THE SUN VITAMIN D3

2018

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The importance of vitamin D3

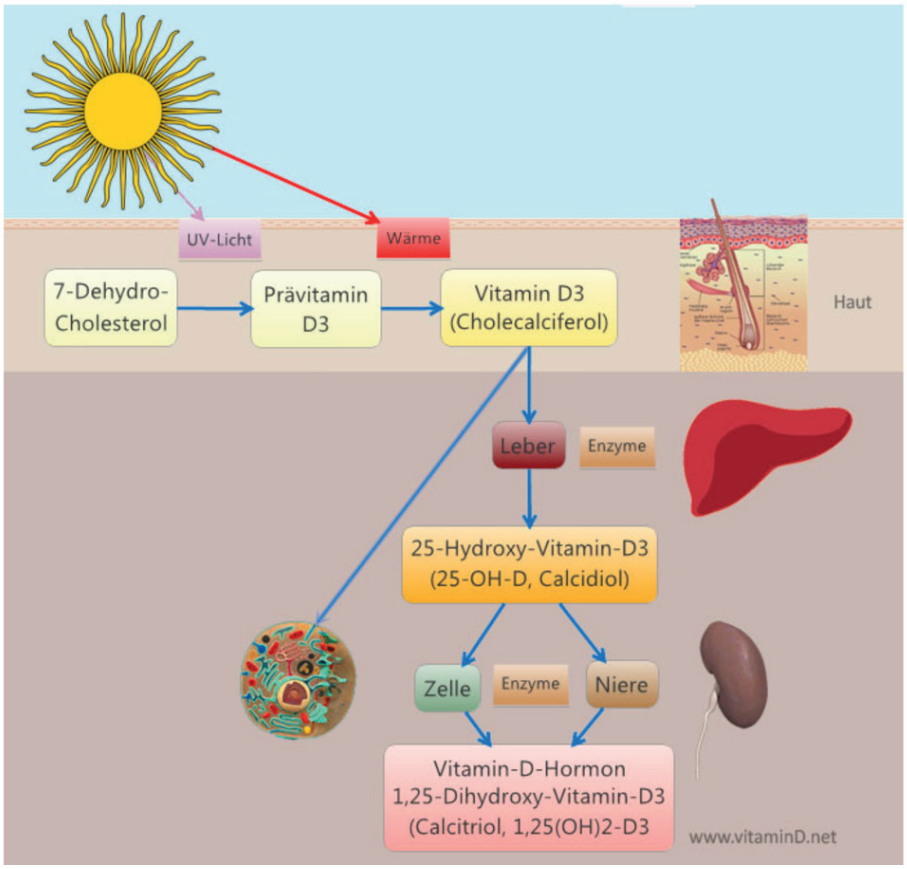
The final stage of vitamin D3 in the cell is a hormone called calcitriol, which together with parathyroid hormone (PTH) is one of the most important hormonal controls of calcium and phosphate content. The parathyroid hormone secreted by the parathyroid gland is released when the calcium level sinks. It activates the osteoclasts („bone-eating cells“) indirectly and mobilizes calcium and phosphate from the bone tissue. The consequence is an increased calcium level in the blood and a reduced content of minerals in the bones (osteopenia, osteoporosis). The synthesis and release of PTH is inhibited by calcitriol. Calcitriol reduces the excretion of calcium from the kidneys and increases the available calcium through absorption in the small intestine. This leads to an increased osteoblast activity; the ability to form healthy new bone.

A study (see Choukroun et al 2014) shows the importance of vitamin D3 in bone formation on which implant healing depends. 1,25- (OH) 2-vitamin D3 (= calcitriol) is the most important hormone involved in bone formation and at the same time it reduces inflammation. [i] Lack of vitamin D3 inhibits the healing of implants and increases the risk of infection. [ii]

Furthermore, an anti-inflammatory effect on the gums and the periodontium is proven. Activated vitamin D3 stimulates the formation of antimicrobial peptides on the skin and mucous membranes and therefore has an antibacterial and anti-inflammatory effect. [iii] (Hieremath, 2013).
A study from 2016 (see. Woelber et al.) proves that a diet low in carbohydrates, while at the same time satisfying the need for omega-3 fatty acids, fiber, vitamins C and D as well as antioxidants, can prevent gum and dental inflammation.
Therefore, periodontitis no longer needs to be treated surgically. It can be prevented and treated by supplementing the needed vitamins and minerals. A study from 2012 (see F.R. Teles et al.) shows that patients with high vitamin D levels had significantly fewer bleeding gums, less pocket depths and less tooth loss. [v]

In addition to the importance of calcium metabolism and bone formation, vitamin D3 has immunological and metabolic effects on our body. Autoimmune diseases such as multiple sclerosis, arthritis and diabetes are more common with low D3 levels. [vi] With sufficient vitamin D3 formation, the acquired (in the case of autoimmune diseases overactive) immune response is regulated down, and the innate non-specific immune response is regulated up. Receptors for vitamin D3 can be found in some cell types of our immune system, i.e. in T lymphocytes and T helper cells. In experiments, the elimination of these receptors led to inflammatory gut diseases. [vii]

Vitamin D3 also strengthens AMPs (anti micro biotic proteins). Those AMPs kill microorganisms, bacteria and viruses often faster and more effective than the immune system, which was gained through activation of specialized defense cells.



The proven resistance against flue by sufficient vitamin D3 is based on the inhibition of NFκB transcriptase factor. The nuclear factor kappa B is a protein that is activated by cell stress and causes both an inflammatory cascade and the formation of free radicals. Vitamin D3 thus plays a regulating role in cell stress reactions, given that there is a sufficient supply of 25-hydroxyvitamin D3 (storage of of vitamin D3).
Likewise, vitamin D can prevent from heart attacks, cancer and chronic fatigue, triggered by the permanent activation of NFκB, secured. Hence, D3 helps to bring the patients into the parasympathetic nervous system. It ensures a healthy sleep and necessary relaxation.

Vitamin D3 is built up to 80% in the skin. For the conversion of the 7-dehydrocholesterol present there, UVB radiation is needed to be converted by photolysis into the pre-vitamin D3. [viii] This pre-vitamin is converted into vitamin D3 (cholecalciferol) by thermal isomerization. After 8 hours, 80% of the pre-vitamin is converted in the skin. As soon as vitamin D3 enters the bloodstream, it is transported to the liver using the vitamin D binding protein (DBP) and hydroxylases to 25-OH-vitamin D3 (calcidiol). Calcidiol is a storage form of vitamin D3. The conversion to the active steroid hormone calcitriol then continues in the kidney. The level of 7-dehydrocholesterol in the skin decreases progressively with age. The ability of older people to form D3 in the skin is reduced by a factor of 3, in comparison to a 20-year-old person.

When using sunscreen or day cream with sun protection factor, already SPF 8 prevents vitamin D3 production by more than 97%. According to the scientific findings of the Karolinska Institute in Stockholm over 20 years and more than 30,000 patients, sunscreen has been shown to be responsible for the development of skin cancer (Dr. Elizabeth Plourde: Sun- screens-Biohazard: Treat as hazardous waste). In addition, nanoparticles of titanium dioxide, which is contained in sunscreen, damages DNA and promotes the onset of Alzheimer's, epilepsy and autism. [ix] The also contained nanoparticles of zinc oxide are suspected to kill intestinal and brain stem cells. [x]

With sunscreen containing Oxybenzone and Octinozate threatening the coral reef's ecosystem, the US state of Hawaii has become the first US state to ban the sale of sunscreen. [xi] Interestingly enough, the press articles address the fatal effect of the toxicity on the corals, but in no word the effect on humans when applying these superpowers several times a day on one of the best absorption organs (the human skin) with an area of 1.5. 2 square meters...

20% of vitamin D can be taken in through the food. [xii] High-fat fish such as salmon and herring have high levels, as well as milk, porcini mushrooms, shiitake mushrooms and avocados. Generally, however, there is an increasing loss of minerals and vitamins in all fruits and vegetables. Leached soils, air pollution, modern processing methods and storage resulted in a drastic loss of valuable ingredients in our food over the last 50 years. [xiii] Today, you would have to eat ten times as many fruits and vegetables to get the same nutrient content as you did fifty years ago.
Due to today's lifestyle and because we mainly stay indoors, the majority of the population has a vitamin D deficiency, today.
It is important to know that in the countries north of the 40th latitude (in Europe north of Rome) vitamin D can only be produced insufficiently in the months October to March. The absorption of UV-B radiation depends on the cloud cover and the angle of incidence of the sun. If the angle is less than 45 °, the path of the sun's rays through the ozone layer is too long to produce vitamin D as the ozone layer absorbs some of the UV radiation. On the website www.timeanddate.com you can track the hours of sunshine with their angles anywhere in the world. For example, on January 11, 2018, in Oslo (40th parallel), there was no sunshine angle of over 45 ° at any time of the day. In Tel Aviv, however, (32nd latitude) vitamin D could be produced on January 11 between 9:28am and 4:03 pm optimally. For mobile phones, an app is available (Dminder by Prof. Molick) which precisely indicates how many units of Vitamin D at what time of day can be built within a certain time. There is a simple rule easy to remember: If the shadow is longer than the height, no vitamin D production takes place. For the production of vitamin D, only the UV-B radiation is responsible, which accounts for the lower proportion of UV radiation. The longer UV-A rays penetrate deeper into the skin and are responsible for possible cell damage and skin aging.

