Current scientific status

Study overview

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

VITAMINS IMPORTANT IN DENTISTRY

4.1 Vitamin C

4.2 Vitamin D3

4.2 Vitamin K2

SWISS BIOHEALTH ACADEMY

CENTER HOČEVAR

4. VITAMINS IMPORTANT IN DENTISTRY

4.1 Vitamin C

4.1.1 Bone Metabolism

J BONE MINER RES. 2015 NOV;30(11):1945-55.
DOI: 10.1002/JBMR.2709. EPUB 2015 OCT 7.

The Roles and Mechanisms of Actions of Vitamin C in Bone: New Developments.

Aghajanian P, Hall S, Wongworawat MD, Mohan S.

ABSTRACT
Vitamin C is an important antioxidant and cofactor that is involved in the regulation of development, function, and maintenance of several cell types in the body. Deficiencies in vitamin C can lead to conditions such as scurvy, which, among other ailments, causes gingivia, bone pain, and impaired wound healing. This review examines the functional importance of vitamin C as it relates to the development and maintenance of bone tissues. Analysis of several epidemiological studies and genetic mouse models regarding the effect of vitamin C shows a positive effect on bone health. Overall, vitamin C exerts a positive effect on trabecular bone formation by influencing expression of bone matrix genes in osteoblasts. Recent studies on the molecular pathway for vitamin C actions that include direct effects of vitamin C on transcriptional regulation of target genes by influencing the activity of transcription factors and by epigenetic modification of key genes involved in skeletal development and maintenance are discussed. With an understanding of mechanisms involved in the uptake and metabolism of vitamin C and knowledge of precise molecular pathways for vitamin C actions in bone cells, it is possible that novel therapeutic strategies can be developed or existing therapies can be modified for the treatment of osteoporotic fractures.

CURR DRUG TARGETS. 2018;19(5):439-450.
DOI: 10.2174/1389450116666150907100838.

Vitamin C and Bone Health: Evidence from Cell, Animal and Human Studies.

Chin KY, Ima-Nirwana S.

ABSTRACT
BACKGROUND:
Vitamin C, traditionally associated with scurvy, is an important nutrient for maintaining bone health. It is essential in the production of collagen in bone matrix. It also scavenges free radicals detrimental to bone health.

OBJECTIVE:
This review aims to assess the current evidence of the bone-sparing effects of vitamin C derived from cell, animal and human studies.

RESULTS:
Cell studies showed that vitamin C was able to induce osteoblast and osteoclast formation. However, high-dose vitamin C might increase oxidative stress and subsequently lead to cell death. Vitamin C-deficient animals showed impaired bone health due to increased osteoclast formation and decreased bone formation. Vitamin C supplementation was able to prevent bone loss in several animal models of bone loss. Human studies generally showed a positive relationship between vitamin C and bone health, indicated by bone mineral density, fracture probability and bone turnover markers. Some studies suggested that the relationship between vitamin C and bone health could be U-shaped, more prominent in certain subgroups and different between dietary and supplemental form. However, most of the studies were observational, thus could not confirm causality. One clinical trial was performed, but it was not a randomized controlled trial, thus confounding factors could not be excluded.

CONCLUSION:
vitamin C may exert beneficial effects on bone, but more rigorous studies and clinical trials should be performed to validate this claim.

CLIN IMPLANT DENT RELAT RES. 2018 OCT;20(5):793-798. DOI: 10.1111/CID.12647. EPUB 2018 JUL 24.

Role of vitamin C in wound healing after dental implant surgery in patients treated with bone grafts and patients with chronic periodontitis.

Li X, Tang L, Lin YF, Xie GF.

ABSTRACT

BACKGROUND:
Postoperative wound healing is an important part of the success of the dental implant surgery. However, in case of complex surgery or unfavorable factors, wound healing is often unsatisfactory.

OBJECTIVE:
The aim of this study was to explore the effects of vitamin C supplementation in wound healing, following the placement of dental implants with or without bone grafts and patients with chronic periodontitis.

METHODS:
This randomized controlled clinical trial included 128 patients requiring dental implants to replace missing teeth. Patients were divided into four groups, group A received dental implants supported by guided bone regeneration (GBR) technique, group B received dental implants with Bio-Oss Collagen, group C received dental implants in patients with chronic periodontitis, and group D received dental implants without any bone grafting or periodontal disease. Each group was divided into an experimental subgroup, who received vitamin C, and a control subgroup. Follow-up appointments were performed at day 3, day 7, and day 14 postsurgery, during which soft tissue healing and pain response scores were evaluated using the Landry index and visual analogue scale, respectively.

RESULTS:
The experimental subgroups had significantly higher healing indices than the controls (P<.05) at day 7 postsurgery for group B and day 14 postsurgery for groups A, B, and C. Group D displayed no difference between the experimental and control groups at any time point. In reference to vitamin C for pain relief, there were no statistically significant differences between the study groups.

CONCLUSION:
Using vitamin C supplementation improves postoperative healing following dental implant surgery in patients with chronic periodontitis and patients treated with GBR or Bio-Oss Collagen grafts. However, vitamin C supplementation does not decrease the postoperative pain associated with dental implant surgery.

BR J NUTR. 2018 APR;119(8):847-858. DOI: 10.1017/S0007114518000430.

Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: a systematic review and meta-analysis of observational studies.

Malmir H, Shab-Bidar S, Djafarian K.

ABSTRACT

We aimed to systematically review available data on the association between vitamin C intake and bone mineral density (BMD), as well as risk of fractures and osteoporosis, and to summarise this information through a meta-analysis. Previous studies on vitamin C intake in relation to BMD and risk of fracture and osteoporosis were selected through searching PubMed, Scopus, ISI Web of Science and Google Scholar databases before February 2017, using MeSH and text words. To pool data, either a fixed-effects model or a random-effects model was used, and for assessing heterogeneity, Cochran's Q and I 2 tests were used. Subgroup analysis was applied to define possible sources of heterogeneity. Greater dietary vitamin C intake was positively associated with BMD at femoral neck (pooled r 0·18; 0·06, 0·30) and lumbar spine (pooled r 0·14; 95 % CI 0·06, 0·22); however, significant between-study heterogeneity was found at femoral neck: I 2=87·6 %, P heterogeneity<0·001. In addition, we found a non-significant association between dietary vitamin C intake and the risk of hip fracture (overall relative risk=0·74; 95 % CI 0·51, 1·08). Significant between-study heterogeneity was found (I 2=79·1 %, P heterogeneity<0·001), and subgroup analysis indicated that study design, sex and age were the main sources of heterogeneity. Greater dietary vitamin C intake was associated with a 33 % lower risk of osteoporosis (overall relative risk=0·67; 95 % CI 0·47, 0·94). Greater dietary vitamin C intake was associated with a lower risk of hip fracture and osteoporosis, as well as higher BMD, at femoral neck and lumbar spine.

NUTRIENTS. 2019 FEB 27;11(3). PII: E506. DOI: 10.3390/NU11030506.

Vitamin C Activates Osteoblastogenesis and Inhibits Osteoclastogenesis via Wnt/β-Catenin/ATF4 Signaling Pathways.

Choi HK, Kim GJ, Yoo HS, Song DH, Chung KH, Lee KJ, Koo YT, An JH.

ABSTRACT

This study evaluated the effects of vitamin C on osteogenic differentiation and osteoclast formation, and the effects of vitamin C concentration on bone microstructure in ovariectomized (OVX) Wistar rats. Micro-computed tomography analysis revealed the recovery of bone mineral density and bone separation in OVX rats treated with vitamin C. Histomorphometrical analysis revealed improvements in the number of osteoblasts, osteoclasts, and osteocytes; the osteoblast and osteoclast surface per bone surface; and bone volume in vitamin C-treated OVX rats. The vitamin C-treated group additionally displayed an increase in the expression of osteoblast differentiation genes, including bone morphogenetic protein-2, small mothers against decapentaplegic 1/5/8, runt-related transcription factor 2, osteocalcin, and type I collagen. Vitamin C reduced the expression of osteoclast differentiation genes, such as receptor activator of nuclear factor kappa-B, receptor activator of nuclear factor kappa-B ligand, tartrate-resistant acid phosphatase, and cathepsin K. This study is the first to show that vitamin C can inhibit osteoporosis by promoting osteoblast formation and blocking osteoclastogenesis through the activation of wingless-type MMTV integration site family/β-catenin/activating transcription factor 4 signaling, which is achieved through the serine/threonine kinase and mitogen-activated protein kinase signaling pathways. Therefore, our results suggest that vitamin C improves bone regeneration.

4.1.2 Oral Health/Periodontitis

INDIAN J DENT RES. 2014 JUL-AUG;25(4):499-504. DOI: 10.4103/0970-9290.142547.

Antioxidant and pro-oxidant activity of Vitamin C in oral environment.

Chakraborthy A, Ramani P, Sherlin HJ, Premkumar P, Natesan A.

ABSTRACT

OBJECTIVE:
To review studies reported in the literature elucidating the activity of Vitamin C and determine whether it is an anti-oxidant or a pro-oxidant.

MATERIALS AND METHODS:
Articles were searched in PubMed, MEDLINE using appropriate key words like "Vitamin C," "antioxidant activity," "pro-oxidant activity," "oral health" "oral disease." Hand search of journals was also performed. Articles were reviewed and analyzed.

RESULTS:
Search strategy reviewed 10 relevant articles which studied the dual role of Vitamin C. 65% of authors analyzed antioxidant action of ascorbic acid compared to 35% of the pro-oxidant potential. Vitamin C acts as an antioxidant and a pro-oxidant by a plethora of mechanisms. Factors determining its bimodal activity were studied, and the frequencies of their occurrence in the literature were depicted in percentage.

CONCLUSION:
The data validates the role of Vitamin C as an antioxidant under physiologic conditions exhibiting a cross over role as a pro-oxidant in pathological conditions. Further studies are required to substantiate its pro-oxidant activity to draw concrete conclusions.

BMC ORAL HEALTH. 2016 JUL 26;17(1):28. DOI: 10.1186/S12903-016-0257-1.

An oral health optimized diet can reduce gingival and periodontal inflammation in humans - a randomized controlled pilot study.

Woelber JP, Bremer K, Vach K, König D, Hellwig E, Ratka-Krüger P, Al-Ahmad A, Tennert C.

ABSTRACT

BACKGROUND:
The aim of this pilot study was to investigate the effects of four weeks of an oral health optimized diet on periodontal clinical parameters in a randomized controlled trial.

METHODS:
The experimental group (n=10) had to change to a diet low in carbohydrates, rich in Omega-3 fatty acids, and rich in vitamins C and D, antioxidants and fiber for four weeks. Participants of the control group (n=5) did not change their dietary behavior. Plaque index, gingival bleeding, probing depths, and bleeding upon probing were assessed by a dentist with a pressure-sensitive periodontal probe.

RESULTS:
Despite constant plaque values in both groups, all inflammatory parameters decreased in the experimental group to approximately half that of the baseline values. This reduction was significantly different compared to that of the control group.

CONCLUSION:
A diet low in carbohydrates, rich in Omega-3 fatty acids, rich in vitamins C and D, and rich in fibers can significantly reduce gingival and periodontal inflammation.

PLOS ONE. 2017 MAY 10;12(5):E0177074. DOI: 10.1371/JOURNAL.PONE.0177074. ECOLLECTION 2017.

The association of dietary vitamin C intake with periodontitis among Korean adults: Results from KNHANES IV.

Lee JH, Shin MS, Kim EJ, Ahn YB, Kim HD.

ABSTRACT

METHOD:

A total of 10,930 Korean adults (≥19 years) from the fourth Korean National Health and Nutrition Examination Survey data set were included in this cross-sectional study. Periodontitis was defined as community periodontal index score of 3 or 4.

RESULTS:

Those with inadequate dietary vit C intake were more likely by 1.16 times to have periodontitis than those with adequate dietary vit C intake (adjusted odds ratio [aOR] = 1.16, 95 % confidence interval = 1.04-1.29). Lowest and middle-low quartile of dietary vit C intake, compared to highest quartile of dietary vit C intake, showed significant association (aOR = 1.28 and 1.22 respectively), which was in a biological-gradient relationship (trend-p <0.05).

CONCLUSIONS:

Our data showed that inadequate dietary vit C intake was independently associated with periodontitis among Korean adults. Hence, adequate intake of dietary vitamin C could be substantially important on the promotion of periodontal health among Korean adults.

INT J ENVIRON RES PUBLIC HEALTH. 2019 JUL 11;16(14). PII: E2472. DOI: 10.3390/IJERPH16142472.

The Relationship between Vitamin C and Periodontal Diseases: A Systematic Review.

Tada A, Miura H.

ABSTRACT

Vitamin C is important for preventing and slowing the progression of many diseases. There is significant evidence linking periodontal disease and vitamin C. We aimed to systematically review the studies addressing the relationship between vitamin C and periodontal disease, and the preventive ability of vitamin C against periodontal disease. The vitamin C intake and blood levels were negatively related to periodontal disease in all seven cross-sectional studies. The subjects who suffer from periodontitis presented a lower vitamin C intake and lower blood-vitamin C levels than the subjects without periodontal disease in the two case-control studies. The patients with a lower dietary intake or lower blood level of vitamin C showed a greater progression of periodontal disease than the controls. The intervention using vitamin C administration improved gingival bleeding in gingivitis, but not in periodontitis. Alveolar bone absorption was also not improved. The present systematic review suggested that vitamin C contributes to a reduced risk of periodontal disease.

4.1.3 Systemic Relevance

INT J VITAM NUTR RES SUPPL. 1982;23:103-13.

Prolongation of survival times of terminal cancer patients by administration of large doses of ascorbate.

Murata A, Morishige F, Yamaguchi H.

ABSTRACT
Clinical trials administering supplemental ascorbate to terminal cancer patients were conducted at two hospitals in Japan. During the period 1973-1977 there were 99 patients with terminal cancer at the Fukuoka Torikai Hospital. The average times of survival after the date of designation as terminal were 43 days for 44 low-ascorbate patients and 246 days for 55 high-ascorbate patients. Three of the high-ascorbate patients were still alive, their average survival being 1550 days, on April 1, 1980. Similar effectiveness of ascorbate was also observed at the Kamioka Kozan Hospital. There were 31 patients with terminal cancer during the period 1975-1979. The average survival times were 48 days for 19 control patients and 115 days for 6 high-ascorbate patients. One of the high-ascorbate patients was still alive, his survival being 215 days. In addition to the increase in survival times, the administration of large doses of ascorbate seemed to improve the quality of life.

CMAJ. 2006 MAR 28;174(7):937-42.

Intravenously administered vitamin C as cancer therapy: three cases.

Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer LJ, Levine M.

ABSTRACT
Early clinical studies showed that high-dose vitamin C, given by intravenous and oral routes, may improve symptoms and prolong life in patients with terminal cancer. Double-blind placebo-controlled studies of oral vitamin C therapy showed no benefit. Recent evidence shows that oral administration of the maximum tolerated dose of vitamin C (18 g/d) produces peak plasma concentrations of only 220 micromol/L, whereas intravenous administration of the same dose produces plasma concentrations about 25-fold higher. Larger doses (50-100 g) given intravenously may result in plasma concentrations of about 14,000 micromol/L. At concentrations above 1000 micromol/L, vitamin C is toxic to some cancer cells but not to normal cells in vitro. We found 3 well-documented cases of advanced cancers, confirmed by histopathologic review, where patients had unexpectedly long survival times after receiving high-dose intravenous vitamin C therapy. We examined clinical details of each case in accordance with National Cancer Institute (NCI) Best Case Series guidelines. Tumour pathology was verified by pathologists at the NCI who were unaware of diagnosis or treatment. In light of recent clinical pharmacokinetic findings and in vitro evidence of anti-tumour mechanisms, these case reports indicate that the role of high-dose intravenous vitamin C therapy in cancer treatment should be reassessed.

J KOREAN MED SCI. 2007 FEB; 22(1): 7–11.
PUBLISHED ONLINE 2007 FEB 28. DOI:
10.3346/JKMS.2007.22.1.7

Changes of Terminal Cancer Patients' Health-related Quality of Life after High Dose Vitamin C Administration

Yeom CH, Jung GC, Song KJ.

ABSTRACT

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients. All patients were given an intravenous administration of 10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C. Quality of life was assessed with EORTC QLQ-C30. In the global health/quality of life scale, health score improved from 36±18 to 55±16 after administration of vitamin C ($p=0.001$). In functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C ($p<0.05$). In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C ($p<0.005$). The other function and symptom scales were not significantly changed after administration of vitamin C. In terminal cancer patients, the quality of life is as important as cure. Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

NUTRIENTS. 2017 NOV 3;9(11). PII: E1211. DOI:
10.3390/NU9111211.

Vitamin C and Immune Function.

