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EVIDENCE-BASED MEDICINE

Vitamin D and bone fracture healing

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Abstract

AIM: To examine whether vitamin D is of potential relevance in the healing process of fractures.

METHODS: The present narrative review examined the bulk of the evidence based literature on the topic of vitamin D and bone healing in key electronic data bases from 1980 onwards using the terms vitamin D and bone healing, callus, fracture healing. All data were examined carefully and categorized according to type of study. A summary of the diverse terms and approaches employed in the research, as well as the rationale for hypothesizing vitamin D has a role in fracture healing was detailed.

RESULTS: The results show very few human studies have been conducted to examine if vitamin D is effective at promoting post fracture healing, and the different animal models that have been studied provide no consensus on this topic. The terms used in the related literature, as well as the methods used to arrive at conclusions on this clinical issue are highly diverse, there is no standardization of either of these important terms and methodologies, hence no conclusive statements or clinical guidelines can be forthcoming. There is a strong rational for continuing to examine if vitamin D supplements should be administered post-fracture, and ample evidence vitamin D is an essential hormone for functioning in general, as well as bone health and muscle as this relates to bone density.

CONCLUSION: Whether those with low vitamin D levels can benefit from supplements if their nutritional practices do not cover recommended daily amounts, remains in question.

Key words: Bone healing; Callus formation; Fractures; Fracture healing; Vitamin D

Core tip: This work describes the status of research on the role of vitamin D in bone healing, and offers suggestions for future research and current clinical practice.

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INTRODUCTION

Bone fractures are an important cause of morbidity and often, premature mortality among the older population. Among athletes and others, bone fractures due to trauma or excessive stress can seriously impair function and future activities and aspirations. In both older persons as well as younger persons minimizing the bone healing time, while maximizing bone strength of the fracture site during healing are important outcomes of the therapeutic process. Because inactivity as a result of a fracture is detrimental both to bone healing and health, and may exacerbate or foster vitamin D insufficiency or deficiency, it appears early or accelerated fracture healing would be highly desirable for returning fracture patents to function as soon as possible with minimal side effects.

The term vitamin D or cholecalciferol, which refers to a group of structurally related metabolites obtained either from dietary sources, supplementation, or sunlight and, bound by vitamin D binding protein is transported to the liver where hydroxylating enzymes initially catalyze it to form 25(OH)D (25-hydroxycholecalciferol). This product is then transported to the kidney where a second hydroxyl group is added to form 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D[1]. Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton. Calcitriol or 1,25$(OH)_2D_3$, the dominant D(3)-hormone and active form produces a wide array of biological responses by interacting with vitamin D nuclear receptors [VDR(nuc)] that regulate gene transcription in over 30 target organs and with a putative cell membrane receptor [VDR(mem1,25)] that mediates rapid biological responses[2]. A second type of receptor is a cell surface vitamin D receptor[1].

Not surprisingly, even though the nomenclature is highly varied in the related literature[1], a substantive body of research implies low vitamin D levels can significantly increase fracture risk, as well as increase the risk of fragility fractures[3]. By contrast, vitamin D supplements can reportedly reduce bone loss, especially at common fracture sites due to its effect on bone mineralization and maintenance[4]. As well, physical activities alone, and especially those that improve muscular loading of bone may enhance bone health and reduce fracture risk, whilst inactivity or muscle weakness may increase the risk of falls and subsequent fractures, and here again vitamin D can play a positive role as suggested by research conducted by Beaudart *et al*[5] and Shuler *et al*[6] and Tieland *et al*[7].

As outlined by Schindeler *et al*[8], fracture healing is a complex event involving a variety of differing processes. To better understand if fracture healing itself can be accelerated by the use of vitamin D supplements, either as a result of its impact on bone, or muscle or both, as suggested by Schunak[2] and Smith *et al*[3] this present review was designed to examine more closely, if vitamin D levels consistently predict the extent or rate of post-fracture bone healing, either directly through their osteogenic effects or indirectly through their effects on muscle function.

Since the literature remains equivocal about whether supplementation may be desirable for promoting bone healing in fracture cases, despite considerable prior discussions on this topic, it was felt a broad examination of the available literature would be helpful in this regard. The term fracture healing in this paper refers to the different stages during one of the four stages of fracture repair, but these are not strictly delineated as there is overlap in these stages, namely inflammation, soft callus formation, hard callus formation, and bone remodeling[8]. The terminology adopted to describe vitamin D in this paper is that most commonly used in the related literature, rather than any generic term as there is considerable diversity in this respect and it is highly challenging to interpret or standardize successfully (Table 1).

