



## Is oral vitamin D a risk factor for prosthetic loosening ?

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**High counts of wear particles and activated macrophages are strong predictors of prosthetic loosening in total joint arthroplasty patients. The tissue response, dominated by macrophages, with production of inflammatory mediators and matrix-degrading enzymes, triggers a self-accelerating cycle of osteolysis, ultimately resulting in failure of the arthroplasty, high treatment cost and poor patient outcome. Vitamin D is frequently used as a treatment for osteoporosis, but might also contribute to osteolysis in inflammatory joints. Here, we review the effects of extrarenal vitamin D<sub>3</sub> activation by macrophages in the joint space. The summarized pathways contribute to increased bone resorption in the setting of the inflammatory micro-environment at the bone-prosthesis interface. If further evidence confirms a role of oral vitamin D<sub>3</sub> as a risk factor for aseptic loosening, this might influence the current treatment strategies for patients at risk for this condition.**

**Keywords :** vitamin D ; macrophages ; metabolic syndrome ; particles ; wear ; loosening ; prosthesis ; joint replacement surgery ; extrarenal activation.

**Abbreviations used :** **1,25-(OH)<sub>2</sub>-D<sub>3</sub>** : Calcitriol ; **24-OH-ase** : 24-hydroxylase ; **25-OH-ase** : Hepatic 25-hydroxylase ; **25-OH-D<sub>3</sub>** : Calcidiol ; **BPs** : Bisphosphonates ; **BMD** : Bone mineral density ; **FPP** : farnesyl diphosphate ; **IA** : Inflammatory arthritis ; **IBD** : Inflammatory bowel disease ; **IL** : Interleukins ; **IR** : Insulin resistance ; **M-CSF** : Macrophage-colony stimulating factor ; **MS** : Metabolic Syndrome ; **ODF**, **RANKL** or **TRANCE** : Osteoclast differentiation factor ; **PGE<sub>2</sub>** : Prostaglandin E<sub>2</sub> ; **PTH** : Parathyroid hormone ; **RA** : Rheumatoid arthritis ; **TNF-α** : Tumour

necrosis factor α ; **TPN** : Total parenteral nutrition ; **UVB** : Ultraviolet light in the B-spectrum ; **Vitamin D<sub>3</sub>** : Cholecalciferol ; **VDR** : Vitamin D receptor.

### INTRODUCTION

Aseptic loosening of prosthetic implants, as it occurs clinically, is attributed to wear particles (20,26), the response of the tissue dominated by macrophages (10) and the production of inflammatory mediators and matrix degrading enzymes (13, 19). A sustained pro-inflammatory condition and high counts of wear particles in the total joint space, shift bone turnover towards increased resorption which at the bone-prosthesis interface ultimately leads to implant failure (26).

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Multiple cell types have been implicated in the development of periprosthetic osteolysis in response to wear debris. Monocytes and tissue macrophages are capable of differentiating into cells that show all the cytochemical and functional features of osteoclasts (32,33). The presence of 1,25-(OH)<sub>2</sub>-D<sub>3</sub>, osteoclast differentiation factor (known as ODF, RANKL or TRANCE ; provided by osteoblasts) and macrophage-colony stimulating factor (M-CSF) is sufficient for osteoclast formation *in vitro* (29). It has been known for over ten years that human arthroplasty-derived macrophages can differentiate into osteoclastic bone resorbing cells. Recent *in vitro* experiments, using macrophages taken from loosening prosthetic joints, revealed induction of osteoclast formation in the presence of 1,25-(OH)<sub>2</sub>-D<sub>3</sub>, without the need for M-CSF (33).

Adequate vitamin D<sub>3</sub> intake and renal handling is paramount for bone health. Orally ingested vitamin precursors (cholecalciferol) bypass the skin's feedback mechanisms that limit endogenous production of precursors during sun exposure (17,28). Combined with lack of feedback control on hepatic 25-OH-ase by its substrate (cholecalciferol), oral ingestion of precursors results in increased concentrations of circulating 25-OH-D<sub>3</sub> at all ages (6). During inflammatory states, extrarenal activation of vitamin D<sub>3</sub> by macrophages occurs, not controlled by the strict Ca-PTH-feedback mechanisms, resulting in a state where bone turnover is unbalanced towards resorption (14).