Stressful living conditions lead to systemic acidosis and thus to calcium absorption from the bone to buffer the blood pH to 7.4. This simulates a sufficiently high D3 level in the body. At the same time, this is responsible for the lack of D3. Since vitamin D3 supports the immune system, a deficiency can have many effects. In addition to a lack of concentration and cardiovascular disorders, reduced muscle strength, growth disorders, osteomalacia, immunodeficiency, insomnia, nervousness, depression, tooth loss and increased susceptibility to fractures can occur. Multiple sclerosis, asthma and cancer are also associated with vitamin D3 deficiency. A study from 2016 by Yehuda Shoenfeld (see Lindqvist et al 2016) has already pointed out that avoiding sunlight is on the same level with smoking as a risk factor for premature death. [xiv]
It has been found that the spread of chronic diseases such as diabetes and multiple sclerosis increases with the distance to the equator and thus the sun and outdoor exposure.

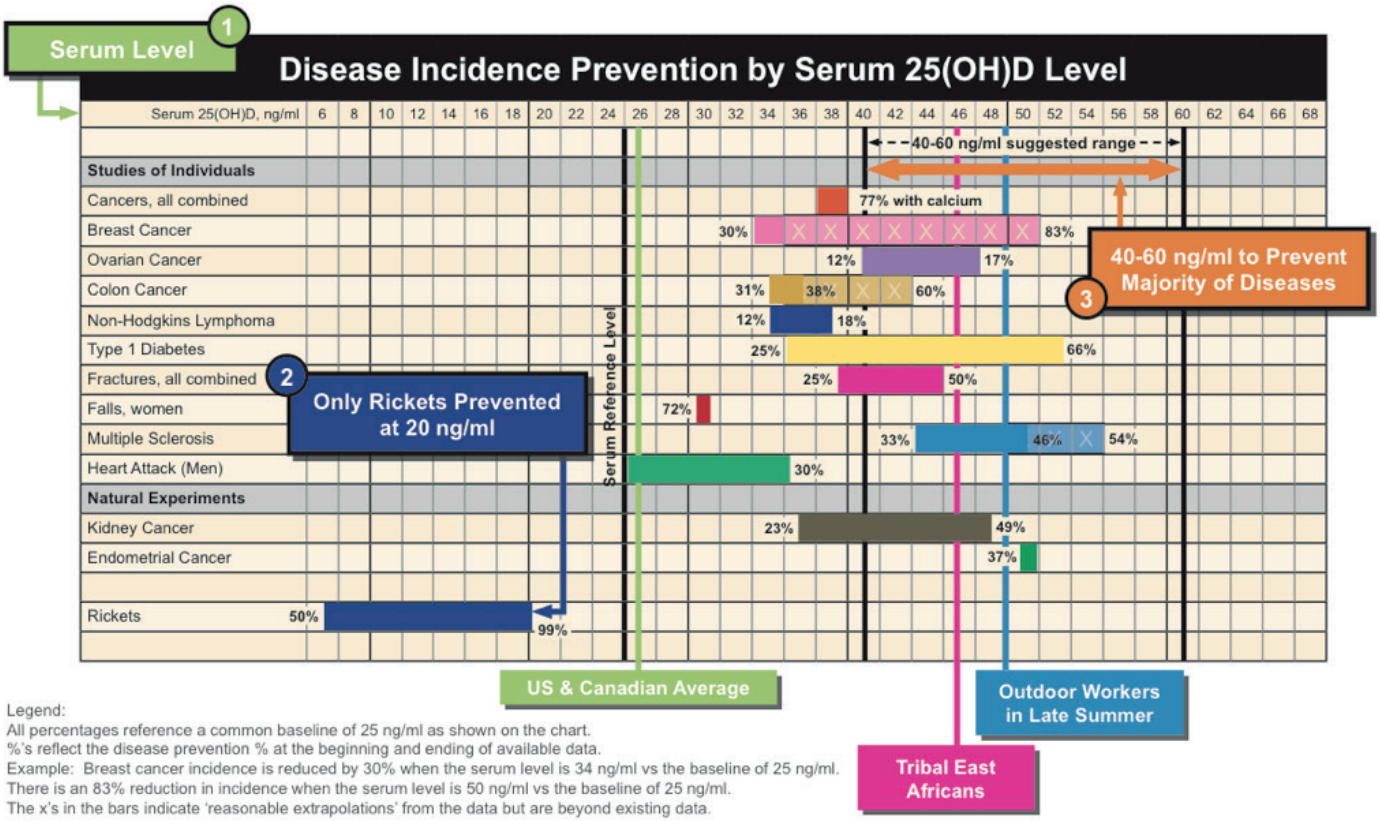
The review meta study shows that patients with a serum level of the storage of 25-OH-vitamin D3 of more than 60 ng / ml are protected by 85% from most chronic diseases!

The 25-OH-D storage form tested in the blood gives information about a lack of vitamin D3. X-ray images can also provide information about vitamin D3 deficiency: in patients with severe vitamin D3 deficiency, the pulp horns are asymmetric and narrowed and visually resemble a chair with a hard back. Healthy pulp resembles a round arch with wider pulp horns. [xv]

On a sunny day at the equator, i.e. humans form 20,000 units of D3. The recommended daily dose was increased from 400 units to 1,000 units daily in Germany in 2015. After scientists confirmed that the low intake recommendations for vitamin D occured due to a calculation error by a factor of 10 (cf. Veuglers et al 2014), they demanded to announce a vitamin D dose recommendation of at least 7,000 units. We estimate that a protective dose of 20,000 units per day should prepare the patient optimally for a surgical procedure.

In prescribing the generalized dosage of 20,000 units/ day for four weeks before the surgery appointment, we reach a blood concentration of about 70 to 120 ng D3 / ml. This corresponds approximately to the vitamin D3 level of a person living in the equatorial region. It prepares the patient optimally for surgery. 85 % of all Germans are even below the governmental target value of 30 ng D3 / ml, which means that they are in „immunological hibernation“ and will not be able to heal bones and wounds completely and without complications.

It is important to combine the intake of vitamin D3 with vitamin K2-mk7 in a long-term use, as vitamin D3 uses up the vitamin K2. High blood calcium levels should be avoided.



Legend:
All percentages reference a common baseline of 25 ng/ml as shown on the chart.
%'s reflect the disease prevention % at the beginning and ending of available data.
Example: Breast cancer incidence is reduced by 30% when the serum level is 34 ng/ml vs the baseline of 25 ng/ml.
There is an 83% reduction in incidence when the serum level is 50 ng/ml vs the baseline of 25 ng/ml.
The x's in the bars indicate 'reasonable extrapolations' from the data but are beyond existing data.

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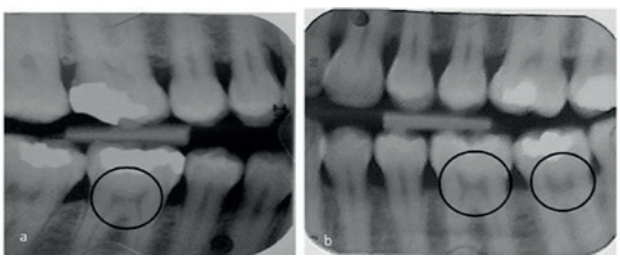
Chart prepared by: Garland CF, Baggerly CA



A vitamin K2 deficiency can manifest itself among other things in heart complaints. The combination of D3 with K2-mk7 also prevents from hypercalcaemia that occurs with D3 overdose. The ratio of vitamin D3 to K2 / mk7 should be 10,000 units of D3 to 100 µg of K2 mk7. In order to convert vitamin D into the active vitamin D hormone and for the further transport in the body, especially magnesium is needed. A lack of magnesium would block the entire household of PTH, calcium and vitamin D. For protein synthesis and activation of some genes, vitamin A in balanced concentration with vitamin D is required. If the ratio is not balanced, the vitamins behave like antagonists and the effect of vitamin D is impaired.

