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Review Article

May Vitamin D Intake be a Risk Factor for Peri-Implant Bone Loss? A Critical Review

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Abstract

Vitamin D has been shown to be of importance in bone mineral homeostasis. However the exact role of 1.25-$(OH)_2D_3$ in osteogenesis still needs to be fully understood.

It is very well demonstrated by epidemiological studies in adults and children that vitamin D deficiency is associated with an increased risk of infections. Endogenous precursors of vitamin D are UVB-unstable and accordingly inactivated before entering the circulation thus preventing an 'endogenous overdose' during prolonged solar exposure. On the opposite cholecalciferol obtained from supplements is not limited by these physiologic feedback mechanisms thus resulting in elevated circulating levels of 25-OH-D_3 in both young and older adults. Furthermore *in vitro* studies have demonstrated that the numbers of osteoclasts formed and their resorption activity is enhanced by the addition of 1.25-$(OH)_2D_3$ thus resulting in a state where bone turnover is unbalanced towards an increased osteoclastic activity. A role for oral vitamin D_3 precursors in conferring adverse effects on bone turnover in an inflammatory prosthetic joint space and maybe a genetic susceptibility can explain part of the osteolitic activity. This patological process may serve also as a novel model to identify patients at risk of peri-implant bone loss related to unbalanced levels of 1.25-$(OH)_2D_3$.

Keywords: *Peri-Implant Bone Loss; Peri-Implantitis; Periimplantitis; Mucositis; Peri-Implant Mucosa; Bone Loss*

Introduction

Vitamin D has been shown to be of importance in bone mineral homeostasis and its active form, 1α,25-dihydroxyvitamin D_3 (1.25-$(OH)_2D_3$), may promote new bone formation [1-3]. In fact, it increases plasma concentrations of calcium and phosphate by regulating their intestinal adsorption [4]. However the exact role of 1.25-$(OH)_2D_3$ in osteogenesis still needs to be fully understood [5,6].

Low concentrations of vitamin D seem to be associated with risk of infections as demonstrated by multiple epidemiological studies in adults and children, in particular regarding the respiratory tract [7,8].

However a very interesting finding is the role of matrix metalloproteinase (MMP-1), interleukin (IL-6) and vitamin D receptor (VDR) in the biological cascade of events that are initiated by bacterial infection and particulate wear debris, resulting in peri-prosthetic bone loss around loosened total hip replacements. The individual responses to such stimuli may be also influenced by genetic variation [9].

Septic loosening of prosthetic implants in orthopedics, as it occurs clinically, is attributed to wear particles [10,11], to the response of the tissue dominated by macrophages [12] and to the production of inflammatory mediators and matrix degrading enzymes [13,14].

Bone turnover may shift towards increased resorption at the bone-prosthesis interface and lead to implant failure [11]. In particular this results seem to be associated with the presence of 1,25-$(OH)_2$-D_3, osteoclast differentiation factor (known as ODF, RANKL or TRANCE; provided by osteoblasts) and macrophage colony stimulating factor (M-CSF): these 3 factors may be sufficient for osteoclasts formation. However it is also well demonstrated the induction of osteoclast formation [15] in the presence only of 1,25-$(OH)_2$-D_3, without the need for M-CSF [16]. Could the same mechanism explain some form of peri-implant bone loss of endosseous dental implants in patients who obtained vitamin D from supplements?

The side effects of high oral doses of vitamin D3 precursors seem to be attributable to extrarenal activation of circulating 25-OH-D_3 by activated macrophages. Furthermore high counts of activated macrophages in the joint space may be a risk factor for aseptic loosening [17]. Also in inflammatory diseases like sarcoidosis and tuberculosis, a high macrophage count sometimes leads to unbalancing of calcium and vitamin D_3 homeostasis. These patients periodically exhibit hypercalcaemia and increased osteolysis [18]. Furthermore dysregulation of these mechanisms and genetic variation seem to module the pathogenesis of aseptic loosening [19-25].

The same mechanism could explain why some dental implants alike hip prosthesis may show bone loss without a relevant infection neither occlusal trauma [26]. The interrelationship between bone metabolism and innate immune responses may explains also why medical conditions typified by chronic inflammation are associated with bone loss, characterized by decreased bone mineral density and deterioration of trabecular bone microarchitecture [9,27,28].

This patological process may serve as a novel model to identify patients at risk of peri-implant bone loss. However the hypothesis that high dosage of oral vitamin D supplements might accelerate peri-prosthetic loosening or peri-implant bone resorption in inflammatory conditions needs further investigation.

Discussion

The exact role of vitamin D status in patients with bone infections or bone loss is still not knowned.