That is, employing the terminology of the authors whose work is reviewed, this review sought to examine whether deficiencies or insufficiencies in serum levels of 25 hydroxyvitamin D, the metabolite recommended for determining vitamin D status in humans[1], and 1,25-dihydroxyvitamin D, the hormone related to bone and muscle health, are specifically related to the fracture healing process.

At the same time it was hoped the review would provide recommendations for future research and practice in this area, given that the paper by Esche *et al*[9] published in 2011 concluded there were too few human based studies to arrive at conclusive recommendations.

MATERIALS AND METHODS

Using the same search strategy as Esche *et al*[9], the search term Vitamin D and Fracture Healing: produced 130 citations (of which 43 were relevant); Vitamin D and Bone Healing: produced 318 cited studies; Vitamin D and Callus Formation: produced 51 cited studies. Compared to Vitamin D alone: that had 59559 cited studies, it can be seen that although the topic is increasing in terms of citations, it is still understudied relative to other topics in the field. Accepted as valid sources of information were literature reviews, case studies, cross-sectional studies, prospective studies, and topics related to healing both direct and indirect that involved the topic of vitamin D and fracture healing or fracture non-union situations, and that appeared to address the topic of interest in this review.

RESULTS

Animal studies

Briggs *et al*[10] mention that dihydroxylated vitamin D metabolites may play a key role on fracture healing as shown by enhanced serum levels of 24R, 25-dihydroxyvitamin D levels in the long bone post fracture period. This idea has been examined for almost three decades and was supported early on by a number of studies using various animal models, such as the chick[11,12], mice[13], rat[14], and rabbit[15].

Melhus *et al*[16] who examined if osteoporosis and the healing of fractured osteoporotic bone were related, studied this issue in vitamin-D depleted ovariectomized rats known to induce weakening of the femoral neck. After initial ovariectomy, the rats were allocated to vitamin D deficient diets and sham operated rates received normal diets. At 12 wk, a fracture was induced in the tibia and fixed with a nail. Bone and callus formation were monitored with bone scans and vitamin D serum levels were measured. The results showed the experimental group had reduced bone mass, but no differences were found in the mechanical properties of the callus between the groups. The authors concluded that vitamin D is not crucial for fracture healing or for enhancing the mechanical properties of callus. This was a similar overall finding to that of Mao *et al*[17] who examined the influence of

Table 1 Diverse vitamin D terminology and modes of assessment in the related literature and related source

Serum 25(OH)D, 24R,25(OH)$_2$D, 1,25(OH)$_2$D[10]
Vitamin D$_2$[25]
24R,25-dihydroxyvitamin D$_3$ [24R,25(OH)$_2$D$_3$], and 1 α,25-dihydroxyvitamin D$_3$[1 α, 25(OH)$_2$D$_3$] hormonally active vitamin D metabolites[24]
Plasma 1,25-dihydroxyvitamin D$_3$ 25(OH)$_2$D$_3$[28]
24R,25-dihydroxyvitamin D$_3$[29]
25OHD concentration[36]
Serum 25-hydroxyvitamin D[37]
Serum 25(OH)D$_3$[38]
Serum 25-hydroxyvitamin D (25-OH-D$_3$, 24,25 dihydroxyvitamin D$_3$ [24,25(OH)$_2$D$_3$], 1,25 dihydroxyvitamin D3 [1,25(OH)$_2$D$_3$][44]
Serum 25-hydroxyvitamin D, 1,25 dihydroxyvitamin D$_3$, 24,25 dihydroxyvitamin D$_3$ metabolites[46]
25-hydroxyvitamin D [25(OH)$_2$D$_3$], 1,25 dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$], and 24,25 dihydroxycholecaciferol; 24,25(OH)$_2$D$_3$-active metabolites of vitamin D$_3$[30]
1,25 dihydroxyvitamin D [1,25(OH)$_2$D]-biologically active metabolite of vitamin D; 24,25(OH)$_2$D$_3$-a metabolite of vitamin D[54]
1,25(OH)D[58]
Vitamin D 25(OH)D[63]

Vitamin D refers to an inactive compound ingested from the diet or produced after exposure of skin to sunlight. 25-hydroxyvitamin D [25-(OH)D] is an inactive metabolite produced in the liver that is hydroxylated in the kidney to form 1-alpha,25-dihydroxyvitamin D [1,25(OH)$_2$D] is the active form of vitamin D that binds to vitamin D receptor or VDR on target tissues[11]. 24R,25-dihydroxyvitamin D3 [24R,25(OH)$_2$D$_3$] is an essential vitamin D metabolite[24,29].

both diabetes and vitamin D deficiency on bone repair in female mice. Although vitamin D deficiency aggravated the decrease in bone mineral density according to the diabetic state of the mice, it did not affect bone repair delayed by the diabetic state.