Furthermore, a zinc deficiency would limit the function of vitamin D. Zinc is needed to form the vitamin D receptors found on almost all cells. This balance of vitamin D3 and vitamin K2 as well as the other co-factors perfectly matched in the BASIC IMMUNE has been confirmed by Dr. med. Klinghardt and Dr. Volz. The intake should be started 4 weeks prior to the surgery.

The German Olympic team in sailing is taking BASIC IMMUNE to prepare optimally for the Olympics. The team members note an enormous increase in performance and faster regeneration time:

Jan Jasper Wagner und Julian Authenried: „We tried out Basic Immune during and after the competition and could immediately identify constant and long-lasting energy, attention and just a general feeling of well-being, even after 6 days of hard work. Usually, right after the competition the body needs some time to rest where all the systems shut down, but with Basic Immune this process could be reconciled. Furthermore, Basic Immune is incredible easy to transport and to take in!
In my opinion, is this one of the great strengths of Basic Immune, as usually it needs a lot of discipline to force oneself to take in all the different supplements".

In our time and especially in our living area far away from the equator and additionally with our high stress levels, it is not possible to achieve the vitamin D3 levels necessary for our health by staying in the sun.
Even if the natural sunshine would be optimal, today we cannot do without the intake of vitamin D to protect ourselves from acute and chronic diseases and to guarantee optimal long-term prognosis for ceramic implants.

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Two Neglected Biologic Risk Factors in Bone Grafting and Implantology: High Low-Density Lipoprotein Cholesterol and Low Serum Vitamin D

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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.

Key Words: cholesterol, LDL cholesterol, vitamin D, failures, implants, bone grafts, infections, immune defense, osseointegration

INTRODUCTION

The search for a biological anomaly labeled as a risk factor before oral surgery is limited to disease states such as diabetes. However, it seems in recent years that cholesterol and vitamin D levels should be more systematically investigated. Good cholesterol (high-density lipoprotein [HDL]) and bad cholesterol (low-density lipoprotein [LDL]) need to be included in this investigation because both could have a negative effect on bone growth and osseointegration (high LDL or low HDL). Vitamin D is one the most important hormones involved in bone growth. In addition, vitamin D also plays a role in reducing the effects of inflammation and helps improve the body's natural immune reactions.

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DYSLIPIDEMIA

LDL cholesterol and bone metabolism

Cholesterol is transported in the plasma predominantly as cholesteryl esters associated with lipopro-

Case Report

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

Surg Lt Cdr G Bryce, Wg Cdr N MacBeth

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.

Case report
A 29-year-old soldier was referred to the Centre for Restorative Dentistry with a painful right mandibular first premolar (LR4) that had been fractured following head trauma relating to the explosion of an Improvised Explosive Device (IED). LR4 suffered a crown fracture that led to an irreversible pulpitis.

Associated injuries included: fractures to second, third and fourth lumbar vertebrae; left third to eighth ribs, left clavicle, left radius, left femur, and right medial malleolus. He also suffered a left pneumothorax and a minor traumatic brain injury. His right ankle had been fused as a component of his stabilisation treatment and the patient had spent approximately twelve months confined, predominantly indoors, within a rehabilitative facility. The patient was a non-smoker, did not drink alcohol and was motivated to maintaining good oral health.

The examination of the LR4 (Figures 1, 2) found prominent enamel crazings extending vertically on the tooth surface. The tooth gave normal responses to pulpal nerve and periodontal ligament tests. The radiographic examination (with a periapical radiograph and subsequent Computerized Tomography (CT) scan) found several fracture lines extending both horizontally and obliquely through the tooth (Figure 3). The LR4 was diagnosed as having a vertical root fracture and was not considered restorable.

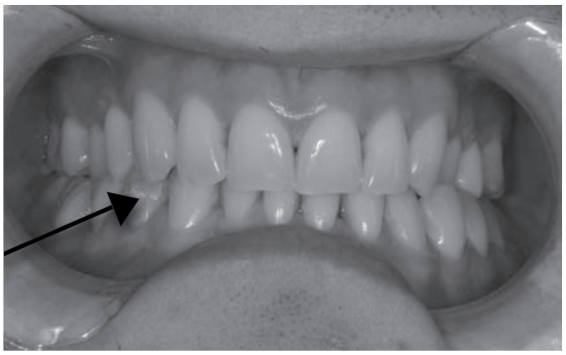

Figure1: Facial view of patient's dentition. LR4 marked with arrow.

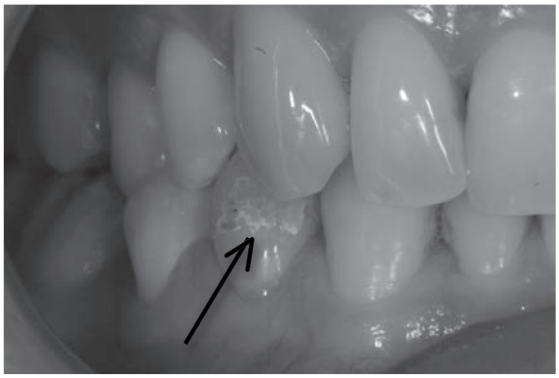

Figure 2: Pre-operative view of fractured tooth LR4.

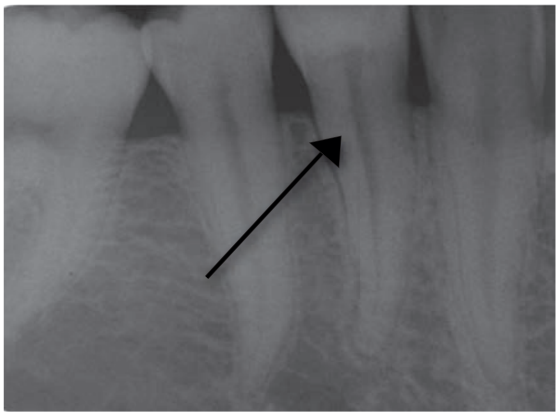

Figure 3: Periapical radiograph and section through CT with arrows indicating oblique fracture of root.

Following discussion and dental implant planning on NobelGuide® software, the patient opted to have the tooth extracted with definitive replacement using an implant-supported crown. All treatment was undertaken followed strict surgical protocols. The LR4 was extracted atraumatically in two fractured parts using periotomes. Curettage of the socket was undertaken, with the cortical plate perforated using a Nobel Biocare® precision drill. A tapered implant (Nobel Replace® RP 4.3x10) was positioned in the extraction site and torqued to achieve primary stability. Xenograft material (Bio-oss® collagen) was placed on the buccal aspect, prior to apposition of the flap using 6.0 Ethilon® non-resorbable sutures. A post-operative radiograph was taken (see figure 4) and the Tooth 44 space was provisionally restored using an immediate resin-bonded cantilever bridge (RBB).

The patient was reviewed five months post-operatively in order to undertake the second-stage surgery to expose the implant. In the interim period, osteopaenia of his fused right ankle had led to an underlying diagnosis of Vitamin D deficiency (<10nmol/L by tandem mass spectrometry)

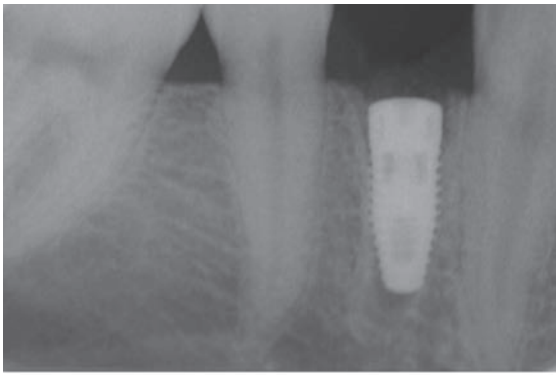

Figure 4: Post-operative radiograph of dental implant placement.

(1) and he had been prescribed oral Vitamin D supplements (Dekristol®). A flap was raised but, although no inflammatory tissue was visualized, the implant was found to be mobile and was removed. The examination of the extracted implant found there to be minimal bony deposition on the fixture and provided good visualisation of the incomplete osseointegration process (see figure 5). The RBB was repositioned and the failure of the implant was discussed with the patient. Following discussion about potential treatment options (including the placement of a further dental implant), the patient decided to accept the RBB as a longer-term restorative measure.

Figure 5: Explanted dental implant.

Vitamin D

The immediate placement of dental implants in sockets following tooth extractions has been shown to have a success rate that is high and similar to that of delayed placement (2, 3). Failure of dental implants to integrate adequately has been related to both general and local factors

General Factors	Local Factors
Systemic Medical Conditions e.g. - Diabetes-mellitus (poorly controlled) - Osteoporosis - Vitamin D deficiency	Site of implant placement 1. maxilla 2. Type IV (highly cancellous) Bone
Medical Therapy: 3. Radiotherapy 4. Chemotherapy	Bone augmentation
Smoking	Poor oral hygiene
Excessive alcohol consumption	Operator factors: Poor surgical technique, ineffective cooling of surgical bur
Malnutrition	

Table 1: General and local factors relating to dental implant failure.

