Review Article

The role of vitamin D and vitamin D deficiency in orthopaedics and traumatology—a narrative overview of the literature

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Abstract: Vitamin D is considered to play an important role in musculoskeletal health. It's classical function is the regulation of calcium and phosphate homeostasis, thus ensuring a balanced bone metabolism that is characterised by an equal amount of bone resorption and bone formation. In the past decades, a plethora of pre-clinical and clinical studies reporting on potential health-beneficial properties of vitamin D have emerged. Moreover, there is an abundance of reports highlighting vitamin D deficiency and insufficiency in patients with almost innumerable diseases. Further, it is estimated that more than one billion people globally are affected by insufficient vitamin D levels. As such, research on vitamin D has been particularly popular over the past years. In orthopaedics and traumatology, most studies describe favourable effects of vitamin D in general. However, the relative importance of vitamin D is oftentimes debated. In this narrative review of the literature, we consider first, the properties of vitamin D and how vitamin D, vitamin D deficiency and the vitamin D receptor (VDR) impact on musculoskeletal health. Secondly, we provide an overview of studies reporting the prevalence of vitamin D deficiency in traumatology and diverse orthopaedic diseases including bone oncology. Lastly, we emphasise recent findings and touch on future perspectives in vitamin D research.

Keywords: Vitamin D; vitamin D deficiency (VDR); orthopaedics; orthopedics; traumatology

Submitted Feb 18, 2021. Accepted for publication May 18, 2021.
doi: 10.21037/atm-21-779
View this article at: http://dx.doi.org/10.21037/atm-21-779

Introduction

In the past decades, a vast quantity of pre-clinical and clinical studies reporting on potential health-beneficial properties of vitamin D have emerged (1-5). While some studies highlight positive effects of vitamin D on a variety of systems in the human body (4,6,7), others have failed to describe favourable characteristics on healthiness (8,9). Moreover, there is a plethora of studies reporting the prevalence of vitamin D deficiency and insufficiency in healthy individuals as well as subgroups of patients with all kinds of diseases (7,10-16).

The aim of this narrative review is to provide an overview of vitamin D status in patients with different orthopaedic diseases. Further, we want to give a broad perspective on vitamin D and its role in orthopaedics and traumatology.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-21-779).

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Background

Vitamin D metabolism

Vitamin D may either be synthesised in the skin via ultraviolet radiation (mostly UVB radiation, 290–315 nm) or ingested in the diet (vitamin D rich foods or supplements) (17,18). In most humans, approximately ninety percent of vitamin D in the body is obtained through cutaneous synthesis (19). Notably, melanin in the skin blocks UVB solar radiation necessary for vitamin D production. Thus, higher dietary vitamin D intake of darker skin people is required to achieve sufficient vitamin D levels (20). Irradiation of the skin converts the cholesterol-derived precursor form, 7-dehydrocholesterol, into previtamin D_3 (cholecalciferol). In the circulation, vitamin D is transported bound to a vitamin D binding protein. In humans, a high proportion of vitamin D is deposited in body fat due to its lipophilic nature. Thus, only a minor proportion of previtamin D_3 is transported to the liver, where it is then further processed into 25-hydroxyvitamin D [25(OH) D or calcidiol] by the enzyme 25-hydroxylase (14,19). Of note, several studies have reported an association of low vitamin D levels and obesity which can best be explained by increased vitamin D deposition in extended body fat compartments (21). Calcidiol is the precursor to the potent steroid hormone calcitriol (1,25 dihydroxyvitamin D). Although 25(OH)D is not the most active metabolite, it is the most abundant circulating form and levels of it are largely used to determine a patient's vitamin D status (19). It is considered the prime candidate marker to assess vitamin D status as the concentration of 25(OH) D in plasma is largely unregulated and it has a relatively long half-life of approximately three weeks (22-25). In the next step, a further hydoxylation process occurs in the kidney where the enzyme 1-alpha-hydroxylase finally produces 1,25-dihydroxyvitamin D (1,25D) which is the biologically active form of vitamin D. The classical function of 1,25D is that of a regulator of calcium and phosphate homeostasis, thus ensuring a balanced bone metabolism that is characterised by an equal amount of bone resorption and bone formation. In addition, it is known to effect cell proliferation, differentiation and apoptosis in numerous tissues, including many cancers such as e.g., skin, breast, prostate or colon (4,26-32). The biological effects of calcitriol are usually mediated through binding of it to the vitamin D receptor (VDR). Upon binding, the VDR forms a heterodimer with the retinoid X receptor (RXR) which then facilitates a translocation of the VDR from the cytoplasm to the nucleus. Eventually the complex then binds to vitamin D responsive elements in the regulatory region of its target genes (33,34). The discovery that nearly all tissues and cells in the body posses a VDR and that several hold the enzymatic machinery to convert the primary circulating form 25(OH)D, to the active form, 1,25D, has provided new insights into the function of this vitamin (14,19).