Hong *et al*[18] examined the potential effects of vitamin D on bone regeneration in dogs. Their results indicated that when combined with calcium, vitamin D supplementation may have positive systemic effects that influence bone regeneration more speedily. Similarly, Fu *et al*[19] found the effect of 1,25-dihydroxy vitamin D on fracture healing and bone remodeling in ovariectomized rat femora to favor fracture healing by improving the histological parameters of the bone, its mechanical strength, and tendency to increase transformation of woven bone into lamellar bone. Blahos *et al*[14] who investigated the impact of 1,25-dihydroxycholecalciferol on local healing of artificially induced tibial fracture in the rat, found the contributory effect to increase the weight of the fractured tibias. This was explained by its stimulatory effect on callus formation. Omeroğlu *et al*[15] found a single high-dose of vitamin D$_3$ did show positive effects in the healthy rabbit as far as fracture healing goes. This was supported by observations of increases in the sites mechanical strength after the administration of the high-dose vitamin D3.

Likewise, Liu *et al*[20] who examined the effect of vitamin D supplementation on the fixation of titanium implants in mice with chronic kidney disease-a problem that negatively affects bone regeneration and fracture healing, showed the bone-implant contact ratio and bone volume around the implant were significantly increased in the vitamin D supplementation group. It was concluded that these results implied vitamin D supplementation is an effective approach for improving titanium implants fixation in cases of chronic kidney disease. This is consistent with the finding by Gigante *et al*[21] that vitamin D is able to stimulate osteoblast differentiation of fracture site derived mesenchymal stem cells, and that administration of 25-OH-vitamin D after a fracture can improve the fractured bone's mechanical strength[22] and accelerate the initial mineralization process in the healing fracture region[23]. It was also consistent with the observation by Kato *et al*[24] that there is a biological role for 24R, and 25 (OH)2D$_3$ forms of vitamin D in the fracture healing process. This group actually found the presence of its receptor/binding protein in a callus membrane fraction of a chick tibial fracture.

Contrary results however, were those of Sun e*t al*[25] who found vitamin D binding protein had no effect on enhancing healing in rat bone defects. Melhus *et al*[16] too found vitamin D deficiency was not crucial for fracture healing or the mechanical properties of the callus, in rats with osteoporosis induced by ovariectomy. Lindgren *et al*[26] produced evidence that 1,25(OH)$_2$D$_3$ actually impairs fracture healing/in the rabbit, as did Andreen and Larsson in the rat[27]. Yet Jingushi *et al*[28] found serum 1 alpha, 25 dihydroxy vitamin D3 does accumulate into the fracture callous during rat femoral fracture healing. The authors suggested that plasma 1,25(OH)$_2$D$_3$ becomes localized in the callous, possibly regulating processes of fracture healing, a finding similar to that of Seo *et al*[29] Dekel *et al*[30] who examined fractures of the right tibia of chicks depleted of vitamin D, or given vitamin D$_3$ that were subsequently tested mechanically with respect to torsional stress, showed benefits of vitamin D. In this respect, they found repletion with 24,25(OH)$_2$D$_3$ and 1,25(OH)$_2$D$_3$ produced the most marked effects.

In sum, it is difficult to arrive at any consensus among the many approaches taken to examine the role of vitamin D on bone healing in the context of animal models. Results vary across models, as well as in the same models, and research approach, compounds, metabolites, and vitamin D derivatives are highly heterogeneous and unstandardized (Table 2).

