

Vitamin D and Fracture Healing: An Ongoing Puzzle

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ABSTRACT

BACKGROUND: Fractures and their repair mechanisms have been topics subject to various forms of investigation for several decades. In both instances, preventing and treating bone fractures and a possible role for vitamin D in both these processes has received increasing attention in the recent literature with no definitive consensus.

QUESTIONS: Whether vitamin D is of potential relevance in preventing future fractures, and especially in the impacting the healing process of current fractures.

METHODS: Building on prior work, the present narrative review specifically examines the related literature housed in key data bases over the last five years and others that have prevailed over the past 30 years.

RESULTS: Despite a large period of time, very few studies covering the present topic can be considered to answer the review questions effectively, and among those that prevail, no conclusive evidence regarding the routine use of vitamin D as a supplement in cases with bone fractures and their prevention has emerged.

CONCLUSION: More research regarding a role for vitamin D in bone fracture healing and prevention is warranted.

Key words: Bone healing; Fractures; Fracture healing; Prevention; Supplementation; Vitamin D

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INTRODUCTION

Fractures, especially those that do not heal optimally are an important cause of excess morbidity and premature disablement, not only among older adults, especially those who are institutionalized, but also among athletes, children, those with comorbid health conditions, those receiving corticosteroid therapy, and oftentimes, otherwise healthy adults. Indeed, even if the bone[s] involved eventually heal, the presence of one or more bone fractures often represents a personal individual challenge in terms of impeding or limiting activities of daily living quite markedly, as well as work capacity, future activities and aspirations, especially those involving sports. Moreover, the medical needs and costs that may arise from surgical failure in the event bone fracture healing is limited^[1] or inadequate, as well as those that arise from excess pain, is likely to be substantive. Minimizing the time required for bone healing, while maximizing the strength of the fracture site during healing are consequently highly desirable outcomes of the therapeutic process for both older adults, as well as younger persons, as well as for primary and secondary fracture prevention purposes. In addition, because inactivity as a result of a fracture is detrimental both to bone healing and health, it appears early or accelerated fracture healing, a process that recapitulates certain aspects of skeletal development and

growth^[2] would be highly desirable for returning fracture patients to function as soon as possible. On the other hand, simply applying some commonly agreed upon standard, rather than claims that have not been verified substantively may prove extremely costly to the patient as well as society.

A substantive body of research in this regard has consequently sought various strategies to offset the healing problems associated with fractures, as well as their causes, and among the most studied topics in this regard is the vitamin known as cholecalciferol or vitamin D. The rationale for this focus is evidence that low levels of vitamin D, a steroid hormone involved in bone remodeling and bone mineralization^[3], plus bone resorption^[3], and calcium homeostasis^[4] can significantly impact fracture risk^[1], especially at common fracture sites^[5]. As well, playing a pivotal role in skeletal health and calcium homeostasis^[6], as well as physical activities, by virtue of its muscle function regulation, especially those that improve muscular loading of bone, the presence of sufficient levels of vitamin D may have a bearing on both bone health and fracture risk as suggested by research conducted by Geusens *et al*^[7], Bischoff *et al*^[8] and Tieland *et al*^[9] among others. Other evidence in favor of a skeletal role for vitamin D is its link to bone development^[10], overall health, and balance capacity, plus general health, as well as the idea that the stronger one is during the recovery stage of a fracture, the more rapidly the fracture site will heal^[11]. Recent evidence suggests the actions of vitamin D in bone appear to be multiple^[12] and can negatively or positively regulate bone mineral content depending on the prevailing physiological and pathological circumstances. However, even though acute hip fracture cases in a sunny climate had lower vitamin D levels than controls^[13], and a globally situated deficiency in vitamin D has been identified as affecting more than one billion people, especially older people prone to fracture^[6,14], the application of vitamin D as a fracture prophylactic remains contentious, despite its possible efficacy for reducing fractures in at risk groups^[1] and for enhancing post-fracture healing efficacy, in particular. Indeed, the recent conclusion that vitamin D has no clinically meaningful effect on the maintenance of bone mineral density^[15] implies the compound is potentially one that has no bearing on bone health or on fracture healing at all despite a number of fairly well established roles for vitamin D as per Box 1 below.

This review examines the status of the literature concerning fracture healing and if this can be mediated or moderated by vitamin D in some way, as this pertains to the controversial use of vitamin D supplements pre and post-fracture. The specific purpose of this present review was to carefully examine the prevailing research findings and overall science based knowledge in this realm to ascertain if this frequently contested issue is nearer a resolution than not.

Since fractures continue to prove highly prevalent, as well as disabling and often lead to second fractures and considerable life-

long disablement, especially in instances of impaired fracture healing^[28], and available meta-analyses on this topic do not always produce uniform conclusions, it appears important to continue to examine the rationale for and the evidence concerning a role for vitamin D in fracture healing.

Simultaneously, we hoped to offer recommendations for future research and practice in this regard, including preventive practices against fractures.