(4) (Table 1). More recently, there have been investigations into the role that mineral and vitamin deficiencies (for example magnesium and vitamin D), may play in dental implant osseointegration (5-7).

Vitamin D is primarily manufactured in the skin, following exposure to solar Ultraviolet-B (UV-B) (wavelengths of 290-315 nm) irradiation. It can also be absorbed via the ingestion of vitamin D-rich foods (oily fish, egg yolks). The exposure of skin to UV-B irradiation initiates the C-photolysis of 7-dehydrocholesterol to previtamin D3 (8). The previtamin D3 undergoes two sequential hydroxylations, in the kidney and liver, prior to reaching its biologically active form, 1,25 dihydroxyvitamin D (1,25[OH]2D) (8).

1,25 (OH)2D is involved in the regulation of bone resorption, formation and mineralisation (8-10). 1,25 (OH)2D can exert an effect on the skeleton by direct interaction with osteoblasts and can also act indirectly, by influencing parathyroid hormone (PTH) production. These interactions, combined with the influence on the intestine to increase calcium and phosphate absorption, help regulate the homeostasis of both calcium and phosphate within the body.

Reduced levels of 1,25 (OH)2D can lead to impaired absorption of calcium and phosphorus from the small intestine (9-11) and so to levels that are deficient for the requirements of both skeletal and extra-skeletal health. In addition, reduced 1,25 (OH)2D encourages increased osteoclast activity, which can result in bone resorption and decreased bone mineral density. 1,25 (OH)2D deficiency may be age-related, but can also result from reduced exposure to UV-B light, fat malabsorption conditions and reduced intake of dietary vitamin D (9).

Although contrasting guidelines as to the cut-off values for vitamin D deficiency exist, it is generally agreed that 1,25 (OH)2D serum levels can be classified as sufficient (>50 ng/ml), inadequate (30-50nmol/L), or deficient (<30nmol/L) (1). The prevalence of vitamin D deficiency is higher than once suspected (9), with service personnel, especially those who serve as submariners, found to be at particular risk (12, 13). For hospital in-patients, the numbers affected by 1,25 (OH)2D deficiency can increase to between 70% and 100% (14). 1,25 (OH)2D deficiency is most commonly associated with childhood bone deformation conditions such as rickets, but may also be associated with bone pain, malignancies, autoimmune disorders, osteomalacia and increased risk of fracture within the adult population (15-17).

Clinical studies into the effects of vitamin D deficiency in adults have generally focused on the increased risk of osteoporosis, osteomalacia and fragility fracture within older populations (14). When studies have investigated osseointegration within osteoporotic patients, there have been conflicting results, with some groups finding impaired integration (18, 19) and others finding no difference (20). However, these studies have not assessed the vitamin D status of their groups and it is impossible to determine a direct correlation between vitamin D deficiency and impaired osseointegration. In-vivo rat models, used to test the effects of vitamin D deficiency on the osseointegration of titanium implants, found that significantly inferior osseointegration occurred when compared to rats with normal serum Vitamin D levels (6). However, currently, there have been very few studies examining the direct relationship of 1,25 (OH)2D deficiency to the success or failure of integration of dental implants.

Discussion

Vitamin D deficiency is more prevalent than previously thought, with some studies indicating that 70% to 100% of

in-patients may be deficient (21, 22). The patient in the case we present had undergone a twelve-month rehabilitation period that confined him indoors; this potentially offers an explanation for his low vitamin D serum level.

The failure of a dental implant to osseointegrate can be the result of a number of different systemic and local factors. General factors such as heavy smoking, diabetes mellitus and chemotherapy have been linked with implant failure. Local factors contributing to failure include: mismanagement of the surgical site; radiotherapy; failure to achieve primary stability; over-heating of the alveolar bone during placement; and the quality and quantity of alveolar bone (4).

In this case, aside from his physical injuries, the patient was an otherwise suitable candidate for implant placement. The implant fixture was placed using an optimal surgical technique into Type II bone (good density for osseointegration) that was free of infection, and a favourable outcome was expected. Although it is impossible to state that his vitamin D deficiency was the sole cause of the implant failure, it may have acted as a contributing factor.

In light of recent research investigating the prevalence of vitamin D deficiency within medical in-patients, at-risk individuals should have their vitamin D levels checked prior to dental implant placement. It is worth noting that 1,25(OH) 2D can be normal or even, in certain cases, elevated in patients who are vitamin D deficient (21). Chemiluminescence protein-binding assays or radioimmunoassay of serum 25(OH)D (the major circulating metabolite of vitamin D) should be employed to measure Vitamin D status (21, 22).

Patients with impaired Vitamin D levels can be managed in two ways: they can be exposed to UV-B rays (increasing the sub-cutaneous synthesis of vitamin D), or managed by dietary loading using supplements. The patient in the case we present was placed on a course of supplemental vitamin D (Dekristol®) tablets, and his serum vitamin D level was monitored until repeated normal values were obtained. Subsequent dental implant placement remains an option for the patient, should he choose to pursue this restorative route.

Conclusion

This case report identifies severe Vitamin D deficiency as a factor that may have contributed to the failure of a dental implant to osseointegrate successfully. Assessment of the Vitamin D status of patients who are long-term in-patients or undergoing prolonged rehabilitative care, is indicated prior to the surgical placement of dental implants.

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Systemic effectors of alveolar bone mass and implications in dental therapy

LYNDON F. COOPER

The relationship of systemic effectors of bone mass to periodontal health and edentulism has been the focus of several reviews (23, 33, 47). Systemic conditions that may provoke bone loss are currently regarded as one factor affecting an individual's susceptibility to periodontal disease. Are systemic determinants of bone mass important determinants of alveolar bone regeneration and osseointegration?

This chapter considers current concepts regarding the determinants of bone mass in the context of alveolar bone regeneration and implant therapies in dentistry. Bone mass represents the balance of bone formation and bone resorption. In health, these processes are coupled by complex interplay of local and systemic biochemical, as well as biomechanical control of osteoblast and osteoclast activity. Various diseases alter this balance. In osteoporosis, for example, bone resorption outweighs bone formation, and a net loss of bone is revealed by the reduction of bone mass and susceptibility to fracture. In states where there is high bone turnover (increased osteoclast activity), treatment by hormone replacement therapy (estrogens), bisphosphonates and more infrequently calcitonin aims to reduce the number of resorptive osteoclasts. In states where there is low turnover (deficient osteoblast activity), a number of experimental protocols, including fluoride and intermittent parathyroid hormone treatment, suggest that osteoblast activity can be enhanced to improve bone mass (25). General approaches to maintaining bone mass focus on proper nutrition and intake of calcium and vitamin D, maintenance of menses and weight-bearing exercise. Does pathologically reduced osteoblast activity or elevated osteoclast activity impact bone formation and maintenance in dental alveolar bone regeneration and implant procedures?

A new look at a previously defined problem

Bone mass is a central factor affecting dental implant treatment planning and prognostication (Fig. 1). In situations where thin cortical bone layer surrounds low density trabecular bone, implant success is difficult to assure. This has been attributed to the inability of installation procedures to assure primary

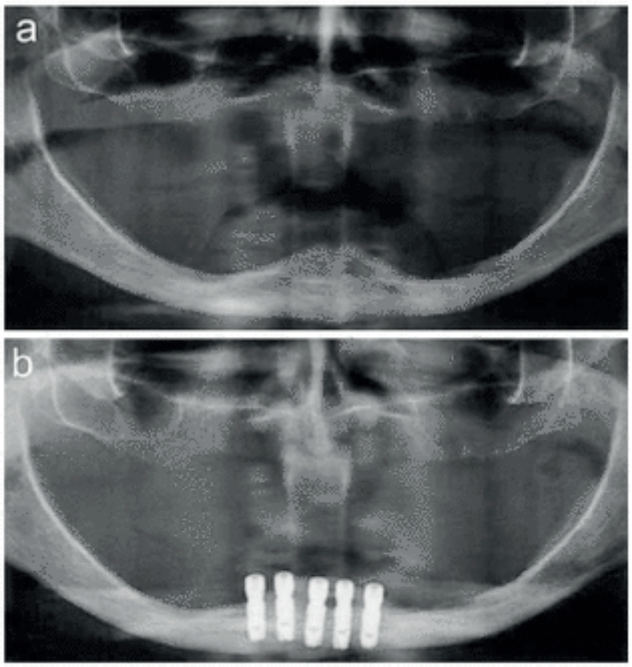

Fig. 1. Successful osseointegration may be beneficial to osteoporotic patients. a. The severely resorbed maindible is well suited for endosseous implant placement. b. Although attempts to achieve osseointegration in poor quality bone associated with osteoporosis may require careful consideration of all factors affecting outcomes, the dense bone of the anterior mandible provides favorable local advantages that contribute to reported high success rates that can be suggested for a vast majority of individuals.