Human studies

A good account of early clinical studies examining the

Table 2 Sample of studies using animal models to examine vitamin D influence on bone healing

Researchers	Model	Finding
Andreen *et al*[27]	Rat	Low doses $1,25(OH)_2D_3$ increased early callus mineralization
Blahos *et al*[14]	Rat tibia	$1,25(OH)_2D_3$ may produce a general response
Brumbaugh *et al*[45]	Chick	Chicks without 1 α, 25 dihydroxy D_3 supplementation showed prolonged fracture healing; 1 α, 25 dihydroxyvitamin D_3 promotes bone repair in the absence vitamin D_3, 25 hydroxyvitamin D_3, and 24, 25 dihydroxyvitamin D_3
Dekel *et al*[30]	Chick	$24,25(OH)_2D_3$, as well as $1,25(OH)_2D_3$ are essential for bone formation after fracture
Fu *et al*[19]	Rat	Vitamin D affected fracture healing positively for up to 12 wk compared to controls both biomechanically and histologically
Lindgren *et al*[49]	Adult rat	Rats given $1,25(OH)_2D_3$ had stronger fracture callus
Lindgren *et al*[26]	Rabbit	$1,25(OH)_2D_3$ impairs fracture healing
Lidor *et al*[12]	Chick	Active metabolites of vitamin D_3 are involved directly in fracture repair
Melhus *et al*[16]	Rat	Vitamin D deficiency does not impact fracture healing
Omeroğlu *et al*[15]	Rabbit	A single high dose of vitamin D_3 had Positive mechanical effects on fractured bone
Seo *et al*[29]	Chicken	$24,25(OH)D_2$ levels increased during fracture repair
Steier *et al*[23]	Rat	Vitamin D_2 accelerated initial mineralization in the fracture healing region

role of vitamin D in fracture healing has been provided by Gorter *et al*[31] Among these studies, research by Doetsch *et al*[32] tried to quantify the healing process of an osteoporotic fracture and to quantify the impact of vitamin D supplementation on the healing process among 30 women randomly assigned to a 800 IU vitamin D plus 1 g calcium or placebo in a double blinded prospective study. The researchers examined the mechanical properties of bone, as well as radiographs to evaluate healing. Bone mineral density was comparable among groups at baseline, and both increased over the 2 wk period. The authors found positive benefits of vitamin D_3 and calcium over the first 6 wk of the fracture for the active group.

Briggs *et al*[10] conducted a prospective study to examine the extent of bioavailable levels of vitamin D metabolites among 28 patients after a cross-shaft fracture of the long bone. They measured serum concentrations of 3 vitamin D metabolites within 48 h of a fracture, and at 1 wk and 6 wk post fracture. They found no change in serum concentrations of 25(OH)D or $24R,25(OH)_2D$ at any time. Mean serum $1,25(OH)_2D$ declined 21% over the course of the study, but no changes in bioavailable concentrations of any vitamin D metabolite were seen over the course of the study.

In a case study reported by Parchi *et al*[33] who examined the impact of vitamin D on the fracture healing process in a child, the authors found deficient vitamin D was a possible cause of the observed inadequate fracture healing process. More specifically, this research showed a significant effect on callus formation with the addition of vitamin D supplementation. Similarly, as reported by Pourfeizi *et al*[34] who conducted a case control study of 30 patients with tibial non union compared with 32 patients with normal bone healing, a high percentage of vitamin D deficiency was observed in tibial unexplained nonunion compared to normal union. Accordingly, the authors suggested vitamin D deficiency was a possible explanation for nonunion of traumatic fractures. This finding, which generally supported the observation of Van Denmark *et al*[35] of a relationship between non union of a distal tibial stress fracture associated with vitamin D deficiency, was contrary to that reported by Boszczyk *et al*[36] who compared vitamin D concentrations in patients with normal and impaired bone union. These authors found a vitamin D deficiency in 86% of examined patients. They found no difference though in 35 patients either with normal or with impaired bone healing. This was a retrospective case-control study, not a prospective randomized controlled study.

Ettehad *et al*[37] who recently examined changes in the vitamin D levels in the serum during healing with respect to fractures of the tibial and femoral shafts found levels of vitamin D declined by the end of the third week after the fracture. They felt this was demonstrative of the fact vitamin D is important in the formation and mineralization of the callus, and consequently supplements of vitamin D administered during the healing process might be helpful in those patients with tibial or femoral shaft fractures. Again, Wölfl *et al*[38] who examined the time course of 25(OH)D during fracture healing in persons with fractures of healthy bone *vs* osteoporotic bone over an eight week period found no inter group differences, making it difficult to establish a definite role for vitamin D in fracture healing in this case controlled study.