Here, we summarize the current knowledge on the pathways supporting a role for extrarenal activation of orally ingested vitamin D<sub>3</sub> precursors by activated tissue macrophages in the total joint space as a hitherto unrecognized risk factor for prosthetic loosening in inflammatory conditions.

## MATERIALS AND METHODS

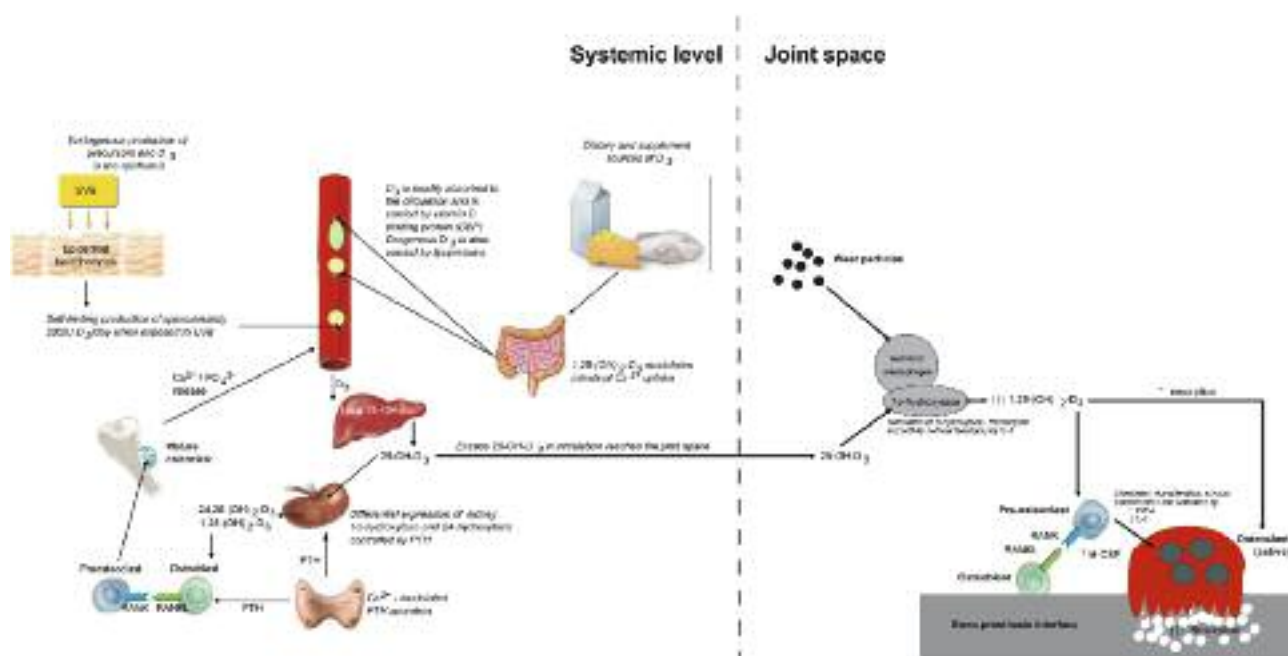
We performed Medline searches for the terms "periprosthetic loosening", "periprosthetic osteolysis", "vitamin D", "extrarenal" and "inflammation" to identify literature relevant to the hypothesis. Articles addressing extrarenal activation of vitamin D, inflammatory disease associated with decreased bone mineral content, wear debris in osteolysis of the hip, animal models of

osteolysis, and *in vitro* models of particle action were selected for further review. We then manually reviewed the references listed in selected articles.