Carr AC, Maggini S.

ABSTRACT

Vitamin C is an essential micronutrient for humans, with pleiotropic functions related to its ability to donate electrons. It is a potent antioxidant and a cofactor for a family of biosynthetic and gene regulatory enzymes. Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C supports epithelial barrier function against pathogens and promotes the oxidant scavenging activity of the skin, thereby potentially protecting against environmental oxidative stress. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. It is also needed for apoptosis and clearance of the spent neutrophils from sites of infection by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage. The role of vitamin C in lymphocytes is less clear, but it has been shown to enhance differentiation and proliferation of B- and T-cells, likely due to its gene regulating effects. Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections. Prophylactic prevention of infection requires dietary vitamin C intakes that provide at least adequate, if not saturating plasma levels (i.e., 100-200 mg/day), which optimize cell and tissue levels. In contrast, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased inflammatory response and metabolic demand.

J TRANSL MED. 2017 APR 14;15(1):77. DOI: 10.1186/S12967-017-1179-7.

The role of vitamin C in the treatment of pain: new insights.

Carr AC, McCall C.

ABSTRACT

The vitamin C deficiency disease scurvy is characterised by musculoskeletal pain and recent epidemiological evidence has indicated an association between suboptimal vitamin C status and spinal pain. Furthermore, accumulating evidence indicates that vitamin C administration can exhibit analgesic properties in some clinical conditions. The prevalence of hypovitaminosis C and vitamin C deficiency is high in various patient groups, such as surgical/trauma, infectious diseases and cancer patients. A number of recent clinical studies have shown that vitamin C administration to patients with chronic regional pain syndrome decreases their symptoms. Acute herpetic and post-herpetic neuralgia is also diminished with high dose vitamin C administration. Furthermore, cancer-related pain is decreased with high dose vitamin C, contributing to enhanced patient quality of life. A number of mechanisms have been proposed for vitamin C's analgesic properties. Herein we propose a novel analgesic mechanism for vitamin C; as a cofactor for the biosynthesis of amidated opioid peptides. It is well established that vitamin C participates in the amidation of peptides, through acting as a cofactor for peptidyl-glycine α-amidating monooxygenase, the only enzyme known to amidate the carboxy terminal residue of neuropeptides and peptide hormones. Support for our proposed mechanism comes from studies which show a decreased requirement for opioid analgesics in surgical and cancer patients administered high dose vitamin C. Overall, vitamin C appears to be a safe and effective adjunctive therapy for acute and chronic pain relief in specific patient groups.

BLOOD CELLS, MOLECULES & DISEASES 69, S. 57–64. DOI: 10.1016/J.BCMD.2017.09.005.

Mechanisms of anti-cancer effects of ascorbate: Cytotoxic activity and epigenetic modulation

Mastrangelo D, Pelosi E, Castelli G, Lo-Coco F, Testa U.

ABSTRACT

Vitamin C (Vit C or Ascorbate) is essential for many fundamental biochemical processes. Vit C is an essential nutrient with redox functions at normal physiologic concentrations. The main physiologic function of this vitamin is related to its capacity to act as a co-factor for a large family of enzymes, collectively known as Fe and 2-oxoglutarate-dependent dioxygenases. It also modulates epigenetic gene expression through the control of TET enzymes activity. Vit C also has several biological properties allowing to restore the deregulated epigenetic response observed in many tumors. High-dose Vit C has been investigated as a treatment for cancer patients since the 1969. Pharmacologic ascorbate acts as a pro-drug for hydrogen peroxide formation (H2O2) and, through this mechanism, kills cancer cells. To achieve high in vivo concentrations, Ascorbate must be injected by i.v. route. Initial clinical studies of Ascorbate cancer treatment have provided encouraging results, not confirmed in subsequent studies. Recent clinical studies using i.v. injection of high-dose Ascorbate have renewed the interest in the field, showing that significant anti-tumor activity. Pre-clinical studies have led to identify tumors sensitive to Ascorbate that could potentially benefit from this treatment either through an epigenetic modulator effect or through tumor killing by oxidative stress.

NATURE REVIEWS CANCER VOLUME 19, PAGES271–282(2019).

Targeting cancer vulnerabilities with high-dose vitamin C

Ngo B, Van Riper JM, Cantley LC, Yun J.

ABSTRACT

Over the past century, the notion that vitamin C can be used to treat cancer has generated much controversy. However, new knowledge regarding the pharmacokinetic properties of vitamin C and recent high-profile preclinical studies have revived interest in the utilization of high-dose vitamin C for cancer treatment. Studies have shown that pharmacological vitamin C targets many of the mechanisms that cancer cells utilize for their survival and growth. In this Opinion article, we discuss how vitamin C can target three vulnerabilities many cancer cells share: redox imbalance, epigenetic reprogramming and oxygen-sensing regulation. Although the mechanisms and predictive biomarkers that we discuss need to be validated in well-controlled clinical trials, these new discoveries regarding the anticancer properties of vitamin C are promising to help identify patient populations that may benefit the most from high-dose vitamin C therapy, developing effective combination strategies and improving the overall design of future vitamin C clinical trials for various types of cancer.

4. VITAMINS IMPORTANT IN DENTISTRY

4.2 Vitamin D3

4.2.1 Arteriosclerosis/CVD

HYPERTENSION. 2007 MAY;49(5):1063-9. EPUB 2007 MAR 19.

Plasma 25-hydroxyvitamin D levels and risk of incident hypertension.

Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC.

ABSTRACT

Laboratory studies indicate that 1,25-dihydroxyvitamin D suppresses renin expression and vascular smooth muscle cell proliferation; clinical studies demonstrate an inverse association between ultraviolet radiation, a surrogate marker for vitamin D synthesis, and blood pressure. We prospectively studied the independent association between measured plasma 25-hydroxyvitamin D [25(OH)D] levels and risk of incident hypertension and also the association between predicted plasma 25(OH)D levels and risk of incident hypertension. Two prospective cohort studies including 613 men from the Health Professionals' Follow-Up Study and 1198 women from the Nurses' Health Study with measured 25(OH)D levels were followed for 4 to 8 years. In addition, 2 prospective cohort studies including 38 388 men and 77 531 women with predicted 25(OH)D levels were followed for 16 to 18 years. During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma 25(OH)D levels were <15 ng/mL (ie, vitamin D deficiency) compared with those whose levels were >or=30 ng/mL was 6.13 (95 % confidence interval [CI]: 1.00 to 37.8). Among women, the same comparison yielded a relative risk of 2.67 (95 % CI: 1.05 to 6.79). The pooled relative risk combining men and women with measured 25(OH)D levels using the random-effects model was 3.18 (95 % CI: 1.39 to 7.29). Using predicted 25(OH)D levels in the larger cohorts, the multivariable relative risks comparing the lowest to highest deciles were 2.31 (95 % CI: 2.03 to 2.63) in men and 1.57 (95 % CI: 1.44 to 1.72) in women. Plasma 25(OH)D levels are inversely associated with risk of incident hypertension.

AM J CARDIOL. 2010 OCT 1;106(7):963-8. DOI: 10.1016/J.AMJCARD.2010.05.027. EPUB 2010 AUG 11.

Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population.

Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB; Intermountain Heart Collaborative (IHC) Study Group.

ABSTRACT

We prospectively analyzed a large electronic medical records database to determine the prevalence of vitamin D deficiency and the relation of vitamin D levels to prevalent and incident CV risk factors and diseases, including mortality. The database contained 41,504 patient records with at least one measured vitamin D level. The prevalence of vitamin D deficiency (≤30 ng/ml) was 63.6 %, with only minor differences by gender or age. Vitamin D deficiency was associated with highly significant increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Also, those without risk factors but with severe deficiency had an increased likelihood of developing diabetes, hypertension, and hyperlipidemia. The vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke, as well as with incident death, heart failure, coronary artery disease/myocardial infarction, stroke, and their composite. In conclusion, we have confirmed a high prevalence of vitamin D deficiency in the general healthcare population and an association between vitamin D levels and prevalent and incident CV risk factors and outcomes. These observations lend strong support to the hypothesis that vitamin D might play a primary role in CV risk factors and disease. Given the ease of vitamin D measurement and replacement, prospective studies of vitamin D supplementation to prevent and treat CV disease are urgently needed.

J AM COLL CARDIOL. 2011 JUL 5; 58(2): 186–192. DOI: 10.1016/J.JACC.2011.02.051.

Vitamin D Status Is Associated With Arterial Stiffness and Vascular Dysfunction in Healthy Humans.

Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, Kavtaradze N, Uphoff I, Hooper C, Tangpricha V, Wayne Alexander R, Brigham K, Quyyumi A.

ABSTRACT

METHODS:

We measured serum 25-OH D in 554 subjects. Endothelial function was assessed as brachial artery flow-mediated dilation, and microvascular function was assessed as digital reactive hyperemia index.

RESULTS:

Mean 25-OH D was 31.8 ± 14 ng/ml. After adjustment for age, sex, race, body mass index, total cholesterol, low-density lipoprotein, triglycerides, C-reactive protein, and medication use, 25-OH D remained independently associated with flow-mediated vasodilation, reactive hyperemia index, pulse wave velocity, augmentation index, and subendocardial viability ratio. In 42 subjects with vitamin D insufficiency, normalization of 25-OH D at 6 months was associated with increases in reactive hyperemia index (0.38 ± 0.14, p = 0.009) and subendocardial viability ratio (7.7 ± 3.1, p = 0.04), and a decrease in mean arterial pressure (4.6 ± 2.3 mm Hg, p = 0.02).

CONCLUSIONS:

Vitamin D insufficiency is associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels in humans, irrespective of traditional risk burden. Our findings provide impetus for larger trials to assess the effects of vitamin D therapy in cardiovascular disease.

J NUTR. 2017 SEP;147(9):1607-1615. DOI: 10.3945/JN.117.250209. EPUB 2017 AUG 2.

Vitamin D in the Spectrum of Prediabetes and Cardiovascular Autonomic Dysfunction.

Dimova R, Tankova T, Chakarova N.

ABSTRACT

Cardiovascular autonomic neuropathy (CAN) is an independent risk factor for mortality in patients with diabetes and prediabetes and is associated with an increased risk of developing type 2 diabetes and cardiovascular disease. Accumulating data indicate the presence of peripheral nerve injury at these early stages of dysglycemia and its multifactorial pathogenesis. Prediabetes is associated with vitamin D insufficiency. Vitamin D is proposed to prevent the progression of glucose intolerance. The putative underlying mechanisms include maintenance of the intracellular calcium concentration, direct stimulation of insulin receptor expression, and enhancement of the insulin response to glucose transporters. The effects of vitamin D supplementation on glucose tolerance and related autonomic nerve dysfunction have been a recent focus of scientific interest. Although well-designed observational studies are available, the causative relation between vitamin D deficiency, glucose intolerance, and CAN is still debatable. One reason might be that interventional studies are unpersuasive with regard to the beneficial clinical effects of vitamin D supplementation. Because of its favorable side effect profile, vitamin D supplementation might represent an attractive therapeutic option for treating the pandemic prevalence of prediabetes and vitamin D deficiency. Vitamin D supplementation can improve glucose tolerance and cardiovascular autonomic function and can thus reduce cardiovascular mortality among subjects with different stages of glucose intolerance and autonomic dysfunction. However, more patient-centered trials on the use of vitamin D supplementation in different conditions are needed.

NUTR REV. 2019 DEC 1;77(12):890-902. DOI: 10.1093/NUTRIT/NUZ037.

Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis.

Dibaba DT.

ABSTRACT

CONTEXT:
Vitamin D deficiency is highly prevalent across the world. The existing evidence suggests vitamin D may have beneficial effects on serum lipid profiles and thus cardiovascular health.

OBJECTIVE:
The objective of this systematic review and meta-analysis was to examine the effect of vitamin D supplementation on serum lipid profiles.

DATA SOURCE:
Original randomized controlled trials (RCTs) examining the effect of vitamin D supplementation on serum lipid profiles and published before July 2018 were identified by searching online databases, including PubMed, Google Scholar, and ScienceDirect, using a combination of relevant keywords.

DATA EXTRACTION:
Data on study characteristics, effect size, measure of variation, type of vitamin D supplementation, and duration of follow-up were extracted by the author.

DATA ANALYSIS:
PRISMA guidelines for systematic reviews were followed. Random effects (DerSimonian and Laird [D-V)] models were used to pool standardized mean differences in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides between the active and the placebo arms of RCT studies. Between-study heterogeneities were assessed using Cochrane Q and I2, and publication bias was assessed using Begg's test, Egger's test, and funnel plot.

RESULTS:
A total of 41 RCTs comprising 3434 participants (n = 1699 in the vitamin D supplementation arm and n = 1735 in the placebo arm) were identified and included in the meta-analysis. Approximately 63.4 % of study participants were women, with 14 studies conducted entirely among women. Approximately 24 % of the trials had follow-up duration >6 months, whereas the remaining 76 % had follow-up duration of <6 months. The standardized mean differences (SMDs) and 95 % confidence intervals (CIs) for comparing the change from baseline to follow-up between the vitamin D supplementation arm and the placebo (control) arm were as follows: total cholesterol = -0.17 (-0.28 to -0.06); LDL cholesterol = -0.12 (-0.23 to -0.01); triglycerides = -0.12 (-0.25 to 0.01); and HDL cholesterol = -0.19 (-0.44 to 0.06). After removing a trial that was an outlier based on the magnitude of the effect size, the SMD for triglycerides was -0.15 (-0.24 to -0.06) and that for HDL cholesterol was -0.10 (-0.28 to 0.09). The improvements in total cholesterol and triglycerides were more pronounced in participants with baseline vitamin D deficiency.

CONCLUSIONS:
Vitamin D supplementation appeared to have a beneficial effect on reducing serum total cholesterol, LDL cholesterol, and triglyceride levels but not HDL cholesterol levels. Vitamin D supplementation may be useful in hypercholesterolemia patients with vitamin D insufficiency who are at high risk of cardiovascular diseases.

ASIA PAC J CLIN NUTR. 2018;27(1):231-237.
DOI: 10.6133/APJCN.022017.08.

Vitamin D status and cardiometabolic risk factors in young adults in Hong Kong: associations and implications.

Wang EW, Pang MY, Siu PM, Lai CK, Woo J, Collins AR, Benzie IF.

ABSTRACT

METHODS AND STUDY DESIGN:

In this observational study, fasting venous blood was collected from 196 (63 males, 133 females), young (18-26 years) non-smoking, nonobese, consenting adults in good general health. Plasma 25(OH)D was measured by LC-MS/MS. A panel of established cardiometabolic risk factors (HbA1c, plasma glucose, lipid profile, hsCRP) and blood pressure were also measured.

RESULTS:

Mean (SD) plasma 25(OH)D concxentration was 42.1 (13.0), with range 15.7-86.8 nmol/L; 141/196 subjects (72 %) had vitamin D deficiency (25(OH)D <50 nmol/L); 13/184 (6.6 %) were severely deficient (<25 nmol/L). Inverse association was seen between 25(OH)D and fasting glucose. Higher HbA1c and TC:HDL-C ratio and lower HDL-C were seen in those with plasma 25(OH)D <25 nmol/L ($p<0.05$).

CONCLUSIONS:

Vitamin D deficiency was highly prevalent and associated with poorer cardiometabolic risk profile in these young adults. Public health strategies for addressing vitamin D deficiency are needed urgently. These new data provide support for further study on vitamin D deficiency as a modifiable risk factor for cardiometabolic disease and the ameliorative effects of increased vitamin D intake on cardiometabolic disease risk profile of vitamin D-deficient young adults.

4.2.2 Bone Metabolism

CRIT REV EUKARYOT GENE EXPR. 2001;11(1-3):199-226.

Vitamin D control of osteoblast function and bone extracellular matrix mineralization.

van Leeuwen JP, van Driel M, van den Bemd GJ, Pols HA.

ABSTRACT

Vitamin D is the major regulator of calcium homeostasis and protects the organism from calcium deficiency via effects on the intestine, kidney, parathyroid gland, and bone. Disturbances in the vitamin D endocrine system (e.g., vitamin D-dependent rickets type I and type II), result in profound effects on the mineralization of bone. Recent studies with vitamin D receptor knockout mice also show effects on bone. It is questioned whether vitamin D has a direct effect on bone formation and mineralization. In rickets and particular vitamin D receptor knockout mice, calcium supplementation restores bone mineralization. However, the vitamin D receptor is present in osteoblasts, and vitamin D affects the expression of various genes in osteoblasts. This review focuses on the role of vitamin D in the control of osteoblast function and discusses the current knowledge of the direct effects of vitamin D on mineralization. Moreover, the role of vitamin D metabolism and the mechanism of action of vitamin D and interaction with other hormones and factors are discussed.

CURR PHARM DES. 2004;10(21):2535-55.