Few papers have investigated the association between Vitamin D and peri-implant bone loss. Several articles have always described Vitamin D_3 deficiency as a possible cause of peri-implant bone loss [29-31] and not high concentration of the same vitamin except in the orthopedic literature [11]. The lost of osseointegration is a complex, multifactorial trait concentrated in some treated populations. There has been shown evidence for genetic contribution to dental implant loss. In fact, genetic polymorphisms have been classically considered as genetic risk factors for several diseases and, more recently, for dental implant loss. However the relationship between vitamin D receptor (VDR) and dental implant bone loss has not been statistically significant [32]. Further confirmation of possible negative effects of oral vitamin D_3 supplementation in patients at risk for peri-prosthetic loosening might contribute to implant longevity and improvement of patient outcome [33]. It should be well known that the numbers of osteoclasts formed, and their bone resorption activity, is enhanced by the addition of 1.25-$(OH)_2D_3$ [34,35]. Monocytes and tissue macrophages are capable of differentiating into cells that show all the cytochemical and functional features of osteoclasts. The presence of 1,25-$(OH)_2$-D_3, osteoclast differentiation factor (ODF/RANKL) provided by osteoblasts or pre-adipocytic cell lines and macrophage colony stimulating factor (M-CSF) is sufficient for osteoclast formation *in vitro*. Thus macrophages can differentiate into osteoclastic bone resorbing cells [36].

Higher levels of M-CSF were found at the interface of implant, bone and pseudocapsular tissues in patients with implant loosening compared to the synovial membrane of patients undergoing primary hip replacement [24,37]: the release of M-CSF by activated cells in the peri-implant region may be an important factor in peri-implant bone loss.

Sabokbar., *et al*. [16] recently demonstrated that macrophages taken from loosening prosthetic joints were able to induce osteoclast formation *in vitro* in the presence of 1,25-$(OH)_2$-D_3, also without the need for M-CSF.

Vitamin D precursors are found in over-the-counter multivitamin preparations but the protective effect of these vitamin D supplements against osteoporosis is still not clear-cut, as recent meta-analyses demonstrate [38]. However the role of vitamin D is very important especially because its deficiency can be easily and safely corrected by 6 weeks oral vitamin D supplementation [39,40].

As a consequence, a screening for vitamin D deficiency in individuals at risk, as well as oral vitamin D supplementation before orthopedic or endosseous implant surgery could be advisable, once demonstrated a clear association between vitamin D levels and poorer-functional outcomes.

Scientific findings support the hypothesis that a correct vitamin D_3 intake is paramount for bone health [41]. Prosser., *et al*. [42] more than a decade ago reported that orally ingested vitamin precursors (cholecalciferol) bypasses the skin's feed-back mechanisms that limit endogenous production of precursors during sun exposure. Thus, oral ingestion of precursors may result in increased concentrations of circulating 25-OH-D_3 at all ages [43].

In 1997 Kerr [18] reported already an increased bone resorption during inflammatory states due to a not controlled extrarenal activation of vitamin D_3 by macrophages.

During normal solar exposure to ultraviolet light in the B-spectrum (UVB), precursors of vitamin D_3 are generated in the skin from 7-deoxycholesterol [42]. Besides humans can also acquire vitamin D_3 precursors (cholecalciferol) by oral ingestion of food from animal sources and dietary supplements [41,42].

Althought endogenously synthesized precursors are UVB-unstable and then inactivated before entering the circulation [41], the colecalciferol, obtained from animal food sources or supplements, is not limited by these feedback mechanisms and readily reaches the circulation after intestinal absorption [41,42].

Skin aging can be also associated with the decrease in endogenous synthesis of vitamin D3 precursors; this, combined with a lifestyle with less solar exposure, is the main cause of hypovitaminosis D3 and predisposition to osteoporosis in the elderly [43].

On the other hand, the intestinal ability to absorb oral cholecalciferol and the hepatic 25-hydroxylation capacity do not decline with age. Finally the administration of vitamin D_3 supplements may result in elevated circulating levels of 25-OH-D3 in both young and older adults.

Conclusion

Despite limitations, we evidenced a different scenery in respect to other authors, therefore re-opening the debate on the role of vitamin D status in patients with bone and joint infections. There is an urgent need to define the serum level of vitamin D which is beneficial for bone homeostasys. There is a need to set guidelines to better control dental implants longevity. It is author's opinion that periodic assessment of vitamin D_3, calcium and magnesium intake, bowel problems and the measurement of serum 25(OH)D, PTH, Ca levels, UCa/Cr and bone health may be of help for the integral management of patients undergoing advanced implant therapy. A confirmation of the possible negative effects of oral vitamin D_3 supplementation in patients at risk for peri-prosthetic loosening or peri-implant bone loss may contribute to both implant longevity and improvement of patient outcome. Further research is needed.

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