## Vitamin D<sub>3</sub> Metabolism

Under normal solar exposure conditions, precursors of vitamin D<sub>3</sub> are generated in the skin from 7-deoxycholesterol by exposure to ultraviolet light in the B-spectrum (UVB) (28). Humans can also acquire vitamin D<sub>3</sub> precursors (cholecalciferol) by oral ingestion of food from animal sources and dietary supplements (17,28). Figure 1 illustrates the pathways along which endogenously generated vitamin D<sub>3</sub> precursors and orally ingested vitamin D<sub>3</sub> precursors are handled. Exposure to sunlight will generate approximately 200 IU of cholecalciferol after 10 minutes of whole body irradiation (17) (see figure 1 for vitamin D<sub>3</sub> homeostasis). Endogenously synthesized precursors are UVB-unstable and thus inactivated before entering the circulation, preventing an 'endogenous overdose' during prolonged solar exposure (17). Cholecalciferol, obtained from animal food sources and supplements, is not limited by these feedback mechanisms and readily reaches the circulation after intestinal absorption (17,28). Senescence of the skin underlies the age-related decrease in endogenous synthesis of vitamin D<sub>3</sub> precursors ; combined with a lifestyle with less solar exposure, it is the main cause of hypovitaminosis D<sub>3</sub> and predisposition to osteoporosis in the elderly (6). On the other hand, the intestinal ability to absorb oral cholecalciferol and the hepatic 25-hydroxylation capacity do not decline with age (6). Administration of vitamin D<sub>3</sub> supplements results in elevated circulating levels of 25-OH-D<sub>3</sub> in both young and older adults (6). High oral doses of cholecalciferol induce elevated levels of circulating 25-OH-D<sub>3</sub> that can persist for months, attributable to the lack of inhibition of cholecalciferol on hepatic 25-hydroxylase (14). These high levels of 25-OH-D<sub>3</sub> elicit hypercalcaemia that can persist for months and in extreme cases, cause metastatic calcifications in the liver and the lungs (14).

The principal site of the second hydroxylation, as a result of 1 $\alpha$ -hydroxylase activity in the proximal tubules of the kidney, is central to the endocrine function of vitamin D as a parathyroid hormone (PTH)-stimulated modulator of calcium homeostasis (44). Renal tubular cells express both 24-hydroxylase and 1, $\alpha$ -hydroxylase. Strict transcriptional feedback mechanisms balance the production of 24,25-(OH)<sub>2</sub>-D<sub>3</sub> and 1,25-(OH)<sub>2</sub>-D<sub>3</sub> (calcitriol), the active hormone (28). All target cells for vitamin D, characterized by a vitamin D receptor (VDR)



**Fig. 1.** — Systemic handling of endogenous/exogenous vitamin D and peripheral (extrarenal) activation in the joint space. **1,25-(OH)<sub>2</sub>-D<sub>3</sub>** : Calcitriol ; **25-OH-ase** : Hepatic 25-hydroxylase ; **25-OH-D<sub>3</sub>** : Calcidiol ; **IL-1** : Interleukin 1 ; **M-CSF** : Macrophage-colony stimulating factor ; **ODF, RANKL or TRANCE** : Osteoclast differentiation factor ; **PTH** : Parathyroid hormone ; **TNF- $\alpha$**  : Tumor necrosis factor  $\alpha$  ; **UVB** : Ultraviolet light in the B-spectrum ; **Vitamin D<sub>3</sub>** : Cholecalciferol.

express 24-hydroxylase, to inactivate calcitriol to calcitroic acid (28). The adverse effects of high oral doses of vitamin D<sub>3</sub> precursors are attributable to extrarenal activation of circulating 25-OH-D<sub>3</sub> by activated macrophages. High counts of activated macrophages in the joint space are a risk factor for aseptic loosening (5). In inflammatory diseases like sarcoidosis and tuberculosis, a high macrophage count sometimes leads to unbalancing of calcium and vitamin D<sub>3</sub> homeostasis. Patients periodically exhibit hypercalcaemia and increased osteolysis (14). The underlying mechanism of these hypercalcaemic episodes is peripheral (extrarenal) activation of 25-OH-D<sub>3</sub> to the active 1,25-(OH)<sub>2</sub>-D<sub>3</sub> by activated macrophages. In case of massive macrophage counts, the active hormone spills over to the general circulation (14). Apart from the strictly controlled vitamin D<sub>3</sub> activation in the renal proximal tubules, several other cell types can express 1, $\alpha$ -hydroxylase, enabling extrarenal activation of the circulating liver-derived precursor (25-OH-D<sub>3</sub>) to the active hormonal form. Cell types capable of expressing 1, $\alpha$ -hydroxylase include dermal and intestinal epithelial cells, monocytic cell lines and macrophages, of