Osteoblast differentiation and control by vitamin D and vitamin D metabolites.

van Driel M, Pols HA, van Leeuwen JP.

ABSTRACT

Vitamin D plays a major role in the regulation of mineral homeostasis and affects bone metabolism. Most effects of vitamin D have been attributed to the 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) metabolite. 1,25-(OH)2D3 regulates its own metabolism by mediating the 24-hydroxylase activity, which leads to the degradation of the molecule but intermediate products (24-hydroxylated forms of 25-(OH)D3 and 1,25-(OH)2D3) may be biologically active too. In this review we describe the direct effects of 1,25-(OH)2D3 on osteoblast function (proliferation, apoptosis, expression of specific bone proteins and growth factors) and mineralization. The role of the vitamin D receptor, vitamin D metabolism and the effects on osteoblast gene expression are documented. Vitamin D acts often in interaction with factors. The effects of 1,25-(OH)2D3 on the expression of growth factors and its interaction with growth factors and hormones in the control of osteoblast differentiation are discussed. Finally, the current status of the development of synthetic vitamin D analogs with bone anabolic characteristics for therapeutic application is described.

J PROSTHODONT. 2009 AUG;18(6):473-8. DOI: 10.1111/J.1532-849X.2009.00446.X. EPUB 2009 MAR 26.

Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model.

Kelly J, Lin A, Wang CJ, Park S, Nishimura I.

ABSTRACT

PURPOSE:
The patient population varies in nutritional deficiencies, which may confound the host response to biomaterials. The objective of this study was to evaluate the effect of a common deficiency of vitamin D on implant osseointegration in the rat model.

MATERIALS AND METHODS:
Male Sprague-Dawley rats were maintained under the cessation of vitamin D intake and UV exposure. The serum levels of 1,25(OH)(2)D(3), 25 OHD(3), Ca, and P were determined. Miniature cylindrical Ti6Al4V implants (2-mm long, 1-mm diameter) were fabricated with double acid-etched (DAE) surface or modified DAE with discrete crystalline deposition (DCD) of hydroxyapatite nanoparticles. DAE and DCD implants were placed in the femurs of vitamin D-insufficient and control rats. After 14 days of healing, the femur-implant samples were subjected to implant push-in test and nondecalcified histology. The surfaces of recovered implant specimens after the push-in test were further evaluated by scanning electron microscopy (SEM).

RESULTS:
The decreased serum level of 25 OHD(3) demonstrated the establishment of vitamin D insufficiency in this model. The implant push-in test revealed that DAE and DCD implants in the vitamin D-insufficient group (15.94 +/- 8.20 N, n = 7; 15.63 +/- 3.96 N, n = 7, respectively) were significantly lower than those of the control group (24.99 +/- 7.92 N, n = 7, $p < 0.05$; 37.48 +/- 17.58 N, n = 7, $p < 0.01$, respectively). The transcortical bone-to-implant contact ratio (BIC) was also significantly decreased in the vitamin D-insufficient group. SEM analyses further suggested that the calcified tissues remaining next to the implant surface after push-in test appeared unusually fragmented.

CONCLUSIONS:
The effect of vitamin D insufficiency significantly impairing the establishment of Ti6Al4V implant osseointegration in vivo was unexpectedly profound. The outcome of Ti-based endosseous implants may be confounded by the increasing prevalence of vitamin D insufficiency in our patient population.

FRONT ORAL BIOL. 2009;13:102-109. DOI: 10.1159/000242400. EPUB 2009 SEP 21.

Regulation of enamel and dentin mineralization by vitamin D receptor.

Zhang X, Beck P, Rahemtulla F, Thomas HF.

ABSTRACT

BACKGROUND:
Vitamin D plays an important role in bone mineralization. Enamel and dentin are two mineralized tissues of different origins that are part of the tooth structure, but the mechanism by which vitamin D regulates the mineralization of these tissues remains unclear. We examined the mineral deposition pattern of enamel and dentin in continuously erupting incisors in a vitamin D receptor (VDR) deficient mouse model to determine the effect of vitamin D receptor pathway on enamel and dentin mineralization.

METHODS:
VDR wild-type mice (VDR+/+) and VDR-deficient (VDR--/--) littermates were sacrificed at 70.5 days of age, and their mandibles were dissected. Immunostaining of biglycan and decorin was used to evaluate the dentin maturation. Micro-computerized tomography (micro-CT) was used to compare the mineral density (MD) of enamel and dentin of the two groups at different regions along the axis of the mandibular incisors. Scanning electronic microscopy (SEM) was employed to examine the ultrastructure of enamel and dentin at the levels corresponding to those examined in the micro-CT studies. Furthermore, an accelerated eruption procedure was performed to exclude the effect of delayed eruption on enamel and dentin mineralization.
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RESULTS:
Different mineral deposition patterns of enamel and dentin were observed at different levels of the incisors in the VDR+/+ and VDR--/-- groups. Early enamel maturation and mineralization, and dentin hypomineralization were observed in the VDR--/-- group.

CONCLUSION:
Vitamin D affects enamel and dentin mineralization through different mechanisms. It may affect the mineralization of dentin systemically while enamel mineralization may be regulated locally.

CLIN ORAL IMPLANTS RES. 2012 NOV;23(11):1308-13. DOI: 10.1111/J.1600-0501.2011.02346.X. EPUB 2011 DEC 12.

Impact of dietary vitamin D on osseointegration in the ovariectomized rat.

Dvorak G, Fügl A, Watzek G, Tangl S, Pokorny P, Gruber R.

ABSTRACT

AIM:

Vitamin D deficiency is highly prevalent in the population and associated with impaired peri-implant bone regeneration. Yet, there is a gap in understanding the impact of vitamin D supplementation on the process of osseointegration. In this study, the effect of vitamin D supplementation on peri-implant bone regeneration was investigated.

METHODS:

Fifty ovariectomized Sprague-Dawley rats were divided into three groups. The depletion group was fed a vitamin D-free diet for 8 weeks. The repletion group received vitamin D-free diet for 6 weeks, before animals were switched to standard diet containing 2400 IU/kg vitamin D. The control group was fed the standard diet. Two titanium mini-implants were placed in the tibia. All groups remained on their previous diet until sacrifice. Blood sample testing and histomorphometric analysis were performed.

RESULTS:

Vitamin D depletion caused a significant reduction in 25-hydroxvitamin D in rat serum that returned to control levels in the repletion group. This vitamin deficiency was associated with a decrease in bone-to-implant contact in the cortical area, which was leveled to controls in the repletion group. No significant changes by vitamin D depletion were noticed in the medullar compartment. Moreover, also the peri-implant bone area and the mineral apposition rate remained unchanged upon vitamin D depletion.

CONCLUSION:

These results indicate that vitamin D deficiency has a negative impact on cortical peri-implant bone formation in ovariectomized rats, which can be compensated by vitamin D supplementation. This study provides first insight into the potential beneficial effect of vitamin D supplementation in implant dentistry.

BRATISL LEK LISTY. 2013;114(8):439-45.

The prevalence and risk factors for osteoporosis in patients with inflammatory bowel disease.

Miznerova E, Hlavaty T, Koller T, Toth J, Holociova K, Huorka M, Killinger Z, Payer J.

ABSTRACT

METHODS:

The cohort consisted of 76 IBD patients, 40 with Crohn's disease (CD) and 36 with ulcerative colitis (UC). Clinical characteristics of every patient were recorded, i.e. age, sex, duration of the disease, clinical behavior, location of disease according to Montreal classification, surgeries, steroid medication, sIBDQ, and smoking habits. We examined the serum 25-hydroxyl vitamin D3 (25-OHD3) in each patient.

RESULTS:

Osteoporosis was documented in 10 IBD patients (13.2 %), while osteopenia in 35 of them (46.1 %). Patients with CD have significantly lower femoral Z score than patients with UC. Femoral Z score was strongly associated with disease duration, and in CD patients suffering from stricturing form, with ileic or ileocolic location and history of proctocolectomy or total colectomy. Patients with osteoporosis had a significantly lower level of 25-OHD3 than patients with normal Bone Mineral Density.

CONCLUSION:

Patients with long disease duration and those suffering from stricturing form of CD with ileic/ileocolic location and history of proctocolectomy/total colectomy are at higher risk of developing osteoporosis than other IBD patients. The high proportion of osteopenia/osteoporosis in our study underlines the importance of BMD measurement in all IBD patients as a base for initiating the appropriate treatment.

J R NAV MED SERV. 2014;100(3):328-32.

Vitamin D deficiency as a suspected causative factor in the failure of an immediately placed dental implant: a case report.

Bryce G, MacBeth N.

ABSTRACT

AIM:

To discuss the influence of Vitamin D deficiency in the osseointegration process of a dental implant by way of a case report.

SUMMARY:

A 29-year-old soldier attended clinic with a fractured mandibular premolar (tooth 44) that was traumatised following head trauma related to the detonation of an Improvised Explosive Device (IED) whilst serving on operational duty. The tooth was deemed unsalvageable and was extracted with immediate placement of a dental implant. The patient experienced no problems but at assessment, five months post-operatively, no osseo-integration of the implant was found. Concurrent medical investigations revealed that he was severely Vitamin D deficient and that this may have contributed to the implant failure.

CONCLUSION:

Vitamin D deficiency may play a role in the failure of osseointegration in dental implants. The assessment of vitamin D status in patients who have been in long-term hospital care or rehabilitation should be considered, prior to the placement of dental implants.

J ORAL IMPLANTOL. 2014 FEB;40(1):110-4. DOI: 10.1563/AAID-JOI-D-13-00062. EPUB 2013 OCT 9.

Two neglected biologic risk factors in bone grafting and implantology: high low-density lipoprotein cholesterol and low serum vitamin D.

Choukroun J, Khoury G, Khoury F, Russe P, Testori T, Komiyama Y, Sammartino G, Palacci P, Tunali M, Choukroun E.

ABSTRACT

Following a failure of a bone graft or an implant placement, the hypothesis of a biological abnormality is rarely considered as a possible cause. A systematic search of peer-reviewed literature for dyslipidemia or vitamin D deficiency may explain this lack of consideration. Excess low-density lipoprotein cholesterol (dyslipidemia) is responsible for a slower bone metabolism or lower dental implant osseointegration. In addition, vitamin D is a key factor for linking innate and adaptive immunity. Both of these factors are compromised under the conditions of vitamin D deficiency. Therefore, vitamin D deficiency slows implant osseointegration and increases the risk of graft infection. Vitamin D is also involved in immune function and therefore allergic reactions.

BONEKEY REP. 2014 FEB 5;3:499. DOI: 10.1038/BONEKEY.2013.233. ECOLLECTION 2014.

Vitamin D: direct effects of vitamin D metabolites on bone: lessons from genetically modified mice.

Eisman JA, Bouillon R.

ABSTRACT

The vitamin D endocrine system has clear beneficial effects on bone as demonstrated by prevention of rickets in children and by reducing the risk of osteomalacia or osteoporosis in adults or elderly subjects. Depending on the design of the study of genetically modified animals, however, 1,25(OH)2D and the vitamin D receptor (VDR) may have no effect, beneficial or even deleterious direct effects on bone. We present here a comprehensive model of the direct effects of vitamin D on bone. In case of sufficient calcium supply, vitamin D and its metabolites can improve the calcium balance and facilitate mineral deposition in bone matrix largely without direct effects on bone cells, although some beneficial effects may occur via mature osteoblasts, as demonstrated in mice with osteoblast-specific overexpression of VDR or 1α-hydroxylase. In case of calcium deficiency, however, 1,25(OH)2D enhances bone resorption, whereas simultaneously inhibiting bone mineralization, so as to defend serum calcium homeostasis at the expense of bone mass. This dual role probably provides a survival benefit for land vertebrates living in a calcium-poor environment.

J STEROID BIOCHEM MOL BIOL. 2014 OCT;144 PT A:114-8. DOI: 10.1016/J.JSBMB.2013.10.003. EPUB 2013 OCT 12.

The local production of 1,25(OH)2D3 promotes osteoblast and osteocyte maturation.

Turner AG, Hanrath MA, Morris HA, Atkins GJ, Anderson PH.

ABSTRACT

Maintenance of an adequate vitamin D status, as indicated by the level of circulating 25-hydroxyvitamin D (25(OH)D), is associated with higher bone mass and decreased risk of fracture. However, the molecular actions of vitamin D hormone (1,25(OH)2D3) in bone are complex, and include stimulation of osteoclastogenesis via RANK-ligand up-regulation, as well as the inhibition of mineralisation. We hypothesise that these divergent data may be reconciled by autocrine actions of 1,25(OH)2D3 which effect skeletal maintenance, as opposed to endocrine 1,25(OH)2D3 which acts to maintain serum calcium homeostasis. We have previously described local metabolism of 1,25(OH)2D3 within osteoblasts, with effects on gene expression and cell function. The aim of the current study was to investigate potential autocrine actions of 1,25(OH)2D3 within cells that exhibit osteocyte-like properties. Late osteoblastic MLO-A5 cells were cultured in the presence of 25(OH)D for 9 days with gene expression analysed pre- and post-mineralisation. Gene expression analysis revealed maturation within this time frame to an osteocyte-like stage, evidenced by increased Dmp1 and Phex mRNA expression. Expression of Cyp27b1 in 25(OH)D treated MLO-A5 cells was associated with elevated media levels of 1,25(OH)2D3 ($p<0.05$), induction of Cyp24a1 ($p<0.001$) and elevated ratios of Opg:Rankl mRNA ($p<0.01$). Chronic 25(OH)D exposure also increased osteocalcin mRNA in MLO-A5 cells, which contrasted with the dose-dependent inhibition of osteocalcin mRNA observed with acute treatment in MLO-Y4 cells ($p<0.01$). Treatment of MLO-Y4 cells with 25(OH)D also inhibited Phex mRNA expression ($p<0.05$), whilst Enpp1 gene expression was induced ($p<0.01$). Overall, the current study demonstrates that osteocyte-like cells convert physiological levels of 25(OH)D to 1,25(OH)2D3, with changes in gene expression that are consistent with increased osteocyte maturation. Although the physiological role of local metabolism of 1,25(OH)2D3 within osteocytes requires further investigation, the abundance and diverse functions of this cell type within bone underscore its potential importance. This article is part of a Special Issue entitled '16th Vitamin D Workshop'.

J DENT RES. 2015 FEB;94(2):381-7. DOI: 10.1177/0022034514561657. EPUB 2014 DEC 10.

Elevated serum 25(OH)-vitamin D levels are negatively correlated with molar-incisor hypomineralization.

Kühnisch J, Thiering E, Kratzsch J, Heinrich-Weltzien R, Hickel R, Heinrich J; GINIplus study group; LISAplus study group.

ABSTRACT

To date, the precise etiology of molar-incisor hypomineralization (MIH) is uncertain. Vitamin D plays a key role in hard tissue formation. Therefore, this study aimed to analyze the relationship between serum 25-hydroxy-vitamin D (25(OH)D) status and dental health data obtained from 1,048 children in a 10-year follow-up of the Munich GINIplus and LISAplus birth cohorts. The dental examination included the diagnosis of MIH and recording of (non-) cavitated caries lesions in primary and permanent teeth. Serum 25(OH)D concentrations were taken from blood samples of the 10-year investigation and measured with a fully automated, modular system. Different logistic regression and Poisson hurdle models were calculated. MIH was diagnosed in 13.6 % of the study population. Approximately 16.4 % of the children demonstrated caries-related defects (D3-4MFS > 0). The mean season-adjusted concentration of 25(OH)D was 75.8 nmol/l (standard deviation 22.0 nmol/l). After adjusting for sex, age, body mass index, parental education, equivalent income, and television/personal computer (TV/PC) viewing hours, a 10 nmol/l increase in serum 25(OH)D concentrations was significantly associated with a lower odds ratio of having MIH (OR = 0.89; P = 0.006). Furthermore, higher 25(OH)D values were associated with a lower number of caries-affected permanent teeth. It is concluded that elevated serum 25(OH)D concentrations were associated with better dental health parameters.

CLIN ORAL IMPLANTS RES. 2016 JUN;27(6):701-6. DOI: 10.1111/CLR.12641. EPUB 2015 JUL 14.

Systemic vitamin D supplementation and local bone formation after maxillary sinus augmentation - a randomized, double-blind, placebo-controlled clinical investigation.

Schulze-Späte U, Dietrich T, Wu C, Wang K, Hasturk H, Dibart S.

ABSTRACT

OBJECTIVES:

Maxillary sinus augmentation procedures with bone replacement grafts aimed to increase bone height in the posterior maxilla. During healing, bone particles are partially resorbed and replaced by the patient's own bone. Vitamin D plays an essential role in calcium homeostasis and is critical for bone formation and remodeling.

