

Peer Review File

Article information: [ttp://dx.doi.org/10.21037/atm-21-779](http://dx.doi.org/10.21037/atm-21-779)

Reviewer#1:

Comment 1. Abstract

Lines 28 to 32. I will suggest you re-write the abstract and use alternative phrases. Also support each claim with reference. I suppose this article is meant for the medical community and not just and not an article for the social media. It is therefore relevant to use phrase appropriate for the medical community

For instance, lines 28 to 30 could read: Vitamin D has important role in musculoskeletal metabolism (add ref). There is abundance of studies highlighting the role of vitamin D in the pathogenesis of almost all musculoskeletal diseases (add ref)

Lines 33 to 38 - minor corrections. Check for typos/spellings

Reply: We appreciate the reviewer's comments and have modified the abstract as below:

Changes in the text: "Vitamin D is considered *to play an important role in musculoskeletal health*. 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..."

Moreover, we had a thorough proofreading of the abstract. Please note that references are not usually included in the abstract. For this reason, we decided to omit any references in the abstract.

Comment 2. Introduction

This has been written like an article for a newspaper publication.

Each statement needs to be supported by reference.

Lines 54 to 57. Please indicate which studies highlighted what. Are these studies showing potential or actual benefit of Vit D?

Lines 59 to 61 good

Reply: As suggested by the reviewer, we have modified the introduction and now provide references for each statement. However, as this is meant to be an introduction we decided not provide detailed information on any specific study. All relevant studies for this review manuscript will be touched on later in the specific sections.

Changes in the text: *“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).”*

Comment 3. Background

Lines 66 to 67 Which category of humans does this process differ?

We found a high (not alarming) "rate of vitamin D deficiency and insufficiency in patients with diverse bone tumours...there should be an increased awareness for physicians to assess and if necessary correct vitamin D status of patients with bone tumours."

Reply: We agree with the reviewer that this might be confusing. For further clarification, we added another sentence and two more references as below.

Changes in the text: *“In most humans, approximately 90% 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).”*

Comment 4. Lines 70 – 71. I would rather use figures such as percentage of total or an approximate estimations, and not most of Vitamin D.....

Reply: As suggested by the reviewer we have modified this part and added another sentence and reference for further clarification as below:

Changes in the text: *“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 D₃ 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 (encoded by CYP27A1) (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).”*

Comment 5. Lines 75 – 75 circulating level is this is largely used.....

Reply: We have modified this sentence for further clarification as below:

Changes in the text: “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).

Comment 6. Line 79occurs principally in the kidney....

Reply: We thank the reviewer for pointing out this mistake and have changed the sentence as below:

Changes in the text: “In the next step, a further hydroxylation process occurs in the *principally of the* kidney where the enzyme 1-alpha-hydroxylase (encoded by CYP27B1) finally produces 1,25-dihydroxyvitamin D (1,25D) which is the biologically active form of vitamin D”

Comment 7. Lines 82 – 83 What is a balanced bone metabolism? Please use appropriate phrase or explain further

Reply: As suggested by the reviewer we have changed the sentence for further clarification as below:

Changes in the text: “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.*”

Comment 8. Line 83 to 84.. in many tissues such as..... , then say the role in neoplasm as a separate statement with reference

Reply: As suggested by the reviewer we have modified this sentence now giving examples for cancers involved as below:

Changes in the text: “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).

Comment 9. Lines 84 to 91 ... please avoid use of most, numerous consider reconstructing the sentences to bring out the message clearer.

Reply: As suggested by the reviewer we removed the term “most” and have made changes as below:

Changes in the text: “*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 possess 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).*”

Comment 10. Line 93 consider changing the heading to eg Vitamin D and Bone metabolism

Reply: We agree with the reviewer that the heading “Vitamin D and Bone metabolism” might be more suitable.

Changes in the text: “*Vitamin D and Bone metabolism*”

Comment 11. Lines 95.... This highly regulated process is characterized by

Reply: As suggested by the reviewer we have changed the text accordingly.