METHODS

To achieve the goals of this report, the present search strategy employed the search terms Vitamin D and Fracture Healing as key words, first for all available articles on the topic, and then for those more specific to the time period Dec 29, 2013-Dec 29 2018 in the PUBMED data base as per Eschele and Aeschlimann^[6]. As well, in accord with these authors, the terms Vitamin D and Bone Healing, and Vitamin D and Callus Formation were employed. Other databases explored were: Web of Science, Scopus, Science Direct and Academic Search Complete. To provide some clarity as to whether there is evidence that vitamin D can either heighten fracture risk directly or indirectly, or can impact the healing process associated with a fracture, accepted as valid were relevant preclinical studies, as well as various full length clinical reports, and research publications related to vitamin D and fractures, vitamin D and bone metabolism, plus vitamin D and fracture healing. No abstracts or foreign non-English articles were analyzed. No restriction was placed on the mechanism of injury when fractures were discussed, nor the fracture site, health status, or age of the subject.

After completing a comprehensive review that pertained to the above topics, salient references as well as those cited in some texts were selected for further reading and discussion. With no substantive body of research on any of the above topics, especially in the realm of the specific topic of vitamin D and its impact on clinical fracture healing, a largely narrative and qualitative review approach was selected as the most salient approach to addressing the key questions underpinning this effort. Although very few well-designed studies are evident in the present body of literature, it was believed that by including the most recent material, plus data related to prior work on vitamin D, along with references from other review and research based articles that sufficient material would be available to permit a broad picture of the state of the art regarding the topic of this review to emerge.

To render this heterogeneous material useful to reflect upon, the ensuing discussion below first outlines some general findings, followed by some results observed in animal models that have been attempted and finally those designed to explore any potential clinically relevant association between fractures and vitamin D, especially whether vitamin D supplementation can impact fracture

Box 1 Rationale for hypothesizing a role for vitamin D and its metabolites in fracture healing.

Plays essential role in bone development, mineralization, and maintenance[1,6,16,18]
Positively benefits muscle strength[17]
The 24R,25(OH)(2)D(3) vitamin D metabolite is essential for fostering bone fracture healing[20]
Can enhance fracture implant fixation[19]
May delay osteoporosis development[21]
Facilitates cross-talk between muscle and bone derived hormones[21]
Facilitates calcium, phosphate, and bone metabolism[6,22]
May modulate cognitive health status and pain-hence health behaviors that affect bone physiology
Vitamin D metabolism is an important intrinsic mechanism for optimizing osteoclast differentiation, ameliorating osteoclast activity, and potentially promoting the coupling of bone resorption to formation[23]
Deficiency is associated with skeletal abnormalities and increased risk of fractures[6,17,22]; increased risk of refracture[26], osteoporosis, many diseases[17], non-union[25] increased risk for fragility fractures[24] and falls[8,22]

outcomes in any way. An attempt was made to categorize findings as either supportive of a possible beneficial fracture-vitamin D link, versus a non supportive or contrary view.

It was decided not to focus on cellular studies in this effort, which have been well-reviewed. Gorter *et al*^[30], and Norman *et al*^[20] should be referred to as well for a sound overview of the biological mechanisms of action of vitamin D and its metabolites, a topic not directly discussed in this report. Nonetheless, taken as a whole, it is believed this ensuing review that examined uncontrolled as well as controlled studies of various types, covers almost all, if not all relevant knowledge on the topic of vitamin D and fracture healing, and related issues.

RESULTS

General observations

As an example of the state of the literature on the present topic, as of December, 29, 2018 the entire **PUBMED** data base yielded the following pattern of reports.

However, on careful analysis, fewer than 25 of those articles matching the key words and published in the last five years could be deemed pertinent for purposes of this current review. Of these, very few were clinical studies that could be said to be well-designed or to specifically examine fracture healing outcomes in any way. It was also evident that the term vitamin D was applied in multiple ways in

Table 1 Table depicting search terms and their relative results concerning the current topic

Key word	Number of reports	Number in last 5 years
Vitamin D	78989	21290
Fracture healing	24519	6234
Bone healing	51413	13542
Callus formation	5469	1200
Vitamin D + fracture healing	208	83
Vitamin D + bone healing	433	121
Vitamin D + Callus formation	55	8

Table 2 Sample of studies using animal models to examine vitamin D in the context of fracture healing or prevention, showing most are favorable, but not all.