A more positive finding in favor of supplementation with vitamin D was reported by Gomberg *et al*[39]. This group described the outcome of efforts to heal subtrochanteric stress fractures caused by excessive long term treatment with alendronate. They found treatment with large doses of oral vitamin D increased serum 25-hydroxyvitamin D_3 to normal levels in 2 mo, after which it remained in the normal range using a maintenance dosage. Although fractures appeared worse on magnetic resonance imaging at 2 mo, 6 mo later, in conjunction with teriparatide treatment and calcium, there was faint bridging of cortical bone, and complete fracture healing occurred over the next year. The combined treatment seemed beneficial to the patient. Inklebarger *et al*[40] have also argued recently for the need to consider the presence

of low vitamin D levels when investigating the causes and possible interventions of femoral and tibial stress fractures in soldiers which may delay healing of these fractures, which is consistent with the finding that serum vitamin D levels are generally low in trauma cases in the United States[41]. In accord with the favorable results of Kato *et al*[42] in an *in vitro* experiment, and findings of low vitamin D levels among fallers[43], the most common cause of hip fractures in older people. Alkalay *et al*[44] found serum 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] was significantly reduced in the fracture patient, even though serum 25 hydroxyvitamin D_3(25-OH-D_3) and 24,25 dihydroxyvitamin D_3 [24, 25$(OH)_2D_3$] did not differ significantly between fracture patients and elective patients.

The data is confusing though because while Brumbaugh *et al*[45] indicated 1 alpha, 25-hydroxyvitamin D_3 promotes bone repair, Haining *et al*[46] found vitamin D metabolites had no influence in explaining fracture nonunion, even though vitamin D supplementation after traction avulsion fracture was recommended by Inkelbarger *et al*[47] and may have indirect beneficial bone effects[48] and appeared to have favorable healing effects in adult rats[49]. Tauber *et al*[50] found blood levels of several active vitamin D metabolites were decreased in some fracture patients, but not others, and attributed the decrease to their consumption during fracture healing. Meller *et al*[51] found a significant rise in plasma 24,25$(OH)_2$-D_3 on the day of the fracture compared to the level measured six weeks later, but no significant changes in plasma 25$(OH)D_3$ levels, in young patients with fractures, and suggested a physiological role for 24,25$(OH)_2$-D_3 in human fracture healing. In an animal model, Seo *et al*[29] implied that 24,25$(OH)D_3$ seems to be involved in the early stage of fracture repair and there is some form of physiological communication between the fractured bone and kidney that results in an increase of the renal derived 24-hydroxylase and circulating concentration of this metabolite. However contrary to research by Hoikka *et al*[52], Omeroğlu *et al*[53], and Lidor *et al*[54], Osório *et al*[55] found no changes in serum levels of 24R,25$(OH)_2D$, although levels of 1,25-dihydroxyvitamin D decreased after fracture over a 6 wk period.

In sum, as outlined in Table 1 and Table 3, the limited data in this area is highly variable and there is consequently little definitive data on whether vitamin D is helpful or not to the healing human fracture, although ample rationale for its post-fracture application exists (Table 4).

DISCUSSION

Fractures, especially those that occur among the elderly are considered to place an enormous burden on the individual, as well as on societies and their social and economic wellbeing. Considerable research shows that high rates of vitamin D insufficiency, referring to serum 25(OH)D concentrations less than 20 ng/mL[1], currently prevail in a high proportion of cases who sustain traumatic fractures[41], especially among the elderly. Consequently, improving vitamin D levels for these fracture patients has been advocated[41] to concentrations greater than 30 ng/mL[1] is advocated. But is there sufficient evidence for this idea? Esche *et al*[9] who conducted a short literature review that examined the question of whether vitamin D supplementation is beneficial for fracture healing found only two studies that were clinically oriented, and that most were studies using a wide variety of animal models. As they observed, both in the non human, as well as the human studies, there are negative, as well as positive results supporting vitamin D supplementation for enhancing fracture healing. As indicated by these authors, at a minimum, more research on larger samples, with more robust research designs, and a careful differentiation of baseline vitamin D status and agreed upon methods of determining vitamin D status is strongly recommended. In particular, more follow up studies, including a focus on events that take place at the four distinct phases of healing could be highly revealing, as opposed to those that simply measure short term fluctuations in vitamin D levels post fracture only, often with opposing results. Gorter *et al*[31] who conducted an updated literature review of 75 *in vitro* and 30 *in vivo* studies found inconsistent results concerning the mechanism of action of vitamin D on fracture healing. They found only four studies that examined the effect of vitamin D deficiency on human fracture healing and that indicated no effect. No studies examined the specific benefits of supplementation alone and studies discussing the cellular effect of vitamin D in fracture healing were nonconclusive.