MATERIALS AND METHODS:

This randomized, double-blind, placebo-controlled clinical investigation studied whether oral supplementation with vitamin D3 (5000 IU) combined with calcium (600 mg) impacts bone formation and remodeling after maxillary sinus augmentation compared to a placebo medication containing calcium alone (n = 10/group). Bone cores were harvested at the time of implant placement (6-8 months) for histological analysis.

RESULTS:

Serum 25-hydroxyvitamin D (25-OHD) levels were comparable between both groups at the baseline (P = nonsignificant [n.s.]). Vitamin D3+ calcium supplementation improved significantly serum 25-OHD levels (placebo vs. vitamin D3 group: 25-OHD ng/ml: 31.13 ± 7.06 vs. 61.11 ± 20.42, P ≤ 0.01); however, no statistically significant difference in bone formation or graft resorption was detected between groups. However, in the vitamin D3 group, a significant association was found between increased vitamin D levels and number of bone-resorbing osteoclasts around graft particles suggesting that local bone remodeling might be more pronounced when serum vitamin D levels were improved (r = 0.92, P ≤ 0.05).

CONCLUSIONS:

Vitamin D3+ calcium supplementation improves serum vitamin D levels and potentially impacts local bone remodeling on a cellular level. However, no statistically significant difference in bone formation or graft resorption was detected between groups.

J BIOMED MATER RES A. 2017 JUL;105(7):2075-2089. DOI: 10.1002/JBM.A.36060. EPUB 2017 MAR 28.

Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss.

Insua A, Monje A, Wang HL, Miron RJ.

ABSTRACT

Despite the growing number of publications in the field of implant dentistry, there are limited studies to date investigating the biology and metabolism of bone healing around dental implants and their implications in peri-implant marginal bone loss. The aim of this review article is to provide a thorough understanding of the biological events taking place during osseointegration and the subsequent early and late phases of bone remodeling around dental implants. An update on the coupling mechanism occurring during bone resorption-bone remodeling is provided, focused on the relevance of the osteocytes, bone lining cells and immune cells during bone maintenance. An electronic and manual literature search was conducted by three independent reviewers in several databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register databases for articles up to September 2016 with no language restriction. Local bone metabolism is subject to signals from systemic calcium-phosphate homeostasis and bone remodeling. Three areas of interest were reviewed due to recent reported compromises in bone healing including the putative effects of (1) cholesterol, (2) hyperlipidemia, and (3) low vitamin D intake. Moreover, the prominent influence of osteocytes and immune cells is discussed as being key regulators during dental implant osseointegration and maintenance. These cells are of crucial importance in the presence of biofilm accumulation and their associated byproducts that leads to hard and soft tissue breakdown; the so called peri-implantitis. Factors that could negatively impact osteoclastogenesis or osteal macrophage activation should be monitored in future research including implant placement/torque protocols, bone characteristics, as well as meticulous maintenance programs to favor osseointegration and future long-term stability and success of dental implants.

J BONE MINER RES. 2017 JUN;32(6):1297-1308. DOI: 10.1002/JBMR.3096. EPUB 2017 FEB 22.

VDR in Osteoblast-Lineage Cells Primarily Mediates Vitamin D Treatment-Induced Increase in Bone Mass by Suppressing Bone Resorption.

Nakamichi Y, Udagawa N, Horibe K, Mizoguchi T, Yamamoto Y, Nakamura T, Hosoya A, Kato S, Suda T, Takahashi N.

ABSTRACT

Long-term treatment with active vitamin D [1α,25(OH)2 D3] and its derivatives is effective for increasing bone mass in patients with primary and secondary osteoporosis. Derivatives of 1α,25(OH)2 D3 , including eldecalcitol (ELD), exert their actions through the vitamin D receptor (VDR). It is reported that ELD treatment causes a net increase in bone mass by suppressing bone resorption rather than by increasing bone formation in animals and humans. VDR in bone and extraskeletal tissues regulates bone mass and secretion of osteotropic hormones. Therefore, it is unclear what types of cells expressing VDR preferentially regulate the vitamin D-induced increase in bone mass. Here, we examined the effects of 4-week treatment with ELD (50 ng/kg/day) on bone using osteoblast lineage-specific VDR conditional knockout (Ob-VDR-cKO) and osteoclast-specific VDR cKO (Ocl-VDR-cKO) male mice aged 10 weeks. Ob-VDR-cKO mice showed normal bone phenotypes, despite no appreciable immunostaining of VDR in bone. Ob-VDR-cKO mice failed to increase bone mass in response to ELD treatment. Ocl-VDR-cKO mice also exhibited normal bone phenotypes, but normally responded to ELD. ELD-induced FGF23 production in bone was regulated by VDR in osteoblast-lineage cells. These findings suggest that the vitamin D treatment-induced increase in bone mass is mediated by suppressing bone resorption through VDR in osteoblast-lineage cells.

4.2.3 Oral Health/Cari es/Periodontitis

J TENN DENT ASSOC. 2011 SPRING;91(2):30-3; QUIZ 34-5.

Vitamin D and its impact on oral health - an update.

Stein SH, Tipton DA.

ABSTRACT
Vitamin D has been shown to regulate musculoskeletal health by mediating calcium absorption and mineral homeostasis. Evidence has demonstrated that vitamin D deficiency may place subjects at risk for not only low mineral bone density/osteoporosis and osteopenia but also infectious and chronic inflammatory diseases. Studies have shown an association between alveolar bone density, osteoporosis and tooth loss and suggest that low bone mass may be a risk factor for periodontal disease. Several recent reports demonstrate a significant association between periodontal health and the intake of vitamin D. An emerging hypothesis is that vitamin D may be beneficial for oral health, not only for its direct effect on bone metabolism but also due to its ability to function as an anti-inflammatory agent and stimulate the production of anti-microbial peptides.

COMPEND CONTIN EDUC DENT. 2012 MAR;33(3):166-71; QUIZ 172, 182.

A review of vitamin D as it relates to periodontal disease.

Yao SG, Fine JB.

ABSTRACT
Vitamin D has classically been known as a "bone hormone." But recently, vitamin D has been found to play a role in respect to systemic diseases such as cardiovascular disease, cancer, and periodontal disease. It has been reported that approximately 1 billion people worldwide are either vitamin D deficient or insufficient. This paper will address the various roles that vitamin D plays in respect to systemic diseases, the effects of vitamin D deficiency, and how it is diagnosed and treated.

NUTR REV. 2013 FEB;71(2):88-97. DOI: 10.1111/J.1753-4887.2012.00544.X. EPUB 2012 NOV 9.

Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis.

Hujoel PP.

ABSTRACT

Vitamin D has been used to prevent and treat dental caries. The objective of this study was to conduct a systematic review of controlled clinical trials (CCTs) assessing the impact of vitamin D on dental caries prevention. Random-effects and meta-regression models were used to evaluate overall and subgroup-specific relative-rate estimates. Twenty-four CCTs encompassing 2,827 children met the inclusion criteria. Twenty-two of the 24 CCTs predated modern clinical trial design, some of which nonetheless reported characteristics such as pseudo-randomization (n = 2), blinding (n = 4), or use of placebos (n = 8). The relative-rate estimates of the 24 CCTs exhibited significant heterogeneity (P < 0.0001), and there was evidence of significant publication bias (P < 0.001). The pooled relative-rate estimate of supplemental vitamin D was 0.53 (95 % CI, 0.43-0.65). No robust differences were identified between the caries-preventive effects of vitamin D(2) , vitamin D(3) , and ultraviolet radiation (Prob > F = 0.22). The analysis of CCT data identified vitamin D as a promising caries-preventive agent, leading to a low-certainty conclusion that vitamin D may reduce the incidence of caries.

J PERIODONTAL RES. 2014 OCT;49(5):545-53. DOI: 10.1111/JRE.12149. EPUB 2013 NOV 21.

Re-evaluating the role of vitamin D in the periodontium.

Stein SH, Livada R, Tipton DA.

ABSTRACT

The importance of vitamin D in maintaining skeletal health via the regulation of calcium has long been recognized as a critical function of this secosteroid. An abundance of literature shows an association between oral bone mineral density and some measure of systemic osteoporosis and suggests that osteoporosis/low bone mass may be a risk factor for periodontal disease. Recently, nonskeletal functions of vitamin D have gained notoriety for several reasons. Many cells that are not associated with calcium homeostasis have been demonstrated to possess membrane receptors for vitamin D. These include activated T and B lymphocytes, and skin, placenta, pancreas, prostate and colon cancer cells. In addition, vitamin D "insufficiency" is a worldwide epidemic and epidemiologic evidence has linked this condition to multiple chronic health problems, including cardiovascular and autoimmune diseases, hypertension and a variety of cancers. Interestingly, there is mounting evidence connecting diminished serum levels of vitamin D with increased gingival inflammation and supporting the concept of "continual vitamin D sufficiency" in maintaining periodontal health. The ability of vitamin D to regulate both the innate and the adaptive components of the host response may play an important role in this process. This review will examine the skeletal and nonskeletal functions of vitamin D, and explore its potential role in protecting the periodontium as well as in regulating periodontal wound healing.

J DENT CHILD (CHIC). 2016 SEP 15;83(3):114-119.

Vitamin D and Dental Caries in Primary Dentition.

Seminario AL, Velan E.

ABSTRACT

Traditionally classified as a vitamin, vitamin D represents a group of fat-soluble secosteroids with D2 (ergocalciferol) and D3 (cholecalciferol) being the most relevant of the group. The importance of this prohormone exceeds its known ability to maintain intra- and extracellular calcium and phosphate concentrations, thereby preserving essential metabolic functions such as the promotion of mineralization and maintenance and remodeling of the bone. Current observational research recognizes the potential antiproliferative, prodifferentiative, and immunomodulatory effects of vitamin D and its metabolites in the human body. The purposes of this paper are to: (1) review how vitamin D interacts in the body, its deficiency at the population level, and how it relates to oral health in children; and (2) assess proposed biological mechanisms by which vitamin D may play a preventive role in the development of dental caries.

J CLIN PERIODONTOL. 2017 MAR;44 SUPPL 18:S79-S84. DOI: 10.1111/JCPE.12672.

Nutrition, dental caries and periodontal disease: a narrative review.

Hujoel PP, Lingström P.

ABSTRACT

AIM:

To provide a narrative review of the role of macro- and micronutrients in relation to dental caries, gingival bleeding and destructive periodontal disease.

MATERIALS & METHODS:

This review is based on systematic reviews (when available) and comparative human studies.

RESULTS:

Dental caries cannot develop without the presence of dietary fermentable carbohydrates, in particular sugar. The susceptibility to develop caries in the presence of carbohydrates may be influenced by genetics and micronutrients such as vitamin D. Gingival bleeding and destructive periodontal disease are sensitive markers to both abnormalities in macronutrient content (excessive carbohydrates or polyunsaturated fat intake, deficient protein intake) and micronutrient intake (e.g. vitamin C and B12).

CONCLUSION:

Dental caries and periodontal diseases are a sensitive alarm bell for an unhealthy diet, which predicts the future onset of the diseases of civilizations.

PEDIATR DENT J. 2017 APR;27(1):21-28. DOI: 10.1016/J.PDJ.2016.08.001. EPUB 2016 DEC 19.

Prenatal vitamin D and enamel hypoplasia in human primary maxillary central incisors: a pilot study.

Reed SG, Voronca D, Wingate JS, Murali M, Lawson AB, Hulsey TC, Ebeling MD, Hollis BW, Wagner CL.

ABSTRACT

BACKGROUND:
Enamel hypoplasia (EH) increases risk for dental caries and also is associated with vitamin D deficiencies. This pilot study evaluates the feasibility to determine the association of human maternal circulating vitamin D concentrations during pregnancy and EH in infant's teeth that develop in utero.

METHODS:
A pilot population of 37 children whose mothers participated in a RCT of vitamin D supplementation during pregnancy was evaluated. Major outcome was EH and major exposure was maternal monthly serum circulating 25(OH) D concentrations during pregnancy. EH was assessed using the Enamel Defect Index and digital images made by a ProScope High Resolution™ handheld digital USB microscope at 50x magnification.

RESULTS:
During initial 8 weeks of study, 29/37 children had evaluable data with mean age of 3.6 ± 0.9 years; 48 % male; and 45 % White, 31 % Hispanic, and 24 % Black. EH was identified in 13 (45 %) of the children. Maternal mean 25(OH)D concentrations were generally lower for those children with EH.

CONCLUSIONS:
Preliminary results suggest follow-up of children of mothers in a vitamin D supplementation RCT during pregnancy provides an important approach to study the etiology of EH in the primary teeth. Further study is needed to discern thresholds and timing of maternal serum 25(OH)D concentrations during pregnancy associated with absence of EH in teeth that develop in utero. Potential dental public health implications for prevention of early childhood caries via sound tooth structure as related to maternal vitamin D sufficiency during pregnancy need to be determined.

MEDICINA (KAUNAS). 2018 JUN 12;54(3). PII: E45. DOI: 10.3390/MEDICINA54030045.

The Relationship between Vitamin D and Periodontal Pathology.

Jagelavičienė E, Vaitkevičienė I, Šilingaitė D, Šinkūnaitė E, Daugėlaitė G.

ABSTRACT

Osteoporosis and periodontal diseases are common problems among the elderly population. Vitamin D is a secosteroid hormone that is either synthesized by human skin cells under the effect of UV radiation or consumed through diet. Deficiency in vitamin D leads to reduced bone mineral density, osteoporosis, the progression of periodontal diseases and causes resorption to occur in the jawbone. Sufficient intake of vitamin D can decrease the risk of gingivitis and chronic periodontitis, as it has been shown to have immunomodulatory, anti-inflammatory, antiproliferative effects and initiates cell apoptosis. In addition, vitamin D is also important for bone metabolism, alveolar bone resorption and preventing tooth loss. It increases antibacterial defense of gingival epithelial cells and decrease gingival inflammation, improves postoperative wound healing after periodontal surgery and is an important supplement used as prophylaxis in periodontology. This publication aims to update the recent advances, stress the clinical importance, and evaluate vitamin D in the prevention of periodontal diseases to reach a successful outcome of conservative and surgical treatment. An analysis of the literature shows that vitamin D plays a significant role in maintaining healthy periodontal and jaw bone tissues, alleviating inflammation processes, stimulating post-operative healing of periodontal tissues and the recovery of clinical parameters. However, further research is needed to clarify the required vitamin D concentration in plasma before starting periodontal treatment to achieve the best outcome.

J STEROID BIOCHEM MOL BIOL. 2018 JAN;175:190-194. DOI: 10.1016/J.JSBMB.2017.01.020. EPUB 2017 FEB 1.

Effects of vitamin D status on oral health.

Uwitonze AM, Murererehe J, Ineza MC, Harelimana EI, Nsabimana U1, Uwambaye P, Gatarayiha A, Haq A, Razzaque MS.

ABSTRACT

Normal humans of all ages have the innate ability to produce vitamin D following sunlight exposure. Inadequate vitamin D status has shown to be associated with a wide variety of diseases, including oral health disorders. Insufficient sunlight exposure may accelerate some of these diseases, possibly due to impaired vitamin D synthesis. The beneficial effects of vitamin D on oral health are not only limited to the direct effects on the tooth mineralization, but are also exerted through the anti-inflammatory functions and the ability to stimulate the production of anti-microbial peptides. In this article, we will briefly discuss the genesis of various oral diseases due to inadequate vitamin D level in the body and elucidate the potential benefits of safe sunlight exposure for the maintenance of oral and general health.

PEDIATR INT. 2019 APR;61(4):327-338. DOI: 10.1111/PED.13801.

Dental caries and vitamin D status in children in Asia.

Almoudi MM, Hussein AS, Abu Hassan MI, Schroth RJ.

ABSTRACT

Dental caries and vitamin D inadequacy are known to affect children worldwide. Vitamin D has a vital role in tooth formation. There is growing evidence linking suboptimal serum vitamin D level with dental caries in children. This paper reviews the literature on both the prevalence of dental caries and of vitamin D deficiency in children in four Asian regions, discusses their associated risk factors, and reviews the global evidence on the association between dental caries and vitamin D in children. Caries prevalence in children ranged from 40 % to 97 % in Eastern Asia, 38-73.7 % in Southern Asia, and 26.5-74.7 % in Western Asian countries. Moreover, a higher prevalence of vitamin D deficiency in Asian children was identified, even in countries in equatorial regions, ranging from 2.8 % to 65.3 % in Eastern Asia, 5-66.7 % in Southern Asia, 4-45.5 % in Western Asia and 38.1-78.7 % in Central Asian countries. Obesity, age, female gender, higher latitude, season, darker skin pigmentation, sunlight protection behaviors, less sunlight exposure and low intake of food containing vitamin D were important factors associated with lower serum vitamin D in Asia. Suboptimal vitamin D level in children may be a significant risk factor for dental caries, and requires further research to ascertain such an association in children in Asia, as well as to understand its exact influence on caries risk and development.

