Aktueller wissenschaftlicher Stand

Eine Studienübersicht

Keramik-Implantologie | Störfelder der Mundhöhle | für die Zahnmedizin relevante Vitamine

Current scientific status

Study overview

Ceramic-implantology | Interference fields of the oral cavity | Vitamins relevant for dentistry

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Liebe Kolleginnen und Kollegen!

Als ich im Jahre 2001 die ersten Keramikimplantate gesetzt habe, wurde mir aufgrund des hervorragenden Einheilverhaltens und der unglaublichen Weichteilverhältnisse sehr schnell klar, dass dies die Zukunft der Implantologie darstellen würde.

Was ich allerdings unterschätzt hatte, war die Tatsache, dass es doch viel länger dauern würde, bis sich diese neue Technologie schrittweise im Mainstream etablieren wird. Auch Heliane Canepa, damals CEO des damaligen Weltmarktführers Nobel Biocare hatte diese Entwicklung unterschätzt, als sie 2005 auf dem Worldmeeting die Aussage machte: «Im Jahre 2010 wird sich kein Mensch mehr Metall einsetzen lassen!». Doch schon lange vor meiner Zeit hatten Pioniere wie Prof. Schulte, Prof. Sandhaus und auch Dr. Dr. Rudelt aus Hamburg-Eppendorf mit Keramikimplantaten experimentiert und im Falle von Aluminiumoxid zwar hohe Frakturraten hinnehmen müssen, jedoch schon damals die perfekte Osseointegration und das hervorragende Weichgewebeverhalten dokumentiert.

Seit dem Jahre 2019 sieht es so aus, dass Keramik tatsächlich im Mainstream angekommen ist, wenn bereits traditionelle Gesellschaften wie die Neue Gruppe, welche seit 60 Jahren existiert, einen gesamten Kongress der Keramikimplantologie widmet und durchweg alle namenhaften Referenten sich für Keramik aussprechen. Aber auch nicht auf Keramik bezogene Kongresse wie die Esthetic-Days in Baden-Baden hatten 2019 fünf Referenten, welche zum Thema Keramikimplantate sprachen. Laut Prof. Terheyden (ehemaliger Präsident der DGI, der größten implantologischen Gesellschaft Europas) ist Keramik materialmäßig dem Titan deutlich überlegen, handelt es sich hierbei doch um ein ausreagiertes Material, welches bereits oxidiert ist und dadurch keine freien Elektronen mehr besitzt, um irgendwelche Reaktionen einzugehen. Ganz im Gegensatz zum Titan, bei dem es sich um ein hochreaktives Material handelt.

Auf dem Keramik-Kongress der Neuen Gruppe 2019 in Köln wurde durch die Vorträge von Prof. Terheyden, Prof. Bosshardt, Prof. Strub und Prof. Mombelli sehr deutlich, dass Keramik von den Erfolgsraten der Osseointegration und allen sonstigen Parametern, welche den Erfolg beim Patienten ausmachen, Titan auf jeden Fall ebenbürtig ist und im Bereich des Weichgewebeverhaltens sogar deutliche Vorteile zeigt. Einig sind sich dabei alle, dass für Keramik die Datenlage noch deutlich schwächer ist als für Titan, welches einen Vorsprung von 40 Jahren und vier Millionen gesetzten Implantaten aufweist. Mit der ersten Ausgabe einer Studienübersicht zur Keramikimplantologie hatten wir Ihnen gezeigt, welche Studien von mir und Swiss Dental Solutions (SDS) durchgeführt wurden und welche Studien aktuell bereits laufen bzw. in der Planung sind. Darüber hinaus sollte sie einen guten Überblick über die aktuelle Studienlage geben.

Dear Colleagues!

After inserting the first ceramic implants in 2001 I quickly realized, this would be the future of implantology due to the excellent osseointegration and the perfect soft tissue conditions.

But I completely underestimated that this new technology would take much longer to establish itself in the mainstream market. Heliane Canepa, CEO of the former world market leader Nobel Biocare, also underestimated this development by declaring at the 2005 World Meeting: "In 2010, no person wants metal replacements anymore!" Before I started using this new technology Prof. Schulte, Prof. Sandhaus and Dr. Dr. Rudelt from Hamburg-Eppendorf pioneered in the field of ceramic implants. Even though they had to accept high fracture rates with aluminum oxide implants, they documented the perfect osseointegration and excellent soft tissue behavior.

Since 2019, there are growing indications that ceramics have entered the mainstream market. In September 2019 traditional societies such as the New Group, which has existed for 60 years, dedicated an entire congress to ceramic implantology and all renowned speakers spoke in favor of ceramics. At different conferences, which are not directly related to ceramics, talks on ceramic implantology were given such as by five speakers at the Esthetic-Days in Baden-Baden in September 2019. According to Prof. Terheyden (former president of the DGI, the largest implantological society in Europe), as a material, ceramic is superior to titanium, because it is already oxidized and does not have free electrons to undergo any further reactions. This is in contrast to titanium, which is a highly reactive material.

At the Ceramic Congress of the "Neuen Gruppe" in Cologne 2019, Prof. Terheyden, Prof. Bosshardt, Prof. Strub and Prof. Mombelli presented evidence for ceramics: the success rate of osseointegration and other criteria for the patient's acceptance rate are on the same level as titanium. Ceramics have a significant advantage in the field of soft tissue behavior. All of the speakers agreed that the data available for ceramic implants are much weaker than for titanium. Titanium implants have an advantage of around 40 years and millions of implants have been already inserted. In our first study review of ceramic implantology we presented you the studies from myself and the SDS Swiss Dental Solutions and also the ongoing and planned studies. In addition, the review should provide a good overview of the existing studies.

In der vorliegenden zweiten Ausgabe wurde diese Übersicht ergänzt und es wurden weitere Themen hinzugefügt. Für den vorliegenden Kontext relevante Studien aus der Welt der Titanimplantate wurden ausgewählt mit besonderer Beachtung des Aspektes der Periimplantitis.

Daran schließt sich eine Zusammenstellung von Studien an, die weitere Belastungen und pathologische Prozesse thematisieren, die aus der Mundhöhle heraus als sog. Störfelder an der Entstehung oder Aufrechterhaltung chronischer systemischer Erkrankungen mitwirken können. Zu ihnen zählen wurzelbehandelte Zähne, Belastungen durch Metalllegierungen (insbesondere, aber nicht nur Amalgam) sowie FDOKs. Die Verstärkung der Problematik von Dentalmetallen durch die zunehmenden Interferenzen mit künstlichen elektromagnetischen Feldern (EMF) wird hier gesondert herausgestellt, wobei diese erst rudimentäre Sektion in kommenden Jahren mit Sicherheit einen enormen Zuwachs an wissenschaftlichen Arbeiten erfahren wird, Stichwort Mobilfunknetz 5G!

Das abschließende Kapitel führt erstmals Studien der für die Mundhöhle so wichtigen Vitamine C, D3 und K2 auf, wobei sich die Gliederung jeweils an für die Zahnheilkunde wichtigen Aspekten orientiert.

Wir hoffen, dass wir Ihnen mit dieser wesentlich erweiterten zweiten Ausgabe ein erneut interessantes und spannendes Dokument an die Hand geben, welches Ihnen bei der Arbeit im Rahmen der biologischen Zahnmedizin mit Keramikimplantaten den Rücken stärkt, und würden uns freuen, wenn Sie uns weitere Studien, welche hier nicht aufgeführt sind, zukommen lassen, sodass diese in der nächsten Ausgabe erscheinen können.

In this second edition, the overview has been extended and more topics have been included. Studies on titanium implants which are relevant to the present context were selected with special attention to the aspect of peri-implantitis.

It is followed by a collection of studies that focus on further stressors and pathological processes located in the oral cavity. As so-called interference fields they might contribute to the development or maintenance of chronic systemic diseases. These include root-treated teeth, exposure to metal alloys (especially, but not only, amalgam) and FDOJs. The increasing interaction of dental metals and artificial electromagnetic fields (EMF) will be mentioned, although this rather rudimentary section will certainly experience an enormous increase in research in the coming years, keyword: mobile phone network 5G!

The final chapter presents studies on the vitamins C, D3 and K2, which are important for the oral cavity. The classification is based on aspects that are important for dentistry.

With this expanded second edition we hope to provide you again an interesting and inspiring document that will support you in applying biological dentistry and using ceramic implants. We would be grateful if you would send us further studies that are not listed in this document, so we can publish them in the next issue.

Mit kollegialen Grüßen / Yours sincerely,

Dr. Ulrich Volz

Dr. Karl Ulrich Volz

1. Ceramic Implantology

1.1 Own Studies/Dissertations

1.1.1 Finished Studies/Dissertations

Dissertation University Ulm 2006.

Klinische Nachuntersuchung von Zirkondioxidkeramik-Implantaten – Funktion als Kalzium-Kathode.

First long term results - A clinical report of zirkondioxide-implants.

Schlömer G, Volz KU, Sidharta J, Haase S

ABSTRACT

The study should give more information to the question if dental implants built of zircondioxide (producer: Z-Systems, Konstanz, GER) will show the same success rates as titanium implants have shown over the years. Present studies raise the question if titanium may cause harm to the human immune system, therefore it is necessary to find a material which can replace titanium implants. In the study 92 zircondioxide-implants were examined which were placed in 34 patients. 66 Z1/Z2-implants were placed with a mean incorporating time of 3.5 years. 26 implants were Z3-implants which were first placed in 2003. They were incoporated with a mean time of 1.8 years. 6 implants were placed in the anterior region, 86 implants in the posterior region. Nearly all implants were single tooth restorations (85), 7 implants were restored in short span bridges.

Success of the implants were measured by the means of sulcus depth measurements, attachment levels, radiographic analysis of bone density around the implants, acoustic tests of osseointegration, API, SBI and by asking patient opinions to assess the implant success. The overall implant success rate was 96.7% which is comparable to success rates with titanium implants.

In the radiographic density analysis of the implant surrounding bone, 98% of all zircondioxide-implants showed a significant increase of bone matrix in the compacta zone compared to time of placement. Obviosly the ceramic implants lead to a gain in marginal bone strength which is according to literature not that often seen with titanium implants. This may be observed due to an optimal physiological loading of the marginal bone through the one-piece-implants, or a biological influence of the zircondioxide may lead to a strengthened bone around these implants.

No implant showed a sulcus depth of more than 3 mm. 89 of 92 implants sounded perfectly while tapped with a metal instrument which is a manual test of osseointegration. Plaque accumulation tests showed a similar results compared to other testings of ceramic materials in the literature: the plaque accumulation on zircondioxide-implants is very low, 12 of 34 patients had less plaque accumulation on the implants than on the natural teeth. The implants showed no recessions or changes in attachment levels concerning the soft tissues.

The study underlines the capacity of zircondioxide-implants (Z-Systems) to be a substitute of titanium based implants. The success rates show similar results, the observation of a strengthened marginal bone is encouraging for the long term results.

Zirconia implants of the first generation. Late implants without application of the Swiss Biohealth Concept.

Dissertation University Hamburg 2017.

Erfolg von dentalen Keramikimplantaten und Patientenzufriedenheit nach Sofortimplantation.

Success of dental ceramic implants and patient satisfaction after immediate implant placement.

Henningsen A, Neuhöffer L, Stolzer C, Volz KU, Gosau M, Smeets R.

ABSTRACT

The aim of this study was the investigation of the outcome of immediate implants of a ceramic implant system (Swiss Dental Solutions) after immediate and conventional loading in the upper and lower jaw and their osseointegration. The success rate with regard to peri-implant bone height and soft tissue behavior of this procedure were determined with regard to patient-related and prosthetic factors. Additionally patient satisfaction was determined by a questionnaire (OHIP). The study included patients treated from June 2013 to June 2015 in the dental practices of Dr. Scholz (former Dr. Volz and Dr. Scholz), Konstanz, Dr. Steinbach & colleagues, Stuttgart and Paracelsus Klinik Lustmühle, CH-Teufen with immediate and late implants and immediate and conventional loading.

After 783 days of maximum observation time survival rate was 92% and a success rate 91.3%. Bone loss over the entire study period was -0.58 mm for immediate implants and -0.73 mm for late implants. A statistically significant influence of type of loading and time point of placement on the implant success and the peri-implant radiological bone loss was not found. The mean pink esthetic score for the immediate implants was 12.14 and 12.3 points, and for the OHIP questionnaire the response rate was n = 22 (53.7%) with an average of 0.54 points.

The survival probability after about 26 months in this study was for immediate implants 90.3% and for late implants 97.3%. Depending on the type of loading, a survival probability of 93.5% for implants with immediate loading after approximately 20 months and of 86.5% for implants without immediate loading after 26 months was found. Taking into account the inclusion criteria dental zirconia implants are suitable for immediate implantation and immediate loading after a strict indication.

Immediate implantations without application of the Swiss Biohealth Concept.

1.1.2 Ongoing Studies/Dissertations

Study in cooperation with the Clinic Dental Cosmetics Costa Rica, San Josè,

BISS - Bilateral Implant Stabilization System - Eine klinische Studie.

BISS - Bilateral Implant Stabilization System – A clinical study.

Fernández A, Hueber R.

BACKGROUND:
With pronounced bone resorption, immediate implantation with primary stable implant integration is not always possible. A new development by Dr. med. dent. Karl Ulrich Volz, Swiss Dental Solutions, which will offer new opportunities in this area, is the new Bilateral Implant Stabilization System (BISS).

METHODS:
The Bilateral Implant Stabilization System is incorporated in patients with severe bone loss, where a primary stability of an implant is not possible. A stabilization of the augmented bone is achieved by the flexible osteosynthesis plate of the BISS, which simultaneously forms a firm screw connection with the interface of the SDS-implants. On the one hand, it acts as a parasol that keeps the periosteum at a distance, while at the same time allowing for immediate osseointegration of the stabilized implants with lamellar bone.

Dissertation University Hamburg.

Untersuchung des Implantationszeitpunktes auf das krestale Knochenniveau bei einteiligen Keramikimplantaten.
Crestal bone level changes in immediate vs. delayed placed zirconia implants (one-piece zirconia implants).

Stolzer C [1], Smeets R [1], Alkhouri S.

AUTHOR INFORMATION:
1 Dptm. Of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Division of Orofacial Reconstruction.

MATERIAL:
A retrospective study, evaluation of 300 implants: 150 immediate implants / 150 late implants.

FUNDING PROGRAM:
SDS

MULTICENTER STUDY:
Dental office Dr. Witthöft, dental office Dr. Vajen, dental office Dr. Nischwitz.

METHODS:
Evaluation of the data: crestal bone level, oral hygiene indices, prosthetic success and evaluation of all X-ray images.

CURRENT STATUS:
Recording the parameters of treatment documentation.

With application of the Swiss Biohealth Concept.

Dissertation University Hamburg.

Untersuchung des Implantationszeitpunktes auf das krestale Knochenniveau bei zweiteiligen Keramikimplantaten.

Crestal bone level changes in immediate vs. delayed placed zirconia implants (two-piece zirconia implants).

Stolzer C[1], Smeets R[1], Arnim L.

AUTHOR INFORMATION:
1 Dptm. Of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Division of Orofacial Reconstruction.

MATERIAL:
A retrospective study, evaluation of 300 implants: 150 immediate implants / 150 late implants.

FUNDING PROGRAM:
SDS

SINGLECENTER STUDY:
Dental office Dr. NischwitzZ

METHODS:
Evaluation of the data: crestal bone level, oral hygiene indices, prosthetic success and evaluation of all X-ray images post-operative and 12 months and/or 24 months after prosthetics.

With application of the Swiss Biohealth Concept

Dissertation University Hamburg.

Korrelation des Vitamin D3-Spiegels im Blut in Bezug auf die Verlustrate von Keramikimplantaten – in vivo Humanstudie.

Correlation of blood vitamin D3 levels in relation to the loss rate of zirconia implants - in vivo human study.

Stolzer C[1], Smeets R[1], Eberhard L.

AUTHOR INFORMATION:
1 Dptm. Of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Division of Orofacial Reconstruction

AIM:
The aim of this study is to evaluate the clinical significance of vitamin D blood levels in relation to the loss rate of dental zirconia and titanium implants.

MATERIAL:
A case-control study on 200 zirconia implants.

METHODS:
Evaluation of the following data: `Percussion test` (manual and Ostell-/Periotest measurement -> Opt. stability: 0-8), insertion test (insertion torque 15 N/cm), blood test and loss rates.

CURRENT STATUS:
Votum of ethic committee, data collection, further parameters where required: Osteocalcin, Betacrossleps, PIMP, AP and if indicated bone AP, K2, DPD and crosslinks in urine.

Dissertation University Hamburg.

Simultaneous sinuslift and implantation using Bone growing Zirconiumoxide implants and advanced platelet-rich fibrin (A-PRF) as sole grafting material.

Stolzer C[1], Smeets R[1], Hutfilz S[2]

AUTHOR INFORMATION:
1 Dptm. Of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Division of Orofacial Reconstruction.
2 SHBZ Dptm. of Oralsurgery and Biological Dentistry Chemnitz.

PURPOSE:
To assess the relevance of simultaneous sinuslift with a modified zirconoxid implant and implantation with advanced - and platelet-rich fibrin (A-PRF, Choukroun's technique) as sole subsinus filling material.

MATERIALS:
A modified zirconoxide implant from the company SDS Swiss Dental Solutions is used. At its apical end, this has a discus-shaped plateau to support the Schneiderian membrane on a large area and at the same time minimising the risk of perforations of the Schneiderian membrane The creation of a large peri-implant cavity creates a "bioactive container" by initiating predictable bone formation by supporting and using the APRF as a sole grafting material. Clinical and radiographic follow-up will be performed just after implant placement and after six months.

Dissertation University Hamburg.

Blutlaborparameter in Bezug auf ihre klinische Aussagekraft bezüglich der Prädiktierbarkeit des Erfolges auf Implantationen zu prüfen (Titan).

Blood laboratory parameters in relation to their clinical significance in regard to the predictibility of success on implantations (titanium).

Stolzer C1, Smeets R1, Wegener A.

AUTHOR INFORMATION:
1 Dptm. Of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Division of Orofacial Reconstruction

MATERIAL:
300 CaseS

SINGLECENTER STUDY:
Swiss Biohealth Clinic, Kreuzlingen

METHODS:
Laboratory chemical analysis.

CURRENT STATUS:
Determination of the parameters in cooperation with the Institute of Osteology at the UKE. Several parameters are important (Barvencic) Osteocalcin, Betacrossleps, PIMP, AP and if indicated bone AP, K2, DPD and crosslinks in urine.

Dissertation University Bonn.

Auswirkungen der biologischen Zahnmedizin auf den allgemeinen Gesundheitszustand des Patienten

The effects of biological dentistry on the health status of patients.

Wittmann M, Kneer M, Spalek M.

MATERIAL:
100-300 Patients

SINGLECENTER STUDY:
Swiss Biohealth Clinic, Kreuzlingen

METHODS:
Longitudinal study, use of the Medical Symptoms Questionnaire (MSQ) as a data ascertainment: comparison of MSQ results before and after surgery. Statistical evaluation of the data. The results are tested for significance using a T-test. The Levene test is used to calculate the variance of the variables. At $p > 0.05$, equality of variances is assumed. The frequency distribution of the variables is checked with the chi-square test.

CURRENT STATUS:
The study is in preparation for submission to the Ethics Committee.

Dissertation University Marburg

Untersuchung der Erfolgsquote von keramischen Sofortimplantaten im Oberkiefer-Seitenzahnbereich mit und ohne simultanen internen Sinuslift

Evaluation of the success rate of immediate zirconia implants placed in the maxillary posterior region with and without simultaneous internal sinus lift

Sättele D, Ziebart T, Swiss Biohealth Academy.

DESIGN:
Retrospective study

MATERIAL:
All immediate zirconia implants (SDS) in the maxillary posterior region (regions 14-17 and 24-27) which have been inserted and prosthetically restored at the Swiss Biohealth Clinic, Kreuzlingen/Switzerland, from 01.01.2017 to 31.12.2019 are included. The treatments were carried out by applying the Swiss Biohealth Concept.

METHODS:
The present study is divided into four groups: Immediate implantation without internal sinus lift in inconspicuous extraction sockets, immediate implantation without internal sinus lift in extraction sockets with periapical pathologies, immediate implantation with internal sinus lift in inconspicuous extraction sockets, immediate implantation with internal sinus lift in extraction sockets with periapical pathologies.

Determination of the frequency and extent of periapical pathologies and evaluation of the sinus floor profile (sinus floor inclination angle) by evaluation of the DVT (preoperative). The following parameters are determined on the orthopantomogram: Implant length and marginal bone level.

For immediate implants with simultaneous internal sinus lift further parameters are determined: residual bone height, apical bone deficit, apical bone gain.

CURRENT STATUS:
Recording the parameters in February 2020.

1.1.3 Planned Studies/Dissertations

Dissertation Uni XXX.

Drehmoment bei Sofortimplantation: Welches Drehmoment kann durch das scharfe Gewinde erreicht werden?

The insertion torque and immediate implant placement: Which torque can be achieved with the sharp thread?

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Prospective study

MATERIAL:
100 zirconia implants, anterior and posterior region will be examined separately.

METHODS:
Application of countersinks which correspond to the outer diameter (insertion torque 0 in the cortical bone). Determination which insertion torques can be achieved with the implant thread (up to a maximum of 80N/cm). Evaluation of the data, survival rate after six months with provisional restoration and marginal bone loss.

Dissertation Uni XXX.

Einheilung von Keramikimplantaten in den ersten drei Monate in Bezug auf den Vitamin D3- und LDL-Wert.

Osseointegration of zirconia implants in the first three months in relation to vitamin D3 and LDL levels.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Prospective study

MATERIAL:
100 zirconia implants

METHODS:
Measuring of the patient`s vitamin D3 and LDL-levels at the time of registration at the Swiss Biohealth Clinic, on the day of dental surgery and six months post-operative at the time of final prosthetic restoration. Evaluation of the data: survival rate and subjective parameters of each patient with a questionnaire.

Dissertation Uni XXX.

Einfluss des Implantatwinkels auf die Erfolgsrate von Sofortimplantaten bezogen auf den Limbus alveolaris.

Influence of the implant angle on the success rate of immediate implants in relation to the alveolar limb.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Prospective study

MATERIAL:
100 zirconia implants (50 posterior maxilla – 50 posterior mandible)

METHODS:
Evaluation of the data: survival rate, bone loss and determination of each implant angle by using a DVT post-operative (Sidexis software).

Dissertation Uni XXX.

Knochenaufbau durch Keramikimplantate?
Eine prospektive Studie zur Ermittlung der periimplantären Knochenanlagerung.

Bone growth around zirconia implants?
A prospective study to determine peri-implant bone growth.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Prospective study

MATERIAL:
100 zirconia implants (25 anterior maxilla – 25 anterior mandible – 25 posterior maxilla – 25 posterior mandible).

METHODS:
Measurement of bone density using the Sidexis software at three different positions of the implant: 1. position in the middle of fine thread 2. at the transition of fine thread to coarse thread 3. at the apical end of the implant. Evaluation of the data: measurement of marginal bone loss and determination of the survival rate.

Dissertation Uni XXX.

Der Einfluss des Nahrungsergänzungsmittels Basic Immune auf Gingivitis und Parodontitis.

The influence of the supplement Basic Immune on gingivitis and periodontitis.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
A randomized, blinded study

MATERIAL:
100 patients (50 patients with Basic Immune- and 50 patients with placebo-supplementation.

METHODS:
One subject group and one control group receive Basic Immune or a placebo for four weeks. The influence on gingivitis and periodontitis as well as on other medical parameters (LDL, HRV, stress) should be investigated and evaluated.

Dissertation Uni XXX.

Bone Growth um SDS-Keramikimplantate nach einem Jahr bei Anwendung des Swiss Biohealth Conceptes.

Bone growth around SDS zirconia implants after one year by applying the Swiss Biohealth Concept.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Retrospective study

MATERIAL:
50-200 zirconia implants (SDS)

FUNDING PROGRAM:
SDS

METHODS:
Determination of vertical bone growth (measurement from implant body apical end to crest of bone) and bone density. Detection of vertical bone growth (measurement from implant tip to end of bone) and bone density. X-ray analysis 1. on the day of surgery, 2. three to five months postoperatively at the day of prosthetic restoration and 3. after one year. Measurement of bone gain and soft tissue behavior (soft tissue growth and Esthetic Score) around the implants. Accompanying determination and evaluation of the following data: D3, LDL, if necessary further parameters relating to bone metabolism, state of the patient's health (diagnosis) and intraoperative findings.

Dissertation Uni XXX.

Bestimmung der Knochenklassen in Relation zu Drehmoment und Stabilität (Periotest) von Keramikimplantaten. Einfluss auf die Erfolgsquote und spätere prothetische Versorgung.

Classification of bone in relation to insertion torque and stability (Periotest) of zirconia implants. Influence on the success rate and the final prosthetic restoration.

Swiss Biohealth Academy, Kreuzlingen, Switzerland

DESIGN:
Retrospective study

MATERIAL:
100 zirconia implants (SDS)

METHODS:
Evaluation of the data: Implant type and length, Hounsfield measurement, insertion torque and Periotest measurement, classification of bone, marginal bone loss, determination of survival rate, photo documentation of all inserted implants at the Swiss Biohealth Clinic on the day of surgery and on the day of prosthetics.

1.2 General Studies

1.2.1 Material Properties

Clin Oral Implants Res. 2006 Oct;17(5):565-71.

Zirconia-implant-supported all-ceramic crowns withstand long-term load: a pilot investigation.

Kohal RJ, Klaus G, Strub JR.

ABSTRACT

OBJECTIVES:

The purpose of this pilot investigation was to test whether zirconia implants restored with different all-ceramic crowns would fulfill the biomechanical requirements for clinical use. Therefore, all-ceramic Empress-1 and Procera crowns were cemented on zirconia implants and exposed to the artificial mouth. Afterwards, the fracture strength of the all-ceramic implant-crown systems was evaluated. Conventional titanium implants restored with porcelain-fused-to-metal (PFM) crowns served as controls.

MATERIAL AND METHODS:

Sixteen titanium implants with 16 PFM crowns and 32 zirconia implants with 16 Empress-1 crowns and 16 Procera crowns each--i.e., three implant-crown groups--were used in this investigation. The titanium implants were fabricated using the ReImplant system and the zirconia implants using the Celay system. The upper left central incisor served as a model for the fabrication of the implants and the crowns. Eight samples of each group were submitted to a long-term load test in the artificial mouth (1.2 million chewing cycles). Subsequently, a fracture strength test was performed with seven of the eight crowns. The remaining eight samples of each group were not submitted to the long-term load in the artificial mouth but were fracture-tested immediately. One loaded and one unloaded sample of each group were evaluated regarding the marginal fit of the crowns.

RESULTS:

All test samples survived the exposure to the artificial mouth. Three Empress-1 crowns showed cracks in the area of the loading steatite ball. The values for the fracture load in the titanium implant-PFM crown group without artificial loading ranged between 420 and 610 N (mean: 531.4 N), between 460 and 570 N (mean: 512.9 N) in the Empress-1 crown group, and in the Procera crown group the values were between 475 and 700 N (mean: 575.7 N) when not loaded artificially. The results when the specimens were loaded artificially with 1.2 million cycles were as follows: the titanium implant-PFM crowns fractured between 440 and 950 N (mean: 668.6 N), the Empress-1 crowns between 290 and 550 N (mean: 410.7 N), and the Procera crowns between 450 and 725 N (mean: 555.5 N). No statistically significant differences could be found among the groups without artificial load. The fracture values for the PFM and the Procera crowns after artificial loading were statistically significantly higher than that for the loaded Empress-1 crowns. There was no significant difference between the PFM crown group and the Procera group.

CONCLUSIONS:

Within the limits of this pilot investigation, it seems that zirconia implants restored with the Procera crowns possibly fulfill the biomechanical requirements for anterior teeth. However, further investigations with larger sample sizes have to confirm these preliminary results. As three Empress-1 crowns showed crack development in the loading area of the steatite balls in the artificial mouth, their clinical use on zirconia implants has to be questioned.

Dissertation University Freiburg 2006.

Survival rate and fracture resistance of zirconium dioxide implants after exposure to the artificial mouth: An in-vitro study

Kohal RJ, Strub JR, Andreiotelli M, Peters C, Auschill T.

ABSTRACT

The aim of the present study was to evaluate the survival rate and the fracture strength of zirconium dioxide implants, imitating anterior tooth replacement, and to compare the results with those of titanium implants before and after exposure to the artificial mouth.

A total of 120 ceramic and titanium implants were used for the experiment. The Ti-implants were divided into two control groups A (two-piece implants) and B (one-piece implants) including sixteen titanium implants each. The ceramic implants (one-piece implants) were divided into five groups C (Y-TZP BIO-HIP® implants), D (Y-TZP-A BIO-HIP® implants), E (Y-TZP-A BIO- HIP® implants with special surface topography), F (Y-TZP-A BIO-HIP® implants with special surface topography + preparation of the implant heads) and G (Y-TZP-A BIO-HIP® implants with special surface topography + restoration with ZrO2 crowns, different width of the preparation in each subgroup), using sixteen samples of each, with the exception of group D, which included twenty-four samples. The test and the control groups were divided into 15 subgroups of 8 samples each. One subgroup from groups A (A2), B (B2), C (C2), E (E2) and F (F2), two subgroups from group D (D2, D3) and both subgroups from group G (G1, G2) were exposed to 1.2 million thermomechanical loading cycles in the artificial mouth in order to simulate 5 years of clinical service. Fracture of the implants was considered as failure. Then, all test specimens (exposed and not exposed to the artificial mouth) were loaded until fracture occurred in a universal testing machine. After exposure to the artificial mouth the survival rates reported were as follows: A2 87.5%, C2 50%, D3 (no thermocycling) 87.5% and E2 87.5%. All the other subgroups demonstrated a survival rate of 100%.

The observed mean fracture strength values of the subgroups that were not exposed to the artificial mouth were: A1 825 N, B1 5717 N, C1 1337 N, D1 940 N, E1 850 N and F1 578 N. For the samples that were exposed to the artificial mouth the mean fracture strength values were the following: A2 715 N, B2 2749 N, C2 855 N, D2 879 N, D3 980 N, E2 725 N, F2 607 N, G1 542 N and G2 539 N. Among the different groups no statistically significant differences were found, with the exception of subgroup C1 when compared to subgroup E1 and of subgroup E1 when compared to subgroup F1 ($p<0.05$). The results in the present study showed that the preparation of the abutments had a negative influence in the fracture strength values of the implant.

All mean values obtained were within the limits of clinical acceptance, indicating the use of one- piece zirconia implants may be clinically acceptable. However, long-term clinical data are necessary before one-piece zirconia implants can be recommended for daily practice.

Clin Oral Implants Res. 2007 Oct;18(5):662-8. Epub 2007 Jun 30.

Biomechanical and histomorphometric comparison between zirconia implants with varying surface textures and a titanium implant in the maxilla of miniature pigs.

Gahlert M, Gudehus T, Eichhorn S, Steinhauser E, Kniha H, Erhardt W.

ABSTRACT

BACKGROUND:
Mechanical properties and biocompatibility make zirconia ceramics suitable implant material. The characteristics of tooth-color like, the ability to be machined and the low plaque affinity make zirconia especially suitable as a dental implant material. The influence of surface modification on the osseointegration of this material has not been extensively investigated.

PURPOSE:
Long-term investigations with titanium implants have shown superior biomechanical results with the sandblasted acid-etched (SLA) surface, demonstrating a high bone-implant interaction. The objective of this study was to compare two different zirconia surface topographies biomechanically and histologically with the well-documented titanium SLA surface

MATERIAL AND METHODS:
Zirconia implants with either a machined (ZrO2m) or a sandblasted (rough, ZrO2r) surface were manufactured with the exact same cylindrical shape with a standard ITI thread configuration as the SLA titanium implants. The incisors 2 and 3 were removed from both sides of the maxillae of 13 adult miniature pigs and the tissues left to heal for 6 months. After this time period the animals received a total of 78 implants using a randomized scheme, with the titanium SLA implant used as an only individual reference. After healing periods of 4, 8, and 12 weeks 20, 24, and 25 implants, respectively, were subjected to removal torque tests (RTQ) as the main biomechanical analysis of the study. A fewer number was resected on bloc, embedded in methylmethacrylat and analyzed for their direct bone apposition under a light microscope.

RESULTS:
Surface analysis revealed the highest surface roughness for the SLA-implant, followed by ZrO2r and ZrO2m. The turned ZrO2m implants showed statistically significant lower RTQ values than the other two implants types after 8 and 12 weeks, while the SLA implant showed significantly higher RTQs values than ZrO2r surface after 8 weeks. Differences in the bone apposition were observed in the histomorphometric analysis using light microscopy for all surfaces at any time point.

CONCLUSION:
The findings suggest that ZrO2r implants can achieve a higher stability in bone than ZrO2m implants. Roughening the turned zirconia implants enhances bone apposition and has a beneficial effect on the interfacial shear strength.

Materiali in Tehnologije 2007 Sept;41(5):237-241.

The fracture and fatigue of surface-treated tetragonal zirconia (Y-TZP) dental ceramics

Kosmač T, Oblak C, Jevnikar P.

ABSTRACT

The effects of dental grinding and sandblasting on the biaxial flexural strength of Y-TZP ceramics containing the mass fraction of 3 % yttria were evaluated. Dental grinding at high rotation speed lowers the mean strength under static loading and the survival rate under cyclic loading. Sandblasting, in contrast, may provide a powerful tool for surface strengthening also resulting in a substantially higher survival rate under cyclic loading. Fractographic examination of ground specimens revealed that failure originated from radial cracks extending up to 50 μm from the grinding groves into the bulk of the material. However, no evidence of grinding-induced surface cracks could be obtained by SEM analysis of the ground samples, prepared by a standard bonded-interface technique. Sandblasting, in contrast. introduces lateral cracks, which are not detrimental to the strength of Y-TZP ceramics. The "medical-grade" Y-TZP ceramics also containing 0.25 % of dispersed alumina used in this work exhibited full stability under hydrothermal conditions.

Clin Implant Dent Relat Res. 2009 Jun;11(2):158-66.

Fracture strength of zirconia implants after artificial aging.

Andreiotelli M, Kohal RJ.

ABSTRACT

BACKGROUND:

Zirconia (ZrO(2)) might be an alternative material to titanium (Ti) for dental implant fabrication. However, no data are available on the fracture strength of one-piece ZrO(2) oral implants.

PURPOSE:

The objective of this study was to evaluate the fracture strength of ZrO(2) implants after exposure to the artificial mouth.

MATERIALS AND METHODS:

One hundred twenty ZrO(2) and Ti implants were used. The Ti implants were divided into two control groups (A and B). ZrO(2) implants manufactured from yttria-stabilized tetragonal ZrO(2) polycrystal (Y-TZP) in group C, from Y-TZP dotted with alumina (Y-TZP-A) in group D, and from Y-TZP-A with a modified surface in groups E and F were used. In group F, the implant heads were prepared, and in group G, the implants were restored with ZrO(2) crowns. Each group included 16 samples with the exception of group D, which included 24 samples. A subgroup of each implant type (eight implants) was subjected to thermomechanical cycling in a chewing simulator prior to fracture testing. Test specimens were then loaded until a fracture occurred.

RESULTS:

Seven of the 120 samples failed in the chewing simulator. ZrO(2) implant fracture occurred at 725 to 850 N when the implants were not prepared, and at 539 to 607 N when prepared. The samples in group A fractured at the level of the abutment screw. All ZrO(2) implants fractured at the level of the Technovit resin (Heraeus Kulzer GmbH & Co., Wehrheim, Germany). No fracture of the ZrO(2) crowns in group G was observed.

CONCLUSION:

Mean fracture strength values obtained were all within the limits of clinical acceptance. However, implant preparation had a statistically significant negative influence on the implant fracture strength. Long-term clinical data are necessary before one-piece ZrO(2) implants can be recommended for daily practice.

Clin Implant Dent Relat Res. 2009 Dec;11(4):323-9. doi: 10.1111/j.1708-8208.2008.00116.x. Epub 2008 Sep 9.

Stability of prototype two-piece zirconia and titanium implants after artificial aging: an in vitro pilot study.

Kohal RJ, Finke HC, Klaus G.

ABSTRACT

BACKGROUND:

Zirconia oral implants are a new topic in implant dentistry. So far, no data are available on the biomechanical behavior of two-piece zirconia implants. Therefore, the purpose of this pilot investigation was to test in vitro the fracture strength of two-piece cylindrical zirconia implants after aging in a chewing simulator.

MATERIALS AND METHODS:

This laboratory in vitro investigation comprised three different treatment groups. Each group consisted of 16 specimens. In group 1, two-piece zirconia implants were restored with zirconia crowns (zirconia copings veneered with Triceram; Espident, Ispringen, Germany), and in group 2 zirconia implants received Empress 2 single crowns (Ivoclar Vivadent AG, Schaan, Liechtenstein). The implants, including the abutments, in the two zirconia groups were identical. In group 3, similar titanium implants were reconstructed with porcelain-fused-to-metal crowns. Eight samples of each group were submitted to artificial aging with a long-term load test in the artificial mouth (chewing simulator). Subsequently, all not artificially aged samples and all artificially aged samples that survived the long-term loading of each group were submitted to a fracture strength test in a universal testing machine. For the pairwise comparisons in the different test groups with or without artificial loading and between the different groups at a given artificial loading condition, the Wilcoxon rank-sum test for independent samples was used. The significance level was set at 5%.

RESULTS:

One sample of group 1 (veneer fracture), none of group 2, and six samples of group 3 (implant abutment screw fractures) failed while exposed to the artificial mouth. The values for the fracture strength after artificial loading with 1.2 million cycles for group 1 were between 45 and 377 N (mean: 275.7 N), in group 2 between 240 and 314 N (mean: 280.7 N), and in the titanium group between 45 and 582 N (mean: 165.7 N). The fracture strength results without artificial load for group 1 amounted to between 270 and 393 N (mean: 325.1 N), for group 2 between 235 and 321 N (mean: 281.8 N), and between 474 and 765 N (mean: 595.2 N) for the titanium group. The failure mode during the fracture testing in the zirconia implant groups was a fracture of the implant head and a bending/fracture of the abutment screw in the titanium group.

CONCLUSIONS:

Within the limits of this pilot investigation, the biomechanical stability of all tested prototype implant groups seems to be - compared with the possibly exerted occlusal forces - borderline for clinical use. A high number of failures occurred already during the artificial loading in the titanium group at the abutment screw level. The zirconia implant groups showed irreparable implant head fractures at relatively low fracture loads. Therefore, the clinical use of the presented prototype implants has to be questioned.

Int J Oral Maxillofac Implants. 2010 Jan-Feb;25(1):95-103.

Evaluation of stresses occurring on three different zirconia dental implants: three-dimensional finite element analysis.

Caglar A, Bal BT, Aydin C, Yilmaz H, Ozkan S.

ABSTRACT

PURPOSE:

The aim of this study was to evaluate the von Mises, compressive, and tensile stresses occurring on three different zirconia dental implants and surrounding bone with three-dimensional finite element analysis.

MATERIALS AND METHODS:

Three different zirconia implants (Z-Systems, Ziterion, and White-Sky), 10 mm in length and 4 mm in diameter, and anterior maxillary bone were modeled using three-dimensional finite element analyses. Zirconia implants were placed into the maxillary left central incisor region. Loading was applied in horizontal and oblique axes (at angles of 90 and 30 degrees with respect to the implant long axes). Oblique loading was 178 N and horizontal loading was 25.5 N.

RESULTS:

Under oblique loading, von Mises stresses for all implants were similar, and under horizontal loading conditions, the highest von Mises stress was found at the buccal and palatal neck region of the Ziterion implant (46.57 MPa). In cortical bone, the highest von Mises stresses were observed at the buccal region of the Z-Systems implant under oblique and horizontal loading conditions (26.65 MPa and 10.74 MPa, respectively). The highest compressive stresses were observed at the implant buccal neck region and cortical bone interface of the Z-Systems implant under oblique and horizontal loading conditions. For both loading conditions, the highest tensile stress values were observed at the implant palatal region and cortical bone interface of the Z-Systems implant.

CONCLUSION:

The von Mises, compressive, and tensile stresses that occurred in cortical bone were higher than those observed in trabecular bone. Generally, the stresses in the Z-Systems implant were higher than in the other zirconia implants. The differences between the stress values occurring on the zirconia implants may be related to the different body and thread designs of these implants.

BIOmaterialien 2010 Nov; 11 (1). Epub 2011 Mai 18

Raue Y-TZP Biokeramikoberflächen für die dentale Implantologie.

Rough Y-TZP bioceramic surfaces for dental implantology

Hildebrand G, Strickstrock M, Grohmann S, Rechtenbach A, Moje H-J, Moje J, Zylla I-M, Liefeith K.

ABSTRACT

Compared with conventional bioceramic systems yttrium stabilized tetragonal zirconia (Y-TZP) ceramics possess some superior mechanical properties, ensuring a broad application in dentistry. Based on enhancing bond strength, sandblasting is a popular method used to achieve this purpose by increasing surface roughness and providing undercuts. In this context Moje Keramikimplantate GmbH 8t Co. KG has a long experience concerning the modification of surface topography of yttrium stabilized tetragonal zirconia (Y-TZP) ceramics containing traces of alumina for applications in dental implant surgery. This sophisticated approach for generating micro structured surfaces of high quality and reproducibility include a special ceramic process technology followed by different abrasive sand blasting regimes. The resulting bioceramic surface displays a mean surface roughness (Ra) ranging from rather smooth surface (0.6 pm) to a microtopography widely accepted as the common golden standard (SLA titanium, Ra: 1.7 pm) in dental implantology. Additionally, even rougher surfaces can be achieved with a mean surface roughness (Ra) of approximately 3 pm. Cell biological analysis with the osteosacarcoma cell line MC3T3-E1 (subclone 4) reveal that the introduced microstructure does not result in any cytotoxic effects imposed on the cells. All materials and topographies investigated promote both adhesion and proliferation of osteoblastic cells. Interestingly, the highest cell count was observed on the Y-TZP sample with a mean surface roughness of Ra 3.0 pm indicating that rougher topographies are favoured by the osteoblasts. Furthermore, cells spread well on all sample surfaces with more spindle shaped phenotypes on the roughened titanium reference.

Material testing further comprised bending strength analysis performed on Y-TZP discs according to current standards. The bending strength of different rough Y-TZP bioceramics varied between 720 and 850 MPa and satisfies the common requirements for dental prosthesis. Since manufacturing and the technology for microstructuring bioceramic surfaces still offers some degrees of freedom to adjust the resulting microtexture and phase distribution the biomechanical properties may be further improved in the future. Certainly, Y-TZP bioceramics with good osteoinductive properties and an enhanced product safety may be generated in the near future.

Biomed Tech 2010; 55 (Suppl. 1) 2010 by Walter de Gruyter.

Topografische, zellbiologische und biomechanische Analyse von Y-TZP Keramiken für die dentale Implantologie.

Topographic, cell biological and biomechanical analysis of Y-TZP ceramics in dental implantology.

Liefeith K, Strickstrock M, Zylla IM, Hildebrand G, Grohmann S, Rost J, Moje HJ.

ABSTRACT

Bioceramic surfaces with a similar roughness to the SLA Titanium surface were manufactured and analyzed topographically and cell-biologically. As expected, all rough Y-TZP ceramic surfaces examined here as well as the SLA Titanium surface do not show any cytotoxic influences on the used osteoblasts. In particular the rough Y-TZP ceramic sample with a Ra-value of approx. 3 µm shows the best results in proliferation due to a higher surface area. A FE-analysis performed to estimate the influence of the load on the surrounding bone tissue was accomplished at different ceramic implant geometries.

J Biomed Mater Res A. 2011 Sep 15;98(4):604-13. doi: 10.1002/jbm.a.33145. Epub 2011 Jun 30.

In vivo comparative biokinetics and biocompatibility of titanium and zirconium microparticles.

Olmedo DG, Tasat DR, Evelson P, Rebagliatti R, Guglielmotti MB, Cabrini RL.

ABSTRACT

Titanium and zirconium are biomaterials that present a layer of titanium dioxide (TiO(2)) or zirconium dioxide (ZrO(2)). As a result of corrosion, microparticles can be released into the bioenvironment, and their effect on tissues is seemingly associated with differences in the physicochemical properties of these metals. The aim of this study was to perform a long-term evaluation of the distribution, destination, and potential risk of TiO(2) and ZrO(2) microparticles that might result from the corrosion process. Wistar rats were i.p. injected with an equal dose of either TiO(2) or ZrO(2) suspension. The following endpoints were evaluated at 3, 6, and 18 months: (a) the presence of particles in blood cells and liver and lung tissue, (b) Ti and Zr deposit quantitation, (c) oxidant-antioxidant balance in tissues, and (d) O(2)(-) generation in alveolar macrophages. Ti and Zr particles were detected in blood mononuclear cells and in organ parenchyma. At equal doses and times postadministration, Ti content in organs was consistently higher than Zr content. Ti elicited a significant increase in O(2)(-) generation in the lung compared to Zr. The consumption of antioxidant enzymes was greater in the Ti than in the Zr group. The present study shows that the biokinetics of TiO(2) and ZrO(2) depends on particle size, shape, and/or crystal structure.

Conference Paper 2014 June.

Effect of the Design on the Strength of Ceramic Implants.

Just BA, Schöne A, Fischer J.

ABSTRACT

OBJECTIVE:

Implants are mechanically stressed during insertion and subsequent functional loading. The aim of this investigation was to evaluate the effect of abutment design and implant diameter of one piece ceramic implants on torsional and bending strength.

METHOD:

Three experimental one piece ceramic implants with different abutment designs (A, B, C) and different diameters (d: 4.0, 4.5, 5.0 mm) went under investigation. To evaluate the torsional strength, implants (n = 9) were inserted into a pig jaw. Static fracture load was measured according to ISO 14801 (n = 15) and facture patterns were correlated with the results of finite element analyses.

RESULT:

During implant placement abutment A failed. Abutment B showed sufficient stability against torsional forces while abutment C revealed superior properties regarding force distribution and clinical handling. Loading according to ISO 14801 always resulted in fracture of the endosseous implant portion. Fracture load was correlated to d3. No fractures occurred within the abutments. Finite element analysis reliably predicted fracture pattern.

CONCLUSION:

The abutment design has a strong impact regarding torsional strength during implant placement. During functional loading the implant diameter seems to be more important in respect to fracture resistance.

Dent Mater. 2015 Dec;31(12):e279-88.

Loading capacity of zirconia implant supported hybrid ceramic crowns.

Rohr N, Coldea A, Zitzmann NU, Fischer J.

ABSTRACT

OBJECTIVE:

Recently a polymer infiltrated hybrid ceramic was developed, which is characterized by a low elastic modulus and therefore may be considered as potential material for implant supported single crowns. The purpose of the study was to evaluate the loading capacity of hybrid ceramic single crowns on one-piece zirconia implants with respect to the cement type.

METHODS:

Fracture load tests were performed on standardized molar crowns milled from hybrid ceramic or feldspar ceramic, cemented to zirconia implants with either machined or etched intaglio surface using four different resin composite cements. Flexure strength, elastic modulus, indirect tensile strength and compressive strength of the cements were measured. Statistical analysis was performed using two-way ANOVA (p=0.05).

RESULTS:

The hybrid ceramic exhibited statistically significant higher fracture load values than the feldspar ceramic. Fracture load values and compressive strength values of the respective cements were correlated. Highest fracture load values were achieved with an adhesive cement (1253±148N). Etching of the intaglio surface did not improve the fracture load.

SIGNIFICANCE:

Loading capacity of hybrid ceramic single crowns on one-piece zirconia implants is superior to that of feldspar ceramic. To achieve maximal loading capacity for permanent cementation of full-ceramic restorations on zirconia implants, self-adhesive or adhesive cements with a high compressive strength should be used.

Clin Oral Implants Res. 2016 Feb;27(2):162-6.

Surface micro-structuring of zirconia dental implants.

Fischer J, Schott A, Märtin S.

ABSTRACT

OBJECTIVE:

Sandblasting with subsequent acid etching is a potential procedure to generate microstructured surfaces on zirconia implants. The aim of the study was to systematically analyze the effect of these process steps on surface morphology and mechanical strength of the implants.

MATERIALS AND METHODS:

Zirconia implant blanks (ceramic.implant, VITA) were sandblasted (105-µm alumina, 6 bar), subsequently HF-etched, and finally heat-treated at 1250°C. Surface topographies were documented by SEM. Surface roughness Ra (n = 4), monoclinic volume fraction in the surface layer (n = 1), and static fracture load (n = 4) were measured.

RESULTS:

Surface roughness Ra reached a maximum of 1.2 µm after 4× sandblasting. Scratches and sharp edges dominated the surface aspect. Fracture load increased with the number of sandblasting cycles with a gain of 30% after 20 cycles. HF etching did not change the Ra values, but sharp edges were rounded and small pits created. A minor decrease in fracture load with increasing etching time was observed. Heat treatment of 1 h reduced the fracture load by 1/3. Longer heat treatment had no further effect. The roughness Ra was not modified by heat treatment. Fracture load was strongly correlated with the monoclinic fraction except for the results obtained directly after acid etching, where a constant monoclinic fraction was observed.

CONCLUSIONS:

Sandblasting with 105-µm alumina followed by 1 h HF etching at room temperature and 1 h heat treatment at 1250°C is a reliable and tolerant process to create a surface roughness of about Ra = 1.2 µm on zirconia implants.

Clin Implant Dent Relat Res. 2017 Apr;19(2):245-252.

The Impact of In Vitro Accelerated Aging, Approximating 30 and 60 Years In Vivo, on Commercially Available Zirconia Dental Implants.

Monzavi M, Noumbissi S, Nowzari H.

ABSTRACT

BACKGROUND:

Despite increased popularity of Zirconia dental implants, concerns have been raised regarding low temperature degradation (LTD) and its effect on micro-structural integrity.

PURPOSE:

This study evaluated the effect of LTD on four types of Zirconia dental implants at 0, 30, and 60 years of artificial aging. The impact of aging on t-m transformation and micro crack formation was measured.

MATERIALS AND METHODS:

Accelerated aging at 15 and 30 hours, approximating 30 and 60 years in vivo, aged 36 Zirconia dental implants: Z systems® (A), Straumann® (B), Ceraroot® (C), and Zeramex® (D). Focused ion beam-scanning electron microscopic analysis determined the micro structural features, phase transformation, and the formation of micro cracks.

RESULTS:

At 15 hours, type A implant presented with micro cracks and t-m transformation of 0.9 µm and 3.1 µm, respectively. At 30 hours, micro cracks remained shallow (1 µm). At 15 hours, type B implant presented micro cracks (0.7 µm) and grain transformation (1.2 µm). At 30 hours, these features remained superficial at 0.6 and 1.5 µm, respectively. Type C implant presented surface micro cracks of 0.3 µm at 15 hours. The depth of t-m transformation slightly increased to 1.4 µm. At 30 hours, number of micro cracks increased at the surface to an average depth of 1.5 µm. Depth of t-m transformation increased to an average of 2.5 µm. At 15 hours, micro cracks remained superficial (0.8 µm) for type D implant and depth of t-m transformation increased to 2.3 µm. At 30 hours, the depth of micro cracks increased to an average of 1.3 µm followed by increased t-m transformation to a depth of 4.1 µm.

CONCLUSION:

Depth of grain transformation remained within 1-4 µm from the surface. The effect of aging was minimal for all Zirconia implants.

J Prosthodont Res. 2018 Apr;62(2):258-263.

Ultimate force and stiffness of 2-piece zirconium dioxide implants with screw-retained monolithic lithium-disilicate reconstructions.

Joda T, Voumard B, Zysset PK, Brägger U, Ferrari M.

ABSTRACT

PURPOSE:

The aims were to analyze stiffness, ultimate force, and failure modes of a 2-piece zirconium dioxide (ZrO2) implant system.

METHODS:

Eleven 2-piece ZrO2 implants, each mounted with ZrO2 abutments plus bonded monolithic lithium disilicate (LS2) restorations, were grouped for 3.3mm (A) and 4.1mm (B) diameter samples. Quasi-static load was monotonically applied under a standardized test set-up (loading configuration according to DIN ISO 14801). The ultimate force was defined as the maximum force that implants are able to carry out until fracture; stiffness was measured as the maximum slope during loading. An unpaired t-test was performed between group A and B for ultimate force and stiffness ($p<0.05$).

RESULTS:

Force-displacement curves revealed statistically homogenous inner-group results for all samples. Failure modes showed characteristic fractures at the neck configuration of the implants independent of the diameter. Mean stiffness was 1099N/mm (±192) for group A, and significantly lower compared to group B with 1630N/mm (±274) ($p<0.01$); whereas mean ultimate force was 348N (±53) for group A, and significantly increased for group B with 684N (±29) ($p<0.0001$).

CONCLUSIONS:

The examined 2-piece ZrO2 implant system mounted to LS2-restorations seems to be a stable unit under in-vitro conditions with mechanical properties compared to loading capacity of physiological force. The metal-free implant reconstructions demonstrated high stiffness and ultimate force under quasi-static load for single tooth replacement under consideration of the dental indication of narrow and standard diameter implants.

Dent Mater J. 2018 Mar 30;37(2):222-228.

Correlations between fracture load of zirconia implant supported single crowns and mechanical properties of restorative material and cement.

Rohr N, Märtin S, Fischer J.

ABSTRACT

Zirconia implants that were restored with veneered zirconia displayed severe chipping rates of the restorations in clinical studies. Purpose of this study was to evaluate the fracture load of different zirconia implant supported monolithic crown materials (zirconia, alumina, lithium disilicate, feldspar ceramic and polymer-infiltrated ceramic) cemented with various cements (Harvard LuteCem SE, Harvard Implant Semi-permanent, Multilink Automix, VITA Adiva F-Cem). Flexural strength and fracture toughness of crown materials and compressive strength of the cements were measured. Fracture load values of crowns fabricated from lithium disilicate, feldspar ceramic and polymer-infiltrated ceramic were increased when cement with high compressive strength was used. Fracture loads for zirconia and alumina crowns were not influenced by the cement. Flexural strength and fracture toughness of the ceramics correlated linearly with the respective fracture load when using adhesive cement with high compressive strength. To achieve sufficient fracture load values, cementation with adhesive cement is essential for feldspar and polymer-infiltrated ceramic.

J Prosthet Dent. 2018 Jan;119(1):138-145.

Influence of cement type and ceramic primer on retention of polymer-infiltrated ceramic crowns to a one-piece zirconia implant.

Rohr N, Brunner S, Märtin S, Fischer J.

ABSTRACT

STATEMENT OF PROBLEM:
The best procedure for cementing a restoration to zirconia implants has not yet been established.

PURPOSE:
The purpose of this in vitro study was to measure the retention of polymer-infiltrated ceramic crowns to zirconia 1-piece implants using a wide range of cements. The effect of ceramic primer treatment on the retention force was also recorded. The retention results were correlated with the shear bond strength of the cement to zirconia and the indirect tensile strength of the cements to better understand the retention mechanism.

MATERIAL AND METHODS:
The retention test was performed using 100 polymer-infiltrated ceramic crowns (Vita Enamic) and zirconia implants (ceramic.implant CI) The crowns were cemented with either interim cement (Harvard Implant semipermanent, Temp Bond), glass-ionomer cement (Ketac Cem), self-adhesive cement (Perma Cem 2.0, RelyX Unicem Automix 2, Panavia SA), or adhesive cement (Multilink Implant, Multilink Automix, Vita Adiva F-Cem, RelyX Ultimate, Panavia F 2.0, Panavia V5 or Panavia 21) (n=5). Additionally ceramic primer was applied on the intaglio crown surface and implant abutment before cementation for all adhesive cements (Multilink Implant, Multilink Automix: Monobond plus; RelyX Ultimate Scotchbond Universal; Vita Adiva F-Cem: Vita Adiva Zr-Prime; Panavia F2.0, Panavia V5: Clearfil Ceramic Primer) and 1 self-adhesive cement containing 10-methacryloyloxydecyl dihydrogen phosphate (MDP) (Panavia SA: Clearfil Ceramic Primer). Crown debond fracture patterns were recorded. Shear bond strength was determined for the respective cement groups to polished zirconia (n=6). The diametral tensile strength of the cements was measured (n=10). Statistical analysis was performed using 1-way or 2-way analysis of variance followed by the Fisher LSD test (α=.05) within each test parameter.

RESULTS:
Adhesive and self-adhesive resin cements had shear bond strength values of 0.0 to 5.3 MPa and revealed similar retention forces. Cements containing MDP demonstrated shear bond strength values above 5.3 MPa and displayed increased retention. The highest retention values were recorded for Panavia F 2.0 (318 ±28 N) and Panavia 21 (605attained retention values between 222 ±16 N (Multilink Automix) and 270 ±26 N (Panavia SA), which were significantly higher (P<.05) than glass-ionomer (Ketac Cem: 196 ±34 N) or interim cement (Harvard Implant semipermanent: 43 ±6 N, Temp Bond: 127 ±13 N). Application of manufacturer-specific ceramic primer increased crown retention significantly only for Panavia SA.

CONCLUSIONS:
Products containing MDP provided a high chemical bond to zirconia. Self-adhesive and adhesive resin cements with low chemical bonding capabilities to zirconia provided retention force values within a small range (220 to 290 N).

1.2.2 Soft tissue Behavior and Microflora

J Prosthet Dent. 1992 Aug;68(2):322-6.

Tissue compatibility and stability of a new zirconia ceramic in vivo.

Ichikawa Y, Akagawa Y, Nikai H, Tsuru H.

ABSTRACT

Tissue reaction and stability of partially stabilized zirconia ceramic in vivo was evaluated with the use of the subcutaneous implantation test. During the experimental period, zirconia ceramic was completely encapsulated by a thin fibrous connective tissue with less than 80 microns thickness. No changes of weight and 3-point bending strength were detected after 12 months of implantation. The result suggests that zirconia ceramic is biocompatible and no degradation of zirconia ceramic occurred.

Int J Oral Maxillofac Implants. 2002 NovDec; 17(6): 793-8.

Bacterial colonization of zirconia ceramic surfaces: an in vitro and in vivo study.

Rimondini L, Cerroni L, Carrassi A, Torricelli P.

ABSTRACT

PURPOSE:

The microbial colonization of new ceramic materials developed for abutment manufacturing was assessed.

MATERIALS AND METHODS:

The materials used in these experiments were disks of 'as-fired' and 'rectified' ceramic material made of tetragonal zirconia polycrystals stabilized with yttrium (Y-TZP) and commercially pure grade 2 titanium (Ti) with corresponding eluates. They were tested in vitro with the following bacteria: Streptococcus mutans, S. sanguis, Actinomyces viscosus, A. naeslundii, and Porphyromonas gingivalis. Proliferation was evaluated on plates by inhibitory halos around pits, previously inoculated with eluates obtained from the materials. Bacterial adhesion on materials was quantified by spectrophotometric evaluation of the slime production by the same bacteria. Moreover, early bacterial adhesion was evaluated in human volunteers and observed with SEM.

RESULTS:

No inhibition of bacterial proliferation using eluates was observed. In vitro as-fired and rectified Y-TZP showed significantly more adherent S. mutans than did Ti disks, while S. sanguis seemed to adhere easily to Ti specimens. No differences were noted for Actinomyces spp and P. gingivalis. In vivo Y-TZP accumulated fewer bacteria than Ti in terms of the total number of bacteria and presence of potential putative pathogens such as rods. No differences were observed between rectified and as-fired Y-TZP.

DISCUSSION:

Overall, Y-TZP accumulates fewer bacteria than Ti.

CONCLUSION:

Y-TZP may be considered as a promising material for abutment manufacturing..

Deutscher Ärzte-Verlag Zahnärztl Impl 2010; 26 (1).

Qualität des periimplantären Weichgewebeattachments von Zirkondioxid-Implantaten (Abutments). Vergleich der Ergebnisse einer Literaturrecherche mit den Erfahrungen aus der eigenen Praxis.

Quality of the periimplant soft tissue attachment of zirconia implants (-abutments). Comparison of the results of a literature review with the experiences of dental practioners.

Mellinghoff J.

ABSTRACT

PURPOSE:
In the present work, zirconia implants are discussed solely with respect to their suitability as stock for peri- implant soft tissue. The aim of the study was to compare the results of a literature review with the results of five years of clinical use in our dental practice.

MATERIAL AND METHODS:
A systematic literature research was conducted in the internet database PUBMED using the key- words 'zircon'*; 'implant', 'soft tissue', 'bacterial adhesion', 'mucosa', 'attachment', 'connective tissue', and 'plaque'. In the clinical part of the work, 65 zirconia implants type Z-Lock-III were inserted in 34 patients according to a surgical protocol, cared for during the healing process using protec- tive measures and examined in annual follow-ups after the placement of the prosthetic superstructure. The mean exposure time was approximately 22 month (min. 1.3 months/ max. 59 months).

RESULTS:
In the literature review, 72 hits were generated, with a total of 16 publications that were relevant for our topic. The studies evaluated soft tissue attachment that was histologically examined, plaque adhesion, bacterial colon- ization with germs associated with periodontal diseases, in- flammation factors of the soft tissue, as well as the influence on the color of the periimplant soft tissue. Compared with TiO2, the implants and abutments of zirconia achieved com- parable or better results in all studies. At all times in the in- vestigation, the evaluation of the clinical findings showed average probing depths between 2 and 3 mm. Plaque and bleeding results were described as exceptionally good. In ad- dition, esthetically pleasing results could be achieved even with soft tissue in problematic condition.

CONCLUSIONS:
Zirconia implants and abutments provide a very good periimplant soft tissue interface that achieves an irritation-free attachment. From an esthetic point of view, there are notable advantages for using Zirconia as compared to TiO2 when dealing with a very thin gingiva Typ II and a high smile line.

J Periodontol. 2004 Feb;75(2):292-6.

Bacterial adhesion on commercially pure titanium and zirconium oxide disks: an in vivo human study.

Scarano A, Piattelli M, Caputi S, Favero GA, Piattelli A.

ABSTRACT

BACKGROUND:

Little is known about the mechanisms of bacterial interaction with implant materials in the oral cavity. A correlation between plaque accumulation and progressive bone loss around implants has been reported. Bacterial adhesion shows a direct positive correlation with surface roughness. Other surface characteristics also seem to be extremely important with regard to plaque formation. Different adhesion affinities of bacteria have been reported for different materials. The aim of this study was to characterize the percentage of surface covered by bacteria on commercially pure titanium and zirconium oxide disks.

METHODS:

Ten patients participated in this study. A removable acrylic device was adapted to the molar-premolar region, and commercially pure titanium (control) and zirconium oxide (test) disks were glued to the buccal aspect of each device. The surface roughness of titanium and test specimens was similar. After 24 hours, all disks were removed and processed for scanning electron microscopy, for the evaluation of the portion of surface covered by bacteria.

RESULTS:

In control specimens, the area covered by bacteria was 19.3% +/- 2.9; in test specimens, the area was 12.1% +/- 1.96. The disk surface covered by bacteria on test specimens was significantly lower than that of control specimens (P = 0.0001).

CONCLUSION:

Our results demonstrate that zirconium oxide may be a suitable material for manufacturing implant abutments with a low colonization potential.

J Dent. 2012 Feb;40(2):146-53. doi: 10.1016/j.jdent.2011.12.006. Epub 2011 Dec 9.

Surface properties of titanium and zirconia dental implant materials and their effect on bacterial adhesion.

Al-Radha AS, Dymock D, Younes C, O'Sullivan D.

ABSTRACT

OBJECTIVES:

Zirconia ceramic material has been widely used in implant dentistry. In this in vitro study the physiochemical properties of titanium and zirconia materials were investigated and the affinity of different bacteria to different materials was compared.

METHODS:

Disc samples with different surface states were used: polished partially stabilized zirconia (PZ), titanium blasted with zirconia (TBZ), titanium blasted with zirconia then acid etched (TBZA), and polished titanium (PT) as a control. Surface topography was examined using scanning electron microscopy and profilometry. Contact angle, surface free energy (SFE), surface microhardness and chemical composition were determined. Disc samples were separately incubated with Streptococcus mitis and Prevotella nigrescens, either with or without pre-coating with human saliva, for 6h and the surface area covered by bacteria was calculated from fluorescence microscope images.

RESULTS:

PZ and TBZ exhibited lower surface free energy and lesser surface wettability than PT. Also, PZ and TBZ surfaces showed lower percentage of bacterial adhesion compared with control PT surface.

CONCLUSIONS:

The zirconia material and titanium blasted with zirconia surface (TBZ surface) showed superior effect to titanium material in reducing the adhesion of the experimented bacteria especially after coating with saliva pellicle. Modifying titanium with zirconia lead to have the same surface properties of pure zirconia material in reducing bacterial adhesion. SFE appears to be the most important factors that determine initial bacterial adhesion to smooth surface.

Implantologie 2014 March 22 (1):65-70.

Zirconia and peri-implant soft tissue – A clinical case observation.

Weng D.

ABSTRACT

In previous years, zirconia implants have predominantly been investigated as to their osseointegrative capacity and their fracture resistance. Recently the focus has shifted toward the interaction between zirconia and peri-implant soft tissues or plaque as well as towards the prosthetic connection between a zirconia implant and its superstructure. This update of a previously published clinical case shows that the affinity between peri-implant soft tissues and zirconia might be improved compared with titanium, which might be beneficial regarding the long-term stability of the peri-implant soft tissue.

Implant Dent. 2015 Feb;24(1):37-41. doi: 10.1097/ID.0000000000000167.

Soft tissue biological response to zirconia and metal implant abutments compared with natural tooth: microcirculation monitoring as a novel bioindicator.

Kajiwara N, Masaki C, Mukaibo T, Kondo Y, Nakamoto T, Hosokawa R.

ABSTRACT

INTRODUCTION:

Zirconia is often used for implant abutments for esthetics. The aim of this clinical study was to compare the effects of zirconia and metal abutments on periimplant soft tissue.

MATERIALS AND METHODS:

Ten maxillary anterior implant patients, 5 with metal abutments and 5 with zirconia abutments, were enrolled in this trial. The soft tissue around the implant abutments was evaluated by 2-dimensional laser speckle imaging and thermography. The blood flow in soft tissue around natural teeth was also measured to correct for differences among the subjects.

RESULTS:

Significantly greater blood flow was detected in the zirconia abutment group (95.64 ± 5.17%) relative to the metal abutment group (82.25 ± 8.92%) in free gingiva (P = 0.0317). Reduced blood flow (by almost 18%) was detected in the tissue surrounding metal abutments compared with the tissue surrounding natural teeth. The surface temperature showed no significant difference for all measurements.

CONCLUSIONS:

These results suggest that blood flow in tissue surrounding zirconia abutments is similar to that in soft tissue around natural teeth. Moreover, zirconia abutments could be advantageous for the maintenance of immune function by improving blood circulation.

Clin. Oral Impl. Res. 2015, 26 (Suppl. 12).

In vitro biofilm formation on commercially available machined and micro-roughened titanium and zirconia implant surfaces.

Roehling S, Astasov-Frauenhoffer M, Hauser-Gerspach I, Braissant O, Engelhardt H, Waltimo T, Gahlert M.

ABSTRACT

BACKGROUND:

It has been shown that biofilm formation and subsequent plaque accumulation on implant surfaces can induce peri-implant infections and that besides surface roughness and surface free energy, the type of biomaterial can also influence the bacterial adhesion and colonization on implant surfaces. In recent years, zirconia has become an alternative to titanium for the fabrication of dental implants and it has been hypothesized that zirconia might have a reduced bacterial adhesion compared to titanium; however, results from experimental studies are rather controversial.

AIM/HYPOTHESIS:

The aim of the present experimental study was to investigate and compare biofilm formation on commercially available machined and micro-roughened zirconia and titanium implant surfaces using an in vitro 3-species biofilm and human plaque samples.

MATERIAL AND METHODS:

Experimental disks made of titanium (Ti-M, Ti-SLA) or zirconia (ZrO2-M, ZrO2-ZLA) with a machined or a sandblasted and acid-etched surface topography, respectively, were produced. Initially, disks were coated with an in vitro 3-species biofilm, consisting of Streptococcus sanguinis, Porphyromonas gingivalis and Fusobacterium nucleatum, or with human plaque samples that were collected from 4 patients within the course of a regular oral hygiene recall. Following to that, the disks were incubated in an anaerobic flow chamber. Finally, after 72 h of incubation, structure, amount, thickness and metabolism of the formed biofilms were evaluated by using scanning electron microscopy (SEM), safranin staining, 4',6 – diamidin-2phenylindol (DAPI) staining combined with confocal laser scanning microscopy (CLSM) and isothermal microcalorimetry (IMC). Each microbiological experiment was conducted 3 times (n = 3) on each type of titanium and zirconia disks.

RESULTS:

The 3-species biofilm evaluation showed structured and organized biofilms only on Ti-SLA, whereas ZrO2-ZLA, ZrO2- M and Ti-M showed single aggregates of bacteria. Additionally, zirconia showed statistically significantly reduced 3-species biofilm thickness compared to titanium (ZrO2-M: 8.41 lm; ZrO2-ZLA: 17.47 lm; Ti-M: 13.12 lm; Ti-SLA: 21.97 lm); however, no differences were found with regard to 3-species-biofilm mass and metabolism. Human plaque analysis showed optical density values of 0.06 and 0.08 for ZrO2-M and ZrO2-ZLA, and values of 0.1 and 0.13 for Ti-M and Ti-SLA, respectively, indicating statistically significantly reduced human biofilm mass on zirconia compared to titanium. Additionally, zirconia revealed statistically significantly reduced human plaque thickness (ZrO2-M: 9.04 lm; ZrO2-ZLA: 13.83 lm; Ti-M: 13.42 lm; Ti-SLA: 21.3 lm) but a similar human plaque metabolism compared to titanium.

CONCLUSIONS AND CLINICAL IMPLICATIONS:

After 72 h of incubation, 3-species biofilm evaluation only showed statistically significant differences between zirconia and titanium with regard to biofilm thickness. However, two out of three quantitative microbiological techniques showed statistically significantly reduced human plaque biofilm formation on zirconia compared to titanium implant surfaces. Thus, it might be suggested that zirconia surfaces might have a reduced disposition for peri-implant plaque formation.