Because one fracture is often followed by another, and preliminary evidence strongly supports a role for 24,25$(OH)D_2$, a vitamin D metabolite, in mammalian fracture repair[48], it would seem advantageous to strongly consider the use of nutritious sources, sunlight, and if not available, supplementary resources for those at greatest risk of second fractures, even if healing is not promoted. Given that a sizeable proportion of the population appears to suffer from vitamin D insufficiency[48], and that optimal muscle function is contingent on appropriate vitamin D levels[10-12], this alone might be helpful both in preventing future falls, and in enabling muscle forces around the fracture site to promote healing, while offering better protection of the bone while it is healing, even if the fracture site is not impacted directly. As well, the more generic benefits of vitamin D on physical wellbeing could serve to enhance activity levels that are key to building or maintaining bone mineral density, as well as preventing falls and future fractures, and fostering opportunities to be exposed to sunlight.

Corter *et al*[31] who specifically discussed the influence of vitamin D on bone mineralization and subsequent bone quality did not refer to the importance of vitamin D in fostering muscle function, as well as general wellbeing. Even though this group retrieved over 100 studies on this topic, the fact that they only found five *in vitro* studies performed on material from a fracture site, and only one *in vivo* study in the fracture patient, renders the role of vitamin D in this respect is very hard to discern.

Table 3 Sample of human studies designed to examine vitamin D influence on bone healing

Ref.	Type of Study	Finding
Briggs *et al*[10]	Examined vitamin D levels in 28 patents with diaphyseal long bone fractures at 48 h, 1 wk and 6 wk	Serum 1,25-dihydroxyvitamin D decreased from baseline, but serum 24R,25(OH)$_2$D levels did not change
Delgado-Martínez *et al*[22]	Investigated 25-OH-vitamin D effect in elderly with fractures	The addition of the vitamin D supplement improved strength of the fractured bone
Sun *et al*[25]	Examined effect of vitamin D$_3$ on the differentiation of mesenchymal stem cells from a human fracture site	Vitamin D$_3$ was able to modulate the the differentiation towards osteoblastic phenotype of the cells derived from fracture sites
Doetsch *et al*[32]	Quantified impact of vitamin D$_3$ + calcium on healing of osteoporotic fracture	Bone mineral density at 6 wk was higher in actively treated group suggesting vitamin D$_3$ had a positive effect 6 wk post fracture, but this was not maintained at 12 wk
Parchi *et al*[33]	Case report of child post-fracture	Hypovitaminosis D is a possible cause of inadequate fracture healing and refracture in children Vitamin D has a clear effect on callus formation
Boszczyk *et al*[36]	35 patients with inexplicable fracture healing impairments and controls were studied with regard to vitamin D	No impact of vitamin D deficiency noted
Ettehad *et al*[37]	Determined serum levels of vitamin D during fracture healing of 73 patients	Serum levels of vitamin D were reduced in curative period, suggesting vitamin D plays a role in the formation and mineralization of callus
Alkalay *et al*[44]	Assessed vitamin D metabolite levels in 28 patients after fracture, and 27 undergoing surgery	Serum 1,25-dihydroxyvitamin D$_3$ was significantly reduced in the fracture cases
Tauber *et al*[50]	Determined active metabolites of vitamin D$_3$ in 7 fracture patients	24,25(OH)$_2$D$_3$ levels showed a relative decrease, and a decrease in 1,25(OH)$_2$D$_3$ in 2 cases, suggesting these metabolites are consumed at fracture site during healing
Meller *et al*[51]	Levels of 25(OH)D$_3$ + 24,25(OH)$_2$D$_3$ were determined in 13 young patients with long bone fractures on admission and after 6-8 wk	Plasma 24,25(OH)$_2$,-D$_3$ levels rose over the 6 wk period, but no changes in 25(OH)D$_3$ levels occurred
Hoikka *et al*[52]	Treated 37 osteoporotic fracture cases with 1 α, OHD$_3$ – dosage 1 ug per day, plus 2.5 gm calcium	1 α-OHD$_3$ impacts fracture healing although 5/19 cases developed hypercalcemia