Vitamin D and bone metabolism

The human skeleton is naturally maintained by continuous remodelling, removal and replacement of bone throughout life (35). This highly regulated process is characterised by the coordinated activity of bone forming osteoblasts and locally active osteoclasts breaking down existing bone (36). Bone remodelling generally occurs at a micro-scale and this complex process is further regulated by different cells, hormones, locally acting growth factors and cytokines within the so-called bone microenvironment (36). Vitamin D is essential to maintain a well-balanced metabolism within the bone microenvironment. Consequently, endocrine changes like severe vitamin D deficiency for example may lead to an increased bone turnover altering the bone microenvironment (19). Severe lack of vitamin D can cause the development of osteomalacia in adults which is characterised by the incomplete mineralisation of bone (37). Likewise, severe vitamin D deficiency in children can result in rickets, a decreased mineralisation of bone tissue and the growth plates (38). Moreover, chronic vitamin D deficiency induces secondary hyperparathyroidism, which increases and accelerates bone turnover. Consequently, this results in progressive bone loss and a low bone mineral density with a bone that is prone for musculoskeletal diseases.

Vitamin D and fracture prevention

Vitamin D is a key element in bone mineralisation. Therefore, inadequate vitamin D levels may result in a higher fracture risk. In a recent study, Priemel *et al.* analysed clinically healthy bones of deceased and detected histopathological signs of osteomalacia with vitamin D levels below 30 ng/mL in twenty-five percent of all studied bones. Conversely, bones of patients with vitamin D levels higher than 30 ng/mL did not show a significant loss of bone mineral density (39). The link between vitamin D status and osteoporosis is of high scientific interest. Vitamin D levels below 20 ng/mL lead to malabsorption of intestinal calcium, which in turn may cause osteomalacia

in adults as well as rickets in children and adolescents (14). It was described that serum vitamin D levels may influence outcomes of osteoporosis (40). Osteoporosis often results in fracture. Hip fractures are common fractures in the fragile and elderly population (41). Recent data suggests that measurement of vitamin D serum levels might serve as an indicator for hip fracture risk (42). Several studies described a high incidence of vitamin D deficiency in women with hip fractures (43). These fracture types have devastating consequences and are associated with a high morbidity as well as mortality of elderly. In particular, up to twenty percent of patients will decease within the first twelve months following fracture. In addition, more than 50% of seniors will be permanently functional disable following a hip fracture (44). Consequently, supplementation of vitamin D has been shown to reduce the risk of falls and hip fractures (45,46). For example, one RCT investigated the efficacy of vitamin D supplementation in fracture prevention comparing the effect of 1,200 mg Calcium and 20 microgram Vitamin D supplementation daily versus Placebo in 3,270 French women. In the patient subgroup receiving supplementation, bone mineral density increased and the risk of hip and non-vertebral fractures was reduced by 43% and 32% respectively compared with the placebo group (47). The RECORD study evaluated the efficiency of Calcium and Vitamin D, either alone or in combination, and placebo in 5,292 patients with a low-trauma fracture. In a more than 5-year long follow-up, no difference in the incidence of fractures was found. This is in contrast to other studies and may be best explained by the extremely low compliance with supplementation, especially when this included daily calcium intake (48). The Women's Health initiative study showed a positive effect of oral supplementation of Calcium and Vitamin D on bone mineral density. In particular, a significant reduction of hip fracture risk was observed (49). Furthermore, a meta-analysis showed that optimising vitamin D intake reduced the incidence of non-vertebral fractures, while additional Calcium supplementation had no further effect (50). Osteoporosis often results in vertebral fragility fractures. So far, a distinct correlation between these fractures and vitamin D levels has been described (51). Vertebral fractures have direct and indirect effects on quality of life with increased morbidity and mortality (52). Vitamin D deficiency in postmenopausal women is associated with osteoporotic vertebral fractures (51,52). A recent study showed a possible role of vitamin D status in the occurrence of postkyphoplasty recurrent vertebral compression fractures in elderly patients undergoing kyphoplasty due to osteoporotic fractures (53). In a former research work, we were able to identify a high prevalence of vitamin D insufficiency (89%) in patients with vertebral fractures. Comparing this data to a well-matched group of patients that presented with back pain in the absence of fractures, we found a prevalence of vitamin D insufficiency of 60%. Interestingly however, most patients presenting with back pain had insufficient vitamin D levels, regardless of whether or not a fracture was present (54). In yet another study it was demonstrated that higher serum levels of vitamin D are not only associated with a healthy bone metabolism in general but also reduce the risk of osteoporosis and osteoporotic fractures (55).