J Clin Periodontol. 2015 Oct;42(10):967-75.

Histological analysis of loaded zirconia and titanium dental implants: an experimental study in the dog mandible.

Thoma DS, Benic GI, Muñoz F, Kohal R, Sanz Martin I, Cantalapiedra AG2, Hämmerle CH, Jung RE.

ABSTRACT

OBJECTIVE:

To assess whether or not peri-implant soft tissue dimensions and hard tissue integration of loaded zirconia implants are similar to those of a titanium implant.

MATERIALS AND METHODS:

In six dogs, two one-piece zirconia implants (VC, ZD), a two-piece zirconia implant (BPI) and a control one-piece titanium implant (STM) were randomly placed. CAD/CAM crowns were cemented at 6 months. Six months later, animals were killed and histomorphometric analyses were performed, including: the level of the mucosal margin, the extent of the peri-implant mucosa, the marginal bone loss and the bone-to-implant contact (BIC). Means of outcomes variables were calculated together with their corresponding 95% confidence intervals.

RESULTS:

In general, the mucosal margin was located coronally to the implant shoulder. The buccal peri-implant mucosa ranged between 2.64 ± 0.70 mm (VC) and 3.03 ± 1.71 mm (ZD) (for all median comparisons $p > 0.05$). The relative marginal bone loss ranged between 0.65 ± 0.61 mm (BPI) and 1.73 ± 1.68 mm (ZD) (buccal side), and between 0.55 ± 0.37 mm (VC) and 1.69 ± 1.56 mm (ZD) (lingual side) ($p > 0.05$). The mean BIC ranged between 78.6% ± 17.3% (ZD) and 87.9% ± 13.6% (STM) without statistically significant differences between the groups ($p > 0.05$).

CONCLUSIONS:

One- and two-piece zirconia rendered similar peri-implant soft tissue dimensions and osseointegration compared to titanium implants that were placed at 6 months of loading. Zirconia implants, however, exhibited a relatively high fracture rate.

J Med Microbiol. 2016 Jul;65(7):596-604. doi: 10.1099/jmm.0.000267. Epub 2016 Apr 19.

Bacterial adhesion and biofilm formation on yttria-stabilized, tetragonal zirconia and titanium oral implant materials with low surface roughness - an in situ study.

Al-Ahmad A, Karygianni L, Schulze Wartenhorst M, Bächle M, Hellwig E, Follo M, Vach K, Han JS.

ABSTRACT

Bacterially-driven mucosal inflammation and the development of periimplantitis can lead to oral implant failure. In this study, initial bacterial adhesion after 2 h, and biofilm formation after 1 day and 3 days, were analysed in situ on novel 3 mol% yttria-stabilized tetragonal zirconia polycrystal samples, as well as on alumina and niobium co-doped yttria-stabilized tetragonal zirconia samples. Pure titanium implant material and bovine enamel slabs served as controls. The initially adherent oral bacteria were determined by 4′,6-diamidino-2-phenylindole-staining. Biofilm thickness, surface covering grade and content of oral streptococci within the biofilm were measured by fluorescence in situ hybridization. No significant differences between the ceramic and titanium surfaces were detectable for either initial bacterial adhesion or the oral streptococci content of the in situ biofilm. The oral biofilm thickness on the implant surfaces were almost doubled after three days compared to the first day of oral exposure. Nevertheless, the biofilm thickness values among the different implant surfaces and controls did not differ significantly for any time point of measurement after 1 day or 3 days of biofilm formation. Significant differences in the covering grade were only detected between day 1 and day 3 for each tested implant material group. The content of oral streptococci increased significantly in parallel with the increase in biofilm age from day 1 to day 3. In conclusion, oral implant zirconia surfaces with low surface roughness are comparable to titanium surfaces with respect to initial bacterial adhesion and biofilm formation.

Clin Oral Implants Res. 2016 Mar;27(3):288-94.

Analysis of P. gingivalis, T. forsythia and S. aureus levels in edentulous mouths prior to and 6 months after placement of one-piece zirconia and titanium implants.

Siddiqi A, Milne T, Cullinan MP, Seymour GJ.

ABSTRACT

BACKGROUND:
It has been suggested that completely edentulous patients harbour fewer periodontopathic bacteria compared with dentate patients, due to the removal of the subgingival periodontal environment. However, reappearance of certain microbes has been reported after the placement of implants in these patients.

AIM:
The aim of this study was to determine whether the periodontopathic bacteria Porphyromonas gingivalis and Tannerella forsythia, as well as the non-periodontopathic bacterium, Staphylococcus aureus, emerged in edentulous patients 6 months after placement of one-piece zirconia and titanium implants.

MATERIALS AND METHODS:
Twenty-six patients were included in the study (titanium = 13, zirconia = 13). Microbial samples were collected from the tongue prior to implant placement and 6 months after implant placement from both the tongue and from around the implants. A qRT-PCR assay using SYBR green/ROX chemistry was used for the detection and quantification of rgp, nuc and karilysin single-copy gene of P. gingivalis, T. forsythia and S. aureus, respectively. Positive controls used in the study were pure bacterial gDNA purified from cultures of P. gingivalis and S. aureus, a cloned sequence of the karilysin gene for T. forsythia, a plaque sample positive for P. gingivalis and T. forsythia, and nasal gDNA for S. aureus.

RESULTS:
The results show that prior to implant placement, all three bacterial species were below the lower limit of quantification in all edentulous patients. The samples collected from the tongue and around the implants remained below the lower limit of quantification for each of the three species. However, all positive controls used in the study were detectable in the samples. qPCR standard curves showed correlation coefficients >0.97 and efficiencies >94.5% (slope range -3.19 to -3.46) for each of the SYBR green PCR assays.

CONCLUSION:
The results of this study indicate that the tested organisms did not emerge 6 months after implant placement irrespective of the nature of the implant biomaterial. A further follow-up of at least 2 years post-implantation of these patients is suggested to determine whether there are any changes in the oral microbiota and whether such changes are associated with the development of peri-implant disease.

Int J Oral Maxillofac Surg. 2017 Aug;46(8):1039-1044.

Papilla and alveolar crest levels in immediate versus delayed single-tooth zirconia implants.

Kniha K, Kniha H, Möhlhenrich SC, Milz S, Hölzle F, Modabber A.

ABSTRACT

The aim of this study was to determine the correlation between the papilla deficit and the distance between the bone crest at the neighbouring tooth and the contact point of the clinical crown (distance 4) for immediate and delayed zirconia implants. This prospective observational study included 78 patients with 82 implants investigated at the 1-year follow-up. Patients received single-unit zirconiaimplants (Straumann PURE Ceramic Implant with ZLA surface) that were placed using either the delayed (group A) or immediate (group B) protocol after tooth extraction. The distance of the alveolar crest of the neighbouring tooth to the height of the interdental papilla and the absence of the papilla were also assessed. There was a strong correlation between the papilla deficit and distance 4 in group A (Spearman's rho=0.64). However, in group B, only a weak correlation between the two distances was found (Spearman's rho=0.28). A full soft tissue margin was generated when distance 4 was 7-8mm or less. Delayed implant placement showed a critical distance between the alveolar crest at the neighbouring tooth and the contact point of the crown risking a visible papilla deficit of between 7mm and 8mm.

J Periodontol. 2017 Mar;88(3):298-307. doi: 10.1902/jop.2016.160245. Epub 2016 Oct 7.

In Vitro Biofilm Formation on Titanium and Zirconia Implant Surfaces.

Roehling S, Astasov-Frauenhoffer M, Hauser-Gerspach I, Braissant O, Woelfler H, Waltimo T, Kniha H, Gahlert M.

ABSTRACT

BACKGROUND:

It has been hypothesized that zirconia might have a reduced bacterial adhesion compared with titanium; however, results from experimental studies are rather controversial. The aim of the present study is to compare biofilm formation on zirconia and titanium implant surfaces using an in vitro three-species biofilm and human plaque samples.

METHODS:

Experimental disks made of titanium (Ti) or zirconia (ZrO2) with a machined (M) or a sandblasted (SLA) and acid-etched (ZLA) surface topography were produced. An in vitro three-species biofilm or human plaque samples were applied for bacterial adhesion to each type of disk, which after 72 hours of incubation was assessed using an anaerobic flow chamber model.

RESULTS:

Zirconia showed a statistically significant reduction in three-species biofilm thickness compared with titanium (ZrO2-M: 8.41 μm; ZrO2-ZLA: 17.47 μm; Ti-M: 13.12 μm; Ti-SLA: 21.97 μm); however, no differences were found regarding three-species-biofilm mass and metabolism. Human plaque analysis showed optical density values of 0.06 and 0.08 for ZrO2-M and ZrO2-ZLA, and values of 0.1 and 0.13 for Ti-M and Ti-SLA, respectively; indicating a statistically significant reduction in human biofilm mass on zirconia compared with titanium. Additionally, zirconia revealed a statistically significant reduction in human plaque thickness (ZrO2-M: 9.04 μm; ZrO2-ZLA: 13.83 μm; Ti-M: 13.42 μm; Ti-SLA: 21.3 μm) but a similar human plaque metabolism compared with titanium.

CONCLUSION:

Zirconia implant surfaces showed a statistically significant reduction in human plaque biofilm formation after 72 hours of incubation in an experimental anaerobic flow chamber model compared with titanium implant surfaces.

Cureus. 2017 Jun 16;9(6):e1361. doi: 10.7759/cureus.1361.

Effect of Different Crown Materials on the InterLeukin-One Beta Content of Gingival Crevicular Fluid in Endodontically Treated Molars: An Original Research.

Saravanakumar P, Thallam Veeravalli P, Kumar V A, Mohamed K, Mani U, Grover M, Thirumalai Thangarajan S.

ABSTRACT

INRODUCTION:

Crown materials used in fixed prosthodontics come into close and prolonged contact with the gingiva.

OBJECTIVE:

The purpose of this study was to evaluate the effect of different crown materials on the interleukin-one beta (IL-1 μm) content of the gingival crevicular fluid and to study which crown material causes the highest inflammation on the marginal gingiva on a biochemical basis.

MATERIALS AND METHODS:

Twenty patients with single endodontically treated tooth were examined. Contralateral teeth were taken as controls. The crown materials in contact with the marginal gingiva were divided into three groups: Group 1- metal, Group2-ceramic, Group 3-zirconia. The collected data were analyzed with International Bibliography of the Social Sciences (IBSS). Statistical Package for the Social Sciences (SPSS) Statistics software 23.0 (IBM Corp, Armonk, New York). All assay procedures were carried out and the results of the collected samples were calculated using the ELISA-AIDTM technique.

RESULTS:

Multiple comparisons using one-way analysis of variance (ANOVA) between the materials on day zero, 45th and 90th day was highly significant with p=0.0005. Pairwise comparison using Tukey's honest significant difference (HSD) posthoc test was also highly statistically significant with p= 0.0005 except for ceramic & zirconia which were significant at p=0.04 on the 90th day. Multiple comparison using repeated measure of ANOVA with Bonferroni correction between day zero, 45th and 90th day was found to be statistically significant only for zirconia (p=0.002).

CONCLUSION:

This study was conducted to evaluate the effect of different crown materials on the amount of marginal gingival inflammation by measuring the IL-1 μm content in gingival crevicular fluid (GCF). At the end of the three-month analysis, it was seen that the zirconia crowns exhibited the least marginal gingival inflammation.

Clin Oral Investig. 2018 Jul;22(6):2335-2343.

Oral bacterial colonization on dental implants restored with titanium or zirconia abutments: 6-month follow-up.

de Freitas AR, Silva TSO, Ribeiro RF, de Albuquerque Junior RF, Pedrazzi V, do Nascimento C.

ABSTRACT

OBJECTIVE:

This investigation aimed to characterize in a 6-month follow-up the microbial profile of implants restored with either titanium or zirconia abutments at the genus or higher taxonomic levels.

METHODS:

Twenty healthy individuals indicative for implant-retained single restorations were investigated. Half of participants were restored with titanium and half with zirconia abutments. Biofilm was collected from the implant-related sites after 1, 3, and 6 months of loading. The 16S rDNA genes were amplified and sequenced with Roche/454 platform.

RESULTS:

A total of 596 species were identified in 360 samples and grouped in 18 phyla and 104 genera. Titanium- or zirconia-related sites as well as teeth showed similar total numbers of operational taxonomic units (OTUs) colonizing surfaces over time. Firmicutes, Proteobacteria, Fusobacteria, Bacteroidetes, and Actinobacteria were the most prevalent phyla with significant differences between different surfaces and time point. Unclassified genera were found in lower levels (1.71% up to 9.57%) on titanium and zirconia samples when compared with teeth, with no significant differences.

CONCLUSION:

Titanium- and zirconia-related surfaces are promptly colonized by a bacterial community similar to those found in the remaining adjacent teeth. Results suggest a selective adhesion of different bacterial genotypes for either titanium or zirconia surfaces. Data also indicate a significant interaction between the relative effects taxa, time point, and sampling site.

CLINICAL RELEVANCE:

The present study disclosed a wider spectrum of microorganisms colonizing either titanium- or zirconia-related microbiomes in very early stage of implant colonization, revealing differences and suggesting a probably specific mechanism for selective bacterial adhesion.

Clin Oral Implants Res. 2019 Jul;30(7):660-669. doi: 10.1111/clr.13451. Epub 2019 May 12.

Tissue integration of zirconia and titanium implants with and without buccal dehiscence defects-A histologic and radiographic preclinical study.

Thoma DS, Lim HC, Paeng KW, Jung UW, Hämmerle CHF, Jung RE.

ABSTRACT

OBJECTIVE:

To histologically and radiographically evaluate soft (primary outcome) and hard tissue integration of two-piece titanium and zirconia dental implants with/without buccal dehiscence defects.

MATERIALS AND METHODS:

In six dogs, five implants were randomly placed on both sides of the mandible: (a) Z1: a zirconia implant (modified surface) within the bony housing, (b) Z2: a zirconia implant (standard surface) within the bony housing, (c) T: a titanium implant within the bony housing, (d) Z1_D: a Z1 implant placed with a buccal bone dehiscence (3 mm in height, identical width to implant body), and (e) T_D: a titanium implant placed with a buccal bone dehiscence. Two weeks of healing and 6 months of loading were applied on each hemi-mandible, respectively.

RESULTS:

The median level of the margo mucosae shifted more apically over time in all groups (borderline statistical significance in groups Z1_D: -0.52 mm and T_D: -1.26 mm). The median height of the peri-implant mucosa in groups Z1_D and T_D was greatest at 2 weeks and 6 months, but the linear change in the peri-implant mucosa was statistically significant only for group T_D over time (-1.45 mm). Z1 demonstrated a higher bone-to-implant contact compared to Z2 and T. Minimal change of radiographic marginal bone levels in all groups was observed (<1 mm).

CONCLUSION:

When buccal dehiscence was presented, titanium implants presented significant loss of peri-implant mucosal height compared to zirconia implants with a modified surface, due to greater apical shift of the margo mucosae. A modified zirconia surface enhanced osseointegration.

1.2.3 Osseointegration

J Prosthet Dent. 1993 Jun;69(6):599-604. doi: 10.1016/0022-3913(93)90289-z

Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing.

Akagawa Y, Ichikawa Y, Nikai H, Tsuru H.

ABSTRACT

Clinical and histologic evaluations of partially stabilized zirconia endosseous implants under unloaded and early loaded conditions in four beagle dogs were performed to examine the possibility of osseointegration of a newly developed one-stage zirconia implant during initial bone healing. No clear difference in clinical features was observed. Direct bone apposition to the implant was generally seen in both implants. However, loss of crestal bone height was quite evident around the loaded implants. These findings suggest that the initial unloaded condition is preferable to achieve osseointegration of one-stage zirconia implants.

J Prosthet Dent. 1998 Nov;80(5):551-8. doi:10.1016/s0022-3913(98)70031-9

Comparison between freestanding and tooth-connected partially stabilized zirconia implants after two years' function in monkeys: a clinical and histologic study.

Akagawa Y, Hosokawa R, Sato Y, Kamayama K.

ABSTRACT

STATEMENT OF PROBLEM:

Partially stabilized zirconia implants placed by a 1-stage procedure have been previously shown to obtain initial osseointegration under clinically unloaded condition. However, it is unknown whether freestanding and tooth-connected partially stabilized zirconia implants can maintain a long-term direct bone-implant interface.

PURPOSE:

This study examined the possibility of the long-term stability of osseointegration around partially stabilized zirconia implants with a 1-stage procedure with different loading designs.

MATERIAL AND METHODS:

Thirty-two partially stabilized zirconia implants were placed into the mandibles of 8 monkeys. Three months after implant placement, 3 types of superstructure were provided in each animal to obtain different concepts of support as (1) single freestanding implant support, (2) connected freestanding implant support, and (3) a combination of implant and tooth support. At 12 and 24 months after loading, clinical, histologic, and histomorphometric evaluations of peri-implant tissues were performed on 28 implants.

RESULTS:

No clear difference in clinical features was observed among the different types of support. Direct bone apposition to the implant was generally seen in all groups. Histometrically, bone contact ratio ranged between 66% and 81%, and bone area ratio varied between 49% and 78% at 24 months after loading. These values showed almost no difference among single freestanding, connected freestanding, and implant-tooth supports of partially stabilized zirconia implants.

CONCLUSION:

In a primate model, partially stabilized zirconia implants placed with a 1-stage procedure achieve long-term stability of osseointegration with the use of single freestanding, connected freestanding, and implant-tooth supports.

Deutscher Ärzte-Verlag Köln Zahnärztl Impl 2003;19(2).

Zirkonoxid-Implantate unter Belastung. Eine vergleichende histologische, tierexperimentelle Untersuchung.

Zirconia implants under occlusal load. A histological animal experiment.

Kohal RJ, Weng D, Bächle M, Klaus G.

ABSTRACT

The aim of this project was to investigate the histological behavior (osseointegration) of loaded ZrO2-implants in an animal model. Five months after extractions of the upper anterior teeth twelve custom-made titanium implants (control group) and twelve custom-made zirconia (PSZ=partially stabilized zirconia) implants (test group) were inserted in the regions of teeth 12, 11, 21, and 22 in six monkeys (Macaca fascicularis). Six months after implant insertion abutment connection was performed (titanium- and zirconia-abutments) and impressions were taken for single crowns. Further three months later, the crowns were inserted. Five months after insertion of the crowns the implants with the surrounding hard and soft tissues were histologically prepared and evaluated under the light microscope regarding the mineralized bone-to-implant contact. All implants showed primary stability during insertion. No implant was lost during the investigational period. The mean mineralized bone-to-implant contact after five months of loading and 14 months of healing amounted to 67.4 % (SD: 17 %) for the zirconia implants. The osseointegration values in the different animals were in the range of 42.4 % to 87.7 %. There was no statistically significant difference to the titanium control group (p = 0.29).

Within the limits of this animal experiment it can be concluded that the utilized custom-made ZrO2 -implants do osseointegrate to the same extent as custom-made titanium control implants.

J Periodontol. 2004 Sep;75(9):1262-8.

Loaded custom-made zirconia and titanium implants show similar osseointegration: an animal experiment.

Kohal RJ, Weng D, Bächle M, Strub JR.

ABSTRACT

BACKGROUND:

Zirconia might be an alternative material to titanium for dental implant fabrication. The aim of the present study was to investigate the histological behavior (osseointegration) of loaded zirconia implants in an animal model and to compare it with the behavior of titanium implants.

METHODS:

Five months after extraction of the upper anterior teeth, 12 custom-made titanium implants (control group) and 12 custom-made zirconia implants (test group) were inserted in the extraction sites in six monkeys. Before insertion, the titanium implant surfaces were sandblasted with Al2O3 and subsequently acid-etched. The zirconia implants were only sandblasted. Six months following implant insertion, impressions were taken for the fabrication of single crowns. A further 3 months later, nonprecious metal crowns were inserted. Five months after insertion of the crowns, the implants with the surrounding hard and soft tissues were harvested, histologically prepared, and evaluated under the light microscope regarding the peri-implant soft tissue dimensions and mineralized bone-to-implant contact.

RESULTS:

No implant was lost during the investigational period. The mean height of the soft peri-implant tissue cuff was 5 mm around the titanium implants and 4.5 mm around the zirconia implants. No statistically significant differences were found in the extent of the different soft tissue compartments. The mean mineralized bone-to-implant contact after 9 months of healing and 5 months of loading amounted to 72.9% (SD: 14%) for the titanium implants and to 67.4% (SD: 17%) for the zirconia implants. There was no statistically significant difference between the different implant materials.

CONCLUSION:

Within the limits of this animal experiment, it can be concluded that the custom-made zirconia implants osseointegrated to the same extent as custom-made titanium control implants and show the same peri-implant soft tissue dimensions.

Clin Implant Dent Relat Res. 2005;7 Suppl 1:S13-20.

Bone tissue responses to surface-modified zirconia implants: A histo-morphometric and removal torque study in the rabbit.

Sennerby L, Dasmah A, Larsson B, Iverhed M.

ABSTRACT

BACKGROUND:
Zirconia ceramics are biocompatible and have mechanical properties that make them suitable as materials for dental implants. Little is known about how surface modification influences the stability and bone tissue response to zirconia implants.

PURPOSE:
The objective of the investigation was to histologically and biomechanically evaluate the bone tissue response to zirconia implants with two different surface modifications in comparison with machined, nonmodified zirconia implants and oxidized titanium implants.

MATERIALS AND METHODS:
Threaded zirconia implants with a diameter of 3.75 mm with either a machined surface (Zr-Ctr) or one of two surface modifications (Zr-A and Zr-B) were manufactured. Oxidized titanium (Ti-Ox) implants 3.75 mm in diameter were also used. The implants were characterized with regard to surface topography using an interferometer. Twelve rabbits received 96 implants using a rotational scheme, two in each tibia and two in each femur. The implants in six rabbits were subjected to removal torque (RTQ) tests after a healing period of 6 weeks. The implants in the remaining six animals were removed en bloc for light microscopic analysis. Back-scatter scanning electron microscopic (BS-SEM) analyses were used to evaluate the state of the bone-implant interface at the modified zirconia implants after RTQ testing.

RESULTS:
The Ti-Ox and Zr-A implants showed the highest surface roughness, followed by the Zr-B implants and, finally, the Zr-Ctr implants. The nonmodified ZrO2 implants showed statistically significant lower RTQs than all other implants. No significant differences in bone-implant contact or bone area filling the threads were observed. BS-SEM showed intact surface layers of the surface-modified implants after RTQ testing and revealed fracture of the interface bone rather than a separation.

CONCLUSION:
The present study showed a strong bone tissue response to surface-modified zirconia implants after 6 weeks of healing in rabbit bone. The modified zirconia implants showed a resistance to torque forces similar to that of oxidized implants and a four- to fivefold increase compared with machined zirconia implants. The findings suggest that surface-modified zirconia implants can reach firm stability in bone.

Dissertation University Munich 2006.

"Untersuchung des Einwachsverhaltens von Zirkoniumdioxid-Implantaten in die Kieferknochenstruktur – Eine experimentelle Studie am Miniaturschwein".

Biomechanical and histomorphometric comparison between zirconia implants with varying surface textures and the titanium SLA implant in the maxilla of miniature pigs.

Gahlert M, Erhardt W, Gudehus H, Schmahl W, Märtlbauer E, Matis U.

ABSTRACT

In comparison to titanium, ZrO2 implants offer a variety of advantages for the use as oral implantologic material. As it is well accepted that implant success is dependent on surface roughness it has been proven that the SLA surface achieves a better bone anchorage than all other comparative tested surfaces.

Even though topological treatment of ZrO2 implants is threatening the stiffness of the endosseous zirconium screws, it has been possible to develop a surface whose average surface roughness amounts to half the one of the SLA surface on titanium screws.
The purpose of the present study was to evaluate the bone anchorage to three different screw shaped implants of various materials and surfaces in a well-established animal model on 13 minipigs comparing the modified sandblasted ZrO2with the machined ZrO2 and the well documented titanium SLA implant.

After 4, 8 and 12 weeks of bone healing, removal torque testing was performed to evaluate the interfacial shear strength of each surface type. In addition 13 implants were evaluated histomorphometrically for the apposition of mineralised structures after 4 and 12 weeks of healing. Even though the titanium SLA surface revealed better results after all healing periods the results remain still positive: The blasted ZrO2 implants yielded a higher mean removal torque than the machined ZrO2 implants especially in the 8 and 12 week animal groups without reaching statistical significance. These results are testified by a higher percentage of bone-to-implant contact for the blasted zirconium screws. It is established that the interlock between implant and in-growth bone for the SLA surface is loosened at the 12 weeks time period. This phenomenon could also be seen around the roughened ZrO2 implants but not around those with machined surfaces and is due to active remodelling processes around an implant surface. If it should succeed to create an analogue surface structure for the ZrO2 screws as it has been realised for titanium by developing the SLA surface, the interfacial biomechanical properties should be comparable.

Taking into account the outstanding aesthetic aspect this newly biomaterial could totally replace titanium in the cases of viewable dental rehabilitations.

Clin Oral Implants Res. 2007 Feb;18(1):53-9.

Behavior of CAL72 osteoblast-like cells cultured on zirconia ceramics with different surface topographies.

Bächle M, Butz F, Hübner U, Bakalinis E, Kohal RJ.

ABSTRACT

OBJECTIVES:

Because of its inherent strength, biocompatibility, and tooth-like color, zirconia ceramics have the potential to become an alternative to titanium as dental implant material. This study aimed at investigating the osteoblastic response to yttrium-stabilized tetragonal zirconia polycrystal (Y-TZP) with different surface topographies.

METHODS:

CAL72 osteoblast-like cells were cultured on machined (TZP-m), airborne particle abraded (TZP-s), and airborne particle abraded and acid-etched Y-TZP (TZP-sa) surfaces. Polystyrene and airborne particle abraded with large grit and acid-etched (SLA) titanium served as a reference control. The surface topography was examined by scanning electron microscopy (SEM) and profilometry. At culture days 3, 6, and 12, cell proliferation, at day 12 cell morphology, and cell-covered surface area were determined.

RESULTS:

The surface roughness of Y-TZP was increased by airborne particle abrasion and additionally by acid etching. No statistically significant differences were found between average roughness (R(a)) and maximum peak-to-valley height (R(p-v)) values of airborne particle abraded and acid-etched Y-TZP and SLA titanium. Whereas the cell proliferation assay revealed statistically significant greater values at day 3 for surface-treated Y-TZP and polystyrene cultures as compared with machined Y-TZP, no differences between the Y-TZP groups, SLA titanium, and polystyrene were observed at culture days 6 and 12.

CONCLUSIONS:

Cell morphology and cell-covered surface area were not affected by the type of substrate. The results suggest that roughened Y-TZP is an appropriate substrate for the proliferation and spreading of osteoblastic cells.

Head Face Med. 2008 Dec 11;4:30. doi: 10.1186/1746-160X-4-30.

Osseointegration of zirconia implants compared with titanium: an in vivo study.

Depprich R1, Zipprich H, Ommerborn M, Naujoks C, Wiesmann HP, Kiattavorncharoen S, Lauer HC, Meyer U, Kübler NR, Handschel J.

AUTHOR INFORMATION

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ABSTRACT

BACKGROUND:

Titanium and titanium alloys are widely used for fabrication of dental implants. Since the material composition and the surface topography of a biomaterial play a fundamental role in osseointegration, various chemical and physical surface modifications have been developed to improve osseous healing. Zirconia-based implants were introduced into dental implantology as an alternative to titanium implants. Zirconia seems to be a suitable implant material because of its tooth-like colour, its mechanical properties and its biocompatibility. As the osseointegration of zirconia implants has not been extensively investigated, the aim of this study was to compare the osseous healing of zirconia implants with titanium implants which have a roughened surface but otherwise similar implant geometries.

METHODS:

Forty-eight zirconia and titanium implants were introduced into the tibia of 12 minipigs. After 1, 4 or 12 weeks, animals were sacrificed and specimens containing the implants were examined in terms of histological and ultrastructural techniques.

RESULTS:

Histological results showed direct bone contact on the zirconia and titanium surfaces. Bone implant contact as measured by histomorphometry was slightly better on titanium than on zirconia surfaces. However, a statistically significant difference between the two groups was not observed.

CONCLUSION:

The results demonstrated that zirconia implants with modified surfaces result in an osseointegration which is comparable with that of titanium implants.

Int J Oral Maxillofac Implants. 2008 Jul-Aug;23(4):691-5.

The zirconia implant-bone interface: a preliminary histologic evaluation in rabbits.

Hoffmann O, Angelov N, Gallez F, Jung RE, Weber FE.

ABSTRACT

PURPOSE:

Zirconia ceramics, a biocompatible material with favorable mechanical properties, has been suggested for use in the manufacture of dental implants instead of the commonly used titanium. Not much data exist on the early healing response around zirconia dental implants. The aim of this study was to give a descriptive histologic assessment of the degree of early bone apposition around zirconia dental implants at 2 and 4 weeks after insertion compared to surface-modified titanium implants.

MATERIALS AND METHODS:

Four zirconia and 4 titanium implants were placed in New Zealand white male rabbits. One implant was inserted in the condyle of each distal femur. Specimens were harvested at 2 and 4 weeks and processed with light microscopic analysis. The area of bone-implant contact was evaluated histomorphometrically.

RESULTS:

A high degree of bone apposition could be observed on all implants at both time points. Differences in the percentage of implant surface covered with bone were noted between the 2 time points, with comparable results for the 2 materials.

CONCLUSION:

The results of this limited histologic study demonstrate a similar rate of bone apposition on zirconia and surface-modified titanium implant surfaces during early healing. To confirm these results, further studies need to be conducted, involving larger sample size at more time points.

Int J Prosthodont. 2008 Jan-Feb;21(1):27-36.

Osseointegration and clinical success of zirconia dental implants: a systematic review.

Wenz HJ, Bartsch J, Wolfart S, Kern M.

ABSTRACT

PURPOSE:

Various ceramic implant systems made of yttria-stabilized tetragonal zirconia polycrystals (Y-TZP) have become commercially available in recent years. A systematic search of the literature was performed to assess the clinical success of dental Y-TZP implants and whether the osseointegration of Y-TZP is comparable to that of titanium, the standard implant material.

MATERIALS AND METHODS:

The internet database MEDPILOT was searched cumulatively for the keywords zircon* and dent* and implant as well as for zircon* and osseointegration. The last search was conducted on January 31st, 2007. Subsequently, the reference lists of the relevant publications were searched. Furthermore, a letter was sent to the 5 identified manufacturers of zirconia dental implants to ask for peer-reviewed publications.

RESULTS:

Ninety-six articles were found by the search strategy. No controlled clinical studies in humans regarding clinical outcomes or osseointegration could be identified. Clinical data were restricted to case studies and case series. Only 7 animal studies fulfilled the inclusion criteria. Osseointegration was evaluated at 4 weeks to 24 months after placement in different animal models and sites and under different loading conditions. The mean bone-implant contact percentage was above 60% in almost all experimental groups. In studies that used titanium implants as a control, Y-TZP implants were comparable to or even better than titanium implants. Surface modifications may further improve initial bone healing and resistance to removal torque.

CONCLUSIONS:

Y-TZP implants may have the potential to become an alternative to titanium implants but cannot currently be recommended for routine clinical use, as no long-term clinical data are available.

Clin Oral Implants Res. 2009 Apr;20(4):333-9.

Biomechanical and histological behavior of zirconia implants: an experiment in the rat.

Kohal RJ, Wolkewitz M, Hinze M, Han JS, Bächle M, Butz F.

ABSTRACT

OBJECTIVE:

This study aimed at evaluating the integration of zirconia implants in a rat femur model.

MATERIAL AND METHODS:

Zirconia implants with two distinct surface topographies were compared with titanium implants with similar topographies. Titanium and zirconia implants were placed into the femurs of 42 male Sprague-Dawley rats. Four groups of implants were utilized: machined zirconia implants, zirconia implants with a rough surface, machined titanium implants, and titanium implants with an electrochemically roughened surface. After a healing period of 28 days, the load-bearing capacity between the bone and the implant surface was evaluated by a push-in test. Additionally, after a healing period of 14 and 28 days, respectively, bone tissue specimens containing the implants were processed and histologically analyzed.

RESULTS:

The mean mineralized bone-to-implant contact showed the highest values after 14 and 28 days for the rough surfaces (titanium: 36%/45%; zirconia: 45%/59%). Also, the push-in test showed higher values for the textured implant surfaces, with no statistical significance between titanium (34 N) and zirconia (45.8 N).

CONCLUSIONS:

Within the limits of the animal investigation presented, it was concluded that all tested zirconia and titanium implant surfaces were biocompatible and osseoconductive. The presented surface modification of zirconia implants showed no difference regarding the histological and biomechanical results compared with an established electrochemically modified titanium implant surface.

Clin Oral Implants Res. 2009 Aug;20(8):844-50. doi: 10.1111/j.1600-0501.2009.01727.x.

Surface-modified zirconia implants: tissue response in rabbits.

Rocchietta I, Fontana F, Addis A, Schupbach P, Simion M.

ABSTRACT

AIM:

To evaluate the bone tissue response to zirconia implants with three different surface modifications in comparison with the oxidized titanium surface with the goal to optimize osseointegration in terms of strength and speed.

MATERIALS AND METHODS:

A total of 18 rabbits with 143 implants were used. One hundred and twenty-three were threaded zirconia ceramic implants with three different surface topographies and 20 modified titanium oxide implants were controls. Each rabbit received eight implants and sacrificed after 3 weeks. The removal torque test (RTQ) and histology were performed.

RESULTS:

Sixteen out of 18 rabbits completed the study with a total of 110 implants. No statistical significance was observed between the chemical modification implants compared with the topographically modified zirconia implant in terms of interfacial shear strength proven by the RTQ applied. No statistical significance was also observed in the bone-to-implant contact between the zirconia implants and the control oxidized implants.

CONCLUSIONS:

The findings suggest that additional specific chemical modifications of the topographically modified zirconia implants do not seem to enhance the bone-to-implant contact and appear not to increase the interfacial shear strength.

Clin Oral Implants Res. 2010 Mar;21(3):350-6.

Osseointegration of one-piece zirconia implants compared with a titanium implant of identical design: a histomorphometric study in the dog.

Koch FP, Weng D, Krämer S, Biesterfeld S, Jahn-Eimermacher A, Wagner W.

ABSTRACT

OBJECTIVE:

The aim of this study was to evaluate osseointegration of one-piece zirconia vs. titanium implants depending on their insertion depth by histomorphometry.

MATERIAL AND METHODS:

Four one-piece implants of identical geometry were inserted on each side of six mongrel dogs: (1) an uncoated zirconia implant, (2) a zirconia implant coated with a calcium-liberating titanium oxide coating, (3) a titanium implant and (4) an experimental implant made of a synthetic material (polyetheretherketone). In a split-mouth manner they were inserted in submerged and non-submerged gingival healing modes. After 4 months, dissected blocks were stained with toluidine blue in order to histologically assess the bone-to-implant contact (BIC) rates and the bone levels (BL) of the implants.

RESULTS:

All 48 implants were osseointegrated clinically and histologically. Histomorphometrically, BL in the crestal implant part did not differ significantly with regard to material type or healing modality. The submerged coated zirconia implants tended to offer the most stable crestal BL. The histometric results reflected the different healing modes by establishing different BL. The median BIC of the apical implant part of the zirconia and titanium group amounted to 59.2% for uncoated zirconia, 58.3% for coated zirconia, 26.8% for the synthetic material and 41.2% for titanium implants.

CONCLUSIONS:

Within the limits of this animal study, it is concluded that zirconia implants are capable of establishing close BIC rates similar to what is known from the osseointegration behaviour of titanium implants with the same surface modification and roughness.

J Clin Periodontol. 2010 Sep;37(9):818-28.

Mechanical anchorage and peri-implant bone formation of surface-modified zirconia in minipigs.

Schliephake H[1], Hefti T, Schlottig F, Gédet P, Staedt H.

AUTHOR INFORMATION

[1]Department of Oral and Maxillofacial Surgery, George-Augusta-University, Göttingen, Germany.

ABSTRACT

AIM:

To test the hypothesis that peri-implant bone formation and mechanical stability of surface-modified zirconia and titanium implants are equivalent.

MATERIALS AND METHODS:

Twelve minipigs received three types of implants on either side of the mandible 8 weeks after removal of all pre-molar teeth: (i) a zirconia implant with a sandblasted surface; (ii) a zirconia implants with a sandblasted and etched surface; and (iii) a titanium implant with a sandblasted and acid-etched surface that served as a control. Removal torque and peri-implant bone regeneration were evaluated in six animals each after 4 and 13 weeks.

RESULTS:

The titanium surface was significantly rougher than both tested zirconia surfaces. Mean bone to implant contact (BIC) did not differ significantly between the three implant types after 4 weeks but was significantly higher for titanium compared with both zirconia implants after 13 weeks ($p<0.05$). Bone volume density (BVD) did not differ significantly at any interval. Removal torque was significantly higher for titanium compared with both zirconia surfaces after 4 and 13 weeks ($p<0.001$). The sandblasted and etched zirconia surface showed a significantly higher removal torque after 4 weeks compared with sandblasted zirconia ($p<0.05$); this difference levelled out after 13 weeks.

CONCLUSIONS:

It is concluded that all implants achieved osseointegration with similar degrees of BIC and BVD; however, titanium implants showed a higher resistance to removal torque, probably due to higher surface roughness.

Deutscher Ärzte-Verlag Zahnärztl Impl 2011; 27 (4).

Vergleich der Osseointegration dentaler Zirkonoxidimplantate mit verschiedenen Gewindeparametern und Oberflächentopographien.

Comparison of osseointegration of dental zirconoxid implants with different thread designs as well as surface topographies.

Mueller CK, Solcher P, Peisker A, Mtsariashvilli M, Schlegel KA, Hildebrand G, Rost J, Liefeith K, Chen J, Schultze-Mosgau S.

ABSTRACT

AIM:
Titanium represents the current standard material in dental implantology. Electrochemical corrosion, sensitization potential as well as esthetic comprise resulted in the testing of zirconiumoxid as an alternative material. Taking this into account it was the aim of the present study to evaluate the osseointegration of different zirconiumoxid implants.

MATERIALS AND METHODS:
A total of 6 different implant designs was evaluated in the study: (1) titanium, zylindric + thread design 1, Ra = 1,7 ìm; (2) zirconiumoxid, cylindric + thread design 1, Ra = 1,7 ìm; (3) zirconiumoxid, cylindric + thread design 2, Ra = 1,7 ìm; (4) zirconiumoxid, conical + thread design 2, Ra = 1,7 ìm; (5) zirconiumoxid, cylindric + thread design 1; Ra = 0,3 ìm and (6) zirconiumoxid, cylindric + thread design 1, Ra = 3,0 ìm. Six different implants were inserted in the frontal skull in each of 10 minipigs. Biopsies were harvested after 2 and 4 months respectively and subjected to microradiography.

RESULTS:
No significant differences between titanium and zirconoxid were found regarding the microradiographically detected bone-implant-contact. Irrespective of the thread design cylindric zirconoxid implants showed a higher BIC at the 2 month follow up than conic zirconiumdioxid implants. Among zirconoxid implants, those with an intermediate Ra value showed a significantly higher bone-implant-contact as compared with low (0,3 ìm) and high (3 ìm) Ra implants 4 months ($p < 0,001$) post op.

CONCLUSION:
It is concluded that all implants achieved osseointegration Regarding the biologic process of osseointegration titanium and zirconoxid showed equal properties in the present study. Cylindric implant design and intermediate surface roughness seemed to enhance osseointegration. However, the mechanical properties of zirconoxid under functional loading should be evaluated in further studies.

Clin Oral Implants Res. 2012 Oct;23(10):1210-6.

Biomechanical evaluation of a microstructured zirconia implant by a removal torque comparison with a standard Ti-SLA implant.

Bormann KH, Gellrich NC, Kniha H, Dard M, Wieland M, Gahlert M.

ABSTRACT

OBJECTIVES:

The purpose of this study was to evaluate the biomechanical bone tissue response to novel microstructured zirconia implants in comparison to sandblasted and acid-etched (SLA) titanium implants through the analysis of removal torque (RTQ) measurements.

MATERIALS AND METHODS:

Ti-SLA implants with a sandblasted, large-grit and acid-etched surface were compared with zirconia implants with an acid-etched surface. All implants had the same shape, a diameter of 4.1 mm and a length of 10 mm. A total of 136 implants were placed in the maxillae of 17 miniature pigs. Six animals were sacrificed after both 4 and 8 weeks and five animals were sacrificed after 12 weeks, thus providing a total of 102 implants for RTQ testing (34 implants were reserved for future histological analysis). The RTQ analysis was successfully performed, using a mixed model regression with P-values calculated using the nonparametric Brunner-Langer method, on 100 of the 102 implants, two were excluded from the analysis.

RESULTS:

The adjusted mean RTQ values for Ti-SLA implants were 131 Ncm (95% CI: 107-155) at 4 weeks, 128 Ncm (108-148) Ncm at 8 weeks, and 180 Ncm (153-207 Ncm) at 12 weeks of healing, whereas RTQ values for the zirconia implants were 110 Ncm (86-134), 97 Ncm (76-118) and 147 Ncm (121-174) at the corresponding time intervals. A comparison of the implant materials resulted in P-values of P = 0.114 at 4 weeks, P = 0.034 at 8 weeks and P = 0.105 at 12 weeks (significance set at P < 0.05).

CONCLUSIONS:

Within the limits of the present study, it could be confirmed that the biomechanical bone-tissue response of the investigated zirconia implants is non-inferior to that of the well-documented, roughened titanium surface, at each time point, within the set tolerance. There were no statistically significant differences between the two materials after a healing period of 4 and 12 weeks. The RTQ values of both implant types increased significantly from the 8-week to the 12-week time point.

Clin Oral Implants Res. 2012 Mar;23(3):281-6.

In vivo performance of zirconia and titanium implants: a histomorphometric study in mini pig maxillae.

Gahlert M, Roehling S, Sprecher CM, Kniha H, Milz S, Bormann K.

ABSTRACT

OBJECTIVES:

To compare the bone tissue response to surface-modified zirconia (ZrO2) and titanium implants.

METHODS:

Cylindrical low-pressure injection moulded zirconia (ZrO2) implants were produced with an acid-etched surface. Titanium implants with identical shape, sandblasted and acid-etched surface (SLA) served as controls. Eighteen adult miniature pigs received both implant types in the maxilla 6 months after extraction of the canines and incisors. The animals were euthanized after 4, 8 and 12 weeks and 16 zirconia and 18 titanium implants with the surrounding tissue were retrieved, embedded in methylmethacrylate and stained with Giemsa-Eosin. The stained sections were digitized and histomorphometrically analysed with regard to peri-implant bone density (bone volume/total volume) and bone-implant contact (BIC) ratio. Statistical analysis was performed using Mann-Whitney' U-test.

RESULTS:

Histomorphometrical analysis showed direct osseous integration for both materials. ZrO2 implants revealed mean peri-implant bone density values of 60.4% (SD ± 9.9) at 4 weeks, 65.4% (SD ± 13.8) at 8 weeks, and 63.3% (SD ± 21.5) at 12 weeks after implantation, whereas Ti-SLA implants demonstrated mean values of 61.1% (SD ± 6.2), 63.6% (SD ± 6.8) and 68.2% (SD ± 5.8) at corresponding time intervals. Concerning the BIC ratio, the mean values for ZrO(2) ranged between 67.1% (SD ± 21.1) and 70% (SD ± 14.5) and for Ti-SLA between 64.7% (SD ± 9.4) and 83.7% (SD ± 10.3). For the two parameters investigated, no significant differences between both types of implants could be detected at any time point.

CONCLUSION:

The results indicate that there was no difference in osseointegration between ZrO2 implants and Ti-SLA controls regarding peri-implant bone density and BIC ratio.

Int J Oral Maxillofac Implants. 2012 Mar-Apr;27(2):352-8.

Osseointegration of zirconia implants with different surface characteristics: an evaluation in rabbits.

Hoffmann O, Angelov N, Zafiropoulos GG, Andreana S.

ABSTRACT

PURPOSE:

Zirconia ceramics are a viable alternative to titanium for use as dental implants. However, the smooth surface of zirconia means that longer healing periods are needed to accomplish osseointegration compared to roughened titanium surfaces. Surface modifications can be used to increase the roughness of zirconia. The aim of this study was to assess histologically and compare the degree of early bone apposition around zirconia dental implants with sandblasted, sintered, or laser-modified surfaces to that seen around surface-modified titanium implants. Removal torque was also measured and compared.

MATERIALS AND METHODS:

Ninety-six implants--24 each of four types (sintered zirconia, laser-modified zirconia, sandblasted zirconia, and acid-etched titanium)--were placed in 48 New Zealand White female rabbits. One implant was inserted in each distal femur. Half of the specimens were harvested at 6 or 12 weeks and processed for light microscopic analysis; the area of bone-to-implant contact was measured morphometrically. The other half were evaluated for removal torque at 6 and 12 weeks.

RESULTS:

No statistically significant differences existed in bone apposition between the different surfaces at either time point. Differences in removal torque were significantly different between titanium and sandblasted zirconia and between sintered zirconia and sandblasted zirconia, with the first mentioned demonstrating a higher torque value at 6 weeks. At 12 weeks, the only significant difference in removal torque was between titanium and sandblasted zirconia, with titanium demonstrating the higher value.

CONCLUSION:

Comparable rates of bone apposition in the zirconia and titanium implant surfaces at 6 and 12 weeks of healing were observed. Removal torque values were similar for all implants with a roughened surface.

Int J Oral Maxillofac Surg. 2012 May;41(5):638-45.

A comparison of biocompatibility and osseointegration of ceramic and titanium implants: an in vivo and in vitro study.

Möller B, Terheyden H, Açil Y, Purcz NM, Hertrampf K, Tabakov A, Behrens E, Wiltfang J.

ABSTRACT

This study compared the biocompatibility in vitro and the osseointegration in vivo of zirconium and titanium implants regarding implant surfaces and the bone-implant contacts. The different implant surfaces and the biocompatibility of zirconium versus titanium implants were determined by vitality and cytotoxic tests in vitro. The contact of the osteoblasts to the implant surface was determined by scanning electron microscopy (SEM). The in vivo study for osseointegration was performed in domestic pigs over 4 and 12 weeks. In each animal, 4 zirconium and 4 titanium implants (WhiteSky, BlueSky, Bredent, Germany) were inserted in the os frontale and analysed by histomorphometry. Cytotoxicity and SEM showed good biocompatibility in relation to the investigated implant materials. Histological results showed direct bone-implant contact of the implant surfaces. The zirconium implants showed a slight delay in osseointegration in terms of bone-implant contact as measured by histomorphometry (after 4 weeks, zirconium (59.3 ± 4.6%) versus titanium (64.1 ± 3.9%); after 12 weeks, zirconium (67.1 ± 2.3%) versus titanium (73.6 ± 3.2%). A statistically significant difference between the two groups was not observed. The results indicated similar biocompatibility and osseointegration for zirconium compared to titanium implants.

Dent Mater. 2013 Jul;29(7):763-76.

Osteoblast and bone tissue response to surface modified zirconia and titanium implant materials.

Kohal RJ, Bächle M, Att W, Chaar S, Altmann B, Renz A, Butz F.

ABSTRACT

OBJECTIVE:

This study examined the in vitro and in vivo response of osteoblasts to a novel, acid-etched and sandblasted zirconia surface.

METHODS:

Osteoblastic hFOB 1.19 cells were cultured either on electrochemically anodized titanium (TiUnite(®)), machined titanium (Ti-m), sandblasted and acid-etched zirconia (TZP-proc), and machined zirconia (TZP-A-m). The surface topography of the various substrates was analyzed by 3D laserscan measurements and scanning electron microscopy. At culture days 1, 3, 7, 14, 21, and 28, cell proliferation was determined. Gene expression was analyzed using RT-PCR. Histologic analysis and biomechanical testing was performed on miniature implants placed in the rat femur.

RESULTS:

During the first 7 days, a retarded cell proliferation was observed on the TiUnite(®) surface. After 28 days of cultivation, cell proliferation reached similar levels on all surfaces. An up-regulation of bone and extracellular matrix specific genes could be seen for TZP-proc at day 21. The mean bone-implant contact rate after a healing period of 14 and 28 days, respectively, was higher for TiUnite(®) than for TZP-proc. At 28 day, the biomechanical test showed significantly higher values for TiUnite(®) than for all other surfaces.

SIGNIFICANCE:

The novel, rough zirconia surface was accepted by hFOB 1.19 cells and integrates into rat bone tissue. However, osseointegration seemed to proceed more slowly and to a lesser extent compared to a moderately roughened titanium surface.

Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jul;116(1):e1-8.

Analysis of the influence of the macro- and microstructure of dental zirconium implants on osseointegration: a minipig study.

Mueller CK, Solcher P, Peisker A, Mtsariashvilli M, Schlegel KA, Hildebrand G, Rost J, Liefeith K, Chen J, Schultze-Mosgau S.

ABSTRACT

OBJECTIVES:

It was the aim of this study to analyze the influence of implant design and surface topography on the osseointegration of dental zirconium implants.

STUDY DESIGN:

Six different implant designs were tested in the study. Nine or 10 test implants were inserted in the frontal skull in each of 10 miniature pigs. Biopsies were harvested after 2 and 4 months and subjected to microradiography.

RESULTS:

No significant differences between titanium and zirconium were found regarding the microradiographically detected bone-implant contact (BIC). Cylindric zirconium implants showed a higher BIC at the 2-month follow-up than conic zirconium implants. Among zirconium implants, those with an intermediate Ra value showed a significantly higher BIC compared with low and high Ra implants 4 months after surgery.

CONCLUSIONS:

Regarding osseointegration, titanium and zirconium showed equal properties. Cylindric implant design and intermediate surface roughness seemed to enhance osseointegration.

J Mater Sci Mater Med. 2015 Jan;26(1):5350.

Microstructured zirconia surfaces modulate osteogenic marker genes in human primary osteoblasts.

Bergemann C, Duske K, Nebe JB, Schöne A, Bulnheim U, Seitz H, Fischer J.

ABSTRACT

In dentistry, zirconia has been used since the early 1990s for endodontic posts, more recently for implant abutments and frameworks for fixed dental prostheses. Zirconia is biocompatible and mechanically strong enough to serve as implant material for oral implants. Although several zirconia implant systems are available, currently the scientific and clinical data for zirconia implants are not sufficient to recommend them for routine clinical use. Here the influence of microstructured yttria-stabilized zirconia (YZ) on human primary osteoblast (HOB) behavior was determined. YZ surfaces were treated by sandblasting (YZ-S), acid etching (YZ-SE) and additionally heat treatment (YZ-SEH). Morphological changes of HOB were determined by scanning electron microscopy. Actin cytoskeleton was investigated by laser scanning microscopy and analyzed by novel actin quantification software. Differentiation of HOB was determined by real time RT-PCR. Improved mechanical interlocking of primary HOB into the porous microstructure of the acid etched and additionally heat treated YZ-surfaces correlates with drastically increased osteocalcin (OCN) gene expression. In particular, OCN was considerably elevated in primary HOB after 3 days on YZ-SE (13-fold) as well as YZ-SEH (12-fold) surfaces. Shorter actin filaments without any favored orientation on YZ-SE and YZ-SEH surfaces are associated with higher roughness (Ra) values. Topographically modified yttria-stabilized zirconia is a likely material for dental implants with cell stimulating properties achieving or actually exceeding those of titanium.

Clin Implant Dent Relat Res. 2016 Aug;18(4):686-98. doi: 10.1111/cid.12375. Epub 2015 Sep 17.

Osseointegration of Zirconia in the Presence of Multinucleated Giant Cells.

Chappuis V, Cavusoglu Y, Gruber R, Kuchler U, Buser D, Bosshardt DD.

ABSTRACT

BACKGROUND:

ICurrent strategies to reduce medical device-associated infections propose zirconia as a potential implant material which may limit bacterial adhesion. Because multinucleated giant cells (MNGCs) have been detected on these implant surfaces, concerns have been raised regarding tissue integration.

PURPOSE:

The present study examined the presence of MNGCs and their subsequent effect upon tissue integration. Surface-modified implants made of yttria-stabilized (TZP) and alumina-toughened zirconia (ATZ) were compared with commercially pure titanium (Ti).

MATERIALS AND METHODS:

Seven miniature pigs received three implants on either side of the maxilla. After healing periods of 4 and 8 weeks, the tissue response at the implant surfaces was characterized according to three specific parameters: bone-to-implant contact (BIC), MNGC-to-implant contact (MIC), and the peri-implant bone density (BD).

RESULTS:

Despite being present on all tested implant surfaces, MNGCs were not associated with an inflammatory cell infiltrate or with fibrous encapsulation. MNGCs were less numerous on the Ti implants (range: 3.9-5.2%) compared with the ceramic implants (range: 17.6-30.3%, $p < .0001$). Even though the values of newly formed bone and pristine bone in direct contact with the implant surfaces were high at 4 weeks (tBIC: Ti = 82.3%, TZP = 64.3%, ATZ = 70%), a negative correlation was observed between the presence of MNGCs and newly formed bone at the implant surface ($p < .001$). Interestingly, the newly formed peri-implant bone density, defined as the percentage of new bone area inside the screw threads (nBD), was not diminished by the presence of MNGCs.

CONCLUSIONS:

Differences in the presence of MNGCs and the BIC parameters between Ti and the ceramic implants appear to be a local cellular phenomenon which is restricted to the implant-bone marrow interface and do not affect the peri-implant bone formation. Factors triggering MNGC differentiation and their persistence in response to biomaterial surface need to be investigated in future studies.

Implant Dent. 2016 Apr;25(2):193-8. doi: 10.1097/ID.0000000000000365.

Success Rate of Two-Piece Zirconia Implants: A Retrospective Statistical Analysis.

Jank S, Hochgatterer G.

ABSTRACT

PURPOSE:

About 10 years ago, one-piece zirconia implants were introduced to dentistry. The aim of the study was to evaluate the clinical success of two-piece zirconia implants regarding osseointegration using the manufacturers' warranty data.

MATERIALS AND METHODS:

Over a period of 4 years (2010-2014), the data of warranty replacements of 15,255 sold Zeramex implants were evaluated retrospectively and blinded.

RESULTS:

Three hundred forty-seven (2.2%) nonosseointegrated implants were sent back. Zeramex T showed an average success rate of 96.7%, whereas Zeralock implants exhibited an average success rate of 98.5%. Furthermore, Zeramex Plus implants exhibit an average success rate of 99.4% within the investigated period. Assuming, that 2% of the failed implants were unreturned, the above-mentioned values show no changes. Assuming 5% (10%) of unreturned nonosseointegrated implants, the average success rate of Zeramex T decreases from 96.7% to 96.6% (96.4%) and of Zeralock from 98.5% to 98.4% (98.4%), respectively. The success rate of Zeramex Plus implants remains unchanged at 99.4%.

CONCLUSION:

The results of this study imply that two-piece zirconia implants show competitive success rates, improved from >96.7% to >98.5% over three product generations.

J Biomed Mater Res B Appl Biomater. 2016 Nov;104(8):1622-1631. doi: 10.1002/jbm.b.33512. Epub 2015 Aug 31.

Peri-implant bone response to retrieved human zirconia oral implants after a 4-year loading period: A histologic and histomorphometric evaluation of 22 cases.

Kohal RJ, Schwindling FS, Bächle M, Spies BC.

ABSTRACT

AIM:

To evaluate the bone tissue response to surface modified zirconia oral implants retrieved from humans.

MATERIALS AND METHODS:

Twenty-nine one-piece zirconia implants showed increased marginal bone loss and did not response to the applied peri-implantitis therapy. After their removal using a trephine bur, 22 of the implant-bone biopsies were suitable for an evaluation and immediately immersed in formalin for two weeks. Subsequent, the retrieved specimens were histologically prepared and the regions still showing osseointegration computer-assisted analyzed regarding the bone-to-implant contact (BIC) and bone density using a transmitted-light microscope.

RESULTS:

The removed implants were in situ for a mean time period of 47.7 months. After their removal, compact bone could be depicted at the apical regions. The remaining bone that was attached to the implants contained a regular lamellar structure with osteons and osteocytes. The BIC ranged from 58.1% to 93.7% (mean: 76.5%) and the bone area/density within the implant threads ranged from 57% to 97.2% (mean: 84.8%).

CONCLUSIONS:

The porous zirconia implants showed a sufficient BIC in the areas where bone still was attached. Although the implants had to be removed due to increased bone loss, it seems that the presented zirconia implant surface per se elicited appropriate osseointegration.

Biomed Res Int. 2017; 2017: 9246721.

Effect of Zirconia Dental Implant Surfaces on Bone Integration: A Systematic Review and Meta-Analysis.

Hafezeqoran A, Koodaryan R.

ABSTRACT

BACKGROUND:

The information available about osseointegration and the bone to implant interaction of zirconia implants with various surface modifications is still far from sufficient.

OBJECTIVE:

The purpose of this systematic review and meta-analysis was to evaluate and compare zirconia dental implants with different surface topographies, with a focus on bone to implant contact and removal torque.

METHODS:

The systematic review of the extracted publications was performed to compare the bone to implant contact (BIC) with removal torque (RT) values of titanium dental implants and machined and surfaced modified zirconia implants.

RESULTS:

A total of fifteen articles on BIC and RT values were included in the quantitative analysis. No significant difference in the BIC values was observed between titanium and machined zirconia implants ($p = 0.373$; 95% CI: −0.166 to 0.443). However, a significantly better BIC values were observed for acid etched zirconia implants compared with those of titanium implants ($p = 0.032$; 95% CI: 0.068 to 1.461). Unmodified zirconia implants showed favorable BIC values compared to modified-surface zirconia implants ($p = 0.021$; 95% CI: −0.973 to −0.080).

CONCLUSION:

Acid etched zirconia implants may serve as a possible substitute for successful osseointegration.

Clin Oral Investig. 2017 Mar;21(2):523-532.

Bone tissue response to experimental zirconia implants.

Mihatovic I, Golubovic V, Becker J, Schwarz F.

ABSTRACT

OBJECTIVES:

This study seeks to assess the bone tissue response at experimental zirconia implants in comparison with titanium implants by means of descriptive histology and histomorphometry in a dog model.

MATERIALS AND METHODS:

Experimental zirconia implants with three different surface roughnesses (Z1 < Z2 < Z3) and conventional sandblasted large grit and acid-etched titanium implants were inserted bilaterally in the lower jaws of nine beagle dogs. Tissue biopsies were obtained after 3 and 14 days and 10 weeks of transmucosal healing. The tissue response was investigated by assessing new, old, and total bone-to-implant contact (nBIC, oBIC, and tBIC).

RESULTS:

After 3 days, histological specimens of all groups showed an intimate contact between the implant threads and pristine bone (tBIC: Ti 42.3 % > Z2 30.1 % > Z3 28.9 % > Z1 25.1 %, $p > 0.05$, unpaired t test, respectively). A provisional matrix was evident at all implant surfaces. At 14 days, percentages of BIC increased in all groups (tBIC: Ti 62.1 % > Z3 69.2 % < Z2 44.4 % > Z1 42.3 %; nBIC: Z3 58.9 % > Ti 52.2 % > Z2 35.1 % > Z1 32.5 %). Two implants, one of group Z1 and one of group Z2, were lost. At 10 weeks, 13 of 18 zirconia implants were lost, equally distributed between all three surface modifications. The remaining implants revealed increased BIC values (tBIC: Z3 69.5 % > Ti 58.5 % > Z1 49.7 % > Z2 37.1 %; nBIC: Z3 57.2 % > Ti 46.5 % > Z1 32.3 % > Z2 29.3 %). Histomorphometrical analysis showed comparable mean BIC values in all groups at all healing periods without showing statistical differences ($p > 0.05$, unpaired t test, respectively).

CONCLUSION:

The bone tissue response throughout the healing periods was characterized by a constant bone remodeling accompanied by resorption of old bone in favor of new bone formation at both titanium and zirconia implants. Surface roughness had a positive effect on BIC, although not showing statistical significance. Due to the poor survival rate, the experimental zirconia implants investigated may not be suitable for clinical use.

J Oral Implantol. 2017 Aug;43(4):314-325.

Thirty Years of Translational Research in Zirconia Dental Implants: A Systematic Review of the Literature.

Siddiqi A, Khan AS, Zafar S.

ABSTRACT

Thirty years of transitional research in zirconia (Zr) ceramics has led to significant improvements in the biomedical field, especially in dental implantology. Oral implants made of yttria-tetragonal zirconia polycrystals (Y-TZP) because of their excellent mechanical properties, good biocompatibility, and esthetically acceptable color have emerged as an attractive metal-free alternative to titanium (Ti) implants. The aim of the review was to highlight the translation research in Zr dental implants that has been conducted over the past 3 decades using preclinical animal models. A computer search of electronic databases, primarily PubMed, was performed with the following key words: "zirconia ceramics AND animal trials," "ceramic implants AND animal trials," "zirconia AND animal trials," "zirconia AND in vivo animal trials," without any language restriction. However, the search was limited to animal trials discussing percentage bone-implant contact (%BIC) around zirconia implants/discs. This search resulted in 132 articles (reviews, in vivo studies, and animal studies) of potential interest. We restricted our search terms to "zirconia/ceramic," "bone-implant-contact," and "animal trials" and found 29 relevant publications, which were then selected for full-text reading. Reasons for exclusion included the article's not being an animal study, being a review article, and not discussing %BIC around Zr implants/discs. Most of the studies investigated BIC around Zr in rabbits (30%), pigs (approximately 20%), dogs, sheep, and rats. This review of the literature shows that preclinical animal models can be successfully used to investigate osseointegration around Zr ceramics. Results of the reviewed studies demonstrated excellent %BIC around Zr implants. It should be noted that most of the studies investigated %BIC/removal torque under nonloading conditions, and results would have been somewhat different in functional loading situations because of inherent limitations of Zr ceramics. Further trials are needed to evaluate the performance of Zr ceramics in clinical conditions using implants designed and manufactured via novel techniques that enhance their biomechanical properties.

Clin Oral Implants Res. 2018 Mar;29(3):277-289.

Bone response to functionally loaded, two-piece zirconia implants: A preclinical histometric study.

Janner SFM, Gahlert M, Bosshardt DD, Roehling S, Milz S, Higginbottom F, Buser D, Cochran DL.

ABSTRACT

OBJECTIVE:

To evaluate the bone response to a two-piece zirconia implant in comparison with a control titanium implant in the canine mandible 4 and 16 weeks after restoration.

MATERIAL AND METHODS:

Zirconia and titanium implants were alternately placed bilaterally in healed mandibular molar and premolar sites of five canines. Full-ceramic single-tooth restorations were cemented after 6 weeks of transmucosal healing, allowing for full functional loading of the implants. Histologic and histometric analyses were performed on orofacial and mesiodistal undecalcified sections of the specimens obtained upon sacrifice after 4 and 16 weeks of functional loading. Bone-to-implant contact (BIC), multinucleated giant cells-to-implant contact (MIC), crestal bone level, and peri-implant bone density were histometrically assessed.

RESULTS:

All 60 implants and 60 restorations were still in function after 4 and 16 weeks of loading in both test and control groups. No implant loss, no implant or abutment fracture, and no chipping of the restorations could be detected. Histometric analysis showed no statistically significant differences between zirconia and titanium implants in BIC, crestal bone level, and peri-implant bone density at both time points. Between 4 and 16 weeks, the crestal bone level around zirconia implants showed a small but statistically significant increase in its distance from the implant shoulder. MIC was very low on both implant types and both time points and decreased statistically significantly overtime.

CONCLUSION:

The present two-piece zirconia implant showed a similar bone integration compared to the titanium implant with similar surface morphology after 4 and 16 weeks of loading.

Int J Oral Maxillofac Implants. 2018 January/February;33(1):217–222.

Peri-implant Crestal Bone Changes Around Zirconia Implants in Periodontally Healthy and Compromised Patients.

Kniha K, Milz S, Kniha H, Ayoub N, Hölzle F, Modabber A.

ABSTRACT

PURPOSE:

No consensus regarding the efficacy of zirconia implants in maintaining peri-implant hard and soft tissue health has yet been obtained. The aim of this retrospective follow-up study was to gain knowledge about peri-implant bone behavior and about implant survival and success after treatment with zirconia dental implants in patients with normal and compromised soft and hard tissue conditions.

MATERIALS AND METHODS:

This follow-up study involved 86 patients with 123 zirconia implants (Straumann PURE Ceramic Implant) that were radiographically investigated directly after implant placement (day 0), 3 months after placement, and 1 year after the definitive implant crown placement. The clinical assessment was done at the 1-year postloading appointment and also included the modified Plaque Index, modified Sulcus Bleeding Index, and sulcus pocket depths. Eighteen patients with periodontally compromised conditions were compared to 68 patients with healthy periodontal conditions.

RESULTS:

The survival rate was 100% and success rate was 94.5%, with no differences between the two groups. The alveolar crest around the ceramic implants showed no significant difference between day 0 and 1 year postloading for both groups (P > .05). There was also no significant difference at 1 year postloading between the groups in the distance from the implant shoulder to the peri-implant bone crest (P = .67) or in pocket depth (P = .07).

CONCLUSION:

No significant peri-implant bone loss was observed in the first year. The survival and success rates showed no differences between the periodontally healthy and periodontally compromised groups; however, only a limited number of patients with periodontally compromised conditions were included in this study.

Dent Mater. 2018 Feb;34(2):171-182.

Osseointegration of zirconia dental implants in animal investigations: A systematic review and meta-analysis.

Pieralli S, Kohal RJ, Lopez Hernandez E, Doerken S, Spies BC.

ABSTRACT

OBJECTIVE:

To determine the osseointegration rate of zirconium dioxide (ZrO2) dental implants in preclinical investigations.

DATA:

Data on the osseointegration rate was extracted considering the bone to implant contact (BIC), removal torque analysis (RTQ) and push-in tests. Meta analyses were conducted using multilevel multivariable mixed-effects linear regression models. The Šidák method was used in case of multiple testing.

SOURCES:

An electronic screening of the literature (MEDLINE/Pubmed, Cochrane Library and Embase) and a supplementary manual search were performed. Animal investigations with a minimum sample size of 3 units evaluating implants made of zirconia (ZrO2) or its composites (ZrO2>50vol.%) were included.

STUDY SELECTION:

The search provided 4577 articles, and finally 54 investigations were included and analyzed. Fifty-two studies included implants made from zirconia, 4 zirconia composite implants and 37 titanium implants. In total, 3435 implants were installed in 954 animals.

CONCLUSIONS:

No significant influence of the evaluated bulk materials on the outcomes of interest could be detected. When comparing different animal models, significant differences for the evaluated variables could be found. These results might be of interest for the design of further animal investigations.

Int J Oral Maxillofac Implants. 2019 March/ April;34(2):357–365.

Ligature-Induced Peri-implant Bone Loss Around Loaded Zirconia and Titanium Implants.

Roehling S, Gahlert M, Janner S, Meng B, Woelfler H, Cochran DL.

ABSTRACT

PURPOSE:

To radiographically investigate ligature-induced peri-implant bone loss around loaded titanium (Ti-SLA) and zirconia (ZrO2-ZLA) implants using a canine model.

MATERIALS AND METHODS:

Forty sandblasted and acid-etched titanium and zirconia implants were alternately placed in the mandibles of five canines (20 Ti-SLA, 20 ZrO2-ZLA). Implants were restored after 6 weeks of unloaded healing. After 4 weeks of functional loading, oral hygiene procedures were stopped and experimental peri-implant bone loss was initiated by placing cotton ligatures. After 8 weeks of active progression, ligatures were removed and plaque was allowed to accumulate for another 16 weeks of spontaneous progression (without ligatures). Standardized radiographs were taken at implant placement, at functional loading, and every 2 weeks during active and spontaneous progression of bone loss.

RESULTS:

Before ligature placement, all implants were successfully osseointegrated and no clinical or radiographic signs of peri-implant infections were detectable. Two weeks after ligature removal, one titanium implant was lost; however, no zirconia implant failures were observed during the study. Radiographically, zirconia implants revealed statistically significantly less crestal peri-implant bone loss compared to titanium implants at the end of the active progression period (Ti-SLA: 3.92 mm; ZrO2-ZLA: 2.65 mm; $P < .01$); however, no significant differences occurred after the spontaneous progression period ($P = .6$). Combining the active and spontaneous progression periods together, zirconia implants demonstrated significantly reduced peri-implant bone loss compared to titanium implants (Ti-SLA: 3.76 mm; ZrO2-ZLA: 2.42 mm; $P < .01$).

CONCLUSION:

These results demonstrate a significantly reduced ligature-induced inflammation and bone loss for ZrO2-ZLA implants compared to Ti-SLA implants in the canine model.

1.2.4 Clinically case Series and Studies

Int J Oral Maxillofac Implants. 2007 May-Jun;22(3):430-5.

One-year follow-up of first consecutive 100 zirconia dental implants in humans: a comparison of 2 different rough surfaces.

Oliva J, Oliva X, Oliva JD.

ABSTRACT

PURPOSE:

The aim of this study was to evaluate the success rate of 100 consecutive zirconia dental implants with 2 different rough surfaces after 1 year of follow-up.

MATERIALS AND METHODS:

One-piece zirconia dental implants (CeraRoot, Barcelona, Spain) with 1 of 2 different roughened surfaces were designed and manufactured for this study. Five different implant designs were manufactured. Standard or flapless surgical procedures were used for implant placement. Simultaneous bone augmentation or sinus elevation were performed in the cases where bone height or width was insufficient. Implants in the anterior region (canine to canine) were immediately restored with provisional prostheses. Implants placed using less than 35 N torque were splinted with composite resin using an etched and bonded approach to the neighboring teeth or implants to minimize implant mobility and failure. Definitive all-ceramic restorations were placed 4 months after implant placement (8 months for implants where bone augmentation or sinus elevation was performed).

RESULTS:

The study included 36 patients with a mean age of 50 years. The overall implant success rate after 1 year of follow-up was 98% in both the coated and noncoated groups.

CONCLUSIONS:

From the preliminary results of this investigation, it can be concluded that zirconia dental implants with roughened surfaces might be a viable alternative for tooth replacement. Further follow-up is needed to evaluate the long-term success rates of the implant surfaces studied.

Minerva Stomatol. 2010 Jul-Aug;59(7-8):381-92.