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

Ulrike Schulze-Späte Thomas Dietrich Christina Wu Kun Wang Hatice Hasturk Serge Dibart

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.

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Review

Nonclassical Vitamin D Actions

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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).

Keywords: vitamin D; cancer; cardiovascular; mortality; ultraviolet B radiation; diet

1. Introduction

Vitamin D has long been known for its effects on calcium and bone metabolism. Severe vitamin D deficiency causes a lack of bone mineralization, which manifests as rickets in children and osteomalacia in adults. There is also accumulating evidence that insufficient vitamin D status contributes to the bone disease osteoporosis. Adequate vitamin D supplementation can reduce the risk of osteoporotic fractures by approximately 20% [1]. However, it is now becoming increasingly clear that vitamin D has a much broader range of actions in the human body than believed before. Its physiological effects are not only limited to bone. Various other chronic diseases that are frequently observed in modern societies are probably at least in part caused by inadequate vitamin D supply. The present article describes the potential clinical relevance of nonclassical vitamin D actions. It refers to randomized, controlled clinical trials (RCTs) or meta-analyses of RCTs whenever it is possible. Results from non-RCTs are also presented in fields where no RCTs are available yet. Although the article primarily refers to the literature of the last four years, some useful older data are also included. Note that this article should provide evidence for nonclassical vitamin D actions. It is not a systemic review of the available literature.

2. Vitamin D Metabolism

Vitamin D is unique among vitamins in that humans can produce it themselves in their skin provided they have sufficient exposure to ultraviolet radiation B (290–315 nm). Vitamin D is also found naturally in small amounts in milk and eggs, and in relatively large amounts in fatty fish such as herring and mackerel. Nevertheless, skin synthesis of vitamin D usually contributes 80% to 90% to vitamin D supply in free-living persons. This assumption is based on the fact that in healthy young adults circulating 25(OH)D concentrations usually lie between 30–80 nmol/L [2], dietary vitamin D intake is usually below 5 μg daily [3], and 1 μg vitamin D increases circulating 25(OH)D concentrations by approximately 1–3 nmol/L [4,5]. The exact amount of vitamin D production in human skin depends on the geographic latitude, season, time of day, as well as on the weather conditions (cloudiness), amount of air pollution and surface reflection. In addition, clothing habits, lifestyle, and workplace (e.g., indoor *versus* outdoor), sunscreen use, and sun avoidance practices have a strong impact on vitamin D synthesis. It is also noteworthy that skin type determines a person's effectiveness in producing vitamin D. The darker the skin is pigmented, the more ultraviolet radiation is absorbed by melanin and the less vitamin D is produced [6,7]. Migrant populations and their descendants often have skin types that do not fit to the ambient ultraviolet environment. To achieve a similar effect on vitamin D production compared to a fair-skinned person, the exposure time to ultraviolet radiation in a dark-skinned person living in Europe or North America must be up to six times longer [8].

Vitamin D can be produced very effectively by humans when ultraviolet radiation B (UVB) from sunlight or artificial sources reaches skin cells. A whole body exposure to UVB radiation of 15 to 20 minutes daily is able to produce up to 250 μg vitamin D (10,000 IU) [9,10]. Once in the circulation, vitamin D is converted by a hepatic hydroxylase into 25-hyroxyvitamin D (25(OH)D). The circulating 25(OH)D level is an indicator of vitamin D status. This level reflects both, ultraviolet exposure and dietary vitamin D intake. As needed, 25(OH)D is converted in the kidney to its active hormonal form

1,25-dihydroxyvitamin D_3 (calcitriol) in a process which is usually tightly controlled by parathyroid hormone. In spite of this, inadequate vitamin D supply lowers the circulating level of this important hormone [11]. Circulating calcitriol is also adversely affected by a reduced number of viable nephrons, high serum concentrations of fibroblast growth factor-23, and high levels of inflammatory cytokines [12,13].

If vitamin D production or intake is low, vitamin D insufficiency or even deficiency is the result. Parathyroid hormone levels start rising at 25(OH)D cutoff levels of 75 nmol/l or lower (Table 1). The following cut-offs are used for different stages of vitamin D inadequacy: <25 nmol/L for deficiency (divide by 2.496 to convert into ng/ml), 25-49.9 nmol/L for insufficiency, 50-74.9 nmol/L for hypovitaminosis/suboptimal supply. Although there is still some debate on how to classify vitamin D status, the vast majority of vitamin D researchers agree that 25(OH)D levels below 50 nmol/l are insufficient.

Cellular vitamin D actions are mediated by a membrane-bound and a cytosolic vitamin D receptor (VDR). The VDR is nearly ubiquitously expressed, and almost all cells respond to vitamin D exposure; about 3% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system [14]. Calcitriol is also produced by local 1α-hydroxylases from its precursor 25(OH)D in various extra-renal cells, among them vascular smooth muscle cells, colonocytes, and immune cells such as monocytes, dendritic cells (DCs), and B-lymphocytes [15,16]. Here, calcitriol plays an important paracrine and autocrine role. Uptake of 25(OH)D into extra-renal tissues is reduced in case of low circulating calcitriol levels, e.g., in patients with renal insufficiency [17].

Table 1. Vitamin D status classified according to circulating 25-hydroxyvitamin D concentrations [according to reference 18, with modifications according to reference 6].

Stage	25-hydroxyvitamin D (nmol/l)	Clinical/biochemical alterations
Deficiency	<25	Rickets, osteomalacia, myopathy, calcium malabsorption, severe hyperparathyroidism, low calcitriol concentrations, impaired immune and cardiac function?, death
Insufficiency	25 to 49.9	Reduced bone mineral density, impaired muscle function, low intestinal calcium absorption rates, elevated PTH levels, slightly reduced calcitriol levels
Hypovitaminosis D /suboptimal supply	50 to 74.9	Low bodily stores of vitamin D, slightly elevated PTH levels
Adequacy	75 to 372	No disturbances of vitamin D-dependent functions
Intoxication	>372	Intestinal calcium hyperabsorption, hypercalcemia, soft tissue calcification, death

