Current scientific status

Study overview

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

INTERFERENCE FIELDS IN THE ORAL CAVITY

3.1 Root Canal treated Teeth

3.2 Metals/Amalgam

3.3 Cavitations (Osteonecrosis of the Jawbone/FDOJ)

SWISS BIOHEALTH ACADEMY

CENTER HOČEVAR

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 (5 2%) 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 TAND-HEELKUNDE 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 healthcare 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 physiosomatic 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. INTERFERENCE FIELDS IN THE ORAL CAVITY

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 + 0.24 x 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. INTERFERENCE FIELDS IN THE ORAL CAVITY

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 proinflammatory 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".