which the latter possess the highest capacity to activate vitamin D<sub>3</sub> to its active hormonal form (9). Subsequently, nearly 20 other forms of granulomatous diseases, such as Crohn's disease, have been reported to be associated with increased levels of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> (4). Less infiltrative inflammatory conditions like inflammatory bowel disease (IBD) and inflammatory arthritis (IA) are also characterized by increased bone resorption, resulting in decreased bone mineral content (1) and joint destruction, respectively.

### Vitamin D and bone turnover in inflammatory conditions

A number of growth factors, cytokines, hormones and cell adhesion molecules (e.g. integrins) regulate normal bone cell differentiation, growth, and function. Chronic elevation of pro-inflammatory mediators like tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukins (IL) IL-1 $\beta$ , IL-6, IL-8 and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) can disrupt normal bone remodeling and ultimately lead to bone

loss (11,21,31,39). These mediators act both directly and indirectly to increase osteoclastogenesis, prevent osteoclast apoptosis, and/or inhibit osteoblast activity. Dysregulation of these mechanisms and genetic variation in its components modulates the pathogenesis of aseptic loosening (15,16,21,24,27,35,38). The interrelationship between bone metabolism and innate immune responses likely explains why medical conditions typified by chronic inflammation are associated with bone loss, characterized by decreased bone mineral density (BMD) and deterioration of trabecular bone microarchitecture. In obese patients, characterized by a chronic pro-inflammatory state, osteoporosis risk is increased (2,22).

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)<sub>2</sub>-D<sub>3</sub>, 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* (29). It has been known for over ten years that human arthroplasty-derived macrophages can differentiate into osteoclastic bone resorbing cells (32).

M-CSF is an essential mediator of osteoclast formation. The release of M-CSF by activated cells in the peri-implant region is likely to be an important factor in peri-implant bone loss. M-CSF is present in the synovial fluid and in the synovial-like membrane of peri-implant tissues taken from patients with aseptic loosening. Higher levels of M-CSF were found in the tissue at the interface of implant and bone and pseudocapsular tissues in these patients than in the synovial membrane of patients undergoing primary hip replacement (35,43). Particle-activated macrophages release high levels of M-CSF, suggesting that these macrophages are a major source of M-CSF in the peri-implant tissues (43). Sabokbar *et al* recently demonstrated that macrophages taken from loosening prosthetic joints were able to induce osteoclast formation *in vitro* in the presence of 1,25-(OH)<sub>2</sub>-D<sub>3</sub>, without the need for M-CSF (33). Along similar lines, aspirated knee joint fluid from rheumatoid arthritis (RA) patients is laden with macrophages and contains biologically relevant quantities of 1,25-(OH)<sub>2</sub>-D<sub>3</sub>, resulting from the activation of 25-OH-D<sub>3</sub> by macrophage-expressed 1 $\alpha$ -hydroxylase (34) which underscores the role of uncontrolled vitamin D<sub>3</sub> activation by macrophages in inflammatory conditions associated with increased resorptive activity. Figure 1 (right panel) illustrates the relevant pathways of extrarenal activation of vitamin D and cytokines stimulating osteoclast formation and activation at the bone-prosthesis interface.