Edentulous jaws rehabilitation with yttrium-stabilized zirconium dioxide implants: two years follow-up experience.

Borgonovo AE, Arnaboldi O, Censi R, Dolci M, Santoro G.

ABSTRACT

AIM:

The aim of this study was to present authors' two-year clinical experience with Yttrium-stabilized zirconium dioxide implants placed in native bone or regenerated bone.

METHODS:

Yttrium-stabilized zirconium dioxide implants made of brezirkon (whiteSKY, Bredent medical, Senden, Germany) were used for the treatment of edentulous ridge rehabilitation in the Dental Clinic of the University of Milan (Head of the Department, Prof. F. Santoro). Zirconium dioxide is a highly resistant ceramic material obtained by cleaning zirconium dioxide and zirconium silicate. The implant used in the clinical study featured a conical one piece implant with double cylindrical thread with a sandblasted rough surface. The prosthetic section was smooth.

RESULTS:

Forty-six implants have been inserted in 18 patients from January 2007 to January 2009, the follow-up period was comprised between 6 and 24 months. The overall success rate was 89%; the success rate in native bone was 97% and 74% in augmented bone. It can be stated that the success rate is comparable to titanium fixtures.

CONCLUSION:

It would be logical to use a ceramic material for the esthetic regions; zirconium dioxide is particularly suitable since it features tissue friendliness and resistance comparable to titanium. The good mechanical properties, possibility of easy fabrication of the prosthetic restoration and the good integration into the tissue and the esthetics provide perfect preconditions for yttrium-stabilized zirconium dioxide to become the most commonly used material in implant dentistry.

Eur J Oral Implantol. 2010 Summer;3(2):111-20.

Immediate occlusal versus non-occlusal loading of single zirconia implants. A multicentre pragmatic randomised clinical trial.

Cannizzaro G, Torchio C, Felice P, Leone M, Esposito M.

ABSTRACT

PURPOSE:

To evaluate whether immediate non-occlusal loading of single zirconia implants could reduce early failures when compared to immediate occlusal loading.

MATERIALS AND METHODS:

Forty partially edentulous patients who received one single zirconia implant (Z-Systems) at least 10 mm long and 3.25 mm wide inserted with a torque of at least 35 Ncm were randomised to immediate occlusal or non-occlusal loading groups. All patients received provisional acrylic crowns the same day of implant placement. Provisional crowns were replaced after 4 to 5 months by definitive full ceramic crowns. Outcome measures were implant success, any complications and peri-implant marginal bone levels.

RESULTS:

One year after loading, no patients had dropped out. Five implants (12.5%) failed early: three occlusally loaded and two non-occlusally loaded. Three complications occurred, all after delivery of the definitive crowns: one crown fractured (occlusal loading), one had to be remade after debridement because of hyperplastic tissues (occlusal loading), and one crown decemented (nonocclusal loading). These differences were not statistically significant. Both groups gradually lost periimplant bone in a highly statistically significant way. One year after loading, patients subjected to non-occlusal loading lost an average of 0.7 mm of peri-implant bone versus 0.9 mm in the occlusal group. This difference in bone loss between groups was not statistically significant. There was an association between immediate post-extractive implants and implant failures (P=0.01). Four of the 10 immediate post-extractive implants (40%) failed versus one out of 30 delayed implants (3%).

CONCLUSIONS:

The results of this study do not provide a conclusive answer to whether immediate non-occlusal loading may decrease implant failures. Immediately loaded zirconia implants placed in post-extractive sites had high failure rates.

Int J Oral Maxillofac Implants. 2010 Mar-Apr;25(2):336-44.

Five-year success rate of 831 consecutively placed Zirconia dental implants in humans: a comparison of three different rough surfaces.

Oliva J, Oliva X, Oliva JD.

ABSTRACT

PURPOSE:

The aim of this study was to evaluate the 5-year success rate of zirconia (ZrO2) implants with three different kinds of surfaces.

MATERIALS AND METHODS:

One-piece zirconia dental implants (CeraRoot) with three different roughened surfaces were designed and manufactured for this study: coated, uncoated, and acid-etched. Five different implant designs were manufactured. Standard or flapless surgical procedures were used for implant placement. Simultaneous bone augmentation or sinus elevation was performed when bone height or width was insufficient. Definitive all-ceramic restorations were placed 4 months after implant placement (8 months or more for implants when bone augmentation or sinus elevation was performed). The implants were followed up to 5 years (mean, 3.40 +/- 0.21).

RESULTS:

In all, 831 implants were placed in 378 patients with a mean age of 48 years. The overall implant success rate after 5 years of follow-up was 95% (92.77% for uncoated implants, 93.57% for coated implants, and 97.60% for acid-etched implants). The success rate of the acid-etched surface group was significantly better than that of the other two.

CONCLUSION:

From this midterm investigation, it can be concluded that zirconia dental implants with roughened surfaces might be a viable alternative for tooth replacement. Further follow-up is needed to evaluate the long-term success rates of the implant surfaces studied.

Minerva Stomatol. 2011 May;60(5):229-41.

Use of endosseous one-piece yttrium-stabilized zirconia dental implants in premolar region: a two-year clinical preliminary report.

Borgonovo A, Censi R, Dolci M, Vavassori V, Bianchi A, Maiorana C.

ABSTRACT

OBJECTIVE:

The aim of this work was to clinically and radiographically evaluate survival and success rate of zirconia dental implants positioned in premolar area during a follow-up period of at least 12 months up to 24 months.

METHODS:

Sixteen patients were treated with 26 zirconia implants. All implants received immediate temporary restorations and 6 months after surgery were definitively restored. Twelve to 14 months after implant insertion, a clinical-radiographical evaluation was performed in order to estimate peri-implant tissues health and peri-implant marginal bone loss.

RESULTS:

The survival rate was 96.16%. The success rate was 91.6%.

CONCLUSION:

significant even if results are encouraging. Further scientific information regarding clinical use of zirconia dental implants are needed, as well as prospective long-term clinical studies in order to understand if zirconia implants may represent a valid alternative to titanium implants.

Clin Oral Implants Res. 2013 May;24(5):569-75. doi: 10.1111/j.1600-0501.2012.02425.x. Epub 2012 Feb 15.

Immediate provisional restoration of single-piece zirconia implants: a prospective case series - results after 24 months of clinical function.

Payer M, Arnetzl V, Kirmeier R, Koller M, Arnetzl G, Jakse N.

ABSTRACT

OBJECTIVE:

Aim of this prospective case series was to evaluate the outcome of immediately provisionalized single-piece zirconia implants.

MATERIAL AND METHODS:

A total of 20 zirconia implants were inserted in single-tooth gaps in the maxilla (11) and mandible (9) of 20 patients. Implants were restored with all-ceramic CAD/CAM provisionals without occlusal contacts immediately after placement. Permanent all-ceramic restoration was performed 4 months after surgery. Plaque index (PI), bleeding on probing (BOP), Periotest(®) (PV), pink aesthetic score (PES), mean radiographic marginal bone levels (MBL), implant survival and success were evaluated up to 24 months.

RESULTS:

Assessment of PI at baseline and follow-ups after 6, 12, 18 and 24 months revealed 27% (±5.3), 24% (±6), 23% (±6.1), 23% (±5.3) and 22% (±6.4), respectively. Evaluation of BOP revealed 25% (±5.6), 21% (±6), 21% (±7.2), 18% (±5.9) and 15% (±5.5), respectively. Implants presented stable at follow-ups (PV). PES improved, but not statistically significant from 8.13 (±1.5) at baseline to 10 (±2) 24 months after implantation. Measurements of MBL showed a significant bone loss of 1.01 mm within the first year after placement ($P < 0.001$) and 1.29 mm 24 months post-implant insertion, not reaching further statistically significant levels ($P > 0.05$). One implant was lost 4 months after placement, resulting in a survival and success rate of 95%.

CONCLUSION:

Clinical and radiographic parameters demonstrated a 95% integration of immediately loaded zirconia single-piece implants. A long-term randomized-controlled clinical trial was initiated to confirm evidence of this protocol.

Int J Prosthodont. 2014 Sep-Oct;27(5):461-8. doi: 10.11607/ijp.3626.

Prosthodontic maintenance of overdentures on zirconia implants: 1-year results of a randomized controlled trial.

Osman RB, Ma S.

ABSTRACT

PURPOSE:

The purpose of this study was to determine the prosthodontic outcomes of one-piece zirconia implants and their attachment systems in edentulous participants with maxillary and mandibular overdentures after 1 year of a randomized controlled trial.

MATERIALS AND METHODS:

Random allocation of 24 edentulous participants (age range: 45 to 86 years) into titanium (control) or zirconia (test) groups using onepiece implants and a planned unsplinted prosthodontic design was performed. Four maxillary implants (one midpalatal; three anterior crestal) and three mandibular implants (one midsymphyseal; two bilateral distal) were conventionally loaded with the overdentures. Similar attachment systems were used throughout: ball abutment-type patrices (diameter: 2.25 to 3.1 mm as part of the one-piece implants) and custommade plastic matrices (with or without metal housings depending on the patrix size). Prosthodontic outcomes were documented during the first year of the clinical trial.

RESULTS:

Following three deaths and two dropouts, there were 19 participants who were available at the 1-year recall. Of these participants, 3 had early maxillary implant failure and had to be converted to conventional maxillary complete dentures opposing mandibular implant overdentures. There were 79 maintenance events, 34 in the titanium (control) group and 45 in the zirconia (test) group. Patrix loss occurred as a result of three zirconia implant fractures (one mandibular and two crestal maxillary implants). Maintenance events were principally the replacement of matrices and overdenture fracture. Although relines and replacement overdentures also occurred, overall there were no significant differences in prosthodontic maintenance between the control and test groups. A six-field prosthodontic-success analysis table showed no statistically significant difference between the two groups; however, 50% of participants in each group were allocated to the retreatment (repair) field, which produced a low prosthodontic success rate.

CONCLUSIONS:

Removable overdentures can be used on both one-piece titanium and zirconia implants with these attachment systems, due to no difference in prosthodontic maintenance and success. Before recommending routine use of a "metal-free" overdenture treatment option in clinical practice, consideration must be given to the success of the implants themselves.

Clin Oral Implants Res. 2014 Dec;25(12):1366-77.

Ceramic implants (Y-TZP): are they a viable alternative to titanium implants for the support of overdentures? A randomized clinical trial.

Osman RB, Swain MV, Atieh M, Ma S, Duncan W.

ABSTRACT

OBJECTIVE:

The objective of this study was to assess 1-year clinical success of one-piece zirconia implants compared with similar-design titanium implants, in the context of a novel protocol for implant distribution.

MATERIALS AND METHODS:

Twenty-four edentulous participants were randomly allocated to one-piece titanium or zirconia implant group. Each participant received four implants in the maxilla (mid-palatal and three anterior crestal implants) and three implants in the mandible (mid-symphyseal and two bilateral distal implants). Conventional loading protocol was followed. Marginal bone remodeling and clinical success of implants were evaluated. The data were statistically analyzed, and risk predictors for implant failures were evaluated.

RESULTS:

There was no significant difference in the survival rate between the two groups. In the mandible, the survival rate of titanium implants was 95.8% vs. 90.9% for the zirconia implants. The corresponding values in the maxilla were 71.9% and 55%, respectively. Three implants in the zirconia group fractured. Statistically significant less marginal bone loss was observed around titanium implants (0.18 mm) compared with the zirconia group (0.42 mm). The prediction model revealed a higher risk for implant failures in the maxilla ($P < 0.0001$).

CONCLUSION:

The outcome of this study indicates caution before recommendation can be made for the use of single-piece zirconiaimplants for overdenture support. Their use should be limited to cases with proven allergy to titanium. This is mainly due to the increased bone loss and higher fracture rate observed for zirconia implants. Future biomaterial research should focus on producing surface characteristics on zirconia implants with outcomes similar to those established for the optimum osseointegration of titanium implants.

Clin Oral Implants Res. 2015 Apr;26(4):413-418. doi: 10.1111/clr.12370. Epub 2014 Mar 26.

Two-piece zirconia implants supporting all-ceramic crowns: a prospective clinical study.

Cionca N, Müller N, Mombelli A.

ABSTRACT

OBJECTIVES:

The aim of this prospective clinical study is to evaluate the safety and efficacy of a new all-ceramic implant system to replace missing teeth in partially edentulous patients.

MATERIAL AND METHODS:

Thirty-two partially edentulous, systemically healthy patients were treated with 49 two-piece zirconia implants (ZERAMEX(®) T Implant System). Zirconia abutments were connected with adhesive resin cement. Single-unit full-ceramic crowns were cemented. The cases have been followed for 588 ± 174 days after loading (range 369-889 days). All patients have been re-evaluated 1 year after loading.

RESULTS:

The cumulative survival rate 1 year after loading was 87% implants. All failures were the result of aseptic loosening, and no implants were lost after the first year. The results of the other cases were good, and the patients were very satisfied. The cumulative soft tissue complication rate was 0%, the cumulative technical complication rate was 4% implants, the cumulative complication rate for bone loss >2 mm was 0%, and the cumulative esthetic complication rate was 0%. Including the data from 20 patients treated with an earlier version of the system, an over-all 2-year cumulative survival rate of 86% was calculated for a total of 76 two-piece zirconia implants supporting all-ceramic crowns in 52 patients.

CONCLUSIONS:

Replacement of single teeth in the posterior area was possible with this new full-ceramic implant system. Failures were due to aseptic loosening.

Clin Oral Implants Res. 2015 Apr;26(4):371-376.

All-ceramic restoration of zirconia two-piece implants-a randomized controlled clinical trial.

Payer M, Heschl A, Koller M, Arnetzl G, Lorenzoni M, Jakse N.

ABSTRACT

OBJECTIVES:

Aim of this controlled prospective randomized study was to evaluate the outcome of two-piece zirconia implants compared to titanium implants over a period of up to 24 months.

MATERIAL AND METHODS:

A total of 31 implants (16 zirconia/Ziterion vario Z(®) + 15 titanium/Ziterion vario T(®)) were inserted primary stable (>30 Ncm) in the maxilla (7) and mandible (24) of 22 patients (13 male, nine female) requiring neither bone nor soft tissue augmentation. After a healing period of 6 months in the maxilla and 4 months in the mandible, ceramic abutments were luted adhesively to the zirconia implants and definitive all-ceramic restoration was performed with high-density ceramics. Radiographic bone levels, condition of the peri-implant mucosa, aesthetic outcome, implant survival and success were recorded for up to 24 months.

RESULTS:

Measurements of mean marginal bone levels 24 months after surgery showed a significant bone loss ($P < 0.001$) in both groups (Ti: 1.43 (SD ± 0.67) vs. Zir 1.48 (SD ± 1.05). One zirconia implant was lost 8 months after restoration. No further complications were recorded, giving an overall survival and success rate of 93.3% for zirconia and 100% for titanium implants after a period of up to 24 months.

CONCLUSIONS:

After 24 months, success rates of the two-piece ceramic implants showed no significant difference compared to control two-piece titanium implants. The bonded zirconia implant abutment connection appears to be capable with clinical application over the observed period. However, further control measurements need to confirm the presented data.

Clin Implant Dent Relat Res. 2015 Jun;17(3):483-96.

Soft and Hard Tissue Response to Zirconia versus Titanium One-Piece Implants Placed in Alveolar and Palatal Sites: A Randomized Control Trial.

Siddiqi A, Kieser JA, De Silva RK, Thomson WM, Duncan WJ.

ABSTRACT

BACKGROUND:

Titanium (Ti) implants have been used in the last four decades to replace missing teeth. Alternatives to Ti such as zirconia (Zr) may offer aesthetic advantages and be more acceptable to patients and clinicians concerned about Ti allergy but must show equivalent biological acceptability to Ti.

PURPOSE:

The research aimed to investigate soft and hard tissue response to Ti and Zr implants in edentulous patients.

MATERIALS AND METHODS:

The research included 24 participants (Ti = 12, Zr = 12) restored with one-piece ball-abutment implants to support overdentures. Participants received four maxillary implants (two in the premolar alveolus, one off center in the alveolar midline, and one wide-diameter implant in the anterior median palate) and three mandibular implants (one in the midline and bilateral posterior implants).

RESULTS:

Success rates for both Ti and Zr implants were low, 67.9% for all alveolar implants and a survival rate of 50.0% for the palatal implants. Only 11 (52.4%) of 21 palatal implants survived the follow-up period. Peri-implant health was equivalent for Ti and Zr implants and showed no statistically significant changes from loading to the 1-year follow-up. Statistically significant differences were noted in radiographic bone level between Ti and Zr implants ($p = .02$), with Zr showing greater bone loss.

CONCLUSIONS:

Although the failure rates with the one-piece Zr implants were higher than with the Ti ones, suggesting that the former's clinical usage as in this study cannot be recommended, it should be borne in mind that the fault may also lie with the novel prosthodontic design which was used.

Clin Oral Implants Res. 2016 Jul;27(7):751-61. doi: 10.1111/clr.12670. Epub 2015 Jul 27.

Evaluation of a one-piece ceramic implant used for single-tooth replacement and three-unit fixed partial dentures: a prospective cohort clinical trial.

Jung RE, Grohmann P, Sailer I, Steinhart YN, Fehér A, Hämmerle C, Strub JR, Kohal R.

ABSTRACT

AIM:

The aim of this clinical trial was to evaluate the safety and efficiency of a one-piece zirconia oral implant after 1 year of function.

MATERIALS AND METHODS:

Two centers included 60 subjects in need of implant-supported single-tooth restorations or three-unit bridges. A total of 71 zirconia one-piece implants were placed and immediately restored with a temporary reconstruction for at least 2 months. The final veneered zirconia restorations were then cemented and followed for 6 months and 1 year after insertion of the restorations. At each visit, a clinical evaluation was performed to analyze biological parameters of the implants and the neighboring teeth. A standardized periapical radiograph was taken at implant insertion, at the placement of the restorations and at the 1-year follow-up.

RESULTS:

Sixty patients with 71 implants (48 in the mandible, 23 in the maxilla) were included in this study and provided with 11 bridges and 49 crowns. Two patients with three implants (one bridge and one single crown) could not be evaluated. One patient lost his implant 5 weeks after implant insertion. Based on 58 patients, the mean survival rate was 98.3% after one year when the implants of the two patients that did not show up were not counted as lost. The mean marginal bone loss from implant insertion to the 1-year follow-up after the final prosthetic restoration was 0.78 mm with a standard deviation of 0.79 mm. The probing depth around the implants increased from 2.7 mm at insertion of the prosthetic reconstruction to 3.5 mm one year after insertion. The probing depth around the adjacent teeth remained stable at 2.5 mm. At the 1-year recall, the difference was significant. The clinical attachment levels at implants and teeth were not different at the 1-year follow-up with 3.1 mm at tooth and implant sites.

CONCLUSIONS:

The presently tested one-piece ceramic implant was successful in replacing single tooth and three-unit gaps after one year of function. Further long-term data are necessary to verify these initial findings.

Clin Implant Dent Relat Res. 2015 Jun;17(3):483-96.

A Retrospective Clinical Study with Regard to Survival and Success Rates of Zirconia Implants up to and after 7 Years of Loading.

Roehling S, Woelfler H, Hicklin S, Kniha H, Gahlert M.

ABSTRACT

PURPOSE:

The study aims to retrospectively investigate the clinical performance of first-generation zirconia implants with a sandblasted surface up to and after 7 years of loading.

MATERIALS AND METHODS:

Clinical records of patients treated with zirconia implants between 2004 and 2009 were screened. Consequently, adequate patients were invited to a clinical and radiographic investigation to classify each implant according to strict success criteria.

RESULTS:

Seventy-one patients receiving 161 implants were available for the evaluation. Overall, 36 implants (22.4%) were lost due to early (n = 14) and late failures (n = 4) or fractures (n = 18). All surviving 125 implants fulfilled the success criteria. None of the investigated implants had a history of peri-implant infections. Mean values with regard to gingival index, plaque index, modified sulcus bleeding index, and probing depth were 0.03, 0.23, 0.59, and 2.80 mm, respectively. The radiographically evaluated mean crestal bone loss was 0.97 ± 0.07 mm. Diameter-reduced implants (3.25 mm) showed lower survival (58.5%) compared with implants with a diameter of 4.0 mm (88.9%) and 5.0 mm (78.6%). The overall longitudinal survival rate was 77.3%.

CONCLUSIONS:

First-generation zirconia implants showed low overall survival and success rates. The evaluated clinical and radiographic parameters were consistent with healthy peri-implant tissues. Additionally, nonfractured failures were not associated with peri-implant infections.

Clin Oral Implants Res. 2016 Oct;27(10):1265-1273.

Bi-layered zirconia/fluor-apatite bridges supported by ceramic dental implants: a prospective case series after thirty months of observation.

Spies BC, Witkowski S, Butz F, Vach K, Kohal RJ.

ABSTRACT

OBJECTIVE:

The aim of this study was to determine the success and survival rate of all-ceramic bi-layered implant-supported three-unit fixed dental prostheses (IS-FDPs) 3 years after implant placement.

MATERIAL AND METHODS:

Thirteen patients (seven males, six females; age: 41-78 years) received two one-piece ceramic implants (alumina-toughened zirconia) each in the region of the premolars or the first molar and were finally restored with adhesively cemented bi-layered zirconia-based IS-FDPs (3 in the maxilla, 10 in the mandible) composed of CAD/CAM-fabricated zirconia frameworks pressed-over with fluor-apatite glass-ceramic ingots. At prosthetic delivery and the follow-ups after 1, 2 and 3 years, the restorations were evaluated using modified United States Public Health Service (USPHS) criteria. Restorations with minor veneer chippings, a small-area occlusal roughness, slightly soundable restoration margins, minimal contour deficiencies and tolerable color deviations were regarded as success. In case of more distinct defects that could, however, be repaired to a clinically acceptable level, IS-FDPs were regarded as surviving. Kaplan-Meier plots were used for the success/survival analyses. To verify an impact on subjective patients' perceptions, satisfaction was evaluated by visual analog scales (VAS).

RESULTS:

All patients were seen 3 years after implant installation. No IS-FDP had to be replaced, resulting in 100% survival after a mean observation period of 29.5 months (median: 30.7). At the 3-year follow-up, 7/13 IS-FDPs showed a veneer chipping, 13/13 an occlusal roughness and 12/13 minimal deficiencies of contour/color. Since six restorations showed a major chipping and/or a major occlusal roughness, the Kaplan-Meier success rate was 53.8%. However, patients' significantly improved perceptions of function, esthetics, sense, and speech at prosthetic delivery remained stable over time.

CONCLUSION:

Bi-layered zirconia/fluor-apatite IS-FDPs entirely survived the observation period but showed a high frequency of technical complications. Nevertheless, the treatment highly satisfied patients' expectations.

Clin Oral Implants Res. 2017 Jan;28(1):29-35.

Clinical performance of two-piece zirconia implants in the posterior mandible and maxilla: a prospective cohort study over 2 years.

Becker J, John G, Becker K, Mainusch S, Diedrichs G, Schwarz F.

ABSTRACT

OBJECTIVES:

To assess the clinical performance of two-piece zirconium implants over a period of up to 2 years.

MATERIAL AND METHODS:

A total of 52 patients with single-tooth gaps in the posterior mandible or maxilla received the same type of a two-piece zirconium implant system with customized heights of the transmucosal aspect. Fibreglass abutments were cemented and restored with fixed all-ceramic single crowns using a conventional loading protocol. The cumulative survival rate (primary outcome) was calculated according to the life table method, and Kaplan-Meier survival curves were used to estimate the survival function. Covariates (gender, implant position, implant diameter/length, oral surgeon) were tested using log-rank tests.

RESULTS:

A total of two target implants in 2 patients were lost after a functioning time of 8 months. The cumulative survival rate was 95.8%, and the mean survival time amounted to 32.9 months. Log-rank tests revealed a significant association for the covariate "oral surgeon" (P = 0.047). The Kaplan-Meier estimates of mechanical/technical and biological complications amounted to 2.1% and 37.5%, respectively. All implant sites revealed a marked increase of the vestibular mucosal level and gain of keratinized tissue at 24 months.

CONCLUSION:

Within the limitations of a prospective cohort study, it was concluded that this two-piece zirconium implant/fibreglass abutment system can be successfully used in the clinical indication investigated.

J Dent. 2017 Dec;67:58-65. doi: 10.1016/j.jdent.2017.09.008. Epub 2017 Sep 20.

All-ceramic, bi-layered crowns supported by zirconia implants: Three-year results of a prospective multicenter study.

Spies BC, Balmer M, Jung RE, Sailer I, Vach K, Kohal RJ.

ABSTRACT

OBJECTIVES:
To determine the clinical and patient-reported outcomes of bi-layered, all-ceramic posterior single crowns (SCs) supported by zirconia implants in an uncontrolled, prospective, multicenter study.

METHODS:
In two centers, 60 patients received 71 one-piece zirconia oral implants to be restored with either SCs (n=49) or three-unit fixed dental prostheses (n=11). Of these patients, 45 implants were restored with all-ceramic, zirconia-based posterior SCs (one per patient). Survival rates of implants and reconstructions were assessed, and technical success was evaluated according to modified U.S. Public Health Service (USPHS) criteria. Furthermore, patient-reported outcome measures (PROMs) were assessed by applying visual analog scales (VAS). Kaplan-Meier (KM) plots and log-rank tests were used for success/survival analyses. The Wilcoxon matched-pairs signed-rank test was used to evaluate time effects on response variables (PROMs, USPHS criteria).

RESULTS:
Forty patients with 40 SCs could be evaluated after 36.7±1.2months. No SC was replaced, resulting in 100% survival. The KM success estimate was 87.5% (two chippings, one restoration margin, and one contour were rated Charlie). In general, the incidence of chipping (p=.0005) and occlusal roughness (p=.0003) was frequent. Compared with the pre-treatment patient surveys (67-93%), all surveys at prosthetic delivery except for speech (p=.139) showed significantly improved VAS scores (81-94%; p<.0001). Thereafter, no decrease in satisfaction could be observed over time until the 3-year follow-up (86-93%; p≥.390).

CONCLUSIONS:
Veneered, zirconia-based SCs supported by zirconia implants satisfied patients' needs highly. However, significant incidence of chipping and roughness of the veneering ceramic may compromise the clinical long-term outcome for this indication.

CLINICAL SIGNIFICANCE:
Posterior, zirconia-based SCs supported by zirconia oral implants entirely survived the follow-up period of 3 years, but two major chippings, one a significant marginal opening and one pronounced over-contouring, resulted in a reduced KM success estimate of 87.5% after 36 months of observation.

Clin Oral Impl Res. 2018;29(Suppl. 17). https://doi.org/10.1111/clr.26_13356.

Zirconia implants as abutments for single crowns and fixed dental prostheses - 5 years results of a prospective cohort investigation.

Balmer M, Spies BC, Kohal R, Hämmerle C, Vach K, Jung R.

ABSTRACT

BACKGROUND:

Zirconia implants have been added to the portfolio of an increasing number of implant companies as an alternative to titanium. Their application is generally justified only by patient's request for metal-free reconstructions and promising results from preclinical or short-term human clinical studies. Presently, the long-term scientific evidence is very limited. Prior to their wider use, zirconia implants have to prove their clinical effectiveness in terms of long-term safety and success.

AIM/HYPOTHESIS:

To evaluate the clinical and radiological outcomes of one-piece zirconia implants as abutments for single crowns or fixed dental prostheses over an observation period of 5 years in function.

MATERIAL AND METHODS:

In a prospective clinical study with two investigational centers, 60 patients were included and 71 one-piece zirconia implants were placed. After a healing period with immediate provisional reconstructions of at least 4 month in the upper jaw and 2 month in the lower jaw, the final all-ceramic single crowns (SCs) or 3-unit fixed dental prostheses (FDPs) were cemented on the implants. Patients were followed up 6 months after prosthetic insertion and subsequently on an annual basis up to the 5 years follow-up. Clinical parameters (probing depth, plaque, bleeding on probing and clinical attachment level) and radiological measurements (marginal bone level) of the implants and the neighboring teeth were assessed. For the statistical analysis of the clinical parameters and of the mean marginal bone level linear mixed models were applied.

RESULTS:

Out of the 71 inserted implants, a total of 63 in 53 patients could be evaluated after a mean observation time of 5.59 ± 0.38 years after implantation. 6 patients with a total of 7 implants did not attend the 5 years follow-up for different reasons and were counted as dropouts. One implant, indicated as single crown abutment, did not achieve osseointegration and had to be removed 5 weeks after implantation. No further implant loss was recorded. Therefore, the 5 years survival rate was calculated as 98.44%. A statistically significant mean marginal bone loss could be observed after 5 years in function (0.74 ± 0.62 mm P = 0.001). However, after an initial mean marginal loss (0.68 ± 0.56 mm) between implantation and prosthetic insertion, no further statistic significant change in marginal bone level could be observed (0.05 ± 0.63 mm P = 0.46). Neither type of reconstruction (SC FDP+ P = 0.419) nor implant diameter (P = 0.625) and length (P = 0.174) had a significant influence on marginal bone level changes.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The presently investigated one-piece zirconia implant showed a high survival rate and a stable marginal bone level after prosthetic insertion. It proved its potential indication as abutment for SCs and FDPs. However, more research with longer observation periods and higher numbers of implants are needed to confirm these findings.

Clin Oral Implants Res. 2017 May;28(5):613-619.

Evaluation of zirconia-based posterior single crowns supported by zirconia implants: preliminary results of a prospective multicenter study.

Spies BC, Kohal RJ, Balmer M, Vach K, Jung RE.

ABSTRACT

OBJECTIVE:

The aim of this uncontrolled prospective multicenter study was to determine the success and survival rate of posterior single crowns composed of zirconia frameworks hand-layered with a leucite-reinforced feldspathic ceramic supported by one-piece zirconia oral implants.

MATERIAL AND METHODS:

In two centers, sixty patients received 71 zirconia oral implants. To obtain a clear indication of posterior implant-supported single crowns (ISSCs), 14 patients (25 implants) were excluded from the analysis (11 bridges, three anterior crowns). The remaining patients were provided with single implants in posterior regions. As one patient lost his implant and another refused further participation after final prosthesis insertion, 44 ISSCs/patients (19 females, 25 males) were available for evaluation. Of these patients, all were seen at prosthetic delivery and the 6- and 12-month follow-up appointments. Evaluations were performed using modified United States Public Health Service (USPHS) criteria. Restorations within Alpha and Bravo ratings were regarded as success. This included minor chippings, a slight roughness, slightly soundable restoration margins and minimal contour deficiencies. In case of more distinct defects that could, however, be repaired to a clinically acceptable level, restorations were regarded as surviving. Kaplan-Meier plots and log-rank tests were used for the success/survival analyses and the calculation of potential group differences (gender, jaw and center).

RESULTS:

After a mean observation period of 12.5 months (SD: 0.8 months), no ISSC had to be replaced, resulting in a Kaplan-Meier survival rate of 100%. The Kaplan-Meier success rate was 90.9% (one major chipping, one obvious roughness, one significant crevice and one pronounced over-contouring). Minor chippings and occlusal roughness were frequent complications. No significantly different survival/success rates could be observed between the mentioned groups.

CONCLUSION:

The frequent incidence of minor chippings suggests a high technique sensitivity when providing zirconia implants with veneered zirconia-based crowns questioning its suitability for this indication.

Clin Oral Implants Res. 2018 Mar;29(3):290-299.

Three-year analysis of zirconia implants used for single-tooth replacement and three-unit fixed dental prostheses: A prospective multicenter study.

Balmer M, Spies BC, Vach K, Kohal RJ, Hämmerle CHF, Jung RE.

ABSTRACT

AIM:

The aim of the present investigation was to evaluate clinically and radiographically the outcome of zirconia oral implants after 3 years in function.

MATERIALS AND METHODS:

In 60 patients in need of either a single-tooth replacement or a three-unit fixed dental prosthesis (FDP), a total of 71 one-piece zirconia implants were placed and immediately restored with temporary fixed prostheses. After a period of at least 2 months in the mandible and at least 4 months in the maxilla, zirconia-based reconstructions were cemented. The implants were clinically and radiologically examined at implant insertion, prosthetic delivery, at 6 months and then yearly up to 3 years. A linear mixed model was used to analyze statistically the influence of prognostic factors on changes in the marginal bone level.

RESULTS:

Seventy-one implants (48 in the mandible, 23 in the maxilla) inserted in 60 patients were restored with 49 crowns and 11 FDP. One patient lost his implant after 5 weeks. Five patients with one implant each could not be evaluated after 3 years. Based on 55 patients with a total of 66 implants, the mean survival rate was 98.5% after 3 years in function. A statistically significant mean marginal bone loss (0.70 mm ± 0.72 mm) has been detected from implant insertion to the 3-year follow-up. The largest marginal bone loss occurred between implantation and prosthetic delivery (0.67 mm ± 0.56 mm). After delivery, no statistically significant bone level change was observed (0.02 mm ± 0.59 mm). None of the investigated prognostic factors had a significant influence on changes in the marginal bone level.

CONCLUSIONS:

After 3 years in function, the investigated one-piece zirconia implant showed a high survival rate and a low marginal bone loss. The implant system was successful for single-tooth replacement and three-unit FDPs. Further investigations with long-term data are needed to confirm these findings.

BMC Oral Health. 2018; 18: 181. Published online 2018 Nov 1. doi: 10.1186/s12903-018-0636-x.

A prospective clinical study to evaluate the performance of zirconium dioxide dental implants in single-tooth edentulous area: 3-year follow-up.

Bormann KH, Gellrich NC, Kniha H, Schild S, Weingart D, Gahlert M.

ABSTRACT

BACKGROUND:

Traditionally, dental implants have been made from titanium or titanium alloys. Alternatively, zirconia-based ceramic implants have been developed with similar characteristics of functional strength and osseointegration. Ceramic implants offer advantages in certain settings, e.g. in patients who object to metal dental implants. The aim of this study was to investigate the mid-term (36 months) clinical performance of a ceramic monotype implant in single-tooth edentulous area.

METHODS

This was a prospective, open-label, single-arm study in patients requiring implant rehabilitation in single-tooth edentulous area. Ceramic implants (PURE Ceramic Implant, Institut Straumann AG, Basel, Switzerland) with a diameter of 4.1 mm were placed following standard procedure and loaded with provisional and final prostheses after 3 and 6 months, respectively. Implant survival rate and implant success rate were evaluated and crestal bone levels were measured by analysing standardized radiographs during implant surgery and at 6, 12, 24 and 36 months.

RESULTS:

Forty-four patients received a study implant, of whom one patient withdrew consent after 3 months. With one implant lost during the first 6 months after surgery, the implant survival rate was 97.7% at 6 months. No further implants were lost over the following 30 months, and 3 patients were lost to follow-up during this time frame. This led to a survival rate of 97.5% at 36 months.

Six months after implant surgery 93.0% of the implants were considered "successful", increasing to 97.6% at 12 months and remaining at this level at 24 months (95.1%) and 36 months (97.5%).

Bone loss was most pronounced in the first half-year after implant surgery (0.88 ± 0.86 mm). By contrast, between 12 and 36 months the mean bone level remained stable (minimal gain of 0.06 [± 0.60] mm). Hence, the overall bone loss from implant surgery to 36 months was 0.97 (± 0.88) mm.

CONCLUSIONS:

In the follow-up period ceramic implants can achieve favourable clinical outcomes on a par with titanium implants. For instance, these implants can be recommended for patients who object to metal dental implants. However, longer term studies with different edentulous morphology need to confirm the present data.

J Clin Periodontol. 2018 Jan;45(1):114-124.

One-piece zirconia oral implants for single-tooth replace-ment: Three-year results from a long-term prospective cohort study.

Bormann KH, Gellrich NC, Kniha H, Schild S, Weingart D, Gahlert M.

ABSTRACT

AIM:

This 3-year report of a prospective long-term cohort investigation aimed to evaluate the clinical and radiographic outcomes of a one-piece zirconia oral implant for single-tooth replacement.

MATERIALS AND METHODS

Sixty-five patients received a 1-stage implant surgery with immediate temporization. Standardized radiographs were taken at implant insertion, after 1 year, and after 3 years to monitor peri-implant bone levels. A univariate analysis of the association of different baseline parameters on marginal bone loss from implant insertion to 36 months was performed. Soft-tissue parameters were evaluated at prosthesis insertion, after 6 months, after 1 year, and at the 3-year follow-up.

RESULTS:

After 3 years, six posterior site implants were lost, giving a cumulative survival rate of 90.8%. The mean marginal bone loss was 1.45 mm; 35% of the implants lost at least 2 mm bone, and 22% more than 3 mm. The univariate analysis did not identify any parameter associated with marginal bone loss. Probing depth, clinical attachment level, and bleeding index increased over 3 years, and plaque index decreased.

CONCLUSIONS:

The low survival rate of the presented ceramic implant and especially the high frequency of advanced bone loss are noticeable but remain unexplained.

1.2.5 General Reviews and Meta-Analyses

Clin Oral Implants Res. 2009 Sep;20 Suppl 4:32-47.

Are ceramic implants a viable alternative to titanium implants? A systematic literature review.

Andreiotelli M, Wenz HJ, Kohal RJ.

ABSTRACT

AIM:

The aim of this systematic review was to screen the literature in order to locate animal and clinical data on bone-implant contact (BIC) and clinical survival/success that would help to answer the question 'Are ceramic implants a viable alternative to titanium implants?'

MATERIAL AND METHODS

A literature search was performed in the following databases: (1) the Cochrane Oral Health Group's Trials Register, (2) the Cochrane Central Register of Controlled Trials (CENTRAL), (3) MEDLINE (Ovid), and (4) PubMed. To evaluate biocompatibility, animal investigations were scrutinized regarding the amount of BIC and to assess implant longevity clinical data were evaluated.

RESULTS:

The PubMed search yielded 349 titles and the Cochrane/MEDLINE search yielded 881 titles. Based upon abstract screening and discarding duplicates from both searches, 100 full-text articles were obtained and subjected to additional evaluation. A further publication was included based on the manual search. The selection process resulted in the final sample of 25 studies. No (randomized) controlled clinical trials regarding the outcome of zirconia and alumina ceramic implants could be found. The systematic review identified histological animal studies showing similar BIC between alumina, zirconia and titanium. Clinical investigations using different alumina oral implants up to 10 years showed survival/success rates in the range of 23 to 98% for different indications. The included zirconia implant studies presented a survival rate from 84% after 21 months to 98% after 1 year.

CONCLUSIONS:

No difference was found in the rate of osseointegration between the different implant materials in animal experiments. Only cohort investigations were located with questionable scientific value. Alumina implants did not perform satisfactorily and therefore, based on this review, are not a viable alternative to titanium implants. Currently, the scientific clinical data for ceramic implants in general and for zirconia implants in particular are not sufficient to recommend ceramic implants for routine clinical use. Zirconia, however, may have the potential to be a successful implant material, although this is as yet unsupported by clinical investigations.

J Oral Implantol. 2011 Jun;37(3):367-76.

Zirconia dental implants: a literature review.

Özkurt Z, Kazazoğlu E.

ABSTRACT

Titanium and titanium alloys are widely used for fabrication of dental implants. Because of potential immunologic and possible esthetic compromises with titanium implants, novel implant technologies are being developed. However, these novel technologies must maintain the characteristics that provide titanium implants with their high success rates. Zirconia implants were introduced into dental implantology as an alternative to titanium implants. Zirconia seems to be a suitable implant material because of its toothlike color, mechanical properties, biocompatibility, and low plaque affinity. The aim of this study is to review clinical and research articles conducted on zirconia dental implants, compare them with titanium dental implants, and provide information on zirconia dental implant osseointegration and mechanical strength. Zirconia dental implants have the potential to become alternative dental implants to titanium dental implants, but they are not yet in routine clinical use.

Clin Implant Dent Relat Res. 2014 Feb;16(1):124-37.

Current findings regarding zirconia implants.

Depprich R, Naujoks C, Ommerborn M, Schwarz F, Kübler NR, Handschel J.

ABSTRACT

PURPOSE:

The present article aims to analyze the available clinical data on the survival and success rate of dental zirconia implants (ZI).

MATERIAL AND METHOD:

Studies (2006-2011) listed in the bibliography were obtained by using the key words "zirconia, zirconium, implants, dental, clinical" and combinations of these in different databases and on the internet. These articles served as a basis for the article.

RESULTS:

A total of 17 clinical studies were found, involving 1,675 implants and 1,274 patients. In 16 studies, one-piece implant systems were investigated. The survival rates for ZI range from 74-98% after 12-56 months, with success rates between 79.6-91.6% 6-12 months after prosthetic restoration. However, the design of most of the studies show considerable shortcomings, and only low evidence level.

CONCLUSION:

The small number of studies and the limited period of observation permit only a qualified statement on the clinical success of ZI. The results available to date indicate that ZI are inferior to titanium implants (TI) with regard to survival and success rates. Well-conducted long-term studies are urgently needed to permit a meaningful assessment of the survival or success rates of ZI and a statement concerning their application as an alternative to TI.

Full Dent. Sci. 2014; 5(20):535-545.

Ceramic implants: scientific evidence for its use.

Hochscheidt CJ, Shimizu R, Andrighetto AR, Leme P, Salgado CV, Volz KU.

ABSTRACT

Ceramic zirconia (ZrO2) has been the subject of many biomedical researches due to its excellent biocompatibility and chemical stability. In recent years it has been used as an alternative to metallic dental implants, and mainly for its aesthetic periointegration qualities. The purpose of this literature review was to evaluate some of the characteristics of ceramic Y-TZP (tetra- gonal zirconia polycrystalline yttria stabilized) and ATZ (zirconia toughened alumina), pointing its limitations of use as alternative materials in Implantology. Many in vitro and in vivo studies have demonstrated that the ceramics Y-TZP exhibit aesthetic and biological advantages over other biomaterials. The values of fracture toughness are clinically acceptable, being higher in ATZ composites. Some cyclic loading tests with ATZ dental implants showed resistance equal or superior to titanium (Ti). New surface treatments for ceramics have shortened the cure time, allowing immediate loading. Animal experiments have confirmed the good potential for osseointegration of ceramic, with the amount of BIC comparable to Ti and less accumulation of biofilm. Studies up to 5 years with dental implants Y-TZP one-piece in humans have success rates between 84.4 and 100%, whereas the survival rate in 7 years with ATZ implants was 99%. Despite the good results with the ceramic Y-TZP and ATZ, the authors suggest caution in their indications and further long-term prospective studies are required.

Int J Oral Maxillofac Implants. 2014 Mar-Apr;29(2):311-20. doi: 10.11607/jomi.2817.

Comparison of clinical performance of zirconia implants and titanium implants in animal models: a systematic review.

Manzano G, Herrero LR, Montero J.

ABSTRACT

PURPOSE:

This study aimed to compare the values of removal torque (RT) and bone-implant contact (BIC) reported in different animal studies for zirconia and titanium implants.

MATERIALS AND METHODS:

A systematic review of the literature was performed to analyze BIC and RT of animal studies in which both zirconia and titanium dental implants were used. To identify the studies to include in this systematic review, an exhaustive search of PubMed was performed of animal studies published in English with reports on the quantification of the osseointegration of both titanium and zirconia implants by means of BIC and/or RT. The results were aggregated and analyzed within each of the animal models (pig, rabbit, rat, monkey, dog, and sheep).

RESULTS:

The selection process resulted in a final sample of 16 studies. In general, no significant differences were found between titanium and zirconia. The significant differences in terms of BIC and RT reported by the authors were attributable to the different surface treatments and microporosities of the implant surfaces studied, not to the materials themselves. Only two articles reported significantly lower BIC for modified zirconia implants as compared to modified titanium implants. Four authors described statistically significant differences in terms of RT between zirconia and titanium implants in the different animal models, regardless of the surface treatment received by the implants.

CONCLUSIONS:

Within the limitations of this study, the values for the BIC and RT of zirconia implants in most of the studies analyzed did not show statistical differences compared with titanium implants. Modified-surface zirconia may have potential as a candidate for a successful implant material, although further clinical studies are necessary.

J Int Soc Prev Community Dent. 2015 May-Jun; 5(3): 147–156.

Zirconia in dental implantology: A review.

Apratim A, Eachempati P, Krishnappa Salian KK, Singh V, Chhabra S, Shah S.

ABSTRACT

BACKGROUND:

Titanium has been the most popular material of choice for dental implantology over the past few decades. Its properties have been found to be most suitable for the success of implant treatment. But recently, zirconia is slowly emerging as one of the materials which might replace the gold standard of dental implant, i.e., titanium.

MATERIALS AND METHODS:

Literature was searched to retrieve information about zirconia dental implant and studies were critically analyzed. PubMed database was searched for information about zirconia dental implant regarding mechanical properties, osseointegration, surface roughness, biocompatibility, and soft tissue health around it. The literature search was limited to English language articles published from 1975 to 2015.

RESULTS:

A total of 45 papers met the inclusion criteria for this review, among the relevant search in the database.

CONCLUSION:

Literature search showed that some of the properties of zirconia seem to be suitable for making it an ideal dental implant, such as biocompatibility, osseointegration, favourable soft tissue response and aesthetics due to light transmission and its color. At the same time, some studies also point out its drawbacks. It was also found that most of the studies on zirconia dental implants are short-term studies and there is a need for more long-term clinical trials to prove that zirconia is worth enough to replace titanium as a biomaterial in dental implantology.

J Prosthet Dent. 2015 Sep;114(3):351-7.

Crestal bone loss and periimplant inflammatory parameters around zirconia implants: A systematic review.

Vohra F, Al-Kheraif AA, Ab Ghani SM, Abu Hassan MI, Alnassar T, Javed F.

ABSTRACT

STATEMENT OF PROBLEM:

Zirconia implants have been used for oral rehabilitation; however, evidence of their ability to maintain crestal bone and periimplant soft tissue health is not clear.

PURPOSE:

The purpose of this systematic review was to evaluate crestal bone loss (CBL) around zirconia dental implants and clinical periimplant inflammatory parameters.

MATERIAL AND METHODS:

The focus question addressed was, "Do zirconia implants maintain crestal bone levels and periimplant soft tissue health?" Databases were searched for articles from 1977 through September 2014 with different combinations of the following MeSH terms: "dental implants," "zirconium," "alveolar bone loss," "periodontal attachment loss," "periodontal pocket," "periodontal index." Letters to the editor, case reports, commentaries, review articles, and articles published in languages other than English were excluded.

RESULTS:

Thirteen clinical studies were included. In 8 of the studies, the CBL around zirconia implants was comparable between baseline and follow-up. In the other 5 studies, the CBL around zirconia implants was significantly higher at follow-up. Among the studies that used titanium implants as controls, 2 studies showed significantly higher CBL around zirconia implants, and in 1 study, the CBL around zirconia and titanium implants was comparable. The reported implant survival rates for zirconia implants ranged between 67.6% and 100%. Eleven studies selectively reported the periimplant inflammatory parameters.

CONCLUSIONS:

Because of the variations in study design and methodology, it was difficult to reach a consensus regarding the efficacy of zirconia implants in maintaining crestal bone levels and periimplant soft tissue health.

Clin Oral Investig. 2016 Sep;20(7):1403-17.

A systematic review of the clinical survival of zirconia implants.

Hashim D, Cionca N, Courvoisier DS, Mombelli A.

ABSTRACT

OBJECTIVES:

The aim of this review was to evaluate the clinical success and survival rates of zirconia ceramic implants after at least 1 year of function and to assess if there is sufficient evidence to justify using them as alternatives to titanium implants.

MATERIALS AND METHODS:

An electronic search in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) databases was performed in April 2015 by two independent examiners to retrieve clinical studies focusing on the survival rate of zirconia implants after at least 1 year of function. Implant survival was estimated using the overall proportion reported in the studies with a Clopper-Pearson 95 % confidence interval (random effect model with a Der-Simonian Laird estimate).

RESULTS:

Fourteen articles were selected out of the 1519 titles initially screened. The overall survival rate of zirconia one- and two-piece implants was calculated at 92 % (95 % CI 87-95) after 1 year of function. The survival of implants at 1 year for the selected studies revealed considerable heterogeneity.

CONCLUSIONS:

In spite of the unavailability of sufficient long-term evidence to justify using zirconia oral implants, zirconia ceramics could potentially be the alternative to titanium for a non-metallic implant solution. However, further clinical studies are required to establish long-term results, and to determine the risk of technical and biological complications. Additional randomized controlled clinical trials examining two-piece zirconia implant systems are also required to assess their survival and success rates in comparison with titanium as well as one-piece zirconia implants.

CLINICAL RELEVANCE:

Zirconia implants provide a potential alternative to titanium ones. However, clinicians must be aware of the lack of knowledge regarding long-term outcomes and specific reasons for failure.

Int J Oral Maxillofac Implants. 2017 May/June;32(3):e125–e134.

Zirconia Implants as an Alternative to Titanium: A Systematic Review and Meta-Analysis.

Elnayef B, Lázaro A, Suárez-López Del Amo F, Galindo-Moreno P, Wang HL, Gargallo-Albiol J, Hernández-Alfaro F.

ABSTRACT

PURPOSE:

The aim of the present study was to systematically evaluate the marginal bone loss (MBL), success, and survival of zirconia(Zi) implants and compare them with the widely studied titanium (Ti) implants.

MATERIALS AND METHODS:

An electronic and manual literature search of several databases was performed by two independent reviewers for articles up to July 2015 that reported the use of Zi implants and survival, success, and MBL with at least 12 months' follow-up. In addition, random effects meta-analyses of selected studies were applied to analyze the weighted mean difference of survival, success, and MBL between groups. Meta-regression analysis was conducted to investigate any potential influence of confounding factors.

RESULTS:

Twenty-one articles were included, analyzing a total of 1,948 Zi implants with a survival rate of 91.5% and a success rate of 91.6% for 1,250 Zi implants. In addition, three studies were included in the quantitative synthesis and were meta-analyzed for the comparison of survival between Zi and Ti implants, with Zi implants having an 89% greater risk of failure compared with Ti implants (OR = 1.89). There were no statistically significant differences (P = .968) in the success of Zi and Ti implants (odds ratio [OR] = 1.02; 95% confidence interval [CI], 0.47-2.20). MBL (± SD) for Zi implants was 0.89 ± 0.18 mm, which was greater than the MBL for Ti implants (mean difference = 0.14 mm). Also, survival of Zi implants (91.5%) was significantly lower than that of Ti implants (OR = 1.89). Metaregression analysis revealed a similar survival rate for one-piece versus two-piece implants. Similarly, no significant differences were found between immediate and delayed loading.

CONCLUSIONS:

The survival rate of Zi implants was significantly lower than that for the commonly used Ti implants. However, for certain clinical conditions, such as a thin tissue biotype or in the highly esthetic anterior area, Zi implants may offer some benefit when compared with Ti implants.

J Dent Res. 2017 Jan;96(1):38-46.

Clinical Outcomes of Zirconia Dental Implants: A Systematic Review

Pieralli S, Kohal RJ, Jung RE, Vach K, Spies BC.

ABSTRACT

To determine the survival rate and marginal bone loss (MBL) of zirconia dental implants restored with single crowns or fixed dental prostheses. An electronic search was conducted up to November 2015 (without any restriction regarding the publication time) through the databases MEDLINE (PubMed), Cochrane Library, and EMBASE to identify randomized controlled clinical trials and prospective clinical trials including >15 patients. Primary outcomes were survival rate and MBL. Furthermore, the influence of several covariates on MBL was evaluated. Qualitative assessment and statistical analyses were performed. This review was conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for systematic reviews. With the applied search strategy, 4,196 titles could be identified. After a screening procedure, 2 randomized controlled clinical trials and 7 prospective clinical trials remained for analyses. In these trials, a total of 326 patients received 398 implants. The follow-up ranged from 12 to 60 mo. Implant loss was mostly reported within the first year, especially within the healing period. Thereafter, nearly constant survival curves could be observed. Therefore, separate meta-analyses were performed for the first and subsequent years, resulting in an implant survival rate of 95.6% (95% confidence interval: 93.3% to 97.9%) after 12 mo and, thereafter, an expected decrease of 0.05% per year (0.25% after 5 y). Additionally, a meta-analysis was conducted for the mean MBL after 12 mo, resulting in 0.79 mm (95% confidence interval: 0.73 to 0.86 mm). Implant bulk material and design, restoration type, and the application of minor augmentation procedures during surgery, as well as the modes of temporization and loading, had no statistically significant influence on MBL. The short-term cumulative survival rates and the MBL of zirconia implants in the presented systematic review are promising. However, additional data are still needed to confirm the long-term predictability of these implants.

J Prosthodont Res. 2018 Oct;62(4):397-406.

A systematic review and meta-analysis on the clinical outcome of zirconia implant-restoration complex.

Haro Adánez M, Nishihara H, Att W3.

ABSTRACT

PURPOSE:

This systematic review evaluates the clinical outcome of zirconia implant-associated survival and success rates, marginal bone loss, and implant-restoration complex integrity.

STUDY SELECTION:

Using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, studies including ≥10 patients restored with zirconia implants supporting single crowns (SCs) or fixed dental prostheses (FDPs) prior to January 2017 were identified. Primary outcomes were survival rates and marginal bone loss around one and two-piece zirconia implants and the associated implant-restoration complex integrity.

RESULTS:

1349 studies were selected; after duplicate removal and title screening, 36 remained for full-text screening. 17 studies met the inclusion criteria: 2 randomized controlled clinical studies, 11 prospective clinical studies and 4 retrospective studies. In total, 1704 implants from 1002 patients were evaluated, including 1521 one-piece and 183 two-piece zirconia implants with follow-up between 1 and 7 years. The mean survival rate was 95% (95% CI 91-97%). The overall mean marginal bone loss was 0.98mm (95% CI 0.79-1.18); the mean marginal bone loss after 1year was 0.89mm (95% CI 0.60-1.18). No meta-analysis regarding prosthetic outcomes was possible.

CONCLUSIONS:

Survival and marginal bone loss values after one year for one-piece zirconia implants are acceptable, but long-term studies are required to support their clinical use. No particular restoration material can be recommended; this decision is apparently based on clinicians' preferences. Results from two-piece implants do not provide sufficient data to support their clinical use and no abutment or cementing materials for two-piece zirconia implants can be recommended.

Clin Oral Implants Res. 2018 Oct;29 Suppl 16:135-153. doi: 10.1111/clr.13352.

Performance and outcome of zirconia dental implants in clinical studies: A meta-analysis.

Roehling S, Schlegel KA, Woelfler H, Gahlert M.

ABSTRACT

OBJECTIVES:

To evaluate implant survival, peri-implant marginal bone loss, technical, and biological complications as well as aesthetic outcomes of zirconia implants in clinical studies.

MATERIAL AND METHODS:

Electronic (Medline, Embase) and hand searches were performed to identify clinical studies published between January 2004 and March 2017 investigating zirconia dental implants with a mean follow-up of at least 12 months. Primary outcomes were implant survival and peri-implant marginal bone loss. Secondary outcomes included technical and biological complications as well as aesthetic outcomes. Meta-analyses were performed to estimate implant survival and marginal bone loss.

RESULTS:

From 943 titles, 264 abstracts were selected. Subsequently, 80 full-text articles were screened, and 18 studies were included for data extraction. One- (14 studies) and 2-piece zirconia implants (4 studies) were investigated. Commercially available (CA) (510 implants, 398 patients) and not commercially available (NCA) zirconia implants (618 implants, 343 patients) were identified. For CA implants (follow-up: 12-61.20 months), technical complications (1.6%), implant fractures (0.2%) and biological complications (4.2%) were reported. Meta-analyses estimated 1- and 2-year survival rates of 98.3% (95% CI: 97.0%-99.6%) and 97.2% (95% CI: 94.7%-99.7%), respectively, and a mean 1-year marginal bone loss of 0.7 mm (95% CI: 0.4-1.0 mm).

CONCLUSIONS:

Since 2004, the survival rates of CA implants significantly improved compared with NCA implants. CA 1-piece zirconiaimplants showed similar 1- and 2-year mean survival rates and marginal bone loss after 1 year compared with published data for titanium implants. However, more clinical long-term data are needed to confirm the presently evaluated promising short-term outcomes.

Clin Oral Implants Res. 2018 Oct;29 Suppl 16:199-214. doi: 10.1111/clr.13306.

A systematic review of the survival and complication rates of zirconia-ceramic and metal-ceramic single crowns.

Pjetursson BE, Valente NA, Strasding M, Zwahlen M, Liu S, Sailer I.

ABSTRACT

OBJECTIVES:

The aim of the present systematic review was to analyze the survival and complication rates of zirconia-based and metal-ceramic implant-supported single crowns (SCs).

MATERIALS AND METHODS:

An electronic MEDLINE search complemented by manual searching was conducted to identify randomized controlled clinical trials, prospective cohort and retrospective case series on implant-supported SCs with a mean follow-up time of at least 3 years. Patients had to have been clinically examined at the follow-up visit. Assessment of the identified studies and data extraction was performed independently by two reviewers. Failure and complication rates were analyzed using robust Poisson's regression models to obtain summary estimates of 5-year proportions.

RESULTS:

The search provided 5,263 titles and 455 abstracts, full-text analysis was performed for 240 articles, resulting in 35 included studies on implant-supported crowns. Meta-analysis revealed an estimated 5-year survival rate of 98.3% (95% CI: 96.8-99.1) for metal-ceramic implant supported SCs (n = 4,363) compared to 97.6% (95% CI: 94.3-99.0) for zirconia implant supported SCs (n = 912). About 86.7% (95% CI: 80.7-91.0) of the metal-ceramic SCs (n = 1,300) experienced no biological/technical complications over the entire observation period. The corresponding rate for zirconia SCs (n = 76) was 83.8% (95% CI: 61.6-93.8). The biologic outcomes of the two types of crowns were similar; yet, zirconia SCs exhibited less aesthetic complications than metal-ceramics. The 5-year incidence of chipping of the veneering ceramic was similar between the material groups (2.9% metal-ceramic, 2.8% zirconia-ceramic). Significantly (p = 0.001), more zirconia-ceramic implant SCs failed due to material fractures (2.1% vs. 0.2% metal-ceramic implant SCs). No studies on newer types of monolithic zirconia SCs fulfilled the simple inclusion criteria of 3 years follow-up time and clinical examination of the present systematic review.

CONCLUSION:

Zirconia-ceramic implant-supported SCs are a valid treatment alternative to metal-ceramic SCs, with similar incidence of biological complications and less aesthetic problems. The amount of ceramic chipping was similar between the material groups; yet, significantly more zirconia crowns failed due to material fractures.

J Prosthodont Res. 2018 Apr;62(2):121-133.

Is zirconia a viable alternative to titanium for oral implant? A critical review.

Sivaraman K, Chopra A, Narayan AI, Balakrishnan D.

ABSTRACT

PURPOSE:

Titanium based implant systems, though considered as the gold standard for rehabilitation of edentulous spaces, have been criticized for many inherent flaws. The onset of hypersensitivity reactions, biocompatibility issues, and an unaesthetic gray hue have raised demands for more aesthetic and tissue compatible material for implant fabrication. Zirconia is emerging as a promising alternative to conventional Titanium based implant systems for oral rehabilitation with superior biological, aesthetics, mechanical and optical properties. This review aims to critically analyze and review the credibility of Zirconia implants as an alternative to Titanium for prosthetic rehabilitation.

STUDY SELECTION:

The literature search for articles written in the English language in PubMed and Cochrane Library database from 1990 till December 2016. The following search terms were utilized for data search: "zirconia implants" NOT "abutment", "zirconiaimplants" AND "titanium implants" AND "osseointegration", "zirconia implants" AND compatibility.

RESULTS:

The number of potential relevant articles selected were 47. All the human in vivo clinical, in vitro, animals' studies were included and discussed under the following subheadings: Chemical composition, structure and phases; Physical and mechanical properties; Aesthetic and optical properties; Osseointegration and biocompatibility; Surface modifications; Peri-implant tissue compatibility, inflammation and soft tissue healing, and long-term prognosis.

CONCLUSIONS:

Zirconia implants are a promising alternative to titanium with a superior soft-tissue response, biocompatibility, and aesthetics with comparable osseointegration. However, further long-term longitudinal and comparative clinical trials are required to validate zirconia as a viable alternative to the titanium implant.

Clinical Oral Implants Res. 2019 March. https://doi.org/10.1111/clr.13425.

Zirconia compared to titanium dental implants in preclinical studies — A systematic review and meta-analysis.

Roehling S, Schlegel KA, Woelfler H, Gahlert M.

ABSTRACT

OBJECTIVES:

To evaluate whether zirconia implants demonstrate differences in hard and soft tissue integration compared to titanium implants in preclinical studies.

MATERIAL AND METHODS::

In March 2017, electronic (MEDLINE, EMBASE) and hand search was performed to identify preclinical studies comparing zirconia and titanium implants. Primary outcomes were bone-to-implant contact (BIC) and removal torque out (RTQ), respectively, push-in (PI) measurements. Secondary outcomes included biologic width (BW) dimensions.

RESULTS:

A total of 37 studies were included for data extraction after screening of 91 from 1,231 selected titles. Thirty-seven experimental studies using six different species were identified. The follow-up periods ranged between 0.4 and 56 weeks. For titanium, mean values of 59.1% (95% CI: 53.3 – 64.8), 102.6 Ncm (95% CI: 81.5 – 123.6), and 25.1 N (95% CI: 20.2 – 30.0) for BIC, RTQ, and PI were estimated, respectively. The mean values for zirconia were 55.9% (95% CI: 51.6 – 60.1), 71.5 Ncm (95% CI: 51.1 – 91.9), and 22.0 N (95% CI: 13.2 – 30.7) for corresponding parameters. Confounding factors such as animal species, implant material, loading protocol, and study or loading duration significantly influenced the outcomes. Similar qualitative soft tissue integration was reported for zirconia and titanium implants. However, faster maturation processes of epithelial and connective tissues around zirconia implants were assumed. Quantitatively, similar BW dimensions were evaluated for titanium (3.5 mm; 95% CI: 2.9 – 4.2) and zirconia (3.2 mm; 95% CI: 2.7 – 3.7), whereas the loading protocol significantly influenced the outcomes.

CONCLUSIONS:

Zirconia and titanium implants demonstrate a similar soft and hard tissue integration capacity. However, titanium tended to show a faster initial osseointegration process compared to zirconia. Importantly, not only material characteristics but predominantly animal species and study protocols can significantly influence the outcomes.

2. Titanium Implantology and Periimplantitis

2.1 Basic Research

Int J Oral Maxillofac Surg. 1994 Dec;23(6 Pt 2):450-2.

Titanium deposition in regional lymph nodes after insertion of titanium screw implants in maxillofacial region.

Weingart D, Steinemann S, Schilli W, Strub JR, Hellerich U, Assenmacher J, Simpson J.

ABSTRACT

The deposition of titanium in regional lymph nodes was studied after insertion of endosseous, plasma-spray-coated titanium screw implants in a total of 19 beagle dogs. Five additional animals with no implants served as the control group. After killing the animals 9 months postoperatively, the regional lymph nodes were carefully excised, and samples were prepared for histologic examination. Other samples were used to identify foreign particles by energy-dispersive x-ray analysis and for measurement of the titanium concentration in the tissue by flameless atomic absorption spectroscopy. Very fine foreign-body particles could be seen in the histologic sections, and they were identified as titanium by energy-dispersive x-ray analysis. The atomic absorption analysis for titanium revealed a significantly higher concentration in the group with implants. The presence of very fine, poorly attached particles on the plasma-sprayed titanium surface suggests that these particles may be mechanically dislodged from the surface on insertion of the implants. This suggests that the fine particles may be transported by phagocytes to the regional lymph nodes, where they could be found without any signs of inflammation or foreign-body reaction.

J Bone Joint Surg Am. 1999 May;81(5):603-15.

Signaling pathways for tumor necrosis factor-alpha and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro.

Nakashima Y, Sun DH, Trindade MC, Maloney WJ, Goodman SB, Schurman DJ, Smith RL.

ABSTRACT

BACKGROUND:

Loosening of the implant after total joint arthroplasty remains a serious problem. The activation of macrophages by wear debris from implants, mediated by the release of cytokines that elicit bone resorption, may lead to loosening. The purpose of the present study was to elucidate the mechanisms of macrophage activation by titanium particles from the components of implants and to identify the signaling pathways involved in particle-mediated release of cytokines.

METHODS:

Macrophages were isolated from mononuclear leukocytes obtained from healthy human donors and were exposed to titanium-alloy particles that had been obtained from periprosthetic membranes collected at revision total joint arthroplasties and then enzymatically prepared. The experimental protocols included examination of the effects of the inhibition of phagocytosis and the binding of antibodies to macrophage complement receptors on particle-induced macrophage activation. The release of the proinflammatory cytokines TNF-alpha (tumor necrosis factor-alpha) and IL-6 (interleukin-6) was used to assess macrophage activation. The signaling pathways involved in the induction of cytokine release were analyzed by identification of phosphorylated proteins with use of the Western blot technique and by translocation of the transcription factors nuclear factor-kappa B (NF-kappaB) and nuclear factor-interleukin-6 (NF-IL-6) into the nuclear protein fraction with use of electrophoretic mobility shift assays. The role of serine/threonine and tyrosine kinase pathways in the activation of nuclear factors and the release of cytokines was examined with use of selective pharmacological agents.

RESULTS:

Exposure of macrophages to titanium-alloy particles in vitro for forty-eight hours resulted in a fortyfold increase in the release of TNF-alpha and a sevenfold increase in the release of IL-6 ($p<0.01$). Phagocytosis of particles occurred in approximately 73 percent of the macrophages within one hour of exposure. Pretreatment of the macrophages with cytochalasin B reduced phagocytosis by 95 percent but did not reduce the release of TNF-alpha or IL-6. Thus, phagocytosis of particles was not necessary for induction

of the release of TNF-alpha or IL-6 in the cultured macrophages. Ligation of the macrophage CD11b/CD18 receptors by integrin-specific antibodies also increased the release of TNF-alpha and IL-6. Antibodies to CD11b/ CD18 receptors (macrophage Mac-1 receptors) reduced phagocytosis of particles by 50 percent ($p<0.05$). (The CD11b/ CD18 macrophage receptor is the macrophage receptor for the complement component CR3bi. The CD11b/CD18 macrophage receptor can also bind to ICAM-1 and ICAM-2. CD is the abbreviation for cluster of differentiation, and ICAM is the abbreviation for intercellular adhesion molecule.) Inhibition of phagocytosis was not accompanied by a decrease in the release of TNF-alpha and IL-6. Blocking RNA synthesis with actinomycin D or preventing protein synthesis with cycloheximide abolished or decreased particle-induced release of TNF-alpha and IL-6 from the macrophages. Macrophage release of TNF-alpha and IL-6 in response to particles coincided with increased tyrosine phosphorylation and mitogen-activated protein kinase activation. Inhibition of tyrosine and serine/threonine kinase activity decreased the particle-induced release of cytokines. Exposure of macrophages to either titanium-alloy particles or to antibodies to the receptor proteins CD11b and CD18 for thirty minutes activated the transcription factors NF-kappaB and NF-IL-6. Inhibition of particle phagocytosis did not block activation of the transcription factors. However, inhibition of tyrosine and serine/threonine kinase activity decreased the activation of NF-kappaB and NF-IL-6.

CONCLUSIONS:

These data suggest that particle induced macrophage release of TNF-alpha and IL-6 does not require phagocytosis but is dependent on tyrosine and serine/threonine kinase activity culminating in activation of the transcription factors NF-kappa B and NF-IL-6.

CLINICAL RELEVANCE:

Retrieval studies have documented numerous macrophages in association with particulate debris in granulomatous tissue surrounding failed total joint replacements. However, the molecular basis on which wear particles induce macrophage expression of proinflammatory cytokines and bone-resorbing factors remains unclear. This in vitro study showed that particles incite the release of proinflammatory cytokines from macrophages in the absence of phagocytosis. These results imply that contact of wear particles with macrophage cell-surface membrane proteins, such as the complement receptor CD11b/CD18, is sufficient signal for release of proinflammatory cytokines. The data further suggest that release of proinflammatory cytokines follows transmission of a membrane recognition event through intracellular signaling pathways that effect gene activation and protein synthesis. Therefore, these data indicate that a reduction in the formation of wear particles can be expected to improve the outcome after total joint arthroplasty by decreasing macrophage activation.

Aust Dent J. 2002 Sep;47(3):214-7.

A study of titanium release into body organs following the insertion of single threaded screw implants into the mandibles of sheep.

Frisken KW, Dandie GW, Lugowski S, Jordan G.

ABSTRACT

BACKGROUND:

Titanium is generally considered a safe metal to use in implantation but some studies have suggested that particulate titanium may cause health problems either at the site overlying the implant or in distant organs, particularly after frictional wear of a medical prosthesis. It was the purpose of this investigation to study the levels of dissemination of titanium from threaded screw type implants following placement of single implants in sheep mandibles.

METHOD:

Twelve sheep were implanted with a single 10x3.75mm self-tapping implant for time intervals of one, four and eight to 12 weeks. Four unoperated sheep served as controls. Regional lymph nodes, lungs, spleens and livers were dissected, frozen and subsequently analysed by Graphite Furnace Atomic Absorption Spectroscopy.

RESULTS:

Results associated with successful implants showed no statistically significant different levels of titanium in any organ compared to controls, although some minor elevations in titanium levels within the lungs and regional lymph nodes were noted. Two implants failed to integrate and these showed higher levels of titanium in the lungs (2.2-3.8 times the mean of the controls) and regional lymph nodes (7-9.4 times the levels in controls).

CONCLUSIONS:

Debris from a single implant insertion is at such a low level that it is unlikely to pose a health problem. Even though the number of failed implants was low, multiple failed implants may result in considerably more titanium release which can track through the regional lymph nodes. Results suggest that sheep would be an excellent model for following biological changes associated with successful and failed implants and the effect this may have on titanium release.

Implant Dent. 2003;12(1):75-80.

Macrophages related to dental implant failure.

Olmedo D, Fernández MM, Guglielmotti MB, Cabrini RL.

ABSTRACT

PURPOSE:

The aim of this study was to evaluate, histologically and quantitatively, the presence of macrophages loaded with metallic particles in the periimplant soft tissues of failed titanium (Ti) dental implants.