Abbreviation: PTH, parathyroid hormone

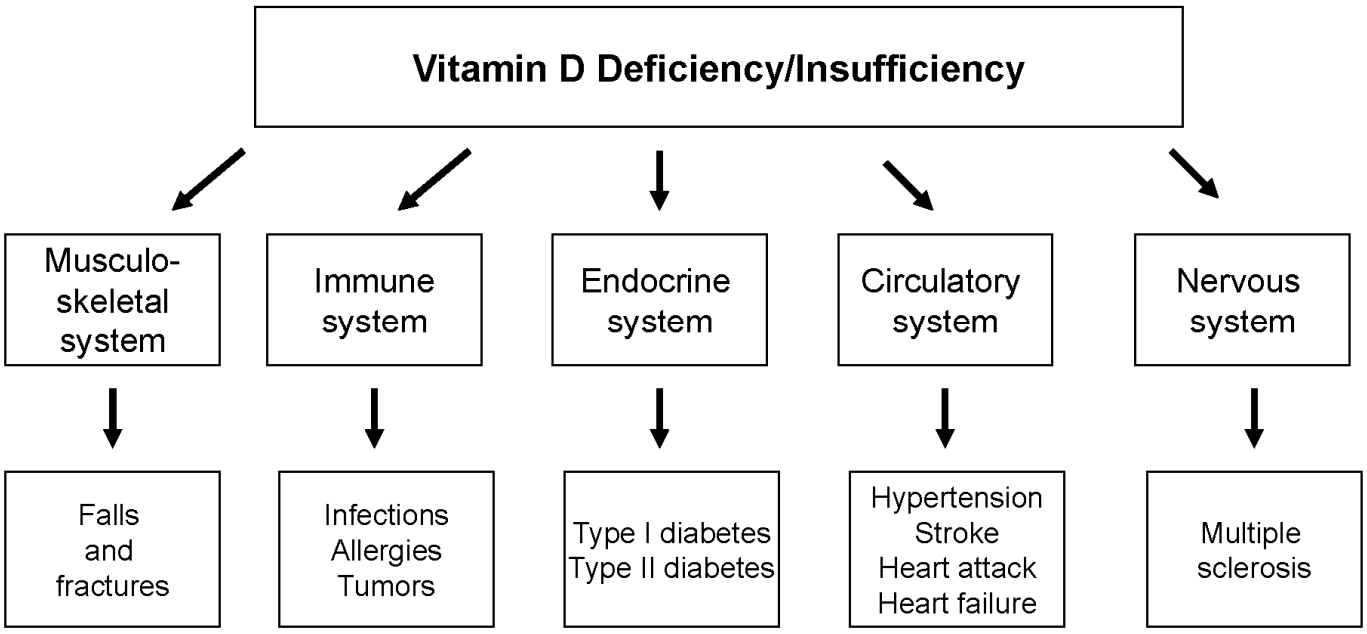
3. Worldwide Vitamin D Status

A recent review [19] summarized human vitamin D status according to region of the world. Six regions of the world were reviewed - Asia, Europe, Middle East and Africa, Latin America, North America, and Oceania–through a survey of published literature. Based on the articles referred to in this review, it was concluded that insufficient vitamin D status is prevalent in every of the six regions studied. Depending on the region, between 50% and more than 90% of people had 25(OH)D concentrations below 50 nmol/L. Low vitamin D status is most common in regions such as South Asia and the Middle East. Data demonstrate that insufficient vitamin D status is widespread and is re-emerging as a major health problem globally. Urbanization in combination with modern and also traditional lifestyles such as indoor working, indoor leisure time activities, and traditional Islamic clothing, and in combination with the aging process (institutionalization) is an important risk factor for vitamin D insufficiency/deficiency in large parts of the adult population. In highly urbanized areas, individual daily sun exposure is usually too low to achieve a 25(OH)D level of 75 nmol/L. Due to the fact that the vast majority of foods naturally contain no or only modest amounts of vitamin D, diet is not able to close the gap in vitamin D supply. It is noteworthy that urbanization and industrialization has long been known as a major cause of childhood rickets in western countries [7]. Rickets is now on the increase in many developing countries, and is also re-emerging as an important health problem in countries with strong sun avoidance policies and cultures requiring modest dress.

4. Diseases Associated with Nonclassical Vitamin D Actions

Figure 1 illustrates that vitamin D deficiency/insufficiency can result in impaired musculo-skeletal function, impaired immune function, cardiac and vascular impairment and impaired nervous function. As outlined in Figure 1, the development of various chronic diseases may be the consequence.

Figure 1. Suggested association of vitamin D deficiency/insufficiency with chronic diseases.



4.1. Vitamin D and Muscle Strengthening

Vitamin D deficiency causes reduced aktomyosin content of myofibrils, low calcium content of mitochondria, reduced calcium uptake into the sarcoplasmic reticulum, and low serum levels of muscle enzymes [3]. The importance of vitamin D-repletion for adequate muscle function was underscored in a recent study in institutionalized people ≥60 years of age with insufficient vitamin D status [20]: This RCT demonstrated that six-month supplementation (December to May) of oral vitamin D (3,750 μg once a month during the first two months, followed by 2,250 μg once a month for the last four months) was able to improve lower limb muscle strength by 16–24%. Data support results of a recently performed meta-analysis of randomized controlled trials (RCTs), indicating that daily doses of 17.5 to 20 μg supplemental vitamin D are able to prevent falls in elderly adults [21]. The relative risk of falls was reduced by approximately 20% if the achieved serum 25(OH)D concentrations is 60 nmol/l or more. In contrast to "high dose" supplemental vitamin D, low dose daily supplemental vitamin D (5 to 15 μg) is not able to prevent falls. Thus, doses of supplemental vitamin D of less than 17.5 μg or serum 25-hydroxyvitamin D concentrations of less than 60 nmol/L may not reduce the risk of falling among older individuals. It is noteworthy that in elderly people the risk of falling predicts the risk of developing osteoporotic fractures. Therefore, the effects of vitamin D on muscle strength may contribute to the preventive effect of vitamin D on osteoporotic fractures. There is also evidence that adequate vitamin D supply is important for muscle function in children. Already more than 50 years ago, Ronge [22] has demonstrated that children who have hands and face exposed to UVB radiation in their classroom at school for 3–5 hours during wintertime show better endurance performance compared to a control group without UVB exposure. Endurance performance was assessed by bicycle ergometry. In that study, a similar positive effect on endurance performance was seen in children who received a single vitamin D bolus of 6.25 mg vitamin D in February.

4.2. Infections

There is mounting evidence for a pivotal role of vitamin D in the immune system. Calcitriol is able to induce the differentiation of monocytes into macrophages. In addition, calcitriol increases the activity of macrophages and facilitates their cytotoxic activity. Macrophages represent the first unspecific defence line of the immune system. It is well known that the prevalence of infections such as pneumonia is high in infants with rickets [3]. The use of vitamin D (or cod liver oil) as a treatment of infections have been practised for over 150 years. As early as 1903, Niels Finsen was awarded the Nobel Prize for Medicine and Physiology for his theory to cure Lupus vulgaris (skin-tuberculosis) using phototherapy. In 2007, Schauber *et al.* [23] published data demonstrating that vitamin D is able to stimulate synthesis of the anti-microbial peptide cathelicidin in human skin cells to enhance innate immunity. A meta-analysis of observational studies has demonstrated that patients with tuberculosis have lower circulating 25(OH)D concentrations compared to healthy controls [24]. Ecological studies also support a preventive role of vitamin D in influenza: the seasonal and latitudinal distribution of outbreaks of influenza A in the world in 1967–1975, and weekly consultation rates for illnesses diagnosed clinically as influenza or influenza-like in England 1968-1970 were inversely associated with solar UVB radiation [25]. Very recently, it has been demonstrated in an RCT that supplementation with 30 μg vitamin D daily reduces the risk of wintertime influenza A in Japanese

nursery school children [26]. Some epidemiological data support the assumption that vitamin D may reduce the susceptibility to respiratory tract infections [27,28]. In addition, vitamin D users of the RECORD trial [29], an RCT with approximately 3,500 participants who received 20 μg vitamin D or placebo, reported a lower tendency for infections and antibiotic use in March compared to vitamin D nonusers. In another RCT in individuals with baseline circulating concentrations below 50 nmol/L, supplementation with 20 μg or 50 μg vitamin D daily for three years significantly reduced upper respiratory tract infections compared to placebo [30]. In contrast, a daily vitamin D supplement of 50 μg for 12 weeks did not prevent upper respiratory tract infections in individuals with baseline circulating 25(OH)D concentrations above 50 nmol/L [31]. Consequently, there is currently insufficient data to conclusively state that vitamin D supplementation could result in lowered infection [32]. One factor that has to be considered in future studies is baseline 25(OH)D concentration. In addition, the relation between vitamin D supplementation, local calcitriol, and local cathelicidin production has to be investigated more detailed. Interestingly, oral intake of activated vitamin D in rickets patients for four weeks significantly increased human cathelicidin expression in neutrophils compared to age-matched healthy controls without administration of activated vitamin D [33], indicating a critical role of adequate calcitriol availability for regulation of the innate immune response.

4.3. Allergies

Activation of the adaptive immune system is complex. Generally, it is of importance that specific pathways of the specific immune system are adequately suppressed in order to avoid autoimmune diseases or allergic reactions. Regulatory T cells are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells. A strong Th2 predominance leads to pathologic conditions such as overproduction of IgE and allergic diseases, whereas a strong Th1 predominance leads to autoimmunity and severe allograft rejection. Of clinical importance is the fact that DCs may induce naïve T cells in an immunogenetic direction but also in a tolerogenic direction, depending on the state of their maturation and their cell surface receptor. Tolerogenic DCs generally are semimature. There is accumulating evidence that vitamin D modulates the adaptive immune system [16]. Calcitriol appears to generate tolerogenic DCs *in vivo*, as demonstrated in models of transplantation and autoimmune disease. DCs appear to be key targets of calcitriol. Calcitriol arrest the differentiation and maturation of DCs, maintaining them in an immature state. Calcitriol is able to enhance the secretion by DCs of the anti-inflammatory and anti-allergic cytokine IL-10.

At present, the vitamin D hypothesis of allergies takes two forms: Some argue that vitamin D deficiency may cause allergic reactions whereas others argue that vitamin D excess leads to an increased allergy risk. Wjst is a representative of the latter hypothesis. He argues that the increase in allergies in Bavaria after 1960 coincided with vitamin D supplementation intervention programs to prevent rickets in childhood. Moreover, both, adherence to these programs and prevalence of allergies in children seem to be lower in farming communities in Bavaria [34]. The farm protection is observed mainly during the first year of life [35], when vitamin D supplementation is also recommended. Wjst's hypothesis is based on the assumption that vitamin D may lead to Th2 predominance and increased IgE production. Generally, his hypothesis is supported by findings that children whose mothers'

concentration of 25(OH)-vitamin D in late pregnancy was >75 nmol/l had an increased risk of eczema on examination at nine months and asthma at age nine years compared to children whose mothers' concentration was <30 nmol/L [36]. In addition, vitamin D supplementation during infancy was associated with a higher allergy risk [37,38], and the prevalence of allergic rhinitis increased across quartile groups of 25(OH)D serum levels in adults of NHANES III [39].