AM J TRANSL RES. 2019 APR 15;11(4):2304-2316. ECOLLECTION 2019.

Calcitriol exerts a mineralization-inductive effect comparable to that of vitamin C in cultured human periodontium cells.

Hong HH, Hong A, Wang CC, Huang EW, Chiang CC, Yen TH, Huang YF.

ABSTRACT

This study inspected whether calcitriol could exert a mineralization-inductive effect comparable to that of vitamin C in cultured human periodontium cells (hPDCs). The mRNA expression of the mineralization-related biomarkers core-binding factor subunit alpha-1 (Cbfa1), collagen 1 α1 (Col-I), alkaline phosphatase (ALP), osteopontin (OPN), bone sialoprotein (BSP), osteocalcin (OCN), vitamin D receptor (VDR), cementum protein 1 (CEMP-1), cementum attachment protein (CAP), interleukin 6 (IL-6), transforming growth factor-β1 (TGF-β1) and osteoprotegerin (OPG) was surveyed after incubation of hPDCs with vitamin C and calcitriol for 2 weeks. It was found that both vitamin C and calcitriol not only increased mineralization-related mRNA fold-changes but also enhanced ALP activity, CEMP-1 immunofluorescence, von Kossa and Alizarin Red staining and TXM-associated calcifications. Generally, 10-8 M calcitriol displayed greater mineralization significance than 10-7 M calcitriol in the assays tested. However, vitamin C stimulated lower Cbfa1, Col-1, ALP, OPN, BSP, OCN, VDR, CEMP-1 and IL-6 mRNA fold-changes than 10-8 M calcitriol. Finally, TXM analysis indicated that a 10-8 M calcitriol treatment stimulated greater calcifications than vitamin C treatment. Therefore, the analytical results confirmed the osteo-inductive potential of vitamin C in cultured hPDCs. In contrast, 10-8 M calcitriol could potentially function as a substitute because it stimulates a greater mineralization effect than vitamin C or 10-7 M calcitriol.

J PERIODONTAL RES. 2019 AUG;54(4):444-452. DOI: 10.1111/JRE.12646. EPUB 2019 FEB 25.

Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss.

Menzel LP, Ruddick W, Chowdhury MH, Brice DC, Clance R, Porcelli E, Ryan LK, Lee J, Yilmaz Ö, Kirkwood KL, McMahon L, Tran A, Diamond G.

ABSTRACT

BACKGROUND AND OBJECTIVE:

Both chronic and aggressive periodontal disease are associated with vitamin D deficiency.

RESULTS:

Dietary restriction of vitamin D led to alveolar bone loss and increased inflammation in the gingiva in the mouse model. In primary human GEC and established human cell lines, treatment of GEC with 1,25(OH)2 D3 inhibited the intracellular growth of P. gingivalis. Cultured GEC expressed two 25-hydroxylases (CYP27A1 and CYP2R1), as well as 1-α hydroxylase, enabling conversion of vitamin D to both 25(OH)D3 and 1,25(OH)2 D3 .

CONCLUSION:

Vitamin D deficiency in mice contributes to PD, recapitulating the association seen in humans, and provides a unique model to study the development of PD. Vitamin D increases the activity of gingival epithelial cells (GEC) against the invasion of periodontal pathogens and inhibits the inflammatory response, both in vitro and in vivo. GEC can convert inactive vitamin D to the active form in situ, supporting the hypothesis that vitamin D can be applied directly to the gingiva to prevent or treat periodontal disease.

JAMA PEDIATR. 2019 AUG 5. DOI: 10.1001/JAMAPEDIATRICS.2019.2545. [EPUB AHEAD OF PRINT]

Association of High-Dose Vitamin D Supplementation During Pregnancy With the Risk of Enamel Defects in Offspring: A 6-Year Follow-up of a Randomized Clinical Trial.

Nørrisgaard PE, Haubek D, Kühnisch J, Chawes BL, Stokholm J, Bønnelykke K, Bisgaard H.

ABSTRACT

IMPORTANCE:
Enamel defects of developmental origin affect up to 38 % of schoolchildren and is recognized as a global public health challenge. The impaired enamel formation results in pain owing to hypersensitivity, posteruptive breakdowns, rapid caries progression, and extractions in some cases. The etiology is unknown; therefore, prevention is currently not possible.

OBJECTIVE:
To assess the association of a high-dose vitamin D supplementation in pregnant women with enamel defects and caries in their offspring.

DESIGN, SETTING, AND PARTICIPANTS:
Post hoc analysis of a double-blind, single-center, randomized clinical trial, the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort (COPSAC2010). Enrollment began March 2009 and included 623 women recruited at 24 weeks of pregnancy and 588 of their children. A dental examination was completed at age 6 years in 496 of 588 children (84 %). Data were analyzed in 2018.

INTERVENTION:
High-dose vitamin D3 (2400 IU/d; N = 315) or matching placebo tablets (N = 308) from pregnancy week 24 to 1 week post partum. In addition, all women received 400 IU/d of vitamin D3 as part of standard care.

MAIN OUTCOMES AND MEASURES:
Enamel defect was defined as having at least 1 molar affected by demarcated opacity, enamel breakdown, and/or atypical restoration. Caries was defined as decayed, missing, or filled surfaces in both the deciduous and permanent dentitions (World Health Organization standard).

RESULTS:
The risk of enamel defects in the permanent dentition was lower in the offspring of mothers who received high-dose vitamin D supplementation during pregnancy compared with standard dose (15.1 % [n = 26 of 172] vs 27.5 % [n = 44 of 160]; odds ratio, 0.47; 95 % CI, 0.27-0.81). A similar association was observed for the deciduous dentition (8.6 % [n = 21 of 244] vs 15.9 % [n = 40 of 252]; odds ratio, 0.50; 95 % CI, 0.28-0.87). There was no association between supplementation and caries.

CONCLUSIONS AND RELEVANCE:
High-dose vitamin D supplementation during pregnancy was associated with approximately 50 % reduced odds of enamel defects in the offspring. This suggests prenatal vitamin D supplementation as a preventive intervention for enamel defects, with a clinically important association with dental health.

4.2.4 Systemic Relevance

J CELL BIOCHEM. 2003 FEB 1;88(2):296-307.

Vitamin D: A millenium perspective.

Holick MF.

ABSTRACT
Vitamin D is one of the oldest hormones that have been made in the earliest life forms for over 750 million years. Phytoplankton, zooplankton, and most plants and animals that are exposed to sunlight have the capacity to make vitamin D.

Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis. It accomplishes this by increasing the efficiency of the intestine to absorb dietary calcium. When there is inadequate calcium in the diet to satisfy the body's calcium requirement, vitamin D communicates to the osteoblasts that signal osteoclast precursors to mature and dissolve the calcium stored in the bone. Vitamin D is metabolized in the liver and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)(2)D]. 1,25(OH)(2)D receptors (VDR) are present not only in the intestine and bone, but in a wide variety of other tissues, including the brain, heart, stomach, pancreas, activated T and B lymphocytes, skin, gonads, etc. 1,25(OH)(2)D is one of the most potent substances to inhibit proliferation of both normal and hyperproliferative cells and induce them to mature. It is also recognized that a wide variety of tissues, including colon, prostate, breast, and skin have the enzymatic machinery to produce 1,25(OH)(2)D. 1,25(OH)(2)D and its analogs have been developed for treating the hyperproliferative disease psoriasis. Vitamin D deficiency is a major unrecognized health problem. Not only does it cause rickets in children, osteomalacia and osteoporosis in adults, but may have long lasting effects. Chronic vitamin D deficiency may have serious adverse consequences, including increased risk of hypertension, multiple sclerosis, cancers of the colon, prostate, breast, and ovary, and type 1 diabetes. There needs to be a better appreciation of the importance of vitamin D for overall health and well being.

EPIDEMIOL INFECT. 2006 DEC;134(6):1129-40. EPUB 2006 SEP 7.

Epidemic influenza and vitamin D.

Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E.

ABSTRACT
In 1981, R. Edgar Hope-Simpson proposed that a 'seasonal stimulus' intimately associated with solar radiation explained the remarkable seasonality of epidemic influenza. Solar radiation triggers robust seasonal vitamin D production in the skin; vitamin D deficiency is common in the winter, and activated vitamin D, 1,25(OH)2D, a steroid hormone, has profound effects on human immunity. 1,25(OH)2D acts as an immune system modulator, preventing excessive expression of inflammatory cytokines and increasing the 'oxidative burst' potential of macrophages. Perhaps most importantly, it dramatically stimulates the expression of potent anti-microbial peptides, which exist in neutrophils, monocytes, natural killer cells, and in epithelial cells lining the respiratory tract where they play a major role in protecting the lung from infection. Volunteers inoculated with live attenuated influenza virus are more likely to develop fever and serological evidence of an immune response in the winter. Vitamin D deficiency predisposes children to respiratory infections. Ultraviolet radiation (either from artificial sources or from sunlight) reduces the incidence of viral respiratory infections, as does cod liver oil (which contains vitamin D). An interventional study showed that vitamin D reduces the incidence of respiratory infections in children. We conclude that vitamin D, or lack of it, may be Hope-Simpson's 'seasonal stimulus'.

AM J CLIN NUTR. 2007 JAN;85(1):54-9.

Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations.

Major GC, Alarie F, Doré J, Phouttama S, Tremblay A.

ABSTRACT

BACKGROUND:
Adequate calcium intake can have a favorable effect on some metabolic variables.

OBJECTIVE:
The objective of the study was to determine the effects of daily calcium intake and of supplementation with calcium and vitamin D (calcium+D) during a weight-loss intervention on blood pressures, plasma lipid and lipoprotein concentrations, and glucose and insulin concentrations in low calcium consumers.

DESIGN:
Healthy, overweight or obese women (n = 63) with a daily calcium intake of < 800 mg/d were randomly assigned in a double-blind manner to 1 of 2 groups: the group consuming 2 tablets/d of a calcium + vitamin D supplement (600 mg elemental calcium and 200 IU vitamin D/tablet) or the group consuming placebo; both groups observed a 700 kcal/d energy restriction. These 63 women then completed a 15-wk weight-loss intervention.

RESULTS:
Initial daily calcium intake was significantly correlated with plasma HDL cholesterol (r = 0.41, P < 0.001) and with 2-h postload glycemia (r = -0.29, P < 0.05) during an oral-glucose-tolerance test, independent of fat mass and waist circumference. After the 15-wk intervention, significantly greater decreases in total:LDL and LDL:HDL (P < 0.01 for both) and of LDL cholesterol (P < 0.05) were observed in the calcium+D group than in the placebo group. The differences in total:HDL and LDL:HDL were independent of changes in fat mass and in waist circumference. A tendency for more beneficial changes in HDL cholesterol, triacylglycerol, and total cholesterol was also observed in the calcium+D group (P = 0.08).

CONCLUSION:
Consumption of calcium+D during a weight-loss intervention enhanced the beneficial effect of body weight loss on the lipid and lipoprotein profile in overweight or obese women with usual low daily calcium intake.

J NEUROIMMUNOL. 2008 FEB;194(1-2):7-17. DOI: 10.1016/J.JNEUROIM.2007.11.014. EPUB 2008 JAN 4.

Vitamin D as an immune modulator in multiple sclerosis, a review.

Smolders J, Damoiseaux J, Menheere P, Hupperts R.

ABSTRACT

The role of vitamin D in calcium homeostasis is well known. More recently vitamin D has become a topic of interest in immune regulation and multiple sclerosis. The main reason for this is the observed geographical distribution of multiple sclerosis. Areas with high sunlight exposure, the principal inducer of vitamin D synthesis, have a relatively low prevalence of multiple sclerosis and vice versa. Furthermore, low levels of the principal vitamin D metabolite (25-hydroxy vitamin D) in the circulation are associated with a high incidence of multiple sclerosis. Other epidemiological evidence also supports the view that vitamin D metabolites have an immune and disease modulating effect in multiple sclerosis. Experimental research in vitro and in animal models has further clarified the interaction of vitamin D metabolites with the immune system. The evidence obtained from these studies strongly supports a model in which vitamin D mediates a shift to a more anti-inflammatory immune response, and in particular to enhanced regulatory T cell functionality. In the current review we link the basic knowledge on vitamin D and immune regulation with the vitamin D related observations in multiple sclerosis. We conclude that there is a sound basis on which to initiate double-blind placebo-controlled trials that not only address the effect of vitamin D on the clinical outcome of multiple sclerosis, but also on the regulatory T cell compartment.

FUTURE MICROBIOL. 2009 NOV;4(9):1151-65. DOI: 10.2217/FMB.09.87.

The vitamin D-antimicrobial peptide pathway and its role in protection against infection.

Gombart AF.

ABSTRACT
Vitamin D deficiency has been correlated with increased rates of infection. Since the early 19th century, both environmental (i.e., sunlight) and dietary sources (cod liver) of vitamin D have been identified as treatments for TB. The recent discovery that vitamin D induces antimicrobial peptide gene expression explains, in part, the 'antibiotic' effect of vitamin D and has greatly renewed interest in the ability of vitamin D to improve immune function. Subsequent work indicates that this regulation is biologically important for the response of the innate immune system to wounds and infection and that deficiency may lead to suboptimal responses toward bacterial and viral infections. The regulation of the cathelicidin antimicrobial peptide gene is a human/primate-specific adaptation and is not conserved in other mammals. The capacity of the vitamin D receptor to act as a high-affinity receptor for vitamin D and a low-affinity receptor for secondary bile acids and potentially other novel nutritional compounds suggests that the evolutionary selection to place the cathelicidin gene under control of the vitamin D receptor allows for its regulation under both endocrine and xenobiotic response systems. Future studies in both humans and humanized mouse models will elucidate the importance of this regulation and lead to the development of potential therapeutic applications.

CURR OPIN ALLERGY CLIN IMMUNOL. 2009 JUN;9(3):202-7. DOI: 10.1097/ACI.0B013E32832B36CD.

Childhood asthma may be a consequence of vitamin D deficiency.

Litonjua AA.

ABSTRACT
PURPOSE OF REVIEW:
Vitamin D deficiency has been rediscovered as a public-health problem worldwide. It has been postulated that vitamin D deficiency may explain a portion of the asthma epidemic. The purpose of this review is to present the evidence for a role of vitamin D in asthma.

RECENT FINDINGS:
Both animal models and studies in human fetal tissues show that vitamin D plays a role in fetal lung growth and maturation. Epidemiologic studies have also suggested that higher prenatal vitamin D intakes have a protective role against wheezing illnesses in young children. Vitamin D may protect against wheezing illnesses through its role in upregulating antimicrobial proteins or through its multiple immune effects. In addition, vitamin D may play a therapeutic role in steroid resistant asthmatics, and lower vitamin D levels have recently been associated with higher risks for asthma exacerbations.

SUMMARY:
Improving vitamin D status holds promise in primary prevention of asthma, in decreasing exacerbations of disease, and in treating steroid resistance. However, the appropriate level of circulating vitamin D for optimal immune functioning remains unclear. Because vitamin D deficiency is prevalent even in sun-replete areas, clinical trials are needed to definitively answer questions about the role of vitamin D in asthma.

DIABETES. 2010 JAN;59(1):242-8. DOI: 10.2337/DB09-1011. EPUB 2009 OCT 15.

Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study.

Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, Robins SJ, O'Donnell CJ, Hoffmann U, Jacques PF, Booth SL, Vasan RS, Wolf M, Wang TJ.

ABSTRACT

OBJECTIVE:

Because vitamin D deficiency is associated with a variety of chronic diseases, understanding the characteristics that promote vitamin D deficiency in otherwise healthy adults could have important clinical implications. Few studies relating vitamin D deficiency to obesity have included direct measures of adiposity. Furthermore, the degree to which vitamin D is associated with metabolic traits after adjusting for adiposity measures is unclear.

RESEARCH DESIGN AND METHODS:

We investigated the relations of serum 25-hydroxyvitamin D (25[OH]D) concentrations with indexes of cardiometabolic risk in 3,890 nondiabetic individuals; 1,882 had subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured by multidetector computed tomography (CT).

RESULTS:

In multivariable-adjusted regression models, 25(OH)D was inversely associated with winter season, waist circumference, and serum insulin ($P < 0.005$ for all). In models further adjusted for CT measures, 25(OH)D was inversely related to SAT (-1.1 ng/ml per SD increment in SAT, $P = 0.016$) and VAT (-2.3 ng/ml per SD, $P < 0.0001$). The association of 25(OH)D with insulin resistance measures became nonsignificant after adjustment for VAT. Higher adiposity volumes were correlated with lower 25(OH)D across different categories of BMI, including in lean individuals (BMI <25 kg/m(2)). The prevalence of vitamin D deficiency (25[OH]D <20 ng/ml) was threefold higher in those with high SAT and high VAT than in those with low SAT and low VAT ($P < 0.0001$).