MATERIALS AND METHODS::

The study was performed on sections of metallic Ti implants embedded in methyl methacrylate resin that exhibited macrophages in the soft tissues contiguous with the implant. The volume of periimplant soft tissue was evaluated, and the number of macrophages was determined. The particles within macrophages were analyzed by energy-dispersive x-ray analysis.

RESULTS:

Macrophages were more abundant in the zone adjacent to the metallic implant as compared with the zone further away from the implant. Energy-dispersive x-ray analysis revealed the presence of Ti within macrophages.

CONCLUSIONS:

Macrophages loaded with Ti particles can be associated with a corrosion process. The method proposed would allow for the objective evaluation of the presence of macrophages associated with dental implants and other orthopedic materials that contain Ti or other metals.

Dent Mater. 2003 Jan;19(1):54-9.

Galvanic corrosion behavior of implant suprastructure dental alloys.

Taher NM, Al Jabab AS.

ABSTRACT

OBJECTIVE:

The purpose of this study was to evaluate and compare in vitro, the galvanic corrosion behavior of Co-Cr alloys (R2000, R800), Ni-Cr (RCS), silver-palladium (Jelstar), Gold (Pontallor-4) and Ternary Ti (experimental Ter Ti) when coupled with endosseous Ti implant abutment material. Amalgam alloy and commercially pure Ti cylinders (SSTi) were coupled with endosseous Ti implants as negative and positive controls, respectively.

METHODS:

An EG&G Model 263 Scanning Potentiostat was used for this purpose. Specimens were prepared and fresh artificial saliva was used as an electrolyte solution. The experiment run time was 24h for each couple. The common potential, galvanic current and current integration during the last 6h were recorded for each couple.

RESULTS:

The results showed that the best couples were Ti/Pontallor-4, Ti/Ter Ti, Ti/R800 and Ti/Jelstar. The least acceptable couples were Ti/amalgam, SSTi/SSTi and Ti/R2000, while the Ti/RCS couple showed unstable galvanic corrosion behavior.

SIGNIFICANCE:

It is concluded that the following alloys can be used as suprastructure alloys with Ti implants: Pontallor-4, R800, Jelstar and Ter Ti. Although Ter Ti alloy is an experimental alloy, it showed good results, but cannot be used in the clinical field unless extensive investigations are carried out. The SSTi/SSTi couple showed unexpected galvanic corrosion behavior which needs further investigation.

Biomed Tech (Berl). 2004 Dec;49(12):340-4.

Effects of clinically relevant alumina ceramic, zirconia ceramic and titanium particles of different sizes and concentrations on TNF-alpha release in a human macrophage cell line

Sterner T, Schütze N, Saxler G, Jakob F, Rader CP.

ABSTRACT

INTRODUCTION:

Aseptic loosening is considered to be the main problem of modern endoprothesis. Tumor necrosis factor alpha (TNFalpha) seems to be the initiator protein of particle disease. The aim of our study was to investigate the TNFalpha response of macrophage like cells (MLC) after stimulation with periprosthetic particles, typically found during revision surgery. For this purpose alumina ceramic (Al2O3), zirconia ceramic (ZrO2) and titanium (Ti) particles of different sizes and concentrations were used. Important was to study the effects of different sizes due to TNFalpha secretion and the comparison of the biological effects of alumina ceramic and titanium.

METHOD:

To obtain an TNFalpha profile we used an established macrophage model (Rader et al.) with THP-1 cells (human monocytic cell line). Therefore 106 MLC were incubated with different particle concentrations and sizes for 6 h. The supernatant was then investigated for TNF using ELISA assay.

RESULTS:

Ti-particles provoked in both sizes (0.2 microm and 2.5 microm) the greatest TNFalpha response, 8 times and 17 times as high in comparison with control. But substantially more 0.2 microm sized Ti-particles were necessary to get the above mentioned results. Al2O3-particles were not as effective as Ti, but they released fourfold more TNFalpha compared to control. There was no difference in TNFalpha-secretion comparing Al2O3-particles of different sizes (0.6 microm and 2 microm), but a 1000 times greater concentration of the 0.6 microm sized particles were needed. Using Al2O3- and Ti-particles of the same size and concentration, Ti provoked a significant higher TNFalpha response. ZrO2 showed no effects on TNFalpha release.

CONCLUSION:

Because of our results we recommend ceramic articulating surfaces, which are superior to metal on metal matings ion term of biological reactions. Additionally bigger wear particles should be avoided. Revisionoperation should be done early to avoid huge amount of wear particles and to minimize local osteolysis.

Wiley Periodicals, Inc. J Biomed Mater Res, 2007. https://doi.org/10.1002/jbm.a.31514

Biological response of tissues with macrophagic activity to titanium dioxide

Olmedo DG, Tasat DR, Evelson P, Guglielmotti MB, Cabrini RL

ABSTRACT

The titanium dioxide layer is composed mainly of anatase and rutile. This layer is prone to break, releasing particles to the milieu. Therefore, corrosion may cause implant failure and body contamination. We have previously shown that commercial anatase–titanium dioxide (TiO2–anatase) is deposited in organs with macrophagic activity, transported in the blood by phagocytic-mononuclear cells, and induces an increase in the production of reactive oxygen species (ROS). In this study, we evaluated the effects of rutile–titanium dioxide (TiO2–rutile). Male Wistar rats were injected i.p. with a suspension of TiO2–rutile powder at a dose of 1.60 g/100 g b.w. Six months postinjection, the presence of Ti was assessed in serum, blood cells, liver, spleen, and lung. Titanium was found in phagocytic mononuclear cells, serum, and in the parenchyma of all the organs tested. TiO2–rutile generated a rise in the percentage of reactive cells, which was smaller than that observed when TiO2–anatase was employed in a previous study. Although TiO2–rutile provoked an augmentation of ROS, it failed to induce damage to membrane lipids, possibly due to an adaptive response. The present study reveals that TiO2–rutile is less bioreactive than TiO2–anatase.

Int J Oral Maxillofac Surg. 2008 Nov;37(11):1032-8. doi: 10.1016/j.ijom.2008.05.013. Epub 2008 Jul 7.

Local effect of titanium implant corrosion: an experimental study in rats.

Olmedo DG, Duffó G, Cabrini RL, Guglielmotti MB.

ABSTRACT

The aim of this study was to evaluate histologically the biological effect of pitting corrosion and to contribute clinically relevant data on the permanence of titanium metal structures used in osteosynthesis in the body. Commercially pure titanium laminar implants (control) and commercially pure titanium laminar implants with pitting corrosion (experimental) were implanted in the tibiae of rats. At 14 days post-implantation the animals were killed. The tibiae were resected, fixed, radiographed and processed for embedding in methyl methacrylate. Percentage of bone-implant contact and peri-implant bone volume were evaluated. The histological study of the titanium implants submitted to pitting corrosion showed scarce bone-implant contact, it was only present in the areas with no pitting and/or surface alterations. There was a statistically significant lower percentage of bone-implant contact in the experimental group (6%+/-4) than in the control group (26%+/-6) ($p<0.001$). Products of corrosion in the peri-implant bed, especially around the blood vessels and areas of bone marrow in the metal-tissue interface, were observed. The microchemical analysis of corrosion products revealed the presence of titanium. The adverse local effects caused by pitting corrosion suggest that titanium plates and grids should be used with caution as permanent fixation structures.

J Mater Sci Mater Med. 2008 Sep;19(9):3049-56. doi: 10.1007/s10856-008-3438-x. Epub 2008 Apr 4.

Biodistribution of titanium dioxide from biologic compartments.

Olmedo DG, Tasat DR, Guglielmotti MB, Cabrini RL.

ABSTRACT

The layer of titanium dioxide (TiO(2)) of the implant is chronically exposed to the internal electrolyte milieu in the peri-implant biological compartment. Corrosion results from electrochemical attack and ensuing gradual degradation of the metallic materials and is thus of biological interest when these biomaterials are employed in clinical implantology. Herein we evaluated and compared the chronic effect and the biodistribution of TiO(2) administered subcutaneously or intraperitoneally. We propose that the compartmentalization of titanium in the area of subcutaneous injection would reproduce the biological compartment of the implant and its microenvironment from which metal ions could be released and migrate systemically. Potential TiO(2) deposits were identified and characterized in skin, liver and lung by histological and EDX analyses. After both treatments, the skin, liver, and lungs exhibited histological evidence of TiO(2) deposits. In order to characterize in situ macrophage-like cells, tissue sections were immunohistochemically stained for CD68. Tissue specimens from all organs assayed showed positive staining for anti-macrophage monoclonal antibody CD68 (PGM1). Despite the compartmentalization of titanium within nodular areas in rats treated subcutaneously, systemic migration occurred. We concluded that systemic migration of TiO(2) occurred regardless of the administration route.

J Biomed Mater Res A. 2009 Oct;91(1):29-36. doi: 10.1002/jbm.a.32183.

Titanium IV ions induced human osteoclast differentiation and enhanced bone resorption in vitro.

Cadosch D, Chan E, Gautschi OP, Meagher J, Zellweger R, Filgueira L.

ABSTRACT

There is increasing evidence that titanium (Ti) ions are released from orthopedic implants, with concentrations in the range of 1 microM in tissue and blood, and may play a role in aseptic loosening of orthopedic implants. This study investigated whether Ti(IV) ions induce differentiation of monocytic osteoclast precursors into osteo-resorptive multinucleated cells and influence the activation and function of in vitro generated osteoclasts. Human monocytes and in vitro generated osteoclasts were exposed to 1 microM Ti(IV) ions for 10 days. Thereafter, osteoclast differentiation, activation, and function were evaluated. Transcription of specific osteoclastic genes was measured using quantitative reverse transcription polymerase chain reactions, which showed increased expression of tartrate-resistant acid phosphatase (TRAP) in approximately 20% of Ti(IV)-treated monocytes. Detection and quantification of intracellular TRAP activity using ELF97 as a fluorescent substrate revealed a significant increase of TRAP-positive cells in Ti(IV)-treated monocytes. Additionally, as demonstrated on dentin slide cultures, Ti(IV)-treated monocytes became functional bone resorbing cells, significantly increasing their osteo-resorptive activity to similar levels as osteoclasts in vitro. These results suggest that Ti(IV) ions released by biocorrosion from orthopedic implants induce differentiation of monocytes toward mature, functional osteoclasts, which may well contribute the pathomechanism of aseptic loosening.

J Neurosci Methods. 2009 Mar 30;178(1):182-7. doi: 10.1016/j.jneumeth.2008.12.008. Epub 2008 Dec 14.

Uptake and intracellular distribution of various metal ions in human monocyte-derived dendritic cells detected by Newport Green DCF diacetate ester.

Cadosch D, Meagher J, Gautschi OP, Filgueira L.

ABSTRACT

BACKGROUND:

The attempt to visualise intracellular protein metal complexes has currently been difficult due to the unavailability of probes for such molecular structures. Newport Green DCF diacetate ester is a cell permeant acetate ester, which b comes fluorescent after hydrolysis. This molecule is initially uncharged, allowing it to pass through cell membranes. Once in the cell, it is hydrolysed and becomes charged, hindering its escape from the cell and allowing it to bind charged protein metal complexes, which then become fluorescent.

METHODS:

In this study, we exposed cultured human monocyte-derived dendritic cells (mDC) to a variety of metal ions with the aim of having the cells take up and process protein metal complexes. Newport Green DCF diacetate ester was used to fluorescently label intracellular protein metal complexes.

RESULTS:

Flow cytometry analysis and confocal imaging showed specific staining for mDC exposed to aluminium, chromium, nickel, titanium and zirconium ions. The intensity of staining varied between ion types, whereby Ti(III) resulted in the brightest fluorescence signal. Aluminium, Cr(III), Ni, Ti(IV) and Zr(IV) were also clearly detectable.

CONCLUSION:

For the first time, intracellular metal ion protein complexes undergoing cellular processing were successfully visualised in human mDC using flow cytometry and confocal microscopy.

Bull NYU Hosp Jt Dis. 2009;67(2):182-8.

Biologic effects of implant debris.

Hallab NJ, Jacobs JJ.

ABSTRACT

Biologic response to orthopedic implants debris is central to clinical performance. Eventual implant loosening due to aseptic osteolysis has been attributed to local inflammatory responses to wear and corrosion products that are produced by articulating implant interfaces. The response to implant debris is dominated by local immune activation, e.g. macrophages. Immune reactivity has been shown to depend on the number of particles produced or the dose (i.e., the concentration of phagocytosable particles per tissue volume, which can be characterized by knowing the size distribution and amount of debris). Elongated particles (fbers) are generally more pro-inflammatory than round particles, and there is a growing consensus that metals particles are more proinflammatory than polymers in vivo. Generally, to produce an in vitro inflammatory response, particles need to be less than 10 mum, i.e. phagocytosable. However, both soluble and particulate debris derived from Co-Cr-Mo alloy implants can induce monocyte/macrophage activation and secretion of pro-inflammatory cytokines such as IL-1beta, TNFalpha, IL-6 and IL-8 via up-regulation of transcription factor NFkappabeta, and activation of inflammasome danger signaling in human macrophages. Not only does activation of local (and systemic) inflammation result in decreased osteoblast function but osteoclast activity increases. Some people are more predisposed to implant debris induced inflammation and metal "allergy" testing services are becoming available. New pathways of implant debris-induced inflammatory reactions continue to be discovered, such as the "danger signaling" inflammasome pathway, which provides new targets for pharmaceutical intervention and improved implant performance.

J Biomed Mater Res A. 2010 Dec 15;95(4):1004-10. doi: 10.1002/jbm.a.32914. Epub 2010 Sep 24.

Biocorrosion and uptake of titanium by human osteoclasts.

Cadosch D, Al-Mushaiqri MS, Gautschi OP, Meagher J, Simmen HP, Filgueira L.

ABSTRACT

All metals in contact with a biological system undergo corrosion through an electrochemical redox reaction. This study investigated whether human osteoclasts (OC) are able to grow on titanium and aluminum, and directly corrode the metals leading to the release of corresponding metal ions, which are believed to cause inflammatory reactions and activate osteoclastic differentiation. Scanning electron microscopy analysis demonstrated long-term viable OC cultures on the surface of titanium and aluminum foils. Atomic emission spectrometry investigations showed significantly increased levels of aluminum in the supernatant of OC cultured on aluminum; however, all measurements in the supernatants of cell cultures on titanium were below detection limits. Despite this, confocal microscopy analysis with Newport Green DCF diacetate ester staining depicted intense fluorescence throughout the cytoplasm and nucleolus of OC cultured on titanium foils. Comparable fluorescence intensities were not observed in monocytes and control cells cultured on glass. The present study demonstrated that human osteoclast precursors are able to grow and differentiate toward mature OC on titanium and aluminum. Furthermore, it established that the mature cells are able to directly corrode the metal surface and take up corresponding metal ions, which subsequently may be released and thereby induce the formation of osteolytic lesions in the periprosthetic bone, contributing to the loosening of the implant.

J Biomed Mater Res A. 2010 Feb;92(2):475-83. doi: 10.1002/jbm.a.32390.

Titanium induced production of chemokines CCL17/TARC and CCL22/MDC in human osteoclasts and osteoblasts.

Cadosch D, Gautschi OP, Chan E, Simmen HP, Filgueira L.

ABSTRACT

There is increasing evidence that titanium (Ti(IV)) ions are released from orthopedic implants and play a role in aseptic loosening. This study aimed to investigate whether titanium induces expression of chemokines and cytokines that are important in osteoclastogenesis in human osteoclasts and osteoblasts. Incubation of those cells with 1 muM Ti(IV) significantly upregulated expression of CCL17/TARC and CCL22/MDC, RANK-L, M-CSF and pro-inflammatory cytokines as determined by quantitative real-time PCR and ELISA assays. Additionally, flow cytometry was used to show Ti(IV) related increased expression of CCR4, the cognate receptor for CCL17 and CCL22 in challenged osteoclast precursors. These results strongly suggest that Ti(IV) ions play a role in the recruitment of osteoclast precursors to the bone-implant interface by increasing CCL17 and CCL22 expression and by upregulating their cognate receptor. Moreover the increased expression of RANK-L and M-CSF by osteoblasts together with increased levels of pro-inflammatory cytokines may enhance osteoclast differentiation and activity, and subsequently contribute to the pathomechanism of aseptic loosening.

J Orthop Res. 2010 Mar;28(3):341-7. doi: 10.1002/jor.21013.

Titanium uptake, induction of RANK-L expression, and enhanced proliferation of human T-lymphocytes.

Cadosch D, Sutanto M, Chan E, Mhawi A, Gautschi OP, von Katterfeld B, Simmen HP, Filgueira L.

ABSTRACT

There is increasing evidence that titanium ions are released from orthopedic implants by biocorrosion. The aim of this study was to investigate titanium uptake by human T-lymphocytes and its effects on phenotype and proliferation. Freshly isolated human nonadherent peripheral blood mononuclear cells (NA-PBMC), were exposed to TiCl4 [Ti(IV)]. Bioavailability and distribution of Ti(IV) in T-lymphocytes was determined by energy-filtered electron microscopy (EFTEM). The effects of Ti(IV) challenge on nonactivated and PHA-activated cells were assessed by flow cytometric analysis of surface markers, RANK-L production, and proliferation assays. EFTEM colocalized Ti(IV) with phosphorus in the nucleus, ribosomes, cytoplasmic membranes, and the surface membrane of T-lymphocytes. Ti(IV) increased significantly the expression of CD69, CCR4, and RANK-L in a concentration-dependent manner. Titanium enters T-lymphocytes through a currently unknown mechanism and binds to phosphorus-rich cell structures. Titanium influences phenotype and function of T-lymphocytes, resulting in activation of a CD69+ and CCR4+ T-lymphocyte population and secretion of RANK-L. These results strongly suggest the involvement of titanium ions challenged T-lymphocytes in the complex pathophysiological mechanisms of aseptic loosening of orthopedic implants.

ZWR 2010; 119(5): 222-232. DOI: 10.1055/s-0030-1261273

Hyperreaktivität von Gewebemakrophagen nach Kontakt mit Titanoxidpartikeln als Ursache einer verstärkten lokalen Entzündungsreaktion bei Patienten mit Periimplantitis

Hyperactivity of Tissue-macrophages after Contact with Particles of Oxidated Titan as the Cause of an Enhanced Local Inflammatory Reaction in Patients with Periimplantitis.

Schütt S, Von Baehr V.

ABSTRACT

One of the main reasons for the high immunological tolerance of Titan in comparence to other metals is its excellent corrosive behaviour. On the other side it is well known by orthopedists and dentists that in some patients titanium implants induce inflammatory reactions that not seldom cause the integration of the implant to fail.

Until today the responsible mechanisms of this „titanium sensibilisation“ are only partially known. Contrary to allergies towards other metals, real cellular induced allergies for titan are very seldom. Due to their high affinity to oxygen, titan-ions directly after their release form oxides. Other than free ions, oxides can not bind to proteins en therefore can not act as a hapten.

A common cause of this „titanium sensibilisation“ is the exaggerated pro-inflammatory reactivity of tissue-macrophages after contact with titan(oxid)particles. This reaction is as well in vivo as in vitro measurable by the pro-inflammatory key-cytokines interleucine-1 and TNF-α. The cytokine response is not caused by the presence of specific lymphocytes but is based upon an enhanced inflammatory readiness of unspecific inflammatory cells after contact with debris (titan-particle-abrasion). The intensity of the inflammatory reaction of tissue-macrophages towards titan-particle-abrasion is mainly dependant upon genetical factors.

J Oral Pathol Med. 2011 May;40(5):412-20. doi: 10.1111/j.1600-0714.2010.00958.x. Epub 2010 Oct 24.

Mapping of titanium particles in peri-implant oral mucosa by laser ablation inductively coupled plasma mass spectrometry and high-resolution optical darkfield microscopy.

Flatebø RS, Høl PJ, Leknes KN, Kosler J, Lie SA, Gjerdet NR.

ABSTRACT

The present study examines the quantity, size, element signatures and distribution of titanium particles in normal oral mucosal tissue and in oral mucosa exposed to a titanium implant. Tissue samples from six healthy patients were obtained by a full thickness biopsy taken from the edge of the oral mucosa when inserting a titanium dental implant. At the abutment insertion 6 months later, a punch test biopsy of oral mucosa was taken over the implant site. Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) is a sensitive and specific multi-element microanalytical technique that demonstrated the presence of Ti particles in the tissue adjacent to implant cover-screws. The epithelial part of the control samples revealed more particles than the corresponding area of the test samples, consisting partly of newly formed scar tissue. High-Resolution Optical Darkfield Microscope (HR-ODM) confirmed the presence of particles in both the control and the test samples. The combination of LA-ICP-MS and HR-ODM appears to be a powerful combination for detection of particles in oral tissues; optical microscopy provides an overview with histological references, whereas LA-ICP-MS identifies the chemical composition.

J Biomed Mater Res A. 2011 Dec 15;99(4):630-7. doi: 10.1002/jbm.a.33222. Epub 2011 Sep 27.

Macrophage response to high number of titanium particles is cytotoxic and COX-2 mediated and it is not affected by the particle's endotoxin content or the cleaning treatment.

Schwab LP, Marlar J, Hasty KA, Smith RA.

ABSTRACT

Periprosthetic osteolysis is a progressive deterioration of bone around prostheses resulting primarily from the presence of wear debris. Particulate material, number, and their interactions with environmental factors play important roles in macrophage activation around implants. We have previously shown that macrophages cultured in the presence of high numbers of cleaned titanium (Ti) particles released significant amounts of PGE_2 that is potentially detrimental for bone. Cleaning of particles has become routine in most studies of macrophage/particle interactions as contaminating endotoxin elicits a macrophage cytokine response and since numerous studies have suggested that endotoxins may be present on implant materials. However, the strenuous cleaning procedure itself represents a possible source of other contaminants (such as material by-products) that may be relevant to the prostanoid response of macrophages. To analyze this hypothesis, the macrophage response to high numbers of cleaned Ti particles was compared to that of unclean particles and to particles that were subjected to a short version of the cleaning procedure. It was found that neither the high amount of endotoxin on the unclean particles nor the duration of the cleaning procedure had an effect on the release of PGE_2 and the decrease in cell viability in response to high number of Ti particles. Evidence of a possible relationship between these two variables is presented.

J R Soc Interface. 2012 Nov 7;9(76):3161-4. Epub 2012 Jul 25.

Do 'passive' medical titanium surfaces deteriorate in service in the absence of wear?

Addison O, Davenport AJ, Newport RJ, Kalra S, Monir M, Mosselmans JF, Proops D, Martin RA.

ABSTRACT

Globally, more than 1000 tonnes of titanium (Ti) is implanted into patients in the form of biomedical devices on an annual basis. Ti is perceived to be 'biocompatible' owing to the presence of a robust passive oxide film (approx. 4 nm thick) at the metal surface. However, surface deterioration can lead to the release of Ti ions, and particles can arise as the result of wear and/or corrosion processes. This surface deterioration can result in peri-implant inflammation, leading to the premature loss of the implanted device or the requirement for surgical revision. Soft tissues surrounding commercially pure cranial anchorage devices (bone-anchored hearing aid) were investigated using synchrotron X-ray micro-fluorescence spectroscopy and X-ray absorption near edge structure. Here, we present the first experimental evidence that minimal load-bearing Ti implants, which are not subjected to macroscopic wear processes, can release Ti debris into the surrounding soft tissue. As such debris has been shown to be pro-inflammatory, we propose that such distributions of Ti are likely to effect to the service life of the device.

J Periodontol. 2012 Aug;83(8):973-80. doi: 10.1902/jop.2011.110392. Epub 2011 Dec 5.

Oral mucosa tissue response to titanium cover screws.

Olmedo DG, Paparella ML, Spielberg M, Brandizzi D, Guglielmotti MB, Cabrini RL.

ABSTRACT

BACKGROUND:

Titanium is the most widely used metal in dental implantology. The release of particles from metal structures into the biologic milieu may be the result of electrochemical processes (corrosion) and/or mechanical disruption during insertion, abutment connection, or removal of failing implants. The aim of the present study is to evaluate tissue response of human oral mucosa adjacent to titanium cover screws.

METHODS:

One hundred fifty-three biopsies of the supra-implant oral mucosa adjacent to the cover screw of submerged dental implants were analyzed. Histologic studies were performed to analyze epithelial and connective tissue as well as the presence of metal particles, which were identified using microchemical analysis. Langerhans cells, macrophages, and T lymphocytes were studied using immunohistochemical techniques. The surface of the cover screws was evaluated by scanning electron microscopy (SEM).

RESULTS:

Forty-one percent of mucosa biopsies exhibited metal particles in different layers of the section thickness. Particle number and size varied greatly among specimens. Immunohistochemical study confirmed the presence of macrophages and T lymphocytes associated with the metal particles. Microchemical analysis revealed the presence of titanium in the particles. On SEM analysis, the surface of the screws exhibited depressions and irregularities.

CONCLUSIONS:

The biologic effects seen in the mucosa in contact with the cover screws might be associated with the presence of titanium or other elements, such as aluminum or vanadium. The potential long-term biologic effects of particles on soft tissues adjacent to metallic devices should be further investigated because these effects might affect the clinical outcome of the implant.

J Periodontol. 2013 Jan;84(1):78-83. doi: 10.1902/jop.2012.110757. Epub 2012 Mar 13.

Exfoliative cytology and titanium dental implants: a pilot study.

Olmedo DG, Nalli G, Verdú S, Paparella ML, Cabrini RL.

ABSTRACT

BACKGROUND:

Oral exfoliative cytology is a diagnostic method that involves the study of cells exfoliated from the oral mucosa. Ions/particles released from metallic implants can remain in the peri-implant milieu. The aim of the present study is to assess the presence of metal particles in cells exfoliated from peri-implant oral mucosa around titanium dental implants.

METHODS:

The study comprised 30 patients carrying titanium dental implants, who had neither a metallic prosthesis nor metal restorations in neighboring teeth. Individuals undergoing orthodontic therapy and those who had oral piercing were also excluded from the study. The study sample included patients with and without peri-implantitis. Cytologic samples of the peri-implant area were collected. Samples of the marginal gingiva on the contralateral side of the implant were taken from the same individuals to serve as control. Cytologic analysis was performed using light microscopy. Titanium concentration was determined using inductively coupled plasma-mass spectrophotometry.

RESULTS:

Metal-like particles were observed inside and outside epithelial cells and macrophages in cytologic smears of peri-implant mucosa of both patients with and without peri-implantitis. No particles were found in the control cytologic samples. The concentration of titanium was higher in the peri-implantitis group compared with the group without peri-implantitis; no traces of titanium were observed in controls.

CONCLUSIONS:

Regardless of an inflammatory response, ions/particles are released from the surface of the implant into the biologic milieu. Exfoliative cytology is a simple technique that may be used to detect metal particles in cells exfoliated from the peri-implant mucosa.

Biomed Res Int. 2013; 2013:539834. doi: 10.1155/2013/539834. Epub 2013 Sep 11.

Allergy or tolerance: reduced inflammatory cytokine response and concomitant IL-10 production of lymphocytes and monocytes in symptom-free titanium dental implant patients.

Thomas P, Iglhaut G, Wollenberg A, Cadosch D, Summer B.

ABSTRACT

Hypersensitivity reactions to titanium (Ti) are very rare. Thus, we assessed the proinflammatory response and also potential tolerance favoring in vitro reactivity of human blood lymphocytes and monocytes (PBMC) to Ti in healthy individuals (14 without, 6 with complication-free dental Ti implants). The proliferation index (SI) in lymphocyte transformation test (LTT) and production of cytokines linked to innate immune response (IL-1 β , IL-6, and TNF α) or immune regulation (IL-10) were assessed in response to TiO2 particles or Ti discs. In both groups, the Ti-LTT reactivity was not enhanced (e.g., SI < 3). The control antigen tetanus toxoid (TT) gave adequate reactivity (median SI individuals without/with implant: 20.6 ± 5.97/19.58 ± 2.99). Individuals without implant showed higher cytokine response to Ti materials than individuals with symptom-free implants; for example, TiO2 rutile particle induced increase of IL-1 β 70.27-fold/8.49-fold versus control medium culture. PBMC of 5 of the 6 individuals with complication-free Ti implants showed an ex vivo ongoing production of IL-10 (mean 4.18 ± 2.98 pg/mL)-but none of the 14 controls showed such IL-10 production. Thus in vitro IL-1 β -, IL-6-, and TNF-α production reflects "normal" unspecific immune response to Ti. This might be reduced by production of tolerogenic IL-10 in individuals with symptom-free Ti dental implants.

J Periodontol. 2014 Sep;85(9):1275-82. doi: 10.1902/jop.2014.130595. Epub 2014 Jan 20.

Attachment of Porphyromonas gingivalis to corroded commercially pure titanium and titanium-aluminum-vanadium alloy.

Barão VA, Yoon CJ, Mathew MT, Yuan JC, Wu CD, Sukotjo C.

ABSTRACT

BACKGROUND:

Titanium dental material can become corroded because of electrochemical interaction in the oral environment. The corrosion process may result in surface modification. It was hypothesized that a titanium surface modified by corrosion may enhance the attachment of periodontal pathogens. This study evaluates the effects of corroded titanium surfaces on the attachment of Porphyromonas gingivalis.

METHODS:

Commercially pure titanium (cp-Ti) and titanium-aluminum-vanadium alloy (Ti-6Al-4V) disks were used. Disks were anodically polarized in a standard three-electrode setting in a simulated oral environment with artificial saliva at pH levels of 3.0, 6.5, or 9.0. Non-corroded disks were used as controls. Surface roughness was measured before and after corrosion. Disks were inoculated with P. gingivalis and incubated anaerobically at 37°C. After 6 hours, the disks with attached P. gingivalis were stained with crystal violet, and attachment was expressed based on dye absorption at optical density of 550 nm. All assays were performed independently three times in triplicate. Data were analyzed by two-way analysis of variance, the Tukey honestly significant difference test, t test, and Pearson's correlation test ($\alpha = 0.05$).

RESULTS:

Both cp-Ti and Ti-6Al-4V alloy-corroded disks promoted significantly more bacterial attachment (11.02% and 41.78%, respectively; $P < 0.0001$) than did the non-corroded controls. Significantly more (11.8%) P. gingivalis attached to the cp-Ti disks than to the Ti-6Al-4V alloy disks ($P < 0.05$). No significant difference in P. gingivalis attachment was noted among the corroded groups for both cp-Ti and Ti-6Al-4V alloy ($P > 0.05$). There was no significant correlation between surface roughness and P. gingivalis attachment.

CONCLUSION:

A higher degree of corrosion on the titanium surface may promote increased bacterial attachment by oral pathogens.

J Biomed Mater Res A. 2014 May;102(5):1439-48. doi: 10.1002/jbm.a.34822. Epub 2013 Jun 21.

Impact through time of different sized titanium dioxide particles on biochemical and histopathological parameters.

Bruno ME, Tasat DR, Ramos E, Paparella ML, Evelson P, Rebagliati RJ, Cabrini RL, Guglielmotti MB, Olmedo DG.

ABSTRACT

Due to corrosion, a titanium implant surface can be a potential source for the release of micro (MPs) and nano-sized particles (NPs) into the biological environment. This work sought to evaluate the biokinetics of different sized titanium dioxide particles (TiO_2) and their potential to cause cell damage. Wistar rats were intraperitoneally injected with 150 nm, 10 nm, or 5nm TiO_2 particles. The presence of TiO_2 particles was evaluated in histologic sections of the liver, lung, and kidney and in blood cells at 3 and 12 months. Ultrastructural analysis of liver and lung tissue was performed by TEM, deposit concentration in tissues was determined spectroscopically, and oxidative metabolism was assessed by determining oxidative membrane damage, generation of superoxide anion ($O_2^{(-)}$), and enzymatic and non-enzymatic antioxidants. TiO_2 particles were observed inside mononuclear blood cells and in organ parenchyma at 3 and 12 months. TiO_2 deposits were consistently larger in liver than in lung tissue. Alveolar macrophage $O_2^{(-)}$ generation and average particle size correlated negatively ($p < 0.05$). NPs were more reactive and biopersistent in lung tissue than MPs. Antioxidant activity, particularly in the case of 5 nm particles, failed to compensate for membrane damage in liver cells; the damage was consistent with histological evidence of necrosis.

Toxicol Rep. 2015 Feb 19;2:765-774. doi: 10.1016/j.toxrep.2015.02.004. eCollection 2015.

Comparative study of the cytotoxic and genotoxic potentials of zinc oxide and titanium dioxide nanoparticles.

Khan M, Naqvi AH, Ahmad M.

ABSTRACT

Nanoparticles (NPs) of zinc oxide (ZnO) and titanium dioxide (TiO2) are receiving increasing attention due to their widespread applications. The aim of this study was to evaluate the toxic effect of ZnO and TiO2 NPs at different concentrations (50, 100, 250 and 500 ppm) and compare them with their respective salts using a battery of cytotoxicity, and genotoxicity parameters. To evaluate cytotoxicity, we have used human erythrocytes and for genotoxic studies human lymphocytes have been used as in vitro model species. Concentration dependent hemolytic activity to RBC's was obtained for both NPs. ZnO and TiO2 NPs resulted in 65.2% and 52.5% hemolysis at 250 ppm respectively indicating that both are cytotoxic to human RBCs. Antioxidant enzymes assays were also carried out in their respective hemolysates. Both nanoparticles were found to generate reactive oxygen species (ROS) concomitant with depletion of glutathione and GST levels and increased SOD, CAT and lipid peroxidation in dose dependent manner. ZnO and TiO2 NPs exerted roughly equal oxidative stress in terms of aforementioned stress markers. Genotoxic potential of both the NPs was investigated by in vitro alkaline comet assay. DNA damage induced by the NPs was concentration dependent and was significantly greater than their ionic forms at 250 and 500 ppm concentrations. Moreover, the nanoparticles of ZnO were significantly more genotoxic than those of TiO2 at higher concentrations. The toxicity of these NPs is due to the generation of ROS thereby causing oxidative stress.

Clin Implant Dent Relat Res. 2015 Aug;17(4):681-92. doi: 10.1111/cid.12167. Epub 2013 Nov 28.

Surface Damage on Dental Implants with Release of Loose Particles after Insertion into Bone.

Senna P, Antoninha Del Bel Cury A, Kates S, Meirelles L.

ABSTRACT

BACKGROUND:

Modern dental implants present surface features of distinct dimensions that can be damaged during the insertion procedure into bone.

PURPOSE:

The aims of this study were (1) to quantify by means of roughness parameters the surface damage caused by the insertion procedure of dental implants and (2) to investigate the presence of loose particles at the interface.

MATERIALS AND METHODS:

Three groups of dental implants representing different surface topographies were inserted in fresh cow rib bone blocks. The surface roughness was characterized by interferometry on the same area before and after the insertion. Scanning electron microscopy (SEM)-back-scattered electron detector (BSD) analysis was used to identify loose particles at the interface.

RESULTS:

The amplitude and hybrid roughness parameters of all three groups were lower after insertion. The surface presenting predominance of peaks (Ssk [skewness] > 0) associated to higher structures (height parameters) presented higher damage associated to more pronounced reduction of material volume. SEM-BSD images revealed loose titanium and aluminum particles at the interface mainly at the crestal cortical bone level.

CONCLUSIONS:

Shearing forces during the insertion procedure alters the surface of dental implants. Loose metal particles can be generated at bone-implant interface especially around surfaces composed mainly by peaks and with increased height parameters.

J Med Microbiol. 2016 Jul;65(7):596-604. doi: 10.1099/jmm.0.000267. Epub 2016 Apr 19.

Bacterial adhesion and biofilm formation on yttria-stabilized, tetragonal zirconia and titanium oral implant materials with low surface roughness - an in situ study.

Al-Ahmad A, Karygianni L, Schulze Wartenhorst M, Bächle M, Hellwig E, Follo M, Vach K, Han JS.

ABSTRACT

Bacterially-driven mucosal inflammation and the development of periimplantitis can lead to oral implant failure. In this study, initial bacterial adhesion after 2 h, and biofilm formation after 1 day and 3 days, were analysed in situ on novel 3 mol% yttria-stabilized tetragonal zirconia polycrystal samples, as well as on alumina and niobium co-doped yttria-stabilized tetragonal zirconia samples. Pure titanium implant material and bovine enamel slabs served as controls. The initially adherent oral bacteria were determined by 4′,6-diamidino-2-phenylindole-staining. Biofilm thickness, surface covering grade and content of oral streptococci within the biofilm were measured by fluorescence in situ hybridization. No significant differences between the ceramic and titanium surfaces were detectable for either initial bacterial adhesion or the oral streptococci content of the in situ biofilm. The oral biofilm thickness on the implant surfaces were almost doubled after three days compared to the first day of oral exposure. Nevertheless, the biofilm thickness values among the different implant surfaces and controls did not differ significantly for any time point of measurement after 1 day or 3 days of biofilm formation. Significant differences in the covering grade were only detected between day 1 and day 3 for each tested implant material group. The content of oral streptococci increased significantly in parallel with the increase in biofilm age from day 1 to day 3. In conclusion, oral implant zirconia surfaces with low surface roughness are comparable to titanium surfaces with respect to initial bacterial adhesion and biofilm formation.

Int J Mol Sci. 2018 Apr 6;19(4). pii: E1101. doi: 10.3390/ijms19041101.

Novel Nanoparticulate and Ionic Titanium Antigens for Hypersensitivity Testing.

Høl PJ, Kristoffersen EK, Gjerdet NR, Pellowe AS.

ABSTRACT

Titanium is used in a wide variety of materials ranging from medical devices to materials used in everyday life. Adverse biological reactions that could occur in patients, consumers, and workers should be monitored and prevented. There is a lack of available agents to test and predict titanium-related hypersensitivity. The aim of this study was to develop two bioavailable titanium substances in ionic and nanoparticulate form to serve as antigens for hypersensitivity testing in vitro. Peripheral blood mononuclear cells from 20 test subjects were stimulated with the antigens and secretion of monocytic and lymphatic cytokines and chemokines were measured by a multiplex bead assay. Lymphocyte stimulation indices were also determined in a subset of test subjects by measuring CD69 and HLA-DR expression by flow cytometry. Cytokine profiling revealed that both antigens increased production of typical monocyte and macrophage secreted cytokines after 24 h, with significant increases in IL-1β IL-7, IL-10, IL-12, IL-2R, IL-6, GM-CSF, TNF-α, IL-1RA, MIP-1α, MIP-1β, IFN-α, and IL-15. Lymphatic cytokines and chemokines were not significantly induced by activation. After seven days of stimulation, ionic-Ti (2.5 μg/mL) caused proliferation (stimulation index > 2) of CD4+ cells and CD8+ cells in all persons tested (N = 6), while titanium dioxide nanoparticles (50 μg/mL) only caused significant proliferation of CD4+ cells. Our preliminary results show that the experimental titanium antigens, especially the ionic form, induce a general inflammatory response in vitro. A relevant cohort of test subjects is required to further elucidate their potential for predictive hypersensitivity testing.

2.2 Clinically relevant Studies and Papers

J Bone Joint Surg Am. 2000 Apr;82(4):457-76.

Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement.

Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M.

ABSTRACT

BACKGROUND:

The importance of particles generated by wear and corrosion of joint replacement prostheses has been understood primarily in the context of the local effects of particle-induced periprosthetic osteolysis and aseptic loosening. We studied dissemination of wear particles in patients with total hip and knee replacement to determine the prevalence of and the histopathological response to prosthetic wear debris in the liver, spleen, and abdominal para-aortic lymph nodes.

METHODS:

Postmortem specimens from twenty-nine patients and biopsy specimens from two living patients with a failed replacement were analyzed. Specimens of tissue obtained from the cadavera of fifteen patients who had not had a joint replacement served as controls. The concentration of particles and the associated tissue response were characterized with the use of light microscopy of stained histological sections. Metallic particles were identified by electron microprobe analysis. Polyethylene particles were studied with the use of oil-red-O stain and polarized light microscopy. The composition of polyethylene particles was confirmed in selected cases by Fourier transform infrared spectroscopy and hot-stage thermal analysis. Twenty-one of the patients studied post mortem had had a primary total joint replacement. Eleven of them had had a hip prosthesis for a mean of sixty-nine months (range, forty-three to 171 months), and ten had had a knee replacement for a mean of eighty-four months (range, thirty-one to 179 months). The other eight patients studied post mortem had had a hip replacement in which one or more components had loosened and had been revised. The mean time between the initial arthroplasty and the time of death was 174 months (range, forty-seven to 292 months), and the mean time between the last revision procedure and the time of death was seventy-one months (range, one to 130 months).

RESULTS:

Metallic wear particles in the liver or spleen were more prevalent in patients who had had a failed hip arthroplasty (seven of eight) than in patients who had had a primary hip (two of eleven) or knee replacement (two of ten). The principal source of wear particles in the majority of these patients involved secondary nonbearing surfaces rather than wear between the two primary bearing surfaces as intended. In one living patient, dissemination of titanium alloy particles from a hip prosthesis with mechanical failure was associated with a visceral granulomatous reaction and hepatosplenomegaly, which required operative and medical treatment. Metallic wear particles were detected in the paraaortic lymph nodes in 68 percent (nineteen) of the twenty-eight patients with an implant from whom lymph nodes were available for study. In 38 percent (eleven) of all twenty-nine patients with an implant who were studied post mortem, metallic particles had been further disseminated to the liver or spleen, where they were usually found within small aggregates of macrophages occurring as infiltrates without apparent pathological importance. Polyethylene particles elicited a similar response. They were identified in the paraaortic lymph nodes of 68 percent (nineteen) of the twenty-eight patients and the liver or spleen of 14 percent (four) of the twenty-nine patients. The majority of the disseminated wear particles were less than one micrometer in size. Currently available methods lack the sensitivity and specificity necessary to detect very low concentrations of submicrometer polyethylene particles and probably underestimated the prevalence of polyethylene wear debris in the liver and spleen.

CONCLUSIONS:

In this study, systemic distribution of metallic and polyethylene wear particles was a common finding, both in patients with a previously failed implant and in those with a primary total joint prosthesis. The prevalence of particles in the liver or spleen was greater after reconstructions with mechanical failure. (ABSTRACT TRUNCATED)

Clin Implant Dent Relat Res. 2007 Jun;9(2):112-5.

Breast metastasis around dental implants: a case report.

Dib LL, Soares AL, Sandoval RL, Nannmark U.

ABSTRACT

BACKGROUND:
Metastases to the oral cavity and to the jaws are rare; hence, the clinical manifestations of the oral metastasis lesion could frequently be simulating general pathologic entities, making the diagnosis a challenging process to the dental team. Local factors, such as trauma, have been observed to facilitate the growth of blood-borne tumors. To this end, surgical procedures such as fixture placement might cause cancer cells to spread.

PURPOSE:
Careful clinical examination is a valuable help in diagnosing oral lesions, which can improve the quality of life of patients and reduce the risks of oral complications.

MATERIALS AND METHODS:
A female patient was referred to the clinic with symptoms of irritation, swelling, and pain associated with implants in the mandible and the maxilla.

RESULTS:
Clinical examination, x-ray, and histopathology revealed that the patients suffered from a metastatic lesion, primary tumor being an adenocarcinoma of the breast diagnosed at the same time.

CONCLUSION:
Optimal clinical examination in conjunction with radiography and histopathology is a necessity in order to discover malignant lesions in time. Routine dental check-ups must comprise more thorough soft-tissue examination.

Clin Oral Implants Res. 2007 Aug;18(4):540-3. Epub 2007 Apr 30.

Plasmacytoma of the mandible associated with a dental implant failure: a clinical report.

Poggio CE.

ABSTRACT

The case report of a patient is presented who had been suffering from a plasmacytoma of the spine several years back, and who had developed a new plasmacytoma of the mandible, 3 years subsequent to the insertion of a dental implant. This second solitary lesion occurred 15 years after the first one, and without signs of conversion to multiple myeloma. Research in animal models has shown multinucleated giant cells, belonging to the monocyte-macrophage lineage, persisting between the titanium surface and the lymphohemopoietic compartment, at least 1.5 years after implant insertion. Factors that increase the proliferative activity of precursor B cells, for example a protracted macrophage activation, are likely to increase the risk of B cell oncogenesis. A possible role of the titanium surface in an increase of precursor B cell proliferative activity, thus facilitating a new localization, was evaluated.

Int J Prosthodont. 2007 Jan-Feb;20(1):51-4.

An unusual case of implant failure.

Verhoeven JW, Cune MS, van Es RJ.

ABSTRACT

A 67-year-old woman was referred with a rapidly progressing swelling in the left canine region of the edentulous mandible. Nine months earlier, 2 permucosal implants had been placed in her atrophic anterior mandible. A few weeks after implant placement, an inoperable carcinoma of the lung had been diagnosed. This tumor was treated with a combination of chemotherapy and radiotherapy. After 3 months, the implants were provided with a Dolder bar supporting an overdenture. Subsequently, progressive inflammation developed around the left implant and removal of the implant was necessary. When progressive swelling of the mucosa developed at the previous implant site, the patient was referred to an oral and maxillofacial surgeon. The swelling measured 35 mm in diameter and was biopsied. It was diagnosed as a metastasis of the lung carcinoma to the mandible. The tumor of the jaw was treated with local radiotherapy.

J Am Dent Assoc. 2008 Aug;139(8):1061-5.

Oral squamous cell carcinoma associated with symphyseal dental implants: an unusual case report.

Gallego L, Junquera L, Baladrón J, Villarreal P.

ABSTRACT

BACKGROUND:

The development of squamous cell carcinoma (SCCa) around dental implants is an uncommon pathological manifestation. This case report describes a patient with history of oral lichen planus (OLP) and previous SCCa of the gingiva who developed SCCa adjacent to symphyseal implants.

CASE DESCRIPTION:

An 81-year-old edentulous woman with history of OLP developed an in situ SCCa on the left mandibular edentulous ridge. One of the authors, an oral and maxillofacial surgeon, performed a marginal mandibular resection of the lesion. Functional oral rehabilitation was achieved by means of two endosseous symphyseal implants. Three years after the patient underwent implant-supported reconstruction, the oral and maxillofacial surgeon detected an exophytic mass adjacent to the right implant and diagnosed it as recurrent SCCa. Two of the authors performed a marginal mandibular resection. One year later, the patient developed a recurrence over the resected area, requiring segmental mandibulectomy.

CLINICAL IMPLICATIONS:

This case report demonstrates that recurrent primary malignancy can masquerade as benign peri-implant complications. A high degree of vigilance is required in the follow-up of patients with previous cancer or premalignant lesions.

J Am Dent Assoc. 2008 Aug;139(8):1052-9.

Maxillary osteosarcoma associated with a dental implant: report of a case and review of the literature regarding implant-related sarcomas.

McGuff HS, Heim-Hall J, Holsinger FC, Jones AA, O'Dell DS, Hafemeister AC.

ABSTRACT

BACKGROUND:

The development of malignant neoplasms has been reported as a rare complication of the use of implanted biomaterials. The majority of these cases have been sarcomas related to orthopedic hardware. The authors present the first reported case of a sarcoma arising in association with a dental implant.

CASE DESCRIPTION:

A 38-year-old woman developed a low-grade chondroblastic osteosarcoma of the right maxilla 11 months after receiving a titanium dental implant. She was treated with systemic chemotherapy and then a maxillary resection. As of this publication, 47 months later, she is alive and disease-free.

CLINICAL IMPLICATIONS:

The use of endosseous implants has been associated with a low risk for the development of cancer. As the use of dental implants continues to expand, dentists need to be aware of this rare but devastating complication.

Clin Oral Implants Res. 2008 Aug;19(8):823-35. doi: 10.1111/j.1600-0501.2008.01544.x.

Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients.

Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, Maestro A.

ABSTRACT

BACKGROUND:

In dentistry, allergic reactions to Ti implants have not been studied, nor considered by professionals. Placing permanent metal dental implants in allergic patients can provoke type IV or I reactions. Several symptoms have been described, from skin rashes and implant failure, to non-specific immune suppression.

OBJECTIVE:

Our objective was to evaluate the presence of titanium allergy by the anamnesis and examination of patients, together with the selective use of cutaneous and epicutaneous testing, in patients treated with or intending to receive dental implants of such material.

MATERIAL AND METHODS:

Thirty-five subjects out of 1500 implant patients treated and/or examined (2002-2004) were selected for Ti allergy analysis. Sixteen presented allergic symptoms after implant placement or unexplained implant failures [allergy compatible response group (ACRG)], while 19 had a history of other allergies, or were heavily Ti exposed during implant surgeries or had explained implant failures [predisposing factors group (PFG)]. Thirty-five controls were randomly selected (CG) in the Allergy Centre. Cutaneous and epicutaneous tests were carried out.

RESULTS:

Nine out of the 1500 patients displayed positive (+) reactions to Ti allergy tests (0.6%): eight in the ACRG (50%), one in the PFG (5.3%)(P=0.009) and zero in the control group. Five positives were unexplained implant failures (five out of eight).

CONCLUSIONS:

Ti allergy can be detected in dental implant patients, even though its estimated prevalence is low (0.6%). A significantly higher risk of positive allergic reaction was found in patients showing post-op allergy compatible response (ACRG), in which cases allergy tests could be recommended.

Int J Oral Maxillofac Surg. 2010 May;39(5):503-7. doi: 10.1016/j.ijom.2009.11.007. Epub 2009 Dec 11.

Reactive lesions of peri-implant mucosa associated with titanium dental implants: a report of 2 cases.

Olmedo DG, Paparella ML, Brandizzi D, Cabrini RL.

ABSTRACT

The aim of this study was to report 2 novel clinical cases of reactive lesions of the peri-implant mucosa associated with titanium dental implants where metal-like particles were observed histologically. In both cases, the lesions were diagnosed as epulis, based on clinical evidence. Extirpation biopsies were carried out. Case 1 was diagnosed as pyogenic granuloma and case 2 as peripheral giant cell granuloma. The presence of metal-like particles in the tissues suggests that the etiology of the lesions might be related to the corrosion process of the metal structure. This is the first case of pyogenic granuloma to be reported in association with dental implants. All clinical cases of soft tissue lesions associated with implants should be reported to contribute to the understanding of the etiology and pathogeny of these lesions.

Clin Cosmet Investig Dent. 2013; 5: 57–61. Published online 2013 Aug 19. doi: 10.2147/CCIDE.S35170.

Allergy related to dental implant and its clinical significance.

Chaturvedi TP.

ABSTRACT

The oral cavity provides an ideal and unique environment for study of biological processes involving metallic dental aids. Dental materials within the mouth interact continually with physiological fluids. Oral tissues are exposed to a veritable bombardment of both chemical and physical stimuli as well as the metabolism of many species of bacteria; yet, for the most part, oral tissues remain healthy. The pH of saliva varies from 5.2 to 7.8. Teeth, restorations, or any prosthesis including dental implants in the oral cavity have to function in one of the most inhospitable environments in the human body. They are subject to larger temperature and pH variations than most other parts of the body. Corrosion, the graded degradation of materials by electrochemical attack, is of concern particularly when dental implants are placed in the hostile electrolytic environment provided by the human mouth. Allergic reactions may occur from the presence of ions produced from the corrosion of implants. The present article describes various manifestations of allergic reactions due to implant material in the oral cavity.

Biomed Res Int. 2015; 2015:137287. doi: 10.1155/2015/137287. Epub 2015 Mar 25.

Biomaterial hypersensitivity: is it real? Supportive evidence and approach considerations for metal allergic patients following total knee arthroplasty.

Mitchelson AJ, Wilson CJ, Mihalko WM, Grupp TM, Manning BT, Dennis DA, Goodman SB, Tzeng TH, Vasdev S, Saleh KJ.

ABSTRACT

The prospect of biomaterial hypersensitivity developing in response to joint implant materials was first presented more than 30 years ago. Many studies have established probable causation between first-generation metal-on-metal hip implants and hypersensitivity reactions. In a limited patient population, implant failure may ultimately be related to metal hypersensitivity. The examination of hypersensitivity reactions in current-generation metal-on-metal knee implants is comparatively limited. The purpose of this study is to summarize all available literature regarding biomaterial hypersensitivity after total knee arthroplasty, elucidate overall trends about this topic in the current literature, and provide a foundation for clinical approach considerations when biomaterial hypersensitivity is suspected.

Hautarzt. 2016 May;67(5):373-9. doi: 10.1007/s00105-016-3790-6.

Metal implant sensitivity: clinical and histological presentation.

Hartmann D, Letulé V, Schneider JJ, Flaig MJ.

ABSTRACT

Metal implant sensitivity (intolerance) can cause pain, reduced mobility, loosening of the implant and skin rashes. Knowledge of differential diagnoses, histology and appropriate diagnostics are essential for proper diagnosis. To outline typical clinical signs and histology in metal-implant-associated skin lesions we present three exemplary patients from our implant allergy outpatient department and give an overview of the current literature regarding metal implant sensitivity. In patients with a negative patch test the lymphocyte transformation test may reveal metal sensitization. Even "pure" titanium alloys may contain traces of nickel. The histology of implant-associated skin reactions goes from teleangiectatic postimplantation erythema to eczema and vasculitis. Based on the synopsis of history, clinical picture, allergological testing and histology, metal implant sensitivity can be diagnosed more precisely.

J Prosthodont Res. 2016 Jul;60(3):213-9. doi: 10.1016/j.jpor.2015.12.004. Epub 2016 Jan 8.

Allergic contact dermatitis caused by titanium screws and dental implants.

Hosoki M, Nishigawa K, Miyamoto Y, Ohe G, Matsuka Y.

ABSTRACT

PATIENTS:

Titanium has been considered to be a non-allergenic material. However, several studies have reported cases of metal allergy caused by titanium-containing materials. We describe a 69-year-old male for whom significant pathologic findings around dental implants had never been observed. He exhibited allergic symptoms (eczema) after orthopedic surgery. The titanium screws used in the orthopedic surgery that he underwent were removed 1 year later, but the eczema remained. After removal of dental implants, the eczema disappeared completely.

DISCUSSION:

Titanium is used not only for medical applications such as plastic surgery and/or dental implants, but also for paints, white pigments, photocatalysts, and various types of everyday goods. Most of the usage of titanium is in the form of titanium dioxide. This rapid expansion of titanium-containing products has increased percutaneous and permucosal exposure of titanium to the population.

CONCLUSIONS:

In general, allergic risk of titanium material is smaller than that of other metal materials. However, we suggest that pre-implant patients should be asked about a history of hypersensitivity reactions to metals, and patch testing should be recommended to patients who have experienced such reactions.

Orthopedics. 2016 May;39(3 Suppl):S24-30. doi: 10.3928/01477447-20160509-08.

Influence of Surface Coating on Metal Ion Release: Evaluation in Patients With Metal Allergy.

Thomas P, Weik T, Roider G, Summer B, Thomsen M.

ABSTRACT

Nickel, chromium, and cobalt in stainless steel and Cobalt-chrome-molybdenum (CoCrMo) alloys may induce allergy. The objectives of this study were to evaluate surface coating regarding ion release, patch test reactivity, and arthroplasty performance. Materials and methods included patch test in 31 patients with metal allergy and 30 patients with no allergy to stainless steel and CoCrMo disks that are uncoated or coated by titanium nitride/zirconium nitride (TiN/ZrN). Assessment include atomic absorption spectrometry of released nickel, cobalt, and chromium from the disks after exposure to distilled water, artificial sweat and culture medium. Results showed that both coatings reduced the nickel and chromium release from stainless steel and CoCrMo disks and mostly the cobalt release from the disks (maximally 11.755 μg/cm(2)/5 d to 1.624 by Ti-N and to 0.442 by ZrN). Six of the 31 patients with metal allergy reacted to uncoated disks, but none reacted to the coated disks. The current authors report on exemplary patients with metal allergy who had symptom relief by revision with surface-coated arthroplasty. The authors concluded that the surface coating may prevent cutaneous and peri-implant allergic reactions. [Orthopedics. 2016; 39(3):S24-S30.].

J Indian Soc Periodontol. 2017 May-Jun;21(3):192-194. doi: 10.4103/jisp.jisp_184_16.

Titanium particles in tissues from peri-implant mucositis: An exfoliative cytology-based pilot study.

Penmetsa SLD, Shah R, Thomas R, Kumar ABT, Gayatri PSD, Mehta DS.

ABSTRACT

BACKGROUND:

To evaluate the presence of titanium particles in the peri-implant mucosa of unloaded single implants.

MATERIALS AND METHODS:

Forty participants with single unloaded implants were selected. They were divided equally into two groups: Group 1 with mild and Group 2 with moderate-to-severe peri-implant mucositis. Cytologic smears of peri-implant mucosa were obtained using cytobrush during second-stage surgery.

RESULTS:

Study states that 60% of participants of Group 2 were positive for titanium particles in peri-implant cytology.

CONCLUSION:

This study concludes that the titanium particles might be the initiators of the inflammation around implant.

J Periodontol. 2017 May;88(5):436-442. doi: 10.1902/jop.2016.160524. Epub 2016 Nov 18.

Increased Levels of Dissolved Titanium are Associated With Peri-Implantitis - A Cross-Sectional Study.

Safioti LM, Kotsakis GA, Pozhitkov AE, Chung WO, Daubert DM.

ABSTRACT

BACKGROUND:

Peri-implantitis represents a disruption of the biocompatible interface between the titanium dioxide layer of the implant surface and the peri-implant tissues. Increasing preclinical data suggest that peri-implantitis microbiota not only triggers an inflammatory immune response but also causes electrochemical alterations of the titanium surfaces, i.e., corrosion, that aggravate this inflammatory response. Thus, it was hypothesized that there is an association between dissolution of titanium from dental implants, which suggests corrosion, and peri-implantitis in humans. The objective of this study is to compare levels of dissolved titanium in submucosal plaque collected from healthy implants and implants with peri-implantitis.

METHODS:

Submucosal plaque from 20 implants with peri-implantitis and 20 healthy implants was collected with sterile curets from 30 participants. Levels of titanium were quantified using inductively coupled plasma mass spectrometry and normalized for mass of bacterial DNA per sample to exclude confounding by varying amounts of plaque per site. Statistical analysis was performed using generalized estimated equations to adjust for clustering of implants per participant.

RESULTS:

Implants with peri-implantitis harbored significantly higher mean levels of titanium (0.85 ± 2.47) versus healthy implants (0.07 ± 0.19) after adjusting for amount of plaque collected per site (P = 0.033).

CONCLUSIONS:

Greater levels of dissolved titanium were detected in submucosal plaque around implants with peri-implantitis compared with healthy implants, indicating an association between titanium dissolution and peri-implantitis. Factors triggering titanium dissolution, as well as the role of titanium corrosion in the peri-implant inflammatory process, warrant further investigation.

Clin Implant Dent Relat Res. 2018 Dec;20(6):945-953. doi: 10.1111/cid.12676. Epub 2018 Sep 25.

Titanium as a modifier of the peri-implant microbiome structure.

Daubert D, Pozhitkov A, McLean J, Kotsakis G.

ABSTRACT

BACKGROUND:
Recent data support the implication of accelerated titanium dissolution products in peri-implantitis. It is unknown whether these dissolution products have an effect on the peri-implant microbiome, the target of existing peri-implantitis therapies.

PURPOSE:
This study assessed the relationship between the peri-implant microbiome, dissolved titanium levels, and peri-implantitis.

MATERIALS AND METHODS:
Clinical, microbiome, and titanium data were collected from a periodontal population having implants in function for 10 years. Clinical examinations were performed, and submucosal plaque samples were collected from the deepest site per implant. An aliquot of the sample was used for 16S rRNA gene sequencing, with the remainder analyzed for titanium quantity using mass spectrometry. Sequences were clustered into taxonomic units at 97% minimum sequence similarity using the QIIME pipeline approach.

RESULTS:
Fifteen implants were assessed. According to established case definitions, six had a diagnosis of peri-implantitis; nine were healthy. The genera Streptococcus, Prevotella and Haemophilus characterized peri-implant health. Peri-implantitis was associated with a marked increase in Veillonella. Quantities of dissolved titanium were identified in 40% of sites. Titanium presence was associated with peri-implant disease status (P = .02) and correlated to the first principal component of the microbiome (rho = 0.552) and its alpha-diversity (rho = -0.496). Canonical correlation analyses found that titanium levels, but not health or disease status of the implant, were significantly associated with the microbiota composition (P = .045).

CONCLUSIONS:
These findings suggest an association between titanium dissolution products and peri-implantitis and support a role for these products in modifying the peri-implant microbiome structure and diversity.

J Prosthodont Res. 2018 Oct;62(4):426-431. doi: 10.1016/j.jpor.2018.03.003. Epub 2018 Apr 16.

Cross-sectional observational study exploring clinical risk of titanium allergy caused by dental implants.

Hosoki M, Nishigawa K, Tajima T, Ueda M, Matsuka Y.

ABSTRACT

PURPOSE:
Studies have reported cases of metal allergy caused by titanium-containing materials. We wished to clarify the relationship between titanium allergy and dental implants by describing patients who suffered allergic symptoms after they had received such implants.

METHODS:
A total of 270 patients who visited a Dental Metal Allergy Clinic at Tokushima University Hospital from April 2010 to March 2014 were the study cohort. Patch testing with 28 types of metal allergens (including four titanium allergens) was undertaken for patients.

RESULTS:
A total of 217 patients (80.4 %) exhibited allergy-positive reactions to at least one type of metal allergen. Mercury, palladium, chromium and nickel exhibited a higher prevalence of allergy-positive reactions than other metals. Sixteen patients visited our clinic suffering allergic symptoms after receiving dental implants. Eleven of those patients exhibited allergy-positive reactions for any of the metal allergens, and 4 of these patients had allergy-positive reactions against titanium allergens. The total number of allergy-positive reactions for titanium allergens among all 270 patients was 17 (6.3 %). No patient exhibited a positive reaction only for the titanium allergen.

CONCLUSIONS:
The prevalence of allergy-positive reactions for titanium allergens was lower than for other metal allergens. We suggest examination of pre-implant patients who have a history of hypersensitivity reactions to metals.

EPMA J. 2018 Jun 8;9(3):331-343. doi: 10.1007/s13167-018-0138-6. eCollection 2018 Sep.

Titanium implants and silent inflammation in jawbone-a critical interplay of dissolved titanium particles and cytokines TNF-α and RANTES/CCL5 on overall health?

Lechner J, Noumbissi S, von Baehr V.

ABSTRACT

BACKGROUND AND INTRODUCTION:

It is a well-known fact that titanium particles deriving from dental titanium implants (DTI) dissolve into the surrounding bone. Although titanium (TI) is regarded as a compatible implant material, increasing concern is coming up that the dissolved titanium particles induce inflammatory reactions around the implant. Specifically, the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) is expressed in the adjacent bone. The transition from TNF-α-induced local inflammation following insertion of DTI surgery to a chronic stage of "silent inflammation" could be a neglected cause of unexplained medical conditions.

MATERIAL AND METHODS:

The signaling pathways involved in the induction of cytokine release were analyzed by multiplex analysis. We examined samples of jawbone (JB) for seven cytokines in two groups: specimens from 14 patients were analyzed in areas of DTI for particle-mediated release of cytokines. Each of the adjacent to DTI tissue samples showed clinically fatty degenerated and osteonecrotic medullary changes in the JB (FDOJ). Specimens from 19 patients were of healthy JB. In five cases, we measured the concentration of dissolved Ti particles by spectrometry.

RESULTS:

All DTI-FDOJ samples showed RANTES/CCL5 (R/C) as the only extremely overexpressed cytokine. DTI-FDOJ cohort showed a 30-fold mean overexpression of R/C as compared with a control cohort of 19 healthy JB samples. Concentration of dissolved Ti particles in DTI-FDOJ was 30-fold higher than an estimated maximum of 1.000 μg/kg.

DISCUSSION:

As R/C is discussed in the literature as a possible contributor to inflammatory diseases, the here-presented research examines the question of whether common DTI may provoke the development of chronic inflammation in the jawbone in an impaired state of healing. Such changes in areas of the JB may lead to hyperactivated signaling pathways of TNF-α induced R/C overexpression, and result in unrecognized sources of silent inflammation. This may contribute to disease patterns like rheumatic arthritis, multiple sclerosis, and other systemic-inflammatory diseases, which is widely discussed in scientific papers.

CONCLUSION:

From a systemic perspective, we recommend that more attention be paid to the cytokine cross-talk that is provoked by dissolved Ti particles from DTI in medicine and dentistry. This may contribute to further development of personalized strategies in preventive medicine.

2.3 General Reviews and Overviews

Indian J Dent Res. 2009 Jan-Mar;20(1):91-8.

An overview of the corrosion aspect of dental implants (titanium and its alloys).

Chaturvedi TP.

ABSTRACT

Titanium and its alloys are used in dentistry for implants because of its unique combination of chemical, physical, and biological properties. They are used in dentistry in cast and wrought form. The long term presence of corrosion reaction products and ongoing corrosion lead to fractures of the alloy-abutment interface, abutment, or implant body. The combination of stress, corrosion, and bacteria contribute to implant failure. This article highlights a review of the various aspects of corrosion and biocompatibility of dental titanium implants as well as suprastructures. This knowledge will also be helpful in exploring possible research strategies for probing the biological properties of materials.

Hindawi Publishing Corporation Advances in Tribology. Volume 2009, Article ID 250986, 12 pages doi:10.1155/2009/250986.

Significance of Tribocorrosion in Biomedical Applications: Overview and Current Status

Mathew MT, Pai PS, Pourzal R, Fischer A, Wimmer MA.

ABSTRACT

Recently, "tribocorrosion," a research area combining the science of tribology and corrosion, has drawn attention from scientists and engineers belonging to a wide spectrum of research domains. This is due to its practical impact on daily life and also the accompanying economical burdens. It encompasses numerous applications including the offshore, space, and biomedical industry, for instance, in the case of artificial joints (Total Hip Replacement, THR) in orthopedic surgery, where implant metals are constantly exposed to tribological events (joint articulations) in the presence of corrosive solutions, that is, body fluids. Keeping the importance of this upcoming area of research in biomedical applications in mind, it was thought to consolidate the work in this area with some fundamental aspects so that a comprehensive picture of the current state of knowledge can be depicted. Complexity of tribocorrosion processes has been highlighted, as it is influenced by several parameters (mechanical and corrosion) and also due to the lack of an integrated/efficient test system. Finally a review of the recent work in the area of biotribocorrosion is provided, by focusing on orthopedic surgery and dentistry.

Acta Odontol Latinoam. 2009;22(1):3-9.

The issue of corrosion in dental implants: a review.

Olmedo DG, Tasat DR, Duffó G, Guglielmotti MB, Cabrini RL.

ABSTRACT

Pure titanium or titanium alloys, and to a lesser extent, zirconium, are metals that are often used in direct contact with host tissues. These metallic biomaterials are highly reactive, and on exposure to fluid media or air, quickly develop a layer of titanium dioxide (TiO2) or zirconium dioxide (ZrO2). This layer of dioxide forms a boundary at the interface between the biological medium and the metal structure, determining the degree of biocompatibility and the biological response of the implant. Corrosion is the deterioration a metal undergoes as a result of the surrounding medium (electrochemical attack), which causes the release of ions into the microenvironment. No metal or alloy is entirely inert in vivo. Corrosion phenomena at the interlace are particularly important in the evolution of both dental and orthopedic implants and one of the possible causes of implant failure after initial success. This paper comprises a review of literature and presents results of our laboratory experiments related to the study of corrosion, with special emphasis on dental implants. In situ degradation of a metallic implant is undesirable because it alters the structural integrity of the implant. The issue of corrosion is not limited to a local problem because the particles pmduced as a result could migrate to distant sites, whose evolution would require further studies.

Clin Oral Implants Res. 2011 Jul;22(7):673-680. doi: 10.1111/j.1600-0501.2010.02081.x. Epub 2011 Jan 20.

Titanium allergy: could it affect dental implant integration?

Siddiqi A, Payne AGT, De Silva RK, Duncan WJ.

ABSTRACT

PURPOSE:

Degradation products of metallic biomaterials including titanium may result in metal hypersensitivity reaction. Hypersensitivity to biomaterials is often described in terms of vague pain, skin rashes, fatigue and malaise and in some cases implant loss. Recently, titanium hypersensitivity has been suggested as one of the factors responsible for implant failure. Although titanium hypersensitivity is a growing concern, epidemiological data on incidence of titanium-related allergic reactions are still lacking.

MATERIALS AND METHODS:

A computer search of electronic databases primarily MEDLINE and PUBMED was performed with the following key words: 'titanium hypersensitivity', 'titanium allergy', 'titanium release' without any language restriction. Manual searches of the bibliographies of all the retrieved articles were also performed. In addition, a complementary hand search was also conducted to identify recent articles and case reports.

RESULTS:

Most of the literature comprised case reports and prospective in vivo/in vitro trials. One hundred and twenty-seven publications were selected for full text reading. The bulk of the literature originated from the orthopaedic discipline, reporting wear debris following knee/hip arthroplasties. The rest comprised osteosynthesis (plates/screws), oral implant/dental materials, dermatology/cardiac-pacemaker, pathology/cancer, biomaterials and general reports.

CONCLUSION:

This review of the literature indicates that titanium can induce hypersensitivity in susceptible patients and could play a critical role in implant failure. Furthermore, this review supports the need for long-term clinical and radiographic follow-up of all implant patients who are sensitive to metals. At present, we know little about titanium hypersensitivity, but it cannot be excluded as a reason for implant failure.

Clin Implant Dent Relat Res. 2013 Feb;15(1):47-52. doi: 10.1111/j.1708-8208.2010.00330.x. Epub 2011 Mar 17.

Is titanium sensitivity associated with allergic reactions in patients with dental implants? A systematic review.

Javed F, Al-Hezaimi K, Almas K, Romanos GE.

ABSTRACT

BACKGROUND:

A worrying correlation which seems to be overlooked by clinicians is allergic reactions to titanium (Ti) in patients with dental implants.

PURPOSE:

The aim of the present review study was to assess whether or not Ti sensitivity is associated with allergic reactions in patients with dental implants.

MATERIALS AND METHODS:

To address the focused question "Can Ti cause allergic reactions in patients with dental implants?", databases were explored from 1977 until May 2010 using a combination of the following keywords: "allergy,""dental,""hypersensitivity,""implant,""oral," and "Titanium." Letters to the editor and unpublished data were excluded.