It is, however, noteworthy that several other epidemiological studies support the vitamin D deficiency hypothesis of allergic reactions [40-44]. Moreover, administration of calcitriol to blood cells of healthy persons and steroid-resistant asthmatic patients enhanced subsequent responsiveness to dexamethasone for induction of IL-10 [43]. Very few intervention trials are available so far. In a small, randomized, double-blind, placebo-controlled trial, vitamin D_2 supplementation (25 μg/day) significantly improved skin symptoms in children with winter-related atopic dermatitis [45]. In a study in heart failure patients, vitamin D_3 supplementation (50 μg/day) was able to increase blood levels of the anti-allergic cytokine IL-10 [46]. However, the effect on allergic reactions has not been elucidated in that earlier investigation.

In total, it cannot be ruled out that vitamin D deficiency as well as vitamin D excess may increase the risk of allergic reactions. This assumption is supported by recent findings. Hyppönen *et al.* [47] observed a biphasic effect of vitamin D with both low and high 25(OH)D levels associated with elevated IgE concentrations in participants of the 1958 British birth cohort. Compared with the reference group with the lowest IgE concentrations [25(OH)D 100–125 nmol/L], adjusted IgE concentrations were 29% higher for participants with the 25(OH)D < 25 nmol/L, and 56% higher for participants with 25(OH)D > 135 nmol/L.

4.4. Cancer

Since vitamin D is a key regulator of various cellular metabolic pathways, it is important for cellular maturation, differentiation, and apoptosis [3]. In 2008, the WHO published a report from the International Agency for Research on cancer [48] that came to the conclusion that there is (i) consistent epidemiological evidence for an inverse association between 25(OH)D and colorectal cancer and colorectal adenomas, (ii) suggested epidemiological evidence for an inverse association between 25(OH)D and breast cancer, (iii) insufficient evidence for an inverse association between 25(OH)D and other types of cancer, and (iv) the need for new randomized controlled trials (RCTs). One such RCT has already been published [49]: In a four-year, population-based study, where the primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence, 1179 community-dwelling women were randomly assigned to receive 1500 mg supplemental calcium/d alone (Ca-only), supplemental calcium plus 27.5 μg vitamin D/d (Ca + D), or placebo. Cancer incidence was 60–77% lower in the Ca + D women and 43% lower in the Ca-only group than in the placebo control subjects ($P < 0.03$). Gorham *et al.* [50] have estimated that in North America, Europe, and East Asia approximately 32% of colon cancer and approximately 26% of breast cancer can be prevented with 50 μg vitamin D daily and 3–10 min daily of noon sunlight seasonality, when weather permits. Garland *et al.* [51] estimated that raising the minimum year-around serum 25(OH)D level to 100–150 nmol/L would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada. Such intakes also are expected to reduce case-fatality rates of patients who have

breast, colorectal, or prostate cancer by half. Nevertheless, there is also some concern that cancer risk is not only enhanced in individuals with deficient/insufficient vitamin D status, but also if 25(OH)D concentrations rise above 80 nmol/L [52], a concentration several vitamin D researchers consider adequate. However, this increase in cancer risk has only been observed in observational studies after multivariable adjustments have been made for confounding factors. This kind of exploratory data analysis has been criticized by some researchers [53].

4.5. Diabetes Mellitus

In vitro and *in vivo* studies suggest that vitamin D can prevent pancreatic beta-cell destruction and reduces the incidence of autoimmune diabetes. This may at least in part be due to a suppression of proinflammatory cytokines such as tumor necrosis factor (TNF)-α. Recently, the relationship between UVB irradiance, the primary source of circulating vitamin D in humans, and age-standardized incidence rates of type 1 diabetes mellitus in children aged <14 years, was analyzed according to 51 regions of the world [54]. Incidence rates were generally higher at higher latitudes and were inversely associated with UVB irradiance. As early as 2001, Hyppönen *et al.* [55] has demonstrated in a birth cohort study that vitamin D supplementation was associated with a decreased frequency of type 1 diabetes. In contrast, children suspected of having rickets during the first year of life had a three times higher relative risk compared with those without such a suspicion. Meanwhile, a meta-analysis of four case-control studies has shown that the risk of type 1 diabetes is reduced by 29% in infants who are supplemented with vitamin D compared to those who are not supplemented [56]. There is also some evidence of a dose-response effect, with those using higher amounts of vitamin D being at lower risk of developing type 1 diabetes. Finally, timing of supplementation might also be important for the subsequent development of type 1 diabetes. In a recent RCT [57], the majority of patients with latent autoimmune diabetes in adults increased their concentrations of plasma C–peptide levels in fasting state after 1 year of treatment with activated vitamin D, whereas only a minority of patients treated with insulin alone maintained stable fasting C-peptide levels.

In 2007, Pittas *et al.* [58] conducted a systemic review and meta-analysis for observational studies and clinical trials in adults with outcomes related to glucose homeostasis in type 2 diabetes mellitus. Observational studies show a relatively consistent association between low vitamin D status and prevalent type 2 diabetes, with an odds ratio of 0.36 among non-Blacks for highest *versus* lowest 25-hydroxyvitamin D. Evidence from RCTs with vitamin D and/or calcium supplementation suggests that combined vitamin D and calcium supplementation may have a role in the prevention of type 2 diabetes only in populations at high risk (*i.e,.* glucose intolerance). Whereas vitamin D supplementation did not improve glycemic control in diabetic subjects with normal serum 25(OH)D levels [59], administration of 100 μg vitamin D3 improved insulin sensitivity in vitamin D deficient and insulin resistant South Asian women [60]. Insulin resistance was most improved when endpoint serum 25(OH)D reached ≥ 80 nmol/L. Optimal vitamin D concentrations for reducing insulin resistance were shown to be 80–119 nmol/L.

4.6. Cardiovascular Disease

Globally, cardiovascular disease (CVD) is the number one cause of death. In 2005, CVD was responsible for approximately 30% of deaths worldwide. CVD includes various illnesses such as coronary heart disease (CHD), peripheral arterial disease, cerebrovascular disease such as stroke, and congestive heart failure. There is accumulating evidence that the vitamin D hormone calcitriol exerts important physiological effects in cardiomyocytes, vascular smooth muscle cells, and the vascular endothelium. The mechanisms have been reviewed in detail elsewhere [61]. Hypertension is a key risk factor for CVD. A recently published systematic review and meta-analysis came to the conclusion that vitamin D produces a fall in systolic blood pressure of −6.18 mm Hg and a nonsignificant fall in diastolic blood pressure of −2.56 mm Hg in hypertensive patients. No reduction in blood pressure is seen in studies examining patients who are normotensive at baseline [62]. Since these studies had small sample sizes, future studies should investigate their generalizability.

Several large prospective observational or cohort studies have demonstrated that a higher vitamin D status is associated with approximately 50% lower cardiovascular morbidity and mortality risk compared with low vitamin D status (Table 2).

Table 2. Evidence for association of circulating 25-hydroxyvitam in D level with cardiovascular morbidity and mortality.

Study	Design	Number of individuals	Comparator	Odds/hazard ratio or Relative risk (95% CI)
Fatal stroke				
Pilz *et al.* 2009 [63]	Prospective cohort study with coronary angiography	3258	Per z value of 25(OH)D	OR 0.58 (0.43 to 0.78)
Cardiovascular morbidity				
Wang *et al.* 2008 [64]	Prospective observational study	1739	25(OH)D > 37.5 nmol/L *versus* < 25 nmol/L	HR 0.55 (0.32 to 0.97)
Myocardial infarction				
Giovannucci *et al.* 2008 [65]	Nested case control study	1354	25(OH)D > 75 nmol/L *versus* < 37.5 nmol/L	RR 0.48 (0.28 to 0.81)
Cardiovascular mortality				
Dobnig *et al.* 2008 [66]	Prospective cohort study with coronary angiography	3258	Median 25(OH)D 70 nmol/L *versus* 19 nmol/L	HR 0.45 (0.32 to 0.64)
Pilz *et al.* 2009 [67]	Prospective observational study in individuals 50-75 years	614	Three highest *versus* lowest 25 (OH)D quartile	HR 0.19 (0.07 to 0.50)
Ginde *et al.* 2009 [68]	Prospective observational study in individuals > 65 years.	3408	25(OH)D > 100 nmol/L *versus* < 25 nmol/L	HR 0.42 (0.21 to 0.86)

The Women's Health Initiative (WHI) calcium/vitamin D (CaD) trial could however not demonstrate a reduction in cardiovascular mortality by daily supplementation of 1,000 mg calcium and 10 μg vitamin D [69]. Meanwhile it is clear that an amount of 10 μg vitamin D is far too low to result in a meaningful increase in serum 25(OH)D levels (see before) and that a daily calcium supplement of 1,000 mg increases the risk for cardiovascular events in healthy older women. Both, the supplemental calcium in the vitamin D arm of the WHI study and the low amount of vitamin D might have countermanded its cardiovascular benefits. In line with this assumption, a recent meta-analysis of seven randomized trials showed a slight but statistically nonsignificant reduction in CVD risk (relative risk: 0,90; 95% CI: 0.77 to 1.05) with vitamin D supplementation at moderate to high doses (approximately 25μg/d) but not with calcium supplementation (relative risk: 1,14; 95% CI: 0.92 to 1.41) or a combination of vitamin D and calcium supplementation (relative risk: 1.04; 95% CI: 0.92 to 1.18) [70].