CONCLUSIONS:

Vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity. The mechanisms by which adiposity promotes vitamin D deficiency warrant further study.

NUTRIENTS. 2010 APR; 2(4): 408–425. PUBLISHED ONLINE 2010 MAR 25. DOI: 10.3390/NU2040408.

Nonclassical Vitamin D Action.

Zittermann A, Gummert JF.

ABSTRACT

It is becoming increasingly clear that vitamin D has a broad range of actions in the human body. Besides its well-known effects on calcium/phosphate homeostasis, vitamin D influences muscle function, cardiovascular homeostasis, nervous function, and the immune response. Vitamin D deficiency/insufficiency has been associated with muscle weakness and a high incidence of various chronic diseases such as cardiovascular disease, cancer, multiple sclerosis, and type 1 and 2 diabetes. Most importantly, low vitamin D status has been found to be an independent predictor of all-cause mortality. Several recent randomized controlled trials support the assumption that vitamin D can improve muscle strength, glucose homeostasis, and cardiovascular risk markers. In addition, vitamin D may reduce cancer incidence and elevated blood pressure. Since the prevalence of vitamin D deficiency/insufficiency is high throughout the world, there is a need to improve vitamin D status in the general adult population. However, the currently recommended daily vitamin D intake of 5-15 μg is too low to achieve an adequate vitamin D status in individuals with only modest skin synthesis. Thus, there is a need to recommend a vitamin D intake that is effective for achieving adequate circulating 25-hydroxyvitamin D concentrations (>75 nmol/L).

BR J NUTR. 2011 NOV;106(9):1433-40. DOI: 10.1017/S0007114511001991. EPUB 2011 JUN 6.

Vitamin D status has a linear association with seasonal infections and lung function in British adults.

Berry DJ, Hesketh K, Power C, Hyppönen E.

ABSTRACT

Higher vitamin D concentrations have been proposed as a protective 'seasonal stimulus' against influenza, and there are suggestions for associations with other aspects of respiratory health. The aim of the present study was to investigate the relationship of current vitamin D status (measured by 25-hydroxyvitamin D, 25(OH)D) with respiratory infections and lung function. We used cross-sectional data from 6789 participants in the nationwide 1958 British birth cohort who had measurements of 25(OH)D, lung function (forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC)) and respiratory infections available from the age of 45 years. In this population, the prevalence of respiratory infections had a strong seasonal pattern in the opposite direction to the pattern for 25(OH)D concentrations. Each 10 nmol/l increase in 25(OH)D was associated with a 7 % lower risk of infection (95 % CI 3, 11 %) after adjustment for adiposity, lifestyle and socio-economic factors. For FEV1 and FVC, each 10 nmol/l increase in 25(OH)D was associated with 8 (95 % CI 3, 13) ml and 13 (95 % CI 7, 20) ml higher volume, respectively, after controlling for covariates. Associations of 25(OH)D with FEV1 and FVC were only slightly attenuated after further adjustment for infection and other respiratory illness. In conclusion, vitamin D status had a linear relationship with respiratory infections and lung function. Randomised controlled trials are warranted to investigate the role of vitamin D supplementation on respiratory health and to establish the underlying mechanisms.

AIDS. 2011 FEB 20;25(4):525-9. DOI: 10.1097/QAD.0B013E328342FDFD.

Vitamin D deficiency is associated with type 2 diabetes mellitus in HIV infection.

Szep Z, Guaraldi G, Shah SS, Lo Re V 3rd, Ratcliffe SJ, Orlando G, Carli F, Rossi R, Rochira V, Tebas P.

ABSTRACT

BACKGROUND:

Metabolic complications, including type 2 diabetes mellitus and metabolic syndrome, are increasingly recognized among HIV-infected individuals. Low vitamin D levels increase the risk of type 2 diabetes mellitus, and vitamin D supplementation has been shown to decrease the risk of type 2 diabetes mellitus in patients without HIV infection.

OBJECTIVES:

The primary objective was to determine whether vitamin D deficiency (serum 25-hyrdoxyvitamin D <20 ng/ml) was associated with type 2 diabetes mellitus among HIV-infected patients. Our secondary objective was to determine whether vitamin D deficiency was associated with metabolic syndrome in HIV.

METHODS:

We conducted a cross-sectional study among participants enrolled in the prospective Modena (Italy) HIV Metabolic Clinic Cohort. Clinical and laboratory data, including history of type 2 diabetes mellitus, fasting blood glucose, components of metabolic syndrome, and 25-hydroxyvitamin D levels, were obtained for all participants.

RESULTS:

After adjusting for vitamin D supplementation, sex, age, body mass index, and hepatitis C virus co-infection, vitamin D deficiency was associated with type 2 diabetes mellitus [adjusted odds ratio (OR) 1.85; 95 % confidence interval (CI) 1.03-3.32; P = 0.038]. The association between vitamin D deficiency and metabolic syndrome was not significant after adjusting for vitamin D supplementation, sex, age and body mass index (adjusted OR 1.32; 95 % CI 1.00-1.75; P = 0.053).

CONCLUSIONS:

Our study demonstrates an association between vitamin D deficiency and type 2 diabetes mellitus. Clinical trials are needed to better characterize the association between vitamin D deficiency and type 2 diabetes mellitus in HIV infection and to evaluate whether vitamin D is able to prevent or delay the onset of type 2 diabetes mellitus.

J NUTR. 2013 OCT;143(10):1679-86. DOI: 10.3945/JN.113.180794. EPUB 2013 AUG 21.

Vitamin D regulates the gut microbiome and protects mice from dextran sodium sulfate-induced colitis.

Ooi JH, Li Y, Rogers CJ, Cantorna MT.

ABSTRACT

The active form of vitamin D [1,25-dihydroxycholecalciferol, 1,25(OH)2D3] and the vitamin D receptor (VDR) regulate susceptibility to experimental colitis. The effect of the bacterial microflora on the susceptibility of C57BL/6 mice to dextran sodium sulfate-induced colitis was determined. Mice that cannot produce 1,25(OH)2D3 [Cyp27b1 (Cyp) knockout (KO)], VDR KO as well as their wild-type littermates were used. Cyp KO and VDR KO mice had more bacteria from the Bacteroidetes and Proteobacteria phyla and fewer bacteria from the Firmicutes and Deferribacteres phyla in the feces compared with wild-type. In particular, there were more beneficial bacteria, including the Lactobacillaceae and Lachnospiraceae families, in feces from Cyp KO and VDR KO mice than in feces from wild-type. Helicobacteraceae family member numbers were elevated in Cyp KO compared with wild-type mice. Depletion of the gut bacterial flora using antibiotics protected mice from colitis. 1,25(OH)2D3 treatment (1.25 μg/100 g diet) of Cyp KO mice decreased colitis severity and reduced the numbers of Helicobacteraceae in the feces compared with the numbers in the feces of untreated Cyp KO mice. The mechanisms by which the dysbiosis occurs in VDR KO and Cyp KO mice included lower expression of E-cadherin on gut epithelial and immune cells and fewer tolerogenic dendritic cells that resulted in more gut inflammation in VDR and Cyp KO mice compared with wild-type mice. Increased host inflammation has been shown to provide pathogens with substrates to out-compete more beneficial bacterial species. Our data demonstrate that vitamin D regulates the gut microbiome and that 1,25(OH)2D3 or VDR deficiency results in dysbiosis, leading to greater susceptibility to injury in the gut.

SKIN PHARMACOL PHYSIOL. 2013;26(2):101-7. DOI: 10.1159/000346698. EPUB 2013 FEB 20.

Serum ferritin and vitamin d in female hair loss: do they play a role?

Rasheed H, Mahgoub D, Hegazy R, El-Komy M, Abdel Hay R, Hamid MA, Hamdy E.

ABSTRACT

AIM:

Evaluation of serum ferritin and vitamin D levels in females with chronic telogen effluvium (TE) or female pattern hair loss (FPHL), in order to validate their role in these common hair loss diseases.

METHODS:

Eighty females (18 to 45 years old) with hair loss, in the form of TE or FPHL, and 40 age-matched females with no hair loss were included in the study. Diagnosis was based upon clinical examination as well as trichogram and dermoscopy. Serum ferritin and vitamin D2 levels were determined for each participant.

RESULTS:

Serum ferritin levels in the TE (14.7 ± 22.1 μg/l) and FPHL (23.9 ± 38.5 μg/l) candidates were significantly lower than in controls (43.5 ± 20.4 μg/l). Serum vitamin D2 levels in females with TE (28.8 ± 10.5 nmol/l) and FPHL (29.1 ± 8.5 nmol/l) were significantly lower than in controls (118.2 ± 68.1 nmol/l; $p < 0.001$). These levels decreased with increased disease severity. Serum ferritin cut-off values for TE and FPHL were 27.5 and 29.4 μg/l, respectively, and those for vitamin D were 40.9 and 67.9 nmol/l.

CONCLUSION:

Low serum ferritin and vitamin D2 are associated with hair loss in females with TE and FPHL. Screening to establish these levels in cases of hair loss and supplementing with them when they are deficient may be beneficial in the treatment of disease.

NUTRIENTS. 2013 JUN 26;5(7):2268-75. DOI: 10.3390/NU5072268.

Vitamin D status is associated with disease activity among rheumatology outpatients.

Sabbagh Z, Markland J, Vatanparast H.

ABSTRACT

The co-existence of high prevalence of vitamin D inadequacy among Canadians and high prevalence of systematic autoimmune rheumatic diseases (SARDs) raise the question on relationship between the two situations.

OBJECTIVE:
To determine vitamin D status in known cases of common SARDs and compare to those with non-autoimmune diseases; further, to evaluate the impact of vitamin D on disease activity in rheumatoid arthritis (RA) cases.

METHODS:
In a retrospective case-control study design, we evaluated 116 patients in a community clinic classified in two groups,

CONTROL GROUP:
patients with non-rheumatic disease (n = 56), and Case group: those with rheumatic diseases (n = 60). We compared plasma vitamin D status (25(OH)D), indicators of disease activity and other potential confounders. Further, we determined factors associated with disease activity in RA cases.

RESULTS:
The plasma 25(OH)D was significantly lower in Case group (64.8 ± 29.8) compared to CONTROL GROUP (86.8 ± 37.7). High number of SARDs outpatients 56 %) had considerably low plasma 25(OH)D concentration. RA cases with low plasma 25(OH)D had over five times higher risk of disease activity (OR = 5.15 95 % CI 1.16, 22.9; p = 0.031).

CONCLUSION:
Inadequate vitamin D status in SARDs cases, along with considerably strong association with disease activity in RA cases, indicate the need for proper evaluation of vitamin D status in this clinical population. Moreover, appropriate training should be given to the patients to ensure the intake of the recommended amount of vitamin D per day through diet or supplement.

MUCOSAL IMMUNOL. 2015 MAY;8(3):618-26. DOI: 10.1038/MI.2014.94. EPUB 2014 OCT 15.

Dysbiosis caused by vitamin D receptor deficiency confers colonization resistance to Citrobacter rodentium through modulation of innate lymphoid cells.

Chen J, Waddell A, Lin YD, Cantorna MT.

ABSTRACT

Vitamin D receptor (VDR) knockout (KO) mice had fewer Citrobacter rodentium in the feces than wild-type (WT) mice and the kinetics of clearance was faster in VDR KO than WT mice. VDR KO mice had more interleukin-22 (IL-22)-producing innate lymphoid cells (ILCs) and more antibacterial peptides than WT mice. The increased ILCs in the VDR KO mice was a cell-autonomous effect of VDR deficiency on ILC frequencies. Bone marrow (BM) transplantation from VDR KO mice into WT resulted in higher ILCs and colonization resistance of the WT mice. Disruption of the gut microbiota using antibiotics in VDR KO mice reversed colonization resistance to C. rodentium infection. Confirming the role of the microbiota in the colonization resistance of VDR KO mice, transfer of the VDR KO microbiota to WT germ-free mice resulted in colonization resistance. Once colonization resistance was overcome, VDR KO mice had increased susceptibility to C. rodentium. VDR expression is a regulator of ILC frequencies, IL-22, dysbiosis, and C. rodentium susceptibility.

BMJ 2014;348:G1903 DOI: 10.1136/BMJ.G1903
(PUBLISHED 1 APRIL 2014)

Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies

Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, Feldman BS, Pan A, Johnson L, Crowe F, Hu FB, Franco OH.

ABSTRACT

OBJECTIVE:
To evaluate the extent to which circulating biomarker and supplements of vitamin D are associated with mortality from cardiovascular, cancer, or other conditions, under various circumstances.

DESIGN:
Systematic review and meta-analysis of observational studies and randomised controlled trials.

DATA SOURCES:
Medline, Embase, Cochrane Library, and reference lists of relevant studies to August 2013; correspondance with investigators.

STUDY SELECTION:
Observational cohort studies and randomised controlled trials in adults, which reported associations between vitamin D (measured as circulating 25-hydroxyvitamin D concentration or vitamin D supplement given singly) and cause specific mortality outcomes.

DATA EXTRACTION:
Data were extracted by two independent investigators, and a consensus was reached with involvement of a third. Study specific relative risks from 73 cohort studies (849 412 participants) and 22 randomised controlled trials (vitamin D given alone versus placebo or no treatment; 30 716 participants) were meta-analysed using random effects models and were grouped by study and population characteristics.

RESULTS:
In the primary prevention observational studies, comparing bottom versus top thirds of baseline circulating 25-hydroxyvitamin D distribution, pooled relative risks were 1.35 (95 % confidence interval 1.13 to 1.61) for death from cardiovascular disease, 1.14 (1.01 to 1.29) for death from cancer, 1.30 (1.07 to 1.59) for non-vascular, non-cancer death, and 1.35 (1.22 to 1.49) for all cause mortality. Subgroup analyses in the observational studies indicated that risk of mortality was significantly higher in studies with lower baseline use of vitamin D supplements. In randomised controlled trials, relative risks for all cause mortality were 0.89 (0.80 to 0.99) for vitamin D3 supplementation and 1.04 (0.97 to 1.11) for vitamin D2 supplementation. The effects observed for vitamin D3 supplementation remained unchanged when grouped by various characteristics. However, for vitamin D2 supplementation, increased risks of mortality were observed in studies with lower intervention doses and shorter average intervention periods.

CONCLUSIONS:
Evidence from observational studies indicates inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease, cancer, and other causes. Supplementation with vitamin D3 significantly reduces overall mortality among older adults; however, before any widespread supplementation, further investigations will be required to establish the optimal dose and duration and whether vitamin D3 and D2 have different effects on mortality risk.

INT UROL NEPHROL. 2019 SEP;51(9):1567-1580. DOI: 10.1007/S11255-019-02236-9. EPUB 2019 JUL 23.

The effects of vitamin D treatment on glycemic control, serum lipid profiles, and C-reactive protein in patients with chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials.

Milajerdi A, Ostadmohammadi V, Amirjani S, Kolahdooz F, Asemi Z.

ABSTRACT

PURPOSE:
Insulin resistance, dyslipidemia and increased systemic inflammation are important risk factors for chronic kidney disease (CKD). Hence, vitamin D administration might be an appropriate approach to decrease the complications of CKD. Randomized controlled trials assessing the effects of vitamin D supplementation or treatment on glycemic control, lipid profiles, and C-reactive protein (CRP) among patients with CKD were included.

METHODS:
Two independent authors systematically searched online databases including EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science in November 2018 with no time restriction. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. Between-study heterogeneity was estimated using the Cochran's Q test and I-square (I2) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size.

RESULTS:
Of the 1358 citations identified from searches, 17 full-text articles were reviewed. Pooling findings from five studies revealed a significant reduction in fasting glucose (WMD: - 18.87; 95 % CI: - 23.16, - 14.58) and in homeostatic model assessment of insulin resistance (HOMA-IR) through three studies (WMD: - 2.30; 9 5 % CI: - 2.88, - 1.72) following the administration of vitamin D. In addition, pooled analysis revealed a significant reduction in triglycerides (WMD: - 32.52; 95 % CI: - 57.57, - 7.47) through six studies and in cholesterol concentrations (WMD: - 7.93; 95 % CI: - 13.03, - 2.83) through five studies, following vitamin D supplementation or treatment, while there was no effect on insulin, HbA1c, LDL and HDL cholesterol, and CRP levels.

CONCLUSIONS:
This meta-analysis demonstrated the beneficial effects of vitamin D supplementation or treatment on improving fasting glucose, HOMA-IR, triglycerides and cholesterol levels among patients with CKD, though it did not influence insulin, HbA1c, LDL and HDL cholesterol, and CRP levels.