## DISCUSSION & CONCLUSION

Maintaining an adequate vitamin D status throughout life, in concert with adequate calcium intake is one of the major modifiable risk factors for osteoporosis. Upon the discovery of low cholecalciferol levels as the culprit for rachitis in the previous century, the beneficial effects of irradiated plant derivatives containing cholecalciferol were observed in patients affected by this debilitating condition, and 'vitamin D' was born (14). The steroidal structure does not fit the semantical 'vital - amine' definition, a compound which the human body cannot generate in adequate quantities to assure normal homeostasis. On the other hand, vitamin D precursors are found in over-the-counter multivitamin preparations and are regarded as a fat-soluble vitamin. The protective effect of these vitamin D supplements against osteoporosis is still not clear-cut, as recent meta-analyses demonstrate (12).

In some cases vitamin D intoxication from supplements or fortified foodstuffs occurs, resulting in hypercalcaemia and sometimes metastatic calcifications. Intoxicated patients are usually treated with bisphosphonates (BPs) (25). These effective inhibitors of bone resorption have proven to be effective, besides their extensive use for the treatment of systemic or local bone loss (23,36,41), in the prevention of aseptic loosening in animal models (42). After intracellular absorption of BPs by osteoclasts, these compounds inhibit the mevalonate pathway enzyme farnesyl diphosphate (FPP) synthase in osteoclasts both *in vitro* and *in vivo* (37), reducing both endogenous synthesis as well as bone resorption and the inherent hypercalcaemia (8,18). The above findings support a role for oral vitamin D<sub>3</sub> precursors in conferring adverse effects on bone turnover in an inflammatory prosthetic joint space.

Tauber's group measured blood levels of the active metabolites of 25-OH-D<sub>3</sub>, 1,25-OH<sub>2</sub>-D<sub>3</sub> and 24, 25-OH<sub>2</sub>-D<sub>3</sub>, which were normal in 15 patients suffering from arthrosis of the hip and in 13 patients with aseptic loosening of total hip endoprostheses. In one case, 24,25-OH<sub>2</sub>-D<sub>3</sub> was not detectable (40). Locally produced 1,25-OH<sub>2</sub>-D<sub>3</sub> does not generally spill over to the circulation, after binding the VDR, it elicits its own catabolism by inducing swift

transcription of CYP-24, resulting in the production of the metabolically inert end-product  $1\alpha,24,25\text{-OH}_3\text{-D}_3$  (14,28). Measuring the ratio of excreted  $1\alpha,24,25\text{-OH}_3\text{-D}_3$  /circulating  $1,25\text{-OH}_2\text{-D}_3$  is not common practice, but might provide an estimate of the degree of extrarenal activation to serve as a novel way to identify patients at risk.

The above findings, in the light of the hypothesis that oral vitamin D supplements might accelerate periprosthetic loosening in inflammatory conditions, should be verified through measurement of both circulating precursors as well as excreted vitamin D metabolites. Circulating concentrations of  $25\text{-OH-D}_3$  are highly variable in the general population, and vary with geographical latitude, solar exposure and age, acting as an important confounder in the quantification of the net effects of vitamin  $D_3$ . Activation of the vitamin D receptor by active vitamin  $D_3$ , regardless of its  $1\alpha$ -hydroxylation site, elicits a plethora of genomic (modulation of the expression of more than 200 genes) and non-genomic effects that vary by cell type (28). We therefore recommend further confirmation of the possible negative effects of oral vitamin  $D_3$  supplementation in patients at risk for periprosthetic loosening, which might contribute to both implant longevity and improvement of patient outcome prediction.

The body is able to produce this substance in sufficient quantities, given UVB-irradiation, to catalyze the generation of precursors from the body's abundant supply of cholesterol. Circulating concentrations of  $25\text{-OH-D}_3$  are highly variable in the general population, and vary with geographical latitude, solar exposure and age, acting as an important confounder in the quantification of the net effects of vitamin  $D_3$ . Activation of the vitamin D receptor by active vitamin  $D_3$ , regardless of its  $1\alpha$ -hydroxylation site, elicits a plethora of genomic (modulation of the expression of more than 200 genes) and non-genomic effects that vary by cell type (3,7,30).

Further confirmation of possible negative effects of oral vitamin  $D_3$  supplementation in patients at risk for periprosthetic loosening might contribute to implant longevity and improvement of patient outcome.

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