Nakamura *et al.* described in a 6-year cohort study of 773 senior Japanese women, an association between sufficient vitamin D levels (>71 nmol/L) and a 58% reduction of osteoporotic fractures compared to patients with vitamin D deficient serum concentrations. Maintaining sufficient serum levels of vitamin D may result in a reduction of fracture risk (40). Another study described that serum vitamin D levels under 20 ng/mL doubled the risk of osteoporotic fractures in comparison to vitamin D levels above this threshold (56). A Brazilian study showed that vitamin D deficiency was one of the most important factors in women with vertebral fragility fractures (57). El-Maghraoui *et al.* enrolled 178 menopausal Moroccan women in their cohort study to evaluate serum vitamin D concentrations and to evaluate the relationship of bone mineral density and vertebral fractures. A widespread rate of insufficient vitamin D levels (85% of enrolled women) and deficiency (52%) was detected. In addition, insufficient vitamin D concentrations were reported as an independent risk factor for vertebral fractures in postmenopausal women (51). There is a certain discrepancy regarding the association of sex with vitamin D levels and osteoporosis. While some studies indicate that females have a higher risk to be vitamin D deficient than men, other data identified male sex as a risk factor (58). This conflicting literature indicates that gender may not necessarily be of importance for vitamin D deficiency, which is also supported by our own data. As such, both males and females need to be monitored for hypovitaminosis D as both groups are at risk. In a study on 1,083 elderly orthopaedic patients aged over 70 years, we found a mean vitamin D level of 17.1 ng/mL (16). Data on geriatric orthopaedic patients is rare, but they all consent to a widespread rate of low serum vitamin D in the elderly. This is distressing, especially as a minimum serum 25(OH)D level of 30 ng/mL is

recommended for fragile elderly subjects with an elevated risk of falls and fractures (59). Further, Bischoff-Ferrari *et al.* showed a 22% reduction in falls of patients taking vitamin D supplements (60). Gerdhem *et al.* evaluated 986 postmenopausal women and showed a twofold increased fracture risk for patients with 25(OH)D levels below 20 ng/mL compared to patients with higher serum vitamin D levels (56). Moreover, a contributing role of vitamin D deficiency in the occurrence of simultaneous fractures has recently been described in a study of 472 elderly hip fracture patients (61).

In summary, vitamin D deficiency is frequent in patients with osteoporotic fractures around the world. Further, vitamin D supplements may not only reduce the risk of fractures due to an increase in bone mineral density but also via reduction of falls.