RESULTS:

Seven studies (six clinical and one experimental) were included. The participants were aged between 14.3 and 84.1 years. In five clinical studies, Ti implants were inserted in the mandible. Five studies reported dermal inflammatory conditions and gingival hyperplasia as allergic reactions in patients with Ti dental implants. A case report presented swelling in submental and labial sulcus and hyperemia of soft tissues in a patient with Ti dental implants. Two studies reported that Ti implants are well tolerated in host tissues. The patch test was performed in two clinical studies for the diagnosis of allergic reactions. Memory lymphocyte immunostimulation assay and lymphocyte transformation tests were also performed.

CONCLUSION:

The significance of Ti as a cause of allergic reactions in patients with dental implants remains unproven.

Dermatitis. 2015 Jan-Feb;26(1):7-25. doi: 10.1097/DER.0000000000000091.

Hypersensitivity reactions to titanium: diagnosis and management.

Wood MM, Warshaw EM.

ABSTRACT

Titanium is notable for its biocompatibility and is used as biologic implant material across surgical specialties, especially in metal-sensitive individuals. However, rare cases of titanium hypersensitivity reactions are reported in the literature. This article discusses the properties and biological behavior of titanium and provides a thorough review of the literature on reported cases, diagnostic techniques, and approach to management of titanium hypersensitivity.

Int J Mol Sci. 2016 Jun; 17(6): 798. Published online 2016 May 24. doi: 10.3390/ijms17060798.

Adverse Biological Effect of TiO2 and Hydroxyapatite Nanoparticles Used in Bone Repair and Replacement

Wang J, Wang L, Fan Y.

ABSTRACT

The adverse biological effect of nanoparticles is an unavoidable scientific problem because of their small size and high surface activity. In this review, we focus on nano-hydroxyapatite and TiO2 nanoparticles (NPs) to clarify the potential systemic toxicological effect and cytotoxic response of wear nanoparticles because they are attractive materials for bone implants and are widely investigated to promote the repair and reconstruction of bone. The wear nanoparticles would be prone to binding with proteins to form protein-particle complexes, to interacting with visible components in the blood including erythrocytes, leukocytes, and platelets, and to being phagocytosed by macrophages or fibroblasts to deposit in the local tissue, leading to the formation of fibrous local pseudocapsules. These particles would also be translocated to and disseminated into the main organs such as the lung, liver and spleen via blood circulation. The inflammatory response, oxidative stress, and signaling pathway are elaborated to analyze the potential toxicological mechanism. Inhibition of the oxidative stress response and signaling transduction may be a new therapeutic strategy for wear debris–mediated osteolysis. Developing biomimetic materials with better biocompatibility is our goal for orthopedic implants.

J Periodontal Res. 2017 Dec;52(6):946-954. doi: 10.1111/jre.12469. Epub 2017 Jun 14.

Synergistic interactions between corrosion and wear at titanium-based dental implant connections: A scoping review.

Apaza-Bedoya K, Tarce M, Benfatti CAM, Henriques B, Mathew MT, Teughels W, Souza JCM.

ABSTRACT

Two-piece implant systems are mainly used in oral implantology involving an osseointegrated implant connected to an abutment, which supports prosthetic structures. It is well documented that the presence of microgaps, biofilms and oral fluids at the implant-abutment connection can cause mechanical and biological complications. The aim of this review paper was to report the degradation at the implant-abutment connection by wear and corrosion processes taking place in the oral cavity. Most of the retrieved studies evaluated the wear and corrosion (tribocorrosion) of titanium-based materials used for implants and abutments in artificial saliva. Electrochemical and wear tests together with microscopic techniques were applied to validate the tribocorrosion behavior of the surfaces. A few studies inspected the wear on the inner surfaces of the implant connection as a result of fatigue or removal of abutments. The studies reported increased microgaps after fatigue tests. In addition, data suggest that micromovements occurring at the contacting surfaces can increase the wear of the inner surfaces of the connection. Biofilms and/or glycoproteins act as lubricants, although they can also amplify the corrosion of the surfaces. Consequently, loosening of the implant-abutment connection can take place during mastication. In addition, wear and corrosion debris such as ions and micro- and nanoparticles released into the surrounding tissues can stimulate peri-implant inflammation that can lead to pathologic bone resorption.

Int J Mol Sci. 2018 Nov 13;19(11). pii: E3585. doi: 10.3390/ijms19113585.

Potential Causes of Titanium Particle and Ion Release in Implant Dentistry: A Systematic Review.

Delgado-Ruiz R, Romanos G.

ABSTRACT

Implant surface characteristics, as well as physical and mechanical properties, are responsible for the positive interaction between the dental implant, the bone and the surrounding soft tissues. Unfortunately, the dental implant surface does not remain unaltered and changes over time during the life of the implant. If changes occur at the implant surface, mucositis and peri-implantitis processes could be initiated; implant osseointegration might be disrupted and bone resorption phenomena (osteolysis) may lead to implant loss. This systematic review compiled the information related to the potential sources of titanium particle and ions in implant dentistry. Research questions were structured in the Population, Intervention, Comparison, Outcome (PICO) framework. PICO questionnaires were developed and an exhaustive search was performed for all the relevant studies published between 1980 and 2018 involving titanium particles and ions related to implant dentistry procedures. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for the selection and inclusion of the manuscripts in this review. Titanium particle and ions are released during the implant bed preparation, during the implant insertion and during the implant decontamination. In addition, the implant surfaces and restorations are exposed to the saliva, bacteria and chemicals that can potentially dissolve the titanium oxide layer and, therefore, corrosion cycles can be initiated. Mechanical factors, the micro-gap and fluorides can also influence the proportion of metal particles and ions released from implants and restorations.

J Dent Res. 2018 Mar;97(3):259-265. doi: 10.1177/0022034517740560. Epub 2017 Nov 12.

Is Metal Particle Release Associated with Peri-implant Bone Destruction? An Emerging Concept.

Fretwurst T, Nelson K, Tarnow DP, Wang HL, Giannobile WV.

ABSTRACT

Peri-implant diseases affecting the surrounding structures of endosseous dental implants include peri-implant mucositis and peri-implantitis. The prevalence of peri-implantitis ranges between 15% and 20% after 10 y, highlighting the major challenge in clinical practice in the rehabilitation of dental implant patients. The widespread nature of peri-implant bone loss poses difficulties in the management of biological complications affecting the long-term success of osseointegrated implant reconstructions. Metal and titanium particles have been detected in peri-implant supporting tissues. However, it remains unclear what mechanisms could be responsible for the elicitation of particle and ion release and whether these released implant-associated materials have a local and/or systemic impact on the peri-implant soft and hard tissues. Metal particle release as a potential etiologic factor has been intensively studied in the field of orthopedics and is known to provoke aseptic loosening around arthroplasties and is associated with implant failures. In dental medicine, emerging information about metal/titanium particle release suggests that the potential impact of biomaterials at the abutment or bone interfaces may have an influence on the pathogenesis of peri-implant bone loss. This mini-review highlights current evidence of metal particle release around dental implants and future areas for research.

Clin Oral Implants Res. 2018 Oct;29 Suppl 18:37-53. doi: 10.1111/clr.13305.

What is the impact of titanium particles and biocorrosion on implant survival and complications? A critical review.

Mombelli A, Hashim D, Cionca N.

ABSTRACT

OBJECTIVES:

To compile the current evidence regarding the association between the release of titanium particles and biologic complications of dental implants.

MATERIAL AND METHODS:

This is a critical review. We searched the literature using the terms "corrosion," "allergy," "hypersensitivity," or "particles" together with "titanium," "Ti," "TiO2. " The bibliographies of identified publications and previously published review articles were scanned to find additional related articles. We included clinical studies, in vivo and in vitro experiments.

RESULTS:

Titanium particles and degradation products of titanium have been detected in oral and nonoral tissues. Particles are released from surfaces of dental implants because of material degradation in a process called tribocorrosion. It involves mechanical wear and environmental factors, notably contact to chemical agents and interaction with substances produced by adherent biofilm and inflammatory cells. In vitro, titanium particles can interfere with cell function and promote inflammation. A temporal association between exposure to titanium and occurrence of tissue reactions suggested hypersensitivity in a limited number of cases. However, there is poor specificity as the observed reactions could be initiated by other factors associated with the placement of implants. Titanium particles are commonly detected in healthy and diseased peri-implant mucosa alike, at low levels even in gingiva of individuals without titanium implants. Rather than being the trigger of disease, higher concentrations of titanium in peri-implantitis lesions could be the consequence of the presence of biofilms and inflammation.

CONCLUSION:

There is an association between biocorrosion, presence of titanium particles, and biological implant complications, but there is insufficient evidence to prove a unidirectional causal relationship.

Int J Implant Dent. 2019 Mar 11;5(1):10. doi: 10.1186/s40729-019-0162-x.

General review of titanium toxicity.

Kim KT, Eo MY, Nguyen TTH, Kim SM.

ABSTRACT

BACKGROUND:

Titanium is a commonly used inert bio-implant material within the medical and dental fields. Although the use of titanium is thought to be safe with a high success rate, in some cases, there are rare reports of problems caused by titanium. In most of these problematic reports, only individual reports are dominant and comprehensive reporting has not been performed. This comprehensive article has been prepared to review the toxicity of titanium materials within the medical and dental fields.

METHODS:

We used online searching tools including MEDLINE (PubMed), Embase, Cochrane Library, and Google Scholar by combining keywords such as "titanium implant toxicity," "titanium implant corrosion," "titanium implant allergy," and "yellow nail syndrome." Recently updated data has been collected and compiled into one of four categories: "the toxicity of titanium," "the toxicity of titanium alloys," "the toxicity of titanium implants," and "diseases related to titanium."

RESULTS:

Recent studies with regard to titanium toxicity have been increasing and have now expanded to the medical field in addition to the fields of environmental research and basic science. Problems that may arise in titanium-based dental implants include the generation of titanium and titanium alloy particles and ions deposited into surrounding tissues due to the corrosion and wear of implants, resulting in bone loss due to inflammatory reactions, which may lead to osseointegration failure of the dental implant. These titanium ions and particles are systemically deposited and can lead to toxic reactions in other tissues such as yellow nail syndrome. Additionally, implant failure and allergic reactions can occur due to hypersensitivity reactions. Zirconia implants can be considered as an alternative; however, limitations still exist due to a lack of long-term clinical data.

CONCLUSIONS:

Clinicians should pay attention to the use of titanium dental implants and need to be aware of the problems that may arise from the use of titanium implants and should be able to diagnose them, in spite of very rare occurrence. Within the limitation of this study, it was suggested that we should be aware the rare problems of titanium toxicity.

3. Interference Fields in the Oral Cavity

3.1 Root Canal treated Teeth

3.1.1 Basic Research

International Endodontic Journal. 2009 Sept; Volume 42, Issue 10. https://doi org/10.1111/j.1365-2591.2009.01594.x

Microflora in teeth associated with apical periodontitis: a methodological observational study comparing two protocols and three microscopy techniques

Richardson N, Mordan NJ, Figueiredo JAP, Ng Y-L, Gulabivala K.

ABSTRACT

AIM:

The aim of this study was to compare two protocols to examine bacterial colonization in teeth associated with chronic apical periodontitis with acute episodes (ap), using light microscopy (LM), transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

METHODOLOGY:

Nine root samples (seven teeth) were processed using either Eastman Dental Institute (EDI) (n = 4 teeth/4 roots) or Zurich (n = 3 teeth/5 roots) protocols. The roots were sectioned longitudinally; one root portion was viewed with SEM, descriptively dividing its length into apical, middle and coronal; semi-thin and ultra-thin transverse sections were viewed under LM and TEM from each third of the other root portion. Each root was therefore examined using all microscopy techniques. Observations of bacterial presence, description and distribution within the root canal lumen and root dentine were systematically recorded using pre-determined criteria.

RESULTS:

The Zurich technique gave a more predictable division of the root, but the surface was slightly smeared and demineralization was incomplete. The Eastman Dental Institute (EDI) approach appeared to provide better ultrastructural detail. Bacteria were detected in eight of the nine roots. Bacterial biofilms were commonly seen adhering to the root canal surface, containing various cellular morphotypes: rods, cocci, filaments and spirochaetes. Bacteria were more evident apically than coronally, associated with the canal wall but were more commonly evident coronally than apically within the dentinal tubules. Polymorphs (PMNs) were found in all the root thirds, especially apically, often numerous and walling off the bacterial biofilm from the remaining canal lumen.

CONCLUSIONS:

Both protocols had merits and de-merits. The combination of microscopy techniques offered complementary views of intra-radicular bacterial colonization. The perception of confinement of the host/microbial interface at the apical foramen is not entirely correct; PMNs may be found even in the coronal third of root canals containing necrotic pulp tissue.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 May;107(5):721-6. doi: 10.1016/j.tripleo.2009.01.042.

Bacteria in the apical root canal of teeth with primary apical periodontitis.

Siqueira JF Jr, Rôças IN, Alves FR, Silva MG.

ABSTRACT

OBJECTIVE:

Bacteria settled in the apical root canal are in a privileged position to inflict damage to the periradicular tissues. Therefore, the species identified in this region can be of special relevance for the pathogenesis of apical periodontitis. This study investigated the occurrence and levels of several bacterial taxa in the apical root canal of teeth with apical periodontitis.

STUDY DESIGN:

DNA extracts from samples taken from the apical part of the root canal of extracted teeth evincing chronic apical periodontitis lesions served as templates for analysis of the presence and levels of 28 bacterial species/phylotypes using a 16S ribosomal RNA gene-based reverse-capture checkerboard hybridization assay.

RESULTS:

Bacterial DNA was detected in 19 out of 20 samples. Detected taxa included Pseudoramibacter alactolyticus (32%), Bacteroidetes clone X083 (26%), Streptococcus species (21%), Olsenella uli (10.5%), Synergistes clone BA121 (10.5%), Fusobacterium nucleatum (10.5%), Porphyromonas endodontalis (10.5%), Dialister clone BS016 (5%), Filifactor alocis (5%), Parvimonas micra (5%), and Treponema denticola (5%). Of these, only Bacteroidetes clone X083 and Synergistes clone BA121 were found at levels above 10(5).

CONCLUSION:

Occurrence of these bacterial taxa in the apical part of infected root canals indicates their potential pathogenetic role in the etiology of apical periodontitis.

J Endod. 2014 May;40(5):670-7. doi: 10.1016/j.joen.2013.10.005. Epub 2013 Nov 19.

New bacterial composition in primary and persistent/secondary endodontic infections with respect to clinical and radiographic findings.

Tennert C, Fuhrmann M, Wittmer A, Karygianni L, Altenburger MJ, Pelz K, Hellwig E, Al-Ahmad A.

ABSTRACT

INTRODUCTION:

The aim of the present study was to analyze the microbiota of primary and secondary/persistent endodontic infections of patients undergoing endodontic treatment with respect to clinical and radiographic findings.

METHODS:

Samples from the root canals of 21 German patients were taken using 3 sequential sterile paper points. In the case of a root canal filling, gutta-percha was removed with sterile files, and samples were taken using sterile paper points. The samples were plated, and microorganisms were then isolated and identified morphologically by biochemical analysis and sequencing the 16S rRNA genes of isolated microorganisms.

RESULTS:

In 12 of 21 root canals, 33 different species could be isolated. Six (50%) of the cases with isolated microorganisms were primary, and 6 (50%) cases were endodontic infections associated with root-filled teeth. Twelve of the isolated species were facultative anaerobic and 21 obligate anaerobic. Monomicrobial infections were found for Enterococcus faecalis and Actinomyces viscosus. E. faecalis was most frequently isolated in secondary endodontic infections (33%). Moraxella osloensis was isolated from a secondary endodontic infection that had an insufficient root canal filling accompanied by a mild sensation of pain. A new bacterial composition compromising Atopobium rimae, Anaerococcus prevotii, Pseudoramibacter alactolyticus, Dialister invisus, and Fusobacterium nucleatum was recovered from teeth with chronic apical abscesses.

CONCLUSIONS:

New bacterial combinations were found and correlated to clinical and radiographic findings, particularly to chronic apical abscesses. M. osloensis was detected in root canals for the second time and only in German patients.

J Endod. 2015 Jul;41(7):1037-42. doi: 10.1016/j.joen.2015.03.008. Epub 2015 Apr 17.

Total and Specific Bacterial Levels in the Apical Root Canal System of Teeth with Post-treatment Apical Periodontitis.

Antunes HS, Rôças IN, Alves FR, Siqueira JF Jr.

ABSTRACT

INTRODUCTION:

Most studies of the microbiota in root canal-treated teeth focused only on the main canal, not distinguishing regions nor incorporating the intricate anatomy in the analysis. Moreover, most of them provided only prevalence data. This study was designed to evaluate the total bacterial counts and the presence, levels, and relative abundance of candidate endodontic pathogens exclusively in the apical root canal system associated with post-treatment apical periodontitis.

METHODS:

Apical root specimens obtained during periradicular surgery of 27 adequately treated teeth with persistent apical periodontitis were cryogenically ground. DNA was extracted from the powder, and real-time polymerase chain reaction was used to quantify the total bacteria and 7 bacterial taxa.

RESULTS:

Samples from 21 teeth were positive for bacteria. Streptococcus species were the most prevalent (76%) followed by members of the Actinobacteria phylum (52%) and Pseudoramibacter alactolyticus (19%). The mean total bacterial load in the apical root segments was 5.7 × 10(4) cell equivalents per root apex (or 2.1 × 10(4)/100 mg root powder). Streptococci comprised from 0.02%-99.9% of the total bacterial counts, Actinobacteria from 0.02%-84.7%, and P. alactolyticus from 67.9%-99%. Although Enterococcus faecalis was found in only 3 (14%) cases, it was dominant in 2.

CONCLUSIONS:

Streptococcus species, members of the Actinobacteria phylum, and P. alactolyticus were the most prevalent taxa in the apical canal system and dominated the bacterial populations in many cases of post-treatment apical periodontitis.

Journal of Dental Sciences, 2015 March, Volume 10, Issue 1, Pages 95-101.

Status of bacterial colonization in teeth associated with different types of pulpal and periradicular disease: A scanning electron microscopy analysis

Huang YH, Xie SJ, Wang NN, Ge JY.

ABSTRACT

BACKGROUND/PURPOSE:

The purpose of this study was to use scanning electron microscopy (SEM) to investigate the status of bacterial colonization in differently infected root canals and the damage to radicular dentin.

MATERIALS AND METHODS:

Twenty-five freshly extracted teeth were selected for this study (Group A: 8 teeth with pulpitis; Group B: 10 teeth with periapical lesions; and Group C: 7 teeth with failed root canal treatment). After fixation, the teeth were longitudinally split into two halves. The halves were then dehydrated, sputter-coated with gold, and viewed using SEM, descriptively dividing their lengths into apical, middle, and coronal thirds.

RESULTS:

In Group A, bacterial infection was mainly located in the coronal third of the root canals and bacteria failed to penetrate into the dentinal tubules. In Group B, bacterial infection was distributed over the entire length of the root canal. The invasion depth of bacteria into the dentinal tubules was approximately 300 μm. In Group C, bacterial infection was mainly focused on the apical third of the root canals. Most of the dentinal tubules had collapsed, and the root canal walls were heavily colonized with dense bacterial biofilm, primarily consisting of cocci. Compared to Group B, the invasion depths were deeper in the apical thirds of root canals ($P < 0.05$).

CONCLUSION:

Bacterial infection was lighter in the root canals with pulpitis than in those with apical periodontitis, which might require special considerations regarding different stages of pulp and periapical pathology in root canal treatment.

3.1.2 Clinically relevant Studies and Papers

J Am Dent Assoc. 2001 Feb;132(2):191-5.

Implant failures associated with asymptomatic endodontically treated teeth.

Brisman DL, Brisman AS, Moses MS.

ABSTRACT

BACKGROUND:

Endosseous root-formed implants occasionally fail to osseointegrate. Causes of failure include infection, overheating of the bone, habitual smoking, systemic disease, transmucosal overloading, excessive surgical trauma and implant placement adjacent to teeth demonstrating periapical pathology.

CASE DESCRIPTION:

In this article, the authors present another possible cause of implant failure. The cases of four patients who received endosseous root-formed implants are discussed. Each patient demonstrated signs of infection after initial implant placement. The common factor in each failing implant was its placement adjacent to an asymptomatic endodontically treated tooth with no clinical or radiographic evidence of pathology.

CLINICAL IMPLICATIONS:

These patients demonstrate the importance of evaluating and possibly retreating or extracting adjacent endodontically treated teeth before placing implants.

Nederlands tijdschrift voor tandheelkunde 112(11):416-9 · December 2005

Local and potential systemic consequences of endodontic root infection

Wu MK, Wesselink P.

ABSTRACT

In root infections, bacteria are present not only in planktonic cells but also in biofilms, which are more resistant to host defence mechanisms and disinfectans. Apical periodontitis, which may be radiographically undetectable, may develop or persist as a host defence mechanism to prevent the systemic spread of bacteria and their by-products to other sites of the body. The risk of spreading microorganisms and septic emboli is present especially in compromised hosts; furthermore, long-standing inflammation may have systemic effects and affect general health. Effective procedures should be developed to minimize the burden of root infection.

J Dent Res. Author manuscript; available in PMC 2008 Feb 6.Published in final edited form as: J Dent Res. 2006 Nov; 85(11): 996–1000.

Lesions of Endodontic Origin and Risk of Coronary Heart Disease

Caplan DJ, Chasen JB, Krall EA, Cai J, Kang S, Garcia RI, Offenbacher S, Beck JD.

ABSTRACT

A paucity of epidemiologic research exists regarding systemic health consequences of endodontic disease. This study evaluated whether incident radiographically evident lesions of endodontic origin were related to development of coronary heart disease (CHD) among 708 male participants in the VA Dental Longitudinal Study. At baseline and every three years for up to 32 years, participants (who were not VA patients) received complete medical and dental examinations, including full-mouth radiographs. Cox regression models estimated the relationship between incident lesions of endodontic origin and time to CHD diagnosis. Among those ≤ 40 years old, incident lesions of endodontic origin were significantly associated with time to CHD diagnosis ($p < 0.05$), after adjustment for covariates of interest, with hazard ratios decreasing as age increased. Among those > 40 years old, no statistically significant association was observed. These findings are consistent with research that suggests relationships between chronic periodontal inflammation and the development of CHD, especially among younger men.

J Endod. 2009 May;35(5):626-30. doi: 10.1016/j.joen.2009.01.012.

Association between chronic dental infection and acute myocardial infarction.

Willershausen B, Kasaj A, Willershausen I, Zahorka D, Briseño B, Blettner M, Genth-Zotz S, Münzel T.

ABSTRACT

INTRODUCTION:

In patients with cardiovascular diseases several risk factors such as high blood pressure, diabetes, smoking and drinking habits, genetic disposition, and chronic inflammation must be considered. The aim of this study was to investigate whether there is a correlation between dental origin infections and the presence of an acute myocardial infarction (AMI).

METHODS:

A total of 125 patients who had experienced a myocardial infarction and 125 healthy individuals were included in this study. The oral examination was carried out following the consent of the ethics committee and the National Board for Radiation Protection and included the number of teeth, endodontically treated teeth, periodontal screening index (PSI), clinical attachment level, and radiographic apical lesions (radiograph examination). The medical examination included, among others, blood glucose level, C-reactive protein (CRP) serum levels, and leukocyte number.

RESULTS:

The study demonstrated that patients with AMI exhibited an unfavorable dental state of health. After statistical adjustment for age, gender, and smoking, they exhibited a significantly higher number of missing teeth ($P = .001$), less teeth with root canal fillings ($P = .0015$), a higher number of radiologic apical lesions ($P = .001$), and a higher PSI value ($P = .001$) compared with individuals without myocardial infarction. The medical data showed a nonsignificant correlation between CRP and the number of radiologic apical lesions.

CONCLUSIONS:

This study presents evidence that patients who have experienced myocardial infarction also exhibit an unfavorable dental state of health in comparison to healthy patients and suggests an association between chronic oral infections and myocardial infarction.

J Endod. 2011 Dec;37(12):1624-9. doi: 10.1016/j.joen.2011.09.006.

Association of endodontic infection with detection of an initial lesion to the cardiovascular system.

Cotti E, Dessì C, Piras A, Flore G, Deidda M, Madeddu C, Zedda A, Longu G, Mercuro G.

ABSTRACT

INTRODUCTION:

Dental infections might predispose toward the onset of cardiovascular disease (CVD). To date, only a few studies, yielding inconclusive findings, have investigated the potential correlation between apical periodontitis (AP) and CVD. The aim of this study (as the first part of a prospective study) was to evaluate, in the absence of CV risk factors, whether subjects with AP were more exposed to the pathogenetic indices of an atherosclerotic lesion.

METHODS:

Forty men between the ages of 20 and 40 years who were free from periodontal disease, CVD, and traditional CV risk factors were enrolled in the study; 20 subjects had AP, and 20 acted as controls. All subjects underwent dental examination and complete cardiac assessment: physical examination, electrocardiogram, conventional and tissue Doppler echocardiography, and measurement of endothelial flow reserve (EFR). The following laboratory parameters were tested: interleukins -1, -2, and -6 (IL-1, IL-2, IL-6), tumor necrosis factor alpha, and asymmetrical dimethylarginine (ADMA). Data were analyzed by using the 2-tailed Student's t test, Pearson t test (or Spearman t test for nonparametric variables), and multivariate linear regression analysis.

RESULTS:

Echocardiography revealed no abnormalities in any of the subjects studied. ADMA levels were inversely correlated with EFR ($P < .05$) and directly correlated with IL-2 ($P < .001$). Patients with AP presented with significantly greater blood concentrations of IL-1 ($P < .05$), IL-2 ($P < .01$), IL-6 ($P < .05$), and ADMA ($P < .05$) and a significant reduction of EFR ($P < .05$).

CONCLUSIONS:

Increased ADMA levels and their relationship with poor EFR and increased IL-2 might suggest the existence of an early endothelial dysfunction in young adults with AP.

J Endod. 2012 Dec;38(12):1570-7. doi: 10.1016/j.joen.2012.08.013. Epub 2012 Oct 12.

Association among oral health, apical periodontitis, CD14 polymorphisms, and coronary heart disease in middle-aged adults.

Pasqualini D, Bergandi L, Palumbo L, Borraccino A, Dambra V, Alovisi M, Migliaretti G, Ferraro G, Ghigo D, Bergerone S, Scotti N, Aimetti M, Berutti E.

ABSTRACT

INTRODUCTION:

There is evidence to suggest that an association exists between oral infections and coronary heart disease (CHD). Subjects presenting lesions of endodontic origin (LEOs) or pulpal inflammation had an increased risk of developing CHD. However, findings concerning systemic manifestations of apical periodontitis (AP) remain controversial. An association between CD14 gene polymorphisms and atherosclerosis-associated diseases has been shown, but there are no data regarding an association between CD14 polymorphism and AP. This study evaluated associations between clinical oral health status, CD14 polymorphisms, and CHD.

METHODS:

A case-controlled clinical trial was designed to compare middle-aged adults with acute myocardial infarction or unstable angina (n = 51) within 12 months of the acute event defined as first manifestation with healthy controls (n = 49). Participants were matched for age, sex, and socioeconomic status. Indicators of oral disease and compliance were evaluated. CD14 polymorphisms were analyzed by restriction fragment length polymorphism-polymerase chain reaction.

RESULTS:

CHD subjects had a higher prevalence of oral diseases and lower compliance to oral preventive strategies than healthy controls. Multivariate analysis showed a positive association between missing teeth (odds ratio [OR] = 1.37; 95% confidence interval [CI], 1.02-1.85), the number of LEOs (OR = 4.37; 95% CI, 1.69-11.28), chronic periodontitis (OR = 5.87; 95% CI, 1.17-29.4), and CHD. No statistically significant association emerged between the CD14 C(-260)T and the CD14 C(-159)T polymorphism, endodontic or periodontal disease, and CHD.

CONCLUSIONS:

Chronic oral diseases may increase the risk of CHD and may be an unconventional risk factor for CHD.

J Dent Res. 2016 Nov;95(12):1358-1365. doi: 10.1177/0022034516660509. Epub 2016 Jul 28.

Association of Endodontic Lesions with Coronary Artery Disease.

Liljestrand JM, Mäntylä P, Paju S, Buhlin K, Kopra KA, Persson GR, Hernandez M, Nieminen MS, Sinisalo J, Tjäderhane L, Pussinen PJ.

ABSTRACT

An endodontic lesion (EL) is a common manifestation of endodontic infection where Porphyromonas endodontalis is frequently encountered. EL may associate with increased risk for coronary artery disease (CAD) via similar pathways as marginal periodontitis. The aim of this cross-sectional study was to delineate the associations between EL and CAD. Subgingival P. endodontalis, its immune response, and serum lipopolysaccharide were examined as potential mediators between these 2 diseases. The Finnish Parogene study consists of 508 patients (mean age, 62 y) who underwent coronary angiography and extensive clinical and radiographic oral examination. The cardiovascular outcomes included no significant CAD (n = 123), stable CAD (n = 184), and acute coronary syndrome (ACS; n = 169). EL was determined from a panoramic tomography. We combined data of widened periapical spaces (WPSs) and apical rarefactions to a score of EL: 1, no EL (n = 210); 2, ≥1 WPS per 1 apical rarefaction (n = 222); 3, ≥2 apical rarefactions (n = 76). Subgingival P. endodontalis was defined by checkerboard DNA-DNA hybridization analysis, and corresponding serum antibodies were determined by ELISA. In our population, 50.4% had WPSs, and 22.8% apical rarefactions. A total of 51.2% of all teeth with apical rarefactions had received endodontic procedures. Subgingival P. endodontalis levels and serum immunoglobulin G were associated with a higher EL score. In the multiadjusted model (age, sex, smoking, diabetes, body mass index, alveolar bone loss, and number of teeth), having WPSs associated with stable CAD (odds ratio [OR] = 1.94, 95% confidence interval [95% CI] = 1.13 to 3.32, P = 0.016) and highest EL score were associated with ACS (OR = 2.46, 95% CI = 1.09 to 5.54, P = 0.030). This association was especially notable in subjects with untreated teeth with apical rarefactions (n = 59, OR = 2.72, 95% CI = 1.16 to 6.40, P = 0.022). Our findings support the hypothesis that ELs are independently associated with CAD and in particular with ACS. This is of high interest from a public health perspective, considering the high prevalence of ELs and CAD.

BMC Oral Health. 2017 Jul 11;17(1):107. doi: 10.1186/s12903-017-0401-6.

Apical periodontitis associates with cardiovascular diseases: a cross-sectional study from Sweden.

Virtanen E, Nurmi T, Söder PÖ, Airila-Månsson S, Söder B, Meurman JH.

ABSTRACT

BACKGROUND:

Periodontal disease associates with systemic diseases but corresponding links regarding apical periodontitis (AP) are not so clear. Hence our aim was to study association between AP and the prevalence of systemic diseases in a study population from Sweden.

METHODS:

The subjects were 150 patients from a randomly selected epidemiological sample of 1676 individuals. 120 accepted to participate and their basic and clinical examination data were available for these secondary analyses where dental radiographs were used to record signs for endodontic treatments and AP. Periapical Index and modified Total Dental Index scores were calculated from the x-rays to classify the severity of AP and dental infection burden, respectively. Demographic and hospital record data were collected from the Swedish National Statistics Center. T-test, chi-square and univariate analysis of covariance (ANCOVA) and regressions analyses were used for statistics.

RESULTS:

Of the 120 patients 41% had AP and 61% had received endodontic treatments of which 52% were radiographically unsatisfactory. AP patients were older and half of them were smokers. AP and periodontitis often appeared in the same patient (32.5%). From all hospital diagnoses, cardiovascular diseases (CVD) were most common, showing 20.4% prevalence in AP patients. Regression analyses, controlled for age, gender, income, smoking and periodontitis, showed AP to associate with CVD with odds ratio 3.83 (95% confidence interval 1.18-12.40; p = 0.025).

CONCLUSIONS:

The results confirmed our hypothesis by showing that AP statistically associated with cardiovascular diseases. The finding that subjects with AP also often had periodontitis indicates an increased oral inflammatory burden.

Indian Heart J. 2018 Dec;70 Suppl 3:S431-S434. doi: 10.1016/j.ihj.2018.07.004. Epub 2018 Aug 7.

Lesions of endodontic origin: An emerging risk factor for coronary heart diseases.

Bains R, Bains VK.

ABSTRACT

A high inflammatory state, such as atherosclerosis, is a major underlying cause of coronary heart diseases (CHDs). Inflammatory mediators are known to lead to endothelial dysfunction and play a key role in initiation, progression, and rupture of atherothrombotic plaque. Chronic inflammatory dental infections such as periodontitis and lesions of endodontic origin or chronic apical periodontitis (CAP) may provide an environment conducive for such events. Atherosclerosis has shown to share a common spectrum of inflammatory markers with apical periodontitis. The possible correlation between CHD and CAP is emerging at microbiological, clinical, inflammatory, and molecular levels. This less recognized fact should be discussed more among the dental and medical fraternity so that more awareness and positive approach toward oral health can be created among patients and health-care providers.

Mol Neurobiol. 2018 Apr;55(4):2814-2827. doi: 10.1007/s12035-017-0545-z. Epub 2017 Apr 28.

Increased Root Canal Endotoxin Levels are Associated with Chronic Apical Periodontitis, Increased Oxidative and Nitrosative Stress, Major Depression, Severity of Depression, and a Lowered Quality of Life.

Gomes C, Martinho FC, Barbosa DS, Antunes LS, Póvoa HCC, Baltus THL, Morelli NR, Vargas HO, Nunes SOV, Anderson G, Maes M.

ABSTRACT

Evidence indicates that major depression is accompanied by increased translocation of gut commensal Gram-negative bacteria (leaky gut) and consequent activation of oxidative and nitrosative (O&NS) pathways. This present study examined the associations among chronic apical periodontitis (CAP), root canal endotoxin levels (lipopolysaccharides, LPS), O&NS pathways, depressive symptoms, and quality of life. Measurements included advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), lipid peroxides (LOOH), -sulfhydryl (SH) groups, total radical trapping antioxidant parameter (TRAP), and paraoxonase (PON)1 activity in participants with CAP, with and without depression, as well as healthy controls (no depression, no CAP). Root canal LPS levels were positively associated with CAP, clinical depression, severity of depression (as measured with the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory) and O&NS biomarkers, especially NOx and TRAP. CAP-related depression was accompanied by increased levels of NOx, LOOH, AOPP, and TRAP. In CAP participants, there was a strong correlation ($r = 0.734$, $p < 0.001$) between root canal LPS and the HDRS score. There were significant and positive associations between CAP or root canal endotoxin with the vegetative and physio-somatic symptoms of the HDRS as well as a significant inverse association between root canal endotoxin and quality of life with strong effects on psychological, environmental, and social domains. It is concluded that increased root canal LPS accompanying CAP may cause depression and a lowered quality of life, which may be partly explained by activated O&NS pathways, especially NOx thereby enhancing hypernitrosylation and thus neuroprogressive processes. Dental health and "leaky teeth" may be intimately linked to the etiology and course of depression, while significantly impacting quality of life.

Research Article Dentistry· 8:4 January 2018 DOI: 10.4172/2161-1122.1000476

Impact of Endodontically Treated Teeth on Systemic Diseases

Lechner J, Von Baehr V

ABSTRACT

BACKGROUND:

This study compares the radiographic distribution of apical periodontitis (AP) in root- filled and endodontically treated teeth among healthy controls and patients with systemic diseases; the incidence of AP was almost twice as high in the latter group.

OBJECTIVE:

The question arises as to whether the biogenic amines (mercaptan/thioether/hydrogen sulfide) originating from endodontically treated teeth have systemic, subtoxic and immunological effects.

METHOD:

In order to determine this, local hydrogen sulfide measurements of endodontically treated teeth were combined with the laboratory serum analyses of modified proteins to assess the relationship of these compounds with type IV immune reactions.

RESULTS:

It was found that 42.5% of the group with systemic diseases showed immunological disturbance as a result of root-filled teeth. Furthermore, the presence of AP was almost three times higher than in the control group (17.2% versus 5.9%, respectively).

CONCLUSION:

In summary, the data demonstrates that local pathologies caused by endodontically treated teeth may increase immunological and systemic dysfunction.

3.1.3 General Reviews and Overviews

Int Endod J. 2000 Jan;33(1):1-18.

Root canal treatment and general health: a review of the literature.

Murray CA, Saunders WP.

ABSTRACT

The focal infection theory was prominent in the medical literature during the early 1900s and curtailed the progress of endodontics. This theory proposed that microorganisms, or their toxins, arising from a focus of circumscribed infection within a tissue could disseminate systemically, resulting in the initiation or exacerbation of systemic illness or the damage of a distant tissue site. For example, during the focal infection era rheumatoid arthritis (RA) was identified as having a close relationship with dental health. The theory was eventually discredited because there was only anecdotal evidence to support its claims and few scientifically controlled studies. There has been a renewed interest in the influence that foci of infection within the oral tissues may have on general health. Some current research suggests a possible relationship between dental health and cardiovascular disease and published case reports have cited dental sources as causes for several systemic illnesses. Improved laboratory procedures employing sophisticated molecular biological techniques and enhanced culturing techniques have allowed researchers to confirm that bacteria recovered from the peripheral blood during root canal treatment originated in the root canal. It has been suggested that the bacteraemia, or the associated bacterial endotoxins, subsequent to root canal treatment, may cause potential systemic complications. Further research is required, however, using current sampling and laboratory methods from scientifically controlled population groups to determine if a significant relationship between general health and periradicular infection exists.

Med Sci Monit. 2003 Dec;9(12):RA291-9.

The impact of periodontal infection on systemic diseases.

Amar S, Han X.

ABSTRACT

Systemic health is often closely linked to the state of the oral cavity: many systemic diseases and conditions have oral manifestations. Likewise, oral microbiological infections may also affect one's general health status. Indeed, animal and population-based studies now suggest that periodontal diseases may be linked with systemic diseases and conditions including cardiovascular diseases, diabetes, respiratory diseases, adverse pregnancy outcomes, and osteoporosis. Better understanding of this correlation will help both dental and medical professionals to determine the best approach to patient care. This review will focus on the current knowledge linking periodontal infections to a set of systemic diseases. While a number of interactions have been identified, additional research will be required to determine whether these associations are causal or coincidental, and to evaluate disease pathogenesis and potential therapeutic interventions. These findings place oral health in the perspective of systemic health, and they suggest that the dental and medical professions should develop even closer ties in the future.

Int J Cardiol. 2011 Apr 1;148(1):4-10. doi: 10.1016/j.ijcard.2010.08.011. Epub 2010 Sep 18.

Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature.

Cotti E, Dessì C, Piras A, Mercuro G.

ABSTRACT

Cardiovascular diseases (CVD) have a complex etiology determined by risk factors, which are in turn associated to a strong genetic component and to environmental factors. In the biological background for the development of CVD, low-grade chronic inflammation plays a role as a pathogenetic determinant of atherosclerosis. Dental infections have been associated with CVD. Periodontal disease is a chronic infection of the supporting tissues of the tooth that can lead to teeth loss. In recent years, a number of reports have demonstrated the possible relationship between periodontal disease and CVD. Apical periodontitis, on the other hand, is the late consequence of an endodontic infection, which is caused by the persistence of coronal caries and involves the root canal system of the tooth. Most of the time, it is a chronic infection. Some studies have found a correlation between a "composite status" of oral health (eg. caries, tooth loss, periodontal disease) and CVD, but only a few of them have addressed the association between apical periodontitis and CVD. This "state of the art" paper represents the first stage of an incoming study on the relationship between chronic endodontic infection and CVD.

J Endod. 2013 Oct;39(10):1205-17. doi: 10.1016/j.joen.2013.06.014. Epub 2013 Aug 16.

Can apical periodontitis modify systemic levels of inflammatory markers? A systematic review and meta-analysis.

Cotti E, Dessì C, Piras A, Mercuro G.

ABSTRACT

INTRODUCTION:

This systematic review and meta-analysis investigated evidence to support whether apical periodontitis (AP) can modify the systemic levels of inflammatory markers (IM) in humans.

METHODS:

The MEDLINE, Embase, Cochrane, and PubMed databases were searched between 1948 and 2012, with no language restriction. Additionally, the bibliography of all relevant articles and textbooks were manually searched. Based on inclusion and exclusion criteria, 2 reviewers independently rated the quality of each study based on the Newcastle-Ottawa Scale. The primary outcome variable for meta-analysis was determined by the serum levels of IMs in AP subjects versus healthy controls or in AP subjects before versus after treatment intervention.

RESULTS:

Among the 531 initially identified articles, 20 comprised the final analysis. Thirty-one different IMs were analyzed, with immunoglobulin (Ig) A, IgM, IgG, and C-reactive protein (CRP) being the most commonly investigated. CRP, interleukin (IL)-1, IL-2, IL-6, asymmetrical dimethylarginine, IgA, IgG, and IgM were shown to be increased in patients with AP compared with controls in most studies. Meta-analyses showed that serum levels of IgA ($P = .001$), IgG ($P = .04$), and IgM ($P < .00001$) were increased in humans with AP compared with healthy controls and serum levels of CRP, IgA, IgE, IgG, and IgM were not significantly different between patients with AP before and after treatment ($P > .05$).

CONCLUSIONS:

Available evidence is limited but consistent, suggesting that AP is associated with increased levels of CRP, IL-1, IL-2, IL-6, asymmetrical dimethylarginine, IgA, IgG, and IgM in humans. These findings suggest that AP may contribute to a systemic immune response not confined to the localized lesion, potentially leading to increased systemic inflammation.

Int Endod J. 2015 Oct;48(10):933-51. doi: 10.1111/iej.12507. Epub 2015 Aug 3.

Endodontic medicine: connections between apical periodontitis and systemic diseases.

Segura-Egea JJ, Martín-González J, Castellanos-Cosano L.

ABSTRACT

The prevalence of apical periodontitis (AP) in Europe has been reported to affect 61% of individuals and 14% of teeth, and increase with age. Likewise, the prevalence of root canal treatment (RCT) in Europe is estimated to be around 30-50% of individuals and 2-9% of teeth with radiographic evidence of chronic persistent AP in 30-65% of root filled teeth (RFT). AP is not only a local phenomenon and for some time the medical and dental scientific community have analysed the possible connection between apical periodontits and systemic health. Endodontic medicine has developed, with increasing numbers of reports describing the association between periapical inflammation and systemic diseases. The results of studies carried out both in animal models and humans are not conclusive, but suggest an association between endodontic variables, that is AP and RCT, and diabetes mellitus (DM), tobacco smoking, coronary heart disease and other systemic diseases. Several studies have reported a higher prevalence of periapical lesions, delayed periapical repair, greater size of osteolityc lesions, greater likelihood of asymptomatic infections and poorer prognosis for RFT in diabetic patients. On the other hand, recent studies have found that a poorer periapical status correlates with higher HbA1c levels and poor glycaemic control in type 2 diabetic patients. However, there is no scientific evidence supporting a causal effect of periapical inflammation on diabetes metabolic control. The possible association between smoking habits and endodontic infection has also been investigated, with controversial results. The aim of this paper was to review the literature on the association between endodontic variables and systemic health (especially DM and smoking habits).

J Endod. 2016 Oct;42(10):1427-34. doi: 10.1016/j.joen.2016.07.007. Epub 2016 Aug 31.

Association between Systemic Diseases and Apical Periodontitis.

Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF.

ABSTRACT

INTRODUCTION:

To date, the relationships between systemic diseases and periapical microbial infection remain unknown. Thus the purpose of this systematic review was to evaluate the relationship between host modifying factors and their association with endodontic pathosis.

METHODS: :

Two reviewers independently conducted a comprehensive literature search. The MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliographies of all relevant articles and textbooks were manually searched. There was no disagreement between the 2 reviewers.

RESULTS:

Sixteen articles were identified and included. The overall quality of the studies and the risk of bias were rated to be moderate. Only 3 studies demonstrated a low level of bias.

CONCLUSIONS:

The results of this review suggest that there may be a moderate risk and correlation between some systemic diseases and endodontic pathosis. More prospective and longitudinal research in this area is warranted to determine greater specificity in these possible interactions to potentially decrease or minimize the effects of systemic disease on the formation of apical periodontitis.

J Endod. 2017 Apr;43(4):514-519. doi: 10.1016/j.joen.2016.11.008. Epub 2017 Feb 9.

Association between Systemic Diseases and Endodontic Outcome: A Systematic Review.

Aminoshariae A, Kulild JC, Mickel A, Fouad AF.

ABSTRACT

INTRODUCTION:

To date, the relationships between systemic diseases and endodontic treatment outcomes remain poorly studied. Thus, the purpose of this systematic review was to evaluate the relationship between host-modifying factors and their association with endodontic outcomes.

METHODS:

Two reviewers independently conducted a comprehensive literature search. The MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliographies and gray literature of all relevant articles and textbooks were manually searched. There was no disagreement between the 2 reviewers.

RESULTS:

Sixteen articles met the inclusion criteria with moderate to high risk of bias. There was no article with low risk of bias. Available scientific evidence remains inconclusive as to whether diabetes and/or cardiovascular disease(s) may be associated with endodontic outcomes. Human immunodeficiency virus and oral bisphosphonate did not appear to be associated with endodontic outcomes.

CONCLUSIONS:

Although additional well-designed longitudinal clinical studies are needed, the results of this systematic review suggest that some systemic diseases may be correlated with endodontic outcomes.

Int Endod J. 2017 Sep;50(9):847-859. doi: 10.1111/iej.12710. Epub 2016 Nov 19.

Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature.

Berlin-Broner Y, Febbraio M, Levin L.

ABSTRACT

A systematic review was conducted to assess the association between apical periodontitis (AP) and cardiovascular disease (CVD). Studies published from the earliest date available until September 2015 were retrieved from the Medline, PubMed and Embase databases. The included studies reported the results from observational studies and assessed the link between AP and CVD as confirmed by one of the following criteria: diagnosed coronary artery disease, angina pectoris, acute myocardial infarction, stroke or mortality caused by cardiac pathology. The study characteristics were abstracted by independent researchers following the PRISMA standard protocol. NOS criteria were used to rate the quality of the studies, and the GRADE was used for level of evidence evaluation. Nineteen epidemiological studies fulfilled the predetermined inclusion criteria: 10 case-control studies, five cross-sectional studies and four cohort studies. There was considerable heterogeneity amongst the included studies in terms of their study design, population, outcomes of interest and AP evaluation methods. Considering the limited availability and the heterogeneity amongst the studies, meta-analysis was not attempted. Thirteen of the 19 included studies found a significant positive association between apical periodontitis and cardiovascular disease, although in two of them, the significance was present only in univariate analysis. Five studies failed to reveal positive significance, and one study reported a negative association. In conclusion, although most of the published studies found a positive association between apical periodontitis and cardiovascular disease, the quality of the existing evidence is moderate-low and a causal relationship cannot be established.

3.2 Metals/Amalgam

3.2.1 Basic Research

J Prosthet Dent. 1987 Dec;58(6):704-7.

Correlation of dental amalgam with mercury in brain tissue.

Eggleston DW, Nylander M.

ABSTRACT

Data from this project demonstrate a positive correlation between the number of occlusal surfaces of dental amalgam and mercury levels in the brain (p less than .0025 in white matter). This is indirect evidence suggesting that mercury from dental amalgam fillings may contribute to the body burden of mercury in the brain. The toxic levels of mercury in human tissues have not been sufficiently investigated and the amount of mercury in human brain tissue from dental amalgam may or may not be clinically significant. Nevertheless, dental amalgam exposure should be considered in monitoring sources of mercury accumulation in human brain tissue.

J Prosthet Dent. 1987 Dec;58(6):704-7.

Mercury concentrations in the human brain and kidneys in relation to exposure from dental amalgam fillings.

Nylander M, Friberg L, Lind B.

ABSTRACT

Samples from the central nervous system (occipital lobe cortex, cerebellar cortex and ganglia semilunare) and kidney cortex were collected from autopsies and analysed for total mercury content using neutron activation analyses. Results from 34 individuals showed a statistically significant regression between the number of tooth surfaces containing amalgam and concentration of mercury in the occipital lobe cortex (mean 10.9, range 2.4-28.7 ng Hg/g wet weight). The regression equation y = 7.2 + 0.24x has a 95% confidence interval for the regression coefficient of 0.11-0.37. In 9 cases with suspected alcohol abuse mercury levels in the occipital lobe were, in most cases, somewhat lower than expected based on the regression line. The observations may be explained by an inhibition of oxidation of mercury vapour. The regression between amalgams and mercury levels remained after exclusion of these cases. The kidney cortex from 7 amalgam carriers (mean 433, range 48-810 ng Hg/g wet weight) showed on average a significantly higher mercury level than those of 5 amalgam-free individuals (mean 49, range 21-105 ng Hg/g wet weight). In 6 cases analysis of both inorganic and total mercury was carried out. A high proportion (mean 77% SD 17%) of inorganic mercury was found. It is concluded that the cause of the association between amalgam load and accumulation of mercury in tissues is the release of mercury vapour from amalgam fillings.

FASEB J. 1995 Apr;9(7):504-8.

Mercury exposure from "silver" tooth fillings: emerging evidence questions a traditional dental paradigm.

Lorscheider FL, Vimy MJ, Summers AO.

ABSTRACT

For more than 160 years dentistry has used silver amalgam, which contains approximately 50% Hg metal, as the preferred tooth filling material. During the past decade medical research has demonstrated that this Hg is continuously released as vapor into mouth air; then it is inhaled, absorbed into body tissues, oxidized to ionic Hg, and finally covalently bound to cell proteins. Animal and human experiments demonstrate that the uptake, tissue distribution, and excretion of amalgam Hg is significant, and that dental amalgam is the major contributing source to Hg body burden in humans. Current research on the pathophysiological effects of amalgam Hg has focused upon the immune system, renal system, oral and intestinal bacteria, reproductive system, and the central nervous system. Research evidence does not support the notion of amalgam safety.

Clin Neuropathol. 1996 May-Jun;15(3):139-44.

Demonstration of mercury in the human brain and other organs 17 years after metallic mercury exposure.

Opitz H, Schweinsberg F, Grossmann T, Wendt-Gallitelli MF, Meyermann R.

ABSTRACT

A male subject became exposed to metallic mercury vapor at work in 1973. He excreted 1,850 mg Hg/l urine initially. Controls of urine mercury excretion after D-penicillamine administration led to the assumption of a total body clearance of mercury latest since 1976. Subsequently he developed an organic psychosyndrome without detectable signs of classical mercurialism. He never returned to work again and died of lung cancer in 1990. In different organs (brain, kidney, and lung) which were sampled at autopsy elevated levels of mercury were documented by atomic absorption analysis. Histological examination of the tissue by the Danscher and Schroder method, which is specific for mercury, showed a highly positive staining in the majority of nerve cells and cells of other organs. Ultrastructurally mercury could be demonstrated by elemental x-ray analysis within lipofuscin deposits. The lipofuscin content was increased in the mercury positive nerve cells as demonstrated by a strong positive autofluorescence.

Arch Environ Health. 1996 May-Jun;51(3):234-41.

Total and inorganic mercury in breast milk in relation to fish consumption and amalgam in lactating women.

Oskarsson A, Schültz A, Skerfving S, Hallén IP, Ohlin B, Lagerkvist BJ.

ABSTRACT

Total mercury concentrations (mean +/- standard deviation) in breast milk, blood, and hair samples collected 6 wk after delivery from 30 women who lived in the north of Sweden were 0.6 +/- 0.4 ng/g (3.0 +/- 2.0 nmol/kg), 2.3 +/- 1.0 ng/g (11.5 +/- 5.0 nmol/kg), and 0.28 +/- 0.16 microg/g (1.40 +/- 0.80 micromol/kg), respectively. In milk, an average of 51% of total mercury was in the form of inorganic mercury, whereas in blood an average of only 26% was present in the inorganic form. Total and inorganic mercury levels in blood (r = .55, p = .003; and r = .46, p = .01 6; respectively) and milk (r = .47, p = .01; and r = .45, p = .018; respectively) were correlated with the number of amalgam fillings. The concentrations of total mercury and organic mercury (calculated by subtraction of inorganic mercury from total mercury) in blood (r = .59, p = .0006, and r = .56, p = .001; respectively) and total mercury in hair (r = .52, p = .006) were correlated with the estimated recent exposure to methylmercury via intake of fish. There was no significant between the milk levels of mercury in any chemical form and the estimated methylmercury intake. A significant correlation was found between levels of total mercury in blood and in milk (r = .66, p = .0001), with milk levels being an average of 27% of the blood levels. There was an association between inorganic mercury in blood and milk (r = .96, p < .0001); the average level of inorganic mercury in milk was 55% of the level of inorganic mercury in blood. No significant correlations were found between the levels of any form of mercury in milk and the levels of organic mercury in blood. The results indicated that there was an efficient transfer of inorganic mercury from blood to milk and that, in this population, mercury from amalgam fillings was the main source of mercury in milk. Exposure of the infant to mercury from breast milk was calculated to range up to 0.3 microg/kg x d, of which approximately one-half was inorganic mercury. This exposure, however, corresponds to approximately one-half the tolerable daily intake for adults recommended by the World Health Organization. We concluded that efforts should be made to decrease mercury burden in fertile women.

J Trace Elem Med Biol. 1998 Mar;12(1):23-7.

Mercury in human colostrum and early breast milk. Its dependence on dental amalgam and other factors.

Drasch G, Aigner S, Roider G, Staiger F, Lipowsky G.

ABSTRACT

The mercury concentration in 70 breast milk samples (Hg-M) from 46 mothers, collected within the first 7 days after delivery, was determined by cold vapour atomic absorption spectrometry. For comparison, 9 formula milk samples (reconstituted with Hg-free water) were investigated. The Hg-M in the human milk samples ranged from < 0.2 to 6.86 micrograms/L (median 0.37), in the formula milk samples from 0.4 to 2.5 micrograms/L (median 0.76). The Hg-M in the breast milk samples correlates positively with the number of maternal teeth with dental amalgam. The mean Hg-M of amalgam-free mothers was < 0.2 microgram/L, while milk from mothers with 1-4 amalgam fillings contained 0.57 microgram/L, with 5-7 fillings 0.50 microgram/L and with more than 7 fillings 2.11 micrograms/L. Hg-M correlated negatively to the day after delivery. Frequency of fish consumption tends to influence Hg-M positively, while the age of the mother shows no significant correlation. In the first 2 to 3 days after delivery some colostrum samples with Hg-M higher than in formula milk were found. Later on, the Hg-concentration in the breast milk was equal or even lower to that in formula milk. The higher Hg burden of infants' tissues from mothers with dental amalgam, as reported previously, must be explained (1) by a prenatal transfer of Hg from the mother's fillings through the placenta to the fetus, followed by a redistribution of this Hg in the body of the newborn, and (2) an additional burden via breast milk. Nevertheless, the comparison of Hg-M in breast and formula milk, the relatively moderate Hg burden in both kinds of milk, and the multiple manifest advantages of breast feeding speak against any limitation of nursing, even for mothers with a large number of dental amalgam fillings.

J Dent Res. 1998 Mar;77(3):461-71.

Mercury concentrations in urine and whole blood associated with amalgam exposure in a US military population.

Kingman A, Albertini T, Brown LJ.

ABSTRACT

Minute amounts of mercury vapor are released from dental amalgams. Since mercury vapor is known to be associated with adverse health effects from occupationally exposed persons, questions regarding the margin of safety for exposure to mercury vapor in the general population continue to be raised. To address this issue, one needs information regarding exposure to mercury vapor from dental amalgam fillings and its possible consequences for health in the general population. The NIDR Amalgam Study is designed to obtain precise information on amalgam exposure and health outcomes for a non-occupationally-exposed population of US adults. One hypothesis was that in a generally healthy population a significant association between amalgam exposure and Hg levels in urine and/or whole blood could be detected. The cohort investigated was an adult military population of 1127 healthy males. Their average age was 52.8 years, and their ages varied from 40 to 78 years. Ninety-five percent of the study participants were white males, and slightly over 50% had some college education. Five percent were edentulous. The dentate participants, on average, had 25 natural teeth, 36.9 decayed or filled surfaces (DFS), and 19.9 surfaces exposed to amalgam, with amalgam exposure varying from 0 to 66 surfaces. Their average total and inorganic urinary mercury concentrations were 3.09 microg/L and 2.88 microg/L. The average whole-blood total and inorganic mercury concentrations were 2.55 microg/L and 0.54 microg/L. Significant correlations were detected between amalgam exposure and the total ($r = 0.34$, $p < 0.001$) and inorganic 0.34 ($r = 0.34$, $p < 0.001$) urinary mercury concentrations on the original scale. Stronger correlations were found for total ($r = 0.44$, $p < 0.001$) and inorganic ($r = 0.41$, $p < 0.001$) urinary Hg on the log scale, as well as for creatinine-corrected total ($r = 0.43$, $p < 0.001$) and inorganic ($r = 0.43$, $p < 0.001$) urine concentrations. In whole blood, statistically significant, but biologically weak, correlations were detected for total ($r = 0.09$, $p = 0.005$) and inorganic ($r = 0.15$, $p < 0.001$) Hg concentrations, respectively. Based on these cross-sectional data, it is estimated that, on average, each ten-surface increase in amalgam exposure is associated with an increase of 1 microg/L mercury in urine concentration.

Environ Health Perspect. 1999 Nov;107(11):867-71.

Cadmium, mercury, and lead in kidney cortex of the general Swedish population: a study of biopsies from living kidney donors.

Barregård L, Svalander C, Schütz A, Westberg G, Sällsten G, Blohmé I, Mölne J, Attman PO, Haglind P.

ABSTRACT

Cadmium, mercury, and lead concentrations were determined in deep-frozen kidney cortex biopsies taken from 36 living, healthy Swedish kidney donors (18 males and 18 females), who were 30-71 (mean 53) years of age. Information about occupation, smoking, the presence of dental amalgam, and fish consumption could be obtained for 27 of the donors. The samples (median dry weight 0.74 mg) were analyzed using inductively coupled plasma mass spectrometry, and the results were transformed to wet-weight concentrations. The median kidney Cd was 17 micrograms/g (95% confidence interval, 14-23 micrograms/g), which was similar in males and females. In 10 active smokers, the median kidney Cd was 24 micrograms/g, and in 12 who never smoked, it was 17 micrograms/g. The median kidney Hg was 0.29 micrograms/g, with higher levels in females (median 0.54 micrograms/g) than in males (median 0.16 micrograms/g). Subjects with amalgam fillings had higher kidney Hg (median 0.47 micrograms/g, $n = 20$) than those without dental amalgam (median 0.15 micrograms;g/g, $n = 6$), but kidney Hg was below the detection limit in some samples. Nearly half of the samples had kidney Pb below the detection limit. The median kidney Pb was estimated as 0. 14 micrograms/g. This is the first study of heavy metals in kidney cortex of living, healthy subjects, and the results are relatively similar to those of a few previous autopsy studies, indicating that results from autopsy cases are not seriously biased in relation to kidney metal concentrations in the general population. Cd concentrations in those who never smoked were relatively high, indicating considerable Cd intake from the diet in Sweden. The effect of dental amalgam on kidney Hg was as expected, although the reason for the difference in Hg levels between males and females is unclear.

Neuro Endocrinol Lett. 1999;20(6):351-364.

The role of metals in autoimmunity and the link to neuroendocrinology.

Stejskal J, Stejskal VD.

ABSTRACT

Current available literature indicates a risk for metal-induced autoimmunity in man. Metal pathology may be due to toxic or allergic mechanisms where both may play a role. The main factors decisive for disease induced by metals are exposure and genetics which determine the individual detoxifying capacity and sensitivity to metals. This paper reviews the possible mechanisms which may play a role in metal-induced autoimmunity with the emphasis on multiple sclerosis (MS), rheumatoid arthritis (RA) and amyotrophic lateral sclerosis (ALS). We also discuss the role of inflammation-induced changes in the hypothalamus-pituitary-adrenal (HPA) axis as a possible explanation of fatigue, depression and other psychosomatic symptoms observed in these diseases. The increased knowledge about individual sensitivity based on genotype and phenotype variability together with the use of biomarkers for the diagnosis of this individual susceptibility seems to be the key in elucidation of the operating mechanisms. Since metal-induced sensitization may be induced by chronic low-dose exposure, the conventional toxicological approach comparing concentrations of metals in brain autopsies, organ biopsies and body fluids in patients and controls may not provide answers regarding the metal-pathology connection. To address this issue, longitudinal studies of metal-sensitive patients are preferable to the traditional case-control studies.

Environ Health Perspect. 2002 May;110(5):523-6.

Inorganic mercury and methylmercury in placentas of Swedish women.

Ask K, Akesson A, Berglund M, Vahter M.

ABSTRACT

We determined levels of inorganic mercury (I-Hg) and methylmercury in placentas from 119 Swedish women, not selected with respect to high exposure of mercury. Our objective was to relate placental Hg species with maternal and fetal blood concentrations and to evaluate possible associations with selenium. We performed the analyses using automated alkaline solubilization/reduction and cold-vapor atomic fluorescence spectrophotometry. I-Hg levels in placenta increased with an increasing number of maternal dental amalgam fillings ($p < 0.001$). Despite placental accumulation (median, 1.3 microg/kg; range, 0.18-6.7 microg/kg wet weight), a substantial fraction of maternal blood I-Hg, probably as Hg(0), reached the fetus. Although MeHg transferred easily to the fetus, it also accumulated in the placenta. On average, 60% of placental Hg was in the form of MeHg. The median concentration was 1.8 microg/kg (range, 0-6.2 microg/kg wet weight), more than twice the maternal blood concentration. We found significant associations between MeHg and selenium in both maternal and umbilical cord blood but not in the placenta. The associations were particularly obvious in freshwater fish consumers, probably reflecting that fish is a source of both MeHg and selenium. We found no correlations between I-Hg and selenium. This study increases the understanding of Hg, in its different forms, in human placenta and how they are related to maternal and fetal exposure.

Int J Hyg Environ Health. 2002 Apr;205(3):205-11.

Determination of mercury in blood, urine and saliva for the biological monitoring of an exposure from amalgam fillings in a group with self-reported adverse health effects.

Zimmer H, Ludwig H, Bader M, Bailer J, Eickholz P, Staehle HJ, Triebig G.

ABSTRACT

It has been argued that the release of mercury from amalgam fillings is of toxicological relevance. The aim of the study was to determine the internal mercury exposure of two groups differing in their attitude towards possible health hazards by mercury from amalgam fillings. It was to be examined if the two groups differ with regard to the mercury concentration in different biological matrices and to compare the results with current reference values. Blood, urine and saliva samples were analyzed from 40 female subjects who claimed to suffer from serious health damage due to amalgam fillings ("amalgam sensitive subjects"). 43 female control subjects did not claim any association ("amalgam non-sensitive controls"). Mercury was determined by means of cold vapour atomic absorption spectrometry. Number and surfaces of amalgam fillings were determined by dentists for each subject. Median (range) mercury levels in blood were 2.35 (0.25-13.40) micrograms/l for "amalgam sensitive subjects" and 2.40 (0.25-10.50) micrograms/l for "amalgam non-sensitive controls". In urine, the median mercury concentrations were 1.55 (0.06-14.70) micrograms/l and 1.88 (0.20-8.43) micrograms/g creatinine respectively. No significant differences could be found between the two groups. Mercury levels in blood and urine of the examined subjects were within the range of background levels in the general population including persons with amalgam fillings. Stimulated saliva contained 76.4 (6.7-406.0) micrograms mercury/l in "amalgam sensitive subjects" and 57.0 (2.8-559.0) micrograms mercury/l in controls (not significant). Mercury levels in saliva did not correlate with the concentrations in blood and urine, but merely with the number of amalgam fillings or of the filling surfaces. Mercury in saliva is therefore not recommended for a biological monitoring.

Neuro Endocrinol Lett. 2003 Feb-Apr;24(1-2):65-7.

Dental amalgam as one of the risk factors in autoimmune diseases.

Barregård L, Svalander C, Schütz A, Westberg G, Sällsten G, Blohmé I, Mölne J, Attman PO, Haglind P.

ABSTRACT

BACKGROUND:

Experimental and clinical data published recently show that dental amalgam can give rise to undesirable immunological responses in susceptible individuals. In genetically susceptible strains of experimental animals, mercury and silver can induce autoimmune responses. Sera of patients sensitive to mercury were found to have a higher incidence of autoantibodies relative to controls.

OBJECTIVE:

The aim of this study was to determine possible presence of antinuclear SSB/La autoantibodies after the in vitro stimulation of peripheral blood lymphocytes with HgCl2.

METHODS:

Lymphocytes were obtained from patients with autoimmune thyroiditis and increased response to mercury in vitro. Mononuclear cells were cultivated for 6 days with 100 microl HgCl2 solution or with pure medium and the levels of antinuclear autoantibodies SSB/La were assayed by a commercial SSB/La ELISA kit.

RESULTS:

Increased production of SSB/La autoantibodies in the media following stimulation of peripheral blood lymphocytes with HgCl2 was found in all cases. Using the Student's paired test, the results were significant on the p=0.05 significance level.

CONCLUSION:

Results imply that, in some patients with thyroiditis, mercury from dental amalgam can stimulate the production of antinuclear antibodies. Dental amalgam may be a risk factor in some patients with autoimmune disease.

Sci Total Environ. 2003 Jan 1;301(1-3):43-50.

Influence of amalgam fillings on Hg levels and total antioxidant activity in plasma of healthy donors.

Pizzichini M, Fonzi M, Giannerini F, Mencarelli M, Gasparoni A, Rocchi G, Kaitsas V, Fonzi L.

ABSTRACT

In order to evaluate the influence of specific factors on mercury (P-Hg) levels and antioxidant power (P-FRAP) in human plasma, 26 healthy donors were examined by a dentist, their plasma analyzed for Hg by atomic absorption spectrometry and for total antioxidant activity by FRAP method. Hg plasma concentration was found to be correlated with the number of amalgam fillings, suggesting that Hg released from fillings is a source of Hg in non-occupational exposed subjects. P-FRAP correlated negatively with P-Hg suggesting a pro-oxidant role of the Hg released from amalgam fillings. Though age by itself was not significantly correlated with P-FRAP, when considered together with P-Hg in multivariate analysis, it was found to be a major related cofactor. Multivariate analysis showed no influence of fish consumption or cigarette smoking on P-FRAP.

Toxicol Lett. 2003 Apr 11;140-141:75-81.

Interaction of metal salts with cytoskeletal motor protein systems.

Thier R, Bonacker D, Stoiber T, Böhm KJ, Wang M, Unger E, Bolt HM, Degen G.

ABSTRACT

Interactions of chemicals with the microtubular network of cells may lead to genotoxicity. Micronuclei (MN) might be caused by interaction of metals with tubulin and/or kinesin. The genotoxic effects of inorganic lead and mercury salts were studied using the MN assay and the CREST analysis in V79 Chinese hamster fibroblasts. Effects on the functional activity of motor protein systems were examined by measurement of tubulin assembly and kinesin-driven motility. Lead and mercury salts induced MN dose-dependently. The no-effect-concentration for MN induction was 1.1 microM PbCl(2), 0.05 microM Pb(OAc)(2) and 0.01 microM HgCl(2). The in vitro results obtained for PbCl(2) correspond to reported MN induction in workers occupationally exposed to lead, starting at 1.2 microM Hg(II) (Vaglenov et al., 2001, Environ. Health Perspect. 109, 295-298). The CREST Analysis indicate aneugenic effects of Pb(II) and aneugenic and additionally clastogenic effects of Hg(II). Lead (chloride, acetate, and nitrate) and mercury (chloride and nitrate) interfered dose-dependently with tubulin assembly in vitro. The no-effect-concentration for lead salts in this assay was 10 microM. Inhibition of tubulin assembly by mercury started at 2 microM. The gliding velocity of microtubules along immobilised kinesin molecules was affected by 25 microM Pb(NO(3))(2) and 0.1 microM HgCl(2) in a dose-dependent manner. Our data support the hypothesis that lead and mercury genotoxicity may result, at least in part, via disturbance of chromosome segregation via interaction with cytoskeletal proteins.

Environ Res. 2004 Mar;94(3):283-90.

Childhood urine mercury excretion: dental amalgam and fish consumption as exposure factors.

Levy M, Schwartz S, Dijak M, Weber JP, Tardif R, Rouah F.

ABSTRACT

The authors investigated the effect of amalgam fillings and fish consumption on urine mercury level (UHg), in children aged 4-8 years old inclusive. Using a sample of 60 children, we found that children with amalgam fillings had significantly higher UHg levels than children without amalgams (geometric mean=1.412microg Hg/g versus 0.436 microg Hg/g, respectively, P = 0.0001). Subjects with reported higher fish consumption also had significantly higher UHgs (P = 0.004). Univariate analyses provide evidence of an association between elevated UHg level and young age (P = 0.009), short height (P = 0.024), and low weight (P = 0.049) in children with amalgam chewing surfaces. We also found a negative correlation between urine mercury and age (-0.378), height (-0.418), and weight (-0.391). A multiple logistic regression model shows that the presence of amalgam fillings leads to increased odds of high UHg in children (OR=47.18), even after adjusting for high fish consumption (OR=8.66) and height (OR=11.36).

Mutat Res. 2004 Oct 10;563(2):97-106.

Disturbed microtubule function and induction of micronuclei by chelate complexes of mercury(II).

Stoiber T, Bonacker D, Böhm KJ, Bolt HM, Thier R, Degen GH, Unger E.

ABSTRACT

Interactions of mercury(II) with the microtubule network of cells may lead to genotoxicity. Complexation of mercury(II) with EDTA is currently being discussed for its employment in detoxification processes of polluted sites. This prompted us to re-evaluate the effects of such complexing agents on certain aspects of mercury toxicity, by examining the influences of mercury(II) complexes on tubulin assembly and kinesin-driven motility of microtubules. The genotoxic effects were studied using the micronucleus assay in V79 Chinese hamster fibroblasts. Mercury(II) complexes with EDTA and related chelators interfered dose-dependently with tubulin assembly and microtubule motility in vitro. The no-effect-concentration for assembly inhibition was 1 microM of complexed Hg(II), and for inhibition of motility it was 0.05 microM, respectively. These findings are supported on the genotoxicity level by the results of the micronucleus assay, with micronuclei being induced dose-dependently starting at concentrations of about 0.05 microM of complexed Hg(II). Generally, the no-effect-concentrations for complexed mercury(II) found in the cell-free systems and in cellular assays (including the micronucleus test) were identical with or similar to results for mercury tested in the absence of chelators. This indicates that mercury(II) has a much higher affinity to sulfhydryls of cytoskeletal proteins than to this type of complexing agents. Therefore, the suitability of EDTA and related compounds for remediation of environmental mercury contamination or for other detoxification purposes involving mercury has to be questioned.