In line with a potential beneficial effect of vitamin D on CVD risk, a daily vitamin D supplement of 83 μg could improve some traditional and nontraditional cardiovascular risk markers in healthy overweight and obese subjects with mean 25(OH)D concentrations of 30 nmol/L who attended a weight-reduction program [71].

4.7. Multiple Sclerosis

Multiple sclerosis (MS) is a demyellinating disease of the central nervous system that is debilitating and can be fatal. Manifestation of the disease is typically between the age of 20 and 40. In Europe and North America, regions with higher UVB radiation have low rates of MS and vice versa [3]. In Israel, MS prevalence depends on the country of origin. The prevalence is high in people who were born in a country with low UVB irradiance [72], indicating that vitamin D status during the period of early life is of importance for MS susceptibility. MS disease activity shows inverse fluctuations according to season and vitamin D status [73]. In a prospective, nested case-control study among more than seven million US military personnel [74], MS prevalence was lower in those people who had circulating 25-hydroxyvitamin D concentrations between 100 and 150 nmol/L compared with those who had 25-hydroxyvitamin D concentrations below 63 nmol/L. However, this association was only seen in Whites and not in Blacks, indicating that genetic factors play an important role in the pathogenesis of MS. Therefore, the recent finding is of importance that expression of the MS-associated MHC class II allele HLA-DRB1*1501 is regulated by Vitamin D [75].

5. Mortality

As mentioned before, vitamin D status is an important independent predictor of CVD and specific types of cancer. In addition, vitamin D status predicts CVD and cancer mortality. Both, CVD and cancer are the most important causes of mortality in developed countries. In 2007, Autier and Gandini [76] published a meta-analysis of randomized controlled trials (RCTs) on vitamin D and mortality that were not primarily designed to assess mortality. The authors found out that in middle-aged and elderly patients with low serum concentrations of 25-hydroxyvitamin D (25(OH)D) vitamin D supplementation was linked to lower all-cause mortality compared to no vitamin D supplementation.

Daily dose of vitamin D ranged between 10 μg and 50 μg. Risk reduction was 7% during a mean follow-up of 5.7 years.

Based on the aforementioned meta-analysis, several large prospective cohort studies were recently published on all-cause mortality and vitamin D status (Table 3). They demonstrate a consistent increase in mortality risk in patients with insufficient or deficient 25(OH)D concentrations. However, low 25(OH)D was not an independent predictor for mortality in patients with advanced disease [77,78]. One may speculate that in this case, vitamin D supplementation is unable to reverse the already existing severe pathophysiologic derangements.

Table 3. Evidence for association of circulating 25-hydroxyvitamin D level or vitamin D supplementation with all-cause mortality.

Study	Design	Number of individuals	Comparator	Hazard ratio or relative risk (95% CI)
Autier and Gandini, 2007 [76]	Meta-analysis of 18 vitamin D supplementation studies	57,311	Supplemented *versus* unsupplemented	RR 0.93 (0.87 to 0.99)
Dobnig *et al.* 2008 [66]	Prospective cohort study with coronary angiography	3,258	Median 25(OH)D 70 nmol/L *versus* 19 nmol/L	HR 0.48 (0.37 to 0.63)
Kuroda *et al.* 2009 [77]	Prospective observational study in postmenopausal women	1,232	≥ 50 nmol/L *versus* < 50 nmol/L	HR 0.46 (0.27 to 0.79)
Ng *et al.* 2008 [78]	Prospective cohort study in patients with colorectal cancer	304	Mean 41 nmol/L *versus* 100 nmol/L	HR 0.52 (0.29 to 0.94)
Ginde *et al.* 2009 [68]	Prospective observational study in individuals > 65 years.	3,408	25(OH)D > 100 nmol/L *versus* < 25 nmol/L	HR 0.55 (0.34to 0.88)
Pilz *et al.* 2009 [67]	Prospective observational study In individuals 50-75 years	614	Three highest quartiles *versus* lowest quartile	HR 0.51 (0.28 to 0.93)

6. Conclusions

In 2003, a review article had summarized the association of insufficient vitamin D status with various diseases such as myopathy, CVD, cancer, diabetes mellitus, MS, and infections [8]. Meanwhile, evidence has accumulated that vitamin D may indeed play an important role in the etiology of many of these diseases. Meta-analyses of RCTs demonstrate that vitamin D improves muscle function and seems to reduce blood pressure in hypertensive patients. In addition, some RCTs demonstrate that vitamin D reduces cancer incidence, and improves glucose homeostasis in patients with type 2 diabetes and cardiovascular risk markers in overweight people [49,60,71]. The most exiting result is however the fact that vitamin D may reduce mortality rate. This latter finding fits well together with the fact that severe deficiency of several other vitamins such as retinol, thiamine, niacin, and ascorbic acid is also associated with enhanced mortality. Nevertheless, additional large RCTs are needed to confirm whether or not vitamin D is able prolong survival in individuals with inadequate vitamin D status. In this context, the effect of vitamin D in deficient and insufficient individuals should be investigated separately.

Some aforementioned beneficial data on glucose homeostasis and cardiovascular risk markers were not confirmed by recent RCTs [59,81]. All these RCTs performed so far were relative small in sample

seize [59,60,71,81]. In addition, individual medication and baseline circulating 25(OH)D concentrations may have influenced study results. Therefore, additional research is necessary to clarify whether or not vitamin D supplementation is indeed effective in secondary prevention and also in tertiary prevention of chronic diseases. But we should be aware of the fact that many chronic diseases are of multi-factorial origin. Vitamin D is certainly only one factor among others. In addition, there may be individual differences with respect to the metabolic pathways that are disturbed in vitamin D deficient persons. Therefore, we should not be too enthusiastic that future RCTs will show clear beneficial vitamin D effects. For example, the meta-analysis by Autier and Gandini was based on more than 55,000 individuals. None of the single studies included in this analysis showed a significant vitamin D effect on mortality, indicating that huge sample seizes are probably needed to demonstrate a clear vitamin D effect. Even so, the consequences on a population scale may be important because of the large number of people who are affected.

The effect of vitamin D on MS, type 1 diabetes, infections, and allergies is less clear at present. Although newborns usually receive vitamin D supplements for preventing rickets, possible adverse effects of deficient vitamin D concentrations during fetal development such as increased susceptibility for type I diabetes and MS have to be considered as well. It is noteworthy that many women of childbearing age worldwide are vitamin D insufficient or even deficient [19,82]. With respect to MS, type 1 diabetes, and allergies, more birth cohort studies are needed.

Despite some uncertainties with respect to vitamin D and health, there is general agreement that currently a high percentage of people worldwide have low vitamin D status [19,83]. The recommended daily vitamin D intake of 5–15 μg is too low to achieve an adequate vitamin D status in people with only modest UVB exposure. Generally, treating vitamin D deficiency is easy to perform, safe, and inexpensive. Sources of vitamin D could include a combination of food fortification, supplements, and natural and artificial UV-B irradiation, if properly acquired. It has been calculated that 1 μg vitamin D increases circulating 25(OH)D levels by approximately 1 nmol/L [4]. Thus, a daily intake of approximately 50 μg vitamin D would be necessary for increasing the circulating 25(OH)D level from 25 nmol/L to 75 nmol/L. In order to achieve a 25(OH)D concentration above 75 nmol/L in almost all individuals of a group with mean baseline 25(OH)D concentrations of 38 nmol/L, daily supplementation with up to 100 μg vitamin D is necessary [5]. In otherwise healthy adults, the risk of vitamin D intoxication is extremely rare [3,84]. Vitamin D intoxications such as hypercalcemia do not occur until oral vitamin D intake and serum 25(OH)D concentrations exceed 250 μg/day (approximately 3–5 μg/kg body weight) [84] and 372 nmol/L [6], respectively. A daily amount of up to 250 μg vitamin D is similar to the amount that is produced by daily whole body exposure to UVB radiation [10].

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