MATERN CHILD NUTR. 2016 OCT;12(4):898-907.
DOI: 10.1111/MCN.12187. EPUB 2015 APR 7.

Effects of early vitamin D deficiency rickets on bone and dental health, growth and immunity.

Zerofsky M, Ryder M, Bhatia S, Stephensen CB, King J, Fung EB.

ABSTRACT

Vitamin D deficiency is associated with adverse health outcomes, including impaired bone growth, gingival inflammation and increased risk for autoimmune disease, but the relationship between vitamin D deficiency rickets in childhood and long-term health has not been studied. In this study, we assessed the effect of early vitamin D deficiency on growth, bone density, dental health and immune function in later childhood to determine if children previously diagnosed with rickets were at greater risk of adverse health outcomes compared with healthy children. We measured serum 25-hydroxyvitamin D, calcium, parathyroid hormone, bone mineral density, anthropometric measures, dietary habits, dental health, general health history, and markers of inflammation in 14 previously diagnosed rickets case children at Children's Hospital Oakland Research Center. We compared the findings in the rickets cases with 11 healthy children selected from the population of CHO staff families. Fourteen mothers of the rickets cases, five siblings of the rickets cases, and seven mothers of healthy children also participated. Children diagnosed with vitamin D deficiency rickets had a greater risk of fracture, greater prevalence of asthma, and more dental enamel defects compared with healthy children. Given the widespread actions of vitamin D, it is likely that early-life vitamin D deficiency may increase the risk of disease later in childhood. Further assessment of the long-term health effects of early deficiency is necessary to make appropriate dietary recommendations for infants at risk of deficiency.

4.2.5 Pregnancy

MOL CELL ENDOCRINOL. 2017 SEP 15;453:113-130. DOI: 10.1016/J.MCE.2017.01.039. EPUB 2017 FEB 7.

Vitamin D supplementation during pregnancy: Improvements in birth outcomes and complications through direct genomic alteration.

Hollis BW, Wagner CL.

ABSTRACT

Pregnancy represents a time of rapid change, including dramatic shifts in vitamin D metabolism. Circulating concentrations of the active form of vitamin D-1,25(OH)2D skyrocket early in pregnancy to levels that would be toxic to a nonpregnant adult, signaling a decoupling of vitamin D from the classic endocrine calcium metabolic pathway, likely serving an immunomodulatory function in the mother and her developing fetus. In this review, we summarize the unique aspects of vitamin D metabolism and the data surrounding vitamin D requirements during this important period. Both observational and clinical trials are reviewed in the context of vitamin D's health effects during pregnancy that include preeclampsia, preterm birth, and later disease states such as asthma and multiple sclerosis. With enhanced knowledge about vitamin D's role as a preprohormone, it is clear that recommendations about supplementation must mirror what is clinically relevant and evidence-based. Future research that focuses on the critical period(s) leading up to conception and during pregnancy to correct deficiency or maintain optimal vitamin D status remains to be studied. In addition, what effects vitamin D has on genetic signatures that minimize the risk to the mother and her developing fetus have not been elucidated. Clearly, while there is much more research that needs to be performed, our understanding of vitamin D requirements during pregnancy has advanced significantly during the last few decades.

FRONT ENDOCRINOL (LAUSANNE). 2018; 9: 500. PUBLISHED ONLINE 2018 AUG 31. DOI: 10.3389/FENDO.2018.00500

The Implications of Vitamin D Status During Pregnancy on Mother and her Developing Child

Wagner CL, Hollis BW.

ABSTRACT

Pregnancy is a time of tremendous growth and physiological changes for mother and her developing fetus with lifelong implications for the child. The concert of actions that must occur so mother does not reject the foreign tissue of the fetus is substantial. There must be exquisite balance between maternal tolerance to these foreign proteins of paternal origin but also immune surveillance and function such that the mother is not immunocompromised. When this process goes awry, the mother may experience such pregnancy complications as preeclampsia and infections.

Vitamin D deficiency affects these processes. Controversy continues with regard to the optimal daily intake of vitamin D, when sunlight exposure should be taken into account, and how to define sufficiency during such vulnerable and critical periods of development. The importance of vitamin D supplementation during pregnancy in preventing some of the health risks to the mother and fetus appears linked to achieving 25(OH)D concentrations >40 ng/mL, the beginning point of the plateau where conversion of the vitamin D metabolite 25(OH)D, the pre-hormone, to 1,25(OH)2D, the active hormone, is optimized. Throughout pregnancy, the delivery of adequate vitamin D substrate—through sunlight or supplement—is required to protect both mother and fetus, and when in sufficient supply, favorably impacts the epigenome of the fetus, and in turn, long term health. There is a growing need for future research endeavors to focus not only on critical period(s) from pre-conception through pregnancy, but throughout life to prevent certain epigenetic changes that adversely affect health. There is urgency based on emerging research to correct deficiency and maintain optimal vitamin D status. The impact of vitamin D and its metabolites on genetic signaling during pregnancy in both mother and fetus is an area of great activity and still in its early stages. While vitamin D repletion during pregnancy minimizes the risk of certain adverse outcomes (e.g., preterm birth, asthma, preeclampsia, and gestational diabetes), the mechanisms of how these processes occur are not fully understood. As we intensify our research efforts in these areas. it is only a matter of time that such mechanisms will be defined.

CLIN NUTR. 2019 SEP 4. PII: S0261-5614(19)33027-4. DOI: 10.1016/J.CLNU.2019.08.015. [EPUB AHEAD OF PRINT]

Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials.

Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GYH, Blaha MJ, Toth PP, Borghi C, Cicero AFG; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group.

ABSTRACT

BACKGROUND:
Maternal vitamin D deficiency has been associated with an increased risk for preeclampsia. Despite this, the current evidence regarding the efficacy of vitamin D supplementation in preventing preeclampsia is controversial. To assess the impact of vitamin D supplementation on the risk of preeclampsia, we performed a systematic review of the literature and a meta-analysis of the available randomized clinical trials (RCTs).

METHODS:
The primary outcome was preeclampsia. Subgroup analyses were carried out considering the timing of the supplementation, type of intervention and the study design. Meta-regression analysis, including the amount of vitamin D and maternal age, were planned to explore heterogeneity (PROSPERO database registration number: CRD42019119207).

RESULTS:
Data were pooled from 27 RCTs comprising 59 arms, which included overall 4777 participants, of whom 2487 were in the vitamin D-treated arm and 2290 in the control arm. Vitamin D administration in pregnancy was associated with a reduced risk of preeclampsia (odd ratio [OR] 0.37, 95 % confidence interval [CI]: 0.26, 0.52; I2 = 0 %). If the vitamin D supplementation was started up to 20 weeks' gestation, the odds was a little lower (OR 0.35, 95 % CI: 0.24, 0.50, p < 0.001). The effect was largely independent of the supplementation cessation (until delivery or not), type of intervention (vitamin D alone or in association with calcium), and study design. Increasing dose of vitamin D was associated with reduced incidence of preeclampsia (slope of log OR: -1.1, 9 % CI: -1.73, -0.46; p < 0.001).

CONCLUSIONS:
Results suggest that vitamin D supplementation may be useful in preventing preeclampsia. These data are especially useful for health-care providers who engage in the management of pregnant women at risk for preeclampsia. Our findings are a call for action to definitively address vitamin D supplementation as a possible intervention strategy in preventing preeclampsia in pregnancy.

4.3 VITAMIN K2

4.3.1 Arteriosclerosis/CVD

J NUTR. 2004 NOV;134(11):3100-5.

Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study.

Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC.

ABSTRACT

Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990-1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95 % CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59, 0.92), respectively] and severe aortic calcification [odds ratio of 0.71 (0.50, 1.00) and 0.48 (0.32, 0.71), respectively]. Phylloquinone intake was not related to any of the outcomes. These findings suggest that an adequate intake of menaquinone could be important for CHD prevention.

THROMB HAEMOST. 2008 OCT;100(4): 593-603.

Matrix Gla-protein: the calcification inhibitor in need of vitamin K.

Schurgers LJ, Cranenburg EC, Vermeer C.

ABSTRACT

Among the proteins involved in vascular calcium metabolism, the vitamin K-dependent matrix Gla-protein (MGP) plays a dominant role. Although on a molecular level its mechanism of action is not completely understood, it is generally accepted that MGP is a potent inhibitor of arterial calcification. Its pivotal importance for vascular health is demonstrated by the fact that there seems to be no effective alternative mechanism for calcification inhibition in the vasculature. An optimal vitamin K intake is therefore important to maintain the risk and rate of calcification as low as possible. With the aid of conformation-specific antibodies MGP species in both tissue and the circulation have been detected in the healthy population, and significant differences were found in patients with cardiovascular disease (CVD). Using ELISA-based assays, uncarboxylated MGP (ucMGP) was demonstrated to be a promising biomarker for cardiovascular calcification detection. These assays may have potential value for identifying patients as well as apparently healthy subjects at high risk for CVD and/or cardiovascular calcification and for monitoring the treatment of CVD and vascular calcification.

NUTR METAB CARDIOVASC DIS. 2009 SEP;19(7):504-10. DOI: 10.1016/J.NUMECD.2008.10.004.

A high menaquinone intake reduces the incidence of coronary heart disease.

Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witteman JC, Grobbee DE, Peeters PH, van der Schouw YT.

ABSTRACT

BACKGROUND AND AIM:

Vitamin K dependent proteins have been demonstrated to inhibit vascular calcification. Data on the effect of vitamin K intake on coronary heart disease (CHD) risk, however, are scarce. To examine the relationship between dietary vitamins K(1) and K(2) intake, and its subtypes, and the incidence of CHD.

CONCLUSIONS:

A high intake of menoquinones, especially MK-7, MK-8 and MK-9, could protect against CHD. However, more research is necessary to define optimal intake levels of vitamin K intake for the prevention of CHD.

PRZEGL LEK. 2011;68(9):629-32.

Vitamin K, bone metabolism and vascular calcification in chronic kidney disease.

Zak-Gołab A, Okopień B, Chudek J.

ABSTRACT

Atherosclerosis is the main cause of morbidity and mortality in the general population, and premature death in patients with chronic kidney disease (CKD) especially dialysis ones. Vitamin K - dependent proteins play an essential role in the pathogenesis of mineral and bone disorders related to CKD, including vascular calcification. Vitamin K is a family of vitamins, varying in the number of isoprenoid groups (saturated or unsaturated) connected into 2-methyl-1,4-naphthoquinone ring in C3 position. Vitamin K-dependent proteins require carboxylation (VKDPs) for biological activation. The coagulant factors are the most well-known VKDPs, but the role of the other proteins, like Matrix Gla Protein (MGP), Growth Arrest Specific Gene 6 (Gas-6) and osteocalcin has been recently discovered. MGP prevents vascular calcification and Gas-6 affects vascular smooth muscle cell apoptosis and movement. Carboxylation of osteocalcin promotes bone formation. Additionally vitamin K increases proliferation of osteoblasts and apoptosis of osteoclasts, influencing on bone remodeling. There is few studies indicating for decreased consumption of vitamin K in the general population. The restrictive diet recommended for dialysis patients additionally diminishes its daily supply, increasing the chance for vitamin K deficiency in this population. Clinical consequences of inhibition of epoxide reductase by generally used anticoagulants, that inhibiting vitamin K cycle and preventing gamma-carboxylation of Gla proteins, in the peripheral tissue is hardly known. This paper summaries the state of the art knowledge focused on the role of vitamin K in mineral and bone metabolism disorders in CKD patients.

J BONE MINER RES. 2012 NOV;27(11):2271-8. DOI: 10.1002/JBMR.1677.

Vitamin K, vertebral fractures, vascular calcifications, and mortality: VItamin K Italian (VIKI) dialysis study.

Fusaro M, Noale M, Viola V, Galli F, Tripepi G, Vajente N, Plebani M, Zaninotto M, Guglielmi G, Miotto D, Dalle Carbonare L, D'Angelo A, Naso A, Grimaldi C, Miozzo D, Giannini S, Gallieni M; VItamin K Italian (VIKI) Dialysis Study Investigators.

ABSTRACT

Vitamin K (vitamin K1 or phylloquinone and vitamin K2, a series of menaquinones [MKs]) is involved in the production of bone and matrix amino acid γ-carboxyglutamic acid (Gla) proteins, regulating bone and vascular calcification. We carried out an observational study to establish the prevalence of vitamin K deficiency and to assess the relationship between vitamin K status, vertebral fractures, vascular calcification, and survival in 387 patients on hemodialysis for ≥1 year. Important proportions of patients had deficiency of MK7 (35.4 %), vitamin K1 (23.5 %), and MK4 (14.5 %). A total of 55.3 % of patients had vertebral fractures, 80.6 % had abdominal aorta calcification, and 56.1 % had iliac calcification. Vitamin K1 deficiency was the strongest predictor of vertebral fractures. MK4 deficiency was a predictor of aortic calcification, whereas MK5 deficiency actually protected against it. MK7 deficiency was a predictor of iliac calcification. The presence of vertebral fractures was also a predictor of vascular calcifications. Our study suggests that the vitamin K system may be important for preserving bone mass and avoiding vascular calcification in hemodialysis patients, pointing out a possible role of vitamin K in bone and vascular health. Based on our results, we suggest that the general population should also be studied for vitamin K deficiency as a possible cause of both vertebral fractures and vascular calcification.

ADV NUTR. 2012 MAR 1;3(2):166-73. DOI: 10.3945/AN.111.001628.

The role of vitamin K in soft-tissue calcification.

Schurgers LJ, Cranenburg EC, Vermeer C.Theuwissen E, Smit E, Vermeer C.

ABSTRACT

Seventeen vitamin K-dependent proteins have been identified to date of which several are involved in regulating soft-tissue calcification. Osteocalcin, matrix Gla protein (MGP), and possibly Gla-rich protein are all inhibitors of soft-tissue calcification and need vitamin K-dependent carboxylation for activity. MGP is synthesized by vascular smooth muscle cells and is the most important inhibitor of arterial mineralization currently known. Remarkably, the extrahepatic Gla proteins mentioned are only partly carboxylated in the healthy adult population, suggesting vitamin K insufficiency. Because carboxylation of the most essential Gla proteins is localized in the liver and that of the less essential Gla proteins in the extrahepatic tissues, a transport system has evolved ensuring preferential distribution of dietary vitamin K to the liver when vitamin K is limiting. This is why the first signs of vitamin K insufficiency are seen as undercarboxylation of the extrahepatic Gla proteins. New conformation-specific assays for circulating uncarboxylated MGP were developed; an assay for desphospho-uncarboxylated matrix Gla protein and another assay for total uncarboxylated matrix Gla protein. Circulating desphospho-uncarboxylated matrix Gla protein was found to be predictive of cardiovascular risk and mortality, whereas circulating total uncarboxylated matrix Gla protein was associated with the extent of prevalent arterial calcification. This study showed maintenance of vascular elasticity during a 3-y supplementation period, with a parallel 12 % loss of elasticity in the placebo group.

EUR REV MED PHARMACOL SCI. 2013 SEP;17(18):2433-40.

Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis.

Flore R, Ponziani FR, Di Rienzo TA, Zocco MA, Flex A, Gerardino L, Lupascu A, Santoro L, Santoliquido A, Di Stasio E, Chierici E, Lanti A, Tondi P, Gasbarrini A.

ABSTRACT

DISCUSSION:

Vitamin K2 is essential for the function of several proteins, involved in the maintenance of the normal structure of arterial wall, osteoarticular system, teeth, and for the regulation of cell growth. It has been demonstrated to have a pivotal role in the inhibition of vascular foci of calcification, and in the regulation of calcium deposition in the bone. Vitamin K2 deficiency is often subclinic in a large part of healthy population. This deficiency is related to the interaction of various factors, such as the reduced dietary intake, the alteration of intestinal absorption or production, with a possible role of intestinal microbiota and the increased consumption at the vessel wall.

CONCLUSIONS:

Vitamin K2 deficiency has recently been recognized as a protagonist in the development of vascular calcification and osteoporosis. Data reported so far are promising and, dietary supplementation seems a useful tool to contrast these diseases. However, large studies or solid clinical correlations regarding vitamin K2 deficiency and its pathologic consequences are needed to confirm these preliminary experiences.

POL ARCH MED WEWN. 2015;125(9):631-40. EPUB 2015 JUL 15.

Effect of vitamin K2 on progression of atherosclerosis and vascular calcification in nondialyzed patients with chronic kidney disease stages 3-5.

Kurnatowska I, Grzelak P, Masajtis-Zagajewska A, Kaczmarska M, Stefańczyk L, Vermeer C, Maresz K, Nowicki M.

ABSTRACT

PATIENTS AND METHODS:

The study included 42 nondialyzed patients with CKD. The measurements were taken at baseline and after 270 ±12 days of supplementation with vitamin K2 at a dose of 90 μg (menaquinone, MK-7) together with 10 μg of cholecalciferol (K+D group) or 10 μg of cholecalciferol (group D).