Am J Forensic Med Pathol. 2006 Mar;27(1):42-5.

Dental amalgam and mercury levels in autopsy tissues: food for thought.

Guzzi G, Grandi M, Cattaneo C, Calza S, Minoia C, Ronchi A, Gatti A, Severi G.

ABSTRACT

Eighteen cadavers from routine autopsy casework were subject to a study of tissue levels of total mercury in brain, thyroid, and kidney samples by atomic absorption. On these same cadavers, all dental amalgam fillings (the most important source of inorganic mercury exposure in the general population, according to the World Health Organization (WHO) were charted. Total mercury levels were significantly higher in subjects with a greater number of occlusal amalgam surfaces (>12) compared with those with fewer occlusal amalgams (0-3) in all types of tissue (all P < or = 0.04). Mercury levels were significantly higher in brain tissues compared with thyroid and kidney tissues in subjects with more than 12 occlusal amalgam fillings (all P < or = 0.01) but not in subjects with 3 or less occlusal amalgams (all P > or = 0.07).

Neuro Endocrinol Lett. 2006 Dec;27 Suppl 1:61-8.

In vivo effects of dental casting alloys.

Venclíková Z, Benada O, Bártová J, Joska L, Mrklas L, Procházková J, Stejskal V, Podzimek S.

ABSTRACT

OBJECTIVE:

Corrosion products of different metallic alloys used in prosthetic dentistry often cause the development of a bluish-grey pigmentation of gingiva and oral mucosa. The aim of this study was to determine the content of metals in metallic pigmentations and evaluate the immune response to metals found in the oral cavity.

MATERIAL AND METHODS:

The local tissue reactions were investigated clinically by electron microscopy and by energy dispersive x-ray microanalysis. An extensive anamnesis of the patients was recorded as well as earlier contacts with health care institutions. The immunological response to metallic components of dental alloys was evaluated in 34 patients by MELISA, a modified test for lymphocyte proliferation. In addition, cytokines in culture media were determined in 10 persons by the Human Inflammation Antibody Array.

RESULTS:

Dense particles containing metals were found in the matrix among collagen fibrils and in close proximity of the lamina basalis of the gingival epithelium. Particles were also localized intracellularly in fibroblasts, macrophages, and endothelial cells. Metallic depositions consisted predominantly of silver accompanied by selenium and sulphur. Twenty five out of 34 patients revealed high lymphocyte reactivity (positive MELISA test) to one or more metal components of dental restorations. A correlation between the positivity in MELISA test and number of dental alloys in the oral cavity was also found. Twenty MELISA positive patients suffered from serious health problems (various allergies, autoimmune diseases, Parkinson's syndrome etc.). Nickel and inorganic mercury were the most common sensitizers in vitro. The cytokine assay revealed that mercury chloride activated predominantly TH2 lymphocytes, while nickel chloride activated mainly TH1 lymphocytes.

CONCLUSIONS:

Metallic pigmentations in the oral cavity demonstrate a corrosion process and may pose a risk in immunologically susceptible patients.

Dent Mater. 2007 Oct;23(10):1256-61. Epub 2006 Dec 20.

Corrosion by galvanic coupling between amalgam and different chromium-based alloys.

Ciszewski A, Baraniak M, Urbanek-Brychczyńska M.

ABSTRACT

OBJECTIVES:

In recent years there has been an increase in the use of dental casting alloys in prosthodontic treatment. Many patients have metals or alloys, as well as amalgam fillings, in their mouth, and will have them for many years. The aim of this study was to evaluate and compare, in vitro, the galvanic corrosion behavior of chromium-cobalt alloy (Remanium GM 380) and chromium-nickel alloy (Remanium CS) when bound together or coupled with silver-based amalgam (Amalcap plus).

METHODS:

An electrochemical characterization of the alloys was performed by potentiostatic and potentiodynamic methods, i.e. the open circuit potential (OCP), the corrosion potential (E(CORR)), corrosion current density (i(CORR)) and corrosion resistance (R(P)). The electromotive force (EMF) of the bimetallic cells was also tested. Electroanalytical techniques were used to estimate the release of any respective element from the dental alloys under study into the artificial saliva solution.

RESULTS:

It was found that a bimetallic cell consisting of Remanium CS and Remanium GM 380 alloys has a very low EMF (a few mV) and is not a potential source of galvanic currents in the oral cavity. However, galvanic cells prepared from Amalcap plus and Remanium CS or Remanium GM 380 showed a much greater EMF: 104 and 109mV, respectively. This clearly indicates that in these latter cases it is possible to expect some metal ions in the saliva solution as a result of the work of galvanic currents. It was found, by adsorptive stripping voltammetry analysis, that nickel or cobalt, depending on the alloy used, appeared in the saliva solution and increased in concentration over time.

SIGNIFICANCE:

The results indicate that the correct design and use of dental alloys are important when determining the appropriate treatment for a specific patient.

Biochem Biophys Res Commun. 2008 Jul 25;372(2):341-5. doi: 10.1016/j.bbrc.2008.05.052. Epub 2008 May 21.

Heavy metal ions are potent inhibitors of protein folding.

Sharma SK, Goloubinoff P, Christen P.

ABSTRACT

Environmental and occupational exposure to heavy metals such as cadmium, mercury and lead results in severe health hazards including prenatal and developmental defects. The deleterious effects of heavy metal ions have hitherto been attributed to their interactions with specific, particularly susceptible native proteins. Here, we report an as yet undescribed mode of heavy metal toxicity. Cd2+, Hg2+ and Pb2+ proved to inhibit very efficiently the spontaneous refolding of chemically denatured proteins by forming high-affinity multidentate complexes with thiol and other functional groups (IC(50) in the nanomolar range). With similar efficacy, the heavy metal ions inhibited the chaperone-assisted refolding of chemically denatured and heat-denatured proteins. Thus, the toxic effects of heavy metal ions may result as well from their interaction with the more readily accessible functional groups of proteins in nascent and other non-native form. The toxic scope of heavy metals seems to be substantially larger than assumed so far.

Met Ions Life Sci. 2011;8:157-85.

Metal ions affecting the immune system.

Lehmann I, Sack U, Lehmann J.

ABSTRACT

Certain heavy metals have been reported to seriously affect the immune system potentially resulting in a broad range of harmful health effects. Reported alterations in immune cell function include a variety of affected mechanisms. Thereby, depending on the particular metal, its concentration, route and duration of exposure, and biologic availability, the net outcome may be either immunosuppression or stimulation of immune cell activity. Since the key importance of the immune system is protection of the host against pathogenic agents, an impaired immune competence inevitably increases the susceptibility to invading pathogens. However, being aware that the immune system represents a sensitively regulated network of different cells, tissues, and soluble mediators it has to be stated that any form of dys-regulation may result in adverse health effects with overstimulation being as harmful as inhibition of functional activity. Chronic-inflammatory reactions, cancer development, hypersensitivity, allergic and autoimmune diseases are known consequences of persisting overstimulation. All these manifestations were already found to be related with heavy metal exposure.

Curr Opin Immunol. 2016 Oct;42:25-30. doi: 10.1016/j.coi.2016.05.001. Epub 2016 May 23.

Interplay of innate and adaptive immunity in metal-induced hypersensitivity.

McKee AS, Fontenot AP.

ABSTRACT

Metal-induced hypersensitivity is driven by T cell sensitization to metal ions. Recent advances in our understanding of the complex interactions between innate and adaptive immunity have expanded our knowledge of the pathogenesis of these diseases. Metals activate the innate immune system through direct binding to pathogen recognition receptors, activation of the inflammasome, or the induction of cellular death and release of alarmins. Certain metals can serve as adjuvants, promoting dendritic cell activation and migration as well as antigen presentation to metal-specific T cells. These T cells can recognize metals as haptens or as altered MHC-peptide complexes. The ability of metals to create these neoantigens emphasizes the similarity between metal-induced hypersensitivity and autoimmunity.

Biometals. 2017 Apr;30(2):277-283. doi: 10.1007/s10534-017-0004-3. Epub 2017 Feb 20.

Increased mercury emissions from modern dental amalgams.

Bengtsson UG, Hylander LD.

ABSTRACT

All types of dental amalgams contain mercury, which partly is emitted as mercury vapor. All types of dental amalgams corrode after being placed in the oral cavity. Modern high copper amalgams exhibit two new traits of increased instability. Firstly, when subjected to wear/polishing, droplets rich in mercury are formed on the surface, showing that mercury is not being strongly bonded to the base or alloy metals. Secondly, high copper amalgams emit substantially larger amounts of mercury vapor than the low copper amalgams used before the 1970s. High copper amalgams has been developed with focus on mechanical strength and corrosion resistance, but has been sub-optimized in other aspects, resulting in increased instability and higher emission of mercury vapor. This has not been presented to policy makers and scientists. Both low and high copper amalgams undergo a transformation process for several years after placement, resulting in a substantial reduction in mercury content, but there exist no limit for maximum allowed emission of mercury from dental amalgams. These modern high copper amalgams are nowadays totally dominating the European, US and other markets, resulting in significant emissions of mercury, not considered when judging their suitability for dental restoration.

3.2.2 Clinically relevant Studies and Papers

Scand J Work Environ Health. 1989 Aug;15(4):302-4.

A possible case of mercury-related toxicity resulting from the grinding of old amalgam restorations.

Taskinen H, Kinnunen E, Riihimäki V.

ABSTRACT

The potential hazards of metallic mercury in dentistry are well recognized. The present report concerns a patient who experienced an uncommonly high mercury exposure and, possibly, mercury-related toxicity from vapor released during extensive grinding of old amalgam fillings.

Sci Total Environ. 1990 Dec 1;99(1-2):23-35.

The relationship between mercury from dental amalgam and the cardiovascular system.

Siblerud RL.

ABSTRACT

The findings presented here suggest that mercury poisoning from dental amalgam may play a role in the etiology of cardiovascular disorders. Comparisons between subjects with and without amalgam showed amalgam-bearing subjects had significantly higher blood pressure, lower heart rate, lower hemoglobin, and lower hematocrit. Hemoglobin, hematocrit, and red blood cells were significantly lower when correlated to increased levels of urine mercury. The amalgam subjects had a greater incidence of chest pains, tachycardia, anemia, fatigue, tiring easily, and being tired in the morning. The data suggest that inorganic mercury poisoning from dental amalgam does affect the cardiovascular system.

Psychol Rep. 1994 Feb;74(1):67-80.

Psychometric evidence that mercury from silver dental fillings may be an etiological factor in depression, excessive anger, and anxiety.

Siblerud RL, Motl J, Kienholz E.

ABSTRACT

Scores on the Beck Depression Inventory were compared for 25 women who had silver dental fillings (amalgams) and for 23 women without amalgams. Women with amalgams had significantly higher scores and reported more symptoms of fatigue and insomnia. Anger scores from the State-Trait Anger Expression Inventory showed that the women with amalgams had statistically significantly higher mean scores on expressing anger without provocation and experiencing more intense angry feelings. The women without amalgams scored significantly higher on controlling anger, which suggested they invested more energy in monitoring and preventing the experience and expression of anger. Anxiety scores from the State-Trait Anxiety Inventory showed the women with amalgams scored significantly less pleasant, satisfied, happy, secure, and steady, and had a more difficult time making decisions. They had significantly higher Trait Anxiety scores. The women with amalgams also had significantly higher levels of mercury in the oral cavity before and after chewing gum. The study suggests that amalgam mercury may be an etiological factor in depression, excessive anger, and anxiety because mercury can produce such symptoms perhaps by affecting the neurotransmitters in the brain.

Crit Rev Oral Biol Med. 1997;8(4):410-36.

Mercury exposure from dental amalgam fillings: absorbed dose and the potential for adverse health effects.

Mackert JR Jr, Berglund A.

ABSTRACT

This review examines the question of whether adverse health effects are attributable to amalgam-derived mercury. The issue of absorbed dose of mercury from amalgam is addressed first. The use of intra-oral Hg vapor measurements to estimate daily uptake must take into account the differences between the collection volume and flow rate of the measuring instrument and the inspiratory volume and flow rate of air through the mouth during inhalation of a single breath. Failure to account for these differences will result in substantial overestimation of the absorbed dose. Other factors that must be considered when making estimates of Hg uptake from amalgam include the accurate measurement of baseline (unstimulated) mercury release rates and the greater stimulation of Hg release afforded by chewing gum relative to ordinary food. The measured levels of amalgam-derived mercury in brain, blood, and urine are shown to be consistent with low absorbed doses (1-3 micrograms/day). Published relationships between the number of amalgam surfaces and urine levels are used to estimate the number of amalgam surfaces that would be required to produce the 30 micrograms/g creatinine urine mercury level stated by WHO to be associated with the most subtle, pre-clinical effects in the most sensitive individuals. From 450 to 530 amalgam surfaces would be required to produce the 30 micrograms/g creatinine urine mercury level for people without any excessive gum-chewing habits. The potential for adverse health effects and for improvement in health following amalgam removal is also addressed. Finally, the issue of whether any material can ever be completely exonerated of claims of producing adverse health effects is considered.

Neuro Endocrinol Lett. 1999;20(5):289-298.

Metal-specific lymphocytes: biomarkers of sensitivity in man.

Stejskal VD, Danersund A, Lindvall A, Hudecek R, Nordman V, Yaqob A, Mayer W, Bieger W, Lindh U.

ABSTRACT

Many patients attribute their health problems to amalgam and other dental metals. In genetically susceptible indviduals, mercury and gold may function as haptens and elicit allergic and autoimmune reactions. The frequency of metal-induced lymphocyte responses was examined in 3,162 patients in three European laboratories using MELISA(R), an optimized lymphocyte proliferation test. The patients suffered from local and systemic symptoms attributed to dental restorations. The effect of dental metal removal was studied in 111 patients with metal hypersensitivity and symptoms resembling Chronic Fatigue Syndrome (CFS). After consultation with a dentist the patients decided to replace their metal restorations with non-metallic materials. The changes in health and in vitro lymphocyte reactivity were studied by inquiries and follow-up MELISA(R). Lymphocyte reactivity was also analyzed in 116 healthy subjects with no complaints of metal allergy. A significant number of patients had metal-specific lymphocytes in the blood. Nickel was the most common sensitizer, followed by inorganic mercury, gold, phenylmercury, cadmium and palladium. As compared to lymphocyte responses in healthy subjects, the CFS group had significantly increased responses to several metals, especially to inorganic mercury, phenylmercury and gold. Following dental metal removal, 83 patients (76%) reported long-term health improvement. Twenty-four patients (22%) reported unchanged health and two (2%) reported worsening of symptoms. Following dental metal replacement, the lymphocyte reactivity to metals decreased as well. We propose that an inflammatory process induced by metals may modulate the hypothalamic-pituitary-adrenal axis (HPA axis) and trigger multiple non-specific symptoms characterizing CFS and other chronic conditions like myalgic encephalitis (ME) and multiple chemical sensitivity (MCS).

J Nephrol. 2002 Mar-Apr;15(2):171-6.

Mercury in dental restoration: is there a risk of nephrotoxicity?

Mortada WL, Sobh MA, El-Defrawy MM, Farahat SE.

ABSTRACT

BACKGROUND:

Concern has been voiced about exposure to mercury (Hg) from dental amalgam fillings, and there is a need to assess whether this leads to signs of nephrotoxicity.

METHODS:

A total of 101 healthy adults (80 males and 21 females) were included in this study. The population as grouped into those having amalgam fillings (39 males and 10 females) and those without (41 males and 11 females). Hg was determined in blood, urine, hair and nails to assess exposure. Urinary excretion of beta2-microglobulin (beta2M), N-acetyl-beta-D-glucosaminidase (NAG), gamma-glutamyltransferase (gammaGT) and alkaline phosphatase (ALP) were determined as markers of tubular damage. Albuminuria was assayed as an early indicator of glomerular dysfunction. Serum creatinine, beta2M and blood urea nitrogen (BUN) were determined to assess glomerular filtration.

RESULTS:

Hg levels in blood and urine were significantly higher in persons with dental amalgam than those without; in the dental amalgam group, blood and urine levels of Hg significantly correlated with the number of amalgams. Urinary excretion of NAG, gammaGT and albumin was significantly higher in persons with dental amalgam than those without. In the amalgam group, urinary excretion of NAG and albumin significantly correlated with the number of fillings. Albuminuria significantly correlated with blood and urine Hg.

CONCLUSION:

From the nephrotoxicity point of view, dental amalgam is an unsuitable filling material, as it may give rise to Hg toxicity. Hg levels in blood and urine are good markers of such toxicity. In these exposure conditions, renal damage is possible and may be assessed by urinary excretions of albumin, NAG, and gamma-GT.

Int J Toxicol. 2003 Jul-Aug;22(4):277-85.

Reduced levels of mercury in first baby haircuts of autistic children.

Holmes AS, Blaxill MF, Haley BE.

ABSTRACT

Reported rates of autism have increased sharply in the United States and the United Kingdom. One possible factor underlying these increases is increased exposure to mercury through thimerosal-containing vaccines, but vaccine exposures need to be evaluated in the context of cumulative exposures during gestation and early infancy. Differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects. First baby haircut samples were obtained from 94 children diagnosed with autism using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria and 45 age- and gender-matched controls. Information on diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation. Hair mercury levels in the autistic group were 0.47 ppm versus 3.63 ppm in controls, a significant difference. The mothers in the autistic group had significantly higher levels of mercury exposure through Rho D immunoglobulin injections and amalgam fillings than control mothers. Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively. Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group. Hair excretion patterns among autistic infants were significantly reduced relative to control. These data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population. In light of the biological plausibility of mercury's role in neurodevelopmental disorders, the present study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism.

J Occup Environ Med. 2006 Jul;48(7):656.

Parkinson's disease, macular degeneration and cutaneous signs of mercury toxicity.

Dantzig PI.

ABSTRACT

OBJECTIVE:

The objective of this study was to determined if there was a relationship between Grover's disease and Parkinson disease.

METHODS:

Fourteen patients with Parkinson disease and 14 control patients were randomly selected and examined for cutaneous eruptions and blood mercury levels.

RESULTS:

Of the 14 patients with Parkinson's disease, 13 had Grover's disease and detectable blood mercury. None of the patients in the control group had a cutaneous eruption and only 2of the 14 had detectable blood mercury.

CONCLUSION:

Mercury may play a role in the etiology of Parkinson disease and Grover's disease.

Neuro Endocrinol Lett. 2006 Dec;27 Suppl 1:53-8.

Metal alloys in the oral cavity as a cause of oral discomfort in sensitive patients.

Procházková J, Podzimek S, Tomka M, Kucerová H, Mihaljevic M, Hána K, Miksovský M, Sterzl I, Vinsová J.

ABSTRACT

OBJECTIVE OF THE STUDY:

The occurrence of galvanism with its heterogeneous symptomatology is often the source of considerable problems. Abrasion and corrosion not only damage dental alloys but also burden the organism by release of metallic particles. The objective of this study is to evaluate the hypothesis that measurement of galvanic currents could be a useful diagnostic method.

PATIENT GROUPS AND METHODOLOGY:

Three hundred fifty-seven persons with dental metal restorations were divided into groups according to abnormal values of galvanic currents and by oral discomfort. In all persons a detailed examination of the oral cavity was performed, and galvanic currents were measured. In one hundred fifty-nine patients abnormal galvanic currents were found. Measurement of metallic elements in saliva was performed in these patients and in a group of 21 healthy volunteers without any metals in the oral cavity. Thirty-three patients agreed to treatment which involved removal of the causative alloys and their replacement by non-metallic restorations.

RESULTS:

No correlation was found between the values of measured currents and the number of teeth treated by metal restorations. However, patients with metal restorations had significantly higher contents not only of mercury, but also of tin, silver, copper, and gold in the saliva than patients without metallic restorations. After removal of the electro-active restorations, both the contents of metals in saliva and galvanic currents decreased in comparison with the levels before the treatment.

CONCLUSIONS:

Galvanic effects as well as metal particles may induce a series of local or systemic pathological phenomena in sensitive individuals. The occurrence of pathologically acting galvanic effects is influenced not only by the composition and combination of different dental alloys, but to a significant degree also by the quality of used materials and processing.

Neuro Endocrinol Lett. 2006 Aug;27(4):415-23.

Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994-2006).

Wojcik DP, Godfrey ME, Christie D, Haley BE.

ABSTRACT

In a group of 465 patients diagnosed as having chronic mercury toxicity (CMT), 32.3% had severe fatigue, 88.8% had memory loss, and 27.5% had depression. A significant correlation was found between CMT and the Apo-lipoprotein E4 genotype ($p=0.001$). An investigation into an additional 864 consecutively seen general practice patients, resulted in 30.3% having evidence consistent with CMT, and once again a significant correlation was found with the APO-E4 genotype ($p=0.001$). Removal of amalgam mercury fillings when combined with appropriate treatment resulted in a significant symptom reduction ($p<0.001$) to levels reported by healthy subjects.

J Toxicol Environ Health A. 2007 Oct;70(20):1723-30.

A prospective study of mercury toxicity biomarkers in autistic spectrum disorders.

Geier DA, Geier MR.

ABSTRACT

Porphyrins are derivatives formed in the heme synthesis pathway and porphyrins afford a measure of xenobiotic exposure. The steps in the heme pathway most vulnerable to heavy metal inhibition are uroporphyrin decarboxylase (UROD) and coproporphyrinogen oxidase (CPOX) reactions. Mercury toxicity was associated with elevations in urinary coproporphyrin (cP), pentacarboxyporphyrin (5cxP), and precoproporphyrin (prcP) (also known as keto-isocoproporphyrin) levels. Two cohorts of autistic patients in the United States and France had urine porphyrin levels associated with mercury toxicity. A prospective study of urinary porphyrin testing at LabCorp (United States) and the Laboratoire Philippe Auguste (France) involving 71 autism spectrum disorder (ASD) patients, neurotypical sibling controls, and general population controls was undertaken. ASD patients had significant elevations in urinary levels of cP, 5cxP, and prcP relative to controls, and > 50% of ASD patients had urinary cP levels more than 2 standard deviations above the mean values for neurotypical sibling controls. Significant reductions in urinary 5cxP and cP levels were observed in ASD patients following chelation. A significant correlation was found between urinary porphyrins measured at LabCorp and those measured at the Laboratoire Philippe Auguste on individual ASD patients. The established developmental neurotoxicity attributed to mercury and biochemical/genomic evidence for mercury susceptibility/toxicity in ASDs indicates a causal role for mercury. Urinary porphyrin testing is clinically available, relatively inexpensive, and noninvasive. Porphyrins need to be routinely measured in ASDs to establish if mercury toxicity is a causative factor and to evaluate the effectiveness of chelation therapy.

J Neurol Sci. 2009 May 15;280(1-2):101-8. doi: 10.1016/j.jns.2008.08.021. Epub 2008 Sep 25.

Biomarkers of environmental toxicity and susceptibility in autism.

Geier DA, Kern JK, Garver CR, Adams JB, Audhya T, Nataf R, Geier MR.

ABSTRACT

Autism spectrum disorders (ASDs) may result from a combination of genetic/biochemical susceptibilities in the form of a reduced ability to excrete mercury and/or increased environmental exposure at key developmental times. Urinary porphyrins and transsulfuration metabolites in participants diagnosed with an ASD were examined. A prospective, blinded study was undertaken to evaluate a cohort of 28 participants with an ASD diagnosis for Childhood Autism Rating Scale (CARS) scores, urinary porphyrins, and transsulfuration metabolites. Testing was conducted using Vitamin Diagnostics, Inc. (CLIA-approved) and Laboratoire Philippe Auguste (ISO-approved). Participants with severe ASDs had significantly increased mercury intoxication-associated urinary porphyrins (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin) in comparison to participants with mild ASDs, whereas other urinary porphyrins were similar in both groups. Significantly decreased plasma levels of reduced glutathione (GSH), cysteine, and sulfate were observed among study participants relative to controls. In contrast, study participants had significantly increased plasma oxidized glutathione (GSSG) relative to controls. Mercury intoxication-associated urinary porphyrins were significantly correlated with increasing CARS scores and GSSG levels, whereas other urinary porphyrins did not show these relationships. The urinary porphyrin and CARS score correlations observed among study participants suggest that mercury intoxication is significantly associated with autistic symptoms. The transsulfuration abnormalities observed among study participants indicate that mercury intoxication was associated with increased oxidative stress and decreased detoxification capacity.

Contact Dermatitis, 2011 Dec; DOI: 10.5772/28868

Dental Metal Allergy

Hosoki M, Nishigawa K.

CONCLUSION:
All treatments that employ dental metal materials have the potential to cause allergic symptoms, and thus, proper preventive measures and treatment plans are required for these allergy patients. The results of our current research demonstrate the necessity for educating all dental practitioners in the recognition and treatment of dental metal allergy.

Journal of Biomedicine and Biotechnology 2012, Article ID 949048

Toxic Effects of Mercury on the Cardiovascular and Central Nervous Systems

Azevedo BF, Furieri LB, Peçanha FM, Wiggers GA, Vassallo PF, Simões MR, Fiorim J, Rossi de Batista P, Fioresi M, Rossoni L, Stefanon I, Alonso MJ, Salaices M, Vassallo DV.

ABSTRACT
Environmental contamination has exposed humans to various metal agents, including mercury. This exposure is more common than expected, and the health consequences of such exposure remain unclear. For many years, mercury was used in a wide variety of human activities, and now, exposure to this metal from both natural and artificial sources is significantly increasing. Many studies show that high exposure to mercury induces changes in the central nervous system, potentially resulting in irritability, fatigue, behavioral changes, tremors, headaches, hearing and cognitive loss, dysarthria, incoordination, hallucinations, and death. In the cardiovascular system, mercury induces hypertension in humans and animals that has wide-ranging consequences, including alterations in endothelial function. The results described in this paper indicate that mercury exposure, even at low doses, affects endothelial and cardiovascular function. As a result, the reference values defining the limits for the absence of danger should be reduced.

ISRN Hypertension, Volume 2013, Article ID 234034
http://dx.doi.org/10.5402/2013/234034

The Influence of Arsenic, Lead, and Mercury on the Development of Cardiovascular Diseases

Jennrich P.

ABSTRACT

As a group, cardiovascular disease (CVD) is the leading cause of death worldwide. It killed twice as many people as infectious and parasitic disease and three times as many people as all forms of cancer. There are other crucial risk factors next to the major risk factors identified by the Framingham Heart Study. In the last few years, detailed studies showed the correlation between environmental pollution and the development of CVD. The question, which environmental toxin is particularly harmful, is answered by CERCLA Priority List of Hazardous Substances with the following toxins: arsenic, lead, and mercury. The effect of these potential toxic metals on the development of cardiovascular diseases includes pathomechanisms as the accumulation of free radicals, damage of endothelial nitric oxide synthase, lipid peroxidation, and endocrine influences. This leads to the damage of vascular endothelium, atherosclerosis, high blood pressure, and an increased mortality from cardiovascular diseases. The cardiovascular effects of arsenic, lead, and mercury exposure and its impact on cardiovascular mortality need to be included in the diagnosis and the treatment of CVD.

Neuro Endocrinol Lett. 2013;34(6):559-65.

Metal-induced inflammation triggers fibromyalgia in metal-allergic patients.

Stejskal V, Ockert K, Bjørklund G.

ABSTRACT

BACKGROUND:

Fibromyalgia (FM) is a disease of unknown etiology. Inflammation could be one of the mechanisms behind this disease.

OBJECTIVES:

We studied the frequency and clinical relevance of metal allergy in FM patients.

METHODS:

Fifteen female FM patients were included in the study. Metal allergy was measured by a lymphocyte transformation test, MELISA®. Ten healthy age-matched women were used as controls for in vitro studies. Reduction of metal exposure in the FM patients was achieved by replacement of dental metal restorations and by the avoidance of known sources of metal exposure. Objective health assessment was performed 5 years after treatment. Subjective health assessment was established by a questionnaire, completed 2, 5 and in some cases 10 years after the start of the study. Follow-up MELISA was also performed.

RESULTS:

All FM patients tested positive to at least one of the metals tested. The most frequent reactions were to nickel, followed by inorganic mercury, cadmium and lead. Some healthy controls responded to inorganic mercury in vitro but most of the tests were negative. Objective examination 5 years later showed that half of the patients no longer fulfilled the FM diagnosis, 20% had improved and the remaining 30% still had FM. All patients reported subjective health improvement. This correlated with the normalisation of metal-specific responses in vitro.

CONCLUSION:

Metal allergy is frequent in FM patients. The reduction of metal exposure resulted in improved health in the majority of metal-sensitized patients. This suggests that metal-induced inflammation might be an important risk factor in a subset of patients with FM.

Controversies in rheumatology & autoimmunity (CORA), 2013, DOI:10.13140/RG.2.1.4542.3441

Metal allergy - The missing link in autoimmune connective tissue disorders?

Stejskal V, Reynolds TM.

ABSTRACT

Allergy to mercury, nickel, gold and palladium – metals often present in dental restorations – is frequent in patients with autoimmune connective tissue disorders (CTDs). Therefore, exposure to dental metals in hypersensitive individuals should be considered another risk factor for the development of CTDs. Through cytokines, metal-induced inflammation can cause non-specific symptoms (such as chronic fatigue, sleep disturbances and psychiatric symptoms) present in CTDs. The reduction of metal exposure in sensitized patients might result in decreased inflammation and make conventional therapy more efficient. In the future, this kind of approach might contribute to more efficient treatment of patients with autoimmune CTDs.

Isr Med Assoc J. 2014 Dec;16(12):753-8.

Metals as a common trigger of inflammation resulting in non-specific symptoms: diagnosis and treatment.

Stejskal V, Reynolds T, Bjørklund G.

ABSTRACT

BACKGROUND:

The multiple symptoms of chronic fatigue syndrome (CFS) and fibromyalgia resemble those described in patients suffering from autoimmune/inflammatory syndrome induced by adjuvants (ASIA). It has been suggested that chronic metal-induced inflammation might play a role both in CFS and fibromyalgia as well as in ASIA. Humans are exposed to metals mainly through the release of metal ions from corroding dental restorations and orthopedic implants, food, vaccines and jewelry. Metals readily bind to sulphur and other groups in the mitochondria, enzymes and cell proteins. Metal-bound proteins are recognized by the immune system of susceptible subjects and might trigger an abnormal immune response, including allergy and autoimmunity.

OBJECTIVES:

To study three subjects with CFS and two with fibromyalgia, all of whom suspected metal exposure as a trigger for their ill health.

METHODS:

We measured delayed-type hypersensitivity to metals (metal allergy) using a validated lymphocyte transformation test, LTT-MELISA. All patients except one were sensitized to metals present in their dental restorations. The remaining patient reacted to metals in his skull implant. The removal of sensitizing metals resulted in long-term health improvement. Nine healthy controls matched for gender and age showed only marginal reactivity to the metals tested.

CONCLUSIONS:

Patients with CFS and fibromyalgia are frequently sensitized to metals found in the environment or used in dentistry and surgery. This allergy to metals might initiate or aggravate non-specific symptoms in metal-sensitized patients.

J Trace Elem Med Biol. 2015;31:230-6. doi: 10.1016/j.jtemb.2015.01.001. Epub 2015 Jan 14.

Increased frequency of delayed type hypersensitivity to metals in patients with connective tissue disease.

Stejskal V, Reynolds T, Bjørklund G.

ABSTRACT

BACKGROUND:

Connective tissue disease (CTD) is a group of inflammatory disorders of unknown aetiology. Patients with CTD often report hypersensitivity to nickel. We examined the frequency of delayed type hypersensitivity (DTH) (Type IV allergy) to metals in patients with CTD.

METHODS:

Thirty-eight patients; 9 with systemic lupus erythematosus (SLE), 16 with rheumatoid arthritis (RA), and 13 with Sjögren's syndrome (SS) and a control group of 43 healthy age- and sex-matched subjects were included in the study. A detailed metal exposure history was collected by questionnaire. Metal hypersensitivity was evaluated using the optimised lymphocyte transformation test LTT-MELISA(®) (Memory Lymphocyte Immuno Stimulation Assay).

RESULTS:

In all subjects, the main source of metal exposure was dental metal restorations. The majority of patients (87%) had a positive lymphocyte reaction to at least one metal and 63% reacted to two or more metals tested. Within the control group, 43% of healthy subjects reacted to one metal and only 18% reacted to two or more metals. The increased metal reactivity in the patient group compared with the control group was statistically significant ($P<0.0001$). The most frequent allergens were nickel, mercury, gold and palladium.

CONCLUSIONS:

Patients with SLE, RA and SS have an increased frequency of metal DTH. Metals such as nickel, mercury and gold are present in dental restorative materials, and many adults are therefore continually exposed to metal ions through corrosion of dental alloys. Metal-related DTH will cause inflammation. Since inflammation is a key process in CTDs, it is possible that metal-specific T cell reactivity is an etiological factor in their development. The role of metal-specific lymphocytes in autoimmunity remains an exciting challenge for future studies.

Hautarzt. 2016 May;67(5):359-64. doi: 10.1007/s00105-016-3773-7.

Contact allergic gastritis : Rare manifestation of a metal allergy

Pföhler C, Vogt T, Müller CS. (article in german)

ABSTRACT

Only a few cases of contact allergic gastritis in patients with nickel allergy have been reported in the literature. We report a case of probable contact-allergic gastritis in a 46-year-old woman. Clinical examination revealed lichenoid mucosal lesions of the gums adjacent to a bridge and crowns that had been implanted several weeks previously. Since implantation, the patient suffered from gastrointestinal complaints including stomach pain. Gastroscopy and histological investigation of stomach biopsies showed eosinophilic gastritis. Patch testing done under the diagnosis of contact allergic stomatitis showed positive reactions to gold sodium thiosulphate, manganese (II) chloride, nickel (II) sulphate, palladium chloride, vanadium (III) chloride, zirconium (IV) chloride, and fragrances. The crowns and the bridge contained gold, palladium, and zirconium, hence they were replaced by titan-based dentition. Shortly after replacing the artificial dentition, all gastrointestinal symptoms resolved spontaneously without further treatment. Delayed-type allergy to components in the artificial dentition seem to have caused the gastritis.

Environ Pollut. 2018 Jun;237:917-925. doi: 10.1016/j.envpol.2018.01.046. Epub 2018 Feb 21.

Associations of multiple plasma metals with incident type 2 diabetes in Chinese adults: The Dongfeng-Tongji Cohort.

Yuan Y, Xiao Y, Yu Y, Liu Y, Feng W, Qiu G, Wang H, Liu B, Wang J, Zhou L, Liu K, Xu X, Yang H, Li X, Qi L, Zhang X, He M, Hu FB, Pan A, Wu T.

ABSTRACT

The long-term associations between multiple metals and incident diabetes are uncertain. We aimed to examine the relationship between plasma concentrations of 23 metals and the incidence of type 2 diabetes among Chinese senior adults. We quantified fasting plasma concentrations of 23 metals by inductively coupled plasma mass spectrometry among 1039 incident diabetes cases and 1039 controls (age and sex matched) nested in a prospective study, the Dongfeng-Tongji cohort. Both cases and controls were free of diabetes at baseline (2008-2010), incident diabetes were identified using the following criteria: fasting glucose ≥ 7.0 mmoL/l; or hemoglobin A1c (HbA1c) ≥ 6.5%; or self-reported physician diagnosis of diabetes or use of anti-diabetic medication during the follow-up visits in 2013. In the conditional logistic regression models, the multivariable adjusted ORs (95% CIs) of diabetes across quartiles (Q1-Q4) of metal concentrations were as follows: titanium, 1.00, 0.92, 1.31, 1.38 (1.00-1.91, Ptrend = 0.011); selenium, 1.00, 1.08, 1.45, 1.27 (0.93-1.74, Ptrend = 0.05); and antimony, 1.00, 0.79, 0.77, 0.60 (0.44-0.83, Ptrend = 0.002). Arsenic was significantly associated with diabetes in the crude model (ORs comparing extreme quartiles 1.30; 1.02-1.65; Ptrend = 0.006), but was not significant after adjustment for socio-demographic factors. No significant associations were found for other metals. In conclusion, titanium and selenium were positively while antimony was negatively associated with incident diabetes.

3.2.3 Interaction between Metals and EMF

Phys Med Biol. 2005 Jun 7;50(11):2689-700. Epub 2005 May 18.

Interaction of mobile phones with superficial passive metallic implants.

Virtanen H, Huttunen J, Toropainen A, Lappalainen R.

ABSTRACT

The dosimetry of exposure to radiofrequency (RF) electromagnetic (EM) fields of mobile phones is generally based on the specific absorption rate (SAR, W kg(-1)), which is the electromagnetic energy absorbed in the tissues per unit mass and time. In this study, numerical methods and modelling were used to estimate the effect of a passive, metallic (conducting) superficial implant on a mobile phone EM field and especially its absorption in tissues in the near field. Two basic implant models were studied: metallic pins and rings in the surface layers of the human body near the mobile phone. The aim was to find out 'the worst case scenario' with respect to energy absorption by varying different parameters such as implant location, orientation, size and adjacent tissues. Modelling and electromagnetic field calculations were carried out using commercial SEMCAD software based on the FDTD (finite difference time domain) method. The mobile phone was a 900 MHz or 1800 MHz generic phone with a quarter wave monopole antenna. A cylindrical tissue phantom models different curved sections of the human body such as limbs or a head. All the parameters studied (implant size, orientation, location, adjacent tissues and signal frequency) had a major effect on the SAR distribution and in certain cases high local EM fields arose near the implant. The SAR values increased most when the implant was on the skin and had a resonance length or diameter, i.e. about a third of the wavelength in tissues. The local peak SAR values increased even by a factor of 400-700 due to a pin or a ring. These highest values were reached in a limited volume close to the implant surface in almost all the studied cases. In contrast, without the implant the highest SAR values were generally reached on the skin surface. Mass averaged SAR(1 g) and SAR(10 g) values increased due to the implant even by a factor of 3 and 2, respectively. However, at typical power levels of mobile phones the enhancement is unlikely to be problematic.

OJAPr Vol.2 No.3 , September 2014; doi:10.4236/ojapr.2014.23004.

Sensation of Balance Dysregulation Caused/Aggravated by a Collection of Electromagnetic Waves in a Dental Implant

Fujii Y.

ABSTRACT

Cell phone and personal computer users have increased considerably in recent years, particularly in more developed countries. These devices have facilitated communication on a global scale. However, there have been a number of reports of abnormalities occurring in the body due to the electromagnetic waves emitted by such electronic devices. The long lists of both general and severe symptoms, including headaches, fatigue, tinnitus, dizziness, memory loss, irregular heartbeat, and whole-body skin symptoms, have been reported that are apparently associated with the condition of electromagnetic hypersensitivity. In dentistry, titanium dental implants may be commonly associated with antenna-like activity, but the underlying mechanism remains unknown. In the current case studies, balance difficulties were found to occur when the patients had titanium dental implants. These implants seemed to be acting as antennae and collecting harmful electromagnetic waves. Further studies are required to confirm this hypothesis.

3.2.4 General Reviews and Overviews

Neuro Endocrinol Lett. 2005 Oct;26(5):439-46.

Mercury and autism: accelerating evidence?

Mutter J, Naumann J, Schneider R, Walach H, Haley B.

ABSTRACT

The causes of autism and neurodevelopmental disorders are unknown. Genetic and environmental risk factors seem to be involved. Because of an observed increase in autism in the last decades, which parallels cumulative mercury exposure, it was proposed that autism may be in part caused by mercury. We review the evidence for this proposal. Several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal-containing immunoglobulin shots. It was hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism. In vitro, mercury and thimerosal in levels found several days after vaccination inhibit methionine synthetase (MS) by 50%. Normal function of MS is crucial in biochemical steps necessary for brain development, attention and production of glutathione, an important antioxidative and detoxifying agent. Repetitive doses of thimerosal leads to neurobehavioral deteriorations in autoimmune susceptible mice, increased oxidative stress and decreased intracellular levels of glutathione in vitro. Subsequently, autistic children have significantly decreased level of reduced glutathione. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites.

J Occup Med Toxicol. 2011 Jan 13;6(1):2. doi: 10.1186/1745-6673-6-2.

Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission.

Mutter J.

ABSTRACT

It was claimed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)) in a report to the EU-Commission that "....no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease..." [1, available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf].SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review. But the real scientific data show that:(a) Dental amalgam is by far the main source of human total mercury body burden. This is proven by autopsy studies which found 2-12 times more mercury in body tissues of individuals with dental amalgam. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden. (b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys.(c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. SCENIHR only relied on levels in urine or blood.(d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days".(e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals.(f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

J Environ Public Health. 2012;2012:460508. doi: 10.1155/2012/460508. Epub 2011 Dec 22.

Mercury toxicity and treatment: a review of the literature.

Bernhoft RA.

ABSTRACT

Mercury is a toxic heavy metal which is widely dispersed in nature. Most human exposure results from fish consumption or dental amalgam. Mercury occurs in several chemical forms, with complex pharmacokinetics. Mercury is capable of inducing a wide range of clinical presentations. Diagnosis of mercury toxicity can be challenging but can be obtained with reasonable reliability. Effective therapies for clinical toxicity have been described.

Curr Med Chem. 2018;25(19):2198-2214. doi: 10.2174/0929867325666171129124616.

Metals and Parkinson's Disease: Mechanisms and Biochemical Processes.

Bjorklund G, Stejskal V, Urbina MA, Dadar M, Chirumbolo S, Mutter J.

ABSTRACT

Genetic background accounts for only 5 to 10% of the reported cases of Parkinson's disease (PD), while the remaining cases are of unknown etiology. It is believed that environmental factors may be involved in the causality of a large proportion of PD cases. Several PD genes are activated by xenobiotic exposure, and a link between pesticide exposure and PD has been demonstrated. Many epidemiological studies have shown an association between PD and exposure to metals such as mercury, lead, manganese, copper, iron, aluminum, bismuth, thallium, and zinc. This review explores the biological effects, the pathogenetic processes, genetic susceptibilities to metals as well as examining future strategies for PD treatment, such as chelation therapy.

Biol Trace Elem Res. 2019 Feb;187(2):341-356. doi: 10.1007/s12011-018-1380-4. Epub 2018 May 18.

Mercury Involvement in Neuronal Damage and in Neurodegenerative Diseases.

Cariccio VL, Samà A, Bramanti P, Mazzon E.

ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis are characterized by a chronic and selective process of neuronal cell death. Although the causes of neurodegenerative diseases remain still unknown, it is now a well-established idea that more factors, such as genetic, endogenous, and environmental, are involved. Among environmental causes, the accumulation of mercury, a heavy metal considered a toxic agent, was largely studied as a probable factor involved in neurodegenerative disease course. Mercury exists in three main forms: elemental mercury, inorganic mercury, and organic mercury (methylmercury and ethylmercury). Sources of elemental mercury can be natural (volcanic emission) or anthropogenic (coal-fired electric utilities, waste combustion, hazardous-waste incinerators, and gold extraction). Moreover, mercury is still used as an antiseptic, as a medical preservative, and as a fungicide. Dental amalgam can emit mercury vapor. Mercury vapor, being highly volatile and lipid soluble, can cross the blood-brain barrier and the lipid cell membranes and can be accumulated into the cells in its inorganic forms. Also, methylmercury can pass through blood-brain and placental barriers, causing serious damage in the central nervous system. This review describes the toxic effects of mercury in cell cultures, in animal models, and in patients with neurodegenerative diseases. In vitro experiments showed that mercury exposure was principally involved in oxidative stress and apoptotic processes. Moreover, motor and cognitive impairment and neural loss have been confirmed in various studies performed in animal models. Finally, observational studies on patients with neurodegenerative diseases showed discordant data about a possible mercury involvement.

3.3 Cavitations (Osteonecrosis of the Jawbone/FDOJ)

3.3.1 Basic Research

Cytokine. 1996 Jan;8(1):89-98.

RANTES chemokine expression in diseased and normal human tissues.

von Luettichau I, Nelson PJ, Pattison JM, van de Rijn M, Huie P, Warnke R, Wiedermann CJ, Stahl RA, Sibley RK, Krensky AM.

ABSTRACT

RANTES is a member of a large family of cytokines, called chemokines, which are thought to play a regulatory role in inflammatory processes. We have made recombinant human RANTES protein which was used to generate a panel of anti-RANTES monoclonal antibodies. Following characterization, select anti-RANTES monoclonal antibodies were used for immunohistologic staining of a large panel of normal, diseased and fetal tissue sections. Diseased tissues included eleven lymphomas and eight renal tumors. Most tissues were also tested in parallel for RANTES mRNA by in situ hybridization using RANTES mRNA specific oligomeric probes. As expected, most normal adult tissues contain few, if any, RANTES positive cells. In contrast, RANTES expression dramatically increases in inflammatory sites. In addition, megakaryocytes, some tumours, and select fetal tissues express high levels of RANTES message and protein. These results indicate a wider expression of RANTES than previously appreciated and suggest multiple physiologic roles for this soluble factor.

Annu Rev Immunol. 2000;18:217-42.

The biology of chemokines and their receptors.

Rossi D, Zlotnik A.

ABSTRACT

During the last five years, the development of bioinformatics and EST databases has been primarily responsible for the identification of many new chemokines and chemokine receptors. The chemokine field has also received considerable attention since chemokine receptors were found to act as co-receptors for HIV infection (1). In addition, chemokines, along with adhesion molecules, are crucial during inflammatory responses for a timely recruitment of specific leukocyte subpopulations to sites of tissue damage. However, chemokines and their receptors are also important in dendritic cell maturation (2), B (3), and T (4) cell development, Th1 and Th2 responses, infections, angiogenesis, and tumor growth as well as metastasis (5). Furthermore, an increase in the number of chemokine/receptor transgenic and knock-out mice has helped to define the functions of chemokines in vivo. In this review we discuss some of the chemokines' biological effects in vivo and in vitro, described in the last few years, and the implications of these findings when considering chemokine receptors as therapeutic targets.

Trends Immunol. 2001 Feb;22(2):83-7.

RANTES: a versatile and controversial chemokine.

Appay V, Rowland-Jones SL.

ABSTRACT

The activity of the chemokine RANTES is not restricted merely to chemotaxis. It is a powerful leukocyte activator, a feature potentially relevant in a range of inflammatory disorders. RANTES has attracted attention because it can potently suppress and, in some circumstances, enhance HIV replication. These characteristics are critically dependent on its ability to self-aggregate and bind to glycosaminoglycans.

Cancer Res. 2002 Feb 15;62(4):1093-102.

The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity.

Azenshtein E, Luboshits G, Shina S, Neumark E, Shahbazian D, Weil M, Wigler N, Keydar I, Ben-Baruch A.

ABSTRACT

Breast cancer progression may be affected by various cellular components expressed by the tumor cells and/or by microenvironmental factors. Many studies report the correlation between breast cancer progression and monocyte infiltration into the tumor site. We have identified recently the CC chemokine regulated on activation, normal T cell expressed and secreted (RANTES), a major monocyte chemoattractant expressed by breast tumor cells, as a potential contributor to breast cancer progression. In the present study, analysis of the regulation of RANTES expression demonstrates that the expression of RANTES in breast tumor cells is elevated significantly and in a synergistic manner by IFN-gamma and tumor necrosis factor-alpha. Identification of the mechanisms by which RANTES may contribute to breast cancer progression included the analysis of the potential ability of RANTES to act in paracrine and indirect mechanisms, as well as directly on the tumor cells, to promote disease progression. Our results suggest that breast tumor cell-derived RANTES may promote breast cancer progression by its partial contribution to monocyte migration into breast tumor sites. Moreover, RANTES promotes the expression of matrix metalloproteinase (MMP) 9 by THP-1 monocytic cells and elevates vascularity in chick chorioallantoic membrane assays. Tumor necrosis factor-alpha, a major monocyte-derived cytokine, was found to promote the expression of MMP9 and MMP2 by MCF-7 and T47D breast adenocarcinoma cells, respectively, and to induce the de novo expression of an additional proteolytic enzyme by T47D cells, presumably MMP9. The possibility that RANTES may act directly on breast tumor cells was supported by detection of the expression of the CCR5 RANTES receptor in biopsy sections of breast cancer patients and by the ability of RANTES to promote the expression of MMP9 by MCF-7 cells. In all, our study suggests that the expression of RANTES by breast tumor cells results not only in monocyte migration to the tumor site but also in protumorigenic activities of RANTES and of proinflammatory cytokines that may facilitate metastasis formation and contribute to disease progression.

Nature. 2007 Oct 4;449(7162):557-63.

Mesenchymal stem cells within tumour stroma promote breast cancer metastasis.

Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA.

ABSTRACT

Mesenchymal stem cells have been recently described to localize to breast carcinomas, where they integrate into the tumour-associated stroma. However, the involvement of mesenchymal stem cells (or their derivatives) in tumour pathophysiology has not been addressed. Here, we demonstrate that bone-marrow-derived human mesenchymal stem cells, when mixed with otherwise weakly metastatic human breast carcinoma cells, cause the cancer cells to increase their metastatic potency greatly when this cell mixture is introduced into a subcutaneous site and allowed to form a tumour xenograft. The breast cancer cells stimulate de novo secretion of the chemokine CCL5 (also called RANTES) from mesenchymal stem cells, which then acts in a paracrine fashion on the cancer cells to enhance their motility, invasion and metastasis. This enhanced metastatic ability is reversible and is dependent on CCL5 signalling through the chemokine receptor CCR5. Collectively, these data demonstrate that the tumour microenvironment facilitates metastatic spread by eliciting reversible changes in the phenotype of cancer cells.

Horm Metab Res. 2009 Mar;41(3):183-9. doi: 10.1055/s-0028-1093345. Epub 2008 Oct 27.

Expression and secretion of RANTES (CCL5) in human adipocytes in response to immunological stimuli and hypoxia.

Skurk T, Mack I, Kempf K, Kolb H, Hauner H, Herder C.

ABSTRACT

Obesity and related disorders represent states of systemic low-grade inflammation. Chemokine secretion by adipocytes may initiate leukocyte infiltration in obese adipose tissue and thus mediate an important step in the establishment of chronic immune activation. The chemokine RANTES (regulated upon activation normal T cell expressed and secreted)/CCL5 is a chemoattractant for various leukocyte subsets. This study was designed to examine whether RANTES is expressed and released by human adipocytes and how its expression is regulated. RANTES expression under basal conditions was studied in mature adipocytes. Cells were therefore challenged with lipopolysaccharide (LPS), interferon (IFN)-gamma, interleukin (IL)-4, monocyte chemoattractant protein (MCP)-1 or exposed to low oxygen pressure. RANTES was expressed and secreted constitutively in most samples of mature adipocytes from the omental and the subcutaneous depot. RANTES release was dependent on adipocyte size and also seemed to be higher from cells of obese donors. Hypoxia (4% O (2)) caused an approximately 36% increase of RANTES release. Human adipocytes express the chemokine RANTES and are thus identified as a novel cellular source of this immune mediator. LPS and IFNgamma do not seem to play a significant role for the expression of RANTES in contrast to moderate hypoxia, which points to a distinct role in the innate immune system.

Cancer Epidemiol Biomarkers Prev. 2011 Jul;20(7):1543-51. doi: 10.1158/1055-9965.EPI-10-1248. Epub 2011 May 17.

Plasma biomarker profiles differ depending on breast cancer subtype but RANTES is consistently increased.

Gonzalez RM, Daly DS, Tan R, Marks JR, Zangar RC.

ABSTRACT

BACKGROUND:
Current biomarkers for breast cancer have little potential for detection. We determined whether breast cancer subtypes influence circulating protein biomarkers.

METHODS:
A sandwich ELISA microarray platform was used to evaluate 23 candidate biomarkers in plasma samples that were obtained from subjects with either benign breast disease or invasive breast cancer. All plasma samples were collected at the time of biopsy, after a referral due to a suspicious screen (e.g., mammography). Cancer samples were evaluated on the basis of breast cancer subtypes, as defined by the HER2 and estrogen receptor statuses.

RESULTS:
Ten proteins were statistically altered in at least one breast cancer subtype, including four epidermal growth factor receptor ligands, two matrix metalloproteases, two cytokines, and two angiogenic factors. Only one cytokine, RANTES, was significantly increased ($P < 0.01$ for each analysis) in all four subtypes, with areas under the curve (AUC) for receiver operating characteristic values that ranged from 0.76 to 0.82, depending on cancer subtype. The best AUC values were observed for analyses that combined data from multiple biomarkers, with values ranging from 0.70 to 0.99, depending on the cancer subtype. Although the results for RANTES are consistent with previous publications, the multi-assay results need to be validated in independent sample sets.

CONCLUSIONS:
Different breast cancer subtypes produce distinct biomarker profiles, and circulating protein biomarkers have potential to differentiate between true- and false-positive screens for breast cancer.

IMPACT:
Subtype-specific biomarker panels may be useful for detecting breast cancer or as an adjunct assay to improve the accuracy of current screening methods.

Clin Cosmet Investig Dent. 2014; 6: 71–79. Published online 2014 Aug 21. doi: 10.2147/CCIDE.S69807

Validation of dental X-ray by cytokine RANTES – comparison of X-ray findings with cytokine overexpression in jawbone.

Lechner J.

ABSTRACT

INTRODUCTION:
There is a need to clarify the extent to which the most common diagnostic tool in dentistry – two-dimensional panoramic tomography (2D-OPG) – is suitable for identifying fatty degenerative osteolysis of jawbone (FDOJ).

MATERIALS AND METHODS:
To obtain a qualitative assessment of edentulous jawbone sections, the results from 2D-OPG with a defined X-ray density (XrDn), expression of the cytokine RANTES (regulated on activation, normal T-cell expressed and secreted), and a transalveolar ultrasound system for measuring jawbone density were compared.

RESULTS:
The difference in the XrDn of healthy jawbone and FDOJ are minimal, whereas RANTES is up to 25-fold higher in FDOJ. In contrast to 2D-OPG, transalveolar ultrasound showed coincidental findings in FDOJ areas.

DISCUSSION:
Comparisons of the data revealed a discrepancy between the XrDn of 2D-OPGs and the medullary osteopathies in the jawbone like FDOJ.

CONCLUSION:
The data suggest that there is a critical attitude toward the use of 2D-OPG as a sole imaging diagnostic tool for assessing chronic inflammatory processes in the jawbone. Specifically, 2D-OPG is objectively not suitable for depicting FDOJ.

Scientific Reports. (2018) 8:1323 | DOI:10.1038/s41598-018-19643-0

CCR5/CCL5 axis interaction promotes migratory and invasiveness of pancreatic cancer cells.

Singh SK, Mishra MK, Eltoum IA, Bae S, Lillard JW, Singh R.

ABSTRACT

Pancreatic cancer (PC) is one of the deadliest cancers and remains a major challenge due to its invasive and metastatic nature. Increased levels of CCR5 and CCL5 have established indicators for disease status in various cancers, including PC. However, their role in invasion and metastasis of PC is not known. Here we conducted immunohistochemistry of PC tissues and found elevated epithelial staining for CCR5 and CCL5 in metastatic PC tissues compared to non-neoplastic. In vitro experiments, such as flow cytometry, immunofluorescence and western blotting with human PC cell lines (AsPc-1, BxPc-3 and MIA PaCa-2), showed higher expression levels of CCR5. The CCL5 activation of PC cells expressing CCR5 increased their invasive potential, while treatment with CCR5 inhibitor maraviroc inhibited the CCL5 activation. CCL5 induced proliferation of PC cells was mediated through F-actin polymerization, while there was marked reduction when the cells were treated with maraviroc. The direct interaction of CCR5 with CCL5 was verified using a calcium mobilization assay. Taken together, our results demonstrate that CCR5 and CCL5 are potential markers for metastatic PC cancer, and their interaction leads to the increased PC cell invasion. Thus, blocking CCR5/CCL5 axis might prove beneficial to prevent metastasis and provide a more therapeutic strategy to control PC progression.

Oncol Rep. 2019 Dec;42(6):2499-2511. doi: 10.3892/or.2019.7344. Epub 2019 Oct 1.

Effects of CCL5 on the biological behavior of breast cancer and the mechanisms of its interaction with tumor associated macrophages.

An G, Wu F, Huang S, Feng L, Bai J, Gu S, Zhao X.

ABSTRACT

The recurrence and metastasis of breast cancer limit the effectiveness of clinical treatments, making them important issues for clinicians to address. Tumor associated macrophages (TAMs) contribute to regulating the immune system. C C motif chemokine ligand 5 (CCL5) is an inflammatory chemokine that promotes chemotaxis on cells involved in the immune/inflammatory response. Breast cancer cells that secrete CCL5 act on THP 1 cells, influencing the invasion and metastasis of tumors. However, knowledge remains limited regarding the mechanism underlying the effects of CCL5 on breast cancer cells and TAMs, as well as the mechanisms promoting the migration and invasion of breast cancer. The present study demonstrated that the positive expression of CCL5 was associated with lymph node status and tumor node metastasis stage. Treatment with ≥20 ng/ml CCL5 significantly promoted the migration and invasion of MCF 7 and MDA MB 231 cells. CCL5 small interfering RNA intervention significantly decreased the migration and invasion of the two cell types. In vitro, THP 1 cells were successfully induced to become TAMs, which were then recruited via the chemotactic effects of CCL5. This process was achieved through the co stimulation of phorbol 12 myristate 13 acetate, interleukin 4 (IL 4) and IL 13. The nuclear factor κB (NF κB) signaling pathway was activated to regulate EMT, as well as the migration and invasion process of MCF 7 cells, when co cultured with TAMs. We also reported that blocking the expression of CCL5 in vivo may significantly inhibit the growth of human breast cancer xenografts. Therefore, targeting CCL5 may be considered as a novel therapeutic strategy for suppressing the invasion and metastasis of breast cancer.

3.3.2 Clinically relevant Studies and Papers

Oral Surg Oral Med Oral Pathol. 1992 Mar;73(3):307-19; discussion 319-20.

Neuralgia-inducing cavitational osteonecrosis (NICO). Osteomyelitis in 224 jawbone samples from patients with facial neuralgia.

Bouquot JE, Roberts AM, Person P, Christian J.

ABSTRACT

A somewhat obscure etiologic theory for facial neuralgias presumes a low-grade osteomyelitis of the jaws that produces neural degeneration with subsequent production of inappropriate pain signals. Animal investigations and treatment successes with human patients based on this theory lend it credence. The present study examined 224 tissue samples removed from alveolar bone cavities in 135 patients with trigeminal neuralgia or atypical facial neuralgia. All tissue samples demonstrated clear evidence of chronic intraosseous inflammation. The most common microscopic features included dense marrow fibrosis or "scar" formation, a sprinkling of lymphocytes in a relative absence of other inflammatory cells (especially histiocytes), and smudged, nonresorbing necrotic bone flakes. Very little healing or new bone formation was visible. These lesions were able to burrow several centimeters to initiate distant cavities. The present preliminary investigation cannot prove etiology, but the presence of intraosseous inflammation in every single jawbone specimen in these patients and certain clinical and treatment aspects of these lesions (to be reported later) has led the authors to recommend the term neuralgia-inducing cavitational osteonecrosis or NICO for these lesions.

J Egypt Natl Canc Inst. 2005 Mar;17(1):51-5.

Importance of serum IL-18 and RANTES as markers for breast carcinoma progression.

Eissa SA, Zaki SA, El-Maghraby SM, Kadry DY.

ABSTRACT

BACKGROUND:

Interleukin-18 (IL-18), a cytokine that plays an important role in the T-cell-helper response, acts as an angiogenic factor and a tumor suppressor. RANTES (regulated upon activation normal T-cells expressed and secreted) is a member of the C-C chemokine family with chemoattractant activity for a variety of cell types. High incidence and intensity of RANTES were noted in advanced breast carcinoma.

AIM OF THE STUDY:

To correlate the levels of RANTES and IL-18 in serum of breast cancer patients with bone or other organ metastasis compared to breast cancer patients without metastasis and healthy controls and to estimate the role of each of them as a prognostic marker for the progression of the disease.

PATIENTS AND METHODS:

The study was conducted on 60 breast cancer patients (25 cases with no metastasis and 35 cases with metastasis) who were admitted to the outpatient clinic of the NCI, Cairo University during the period from March 2004 to September 2004 and 30 apparently healthy controls who were volunteers at the blood bank of the NCI, Cairo University.

RESULTS:

Showed that there was a statistically significant difference between the level of IL-18 in breast cancer patients without metastasis and the control group ($p<0.05$) while there was a highly significant difference between the metastatic group and the control group ($p<0.001$). There was a significant increase in IL-18 levels between metastatic and non-metastatic cases ($p<0.01$). RANTES showed a significant increase in breast cancer cases with no metastasis and the control group ($p<0.05$) and it showed a highly significant increase in metastatic patients compared to controls ($p<0.001$). There was no significant increase in the level of RANTES in metastatic compared to non-metastatic patients ($p>0.05$).

CONCLUSIONS:

IL-18 is an important non invasive marker suspecting metastasis. Even though RANTES levels were higher in cancer patients compared to controls, its role in staging of breast cancer was not clear in this study.

Spine (Phila Pa 1976). 2013 May 15;38(11):873-80. doi: 10.1097/BRS.0b013e318285ae08.

Expression and relationship of pro-inflammatory chemokine RANTES/CCL5 and cytokine IL-1β in painful human intervertebral discs.

Kepler CK, Markova DZ, Dibra F, Yadla S, Vaccaro AR, Risbud MV, Albert TJ, Anderson DG.

ABSTRACT

STUDY DESIGN:
Laboratory study.

OBJECTIVE:
To evaluate expression of chemokine regulated and normal T cell expressed and secreted (RANTES)/C-C motif ligand 5 (CCL5) and interleukins in intervertebral discs (IVDs) specimens from patients with discogram-proven painful degeneration.

SUMMARY OF BACKGROUND DATA:
Discogenic back pain results in tremendous costs related to treatment and lost productivity. The relationship between inflammation, degeneration (IVD), and cytokine upregulation is well established, but other mediators of the inflammatory cascade are not well characterized.

METHODS:
Painful IVDs were taken from 18 patients undergoing surgery for discogenic pain with positive preoperative discogram. Painless control tissue was taken at autopsy from patients without back pain/spinal pathology or spinal levels with negative discograms resected for deformity. Quantitative real time polymerase chain reaction (qRT-PCR) was performed to evaluate RANTES, IL-1β, IL-6, and IL-8 expression in painful and control discs. RANTES and interleukin expression were analyzed on the basis of Pfirrmann grade.Disc cells were cultured in alginate beads using 2 groups: an untreated group and a group treated with 10 ng/mL IL-1β, 10 ng/mL TNF-α, and 1% fetal bovine serum to induce a degenerative phenotype.

RESULTS:
Nine painless IVD specimens and 7 painful IVD specimens were collected. RANTES expression demonstrated a 3.60-fold increase in painful discs versus painless discs, a significant difference (P = 0.049). IL-1β expression demonstrated significantly higher expression in painful discs (P = 0.03). RANTES expression data demonstrated significant upregulation with increasing Pfirrmann grade (P = 0.045). RANTES expression correlated significantly with IL-1β expression (ρ = 0.67, P < 0.0001). RANTES expression increased more than 200-fold in the alginate culture model in cells treated with IL-1β/TNF-α, 1% fetal bovine serum (P < 0.001).

CONCLUSION:
RANTES and IL-1β expression was significantly elevated in painful IVDs after careful selection of painless versus painful IVD tissue. RANTES expression was found to correlate significantly with expression of IL-1β. RANTES was upregulated by IL-1β/TNF-α/1% fetal bovine serum an in vitro treatment to induce a degenerative phenotype.

Amyotroph Lateral Scler. 2007 Oct;8(5):283-7.

RANTES levels are elevated in serum and cerebrospinal fluid in patients with amyotrophic lateral sclerosis.

Rentzos M, Nikolaou C, Rombos A, Boufidou F, Zoga M, Dimitrakopoulos A, Tsoutsou A, Vassilopoulos D.

ABSTRACT

Immunological disturbances have been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). Chemokines are involved in the recruitment of immune cells. Regulated upon activation, normal T-cell expressed and secreted (RANTES) is a C-C beta-chemokine with strong chemo-attractant activity for T-lymphocytes and monocytes. We examined serum levels of RANTES in 20 patients with amyotrophic lateral sclerosis (ALS), 14 patients with non-inflammatory neurological disorders (NIND) and 13 control subjects (CTRL) and cerebrospinal fluid (CSF) levels of RANTES in ALS and NIND group patients in order to investigate whether RANTES as index of immune activation is present in ALS patients. Patients with ALS had higher RANTES levels compared with the NIND patients and CTRL subjects ($p = 0.005$ and $p = 0.02$, respectively). CSF RANTES levels were also higher compared with the NIND patients ($p = 0.007$). No correlation of serum and CSF RANTES levels with disease duration was found. These results may suggest an activated microglia induced recruitment of peripheral inflammatory cells to sites of inflammation in ALS patients.

Breast Cancer (Auckl). 2014 May 21;8:89-96. doi: 10.4137/BCBCR.S15119. eCollection 2014.

Hyperactivated Signaling Pathways of Chemokine RANTES/CCL5 in Osteopathies of Jawbone in Breast Cancer Patients-Case Report and Research.

Lechner J, von Baehr V.

ABSTRACT

BACKGROUND:

Hollow spaces in the jawbone have been defined as fatty degenerative osteonecrosis of jawbone (FDOJ) and have been linked with a dysregulated immune system. Little is known about the underlying relationship.

OBJECTIVES:

Samples of FDOJ were analyzed to assess expression of cytokines which can play a role in the pathogenesis of breast cancer (MaCa).

MATERIAL AND METHODS:

Samples of FDOJ extracted from 23 patients with MaCa and 19 healthy control jawbone samples were analyzed for 7 immune messengers.

RESULTS:

RANTES was found to be highly overexpressed in disease samples. No change was observed in expression levels of the other immune mediators.

DISCUSSION:

This data provides a compelling confirmation that FDOJ produces high levels of RANTES, a cytokine implicated in MaCa and metastasis. Levels detected in FDOJ are five-fold higher than that previously reported for MaCa tissue suggesting its role as a cytokine source in MaCa.

CONCLUSION:

We thus hypothesize that FDOJ may serve as an expeditor of MaCa progression, through RANTES production.

Int J Gen Med. 2013 Apr 22;6:277-90. doi: 10.2147/IJGM.S43852. Print 2013.

RANTES and fibroblast growth factor 2 in jawbone cavitations: triggers for systemic disease?

Lechner J, von Baehr V.

ABSTRACT

BACKGROUND:
Jawbone cavitations (JC) are hollow dead spaces in jawbones with dying or dead bone marrow. These areas are defined as fatty degenerative osteonecrosis of the jawbone or neuralgia-inducing cavitational osteonecrosis and may produce facial pain. These afflictions have been linked to the immune system and chronic illnesses. Surgical debridement of JC is reported to lead to an improvement in immunological complaints, such as rheumatic, allergic, and other inflammatory diseases (ID). Little is known about the underlying cause/effect relationship.

OBJECTIVES:
JC bone samples were analyzed to assess the expression and quantification of immune modulators that can play a role in the pathogenesis of IDs. The study supports a potential mechanism where JC is a mediating link in IDs.

MATERIALS AND METHODS:
Samples of fatty softened bone taken from JCs were extracted from 31 patients. The specimens were analyzed by bead-based multiplex technology and tested for seven immune messengers.

MATERIALS AND METHODS:
Samples of fatty softened bone taken from JCs were extracted from 31 patients. The specimens were analyzed by bead-based multiplex technology and tested for seven immune messengers.

RESULTS:
Regulated upon activation, normal T-cell expressed, and secreted (RANTES) and fibroblast growth factor (FGF)-2 were found at high levels in the JCs tested. Other cytokines could not be detected at excessive levels.

DISCUSSION:
The study confirms that JC is able to produce inflammatory messengers, primarily RANTES, and, secondarily, FGF-2. Both are implicated in many serious illnesses. The excessive levels of RANTES/FGF-2 in JC patients with amyotrophic lateral sclerosis, multiple sclerosis, rheumatoid arthritis, and breast cancer are compared to levels published in medical journals. Levels detected in JCs are higher than in the serum and cerebrospinal fluid of amyotrophic lateral sclerosis and multiple sclerosis patients and four-fold higher than in breast cancer tissue.

CONCLUSION:
This study suggests that JC might serve as a fundamental cause of IDs, through RANTES/FGF-2 production. Thus, JC and implicated immune messengers represent an integrative aspect of IDs and serve as a possible cause. Removing JCs may be a key to reversing IDs. There is a need to raise awareness about JC throughout medicine and dentistry.

EPMA J. 2015 May 6;6(1):10. doi: 10.1186/s13167-015-0032-4. eCollection 2015.

Chemokine RANTES/CCL5 as an unknown link between wound healing in the jawbone and systemic disease: is prediction and tailored treatments in the horizon?

Lechner J, von Baehr V.

ABSTRACT

BACKGROUND:

This research elucidates the question of whether common and widespread dental procedures (DP) like root filling (RF) and the removal of wisdom teeth (WT) contribute to chronic inflammation in the jawbone. Dentists, in carrying out these DP, can set off defective wound healing in the jawbone in ignorance of its connection to inflammatory mediators and the possibility of it being a hidden cause of chronic systemic diseases (SYD).

MATERIALS AND METHODS:

We examined samples of the jawbone for seven cytokines by multiplex analysis in three groups of jawbone areas. In order to clarify systemic interrelations, specimens from 16 patients were analyzed in areas of former surgery in the retromolar wisdom tooth area; specimens from 16 patients were analyzed in the jawbone, apically of teeth with RF; and specimens from 19 patients were of the healthy jawbone. Each of the retromolar and the apical jawbone samples showed clinically fatty degenerated and osteonecrotic medullary changes.

RESULTS:

All fatty necrotic and osteolytic jawbone (FDOJ) samples showed regulated on activation, normal T-cell expressed and secreted (RANTES) and fibroblast growth factor (FGF)-2 as the only extremely overexpressed cytokines. FDOJ cohorts showed a 30-fold mean overexpression of RANTES and a 20-fold overexpressed level of FGF-2 when compared to healthy controls.