Changes in the text: “*This highly regulated process is characterized by the coordinated activity of bone forming osteoblasts and locally active osteoclasts breaking down existing bone (36).*”

Comment 12. Lines 98 to 104... check for typos and consider reconstructing sentences but otherwise good

Reply: We appreciate the reviewer's comment and conducted another thorough proofreading of the whole manuscript.

Comment 13. Lines 105 to 108 use appropriate term. Weakened bone?

Reply: As suggested by the reviewer we have replaced the term “weakened” bone as below:

Changes in the text: “*Consequently, this results in progressive bone loss and a low bone mineral density with a bone that is prone for musculoskeletal diseases.*”

Comment 14. Line 118.. Did you mean rickets in immature bones or just adolescents? Should this be just rickets in children?

Reply: We agree with the reviewer that this might not be clear enough as it affects immature bones in adolescents and children. For further clarification, we have modified this sentence as below:

Changes in the text: *“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).”*

Comment 15. Line 122 .. did you mean vitamin D deficiency in women with hip fractures?

Reply: Thank you for pointing out this mistake. We have made changes as below:

Changes in the text: *“Several studies described a high incidence of vitamin D **deficiency in women with hip fractures** (43).”*

Comment 16. Lines 122 to 125.... Please rephrase this to make the points clearer.

Reply: As suggested we have rephrased this passage as below:

Changes in the text: *“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).”*

Comment 17. Line 132--- diminished or reduced? By what percentage?

Reply: For further clarification, we have made changes now showing percentages as below:

Changes in the text: *“For example, one RCT investigated the efficacy of vitamin D supplementation in fracture prevention comparing the effect of 1200 mg Calcium and 20 microgram Vitamin D supplementation daily versus Placebo in 3270 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).”*

Comment 18. Lines 132 to 187. Minor alterations in sentence structure and check for typos. Otherwise good.

Reply: As stated before, we conducted another thorough proofreading of the whole manuscript and made some minor changes as below:

Changes in the text: *“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).... 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).**”*

Comment 19. Lines 199 to 205... Check sentence structure and consider reconstructing to make the points clearer

Reply: We agree with the reviewer that this might not be clear enough. For this reason, we have made changes as below:

Changes in the text: *“Vitamin D deficiency **has been demonstrated to negatively impact on fracture healing, thus contributing** to the development of nonunion of fractures (62). 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 23nmol/l (63).**”*

Comment 20. Line 211... missing or lacking?

Reply: To date, there are very few studies that investigate the role of vitamin D on osseointegration of implants. However, these studies are either animal studies or on dental implants that are not comparable to orthopaedic implants. For this reason, we believe that robust data on this topic are currently still missing.

Comment 21. Lines 219 to 222...can use limit the use on the word many?

Reply: As suggested by the reviewer we have replaced the word “many” as below:

Changes in the text: *“**Numerous** studies have reported low vitamin D levels in orthopaedic patients (24, 70, 71). Furthermore, insufficient vitamin D levels have also been described in pediatric orthopaedic patients (38, 72). In general, **a great number of** orthopaedic patients undergoing surgery have been identified to be vitamin D insufficient.”*

Comment 22. Line 222 to 235 ...Good; Lines 236 to 238... consider reconstructing or remove altogether; Lines 241 to 253 . good

Reply: As suggested by the reviewer we have removed lines 236 to 238.

Changes in the text: ~~“Taken together, insufficient vitamin D levels seem to be present in a multitude of orthopaedic patients. Concomitantly, low vitamin D levels are associated with an increased risk for several orthopaedic diseases and a worse patient outcome.”~~

Comment 23. Lines 257 to 259... (We have recently demonstrated....). Are these the current authors' studies?