The role of vitamin D in fracture healing and osseo-integration of orthopaedic implants

Serum vitamin D levels are reduced in the curative phase of a fracture and low activated vitamin D levels correlate with fracture healing (62,63). This may indicate that vitamin D is being utilised and metabolised by healing bone. Furthermore, activated vitamin D improves fracture healing in mice and chickens (63). In addition, 24,25(OH)2D improves the differentiation and maturation of growth plate chondrocytes via a putative membrane receptor in fracture callus (64). Furthermore, vitamin D regulates a range of genes involved in bone remodelling after fracture (65). Vitamin D deficiency has been demonstrated to negatively impact on fracture healing, thus contributing to the development of nonunion of fractures (66). In a case-control study, the prevalence of 25(OH)D levels below 23 nmol/L was found to be 60% in a group of non-union closed tibia fractures. In contrast, only 30% of patients that achieved bone union by 3 to 6 months of follow-up presented with levels less than 23 nmol/L (67). In a large database with more than 300,000 fractures in 18 bones, vitamin D deficiency was associated with an odds ratio of 1.14 of non-union, which affected 4.9% of the fractures (68). As a potential mechanism for non-union, impaired IL-4 and IL-13 production under vitamin D deficiency have been proposed, since these cytokines increase bone formation and fracture bridging (69). Nevertheless, a high-dose therapy of vitamin D3 during recovery did not improve the rate of union of vitamin D deficient patients with a long bone fracture in a randomized double-blind placebo controlled trial (70). Out of 2 trials having tested the effects on fracture healing of proximal humerus or upper and lower limbs fractures of 800 and 1,200 IU vitamin D per day, respectively, the former concluded to some improved fracture healing by higher bone content in the callus with vitamin D. In the latter, the incidence of delayed union was 9.7% in the group who remained vitamin D deficient, whilst it was 0.3% in the vitamin D replete at baseline and 1.7 % in those the deficiency of whom was corrected. In both trials, 1 g calcium supplements were administered as well. The contrasting effects of vitamin D supplementation on fracture healing have previously been reviewed in detail (71).

Few pre-clinical studies have concluded to a lower bone to implant contact and impaired functional osseo-integration in vitamin deficient animals. These effects were corrected by vitamin D or calcitriol administration (72,73). Nonetheless, robust data on this topic are currently still missing.

In summary, the impact of low serum vitamin D levels on fracture healing are not clarified satisfactory. Additionally, clinical studies are rare and mainly inconclusive. However, it seems that vitamin D has a positive influence on fracture healing, however, the mechanism and the magnitude of the effect remain to be determined. The role of vitamin D in implant osseo-integration remains inconsistent and requires further investigation.

Vitamin D in orthopaedics

Numerous studies have reported low vitamin D levels in orthopaedic patients (24,74,75). Furthermore, insufficient vitamin D levels have also been described in pediatric orthopaedic patients (38,76). In general, a great number of orthopaedic patients undergoing surgery have been identified to be vitamin D insufficient. These include patients scheduled for foot and ankle, spine, knee, shoulder and elbow surgery as well as arthroplasty including hip, knee and shoulder arthroplasty (12,24,75,77,78). Several orthopaedic diseases have also been associated with low vitamin D levels (79). For example, it has been demonstrated that patients with decreased articular cartilage thickness were more likely to be vitamin D insufficient and, thus, low vitamin D status might be a risk factor for the development of osteoarthritis (3). Furthermore, orthopaedic diseases that are associated with alterations of bone metabolism, such as bone marrow oedema syndrome and osteochondritis dissecans have been linked to low vitamin D levels (23,75).

Moreover, low vitamin D levels have been associated with an increased risk for muscle injuries and tendinopathy (80). In a study by Oh *et al.* examining patients with rotator cuff disorders, they found that vitamin D levels had a significant negative correlation with the fatty degeneration of the cuff muscle and a positive correlation with isokinetic muscle torque (81). However, low serum vitamin D level does not seem to be related to tear size, extent of retraction, or the degree of fatty infiltration in cuff muscles in a different study (82). Nonetheless, several authors found an association between vitamin D deficiency and insufficiency and the rate of revision rotator cuff surgery (83,84). Barker *et al.* reported an association of serum vitamin D levels and a faster recovery of skeletal muscle strength after muscular injury (85). Though, it has been demonstrated that vitamin D has no effect on functional outcome and graft rupture rates in patients' post-primary ACL reconstruction (86).