CONCLUSIONS:

As RANTES is discussed in the literature as a possible contributor to inflammatory diseases, and though it might have oncogenic effects, we hypothesize that FDOJ in areas of improper and incomplete wound healing in the jawbone might act as hyperactivated signaling pathways, while serving as an unknown source of "silent inflammation". Because of the wide range of RANTES in immune diseases, treating FDOJ can cover many potential prediction or prognosis of individual outcomes.

J Biol Regul Homeost Agents. 2017 Apr-Jun;31(2):321-327.

Impact of Rantes from jawbone on Chronic Fatigue Syndrome.

Lechner J, Huesker K, Von Baehr V.

ABSTRACT

This study elucidates the question of whether chronic inflammation in the jawbone contributes to the development of Chronic Fatigue Syndrome (CFS). Fatty degenerative osteonecrosis in jawbone (FDOJ) may contribute to CFS by induction of inflammatory mediators. We examined seven cytokines by multiplex analysis in jawbone samples from two groups of patients. In order to clarify neurological interrelations, specimens from 21 CFS patients were analyzed from areas of previous surgery in the retromolar wisdom tooth area. Each of the retromolar jawbone samples showed clinically fatty degenerated and osteonecrotic medullary changes. As control, healthy jawbone specimens from 19 healthy patients were analyzed. All fatty necrotic and osteolytic jawbone (FDOJ) samples showed high expression of RANTES and fibroblast growth factor (FGF)-2. FDOJ cohorts showed a 30-fold mean overexpression of RANTES and a 20-fold overexpressed level of FGF-2 when compared to healthy controls. As RANTES is discussed in the literature as a possible contributor to inflammatory diseases, we hypothesize that FDOJ in areas of improper and incomplete wound healing in the jawbone may hyperactivate signaling pathways. Constituting a hidden source of “silent inflammation“ FDOJ may represent a hitherto unknown cause for the development of CFS.

Clin Cosmet Investig Dent. 2017 Nov 9;9:99-109. doi: 10.2147/CCIDE.S149545. eCollection 2017.

Aseptic-avascular osteonecrosis: local "silent inflammation" in the jawbone and RANTES/CCL5 overexpression.

Lechner J, Schuett S, von Baehr V.

ABSTRACT

Of the definitions listed in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), two disease descriptions can be found together: "idiopathic aseptic bone necrosis" and "avascular bone necrosis." The relevant literature on both the conditions abbreviates both as "aseptic ischemic osteonecrosis in the jawbone" (AIOJ). To shed light on the clinical details of this condition, osteolytic jawbone samples of 24 patients with different systemic immunological diseases were examined using four steps: presurgical dental X-ray, postsurgical histology, polymerase chain reaction DNA analysis (PCR DNA) of bacteria, and RANTES/CCL5 (R/C) expression. These four steps showed that neither X-ray nor histology delivered unambiguous results with respect to inflammatory processes; furthermore, the PCR results did not show evidence of any microbial load within the jaw samples. However, there is a striking, coherent overexpression of chemokine R/C in the AIOJ samples. This study proved the aseptic existence of "silent inflammation" within the jawbone. The ICD-10 (AIOJ) definition, which is hard to interpret, can now be substantiated with clinical evidence, while the cytokine expressions described in this report can explain the systemic immunological effects observed within the group of examined patients.

Int J Gen Med. 2018; 11: 155–166. Published online 2018 Apr 27. doi: 10.2147/IJGM.S152873.

The vitamin D receptor and the etiology of RANTES/CCL-expressive fatty-degenerative osteolysis of the jawbone: an interface between osteoimmunology and bone metabolism.

Lechner J, Aschoff J, Rudi T.

ABSTRACT

BACKGROUND:

Recent research on vitamin D indicates that our current understanding of the factors leading to chronic inflammation should be revised. One of the key mechanisms by which microbial immunosuppression occurs is the suppression of one of the most common endogenous cell nucleus receptors: the vitamin D receptor (VDR). Autoimmune diseases may be correlated with VDR deactivation (VDR-deac) which occurs when the receptor is no longer able to transcribe antimicrobial agents. Excess 1,25-dihydroxyvitamin D (1,25D) is not converted to 25-hydroxyvitamin D (25D); thus, high 1,25D levels may be accompanied by low 25D values.

PATIENTS AND METHODS:

Since 1,25D promotes osteoclast activity and may thereby cause osteoporosis, fatty-degenerative osteolysis of the jaw (FDOJ), as described by our team, may also be associated with VDR-deac. In 43 patients, vitamin D conversion, immune system function and the quality of bone resorption and formation in the jawbone were related factors that may enhance chronic inflammatory processes. Here, we examine the relationship between immunology and bone metabolism among 43 FDOJ patients and those with immune system diseases (ISDs).

RESULTS:

We provide a link between FDOJ, RANTES/CCL5 overexpression and VDR-deac.

CONCLUSION:

The clinical data demonstrate the interaction between VDR-deac and proinflammatory RANTES/CCL5 overexpression in FDOJ patients.

EPMA Journal 2019 Dec, Volume 10, Issue 4, pp 351–364.

Immunohistological staining of unknown chemokine RANTES/CCL5 expression in jawbone marrow defects—osteoimmunology and disruption of bone remodeling in clinical case studies targeting on predictive preventive personalized medicine

Lechner J, Schulz T, von Baehr V.

ABSTRACT

BACKGROUND:
Fatty degenerative osteonecrosis in the medullary spaces of the jawbone (FDOJ) may be identified as a lesser known source of RANTES/CCL5 (R/C) overexpression. The chemokine R/C also interferes with bone metabolism leading to osteolysis in areas affected by FDOJ. Many dental surgeries require functioning repair mechanisms and these may be disrupted by R/C overexpression.

OBJECTIVE:
To clarify the way in which R/C expression from adipocytes in FDOJ causes a disturbance in osteogenesis and impacts on medullary stem cells by investigating the detection of R/C expression with immunochemical staining.

MATERIALS AND METHODS:
We examined the tissue samples of 449 patients with FDOJ to assess the level of the chemokine R/C using bead-based Luminex® analysis. In six clinical case studies of FDOJ, we compared bone density, histological findings, R/C expression, and immunohistochemical staining.

RESULTS:
R/C is overexpressed by up to 30-fold in the 449 FDOJ cases when compared with healthy jawbone samples. The comparison of the six clinical cases consistently shows greatly reduced bone density, (i.e., osteolysis), but varies in terms of the level of agreement across the other three parameters.

DISCUSSION:
R/C from FDOJ sources may be implicated in several immune responses and considered a key pathogenetic pathway for increased adipogenesis rather than desirable osteogenesis. Adipocytes pathogenetically act via R/C expression in local FDOJ and systemically on the immune system.

CONCLUSION:
R/C may be regarded as an important trigger for possible pathological developments in the fate of hematopoietic stem cells. FDOJ is not a rigidly uniform process but reflects changing stages of development. The absence of correlating findings should not be interpreted as a misdiagnosis. It seems appropriate to direct further research in the field of "maxillo-mandibular osteoimmunology" focusing on R/C overexpression in FDOJ areas. This may contribute to the development of personalized strategies in preventive medicine.

3.3.3 General Reviews and Overviews

Clin Cosmet Investig Dent. 2018 Nov 9;10:251-262. doi: 10.2147/CCIDE.S184498. eCollection 2018.

Osteoimmunology of tumor necrosis factor-alpha, IL-6, and RANTES/CCL5: a review of known and poorly understood inflammatory patterns in osteonecrosis.

Lechner J, Rudi T, von Baehr V.

ABSTRACT

BACKGROUND:

The immune and bone systems are closely linked via cytokine cross-talk. This interdisciplinary field of research is referred to as osteoimmunology and pertains to inflammatory and osteoarticular diseases that feature the primary expression of tumor necrosis factor-alpha (TNF-α) and IL-6.

OBJECTIVE:

Are there bone resorptive processes wherein chronic inflammatory conditions are not linked to TNF-α and IL-6 expression, but rather to the expression of other cytokines?

MATERIALS AND METHODS:

A comprehensive literature search was performed in PubMed Central.

DISCUSSION:

Although all diseases with cytokines involved in bone resorption (TNF-α and IL-6) are at the forefront of destructive inflammatory processes, there is one exception in the literature: fatty oxide osteoporosis/osteolysis in the jawbone (FDOJ), which is associated with significant bone softening. However, it should be noted that TNF-α and IL-6 fall below the levels found in a healthy jawbone in this condition. Another conspicuous finding is that there is a nearly 35-fold overexpression of the chemokine RANTES/CCL5 (R/C) in all FDOJ cases studied thus far in the literature.

CONCLUSION:

FDOJ appears to represent a unique cytokine and inflammatory pattern from osteolysis in the body. R/C can be defined as the dominant carrier of a "maxillomandibular osteoimmunology".

4. Vitamins important in Dentistry

4.1 Vitamin C

4.1.1 Bone Metabolism

J Bone Miner Res. 2015 Nov;30(11):1945-55. doi: 10.1002/jbmr.2709. Epub 2015 Oct 7.

The Roles and Mechanisms of Actions of Vitamin C in Bone: New Developments.

Aghajanian P, Hall S, Wongworawat MD, Mohan S.

ABSTRACT

Vitamin C is an important antioxidant and cofactor that is involved in the regulation of development, function, and maintenance of several cell types in the body. Deficiencies in vitamin C can lead to conditions such as scurvy, which, among other ailments, causes gingivia, bone pain, and impaired wound healing. This review examines the functional importance of vitamin C as it relates to the development and maintenance of bone tissues. Analysis of several epidemiological studies and genetic mouse models regarding the effect of vitamin C shows a positive effect on bone health. Overall, vitamin C exerts a positive effect on trabecular bone formation by influencing expression of bone matrix genes in osteoblasts. Recent studies on the molecular pathway for vitamin C actions that include direct effects of vitamin C on transcriptional regulation of target genes by influencing the activity of transcription factors and by epigenetic modification of key genes involved in skeletal development and maintenance are discussed. With an understanding of mechanisms involved in the uptake and metabolism of vitamin C and knowledge of precise molecular pathways for vitamin C actions in bone cells, it is possible that novel therapeutic strategies can be developed or existing therapies can be modified for the treatment of osteoporotic fractures.

Curr Drug Targets. 2018;19(5):439-450. doi: 10.2174/1389450116666150907100838.

Vitamin C and Bone Health: Evidence from Cell, Animal and Human Studies.

Chin KY, Ima-Nirwana S.

ABSTRACT

BACKGROUND:

Vitamin C, traditionally associated with scurvy, is an important nutrient for maintaining bone health. It is essential in the production of collagen in bone matrix. It also scavenges free radicals detrimental to bone health.

OBJECTIVE:

This review aims to assess the current evidence of the bone-sparing effects of vitamin C derived from cell, animal and human studies.

RESULTS:

Cell studies showed that vitamin C was able to induce osteoblast and osteoclast formation. However, high-dose vitamin C might increase oxidative stress and subsequently lead to cell death. Vitamin C-deficient animals showed impaired bone health due to increased osteoclast formation and decreased bone formation. Vitamin C supplementation was able to prevent bone loss in several animal models of bone loss. Human studies generally showed a positive relationship between vitamin C and bone health, indicated by bone mineral density, fracture probability and bone turnover markers. Some studies suggested that the relationship between vitamin C and bone health could be U-shaped, more prominent in certain subgroups and different between dietary and supplemental form. However, most of the studies were observational, thus could not confirm causality. One clinical trial was performed, but it was not a randomized controlled trial, thus confounding factors could not be excluded.

CONCLUSION:

vitamin C may exert beneficial effects on bone, but more rigorous studies and clinical trials should be performed to validate this claim.

Clin Implant Dent Relat Res. 2018 Oct;20(5):793-798. doi: 10.1111/cid.12647. Epub 2018 Jul 24.

Role of vitamin C in wound healing after dental implant surgery in patients treated with bone grafts and patients with chronic periodontitis.

Li X, Tang L, Lin YF, Xie GF.

ABSTRACT

BACKGROUND:
Postoperative wound healing is an important part of the success of the dental implant surgery. However, in case of complex surgery or unfavorable factors, wound healing is often unsatisfactory.

OBJECTIVE:
The aim of this study was to explore the effects of vitamin C supplementation in wound healing, following the placement of dental implants with or without bone grafts and patients with chronic periodontitis.

METHODS:
This randomized controlled clinical trial included 128 patients requiring dental implants to replace missing teeth. Patients were divided into four groups, group A received dental implants supported by guided bone regeneration (GBR) technique, group B received dental implants with Bio-Oss Collagen, group C received dental implants in patients with chronic periodontitis, and group D received dental implants without any bone grafting or periodontal disease. Each group was divided into an experimental subgroup, who received vitamin C, and a control subgroup. Follow-up appointments were performed at day 3, day 7, and day 14 postsurgery, during which soft tissue healing and pain response scores were evaluated using the Landry index and visual analogue scale, respectively.

RESULTS:
The experimental subgroups had significantly higher healing indices than the controls ($P < .05$) at day 7 postsurgery for group B and day 14 postsurgery for groups A, B, and C. Group D displayed no difference between the experimental and control groups at any time point. In reference to vitamin C for pain relief, there were no statistically significant differences between the study groups.

CONCLUSION:
Using vitamin C supplementation improves postoperative healing following dental implant surgery in patients with chronic periodontitis and patients treated with GBR or Bio-Oss Collagen grafts. However, vitamin C supplementation does not decrease the postoperative pain associated with dental implant surgery.

Br J Nutr. 2018 Apr;119(8):847-858. doi: 10.1017/S0007114518000430.

Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: a systematic review and meta-analysis of observational studies.

Malmir H, Shab-Bidar S, Djafarian K.

ABSTRACT

We aimed to systematically review available data on the association between vitamin C intake and bone mineral density (BMD), as well as risk of fractures and osteoporosis, and to summarise this information through a meta-analysis. Previous studies on vitamin C intake in relation to BMD and risk of fracture and osteoporosis were selected through searching PubMed, Scopus, ISI Web of Science and Google Scholar databases before February 2017, using MeSH and text words. To pool data, either a fixed-effects model or a random-effects model was used, and for assessing heterogeneity, Cochran's Q and I 2 tests were used. Subgroup analysis was applied to define possible sources of heterogeneity. Greater dietary vitamin C intake was positively associated with BMD at femoral neck (pooled r 0·18; 0·06, 0·30) and lumbar spine (pooled r 0·14; 95 % CI 0·06, 0·22); however, significant between-study heterogeneity was found at femoral neck: I 2=87·6 %, P heterogeneity<0·001. In addition, we found a non-significant association between dietary vitamin C intake and the risk of hip fracture (overall relative risk=0·74; 95 % CI 0·51, 1·08). Significant between-study heterogeneity was found (I 2=79·1 %, P heterogeneity<0·001), and subgroup analysis indicated that study design, sex and age were the main sources of heterogeneity. Greater dietary vitamin C intake was associated with a 33 % lower risk of osteoporosis (overall relative risk=0·67; 95 % CI 0·47, 0·94). Greater dietary vitamin C intake was associated with a lower risk of hip fracture and osteoporosis, as well as higher BMD, at femoral neck and lumbar spine.

Nutrients. 2019 Feb 27;11(3). pii: E506. doi: 10.3390/nu11030506.

Vitamin C Activates Osteoblastogenesis and Inhibits Osteoclastogenesis via Wnt/β-Catenin/ATF4 Signaling Pathways.

Choi HK, Kim GJ, Yoo HS, Song DH, Chung KH, Lee KJ, Koo YT, An JH.

ABSTRACT

This study evaluated the effects of vitamin C on osteogenic differentiation and osteoclast formation, and the effects of vitamin C concentration on bone microstructure in ovariectomized (OVX) Wistar rats. Micro-computed tomography analysis revealed the recovery of bone mineral density and bone separation in OVX rats treated with vitamin C. Histomorphometrical analysis revealed improvements in the number of osteoblasts, osteoclasts, and osteocytes; the osteoblast and osteoclast surface per bone surface; and bone volume in vitamin C-treated OVX rats. The vitamin C-treated group additionally displayed an increase in the expression of osteoblast differentiation genes, including bone morphogenetic protein-2, small mothers against decapentaplegic 1/5/8, runt-related transcription factor 2, osteocalcin, and type I collagen. Vitamin C reduced the expression of osteoclast differentiation genes, such as receptor activator of nuclear factor kappa-B, receptor activator of nuclear factor kappa-B ligand, tartrate-resistant acid phosphatase, and cathepsin K. This study is the first to show that vitamin C can inhibit osteoporosis by promoting osteoblast formation and blocking osteoclastogenesis through the activation of wingless-type MMTV integration site family/β-catenin/activating transcription factor 4 signaling, which is achieved through the serine/threonine kinase and mitogen-activated protein kinase signaling pathways. Therefore, our results suggest that vitamin C improves bone regeneration.

4.1.2 Oral Health/Periodontitis

Indian J Dent Res. 2014 Jul-Aug;25(4):499-504. doi: 10.4103/0970-9290.142547.

Antioxidant and pro-oxidant activity of Vitamin C in oral environment.

Chakraborthy A, Ramani P, Sherlin HJ, Premkumar P, Natesan A.

ABSTRACT

OBJECTIVE:

To review studies reported in the literature elucidating the activity of Vitamin C and determine whether it is an antioxidant or a pro-oxidant.

MATERIALS AND METHODS:

Articles were searched in PubMed, MEDLINE using appropriate key words like "Vitamin C," "antioxidant activity," "pro-oxidant activity," "oral health" "oral disease." Hand search of journals was also performed. Articles were reviewed and analyzed.

RESULTS:

Search strategy reviewed 10 relevant articles which studied the dual role of Vitamin C. 65% of authors analyzed antioxidant action of ascorbic acid compared to 35% of the pro-oxidant potential. Vitamin C acts as an antioxidant and a pro-oxidant by a plethora of mechanisms. Factors determining its bimodal activity were studied, and the frequencies of their occurrence in the literature were depicted in percentage.

CONCLUSION:

The data validates the role of Vitamin C as an antioxidant under physiologic conditions exhibiting a cross over role as a pro-oxidant in pathological conditions. Further studies are required to substantiate its pro-oxidant activity to draw concrete conclusions.

BMC Oral Health. 2016 Jul 26;17(1):28. doi: 10.1186/s12903-016-0257-1.

An oral health optimized diet can reduce gingival and periodontal inflammation in humans - a randomized controlled pilot study.

Woelber JP, Bremer K, Vach K, König D, Hellwig E, Ratka-Krüger P, Al-Ahmad A, Tennert C.

ABSTRACT

BACKGROUND:

The aim of this pilot study was to investigate the effects of four weeks of an oral health optimized diet on periodontal clinical parameters in a randomized controlled trial.

METHODS:

The experimental group (n = 10) had to change to a diet low in carbohydrates, rich in Omega-3 fatty acids, and rich in vitamins C and D, antioxidants and fiber for four weeks. Participants of the control group (n = 5) did not change their dietary behavior. Plaque index, gingival bleeding, probing depths, and bleeding upon probing were assessed by a dentist with a pressure-sensitive periodontal probe.

RESULTS:

Despite constant plaque values in both groups, all inflammatory parameters decreased in the experimental group to approximately half that of the baseline values. This reduction was significantly different compared to that of the control group.

CONCLUSION:

A diet low in carbohydrates, rich in Omega-3 fatty acids, rich in vitamins C and D, and rich in fibers can significantly reduce gingival and periodontal inflammation.

PLoS One. 2017 May 10;12(5):e0177074. doi: 10.1371/journal.pone.0177074. eCollection 2017.

The association of dietary vitamin C intake with periodontitis among Korean adults: Results from KNHANES IV.

Lee JH, Shin MS, Kim EJ, Ahn YB, Kim HD.

ABSTRACT

METHOD:

A total of 10,930 Korean adults (≥19 years) from the fourth Korean National Health and Nutrition Examination Survey data set were included in this cross-sectional study. Periodontitis was defined as community periodontal index score of 3 or 4.

RESULTS:

Those with inadequate dietary vit C intake were more likely by 1.16 times to have periodontitis than those with adequate dietary vit C intake (adjusted odds ratio [aOR] = 1.16, 95% confidence interval = 1.04-1.29). Lowest and middle-low quartile of dietary vit C intake, compared to highest quartile of dietary vit C intake, showed significant association (aOR = 1.28 and 1.22 respectively), which was in a biological-gradient relationship (trend-p <0.05).

CONCLUSIONS:

Our data showed that inadequate dietary vit C intake was independently associated with periodontitis among Korean adults. Hence, adequate intake of dietary vitamin C could be substantially important on the promotion of periodontal health among Korean adults.

Int J Environ Res Public Health. 2019 Jul 11;16(14). pii: E2472. doi: 10.3390/ijerph16142472.

The Relationship between Vitamin C and Periodontal Diseases: A Systematic Review.

Tada A, Miura H.

ABSTRACT

Vitamin C is important for preventing and slowing the progression of many diseases. There is significant evidence linking periodontal disease and vitamin C. We aimed to systematically review the studies addressing the relationship between vitamin C and periodontal disease, and the preventive ability of vitamin C against periodontal disease. The vitamin C intake and blood levels were negatively related to periodontal disease in all seven cross-sectional studies. The subjects who suffer from periodontitis presented a lower vitamin C intake and lower blood-vitamin C levels than the subjects without periodontal disease in the two case-control studies. The patients with a lower dietary intake or lower blood level of vitamin C showed a greater progression of periodontal disease than the controls. The intervention using vitamin C administration improved gingival bleeding in gingivitis, but not in periodontitis. Alveolar bone absorption was also not improved. The present systematic review suggested that vitamin C contributes to a reduced risk of periodontal disease.

4.1.3 Systemic Relevance

Int J Vitam Nutr Res Suppl. 1982;23:103-13.

Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate.

Murata A, Morishige F, Yamaguchi H.

ABSTRACT

Clinical trials administering supplemental ascorbate to terminal cancer patients were conducted at two hospitals in Japan. During the period 1973-1977 there were 99 patients with terminal cancer at the Fukuoka Torikai Hospital. The average times of survival after the date of designation as terminal were 43 days for 44 low-ascorbate patients and 246 days for 55 high-ascorbate patients. Three of the high-ascorbate patients were still alive, their average survival being 1550 days, on April 1, 1980. Similar effectiveness of ascorbate was also observed at the Kamioka Kozan Hospital. There were 31 patients with terminal cancer during the period 1975-1979. The average survival times were 48 days for 19 control patients and 115 days for 6 high-ascorbate patients. One of the high-ascorbate patients was still alive, his survival being 215 days. In addition to the increase in survival times, the administration of large doses of ascorbate seemed to improve the quality of life.

CMAJ. 2006 Mar 28;174(7):937-42.

Intravenously administered vitamin C as cancer therapy: three cases.

Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M.

ABSTRACT

Early clinical studies showed that high-dose vitamin C, given by intravenous and oral routes, may improve symptoms and prolong life in patients with terminal cancer. Double-blind placebo-controlled studies of oral vitamin C therapy showed no benefit. Recent evidence shows that oral administration of the maximum tolerated dose of vitamin C (18 g/d) produces peak plasma concentrations of only 220 micromol/L, whereas intravenous administration of the same dose produces plasma concentrations about 25-fold higher. Larger doses (50-100 g) given intravenously may result in plasma concentrations of about 14,000 micromol/L. At concentrations above 1000 micromol/L, vitamin C is toxic to some cancer cells but not to normal cells in vitro. We found 3 well-documented cases of advanced cancers, confirmed by histopathologic review, where patients had unexpectedly long survival times after receiving high-dose intravenous vitamin C therapy. We examined clinical details of each case in accordance with National Cancer Institute (NCI) Best Case Series guidelines. Tumour pathology was verified by pathologists at the NCI who were unaware of diagnosis or treatment. In light of recent clinical pharmacokinetic findings and in vitro evidence of anti-tumour mechanisms, these case reports indicate that the role of high-dose intravenous vitamin C therapy in cancer treatment should be reassessed.

J Korean Med Sci. 2007 Feb; 22(1): 7–11. Published online 2007 Feb 28. doi: 10.3346/jkms.2007.22.1.7

Changes of Terminal Cancer Patients' Health-related Quality of Life after High Dose Vitamin C Administration

Yeom CH, Jung GC, Song KJ.

ABSTRACT

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients. All patients were given an intravenous administration of 10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C. Quality of life was assessed with EORTC QLQ-C30. In the global health/quality of life scale, health score improved from 36±18 to 55±16 after administration of vitamin C ($p=0.001$). In functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C ($p<0.05$). In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C ($p<0.005$). The other function and symptom scales were not significantly changed after administration of vitamin C. In terminal cancer patients, the quality of life is as important as cure. Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

Nutrients. 2017 Nov 3;9(11). pii: E1211. doi: 10.3390/nu9111211.

Vitamin C and Immune Function.

Carr AC, Maggini S.

ABSTRACT

Vitamin C is an essential micronutrient for humans, with pleiotropic functions related to its ability to donate electrons. It is a potent antioxidant and a cofactor for a family of biosynthetic and gene regulatory enzymes. Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C supports epithelial barrier function against pathogens and promotes the oxidant scavenging activity of the skin, thereby potentially protecting against environmental oxidative stress. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. It is also needed for apoptosis and clearance of the spent neutrophils from sites of infection by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage. The role of vitamin C in lymphocytes is less clear, but it has been shown to enhance differentiation and proliferation of B- and T-cells, likely due to its gene regulating effects. Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections. Prophylactic prevention of infection requires dietary vitamin C intakes that provide at least adequate, if not saturating plasma levels (i.e., 100-200 mg/day), which optimize cell and tissue levels. In contrast, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased inflammatory response and metabolic demand.

J Transl Med. 2017 Apr 14;15(1):77. doi: 10.1186/s12967-017-1179-7.

The role of vitamin C in the treatment of pain: new insights.

Carr AC, McCall C.

ABSTRACT

The vitamin C deficiency disease scurvy is characterised by musculoskeletal pain and recent epidemiological evidence has indicated an association between suboptimal vitamin C status and spinal pain. Furthermore, accumulating evidence indicates that vitamin C administration can exhibit analgesic properties in some clinical conditions. The prevalence of hypovitaminosis C and vitamin C deficiency is high in various patient groups, such as surgical/trauma, infectious diseases and cancer patients. A number of recent clinical studies have shown that vitamin C administration to patients with chronic regional pain syndrome decreases their symptoms. Acute herpetic and post-herpetic neuralgia is also diminished with high dose vitamin C administration. Furthermore, cancer-related pain is decreased with high dose vitamin C, contributing to enhanced patient quality of life. A number of mechanisms have been proposed for vitamin C's analgesic properties. Herein we propose a novel analgesic mechanism for vitamin C; as a cofactor for the biosynthesis of amidated opioid peptides. It is well established that vitamin C participates in the amidation of peptides, through acting as a cofactor for peptidyl-glycine α-amidating monooxygenase, the only enzyme known to amidate the carboxy terminal residue of neuropeptides and peptide hormones. Support for our proposed mechanism comes from studies which show a decreased requirement for opioid analgesics in surgical and cancer patients administered high dose vitamin C. Overall, vitamin C appears to be a safe and effective adjunctive therapy for acute and chronic pain relief in specific patient groups.

Blood cells, molecules & diseases 69, S. 57–64. DOI: 10.1016/j.bcmd.2017.09.005.

Mechanisms of anti-cancer effects of ascorbate: Cytotoxic activity and epigenetic modulation

Mastrangelo D, Pelosi E, Castelli G, Lo-Coco F, Testa U.

ABSTRACT

Vitamin C (Vit C or Ascorbate) is essential for many fundamental biochemical processes. Vit C is an essential nutrient with redox functions at normal physiologic concentrations. The main physiologic function of this vitamin is related to its capacity to act as a co-factor for a large family of enzymes, collectively known as Fe and 2-oxoglutarate-dependent dioxygenases. It also modulates epigenetic gene expression through the control of TET enzymes activity. Vit C also has several biological properties allowing to restore the deregulated epigenetic response observed in many tumors. High-dose Vit C has been investigated as a treatment for cancer patients since the 1969. Pharmacologic ascorbate acts as a pro-drug for hydrogen peroxide formation (H2O2) and, through this mechanism, kills cancer cells. To achieve high in vivo concentrations, Ascorbate must be injected by i.v. route. Initial clinical studies of Ascorbate cancer treatment have provided encouraging results, not confirmed in subsequent studies. Recent clinical studies using i.v. injection of high-dose Ascorbate have renewed the interest in the field, showing that significant anti-tumor activity. Pre-clinical studies have led to identify tumors sensitive to Ascorbate that could potentially benefit from this treatment either through an epigenetic modulator effect or through tumor killing by oxidative stress.

Nature Reviews Cancer volume 19, pages271–282(2019).

Targeting cancer vulnerabilities with high-dose vitamin C

Ngo B, Van Riper JM, Cantley LC, Yun J.

ABSTRACT

Over the past century, the notion that vitamin C can be used to treat cancer has generated much controversy. However, new knowledge regarding the pharmacokinetic properties of vitamin C and recent high-profile preclinical studies have revived interest in the utilization of high-dose vitamin C for cancer treatment. Studies have shown that pharmacological vitamin C targets many of the mechanisms that cancer cells utilize for their survival and growth. In this Opinion article, we discuss how vitamin C can target three vulnerabilities many cancer cells share: redox imbalance, epigenetic reprogramming and oxygen-sensing regulation. Although the mechanisms and predictive biomarkers that we discuss need to be validated in well-controlled clinical trials, these new discoveries regarding the anticancer properties of vitamin C are promising to help identify patient populations that may benefit the most from high-dose vitamin C therapy, developing effective combination strategies and improving the overall design of future vitamin C clinical trials for various types of cancer.

4.2 Vitamin D3

4.2.1 Arteriosclerosis/CVD

Hypertension. 2007 May;49(5):1063-9. Epub 2007 Mar 19.

Plasma 25-hydroxyvitamin D levels and risk of incident hypertension.

Forman JP, Giovannucci E, Holmes MD,
Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC.

ABSTRACT

Laboratory studies indicate that 1,25-dihydroxyvitamin D suppresses renin expression and vascular smooth muscle cell proliferation; clinical studies demonstrate an inverse association between ultraviolet radiation, a surrogate marker for vitamin D synthesis, and blood pressure. We prospectively studied the independent association between measured plasma 25-hydroxyvitamin D [25(OH)D] levels and risk of incident hypertension and also the association between predicted plasma 25(OH)D levels and risk of incident hypertension. Two prospective cohort studies including 613 men from the Health Professionals' Follow-Up Study and 1198 women from the Nurses' Health Study with measured 25(OH)D levels were followed for 4 to 8 years. In addition, 2 prospective cohort studies including 38 388 men and 77 531 women with predicted 25(OH)D levels were followed for 16 to 18 years. During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma 25(OH)D levels were <15 ng/mL (ie, vitamin D deficiency) compared with those whose levels were >or=30 ng/mL was 6.13 (95% confidence interval [CI]: 1.00 to 37.8). Among women, the same comparison yielded a relative risk of 2.67 (95% CI: 1.05 to 6.79). The pooled relative risk combining men and women with measured 25(OH)D levels using the random-effects model was 3.18 (95% CI: 1.39 to 7.29). Using predicted 25(OH)D levels in the larger cohorts, the multivariable relative risks comparing the lowest to highest deciles were 2.31 (95% CI: 2.03 to 2.63) in men and 1.57 (95% CI: 1.44 to 1.72) in women. Plasma 25(OH)D levels are inversely associated with risk of incident hypertension.

Am J Cardiol. 2010 Oct 1;106(7):963-8. doi: 10.1016/j.amjcard.2010.05.027. Epub 2010 Aug 11.

Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population.

Anderson JL, May HT, Horne BD, Bair TL, Hall NL,
Carlquist JF, Lappé DL, Muhlestein JB;
Intermountain Heart Collaborative (IHC) Study Group.

ABSTRACT

We prospectively analyzed a large electronic medical records database to determine the prevalence of vitamin D deficiency and the relation of vitamin D levels to prevalent and incident CV risk factors and diseases, including mortality. The database contained 41,504 patient records with at least one measured vitamin D level. The prevalence of vitamin D deficiency (≤30 ng/ml) was 63.6%, with only minor differences by gender or age. Vitamin D deficiency was associated with highly significant increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Also, those without risk factors but with severe deficiency had an increased likelihood of developing diabetes, hypertension, and hyperlipidemia. The vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke, as well as with incident death, heart failure, coronary artery disease/myocardial infarction, stroke, and their composite. In conclusion, we have confirmed a high prevalence of vitamin D deficiency in the general healthcare population and an association between vitamin D levels and prevalent and incident CV risk factors and outcomes. These observations lend strong support to the hypothesis that vitamin D might play a primary role in CV risk factors and disease. Given the ease of vitamin D measurement and replacement, prospective studies of vitamin D supplementation to prevent and treat CV disease are urgently needed.

J Am Coll Cardiol. 2011 Jul 5; 58(2): 186–192. doi: 10.1016/j.jacc.2011.02.051.

Vitamin D Status Is Associated With Arterial Stiffness and Vascular Dysfunction in Healthy Humans.

Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, Kavtaradze N, Uphoff I, Hooper C, Tangpricha V, Wayne Alexander R, Brigham K, Quyyumi A.

ABSTRACT

METHODS:

We measured serum 25-OH D in 554 subjects. Endothelial function was assessed as brachial artery flow-mediated dilation, and microvascular function was assessed as digital reactive hyperemia index.

RESULTS:

Mean 25-OH D was 31.8 ± 14 ng/ml. After adjustment for age, sex, race, body mass index, total cholesterol, low-density lipoprotein, triglycerides, C-reactive protein, and medication use, 25-OH D remained independently associated with flow-mediated vasodilation, reactive hyperemia index, pulse wave velocity, augmentation index, and subendocardial viability ratio. In 42 subjects with vitamin D insufficiency, normalization of 25-OH D at 6 months was associated with increases in reactive hyperemia index (0.38 ± 0.14, p = 0.009) and subendocardial viability ratio (7.7 ± 3.1, p = 0.04), and a decrease in mean arterial pressure (4.6 ± 2.3 mm Hg, p = 0.02).

CONCLUSIONS:

Vitamin D insufficiency is associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels in humans, irrespective of traditional risk burden. Our findings provide impetus for larger trials to assess the effects of vitamin D therapy in cardiovascular disease.

J Nutr. 2017 Sep;147(9):1607-1615. doi: 10.3945/jn.117.250209. Epub 2017 Aug 2.

Vitamin D in the Spectrum of Prediabetes and Cardiovascular Autonomic Dysfunction.

Dimova R, Tankova T, Chakarova N.

ABSTRACT

Cardiovascular autonomic neuropathy (CAN) is an independent risk factor for mortality in patients with diabetes and prediabetes and is associated with an increased risk of developing type 2 diabetes and cardiovascular disease. Accumulating data indicate the presence of peripheral nerve injury at these early stages of dysglycemia and its multifactorial pathogenesis. Prediabetes is associated with vitamin D insufficiency. Vitamin D is proposed to prevent the progression of glucose intolerance. The putative underlying mechanisms include maintenance of the intracellular calcium concentration, direct stimulation of insulin receptor expression, and enhancement of the insulin response to glucose transporters. The effects of vitamin D supplementation on glucose tolerance and related autonomic nerve dysfunction have been a recent focus of scientific interest. Although well-designed observational studies are available, the causative relation between vitamin D deficiency, glucose intolerance, and CAN is still debatable. One reason might be that interventional studies are unpersuasive with regard to the beneficial clinical effects of vitamin D supplementation. Because of its favorable side effect profile, vitamin D supplementation might represent an attractive therapeutic option for treating the pandemic prevalence of prediabetes and vitamin D deficiency. Vitamin D supplementation can improve glucose tolerance and cardiovascular autonomic function and can thus reduce cardiovascular mortality among subjects with different stages of glucose intolerance and autonomic dysfunction. However, more patient-centered trials on the use of vitamin D supplementation in different conditions are needed.

Nutr Rev. 2019 Dec 1;77(12):890-902. doi: 10.1093/nutrit/nuz037.

Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis.

Dibaba DT.

ABSTRACT

CONTEXT:
Vitamin D deficiency is highly prevalent across the world. The existing evidence suggests vitamin D may have beneficial effects on serum lipid profiles and thus cardiovascular health.

OBJECTIVE:
The objective of this systematic review and meta-analysis was to examine the effect of vitamin D supplementation on serum lipid profiles.

DATA SOURCE:
Original randomized controlled trials (RCTs) examining the effect of vitamin D supplementation on serum lipid profiles and published before July 2018 were identified by searching online databases, including PubMed, Google Scholar, and ScienceDirect, using a combination of relevant keywords.

DATA EXTRACTION:
Data on study characteristics, effect size, measure of variation, type of vitamin D supplementation, and duration of follow-up were extracted by the author.

DATA ANALYSIS:
PRISMA guidelines for systematic reviews were followed. Random effects (DerSimonian and Laird [D-V)] models were used to pool standardized mean differences in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides between the active and the placebo arms of RCT studies. Between-study heterogeneities were assessed using Cochrane Q and I2, and publication bias was assessed using Begg's test, Egger's test, and funnel plot.

RESULTS:
A total of 41 RCTs comprising 3434 participants (n = 1699 in the vitamin D supplementation arm and n = 1735 in the placebo arm) were identified and included in the meta-analysis. Approximately 63.4% of study participants were women, with 14 studies conducted entirely among women. Approximately 24% of the trials had follow-up duration >6 months, whereas the remaining 76% had follow-up duration of <6 months. The standardized mean differences (SMDs) and 95% confidence intervals (CIs) for comparing the change from baseline to follow-up between the vitamin D supplementation arm and the placebo (control) arm were as follows: total cholesterol = -0.17 (-0.28 to -0.06); LDL cholesterol = -0.12 (-0.23 to -0.01); triglycerides = -0.12 (-0.25 to 0.01); and HDL cholesterol = -0.19 (-0.44 to 0.06). After removing a trial that was an outlier based on the magnitude of the effect size, the SMD for triglycerides was -0.15 (-0.24 to -0.06) and that for HDL cholesterol was -0.10 (-0.28 to 0.09). The improvements in total cholesterol and triglycerides were more pronounced in participants with baseline vitamin D deficiency.

CONCLUSIONS:
Vitamin D supplementation appeared to have a beneficial effect on reducing serum total cholesterol, LDL cholesterol, and triglyceride levels but not HDL cholesterol levels. Vitamin D supplementation may be useful in hypercholesterolemia patients with vitamin D insufficiency who are at high risk of cardiovascular diseases.

Asia Pac J Clin Nutr. 2018;27(1):231-237. doi: 10.6133/apjcn.022017.08.

Vitamin D status and cardiometabolic risk factors in young adults in Hong Kong: associations and implications.

Wang EW, Pang MY, Siu PM, Lai CK, Woo J, Collins AR, Benzie IF.

ABSTRACT

METHODS AND STUDY DESIGN:

In this observational study, fasting venous blood was collected from 196 (63 males, 133 females), young (18-26 years) non-smoking, nonobese, consenting adults in good general health. Plasma 25(OH)D was measured by LC-MS/MS. A panel of established cardiometabolic risk factors (HbA1c, plasma glucose, lipid profile, hsCRP) and blood pressure were also measured.

RESULTS:

Mean (SD) plasma 25(OH)D concentration was 42.1 (13.0), with range 15.7-86.8 nmol/L; 141/196 subjects (72%) had vitamin D deficiency (25(OH)D <50 nmol/L); 13/184 (6.6%) were severely deficient (<25 nmol/L). Inverse association was seen between 25(OH)D and fasting glucose. Higher HbA1c and TC:HDL-C ratio and lower HDL-C were seen in those with plasma 25(OH)D <25 nmol/L ($p<0.05$).

CONCLUSIONS:

Vitamin D deficiency was highly prevalent and associated with poorer cardiometabolic risk profile in these young adults. Public health strategies for addressing vitamin D deficiency are needed urgently. These new data provide support for further study on vitamin D deficiency as a modifiable risk factor for cardiometabolic disease and the ameliorative effects of increased vitamin D intake on cardiometabolic disease risk profile of vitamin D-deficient young adults.

4.2.2 Bone Metabolism

Crit Rev Eukaryot Gene Expr. 2001;11(1-3):199-226.

Vitamin D control of osteoblast function and bone extracellular matrix mineralization.

van Leeuwen JP, van Driel M, van den Bemd GJ, Pols HA.

ABSTRACT

Vitamin D is the major regulator of calcium homeostasis and protects the organism from calcium deficiency via effects on the intestine, kidney, parathyroid gland, and bone. Disturbances in the vitamin D endocrine system (e.g., vitamin D-dependent rickets type I and type II), result in profound effects on the mineralization of bone. Recent studies with vitamin D receptor knockout mice also show effects on bone. It is questioned whether vitamin D has a direct effect on bone formation and mineralization. In rickets and particular vitamin D receptor knockout mice, calcium supplementation restores bone mineralization. However, the vitamin D receptor is present in osteoblasts, and vitamin D affects the expression of various genes in osteoblasts. This review focuses on the role of vitamin D in the control of osteoblast function and discusses the current knowledge of the direct effects of vitamin D on mineralization. Moreover, the role of vitamin D metabolism and the mechanism of action of vitamin D and interaction with other hormones and factors are discussed.

Curr Pharm Des. 2004;10(21):2535-55.

Osteoblast differentiation and control by vitamin D and vitamin D metabolites.

van Driel M, Pols HA, van Leeuwen JP.

ABSTRACT

Vitamin D plays a major role in the regulation of mineral homeostasis and affects bone metabolism. Most effects of vitamin D have been attributed to the 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) metabolite. 1,25-(OH)2D3 regulates its own metabolism by mediating the 24-hydroxylase activity, which leads to the degradation of the molecule but intermediate products (24-hydroxylated forms of 25-(OH)D3 and 1,25-(OH)2D3) may be biologically active too. In this review we describe the direct effects of 1,25-(OH)2D3 on osteoblast function (proliferation, apoptosis, expression of specific bone proteins and growth factors) and mineralization. The role of the vitamin D receptor, vitamin D metabolism and the effects on osteoblast gene expression are documented. Vitamin D acts often in interaction with factors. The effects of 1,25-(OH)2D3 on the expression of growth factors and its interaction with growth factors and hormones in the control of osteoblast differentiation are discussed. Finally, the current status of the development of synthetic vitamin D analogs with bone anabolic characteristics for therapeutic application is described.

J Prosthodont. 2009 Aug;18(6):473-8. doi: 10.1111/j.1532-849X.2009.00446.x. Epub 2009 Mar 26.

Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model.

Kelly J, Lin A, Wang CJ, Park S, Nishimura I.

ABSTRACT

PURPOSE:

The patient population varies in nutritional deficiencies, which may confound the host response to biomaterials. The objective of this study was to evaluate the effect of a common deficiency of vitamin D on implant osseointegration in the rat model.

MATERIALS AND METHODS:

Male Sprague-Dawley rats were maintained under the cessation of vitamin D intake and UV exposure. The serum levels of 1,25(OH)(2)D(3), 25 OHD(3), Ca, and P were determined. Miniature cylindrical Ti6Al4V implants (2-mm long, 1-mm diameter) were fabricated with double acid-etched (DAE) surface or modified DAE with discrete crystalline deposition (DCD) of hydroxyapatite nanoparticles. DAE and DCD implants were placed in the femurs of vitamin D-insufficient and control rats. After 14 days of healing, the femur-implant samples were subjected to implant push-in test and nondecalcified histology. The surfaces of recovered implant specimens after the push-in test were further evaluated by scanning electron microscopy (SEM).

RESULTS:

The decreased serum level of 25 OHD(3) demonstrated the establishment of vitamin D insufficiency in this model. The implant push-in test revealed that DAE and DCD implants in the vitamin D-insufficient group (15.94 +/- 8.20 N, n = 7; 15.63 +/- 3.96 N, n = 7, respectively) were significantly lower than those of the control group (24.99 +/- 7.92 N, n = 7, $p < 0.05$; 37.48 +/- 17.58 N, n = 7, $p < 0.01$, respectively). The transcortical bone-to-implant contact ratio (BIC) was also significantly decreased in the vitamin D-insufficient group. SEM analyses further suggested that the calcified tissues remaining next to the implant surface after push-in test appeared unusually fragmented.

CONCLUSIONS:

The effect of vitamin D insufficiency significantly impairing the establishment of Ti6Al4V implant osseointegration in vivo was unexpectedly profound. The outcome of Ti-based endosseous implants may be confounded by the increasing prevalence of vitamin D insufficiency in our patient population.

Front Oral Biol. 2009;13:102-109. doi: 10.1159/000242400. Epub 2009 Sep 21.

Regulation of enamel and dentin mineralization by vitamin D receptor.

Zhang X, Beck P, Rahemtulla F, Thomas HF.

ABSTRACT

BACKGROUND:

Vitamin D plays an important role in bone mineralization. Enamel and dentin are two mineralized tissues of different origins that are part of the tooth structure, but the mechanism by which vitamin D regulates the mineralization of these tissues remains unclear. We examined the mineral deposition pattern of enamel and dentin in continuously erupting incisors in a vitamin D receptor (VDR) deficient mouse model to determine the effect of vitamin D receptor pathway on enamel and dentin mineralization.

METHODS:

VDR wild-type mice (VDR+/+) and VDR-deficient (VDR--/--) littermates were sacrificed at 70.5 days of age, and their mandibles were dissected. Immunostaining of biglycan and decorin was used to evaluate the dentin maturation. Micro-computerized tomography (micro-CT) was used to compare the mineral density (MD) of enamel and dentin of the two groups at different regions along the axis of the mandibular incisors. Scanning electronic microscopy (SEM) was employed to examine the ultrastructure of enamel and dentin at the levels corresponding to those examined in the micro-CT studies. Furthermore, an accelerated eruption procedure was performed to exclude the effect of delayed eruption on enamel and dentin mineralization

.

RESULTS:

Different mineral deposition patterns of enamel and dentin were observed at different levels of the incisors in the VDR+/+ and VDR--/-- groups. Early enamel maturation and mineralization, and dentin hypomineralization were observed in the VDR--/-- group.

CONCLUSION:

Vitamin D affects enamel and dentin mineralization through different mechanisms. It may affect the mineralization of dentin systemically while enamel mineralization may be regulated locally.

Clin Oral Implants Res. 2012 Nov;23(11):1308-13. doi: 10.1111/j.1600-0501.2011.02346.x. Epub 2011 Dec 12.

Impact of dietary vitamin D on osseointegration in the ovariectomized rat.

Dvorak G, Fügl A, Watzek G, Tangl S, Pokorny P, Gruber R.

ABSTRACT

AIM:

Vitamin D deficiency is highly prevalent in the population and associated with impaired peri-implant bone regeneration. Yet, there is a gap in understanding the impact of vitamin D supplementation on the process of osseointegration. In this study, the effect of vitamin D supplementation on peri-implant bone regeneration was investigated.

METHODS:

Fifty ovariectomized Sprague-Dawley rats were divided into three groups. The depletion group was fed a vitamin D-free diet for 8 weeks. The repletion group received vitamin D-free diet for 6 weeks, before animals were switched to standard diet containing 2400 IU/kg vitamin D. The control group was fed the standard diet. Two titanium mini-implants were placed in the tibia. All groups remained on their previous diet until sacrifice. Blood sample testing and histomorphometric analysis were performed.

RESULTS:

Vitamin D depletion caused a significant reduction in 25-hydroxvitamin D in rat serum that returned to control levels in the repletion group. This vitamin deficiency was associated with a decrease in bone-to-implant contact in the cortical area, which was leveled to controls in the repletion group. No significant changes by vitamin D depletion were noticed in the medullar compartment. Moreover, also the peri-implant bone area and the mineral apposition rate remained unchanged upon vitamin D depletion.

CONCLUSION:

These results indicate that vitamin D deficiency has a negative impact on cortical peri-implant bone formation in ovariectomized rats, which can be compensated by vitamin D supplementation. This study provides first insight into the potential beneficial effect of vitamin D supplementation in implant dentistry.

Bratisl Lek Listy. 2013;114(8):439-45.

The prevalence and risk factors for osteoporosis in patients with inflammatory bowel disease.

Miznerova E, Hlavaty T, Koller T, Toth J, Holociova K, Huorka M, Killinger Z, Payer J.

ABSTRACT

METHODS:

The cohort consisted of 76 IBD patients, 40 with Crohn's disease (CD) and 36 with ulcerative colitis (UC). Clinical characteristics of every patient were recorded, i.e. age, sex, duration of the disease, clinical behavior, location of disease according to Montreal classification, surgeries, steroid medication, sIBDQ, and smoking habits. We examined the serum 25-hydroxyl vitamin D3 (25-OHD3) in each patient.

RESULTS:

Osteoporosis was documented in 10 IBD patients (13.2 %), while osteopenia in 35 of them (46.1 %). Patients with CD have significantly lower femoral Z score than patients with UC. Femoral Z score was strongly associated with disease duration, and in CD patients suffering from stricturing form, with ileic or ileocolic location and history of proctocolectomy or total colectomy. Patients with osteoporosis had a significantly lower level of 25-OHD3 than patients with normal Bone Mineral Density.

CONCLUSION:

Patients with long disease duration and those suffering from stricturing form of CD with ileic/ileocolic location and history of proctocolectomy/total colectomy are at higher risk of developing osteoporosis than other IBD patients. The high proportion of osteopenia/osteoporosis in our study underlines the importance of BMD measurement in all IBD patients as a base for initiating the appropriate treatment.

J R Nav Med Serv. 2014;100(3):328-32.

Vitamin D deficiency as a suspected causative factor in the failure of an immediately placed dental implant: a case report.

Bryce G, MacBeth N.

ABSTRACT

AIM:

To discuss the influence of Vitamin D deficiency in the osseointegration process of a dental implant by way of a case report.

SUMMARY:

A 29-year-old soldier attended clinic with a fractured mandibular premolar (tooth 44) that was traumatised following head trauma related to the detonation of an Improvised Explosive Device (IED) whilst serving on operational duty. The tooth was deemed unsalvageable and was extracted with immediate placement of a dental implant. The patient experienced no problems but at assessment, five months post-operatively, no osseo-integration of the implant was found. Concurrent medical investigations revealed that he was severely Vitamin D deficient and that this may have contributed to the implant failure.

CONCLUSION:

Vitamin D deficiency may play a role in the failure of osseointegration in dental implants. The assessment of vitamin D status in patients who have been in long-term hospital care or rehabilitation should be considered, prior to the placement of dental implants.

J Oral Implantol. 2014 Feb;40(1):110-4. doi: 10.1563/AAID-JOI-D-13-00062. Epub 2013 Oct 9.

Two neglected biologic risk factors in bone grafting and implantology: high low-density lipoprotein cholesterol and low serum vitamin D.

Choukroun J, Khoury G, Khoury F, Russe P, Testori T, Komiyama Y, Sammartino G, Palacci P, Tunali M, Choukroun E.

ABSTRACT

Following a failure of a bone graft or an implant placement, the hypothesis of a biological abnormality is rarely considered as a possible cause. A systematic search of peer-reviewed literature for dyslipidemia or vitamin D deficiency may explain this lack of consideration. Excess low-density lipoprotein cholesterol (dyslipidemia) is responsible for a slower bone metabolism or lower dental implant osseointegration. In addition, vitamin D is a key factor for linking innate and adaptive immunity. Both of these factors are compromised under the conditions of vitamin D deficiency. Therefore, vitamin D deficiency slows implant osseointegration and increases the risk of graft infection. Vitamin D is also involved in immune function and therefore allergic reactions.

Bonekey Rep. 2014 Feb 5;3:499. doi: 10.1038/bonekey.2013.233. eCollection 2014.

Vitamin D: direct effects of vitamin D metabolites on bone: lessons from genetically modified mice.

Eisman JA, Bouillon R.

ABSTRACT

The vitamin D endocrine system has clear beneficial effects on bone as demonstrated by prevention of rickets in children and by reducing the risk of osteomalacia or osteoporosis in adults or elderly subjects. Depending on the design of the study of genetically modified animals, however, 1,25(OH)2D and the vitamin D receptor (VDR) may have no effect, beneficial or even deleterious direct effects on bone. We present here a comprehensive model of the direct effects of vitamin D on bone. In case of sufficient calcium supply, vitamin D and its metabolites can improve the calcium balance and facilitate mineral deposition in bone matrix largely without direct effects on bone cells, although some beneficial effects may occur via mature osteoblasts, as demonstrated in mice with osteoblast-specific overexpression of VDR or 1α-hydroxylase. In case of calcium deficiency, however, 1,25(OH)2D enhances bone resorption, whereas simultaneously inhibiting bone mineralization, so as to defend serum calcium homeostasis at the expense of bone mass. This dual role probably provides a survival benefit for land vertebrates living in a calcium-poor environment.

J Steroid Biochem Mol Biol. 2014 Oct;144 Pt A:114-8. doi: 10.1016/j.jsbmb.2013.10.003. Epub 2013 Oct 12.

The local production of 1,25(OH)2D3 promotes osteoblast and osteocyte maturation.

Turner AG, Hanrath MA, Morris HA, Atkins GJ, Anderson PH.

ABSTRACT

Maintenance of an adequate vitamin D status, as indicated by the level of circulating 25-hydroxyvitamin D (25(OH)D), is associated with higher bone mass and decreased risk of fracture. However, the molecular actions of vitamin D hormone (1,25(OH)2D3) in bone are complex, and include stimulation of osteoclastogenesis via RANK-ligand up-regulation, as well as the inhibition of mineralisation. We hypothesise that these divergent data may be reconciled by autocrine actions of 1,25(OH)2D3 which effect skeletal maintenance, as opposed to endocrine 1,25(OH)2D3 which acts to maintain serum calcium homeostasis. We have previously described local metabolism of 1,25(OH)2D3 within osteoblasts, with effects on gene expression and cell function. The aim of the current study was to investigate potential autocrine actions of 1,25(OH)2D3 within cells that exhibit osteocyte-like properties. Late osteoblastic MLO-A5 cells were cultured in the presence of 25(OH)D for 9 days with gene expression analysed pre- and post-mineralisation. Gene expression analysis revealed maturation within this time frame to an osteocyte-like stage, evidenced by increased Dmp1 and Phex mRNA expression. Expression of Cyp27b1 in 25(OH)D treated MLO-A5 cells was associated with elevated media levels of 1,25(OH)2D3 ($p<0.05$), induction of Cyp24a1 ($p<0.001$) and elevated ratios of Opg:Rankl mRNA ($p<0.01$). Chronic 25(OH)D exposure also increased osteocalcin mRNA in MLO-A5 cells, which contrasted with the dose-dependent inhibition of osteocalcin mRNA observed with acute treatment in MLO-Y4 cells ($p<0.01$). Treatment of MLO-Y4 cells with 25(OH)D also inhibited Phex mRNA expression ($p<0.05$), whilst Enpp1 gene expression was induced ($p<0.01$). Overall, the current study demonstrates that osteocyte-like cells convert physiological levels of 25(OH)D to 1,25(OH)2D3, with changes in gene expression that are consistent with increased osteocyte maturation. Although the physiological role of local metabolism of 1,25(OH)2D3 within osteocytes requires further investigation, the abundance and diverse functions of this cell type within bone underscore its potential importance. This article is part of a Special Issue entitled '16th Vitamin D Workshop'.

J Dent Res. 2015 Feb;94(2):381-7. doi: 10.1177/0022034514561657. Epub 2014 Dec 10.

Elevated serum 25(OH)-vitamin D levels are negatively correlated with molar-incisor hypomineralization.

Kühnisch J, Thiering E, Kratzsch J, Heinrich-Weltzien R, Hickel R, Heinrich J; GINIplus study group; LISAplus study group.

ABSTRACT

To date, the precise etiology of molar-incisor hypomineralization (MIH) is uncertain. Vitamin D plays a key role in hard tissue formation. Therefore, this study aimed to analyze the relationship between serum 25-hydroxy-vitamin D (25(OH)D) status and dental health data obtained from 1,048 children in a 10-year follow-up of the Munich GINIplus and LISAplus birth cohorts. The dental examination included the diagnosis of MIH and recording of (non-)cavitated caries lesions in primary and permanent teeth. Serum 25(OH)D concentrations were taken from blood samples of the 10-year investigation and measured with a fully automated, modular system. Different logistic regression and Poisson hurdle models were calculated. MIH was diagnosed in 13.6% of the study population. Approximately 16.4% of the children demonstrated caries-related defects (D3-4MFS > 0). The mean season-adjusted concentration of 25(OH)D was 75.8 nmol/l (standard deviation 22.0 nmol/l). After adjusting for sex, age, body mass index, parental education, equivalent income, and television/personal computer (TV/PC) viewing hours, a 10 nmol/l increase in serum 25(OH)D concentrations was significantly associated with a lower odds ratio of having MIH (OR = 0.89; P = 0.006). Furthermore, higher 25(OH)D values were associated with a lower number of caries-affected permanent teeth. It is concluded that elevated serum 25(OH)D concentrations were associated with better dental health parameters.

Clin Oral Implants Res. 2016 Jun;27(6):701-6. doi: 10.1111/clr.12641. Epub 2015 Jul 14.

Systemic vitamin D supplementation and local bone formation after maxillary sinus augmentation - a randomized, double-blind, placebo-controlled clinical investigation.

Schulze-Späte U, Dietrich T, Wu C, Wang K, Hasturk H, Dibart S.

ABSTRACT

OBJECTIVES:

Maxillary sinus augmentation procedures with bone replacement grafts aimed to increase bone height in the posterior maxilla. During healing, bone particles are partially resorbed and replaced by the patient's own bone. Vitamin D plays an essential role in calcium homeostasis and is critical for bone formation and remodeling.

MATERIALS AND METHODS:

This randomized, double-blind, placebo-controlled clinical investigation studied whether oral supplementation with vitamin D3 (5000 IU) combined with calcium (600 mg) impacts bone formation and remodeling after maxillary sinus augmentation compared to a placebo medication containing calcium alone (n = 10/group). Bone cores were harvested at the time of implant placement (6-8 months) for histological analysis.

RESULTS:

Serum 25-hydroxyvitamin D (25-OHD) levels were comparable between both groups at the baseline (P = nonsignificant [n.s.]). Vitamin D3+ calcium supplementation improved significantly serum 25-OHD levels (placebo vs. vitamin D3 group: 25-OHD ng/ml: 31.13 ± 7.06 vs. 61.11 ± 20.42, P ≤ 0.01); however, no statistically significant difference in bone formation or graft resorption was detected between groups. However, in the vitamin D3 group, a significant association was found between increased vitamin D levels and number of bone-resorbing osteoclasts around graft particles suggesting that local bone remodeling might be more pronounced when serum vitamin D levels were improved (r = 0.92, P ≤ 0.05).

CONCLUSIONS:

Vitamin D3+ calcium supplementation improves serum vitamin D levels and potentially impacts local bone remodeling on a cellular level. However, no statistically significant difference in bone formation or graft resorption was detected between groups.

J Biomed Mater Res A. 2017 Jul;105(7):2075-2089. doi: 10.1002/jbm.a.36060. Epub 2017 Mar 28.

Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss.

Insua A, Monje A, Wang HL, Miron RJ.

ABSTRACT

Despite the growing number of publications in the field of implant dentistry, there are limited studies to date investigating the biology and metabolism of bone healing around dental implants and their implications in peri-implant marginal bone loss. The aim of this review article is to provide a thorough understanding of the biological events taking place during osseointegration and the subsequent early and late phases of bone remodeling around dental implants. An update on the coupling mechanism occurring during bone resorption-bone remodeling is provided, focused on the relevance of the osteocytes, bone lining cells and immune cells during bone maintenance. An electronic and manual literature search was conducted by three independent reviewers in several databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register databases for articles up to September 2016 with no language restriction. Local bone metabolism is subject to signals from systemic calcium-phosphate homeostasis and bone remodeling. Three areas of interest were reviewed due to recent reported compromises in bone healing including the putative effects of (1) cholesterol, (2) hyperlipidemia, and (3) low vitamin D intake. Moreover, the prominent influence of osteocytes and immune cells is discussed as being key regulators during dental implant osseointegration and maintenance. These cells are of crucial importance in the presence of biofilm accumulation and their associated byproducts that leads to hard and soft tissue breakdown; the so called peri-implantitis. Factors that could negatively impact osteoclastogenesis or osteal macrophage activation should be monitored in future research including implant placement/torque protocols, bone characteristics, as well as meticulous maintenance programs to favor osseointegration and future long-term stability and success of dental implants.

J Bone Miner Res. 2017 Jun;32(6):1297-1308. doi: 10.1002/jbmr.3096. Epub 2017 Feb 22.

VDR in Osteoblast-Lineage Cells Primarily Mediates Vitamin D Treatment-Induced Increase in Bone Mass by Suppressing Bone Resorption.

Nakamichi Y, Udagawa N, Horibe K, Mizoguchi T, Yamamoto Y, Nakamura T, Hosoya A, Kato S, Suda T, Takahashi N.

ABSTRACT

Long-term treatment with active vitamin D [1α,25(OH)2 D3] and its derivatives is effective for increasing bone mass in patients with primary and secondary osteoporosis. Derivatives of 1α,25(OH)2 D3 , including eldecalcitol (ELD), exert their actions through the vitamin D receptor (VDR). It is reported that ELD treatment causes a net increase in bone mass by suppressing bone resorption rather than by increasing bone formation in animals and humans. VDR in bone and extraskeletal tissues regulates bone mass and secretion of osteotropic hormones. Therefore, it is unclear what types of cells expressing VDR preferentially regulate the vitamin D-induced increase in bone mass. Here, we examined the effects of 4-week treatment with ELD (50 ng/kg/day) on bone using osteoblast lineage-specific VDR conditional knockout (Ob-VDR-cKO) and osteoclast-specific VDR cKO (Ocl-VDR-cKO) male mice aged 10 weeks. Ob-VDR-cKO mice showed normal bone phenotypes, despite no appreciable immunostaining of VDR in bone. Ob-VDR-cKO mice failed to increase bone mass in response to ELD treatment. Ocl-VDR-cKO mice also exhibited normal bone phenotypes, but normally responded to ELD. ELD-induced FGF23 production in bone was regulated by VDR in osteoblast-lineage cells. These findings suggest that the vitamin D treatment-induced increase in bone mass is mediated by suppressing bone resorption through VDR in osteoblast-lineage cells.

4.2.3 Oral Health/Caries/Periodontitis

J Tenn Dent Assoc. 2011 Spring;91(2):30-3; quiz 34-5.

Vitamin D and its impact on oral health - an update.

Stein SH, Tipton DA.

ABSTRACT

Vitamin D has been shown to regulate musculoskeletal health by mediating calcium absorption and mineral homeostasis. Evidence has demonstrated that vitamin D deficiency may place subjects at risk for not only low mineral bone density/osteoporosis and osteopenia but also infectious and chronic inflammatory diseases. Studies have shown an association between alveolar bone density, osteoporosis and tooth loss and suggest that low bone mass may be a risk factor for periodontal disease. Several recent reports demonstrate a significant association between periodontal health and the intake of vitamin D. An emerging hypothesis is that vitamin D may be beneficial for oral health, not only for its direct effect on bone metabolism but also due to its ability to function as an anti-inflammatory agent and stimulate the production of antimicrobial peptides.

Compend Contin Educ Dent. 2012 Mar;33(3):166-71; quiz 172, 182.

A review of vitamin D as it relates to periodontal disease.

Yao SG, Fine JB.

ABSTRACT

Vitamin D has classically been known as a "bone hormone." But recently, vitamin D has been found to play a role in respect to systemic diseases such as cardiovascular disease, cancer, and periodontal disease. It has been reported that approximately 1 billion people worldwide are either vitamin D deficient or insufficient. This paper will address the various roles that vitamin D plays in respect to systemic diseases, the effects of vitamin D deficiency, and how it is diagnosed and treated.

Nutr Rev. 2013 Feb;71(2):88-97. doi: 10.1111/j.1753-4887.2012.00544.x. Epub 2012 Nov 9.

Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis.

Hujoel PP.

ABSTRACT

Vitamin D has been used to prevent and treat dental caries. The objective of this study was to conduct a systematic review of controlled clinical trials (CCTs) assessing the impact of vitamin D on dental caries prevention. Random-effects and meta-regression models were used to evaluate overall and subgroup-specific relative-rate estimates. Twenty-four CCTs encompassing 2,827 children met the inclusion criteria. Twenty-two of the 24 CCTs predated modern clinical trial design, some of which nonetheless reported characteristics such as pseudo-randomization (n = 2), blinding (n = 4), or use of placebos (n = 8). The relative-rate estimates of the 24 CCTs exhibited significant heterogeneity (P < 0.0001), and there was evidence of significant publication bias (P < 0.001). The pooled relative-rate estimate of supplemental vitamin D was 0.53 (95% CI, 0.43-0.65). No robust differences were identified between the caries-preventive effects of vitamin D(2) , vitamin D(3) , and ultraviolet radiation (Prob > F = 0.22). The analysis of CCT data identified vitamin D as a promising caries-preventive agent, leading to a low-certainty conclusion that vitamin D may reduce the incidence of caries.

J Periodontal Res. 2014 Oct;49(5):545-53. doi: 10.1111/jre.12149. Epub 2013 Nov 21.

Re-evaluating the role of vitamin D in the periodontium.

Stein SH, Livada R, Tipton DA.

ABSTRACT

The importance of vitamin D in maintaining skeletal health via the regulation of calcium has long been recognized as a critical function of this secosteroid. An abundance of literature shows an association between oral bone mineral density and some measure of systemic osteoporosis and suggests that osteoporosis/low bone mass may be a risk factor for periodontal disease. Recently, nonskeletal functions of vitamin D have gained notoriety for several reasons. Many cells that are not associated with calcium homeostasis have been demonstrated to possess membrane receptors for vitamin D. These include activated T and B lymphocytes, and skin, placenta, pancreas, prostate and colon cancer cells. In addition, vitamin D "insufficiency" is a worldwide epidemic and epidemiologic evidence has linked this condition to multiple chronic health problems, including cardiovascular and autoimmune diseases, hypertension and a variety of cancers. Interestingly, there is mounting evidence connecting diminished serum levels of vitamin D with increased gingival inflammation and supporting the concept of "continual vitamin D sufficiency" in maintaining periodontal health. The ability of vitamin D to regulate both the innate and the adaptive components of the host response may play an important role in this process. This review will examine the skeletal and nonskeletal functions of vitamin D, and explore its potential role in protecting the periodontium as well as in regulating periodontal wound healing.

J Dent Child (Chic). 2016 Sep 15;83(3):114-119.

Vitamin D and Dental Caries in Primary Dentition.

Seminario AL, Velan E.

ABSTRACT

Traditionally classified as a vitamin, vitamin D represents a group of fat-soluble secosteroids with D2 (ergocalciferol) and D3 (cholecalciferol) being the most relevant of the group. The importance of this prohormone exceeds its known ability to maintain intra- and extracellular calcium and phosphate concentrations, thereby preserving essential metabolic functions such as the promotion of mineralization and maintenance and remodeling of the bone. Current observational research recognizes the potential antiproliferative, prodifferentiative, and immunomodulatory effects of vitamin D and its metabolites in the human body. The purposes of this paper are to: (1) review how vitamin D interacts in the body, its deficiency at the population level, and how it relates to oral health in children; and (2) assess proposed biological mechanisms by which vitamin D may play a preventive role in the development of dental caries.

J Clin Periodontol. 2017 Mar;44 Suppl 18:S79-S84. doi: 10.1111/jcpe.12672.

Nutrition, dental caries and periodontal disease: a narrative review.

Hujoel PP, Lingström P.

ABSTRACT

AIM:

To provide a narrative review of the role of macro- and micronutrients in relation to dental caries, gingival bleeding and destructive periodontal disease.

MATERIALS & METHODS:

This review is based on systematic reviews (when available) and comparative human studies.

RESULTS:

Dental caries cannot develop without the presence of dietary fermentable carbohydrates, in particular sugar. The susceptibility to develop caries in the presence of carbohydrates may be influenced by genetics and micronutrients such as vitamin D. Gingival bleeding and destructive periodontal disease are sensitive markers to both abnormalities in macronutrient content (excessive carbohydrates or poly-unsaturated fat intake, deficient protein intake) and micronutrient intake (e.g. vitamin C and B12).

CONCLUSION:

Dental caries and periodontal diseases are a sensitive alarm bell for an unhealthy diet, which predicts the future onset of the diseases of civilizations.

Pediatr Dent J. 2017 Apr;27(1):21-28. doi: 10.1016/j.pdj.2016.08.001. Epub 2016 Dec 19.

Prenatal vitamin D and enamel hypoplasia in human primary maxillary central incisors: a pilot study.

Reed SG, Voronca D, Wingate JS, Murali M, Lawson AB, Hulsey TC, Ebeling MD, Hollis BW, Wagner CL.

ABSTRACT

BACKGROUND:

Enamel hypoplasia (EH) increases risk for dental caries and also is associated with vitamin D deficiencies. This pilot study evaluates the feasibility to determine the association of human maternal circulating vitamin D concentrations during pregnancy and EH in infant's teeth that develop in utero.

METHODS:

A pilot population of 37 children whose mothers participated in a RCT of vitamin D supplementation during pregnancy was evaluated. Major outcome was EH and major exposure was maternal monthly serum circulating 25(OH) D concentrations during pregnancy. EH was assessed using the Enamel Defect Index and digital images made by a ProScope High Resolution™ handheld digital USB microscope at 50x magnification.

RESULTS:

During initial 8 weeks of study, 29/37 children had evaluable data with mean age of 3.6 ± 0.9 years; 48% male; and 45% White, 31% Hispanic, and 24% Black. EH was identified in 13 (45%) of the children. Maternal mean 25(OH)D concentrations were generally lower for those children with EH.

CONCLUSIONS:

Preliminary results suggest follow-up of children of mothers in a vitamin D supplementation RCT during pregnancy provides an important approach to study the etiology of EH in the primary teeth. Further study is needed to discern thresholds and timing of maternal serum 25(OH)D concentrations during pregnancy associated with absence of EH in teeth that develop in utero. Potential dental public health implications for prevention of early childhood caries via sound tooth structure as related to maternal vitamin D sufficiency during pregnancy need to be determined.

Medicina (Kaunas). 2018 Jun 12;54(3). pii: E45. doi: 10.3390/medicina54030045.