Table 4 Rationale for hypothesizing vitamin D as beneficial in fracture healing

Plays an essential role in bone formation and maintenance[1,58]
Has positive benefits on muscle strength[5,58]
Is involved in calcium and bone metabolism[1,29,37,54,57,58,64]
Deficiency is associated with fractures[58]
Can modulate cell growth and neuromuscular function[57,65]
May influence the inflammation stage of bone healing positively, as well as the callus formation stage[31]
Can help regulate inflammation and bone marrow and intramuscular fat deposits[58]
Protects older people from osteoporosis[58]
Enhance fixation of implants[58]
Deficiency may be associated with refrature[33]
Deficiency is associated with non union[34,35,67,69]

Although very few studies were evident in the data bases reviewed, this group noted vitamin D deficiency does not seem to hinder fracture healing, while supplementation with calcium increases the extent of the fracture callus at the fracture site and promotes healing.

In other research, Briggs *et al*[10] found decreased serum levels of 1,25-dihydroxyvitamin D in cases with diaphyseal long bone fractures but no changes in serum levels of vitamin D metabolites post fracture. However, Tauber *et al*[50] found a relative decrease in 24,25(OH)$_2$D$_3$ levels as well as a partial decrease in 1,25(OH)$_2$D$_3$ in cases suffering from delayed non unión and/or multiple fractures. Ettehad *et al*[37] too found these metabolites were reduced during the curative period in cases with either tibial or femoral fractures. They related this finding to the possible role of vitamin D in the formation and mineralization of the callus. Suzuki *et al*[43] found excessively low levels of 25(OH)D to be independently and significantly associated with an increased risk of falling in the elderly. Since adequate or high levels of supplementary vitamin D are protective of bone, and many elderly with fractures are already vitamin D deficient at the time of a fall, the most common reason for fracturing a bone, it seems taking supplements as a precaution against future fractures, as well as attempting to enhance fracture healing is potentially of great importance as supported by findings of Hoikka *et al*[52] who observed the addition of 1 alpha-OHD$_3$ to patients with osteoporotic hip fractures seemed to have a beneficial effect on fracture healing. Although this was also found to frequently cause hypercalcemia, and Boszczyk *et al*[36] found no difference in vitamin D concentrations in normal and impaired bone union, and disturbances in vitamin D metabolism are unlikely to play a major role in maintenance of non-union fractures[46],

vitamin D deficiency was present in 86% of examined patients. Inadequate levels of vitamin D were also found to prevail among patients undergoing orthopedic surgery who presented with bone healing complications[47].

Given that hypovitaminosis D could affect bone formation adversely[1], and that muscle strength capacity alone is found to benefit from vitamin D if taken orally[55], and in combination with calcium may decrease the incidence of non-vertebral fractures in older persons with low vitamin D levels[56] the sustained usage of these compounds may be more favorable than not for influencing fracture healing[57-60], despite the negative findings of the RECORD trial[61]. In addition, for those requiring internal fixation surgery post-fracture, the supplementation of vitamin D where this is found deficient may increase the bone-implant contact ratio and bone volume around the implant as reported by Liu *et al*[20] As well as fostering callus mineralization[62], resistance of the implant is also expected to increase favorably with appropriate supplementation[20].

However, the lack of definitive evidence precludes any conclusion or any set of useful guidelines concerning vitamin D supplementation post-fracture, where indicated, despite the magnitude of the societal burden incurred by the high prevalence of adults who experience delayed bone union, non-union, or future fractures due to suboptimal bone and muscle recovery post-fracture. Clearly, while *in vitro* models are helpful, a much greater effort in the clinical research arena appears warranted. In particular, more prospective long term follow-up studies of different vulnerable groups, and exposure to different levels and combinations of supplements appear desirable. For example, in the study by Omeroğlu *et al*[53] 116 guinea pigs who had received 50000 i.u./kg of vitamin D_3 intramuscularly benefited by this administration, suggesting this method of vitamin D delivery might be highly beneficial for accelerating the synthesis and organization of collagen fibers, the proliferation and differentiation of osteoprogenitor cells, and mineralization of the matrix. Alternately, Lidor *et al*[11,54] found the implantation of D_3 compounds directly into the fractures accelerated healing and prevented non-union. Another mode of delivery, namely subcutaneous delivery after an experimental fracture improved fracture strength in a dose dependent manner[22] as did vitamin D injections[20]. Thus different modes of delivering vitamin D post fracture may produce positive, albeit differential impacts on the healing bone that might be worth investigating. Another area for research may extend to testing different vitamin D metabolites and the affinity of callus membrane receptor/binding proteins for these as observed by Kato *et al*[42] in chick tibial fracture healing callus. Another form of study might be focused on assessing the viability of vitamin D receptors, and whether their functional status is linked to the outcomes of vitamin D analyses in the context of fracture healing, bearing in mind that vitamin D measures may not be useful for judging vitamin D in clinical studies. The consistent use of assays to examine plasma concentrations of 25-hydroxyvitamin D [25(OH)D] may provide the best method for assessing the presence of any prevailing vitamin D deficiency[63].