RESULTS:

The increase of carotid intima-media thickness was significantly lower in the K+D group compared with the D group: from 0.95 ±0.2 mm to 1.01 ±0.3, P = 0.003 vs from 1.02 ±0.2 mm to 1.16 ±0.3, P = 0.003. The increase in coronary artery calcification score was slightly lower in the K+D group than in the D group. In the K+D group, a significant decrease in the level of desphosphorylated-uncarboxylated MGP and total osteocalcin was observed.

CONCLUSIONS:

A 270-day course of vitamin K2 administration in patients with CKD stages 3-5 may reduce the progression of atherosclerosis, but does not significantly affect the progression of calcification. Vitamin K2 significantly changes the levels of calcification promoters and inhibitors: dp-ucMGP, OC, and OPG.

CURR NUTR REP. 2016 JUN;5(2):90-98. EPUB 2016 MAR 31.

The Role of Vitamin K in Chronic Aging Diseases: Inflammation, Cardiovascular Disease, and Osteoarthritis.

Harshman SG, Shea MK.

ABSTRACT

Vitamin K is an enzyme cofactor required for the carboxylation of vitamin K dependent proteins, several of which have been implicated in diseases of aging. Inflammation is recognized as a crucial component of many chronic aging diseases and evidence suggests vitamin K has an anti-inflammatory action that is independent of its role as an enzyme co-factor. Vitamin K-dependent proteins and inflammation have been implicated in cardiovascular disease and osteoarthritis, which are leading causes of disability and mortality in older adults. The purpose of this review is to summarize observational studies and randomized trials focused on vitamin K status and inflammation, cardiovascular disease, and osteoarthritis. Although mechanistic evidence suggests a protective role for vitamin K in these age-related conditions, the benefit of vitamin K supplementation is controversial because observational data are equivocal and the number of randomized trials is few.

4.3.2 Bone Metabolism

CURR PHARM DES. 2004;10(21):2557-76.

Effects of vitamin K2 on osteoporosis.

Iwamoto J, Takeda T, Sato Y.

ABSTRACT

Vitamin K2 is a cofactor of gamma-carboxylase, which converts the glutamic acid (Glu) residue in osteocalcin molecules to gamma-carboxyglutamic acid (Gla), and is, therefore, essential for gamma-carboxylation of osteocalcin. Available evidence suggests that vitamin K2 also enhances osteocalcin accumulation in the extracellular matrix of osteoblasts in vitro. The findings suggest that vitamin K2 may not only stimulate bone formation but also suppress bone resorption in vivo. Clinically, vitamin K2 sustains the lumbar bone mineral density (BMD) and prevents osteoporotic fractures in patients with age-related osteoporosis, prevents vertebral fractures in patients with glucocorticoid-induced osteoporosis, increases the metacarpal BMD in the paralytic upper extremities of patients with cerebrovascular disease, and sustains the lumbar BMD in patients with liver-dysfunction-induced osteoporosis. Vitamin K deficiency, as indicated by an increased circulating level of undercarboxylated osteocalcin, may contribute to osteoporotic fractures. Even though the effect of vitamin K2 on the BMD is quite modest, this vitamin may have the potential to regulate bone metabolism and play a role in reducing the risk of osteoporotic fractures. No randomized well-controlled prospective studies conducted on a sufficiently large number of patients have been reported yet, therefore, further studies are needed to confirm the efficacy of vitamin K2 in the treatment of osteoporosis.

CLIN CALCIUM. 2005 JUN;15(6):1034-9.

Vitamin K2 (menatetrenone) and bone quality.

Iinuma N.

ABSTRACT

Vitamin K2 (menatetrenone) treatment was reported to significantly prevent new clinical fracture (chi2 = 10.935;p = 0.0273) in a 2-year group comparison study of patients with osteoporosis, although it only maintained the baseline bone mineral density. This result strongly suggested that another factor was involved in promoting bone strength apart from an increase in bone mineral density. With respect to the therapeutic effect of menatetrenone treatment on corticosteroid-induced osteoporosis over 2 years, the incidence of a new vertebral fracture was 13.3 % in the menatetrenone treatment group versus 4 1% in the control group, indicating that this treatment could prevent fractures. Multivariate logistic regression analysis was performed to investigate independent risk factors for new vertebral fractures, and treatment with menatetrenone showed a preventive effect on fracture with an odds ratio of 0.03 and a risk rate of 0.003.

OSTEOPOROS INT. 2013 SEP;24(9):2499-507. DOI: 10.1007/S00198-013-2325-6. EPUB 2013 MAR 23.

Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women.

Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E.

ABSTRACT

METHODS:

Healthy postmenopausal women (n = 244) received for 3 years placebo or MK-7 (180 μg MK-7/day) capsules. Bone mineral density of lumbar spine, total hip, and femoral neck was measured by DXA; bone strength indices of the femoral neck were calculated. Vertebral fracture assessment was performed by DXA and used as measure for vertebral fractures. Circulating uncarboxylated osteocalcin (ucOC) and carboxylated OC (cOC) were measured; the ucOC/cOC ratio served as marker of vitamin K status. Measurements occurred at baseline and after 1, 2, and 3 years of treatment.

We have investigated whether low-dose vitamin K2 supplements (menaquinone-7, MK-7) could beneficially affect bone health. Next to an improved vitamin K status, MK-7 supplementation significantly decreased the age-related decline in bone mineral density and bone strength. Low-dose MK-7 supplements may therefore help postmenopausal women prevent bone loss.

RESULTS:

MK-7 intake significantly improved vitamin K status and decreased the age-related decline in BMC and BMD at the lumbar spine and femoral neck, but not at the total hip. Bone strength was also favorably affected by MK-7. MK-7 significantly decreased the loss in vertebral height of the lower thoracic region at the mid-site of the vertebrae.

CONCLUSIONS:

MK-7 supplements may help postmenopausal women to prevent bone loss. Whether these results can be extrapolated to other populations, e.g., children and men, needs further investigation.

OSTEOPOROS INT. 2015 MAR;26(3):1175-86. DOI: 10.1007/S00198-014-2989-6. EPUB 2014 DEC 17.

Does vitamin K2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: a meta-analysis of randomized controlled trials.

Huang ZB, Wan SL, Lu YJ, Ning L, Liu C, Fan SW.

ABSTRACT

INTRODUCTION:

Vitamin K2 has been revealed to be effective in the prevention and treatment of osteoporosis in Japan, which was not confirmed in western countries. Thus, we conduct this meta-analysis to verify the hypothesis that vitamin K2 plays a role in the prevention and treatment of osteoporosis for postmenopausal women.

METHODS:

We searched the Cochrane Library, Pub Med, EMBASE, and ISI web of knowledge (until December 1, 2013) and reference lists of eligible articles. A meta-analysis of all-including randomized controlled trials was then performed.

RESULTS:

Nineteen randomized controlled trials encompassing 6759 participants have met the inclusion criteria. Subgroup analysis of postmenopausal women with osteoporosis revealed a significant improvement of vertebral BMD for both medium-term and long-term results favoring vitamin K2 group. However, sensitivity analysis by rejecting the study inducing heterogeneity demonstrated a significant difference in the incidence of fractures favoring vitamin K2. Significant differences were found in undercarboxylated osteocalcin reduction and osteocalcin increment. The result of adverse reaction analysis showed that vitamin K2 group seemed to have a higher adverse reaction rate.

CONCLUSIONS:

This meta-analysis seemed to support the hypothesis that vitamin K2 plays kind of a role in the maintenance and improvement of vertebral BMD and the prevention of fractures in postmenopausal women with osteoporosis. The reduction of undercarboxylated osteocalcin and increment of osteocalcin may have some relation to the process of bone mineralization. However, the effect of vitamin K2 for postmenopausal women without osteoporosis had not been identified. Further high-quality RCTs with large sample size are needed to confirm the role of vitamin K2 in osteoporosis for postmenopausal women.

ORAL DIS. 2017 NOV;23(8):1021-1028. DOI: 10.1111/ODI.12624. EPUB 2017 APR 5.

Regulation of bone remodeling by vitamin K2.

Myneni VD, Mezey E.

ABSTRACT

All living tissues require essential nutrients such as amino acids, fatty acids, carbohydrates, minerals, vitamins, and water. The skeleton requires nutrients for development, maintaining bone mass and density. If the skeletal nutritional requirements are not met, the consequences can be quite severe. In recent years, there has been growing interest in promotion of bone health and inhibition of vascular calcification by vitamin K2. This vitamin regulates bone remodeling, an important process necessary to maintain adult bone. Bone remodeling involves removal of old or damaged bone by osteoclasts and its replacement by new bone formed by osteoblasts. The remodeling process is tightly regulated, when the balance between bone resorption and bone formation shifts to a net bone loss results in the development of osteoporosis in both men and women. In this review, we focus on our current understanding of the effects of vitamin K2 on bone cells and its role in prevention and treatment of osteoporosis. Clin Calcium. 2005 Jun;15(6):1034-9.

BIOMED RES INT. 2018 JUN 27;2018:4629383. DOI: 10.1155/2018/4629383. ECOLLECTION 2018.

Vitamin K and Bone Metabolism: A Review of the Latest Evidence in Preclinical Studies.

Akbari S, Rasouli-Ghahroudi AA.

ABSTRACT

Bone is a metabolically active tissue that renews itself throughout one's life. Cytokines along with several hormonal, nutritional, and growth factors are involved in tightly regulated bone remodeling. Accordingly, vitamin K as a multifunctional vitamin has been recently deemed appreciable as a topic of research as it plays a pivotal role in maintenance of the bone strength, and it has been proved to have a positive impact on the bone metabolism. Vitamin K exerts its anabolic effect on the bone turnover in different ways such as promoting osteoblast differentiation, upregulating transcription of specific genes in osteoblasts, and activating the bone-associated vitamin k dependent proteins which play critical roles in extracellular bone matrix mineralization. There is also credible evidence to support the effects of vitamin k2 on differentiation of other mesenchymal stem cells into osteoblast. The main objective of the present paper is to comprehensively outline the preclinical studies on the properties of vitamin K and its effects on the bone metabolism. The evidence could shed light on further clinical studies to improve osteogenesis in bone graft surgeries.

4.3.3 Caries

MED HYPOTHESES. 2015 MAR;84(3):276-80. DOI: 10.1016/J.MEHY.2015.01.011. EPUB 2015 JAN 19.

A hypothetical role for vitamin K2 in the endocrine and exocrine aspects of dental caries.

Southward Ken, University of Toronto, Canada.

ABSTRACT

The growing interest in oral/systemic links demand new paradigms to understand disease processes. New opportunities for dental research, particularly in the fields of neuroscience and endocrinology will emerge. The role of the hypothalamus portion of the brain cannot be underestimated. Under the influence of nutrition, it plays a significant role in the systemic model of dental caries. Currently, the traditional theory of dental caries considers only the oral environment and does not recognize any significant role for the brain. The healthy tooth, however, has a centrifugal fluid flow to nourish and cleanse it. This is moderated by the hypothalamus/parotid axis which signals the endocrine portion of the parotid glands. High sugar intake creates an increase in reactive oxygen species and oxidative stress in the hypothalamus. When this signaling mechanism halts or reverses the dentinal fluid flow, it renders the tooth vulnerable to oral bacteria, which can now attach to the tooth's surface. Acid produced by oral bacteria such as Strep Mutans and lactobacillus can now de-mineralize the enamel and irritate the dentin. The acid attack stimulates an inflammatory response which results in dentin breakdown from the body's own matrix metalloproteinases. Vitamin K2 (K2) has been shown to have an antioxidant potential in the brain and may prove to be a potent way to preserve the endocrine controlled centrifugal dentinal fluid flow. Stress, including oxidative stress, magnifies the body's inflammatory response. Sugar can not only increase oral bacterial acid production but it can concurrently reduce the tooth's defenses through endocrine signaling. Saliva production is the exocrine function of the salivary glands. The buffering capacity of saliva is critical to neutralizing the oral environment. This minimizes the demineralization of enamel and enhances its re-mineralization. K2, such as that found in fermented cheese, improves salivary buffering through its influence on calcium and inorganic phosphates secreted. Data collected from several selected primitive cultures on the cusp of civilization demonstrated the difference in dental health due to diet. The primitive diet group had few carious lesions compared to the group which consumed a civilized diet high in sugar and refined carbohydrates. The primitives were able to include the fat soluble vitamins, specifically K2, in their diet. More endocrine and neuroscience research is necessary to better understand how nutrition influences the tooth's defenses through the hypothalamus/parotid axis. It will also link dental caries to other inflammation related degenerative diseases such as diabetes.

4TH INTERNATIONAL CONFERENCE AND EXHIBITION ON NUTRITION. OCTOBER 26-28, 2015 CHICAGO, ILLINOIS, USA

The potential role of vitamin K2 in dental caries.

Southward Ken, University of Toronto, Canada.

ABSTRACT

Dental caries has traditionally been viewed as a tooth demineralizing process limited to the oral cavity. New understandings of oral/systemic links propose that dental caries is an uncontrolled inflammatory response controlled by the brain and moderated through the hypothalamus/parotid axis of the endocrine system. The role of reactive oxygen species in the hypothalamus is a signaling factor in establishing tooth vulnerability or resistance. Vitamin K2 appears to have a significant antioxidant role in the brain as well as a key nutrient in the management of calcium in the body including bones and cardiovascular tissues. K2 works in concert with calcium and vitamin D. This systemic paradigm of dental caries places nutrition on the leading edge of prevention because it is focused on the cause of the disease rather than traditional preventive efforts focused on the symptoms. K2 also appears to have a potential salivary buffering role in the exocrine portion of the parotid gland as well as the other salivary glands. In this systemic paradigm, the potential preventive role of nutritionists and public health professionals is elevated to unprecedented levels. Working to broaden current dental recall programs beyond a symptom focus will show benefits but will probably have to be driven by public education programs.

4.3.4 Systemic Relevance

SCIENCE. 2012 JUN 8;336(6086):1306-10. DOI: 10.1126/SCIENCE.1218632. EPUB 2012 MAY 10.

Vitamin K2 is a mitochondrial electron carrier that rescues pink1 deficiency.

Vos M, Esposito G, Edirisinghe JN, Vilain S, Haddad DM, Slabbaert JR, Van Meensel S, Schaap O, De Strooper B, Meganathan R, Morais VA, Verstreken P.

ABSTRACT

Human UBIAD1 localizes to mitochondria and converts vitamin K(1) to vitamin K(2). Vitamin K(2) is best known as a cofactor in blood coagulation, but in bacteria it is a membrane-bound electron carrier. Whether vitamin K(2) exerts a similar carrier function in eukaryotic cells is unknown. We identified Drosophila UBIAD1/Heix as a modifier of pink1, a gene mutated in Parkinson's disease that affects mitochondrial function. We found that vitamin K(2) was necessary and sufficient to transfer electrons in Drosophila mitochondria. Heix mutants showed severe mitochondrial defects that were rescued by vitamin K(2), and, similar to ubiquinone, vitamin K(2) transferred electrons in Drosophila mitochondria, resulting in more efficient adenosine triphosphate (ATP) production. Thus, mitochondrial dysfunction was rescued by vitamin K(2) that serves as a mitochondrial electron carrier, helping to maintain normal ATP production.

J NUTR METAB. 2017;2017:6254836. DOI: 10.1155/2017/6254836. EPUB 2017 JUN 18.

Vitamins K1 and K2: The Emerging Group of Vitamins Required for Human Health.

Schwalfenberg GK.

ABSTRACT

OBJECTIVE:

To review the evidence for the use of vitamin K supplementation in clinical conditions such as osteoporosis, vascular calcification, arthritis, cancer, renal calculi, diabetes, and warfarin therapy.

QUALITY OF EVIDENCE:

PubMed was searched for articles on vitamin K (K1 and K2) along with books and conference proceedings and health conditions listed above. Level I and II evidence supports the use of vitamins K1 and K2 in osteoporosis and Level II evidence supports vitamin K2 in prevention of coronary calcification and cardiovascular disease. Evidence is insufficient for use in diabetes, arthritis, renal calculi, and cancer.

MAIN MESSAGE:

Vitamin K2 may be a useful adjunct for the treatment of osteoporosis, along with vitamin D and calcium, rivaling bisphosphonate therapy without toxicity. It may also significantly reduce morbidity and mortality in cardiovascular health by reducing vascular calcification. Vitamin K2 appears promising in the areas of diabetes, cancer, and osteoarthritis. Vitamin K use in warfarin therapy is safe and may improve INR control, although a dosage adjustment is required.

CONCLUSION:

Vitamin K supplementation may be useful for a number of chronic conditions that are afflicting North Americans as the population ages. Supplementation may be required for bone and cardiovascular health.