The Relationship between Vitamin D and Periodontal Pathology.

Jagelavičienė E, Vaitkevičienė I, Šilingaitė D, Šinkūnaitė E, Daugėlaitė G.

ABSTRACT

Osteoporosis and periodontal diseases are common problems among the elderly population. Vitamin D is a secosteroid hormone that is either synthesized by human skin cells under the effect of UV radiation or consumed through diet. Deficiency in vitamin D leads to reduced bone mineral density, osteoporosis, the progression of periodontal diseases and causes resorption to occur in the jawbone. Sufficient intake of vitamin D can decrease the risk of gingivitis and chronic periodontitis, as it has been shown to have immunomodulatory, anti-inflammatory, antiproliferative effects and initiates cell apoptosis. In addition, vitamin D is also important for bone metabolism, alveolar bone resorption and preventing tooth loss. It increases antibacterial defense of gingival epithelial cells and decrease gingival inflammation, improves postoperative wound healing after periodontal surgery and is an important supplement used as prophylaxis in periodontology. This publication aims to update the recent advances, stress the clinical importance, and evaluate vitamin D in the prevention of periodontal diseases to reach a successful outcome of conservative and surgical treatment. An analysis of the literature shows that vitamin D plays a significant role in maintaining healthy periodontal and jaw bone tissues, alleviating inflammation processes, stimulating post-operative healing of periodontal tissues and the recovery of clinical parameters. However, further research is needed to clarify the required vitamin D concentration in plasma before starting periodontal treatment to achieve the best outcome.

J Steroid Biochem Mol Biol. 2018 Jan;175:190-194. doi: 10.1016/j.jsbmb.2017.01.020. Epub 2017 Feb 1.

Effects of vitamin D status on oral health.

Uwitonze AM, Murererehe J, Ineza MC, Harelimana EI, Nsabimana U1, Uwambaye P, Gatarayiha A, Haq A, Razzaque MS.

ABSTRACT

Normal humans of all ages have the innate ability to produce vitamin D following sunlight exposure. Inadequate vitamin D status has shown to be associated with a wide variety of diseases, including oral health disorders. Insufficient sunlight exposure may accelerate some of these diseases, possibly due to impaired vitamin D synthesis. The beneficial effects of vitamin D on oral health are not only limited to the direct effects on the tooth mineralization, but are also exerted through the anti-inflammatory functions and the ability to stimulate the production of anti-microbial peptides. In this article, we will briefly discuss the genesis of various oral diseases due to inadequate vitamin D level in the body and elucidate the potential benefits of safe sunlight exposure for the maintenance of oral and general health.

Pediatr Int. 2019 Apr;61(4):327-338. doi: 10.1111/ped.13801.

Dental caries and vitamin D status in children in Asia.

Almoudi MM, Hussein AS, Abu Hassan MI, Schroth RJ.

ABSTRACT

Dental caries and vitamin D inadequacy are known to affect children worldwide. Vitamin D has a vital role in tooth formation. There is growing evidence linking suboptimal serum vitamin D level with dental caries in children. This paper reviews the literature on both the prevalence of dental caries and of vitamin D deficiency in children in four Asian regions, discusses their associated risk factors, and reviews the global evidence on the association between dental caries and vitamin D in children. Caries prevalence in children ranged from 40% to 97% in Eastern Asia, 38-73.7% in Southern Asia, and 26.5-74.7% in Western Asian countries. Moreover, a higher prevalence of vitamin D deficiency in Asian children was identified, even in countries in equatorial regions, ranging from 2.8% to 65.3% in Eastern Asia, 5-66.7% in Southern Asia, 4-45.5% in Western Asia and 38.1-78.7% in Central Asian countries. Obesity, age, female gender, higher latitude, season, darker skin pigmentation, sunlight protection behaviors, less sunlight exposure and low intake of food containing vitamin D were important factors associated with lower serum vitamin D in Asia. Suboptimal vitamin D level in children may be a significant risk factor for dental caries, and requires further research to ascertain such an association in children in Asia, as well as to understand its exact influence on caries risk and development.

Am J Transl Res. 2019 Apr 15;11(4):2304-2316. eCollection 2019.

Calcitriol exerts a mineralization-inductive effect comparable to that of vitamin C in cultured human periodontium cells.

Hong HH, Hong A, Wang CC, Huang EW, Chiang CC, Yen TH, Huang YF.

ABSTRACT

This study inspected whether calcitriol could exert a mineralization-inductive effect comparable to that of vitamin C in cultured human periodontium cells (hPDCs). The mRNA expression of the mineralization-related biomarkers core-binding factor subunit alpha-1 (Cbfa1), collagen 1 α1 (Col-I), alkaline phosphatase (ALP), osteopontin (OPN), bone sialoprotein (BSP), osteocalcin (OCN), vitamin D receptor (VDR), cementum protein 1 (CEMP-1), cementum attachment protein (CAP), interleukin 6 (IL-6), transforming growth factor-β1 (TGF-β1) and osteoprotegerin (OPG) was surveyed after incubation of hPDCs with vitamin C and calcitriol for 2 weeks. It was found that both vitamin C and calcitriol not only increased mineralization-related mRNA fold-changes but also enhanced ALP activity, CEMP-1 immunofluorescence, von Kossa and Alizarin Red staining and TXM-associated calcifications. Generally, 10-8 M calcitriol displayed greater mineralization significance than 10-7 M calcitriol in the assays tested. However, vitamin C stimulated lower Cbfa1, Col-1, ALP, OPN, BSP, OCN, VDR, CEMP-1 and IL-6 mRNA fold-changes than 10-8 M calcitriol. Finally, TXM analysis indicated that a 10-8 M calcitriol treatment stimulated greater calcifications than vitamin C treatment. Therefore, the analytical results confirmed the osteoinductive potential of vitamin C in cultured hPDCs. In contrast, 10-8 M calcitriol could potentially function as a substitute because it stimulates a greater mineralization effect than vitamin C or 10-7 M calcitriol.

J Periodontal Res. 2019 Aug;54(4):444-452. doi: 10.1111/jre.12646. Epub 2019 Feb 25.

Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss.

Menzel LP, Ruddick W, Chowdhury MH, Brice DC, Clance R, Porcelli E, Ryan LK, Lee J, Yilmaz Ö, Kirkwood KL, McMahon L, Tran A, Diamond G.

ABSTRACT

BACKGROUND AND OBJECTIVE:

Both chronic and aggressive periodontal disease are associated with vitamin D deficiency.

RESULTS:

Dietary restriction of vitamin D led to alveolar bone loss and increased inflammation in the gingiva in the mouse model. In primary human GEC and established human cell lines, treatment of GEC with 1,25(OH)2 D3 inhibited the intracellular growth of P. gingivalis. Cultured GEC expressed two 25-hydroxylases (CYP27A1 and CYP2R1), as well as 1-α hydroxylase, enabling conversion of vitamin D to both 25(OH)D3 and 1,25(OH)2 D3 .

CONCLUSION:

Vitamin D deficiency in mice contributes to PD, recapitulating the association seen in humans, and provides a unique model to study the development of PD. Vitamin D increases the activity of gingival epithelial cells (GEC) against the invasion of periodontal pathogens and inhibits the inflammatory response, both in vitro and in vivo. GEC can convert inactive vitamin D to the active form in situ, supporting the hypothesis that vitamin D can be applied directly to the gingiva to prevent or treat periodontal disease.

JAMA Pediatr. 2019 Aug 5. doi: 10.1001/jamapediatrics.2019.2545. [Epub ahead of print]

Association of High-Dose Vitamin D Supplementation During Pregnancy With the Risk of Enamel Defects in Offspring: A 6-Year Follow-up of a Randomized Clinical Trial.

Nørrisgaard PE, Haubek D, Kühnisch J, Chawes BL, Stokholm J, Bønnelykke K, Bisgaard H.

ABSTRACT

IMPORTANCE:
Enamel defects of developmental origin affect up to 38% of schoolchildren and is recognized as a global public health challenge. The impaired enamel formation results in pain owing to hypersensitivity, posteruptive breakdowns, rapid caries progression, and extractions in some cases. The etiology is unknown; therefore, prevention is currently not possible.

OBJECTIVE:
To assess the association of a high-dose vitamin D supplementation in pregnant women with enamel defects and caries in their offspring.

DESIGN, SETTING, AND PARTICIPANTS:
Post hoc analysis of a double-blind, single-center, randomized clinical trial, the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort (COPSAC2010). Enrollment began March 2009 and included 623 women recruited at 24 weeks of pregnancy and 588 of their children. A dental examination was completed at age 6 years in 496 of 588 children (84%). Data were analyzed in 2018.

INTERVENTION:
High-dose vitamin D3 (2400 IU/d; N = 315) or matching placebo tablets (N = 308) from pregnancy week 24 to 1 week post partum. In addition, all women received 400 IU/d of vitamin D3 as part of standard care.

MAIN OUTCOMES AND MEASURES:
Enamel defect was defined as having at least 1 molar affected by demarcated opacity, enamel breakdown, and/or atypical restoration. Caries was defined as decayed, missing, or filled surfaces in both the deciduous and permanent dentitions (World Health Organization standard).

RESULTS:
The risk of enamel defects in the permanent dentition was lower in the offspring of mothers who received high-dose vitamin D supplementation during pregnancy compared with standard dose (15.1% [n = 26 of 172] vs 27.5% [n = 44 of 160]; odds ratio, 0.47; 95% CI, 0.27-0.81). A similar association was observed for the deciduous dentition (8.6% [n = 21 of 244] vs 15.9% [n = 40 of 252]; odds ratio, 0.50; 95% CI, 0.28-0.87). There was no association between supplementation and caries.

CONCLUSIONS AND RELEVANCE:
High-dose vitamin D supplementation during pregnancy was associated with approximately 50% reduced odds of enamel defects in the offspring. This suggests prenatal vitamin D supplementation as a preventive intervention for enamel defects, with a clinically important association with dental health.

4.2.4 Systemic Relevance

J Cell Biochem. 2003 Feb 1;88(2):296-307.

Vitamin D: A millenium perspective.

Holick MF.

ABSTRACT

Vitamin D is one of the oldest hormones that have been made in the earliest life forms for over 750 million years. Phytoplankton, zooplankton, and most plants and animals that are exposed to sunlight have the capacity to make vitamin D.

Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis. It accomplishes this by increasing the efficiency of the intestine to absorb dietary calcium. When there is inadequate calcium in the diet to satisfy the body's calcium requirement, vitamin D communicates to the osteoblasts that signal osteoclast precursors to mature and dissolve the calcium stored in the bone. Vitamin D is metabolized in the liver and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)(2)D]. 1,25(OH)(2)D receptors (VDR) are present not only in the intestine and bone, but in a wide variety of other tissues, including the brain, heart, stomach, pancreas, activated T and B lymphocytes, skin, gonads, etc. 1,25(OH)(2)D is one of the most potent substances to inhibit proliferation of both normal and hyperproliferative cells and induce them to mature. It is also recognized that a wide variety of tissues, including colon, prostate, breast, and skin have the enzymatic machinery to produce 1,25(OH)(2)D. 1,25(OH)(2)D and its analogs have been developed for treating the hyperproliferative disease psoriasis. Vitamin D deficiency is a major unrecognized health problem. Not only does it cause rickets in children, osteomalacia and osteoporosis in adults, but may have long lasting effects. Chronic vitamin D deficiency may have serious adverse consequences, including increased risk of hypertension, multiple sclerosis, cancers of the colon, prostate, breast, and ovary, and type 1 diabetes. There needs to be a better appreciation of the importance of vitamin D for overall health and well being.

Epidemiol Infect. 2006 Dec;134(6):1129-40. Epub 2006 Sep 7.

Epidemic influenza and vitamin D.

Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E.

ABSTRACT

In 1981, R. Edgar Hope-Simpson proposed that a 'seasonal stimulus' intimately associated with solar radiation explained the remarkable seasonality of epidemic influenza. Solar radiation triggers robust seasonal vitamin D production in the skin; vitamin D deficiency is common in the winter, and activated vitamin D, 1,25(OH)2D, a steroid hormone, has profound effects on human immunity. 1,25(OH)2D acts as an immune system modulator, preventing excessive expression of inflammatory cytokines and increasing the 'oxidative burst' potential of macrophages. Perhaps most importantly, it dramatically stimulates the expression of potent anti-microbial peptides, which exist in neutrophils, monocytes, natural killer cells, and in epithelial cells lining the respiratory tract where they play a major role in protecting the lung from infection. Volunteers inoculated with live attenuated influenza virus are more likely to develop fever and serological evidence of an immune response in the winter. Vitamin D deficiency predisposes children to respiratory infections. Ultraviolet radiation (either from artificial sources or from sunlight) reduces the incidence of viral respiratory infections, as does cod liver oil (which contains vitamin D). An interventional study showed that vitamin D reduces the incidence of respiratory infections in children. We conclude that vitamin D, or lack of it, may be Hope-Simpson's 'seasonal stimulus'.

Am J Clin Nutr. 2007 Jan;85(1):54-9.

Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations.

Major GC, Alarie F, Doré J, Phouttama S, Tremblay A.

ABSTRACT

BACKGROUND:

Adequate calcium intake can have a favorable effect on some metabolic variables.

OBJECTIVE:

The objective of the study was to determine the effects of daily calcium intake and of supplementation with calcium and vitamin D (calcium+D) during a weight-loss intervention on blood pressures, plasma lipid and lipoprotein concentrations, and glucose and insulin concentrations in low calcium consumers.

DESIGN:

Healthy, overweight or obese women (n = 63) with a daily calcium intake of < 800 mg/d were randomly assigned in a double-blind manner to 1 of 2 groups: the group consuming 2 tablets/d of a calcium + vitamin D supplement (600 mg elemental calcium and 200 IU vitamin D/tablet) or the group consuming placebo; both groups observed a 700 kcal/d energy restriction. These 63 women then completed a 15-wk weight-loss intervention.

RESULTS:

Initial daily calcium intake was significantly correlated with plasma HDL cholesterol (r = 0.41, P < 0.001) and with 2-h postload glycemia (r = -0.29, P < 0.05) during an oral-glucose-tolerance test, independent of fat mass and waist circumference. After the 15-wk intervention, significantly greater decreases in total:LDL and LDL:HDL (P < 0.01 for both) and of LDL cholesterol (P < 0.05) were observed in the calcium+D group than in the placebo group. The differences in total:HDL and LDL:HDL were independent of changes in fat mass and in waist circumference. A tendency for more beneficial changes in HDL cholesterol, triacylglycerol, and total cholesterol was also observed in the calcium+D group (P = 0.08).

CONCLUSION:

Consumption of calcium+D during a weight-loss intervention enhanced the beneficial effect of body weight loss on the lipid and lipoprotein profile in overweight or obese women with usual low daily calcium intake.

J Neuroimmunol. 2008 Feb;194(1-2):7-17. doi: 10.1016/j.jneuroim.2007.11.014. Epub 2008 Jan 4.

Vitamin D as an immune modulator in multiple sclerosis, a review.

Smolders J, Damoiseaux J, Menheere P, Hupperts R.

ABSTRACT

The role of vitamin D in calcium homeostasis is well known. More recently vitamin D has become a topic of interest in immune regulation and multiple sclerosis. The main reason for this is the observed geographical distribution of multiple sclerosis. Areas with high sunlight exposure, the principal inducer of vitamin D synthesis, have a relatively low prevalence of multiple sclerosis and vice versa. Furthermore, low levels of the principal vitamin D metabolite (25-hydroxy vitamin D) in the circulation are associated with a high incidence of multiple sclerosis. Other epidemiological evidence also supports the view that vitamin D metabolites have an immune and disease modulating effect in multiple sclerosis. Experimental research in vitro and in animal models has further clarified the interaction of vitamin D metabolites with the immune system. The evidence obtained from these studies strongly supports a model in which vitamin D mediates a shift to a more anti-inflammatory immune response, and in particular to enhanced regulatory T cell functionality. In the current review we link the basic knowledge on vitamin D and immune regulation with the vitamin D related observations in multiple sclerosis. We conclude that there is a sound basis on which to initiate double-blind placebo-controlled trials that not only address the effect of vitamin D on the clinical outcome of multiple sclerosis, but also on the regulatory T cell compartment.

Future Microbiol. 2009 Nov;4(9):1151-65. doi: 10.2217/fmb.09.87.

The vitamin D-antimicrobial peptide pathway and its role in protection against infection.

Gombart AF.

ABSTRACT

Vitamin D deficiency has been correlated with increased rates of infection. Since the early 19th century, both environmental (i.e., sunlight) and dietary sources (cod liver) of vitamin D have been identified as treatments for TB. The recent discovery that vitamin D induces antimicrobial peptide gene expression explains, in part, the 'antibiotic' effect of vitamin D and has greatly renewed interest in the ability of vitamin D to improve immune function. Subsequent work indicates that this regulation is biologically important for the response of the innate immune system to wounds and infection and that deficiency may lead to suboptimal responses toward bacterial and viral infections. The regulation of the cathelicidin antimicrobial peptide gene is a human/primate-specific adaptation and is not conserved in other mammals. The capacity of the vitamin D receptor to act as a high-affinity receptor for vitamin D and a low-affinity receptor for secondary bile acids and potentially other novel nutritional compounds suggests that the evolutionary selection to place the cathelicidin gene under control of the vitamin D receptor allows for its regulation under both endocrine and xenobiotic response systems. Future studies in both humans and humanized mouse models will elucidate the importance of this regulation and lead to the development of potential therapeutic applications.

Curr Opin Allergy Clin Immunol. 2009 Jun;9(3):202-7. doi: 10.1097/ACI.0b013e32832b36cd.

Childhood asthma may be a consequence of vitamin D deficiency.

Litonjua AA.

ABSTRACT

PURPOSE OF REVIEW:

Vitamin D deficiency has been rediscovered as a public-health problem worldwide. It has been postulated that vitamin D deficiency may explain a portion of the asthma epidemic. The purpose of this review is to present the evidence for a role of vitamin D in asthma.

RECENT FINDINGS:

Both animal models and studies in human fetal tissues show that vitamin D plays a role in fetal lung growth and maturation. Epidemiologic studies have also suggested that higher prenatal vitamin D intakes have a protective role against wheezing illnesses in young children. Vitamin D may protect against wheezing illnesses through its role in upregulating antimicrobial proteins or through its multiple immune effects. In addition, vitamin D may play a therapeutic role in steroid resistant asthmatics, and lower vitamin D levels have recently been associated with higher risks for asthma exacerbations.

SUMMARY:

Improving vitamin D status holds promise in primary prevention of asthma, in decreasing exacerbations of disease, and in treating steroid resistance. However, the appropriate level of circulating vitamin D for optimal immune functioning remains unclear. Because vitamin D deficiency is prevalent even in sun-replete areas, clinical trials are needed to definitively answer questions about the role of vitamin D in asthma.

Diabetes. 2010 Jan;59(1):242-8. doi: 10.2337/db09-1011. Epub 2009 Oct 15.

Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study.

Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, Robins SJ, O'Donnell CJ, Hoffmann U, Jacques PF, Booth SL, Vasan RS, Wolf M, Wang TJ.

ABSTRACT

OBJECTIVE:

Because vitamin D deficiency is associated with a variety of chronic diseases, understanding the characteristics that promote vitamin D deficiency in otherwise healthy adults could have important clinical implications. Few studies relating vitamin D deficiency to obesity have included direct measures of adiposity. Furthermore, the degree to which vitamin D is associated with metabolic traits after adjusting for adiposity measures is unclear.

RESEARCH DESIGN AND METHODS:

We investigated the relations of serum 25-hydroxyvitamin D (25[OH]D) concentrations with indexes of cardiometabolic risk in 3,890 nondiabetic individuals; 1,882 had subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured by multidetector computed tomography (CT).

RESULTS:

In multivariable-adjusted regression models, 25(OH)D was inversely associated with winter season, waist circumference, and serum insulin ($P < 0.005$ for all). In models further adjusted for CT measures, 25(OH)D was inversely related to SAT (-1.1 ng/ml per SD increment in SAT, $P = 0.016$) and VAT (-2.3 ng/ml per SD, $P < 0.0001$). The association of 25(OH)D with insulin resistance measures became nonsignificant after adjustment for VAT. Higher adiposity volumes were correlated with lower 25(OH)D across different categories of BMI, including in lean individuals (BMI <25 kg/m(2)). The prevalence of vitamin D deficiency (25[OH]D <20 ng/ml) was threefold higher in those with high SAT and high VAT than in those with low SAT and low VAT ($P < 0.0001$).

CONCLUSIONS:

Vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity. The mechanisms by which adiposity promotes vitamin D deficiency warrant further study.

Nutrients. 2010 Apr; 2(4): 408–425. Published online 2010 Mar 25. doi: 10.3390/nu2040408.

Nonclassical Vitamin D Action.

Zittermann A, Gummert JF.

ABSTRACT

It is becoming increasingly clear that vitamin D has a broad range of actions in the human body. Besides its well-known effects on calcium/phosphate homeostasis, vitamin D influences muscle function, cardiovascular homeostasis, nervous function, and the immune response. Vitamin D deficiency/insufficiency has been associated with muscle weakness and a high incidence of various chronic diseases such as cardiovascular disease, cancer, multiple sclerosis, and type 1 and 2 diabetes. Most importantly, low vitamin D status has been found to be an independent predictor of all-cause mortality. Several recent randomized controlled trials support the assumption that vitamin D can improve muscle strength, glucose homeostasis, and cardiovascular risk markers. In addition, vitamin D may reduce cancer incidence and elevated blood pressure. Since the prevalence of vitamin D deficiency/insufficiency is high throughout the world, there is a need to improve vitamin D status in the general adult population. However, the currently recommended daily vitamin D intake of 5-15 μg is too low to achieve an adequate vitamin D status in individuals with only modest skin synthesis. Thus, there is a need to recommend a vitamin D intake that is effective for achieving adequate circulating 25-hydroxyvitamin D concentrations (>75 nmol/L).

Br J Nutr. 2011 Nov;106(9):1433-40. doi: 10.1017/S0007114511001991. Epub 2011 Jun 6.

Vitamin D status has a linear association with seasonal infections and lung function in British adults.

Berry DJ, Hesketh K, Power C, Hyppönen E.

ABSTRACT

Higher vitamin D concentrations have been proposed as a protective 'seasonal stimulus' against influenza, and there are suggestions for associations with other aspects of respiratory health. The aim of the present study was to investigate the relationship of current vitamin D status (measured by 25-hydroxyvitamin D, 25(OH)D) with respiratory infections and lung function. We used cross-sectional data from 6789 participants in the nationwide 1958 British birth cohort who had measurements of 25(OH)D, lung function (forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC)) and respiratory infections available from the age of 45 years. In this population, the prevalence of respiratory infections had a strong seasonal pattern in the opposite direction to the pattern for 25(OH)D concentrations. Each 10 nmol/l increase in 25(OH)D was associated with a 7 % lower risk of infection (95 % CI 3, 11 %) after adjustment for adiposity, lifestyle and socio-economic factors. For FEV1 and FVC, each 10 nmol/l increase in 25(OH)D was associated with 8 (95 % CI 3, 13) ml and 13 (95 % CI 7, 20) ml higher volume, respectively, after controlling for covariates. Associations of 25(OH)D with FEV1 and FVC were only slightly attenuated after further adjustment for infection and other respiratory illness. In conclusion, vitamin D status had a linear relationship with respiratory infections and lung function. Randomised controlled trials are warranted to investigate the role of vitamin D supplementation on respiratory health and to establish the underlying mechanisms.

AIDS. 2011 Feb 20;25(4):525-9. doi: 10.1097/QAD.0b013e328342fdfd.

Vitamin D deficiency is associated with type 2 diabetes mellitus in HIV infection.

Szep Z, Guaraldi G, Shah SS, Lo Re V 3rd, Ratcliffe SJ, Orlando G, Carli F, Rossi R, Rochira V, Tebas P.

ABSTRACT

BACKGROUND:

Metabolic complications, including type 2 diabetes mellitus and metabolic syndrome, are increasingly recognized among HIV-infected individuals. Low vitamin D levels increase the risk of type 2 diabetes mellitus, and vitamin D supplementation has been shown to decrease the risk of type 2 diabetes mellitus in patients without HIV infection.

OBJECTIVES:

The primary objective was to determine whether vitamin D deficiency (serum 25-hyrdoxyvitamin D <20 ng/ml) was associated with type 2 diabetes mellitus among HIV-infected patients. Our secondary objective was to determine whether vitamin D deficiency was associated with metabolic syndrome in HIV.

METHODS:

We conducted a cross-sectional study among participants enrolled in the prospective Modena (Italy) HIV Metabolic Clinic Cohort. Clinical and laboratory data, including history of type 2 diabetes mellitus, fasting blood glucose, components of metabolic syndrome, and 25-hydroxyvitamin D levels, were obtained for all participants.

RESULTS:

After adjusting for vitamin D supplementation, sex, age, body mass index, and hepatitis C virus co-infection, vitamin D deficiency was associated with type 2 diabetes mellitus [adjusted odds ratio (OR) 1.85; 95% confidence interval (CI) 1.03-3.32; P = 0.038]. The association between vitamin D deficiency and metabolic syndrome was not significant after adjusting for vitamin D supplementation, sex, age and body mass index (adjusted OR 1.32; 95% CI 1.00-1.75; P = 0.053).

CONCLUSIONS:

Our study demonstrates an association between vitamin D deficiency and type 2 diabetes mellitus. Clinical trials are needed to better characterize the association between vitamin D deficiency and type 2 diabetes mellitus in HIV infection and to evaluate whether vitamin D is able to prevent or delay the onset of type 2 diabetes mellitus.

J Nutr. 2013 Oct;143(10):1679-86. doi: 10.3945/jn.113.180794. Epub 2013 Aug 21.

Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis.

Ooi JH, Li Y, Rogers CJ, Cantorna MT.

ABSTRACT

The active form of vitamin D [1,25-dihydroxycholecalciferol, 1,25(OH)2D3] and the vitamin D receptor (VDR) regulate susceptibility to experimental colitis. The effect of the bacterial microflora on the susceptibility of C57BL/6 mice to dextran sodium sulfate-induced colitis was determined. Mice that cannot produce 1,25(OH)2D3 [Cyp27b1 (Cyp) knockout (KO)], VDR KO as well as their wild-type littermates were used. Cyp KO and VDR KO mice had more bacteria from the Bacteroidetes and Proteobacteria phyla and fewer bacteria from the Firmicutes and Deferribacteres phyla in the feces compared with wild-type. In particular, there were more beneficial bacteria, including the Lactobacillaceae and Lachnospiraceae families, in feces from Cyp KO and VDR KO mice than in feces from wild-type. Helicobacteraceae family member numbers were elevated in Cyp KO compared with wild-type mice. Depletion of the gut bacterial flora using antibiotics protected mice from colitis. 1,25(OH)2D3 treatment (1.25 μg/100 g diet) of Cyp KO mice decreased colitis severity and reduced the numbers of Helicobacteraceae in the feces compared with the numbers in the feces of untreated Cyp KO mice. The mechanisms by which the dysbiosis occurs in VDR KO and Cyp KO mice included lower expression of E-cadherin on gut epithelial and immune cells and fewer tolerogenic dendritic cells that resulted in more gut inflammation in VDR and Cyp KO mice compared with wild-type mice. Increased host inflammation has been shown to provide pathogens with substrates to out-compete more beneficial bacterial species. Our data demonstrate that vitamin D regulates the gut microbiome and that 1,25(OH)2D3 or VDR deficiency results in dysbiosis, leading to greater susceptibility to injury in the gut.

Skin Pharmacol Physiol. 2013;26(2):101-7. doi: 10.1159/000346698. Epub 2013 Feb 20.

Serum ferritin and vitamin d in female hair loss: do they play a role?

Rasheed H, Mahgoub D, Hegazy R, El-Komy M, Abdel Hay R, Hamid MA, Hamdy E.

ABSTRACT

AIM:

Evaluation of serum ferritin and vitamin D levels in females with chronic telogen effluvium (TE) or female pattern hair loss (FPHL), in order to validate their role in these common hair loss diseases.

METHODS:

Eighty females (18 to 45 years old) with hair loss, in the form of TE or FPHL, and 40 age-matched females with no hair loss were included in the study. Diagnosis was based upon clinical examination as well as trichogram and dermoscopy. Serum ferritin and vitamin D2 levels were determined for each participant.

RESULTS:

Serum ferritin levels in the TE (14.7 ± 22.1 μg/l) and FPHL (23.9 ± 38.5 μg/l) candidates were significantly lower than in controls (43.5 ± 20.4 μg/l). Serum vitamin D2 levels in females with TE (28.8 ± 10.5 nmol/l) and FPHL (29.1 ± 8.5 nmol/l) were significantly lower than in controls (118.2 ± 68.1 nmol/l; $p < 0.001$). These levels decreased with increased disease severity. Serum ferritin cut-off values for TE and FPHL were 27.5 and 29.4 μg/l, respectively, and those for vitamin D were 40.9 and 67.9 nmol/l.

CONCLUSION:

Low serum ferritin and vitamin D2 are associated with hair loss in females with TE and FPHL. Screening to establish these levels in cases of hair loss and supplementing with them when they are deficient may be beneficial in the treatment of disease.

Nutrients. 2013 Jun 26;5(7):2268-75. doi: 10.3390/nu5072268.

Vitamin D status is associated with disease activity among rheumatology outpatients.

Sabbagh Z, Markland J, Vatanparast H.

ABSTRACT

The co-existence of high prevalence of vitamin D inadequacy among Canadians and high prevalence of systematic autoimmune rheumatic diseases (SARDs) raise the question on relationship between the two situations.

OBJECTIVE:

To determine vitamin D status in known cases of common SARDs and compare to those with non-autoimmune diseases; further, to evaluate the impact of vitamin D on disease activity in rheumatoid arthritis (RA) cases.

METHODS:

In a retrospective case-control study design, we evaluated 116 patients in a community clinic classified in two groups,

CONTROL GROUP:

patients with non-rheumatic disease (n = 56), and Case group: those with rheumatic diseases (n = 60). We compared plasma vitamin D status (25(OH)D), indicators of disease activity and other potential confounders. Further, we determined factors associated with disease activity in RA cases.

RESULTS:

The plasma 25(OH)D was significantly lower in Case group (64.8 ± 29.8) compared to CONTROL GROUP (86.8 ± 37.7). High number of SARDs outpatients 56%) had considerably low plasma 25(OH)D concentration. RA cases with low plasma 25(OH)D had over five times higher risk of disease activity (OR = 5.15 95% CI 1.16, 22.9; p = 0.031).

CONCLUSION:

Inadequate vitamin D status in SARDs cases, along with considerably strong association with disease activity in RA cases, indicate the need for proper evaluation of vitamin D status in this clinical population. Moreover, appropriate training should be given to the patients to ensure the intake of the recommended amount of vitamin D per day through diet or supplement.

Mucosal Immunol. 2015 May;8(3):618-26. doi: 10.1038/mi.2014.94. Epub 2014 Oct 15.

Dysbiosis caused by vitamin D receptor deficiency confers colonization resistance to Citrobacter rodentium through modulation of innate lymphoid cells.

Chen J, Waddell A, Lin YD, Cantorna MT.

ABSTRACT

Vitamin D receptor (VDR) knockout (KO) mice had fewer Citrobacter rodentium in the feces than wild-type (WT) mice and the kinetics of clearance was faster in VDR KO than WT mice. VDR KO mice had more interleukin-22 (IL-22)-producing innate lymphoid cells (ILCs) and more antibacterial peptides than WT mice. The increased ILCs in the VDR KO mice was a cell-autonomous effect of VDR deficiency on ILC frequencies. Bone marrow (BM) transplantation from VDR KO mice into WT resulted in higher ILCs and colonization resistance of the WT mice. Disruption of the gut microbiota using antibiotics in VDR KO mice reversed colonization resistance to C. rodentium infection. Confirming the role of the microbiota in the colonization resistance of VDR KO mice, transfer of the VDR KO microbiota to WT germ-free mice resulted in colonization resistance. Once colonization resistance was overcome, VDR KO mice had increased susceptibility to C. rodentium. VDR expression is a regulator of ILC frequencies, IL-22, dysbiosis, and C. rodentium susceptibility.

BMJ 2014;348:g1903 doi: 10.1136/bmj.g1903 (Published 1 April 2014)

Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies

Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, Feldman BS, Pan A, Johnson L, Crowe F, Hu FB, Franco OH.

ABSTRACT

OBJECTIVE:
To evaluate the extent to which circulating biomarker and supplements of vitamin D are associated with mortality from cardiovascular, cancer, or other conditions, under various circumstances.

DESIGN:
Systematic review and meta-analysis of observational studies and randomised controlled trials.

DATA SOURCES:
Medline, Embase, Cochrane Library, and reference lists of relevant studies to August 2013; correspondance with investigators.

STUDY SELECTION:
Observational cohort studies and randomised controlled trials in adults, which reported associations between vitamin D (measured as circulating 25-hydroxyvitamin D concentration or vitamin D supplement given singly) and cause specific mortality outcomes.

DATA EXTRACTION:
Data were extracted by two independent investigators, and a consensus was reached with involvement of a third. Study specific relative risks from 73 cohort studies (849 412 participants) and 22 randomised controlled trials (vitamin D given alone versus placebo or no treatment; 30 716 participants) were meta-analysed using random effects models and were grouped by study and population characteristics.

RESULTS:
In the primary prevention observational studies, comparing bottom versus top thirds of baseline circulating 25-hydroxyvitamin D distribution, pooled relative risks were 1.35 (95% confidence interval 1.13 to 1.61) for death from cardiovascular disease, 1.14 (1.01 to 1.29) for death from cancer, 1.30 (1.07 to 1.59) for non-vascular, non-cancer death, and 1.35 (1.22 to 1.49) for all cause mortality. Subgroup analyses in the observational studies indicated that risk of mortality was significantly higher in studies with lower baseline use of vitamin D supplements. In randomised controlled trials, relative risks for all cause mortality were 0.89 (0.80 to 0.99) for vitamin D3 supplementation and 1.04 (0.97 to 1.11) for vitamin D2 supplementation. The effects observed for vitamin D3 supplementation remained unchanged when grouped by various characteristics. However, for vitamin D2 supplementation, increased risks of mortality were observed in studies with lower intervention doses and shorter average intervention periods.

CONCLUSIONS:
Evidence from observational studies indicates inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease, cancer, and other causes. Supplementation with vitamin D3 significantly reduces overall mortality among older adults; however, before any widespread supplementation, further investigations will be required to establish the optimal dose and duration and whether vitamin D3 and D2 have different effects on mortality risk.

Int Urol Nephrol. 2019 Sep;51(9):1567-1580. doi: 10.1007/s11255-019-02236-9. Epub 2019 Jul 23.

The effects of vitamin D treatment on glycemic control, serum lipid profiles, and C-reactive protein in patients with chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials.

Milajerdi A, Ostadmohammadi V, Amirjani S, Kolahdooz F, Asemi Z.

ABSTRACT

PURPOSE:

Insulin resistance, dyslipidemia and increased systemic inflammation are important risk factors for chronic kidney disease (CKD). Hence, vitamin D administration might be an appropriate approach to decrease the complications of CKD. Randomized controlled trials assessing the effects of vitamin D supplementation or treatment on glycemic control, lipid profiles, and C-reactive protein (CRP) among patients with CKD were included.

METHODS:

Two independent authors systematically searched online databases including EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science in November 2018 with no time restriction. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. Between-study heterogeneity was estimated using the Cochran's Q test and I-square (I2) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size.

RESULTS:

Of the 1358 citations identified from searches, 17 full-text articles were reviewed. Pooling findings from five studies revealed a significant reduction in fasting glucose (WMD: -18.87; 95% CI: -23.16, -14.58) and in homeostatic model assessment of insulin resistance (HOMA-IR) through three studies (WMD: -2.30; 95% CI: -2.88, -1.72) following the administration of vitamin D. In addition, pooled analysis revealed a significant reduction in triglycerides (WMD: -32.52; 95% CI: -57.57, -7.47) through six studies and in cholesterol concentrations (WMD: -7.93; 95% CI: -13.03, -2.83) through five studies, following vitamin D supplementation or treatment, while there was no effect on insulin, HbA1c, LDL and HDL cholesterol, and CRP levels.

CONCLUSIONS:

This meta-analysis demonstrated the beneficial effects of vitamin D supplementation or treatment on improving fasting glucose, HOMA-IR, triglycerides and cholesterol levels among patients with CKD, though it did not influence insulin, HbA1c, LDL and HDL cholesterol, and CRP levels.

Matern Child Nutr. 2016 Oct;12(4):898-907. doi: 10.1111/mcn.12187. Epub 2015 Apr 7.

Effects of early vitamin D deficiency rickets on bone and dental health, growth and immunity.

Zerofsky M, Ryder M, Bhatia S, Stephensen CB, King J, Fung EB.

ABSTRACT

Vitamin D deficiency is associated with adverse health outcomes, including impaired bone growth, gingival inflammation and increased risk for autoimmune disease, but the relationship between vitamin D deficiency rickets in childhood and long-term health has not been studied. In this study, we assessed the effect of early vitamin D deficiency on growth, bone density, dental health and immune function in later childhood to determine if children previously diagnosed with rickets were at greater risk of adverse health outcomes compared with healthy children. We measured serum 25-hydroxyvitamin D, calcium, parathyroid hormone, bone mineral density, anthropometric measures, dietary habits, dental health, general health history, and markers of inflammation in 14 previously diagnosed rickets case children at Children's Hospital Oakland Research Center. We compared the findings in the rickets cases with 11 healthy children selected from the population of CHO staff families. Fourteen mothers of the rickets cases, five siblings of the rickets cases, and seven mothers of healthy children also participated. Children diagnosed with vitamin D deficiency rickets had a greater risk of fracture, greater prevalence of asthma, and more dental enamel defects compared with healthy children. Given the widespread actions of vitamin D, it is likely that early-life vitamin D deficiency may increase the risk of disease later in childhood. Further assessment of the long-term health effects of early deficiency is necessary to make appropriate dietary recommendations for infants at risk of deficiency.

4.2.5 Pregnancy

Mol Cell Endocrinol. 2017 Sep 15;453:113-130. doi: 10.1016/j.mce.2017.01.039. Epub 2017 Feb 7.

Vitamin D supplementation during pregnancy: Improvements in birth outcomes and complications through direct genomic alteration.

Hollis BW, Wagner CL.

ABSTRACT

Pregnancy represents a time of rapid change, including dramatic shifts in vitamin D metabolism. Circulating concentrations of the active form of vitamin D-1,25(OH)2D skyrocket early in pregnancy to levels that would be toxic to a nonpregnant adult, signaling a decoupling of vitamin D from the classic endocrine calcium metabolic pathway, likely serving an immunomodulatory function in the mother and her developing fetus. In this review, we summarize the unique aspects of vitamin D metabolism and the data surrounding vitamin D requirements during this important period. Both observational and clinical trials are reviewed in the context of vitamin D's health effects during pregnancy that include preeclampsia, preterm birth, and later disease states such as asthma and multiple sclerosis. With enhanced knowledge about vitamin D's role as a prepro-hormone, it is clear that recommendations about supplementation must mirror what is clinically relevant and evidence-based. Future research that focuses on the critical period(s) leading up to conception and during pregnancy to correct deficiency or maintain optimal vitamin D status remains to be studied. In addition, what effects vitamin D has on genetic signatures that minimize the risk to the mother and her developing fetus have not been elucidated. Clearly, while there is much more research that needs to be performed, our understanding of vitamin D requirements during pregnancy has advanced significantly during the last few decades.

Front Endocrinol (Lausanne). 2018; 9: 500. Published online 2018 Aug 31. doi: 10.3389/fendo.2018.00500

The Implications of Vitamin D Status During Pregnancy on Mother and her Developing Child

Wagner CL, Hollis BW.

ABSTRACT

Pregnancy is a time of tremendous growth and physiological changes for mother and her developing fetus with lifelong implications for the child. The concert of actions that must occur so mother does not reject the foreign tissue of the fetus is substantial. There must be exquisite balance between maternal tolerance to these foreign proteins of paternal origin but also immune surveillance and function such that the mother is not immunocompromised. When this process goes awry, the mother may experience such pregnancy complications as preeclampsia and infections.

Vitamin D deficiency affects these processes. Controversy continues with regard to the optimal daily intake of vitamin D, when sunlight exposure should be taken into account, and how to define sufficiency during such vulnerable and critical periods of development. The importance of vitamin D supplementation during pregnancy in preventing some of the health risks to the mother and fetus appears linked to achieving 25(OH)D concentrations >40 ng/mL, the beginning point of the plateau where conversion of the vitamin D metabolite 25(OH)D, the pre-hormone, to 1,25(OH)2D, the active hormone, is optimized. Throughout pregnancy, the delivery of adequate vitamin D substrate—through sunlight or supplement—is required to protect both mother and fetus, and when in sufficient supply, favorably impacts the epigenome of the fetus, and in turn, long term health. There is a growing need for future research endeavors to focus not only on critical period(s) from pre-conception through pregnancy, but throughout life to prevent certain epigenetic changes that adversely affect health. There is urgency based on emerging research to correct deficiency and maintain optimal vitamin D status. The impact of vitamin D and its metabolites on genetic signaling during pregnancy in both mother and fetus is an area of great activity and still in its early stages. While vitamin D repletion during pregnancy minimizes the risk of certain adverse outcomes (e.g., preterm birth, asthma, preeclampsia, and gestational diabetes), the mechanisms of how these processes occur are not fully understood. As we intensify our research efforts in these areas. it is only a matter of time that such mechanisms will be defined.

Clin Nutr. 2019 Sep 4. pii: S0261-5614(19)33027-4. doi: 10.1016/j.clnu.2019.08.015. [Epub ahead of print]

Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials.

Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GYH, Blaha MJ, Toth PP, Borghi C, Cicero AFG; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group.

ABSTRACT

BACKGROUND:

Maternal vitamin D deficiency has been associated with an increased risk for preeclampsia. Despite this, the current evidence regarding the efficacy of vitamin D supplementation in preventing preeclampsia is controversial. To assess the impact of vitamin D supplementation on the risk of preeclampsia, we performed a systematic review of the literature and a meta-analysis of the available randomized clinical trials (RCTs).

METHODS:

The primary outcome was preeclampsia. Subgroup analyses were carried out considering the timing of the supplementation, type of intervention and the study design. Meta-regression analysis, including the amount of vitamin D and maternal age, were planned to explore heterogeneity (PROSPERO database registration number: CRD42019119207).

RESULTS:

Data were pooled from 27 RCTs comprising 59 arms, which included overall 4777 participants, of whom 2487 were in the vitamin D-treated arm and 2290 in the control arm. Vitamin D administration in pregnancy was associated with a reduced risk of preeclampsia (odd ratio [OR] 0.37, 95% confidence interval [CI]: 0.26, 0.52; I2 = 0%). If the vitamin D supplementation was started up to 20 weeks' gestation, the odds was a little lower (OR 0.35, 95% CI: 0.24, 0.50, $p < 0.001$). The effect was largely independent of the supplementation cessation (until delivery or not), type of intervention (vitamin D alone or in association with calcium), and study design. Increasing dose of vitamin D was associated with reduced incidence of preeclampsia (slope of log OR: -1.1, 95% CI: -1.73, -0.46; $p < 0.001$).

CONCLUSIONS:

Results suggest that vitamin D supplementation may be useful in preventing preeclampsia. These data are especially useful for health-care providers who engage in the management of pregnant women at risk for preeclampsia. Our findings are a call for action to definitively address vitamin D supplementation as a possible intervention strategy in preventing preeclampsia in pregnancy.

4.3 Vitamin K2

4.3.1 Arteriosclerosis/CVD

J Nutr. 2004 Nov;134(11):3100-5.

Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study.

Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC.

ABSTRACT

Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990-1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59, 0.92), respectively] and severe aortic calcification [odds ratio of 0.71 (0.50, 1.00) and 0.48 (0.32, 0.71), respectively]. Phylloquinone intake was not related to any of the outcomes. These findings suggest that an adequate intake of menaquinone could be important for CHD prevention.

Thromb Haemost. 2008 Oct;100(4):593-603.

Matrix Gla-protein: the calcification inhibitor in need of vitamin K.

Schurgers LJ, Cranenburg EC, Vermeer C.

ABSTRACT

Among the proteins involved in vascular calcium metabolism, the vitamin K-dependent matrix Gla-protein (MGP) plays a dominant role. Although on a molecular level its mechanism of action is not completely understood, it is generally accepted that MGP is a potent inhibitor of arterial calcification. Its pivotal importance for vascular health is demonstrated by the fact that there seems to be no effective alternative mechanism for calcification inhibition in the vasculature. An optimal vitamin K intake is therefore important to maintain the risk and rate of calcification as low as possible. With the aid of conformation-specific antibodies MGP species in both tissue and the circulation have been detected in the healthy population, and significant differences were found in patients with cardiovascular disease (CVD). Using ELISA-based assays, uncarboxylated MGP (ucMGP) was demonstrated to be a promising biomarker for cardiovascular calcification detection. These assays may have potential value for identifying patients as well as apparently healthy subjects at high risk for CVD and/or cardiovascular calcification and for monitoring the treatment of CVD and vascular calcification.

Nutr Metab Cardiovasc Dis. 2009 Sep;19(7):504-10. doi: 10.1016/j.numecd.2008.10.004.

A high menaquinone intake reduces the incidence of coronary heart disease.

Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witteman JC, Grobbee DE, Peeters PH, van der Schouw YT.

ABSTRACT

BACKGROUND AND AIM:

Vitamin K dependent proteins have been demonstrated to inhibit vascular calcification. Data on the effect of vitamin K intake on coronary heart disease (CHD) risk, however, are scarce. To examine the relationship between dietary vitamins K(1) and K(2) intake, and its subtypes, and the incidence of CHD.

CONCLUSIONS:

A high intake of menoquinones, especially MK-7, MK-8 and MK-9, could protect against CHD. However, more research is necessary to define optimal intake levels of vitamin K intake for the prevention of CHD.

Przegl Lek. 2011;68(9):629-32.

Vitamin K, bone metabolism and vascular calcification in chronic kidney disease.

Zak-Gołab A, Okopień B, Chudek J.

ABSTRACT

Atherosclerosis is the main cause of morbidity and mortality in the general population, and premature death in patients with chronic kidney disease (CKD) especially dialysis ones. Vitamin K - dependent proteins play an essential role in the pathogenesis of mineral and bone disorders related to CKD, including vascular calcification. Vitamin K is a family of vitamins, varying in the number of isoprenoid groups (saturated or unsaturated) connected into 2-methyl-1,4-naphthoquinone ring in C3 position. Vitamin K-dependent proteins require carboxylation (VKDPs) for biological activation. The coagulant factors are the most well-known VKDPs, but the role of the other proteins, like Matrix Gla Protein (MGP), Growth Arrest Specific Gene 6 (Gas-6) and osteocalcin has been recently discovered. MGP prevents vascular calcification and Gas-6 affects vascular smooth muscle cell apoptosis and movement. Carboxylation of osteocalcin promotes bone formation. Additionally vitamin K increases proliferation of osteoblasts and apoptosis of osteoclasts, influencing on bone remodeling. There is few studies indicating for decreased consumption of vitamin K in the general population. The restrictive diet recommended for dialysis patients additionally diminishes its daily supply, increasing the chance for vitamin K deficiency in this population. Clinical consequences of inhibition of epoxide reductase by generally used anticoagulants, that inhibiting vitamin K cycle and preventing gamma-carboxylation of Gla proteins, in the peripheral tissue is hardly known. This paper summaries the state of the art knowledge focused on the role of vitamin K in mineral and bone metabolism disorders in CKD patients.

J Bone Miner Res. 2012 Nov;27(11):2271-8. doi: 10.1002/jbmr.1677.

Vitamin K, vertebral fractures, vascular calcifications, and mortality: VItamin K Italian (VIKI) dialysis study.

Fusaro M, Noale M, Viola V, Galli F, Tripepi G, Vajente N, Plebani M, Zaninotto M, Guglielmi G, Miotto D, Dalle Carbonare L, D'Angelo A, Naso A, Grimaldi C, Miozzo D, Giannini S, Gallieni M; VItamin K Italian (VIKI) Dialysis Study Investigators.

ABSTRACT

Vitamin K (vitamin K1 or phylloquinone and vitamin K2, a series of menaquinones [MKs]) is involved in the production of bone and matrix amino acid γ-carboxy-glutamic acid (Gla) proteins, regulating bone and vascular calcification. We carried out an observational study to establish the prevalence of vitamin K deficiency and to assess the relationship between vitamin K status, vertebral fractures, vascular calcification, and survival in 387 patients on hemodialysis for ≥1 year. Important proportions of patients had deficiency of MK7 (35.4%), vitamin K1 (23.5%), and MK4 (14.5%). A total of 55.3% of patients had vertebral fractures, 80.6% had abdominal aorta calcification, and 56.1% had iliac calcification. Vitamin K1 deficiency was the strongest predictor of vertebral fractures. MK4 deficiency was a predictor of aortic calcification, whereas MK5 deficiency actually protected against it. MK7 deficiency was a predictor of iliac calcification. The presence of vertebral fractures was also a predictor of vascular calcifications. Our study suggests that the vitamin K system may be important for preserving bone mass and avoiding vascular calcification in hemodialysis patients, pointing out a possible role of vitamin K in bone and vascular health. Based on our results, we suggest that the general population should also be studied for vitamin K deficiency as a possible cause of both vertebral fractures and vascular calcification.

Adv Nutr. 2012 Mar 1;3(2):166-73. doi: 10.3945/an.111.001628.

The role of vitamin K in soft-tissue calcification.

Schurgers LJ, Cranenburg EC, Vermeer C.Theuwissen E, Smit E, Vermeer C.

ABSTRACT

Seventeen vitamin K-dependent proteins have been identified to date of which several are involved in regulating soft-tissue calcification. Osteocalcin, matrix Gla protein (MGP), and possibly Gla-rich protein are all inhibitors of soft-tissue calcification and need vitamin K-dependent carboxylation for activity. MGP is synthesized by vascular smooth muscle cells and is the most important inhibitor of arterial mineralization currently known. Remarkably, the extrahepatic Gla proteins mentioned are only partly carboxylated in the healthy adult population, suggesting vitamin K insufficiency. Because carboxylation of the most essential Gla proteins is localized in the liver and that of the less essential Gla proteins in the extrahepatic tissues, a transport system has evolved ensuring preferential distribution of dietary vitamin K to the liver when vitamin K is limiting. This is why the first signs of vitamin K insufficiency are seen as undercarboxylation of the extrahepatic Gla proteins. New conformation-specific assays for circulating uncarboxylated MGP were developed; an assay for desphospho-uncarboxylated matrix Gla protein and another assay for total uncarboxylated matrix Gla protein. Circulating desphospho-uncarboxylated matrix Gla protein was found to be predictive of cardiovascular risk and mortality, whereas circulating total uncarboxylated matrix Gla protein was associated with the extent of prevalent arterial calcification. This study showed maintenance of vascular elasticity during a 3-y supplementation period, with a parallel 12% loss of elasticity in the placebo group.

Eur Rev Med Pharmacol Sci. 2013 Sep;17(18):2433-40.

Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis.

Flore R, Ponziani FR, Di Rienzo TA, Zocco MA, Flex A, Gerardino L, Lupascu A, Santoro L, Santoliquido A, Di Stasio E, Chierici E, Lanti A, Tondi P, Gasbarrini A.

ABSTRACT

DISCUSSION:

Vitamin K2 is essential for the function of several proteins, involved in the maintenance of the normal structure of arterial wall, osteoarticular system, teeth, and for the regulation of cell growth. It has been demonstrated to have a pivotal role in the inhibition of vascular foci of calcification, and in the regulation of calcium deposition in the bone. Vitamin K2 deficiency is often subclinic in a large part of healthy population. This deficiency is related to the interaction of various factors, such as the reduced dietary intake, the alteration of intestinal absorption or production, with a possible role of intestinal microbiota and the increased consumption at the vessel wall.

CONCLUSIONS:

Vitamin K2 deficiency has recently been recognized as a protagonist in the development of vascular calcification and osteoporosis. Data reported so far are promising and, dietary supplementation seems a useful tool to contrast these diseases. However, large studies or solid clinical correlations regarding vitamin K2 deficiency and its pathologic consequences are needed to confirm these preliminary experiences.

Pol Arch Med Wewn. 2015;125(9):631-40. Epub 2015 Jul 15.

Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5.

Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarska M, Stefańczyk L, Vermeer C, Maresz K, Nowicki M.

ABSTRACT

PATIENTS AND METHODS:

The study included 42 nondialyzed patients with CKD. The measurements were taken at baseline and after 270 ±12 days of supplementation with vitamin K2 at a dose of 90 μg (menaquinone, MK-7) together with 10 μg of cholecalciferol (K+D group) or 10 μg of cholecalciferol (group D).

RESULTS:

The increase of carotid intima-media thickness was significantly lower in the K+D group compared with the D group: from 0.95 ±0.2 mm to 1.01 ±0.3, P = 0.003 vs from 1.02 ±0.2 mm to 1.16 ±0.3, P = 0.003. The increase in coronary artery calcification score was slightly lower in the K+D group than in the D group. In the K+D group, a significant decrease in the level of desphosphorylated-uncarboxylated MGP and total osteocalcin was observed.

CONCLUSIONS:

A 270-day course of vitamin K2 administration in patients with CKD stages 3-5 may reduce the progression of atherosclerosis, but does not significantly affect the progression of calcification. Vitamin K2 significantly changes the levels of calcification promoters and inhibitors: dp-ucMGP, OC, and OPG.

Curr Nutr Rep. 2016 Jun;5(2):90-98. Epub 2016 Mar 31.

The Role of Vitamin K in Chronic Aging Diseases: Inflammation, Cardiovascular Disease, and Osteo-arthritis.

Harshman SG, Shea MK.

ABSTRACT

Vitamin K is an enzyme cofactor required for the carboxylation of vitamin K dependent proteins, several of which have been implicated in diseases of aging. Inflammation is recognized as a crucial component of many chronic aging diseases and evidence suggests vitamin K has an anti-inflammatory action that is independent of its role as an enzyme co-factor. Vitamin K-dependent proteins and inflammation have been implicated in cardiovascular disease and osteoarthritis, which are leading causes of disability and mortality in older adults. The purpose of this review is to summarize observational studies and randomized trials focused on vitamin K status and inflammation, cardiovascular disease, and osteoarthritis. Although mechanistic evidence suggests a protective role for vitamin K in these age-related conditions, the benefit of vitamin K supplementation is controversial because observational data are equivocal and the number of randomized trials is few.

4.3.2 Bone Metabolism

Curr Pharm Des. 2004;10(21):2557-76.

Effects of vitamin K2 on osteoporosis.

Iwamoto J, Takeda T, Sato Y.

ABSTRACT

Vitamin K2 is a cofactor of gamma-carboxylase, which converts the glutamic acid (Glu) residue in osteocalcin molecules to gamma-carboxyglutamic acid (Gla), and is, therefore, essential for gamma-carboxylation of osteocalcin. Available evidence suggests that vitamin K2 also enhances osteocalcin accumulation in the extracellular matrix of osteoblasts in vitro. The findings suggest that vitamin K2 may not only stimulate bone formation but also suppress bone resorption in vivo. Clinically, vitamin K2 sustains the lumbar bone mineral density (BMD) and prevents osteoporotic fractures in patients with age-related osteoporosis, prevents vertebral fractures in patients with glucocorticoid-induced osteoporosis, increases the metacarpal BMD in the paralytic upper extremities of patients with cerebrovascular disease, and sustains the lumbar BMD in patients with liver-dysfunction-induced osteoporosis. Vitamin K deficiency, as indicated by an increased circulating level of undercarboxylated osteocalcin, may contribute to osteoporotic fractures. Even though the effect of vitamin K2 on the BMD is quite modest, this vitamin may have the potential to regulate bone metabolism and play a role in reducing the risk of osteoporotic fractures. No randomized well-controlled prospective studies conducted on a sufficiently large number of patients have been reported yet, therefore, further studies are needed to confirm the efficacy of vitamin K2 in the treatment of osteoporosis.

Clin Calcium. 2005 Jun;15(6):1034-9.

Vitamin K2 (menatetrenone) and bone quality.

Iinuma N.

ABSTRACT

Vitamin K2 (menatetrenone) treatment was reported to significantly prevent new clinical fracture (chi2 = 10.935;p = 0.0273) in a 2-year group comparison study of patients with osteoporosis, although it only maintained the baseline bone mineral density. This result strongly suggested that another factor was involved in promoting bone strength apart from an increase in bone mineral density. With respect to the therapeutic effect of menatetrenone treatment on corticosteroid-induced osteoporosis over 2 years, the incidence of a new vertebral fracture was 13.3% in the menatetrenone treatment group versus 41% in the control group, indicating that this treatment could prevent fractures. Multivariate logistic regression analysis was performed to investigate independent risk factors for new vertebral fractures, and treatment with menatetrenone showed a preventive effect on fracture with an odds ratio of 0.03 and a risk rate of 0.003.

Osteoporos Int. 2013 Sep;24(9):2499-507. doi: 10.1007/s00198-013-2325-6. Epub 2013 Mar 23.

Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women.

Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E.

ABSTRACT

METHODS:

Healthy postmenopausal women (n = 244) received for 3 years placebo or MK-7 (180 μg MK-7/day) capsules. Bone mineral density of lumbar spine, total hip, and femoral neck was measured by DXA; bone strength indices of the femoral neck were calculated. Vertebral fracture assessment was performed by DXA and used as measure for vertebral fractures. Circulating uncarboxylated osteocalcin (ucOC) and carboxylated OC (cOC) were measured; the ucOC/cOC ratio served as marker of vitamin K status. Measurements occurred at baseline and after 1, 2, and 3 years of treatment.

We have investigated whether low-dose vitamin K2 supplements (menaquinone-7, MK-7) could beneficially affect bone health. Next to an improved vitamin K status, MK-7 supplementation significantly decreased the age-related decline in bone mineral density and bone strength. Low-dose MK-7 supplements may therefore help postmenopausal women prevent bone loss.

RESULTS:

MK-7 intake significantly improved vitamin K status and decreased the age-related decline in BMC and BMD at the lumbar spine and femoral neck, but not at the total hip. Bone strength was also favorably affected by MK-7. MK-7 significantly decreased the loss in vertebral height of the lower thoracic region at the mid-site of the vertebrae.

CONCLUSIONS:

MK-7 supplements may help postmenopausal women to prevent bone loss. Whether these results can be extrapolated to other populations, e.g., children and men, needs further investigation.

Osteoporos Int. 2015 Mar;26(3):1175-86. doi: 10.1007/s00198-014-2989-6. Epub 2014 Dec 17.

Does vitamin K2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: a meta-analysis of randomized controlled trials.

Huang ZB, Wan SL, Lu YJ, Ning L, Liu C, Fan SW.

ABSTRACT

INTRODUCTION:

Vitamin K2 has been revealed to be effective in the prevention and treatment of osteoporosis in Japan, which was not confirmed in western countries. Thus, we conduct this meta-analysis to verify the hypothesis that vitamin K2 plays a role in the prevention and treatment of osteoporosis for postmenopausal women.

METHODS:

We searched the Cochrane Library, Pub Med, EMBASE, and ISI web of knowledge (until December 1, 2013) and reference lists of eligible articles. A meta-analysis of all-including randomized controlled trials was then performed.

RESULTS:

Nineteen randomized controlled trials encompassing 6759 participants have met the inclusion criteria. Subgroup analysis of postmenopausal women with osteoporosis revealed a significant improvement of vertebral BMD for both medium-term and long-term results favoring vitamin K2 group. However, sensitivity analysis by rejecting the study inducing heterogeneity demonstrated a significant difference in the incidence of fractures favoring vitamin K2. Significant differences were found in undercarboxylated osteocalcin reduction and osteocalcin increment. The result of adverse reaction analysis showed that vitamin K2 group seemed to have a higher adverse reaction rate.

CONCLUSIONS:

This meta-analysis seemed to support the hypothesis that vitamin K2 plays kind of a role in the maintenance and improvement of vertebral BMD and the prevention of fractures in postmenopausal women with osteoporosis. The reduction of undercarboxylated osteocalcin and increment of osteocalcin may have some relation to the process of bone mineralization. However, the effect of vitamin K2 for postmenopausal women without osteoporosis had not been identified. Further high-quality RCTs with large sample size are needed to confirm the role of vitamin K2 in osteoporosis for postmenopausal women.

Oral Dis. 2017 Nov;23(8):1021-1028. doi: 10.1111/odi.12624. Epub 2017 Apr 5.

Regulation of bone remodeling by vitamin K2.

Myneni VD, Mezey E.

ABSTRACT

All living tissues require essential nutrients such as amino acids, fatty acids, carbohydrates, minerals, vitamins, and water. The skeleton requires nutrients for development, maintaining bone mass and density. If the skeletal nutritional requirements are not met, the consequences can be quite severe. In recent years, there has been growing interest in promotion of bone health and inhibition of vascular calcification by vitamin K2. This vitamin regulates bone remodeling, an important process necessary to maintain adult bone. Bone remodeling involves removal of old or damaged bone by osteoclasts and its replacement by new bone formed by osteoblasts. The remodeling process is tightly regulated, when the balance between bone resorption and bone formation shifts to a net bone loss results in the development of osteoporosis in both men and women. In this review, we focus on our current understanding of the effects of vitamin K2 on bone cells and its role in prevention and treatment of osteoporosis. Clin Calcium. 2005 Jun;15(6):1034-9.

Biomed Res Int. 2018 Jun 27;2018:4629383. doi: 10.1155/2018/4629383. eCollection 2018.

Vitamin K and Bone Metabolism: A Review of the Latest Evidence in Preclinical Studies.

Akbari S, Rasouli-Ghahroudi AA.

ABSTRACT

Bone is a metabolically active tissue that renews itself throughout one's life. Cytokines along with several hormonal, nutritional, and growth factors are involved in tightly regulated bone remodeling. Accordingly, vitamin K as a multifunctional vitamin has been recently deemed appreciable as a topic of research as it plays a pivotal role in maintenance of the bone strength, and it has been proved to have a positive impact on the bone metabolism. Vitamin K exerts its anabolic effect on the bone turnover in different ways such as promoting osteoblast differentiation, upregulating transcription of specific genes in osteoblasts, and activating the bone-associated vitamin k dependent proteins which play critical roles in extracellular bone matrix mineralization. There is also credible evidence to support the effects of vitamin k2 on differentiation of other mesenchymal stem cells into osteoblast. The main objective of the present paper is to comprehensively outline the preclinical studies on the properties of vitamin K and its effects on the bone metabolism. The evidence could shed light on further clinical studies to improve osteogenesis in bone graft surgeries.

4.3.3 Caries

Med Hypotheses. 2015 Mar;84(3):276-80. doi: 10.1016/j.mehy.2015.01.011. Epub 2015 Jan 19.

A hypothetical role for vitamin K2 in the endocrine and exocrine aspects of dental caries.

Southward Ken, University of Toronto, Canada.

ABSTRACT

The growing interest in oral/systemic links demand new paradigms to understand disease processes. New opportunities for dental research, particularly in the fields of neuroscience and endocrinology will emerge. The role of the hypothalamus portion of the brain cannot be underestimated. Under the influence of nutrition, it plays a significant role in the systemic model of dental caries. Currently, the traditional theory of dental caries considers only the oral environment and does not recognize any significant role for the brain. The healthy tooth, however, has a centrifugal fluid flow to nourish and cleanse it. This is moderated by the hypothalamus/parotid axis which signals the endocrine portion of the parotid glands. High sugar intake creates an increase in reactive oxygen species and oxidative stress in the hypothalamus. When this signaling mechanism halts or reverses the dentinal fluid flow, it renders the tooth vulnerable to oral bacteria, which can now attach to the tooth's surface. Acid produced by oral bacteria such as Strep Mutans and lactobacillus can now de-mineralize the enamel and irritate the dentin. The acid attack stimulates an inflammatory response which results in dentin breakdown from the body's own matrix metalloproteinases. Vitamin K2 (K2) has been shown to have an antioxidant potential in the brain and may prove to be a potent way to preserve the endocrine controlled centrifugal dentinal fluid flow. Stress, including oxidative stress, magnifies the body's inflammatory response. Sugar can not only increase oral bacterial acid production but it can concurrently reduce the tooth's defenses through endocrine signaling. Saliva production is the exocrine function of the salivary glands. The buffering capacity of saliva is critical to neutralizing the oral environment. This minimizes the de-mineralization of enamel and enhances its re-mineralization. K2, such as that found in fermented cheese, improves salivary buffering through its influence on calcium and inorganic phosphates secreted. Data collected from several selected primitive cultures on the cusp of civilization demonstrated the difference in dental health due to diet. The primitive diet group had few carious lesions compared to the group which consumed a civilized diet high in sugar and refined carbohydrates. The primitives were able to include the fat soluble vitamins, specifically K2, in their diet. More endocrine and neuroscience research is necessary to better understand how nutrition influences the tooth's defenses through the hypothalamus/parotid axis. It will also link dental caries to other inflammation related degenerative diseases such as diabetes.

4th International Conference and Exhibition on Nutrition. October 26-28, 2015 Chicago, Illinois, USA

The potential role of vitamin K2 in dental caries.

Southward Ken, University of Toronto, Canada.

ABSTRACT

Dental caries has traditionally been viewed as a tooth demineralizing process limited to the oral cavity. New understandings of oral/systemic links propose that dental caries is an uncontrolled inflammatory response controlled by the brain and moderated through the hypothalamus/parotid axis of the endocrine system. The role of reactive oxygen species in the hypothalamus is a signaling factor in establishing tooth vulnerability or resistance. Vitamin K2 appears to have a significant antioxidant role in the brain as well as a key nutrient in the management of calcium in the body including bones and cardiovascular tissues. K2 works in concert with calcium and vitamin D. This systemic paradigm of dental caries places nutrition on the leading edge of prevention because it is focused on the cause of the disease rather than traditional preventive efforts focused on the symptoms. K2 also appears to have a potential salivary buffering role in the exocrine portion of the parotid gland as well as the other salivary glands. In this systemic paradigm, the potential preventive role of nutritionists and public health professionals is elevated to unprecedented levels. Working to broaden current dental recall programs beyond a symptom focus will show benefits but will probably have to be driven by public education programs.

4.3.4 Systemic Relevance

Science. 2012 Jun 8;336(6086):1306-10. doi: 10.1126/science.1218632. Epub 2012 May 10.

Vitamin K2 is a mitochondrial electron carrier that rescues pink1 deficiency.

Vos M, Esposito G, Edirisinghe JN, Vilain S, Haddad DM, Slabbaert JR, Van Meensel S, Schaap O, De Strooper B, Meganathan R, Morais VA, Verstreken P.

ABSTRACT

Human UBIAD1 localizes to mitochondria and converts vitamin K(1) to vitamin K(2). Vitamin K(2) is best known as a cofactor in blood coagulation, but in bacteria it is a membrane-bound electron carrier. Whether vitamin K(2) exerts a similar carrier function in eukaryotic cells is unknown. We identified Drosophila UBIAD1/Heix as a modifier of pink1, a gene mutated in Parkinson's disease that affects mitochondrial function. We found that vitamin K(2) was necessary and sufficient to transfer electrons in Drosophila mitochondria. Heix mutants showed severe mitochondrial defects that were rescued by vitamin K(2), and, similar to ubiquinone, vitamin K(2) transferred electrons in Drosophila mitochondria, resulting in more efficient adenosine triphosphate (ATP) production. Thus, mitochondrial dysfunction was rescued by vitamin K(2) that serves as a mitochondrial electron carrier, helping to maintain normal ATP production.

J Nutr Metab. 2017;2017:6254836. doi: 10.1155/2017/6254836. Epub 2017 Jun 18.

Vitamins K1 and K2: The Emerging Group of Vitamins Required for Human Health.

Schwalfenberg GK.

ABSTRACT

OBJECTIVE:

To review the evidence for the use of vitamin K supplementation in clinical conditions such as osteoporosis, vascular calcification, arthritis, cancer, renal calculi, diabetes, and warfarin therapy.

QUALITY OF EVIDENCE:

PubMed was searched for articles on vitamin K (K1 and K2) along with books and conference proceedings and health conditions listed above. Level I and II evidence supports the use of vitamins K1 and K2 in osteoporosis and Level II evidence supports vitamin K2 in prevention of coronary calcification and cardiovascular disease. Evidence is insufficient for use in diabetes, arthritis, renal calculi, and cancer.

MAIN MESSAGE:

Vitamin K2 may be a useful adjunct for the treatment of osteoporosis, along with vitamin D and calcium, rivaling bisphosphonate therapy without toxicity. It may also significantly reduce morbidity and mortality in cardiovascular health by reducing vascular calcification. Vitamin K2 appears promising in the areas of diabetes, cancer, and osteoarthritis. Vitamin K use in warfarin therapy is safe and may improve INR control, although a dosage adjustment is required.

CONCLUSION:

Vitamin K supplementation may be useful for a number of chronic conditions that are afflicting North Americans as the population ages. Supplementation may be required for bone and cardiovascular health.

Diabetes Res Clin Pract. 2018 Feb;136:39-51. doi: 10.1016/j.diabres.2017.11.020. Epub 2017 Dec 2.

Effect of vitamin K2 on type 2 diabetes mellitus: A review.

Li Y, Chen JP, Duan L, Li S.

ABSTRACT

Type 2 diabetes mellitus (T2DM) continue to be a major public health problem around the world that frequently presents with microvascular and macrovascular complications. Individuals with T2DM are not only suffering from significant emotional and physical misery, but also at increased risk of dying from severe complications. In recent years, evidence from prospective observational studies and clinical trials has shown T2DM risk reduction with vitamin K2 supplementation. We thus did an overview of currently available studies to assess the effect of vitamin K2 supplementation on insulin sensitivity, glycaemic control and reviewed the underlying mechanisms. We proposed that vitamin K2 improved insulin sensitivity through involvement of vitamin K-dependent-protein osteocalcin, anti-inflammatory properties, and lipid-lowering effects. Vitamin K2 had a better effect than vitamin K1 on T2DM. The interpretation of this review will increase comprehension of the development of a therapeutic strategy to prevent and treat T2DM.

Attachment Ceramic Implantology

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Attachment Cavitations (Osteonecrosis of the Jawbone/ FDOJ)

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