Reply: One of the authors of the current manuscript was involved in both studies and is listed as an author on both manuscripts:

89. Horas K, Zheng Y, Fong-Yee C, Macfarlane E, Manibo J, Chen Y, et al. Loss of the Vitamin D Receptor in Human Breast Cancer Cells Promotes Epithelial to Mesenchymal Cell Transition and Skeletal Colonization. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2019;34(9):1721-32.

90. Zheng Y, Trivedi T, Lin RC, Fong-Yee C, Nolte R, Manibo J, et al. Loss of the vitamin D receptor in human breast and prostate cancers strongly induces cell apoptosis through downregulation of Wnt/beta-catenin signaling. *Bone research*. 2017;5:17023.

Comment 24. Lines 253 to 292 . good Check typos please

Comment 24. Lines 253 to 292 . good Check typos please

Reply: As stated before, we conducted another thorough proofreading of the whole manuscript

Reviewer B:

Comments to the author:

1. It is a well-written review article on vitamin D and Vitamin D deficiency in orthopaedics and traumatology. Some contents need to be added to be published.

The aim of the current review is to provide an overview of vitamin D status in patients with different orthopaedic diseases. Therefore, literature about the impact of vitamin D status on osteoarthritis (OA), one of the representative orthopaedic diseases, as well as surgeries for OA such as arthroplasty or osteotomy, needs to be reviewed.

Reply: We agree with the reviewer that the impact of vitamin D on osteoarthritis and arthroplasty is an important topic. For this reason, we added a whole new section on the impact of vitamin D on osteoarthritis and arthroplasty as below:

Changes in the text: “*The impact of vitamin D on osteoarthritis and arthroplasty*

Osteoarthritis is amongst the most prevalent orthopaedic diseases affecting millions of people globally (80). 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 (81). 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 (82). Hence, it has been demonstrated that vitamin D supplementation is effective in improving the WOMAC pain and function in patients with knee osteoarthritis (83, 84). However, vitamin D supplementation does not seem to reduce cartilage volume loss in patients with knee osteoarthritis (83, 85). These findings were supported by several other studies and have recently been reviewed in detail (86, 87). 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 (88, 89). 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, 90, 91). Furthermore, vitamin D levels were found to positively correlate with both pre- and post-operative Harris hip scores (91, 92). Likewise, vitamin D supplements have been shown to improve the functional outcome of patients after total knee arthroplasty (93). In contrast, Hwang et al. reported that low vitamin D level was not a risk factor for unsatisfactory total knee arthroplasty outcome (94). In another study by Visser et al. vitamin D status did not seem to affect physical recovery after total hip arthroplasty (95). 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 (96). In addition, vitamin D deficiency was reported to be associated with longer hospital stay in orthopaedic patients after total hip and knee arthroplasty (79, 93). 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 (97). Vitamin D deficiency has also been associated with a higher rate of all-cause revision in total shoulder arthroplasty (98). Furthermore, there might also be an association between periprosthetic joint infect and low vitamin D levels (73, 76).

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.”.

2. The association of vitamin D deficiency and other orthopaedic surgeries such as cruciate ligament reconstruction or rotator cuff repair also have been reported. These topics also needs to be reviewed.

Reply: As suggested by the reviewer, we have extended the review now including reports on the role of vitamin D in rotator cuff injuries/repair and ACL reconstruction as below:

Changes in the text: *“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 (77). 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 (78). Nonetheless, several authors found an association between vitamin D deficiency and insufficiency and the rate of revision rotator cuff surgery (79, 80). Barker et al. reported an association of serum vitamin D levels and a faster recovery of skeletal muscle strength after muscular injury (81). Though, it has been demonstrated that vitamin D has no effect on functional outcome and graft rupture rates in patients' post-primary ACL reconstruction (82).”*

3. It would be better to suggest a detailed mechanism of action of vitamin D in fracture healing, muscle repair, and cartilage degradation like the authors did in Vitamin D in Bone Oncology section..

Reply: We appreciate the reviewers comment and have extended the part on vitamin D and the mechanism of fracture healing as below:

Changes in the text: *“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).”*