In addition, the outcome of vitamin D deficient orthopaedic patients has been reported to be worse in a variety of orthopaedic surgeries (79). Notably, low vitamin D levels in orthopaedic patients have also been associated with an increased length of hospital stay (87).

The impact of vitamin D on osteoarthritis and arthroplasty

Osteoarthritis is amongst the most prevalent orthopaedic diseases affecting millions of people globally (88). For this reason, several studies have investigated potential associations between the onset, progression and outcome of patients with osteoarthritis. For example, the Framingham Study showed that low vitamin D intake and low serum levels of vitamin D appeared to be associated with an increased risk for progression of osteoarthritis of the knee (89). Moreover, there is evidence that vitamin D plays a role in attenuating inflammation and fatty infiltration as well as in protecting the architecture of the cartilage tissue in the knee joint (90). Hence, it has been demonstrated that vitamin D supplementation is effective in improving the WOMAC pain and function in patients with knee osteoarthritis (91,92). However, vitamin D supplementation does not seem to reduce cartilage volume loss in patients with knee osteoarthritis (91,93). These findings were supported by several other studies and have recently been reviewed in detail (94,95). Similar effects of vitamin D have been observed in osteoarthritis of the hip joint. While some studies report a potential benefit of vitamin D supplementation such as reduction of pain, others do not provide evidence of an independent association between vitamin D serum levels and osteoarthritis of the hip (96,97). Taken together, conflicting evidence exists concerning the supplementation of vitamin D in hip and knee osteoarthritis.

The prevalence of vitamin D deficiency in osteoarthritis patients undergoing knee or hip surgery is high (24,98,99). Furthermore, vitamin D levels were found to positively correlate with both pre- and post-operative Harris hip scores (99,100). Likewise, vitamin D supplements have been shown to improve the functional outcome of patients after total knee arthroplasty (101). In contrast, Hwang *et al*. reported that low vitamin D level was not a risk factor for unsatisfactory total knee arthroplasty outcome (102). In another study by Visser *et al.* vitamin D status did not seem to affect physical recovery after total hip arthroplasty (103). However, preoperative hypovitaminosis D has been reported to have subtle effects on pain intensity scores in the early postoperative period and was identified as a risk factor for moderate-to-severe persistent pain after knee arthroplasty (104). In addition, vitamin D deficiency was reported to be associated with longer hospital stay in orthopaedic patients after total hip and knee arthroplasty (87,101). Of note, vitamin D may also impact on implant survival. Kong *et al*. have recently reported that the combined use of calcium and vitamin D (with a dose of 800 IU or greater for more than 1 year) was associated with the greatest reduction in the risks for revision surgery after total knee arthroplasty (105). Vitamin D deficiency has also been associated with a higher rate of all-cause revision in total shoulder arthroplasty (106). Furthermore, there might also be an association between periprosthetic joint infection and low vitamin D levels (77,107).

Collectively, there is mounting evidence that vitamin D is of importance in osteoarthritis and arthroplasty. However, further studies are still needed to determine whether these effects are of clinical relevance.

Vitamin D in bone oncology

A plethora of epidemiological studies that support the concept that vitamin D has anti-cancer actions have been published (4,108-111). It is therefore not surprising that vitamin D has also been reported to impact on bone oncology. Importantly, two different effects of vitamin D and vitamin D deficiency have to be differentiated. Firstly, vitamin D possesses direct anti-cancer actions which are mediated through binding of 1,25D to the VDR. For example, a multiplicity of studies have demonstrated that vitamin D attenuates cancer cell