In sum, since the elderly in particular, who are highly prone to fractures, are at risk of vitamin D deficiency and insufficiency, as well as reduced exposure to sunlight, accelerated bone[57] loss, skeletal fragility and reduced muscle power[58], the application of post-fracture vitamin D supplements would appear beneficial[64,65]. In particular, as outlined in Table 4, vitamin D in its different physiological forms is implicated in bone metabolism[59], and muscle-bone interactions[58] and potentially promotes fracture healing and mineralization[62,66]. Consequently, identifying the optimal vitamin D level that is desirable in the post-fracture state, as well as the best mode of delivery appears highly warranted. Stressing the importance of compliance with recommendations regarding supplements, if indicated, acknowledging the importance of calcium supplementation when vitamin D levels are deficient, and applying doses of vitamin D known to have clinical efficacy is more likely than not to foster optimal post fracture bone remodeling processes and functional benefits especially for those at risk for osteoporotic fractures[57], falls that lead to fractures[58], fractures requiring fixation[20] or atrophic fracture nonunion in the presence of vitamin D deficiency[35]. As outlined by Maier *et al*[60] about 20% of seniors receive vitamin D at the time of their fracture and after the event despite the documented 81% prevalence of vitamin D deficiency. In this regard, it appears reasonable to suggest efforts to improve vitamin D supplementation in seniors both before and after a fracture event are warranted, especially if it is confirmed that serum levels of 1,25-dihydroxyvitamin D are deficient[61], non-union appears to prevail or is imminent[67], or the diagnosis of a stress fracture is forthcoming[68]. Based on findings of vitamin D deficiencies among patients with non-unions[69], studies that show calcium and vitamin D_3 supplementation may enhance callus formation in the osteopenic or osteoporosis patient[32], and animal models that show a combined effect of 1,25 $(OH)_2D_3$ on serum calcium and phosphate and bone matrix formation[62], fracture healing rates as well as bone quality or both may be forthcoming[70]. Alternately, it is possible, that by inadvertently delaying fracture healing, failure to provide adequate vitamin D supplementation in those suffering from vitamin D insufficiency may result in longer curative periods of inactivity and pain, thus potentially fostering further vitamin D insufficiency or depletion.

COMMENTS

Background

Fractures of the bone and their mechanisms of repair are topics that have been the subject of investigation for more than three decades. In both cases, both preventing and treating fractures and the role of vitamin D in both processes have received increasing attention in the literature due to the importance of minimizing post-fracture complications, especially among the older population.

Research frontiers

While vitamin D is of potential relevance in the healing process of fractures, it is unclear whether supplements should routinely follow fracture injuries, and if so

what is the evidence base for this.

Innovations and breakthroughs

The present narrative review examined the bulk of the literature present in key electronic data bases from 1980 onwards. The results show very few human studies have been conducted to examine if vitamin D is effective at promoting post fracture healing, and the different animal models that have been studied provide no consensus on this topic. While not new, this gap in the literature indicates much more attention is required in this realm than is currently evident.

Applications

Given that vitamin D is an essential hormone for functioning in general, those who have low levels of the hormone in general, can probably benefit from supplements in the post-fracture period if their nutritional practices do not cover recommended daily amounts, and they are at high risk for non union and/or subsequent fractures. Since those who experience non union or delayed union may inadvertently suffer from inadequate vitamin D exposure, and vitamin D insufficiency, or deficiency this approach appears worthwhile to contemplate.

Terminology

The term vitamin D in this paper refers to all forms of this hormone and/or its metabolites. The terms bone healing and fracture healing are used interchangeably.

Peer review

The review by Marks is well written.

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