proliferation while promoting differentiation and apoptosis (27,30,112-114). Notably, these effects have been demonstrated in neoplasms that originate in bone such as osteosarcoma as well as in malignancies that have a high propensity to metastasis to bone. Thus, these direct effects of vitamin D on cancer cells in bone account for primary malignant bone tumours and bone metastases. For example, Thompson *et al.* have demonstrated that osteosarcoma cells express the VDR and respond to 25(OH)D treatment by undergoing differentiation and apoptosis (114). These antiproliferative effects of vitamin D on osteosarcoma cell lines were only recently confirmed in a different study (115). Moreover, recent findings suggest that 1,25D treatment of osteosarcoma cells results in decreased cell proliferation, migration an invasiveness, thus, reducing the aggressive potential of osteosarcoma cells (116). Furthermore, we have recently demonstrated that the VDR itself, and independent of its ligand has a critical function in controlling cancer cell behaviour in bone and cancer metastasis to bone (117,118).

Besides these direct effects of vitamin D on cancer cells in bone, vitamin D is also known to indirectly impact on cancer growth in bone. These indirect effects of vitamin D or vitamin D deficiency on cancer cells are determined by changes in the bone microenvironment. Zheng and Ooi *et al.* have recently shown that vitamin D deficiency promotes the growth of skeletal breast and prostate cancer metastases in mice. These effects were at least in part attributable to changes in the bone microenvironment as a result of secondary hyperparathyroidism and increased bone turnover (119-121). These indirect effects are believed to impact on primary as well as secondary cancer growth in bone. In addition, there is evidence that alterations within the bone microenvironment due to low vitamin D levels might also result in an increased skeletal susceptibility to cancer metastasis (36,122,123).

Collectively, there is mounting evidence that vitamin D is fundamental in bone oncology likely via directs effects of vitamin D on cancer cells but also due to indirect effects of vitamin D deficiency on the bone microenvironment.

Clinically, accelerated bone turnover—as seen in patients with severe vitamin D deficiency—is associated with higher rates of skeletal related events and poorer prognosis in patients with different cancers (79-81). Furthermore, there is increasing evidence that low vitamin D levels are associated with advanced tumour stage in patients with multiple myeloma (124).

Although these health-beneficial effects of vitamin D in patients with bone cancer are known for many years, vitamin D deficiency and insufficiency seems to be highly prevalent in patients with bone tumours. It has become evident that patients with bone metastases and multiple myeloma regularly exhibit insufficient and deficient vitamin D levels (125-127). Furthermore, patients with variety of different bone tumours including primary malignant bone tumours were found to have low vitamin D levels. Remarkably, vitamin D status of patients that are diagnosed with malignant bone tumors were significantly lower compared to patients with benign bone lesions (33,128).

Altogether, there is increasing evidence suggesting that deficient vitamin D status negatively impacts on the growth of bone metastases and possibly fosters skeletal susceptibility to cancer metastases (19,33). Moreover, vitamin D deficiency potentially promotes the formation and growth of primary malignant bone tumors and is known to negatively affect disease stage and progression in patients with multiple myeloma.

Collectively, enormous strides in unravelling the exact function of vitamin D in bone oncology have been made in the past years. Nonetheless, the precise molecular mechanisms of vitamin D involved in tumour initiation and growth, have yet to be elucidated.

Conclusions

Vitamin D is crucial in musculoskeletal health. For this reason, it is not surprising that there is a plethora of studies that link low vitamin D levels to many orthopaedic diseases and an increased fracture risk. There is little doubt that vitamin D is of importance in orthopaedic and trauma surgery. Thus, clinicians should be aware of the high prevalance of vitamin D deficiency in orthopaedic patients. Generally, a closer monitoring of vitamin D status may be beneficial and vitamin D supplements should be considered for patients with insufficient vitamin D status. Lastly, although most studies point to health-beneficial effects of vitamin D in orthopaedics and traumatology, some studies remain inconclusive and there are still many questions that will need to be addressed with future studies.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the

Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-779

Peer Review File: Available at http://dx.doi.org/10.21037/atm-21-779

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-779). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Maier GS, Weissenberger M, Rudert M, Roth KE, Horas K. The role of vitamin D and vitamin D deficiency in orthopaedics and traumatology—a narrative overview of the literature. Ann Transl Med 2021;9(11):942. doi: 10.21037/atm-21-779