Researchers	Population	Key Findings
Andreen <i>et al</i> [55]	Rats	Low doses vitamin D increased early callus mineralization
Aydogan <i>et al</i> [32]	Rats	Vitamin D application was similar to no treatment effect
Blahos <i>et al</i> [47]	Rats	Vitamin D may produce a general response indicative of increased bone formation
Blahos <i>et al</i> [47]	Rats	Dietary vitamin D intake improved general bone health after spinal fusion
Brumbaugh <i>et al</i> [57]	Chicks	Chicks without vitamin D supplementation showed prolonged bone healing
Cao <i>et al</i> [58]	Rats	Fracture healing was unaffected by adding a vitamin D analogue
Dekel <i>et al</i> [59]	Chicks	Vitamin D metabolites appear essential for bone formation post fracture
Delgado-Martinez <i>et al</i> [36]	Rats	Vitamin D strengthened fractured bones of elderly animals
Fu <i>et al</i> [37]	Rats	Vitamin D supplementation affected fracture healing positively
Jinguisha <i>et al</i> [44]	Rats	Serum vitamin D accumulates into callus during healing
Kaastad <i>et al</i> [60]	Rats	Vitamin D depletion reduced femoral bone mineral density/neck fracture strength
Lindgren <i>et al</i> [61]	Rats	Rats given a vitamin D metabolite had stronger callus
Lindgren <i>et al</i> [62]	Rabbits	Vitamin D impairs fracture healing
Lidor <i>et al</i> [63]	Chicks	Active D3 metabolites are directly involved in fracture repair
Martineau <i>et al</i> [31]	Mice	Suboptimal endochondral ossification during fracture repair assisted by vitamin D
Melhus <i>et al</i> [33]	Rats	Vitamin D deficiency does not impact fracture healing
Omeroglu <i>et al</i> [48]	Rabbit	High dose vitamin D3 produced positive fracture healing effects
Seo and Norman [46]	Chicks	Renal and serum vitamin D levels increased during healing
Steier <i>et al</i> [64]	Rats	Vitamin D2 accelerated initial fracture mineralization
Takeda <i>et al</i> [65]	Rats	Long-term treatment of rats with vitamin D complex suppressed bone turnover positively

the prevailing body of literature, and often the terminology reported did not correctly differentiate the active form of vitamin D from its various inert or potentially less active metabolites. In addition to the low numbers of available studies and their heterogeneity, outcomes assessed were often dissimilar, with some focusing on vitamin D deficiency effects, some on vitamin D supplementation effects, some on the functions of active vitamin D and/or inactive vitamin D metabolites, and some on vitamin D and fracture and falls prevention.

It was also evident that in addition to the low numbers of available studies and their heterogeneous samples, outcomes were often assessed over vastly differing time frames, with differing instruments, or not assessed at all in many of the prevailing research efforts. Highly diverse intervention approaches, and dosages of vitamin D applied or measured were similarly evident. Moreover, very few randomized controlled clinically oriented studies were located, and discordant reports were more common than not on any topic examined in the present realm, regardless of substrate. In the forthcoming sections, first some observations from animal based studies are provided, followed by those conducted on or examining various clinical samples.

Overview of laboratory based studies

Among those studies that have explored vitamin D in the context of fracture healing using various animal models, it was observed that very few have been published recently. As well, it was observed that very few examined the four stages of fracture healing, including inflammation, soft callus formation, hard callous formation, and remodeling^[30] in the context of establishing a cause-effect or mediating or moderating relationship between vitamin D and any aspect of these four complex fracture healing stages. Moreover, unlike some other areas of medicine where certain animal models have been developed or preferentially selected to afford a sound basis for clinical applications, Table 2 shows that among those species studied, no consistent model concerning vitamin D and any aspect of fracture healing appears to prevail.

While this lack of consensus may reflect the fact that all these models are indeed similar, there are very few comparison studies to back up this possibility in this regard. Hence the degree to which species differences may account for the lack of overall consensus in establishing the facts in the present realm cannot be discerned with any degree of certitude, despite the importance of such information. In addition, the various animal species used for answering related questions on vitamin D in the context of fracture prevention and healing shown in Table 2 may or may not be optimally appropriate models for examining vitamin D fracture linkages in either animals or humans.

In addition, as depicted in Table 2, the use of diverse bone sites, rather than similar bone sites, study designs that have varied in terms of study durations, outcome measures, and outcomes assessed must surely account for some of the inconsistent findings reported in Table 2. As well, animals of variable ages and genders, subjected to diverse vitamin D agents that may not interact consistently in the distinct stages and mechanisms associated with fracture healing render conclusions about whether or not vitamin D impacts fracture healing in any of the models studied challenging to differentiate. As well, the implications of those studies focusing on vitamin D metabolite influences versus active vitamin D are similarly hard to comprehend.

Thus, while Martineau *et al*^[31] argued for the possibility of vitamin

D metabolites as a potentially important factor in fracture healing, an argument supported by St. Arnaud *et al*^[14], and Avdogan *et al*^[32], Melhus *et al*^[33] provided no strong support for this claim.

Moreover, although findings of Melhus *et al*^[33] were similar to those of Mao *et al*^[34] in this regard, Fischer *et al*^[35] who examined mice aged 26 weeks exposed to ovariectomy, femoral fracture, and external fixation found those mice who received a vitamin D supplemented diet did show improved fracture healing and bone tissue biomechanics, as did Delgado-Martinez *et al*^[36]. Similarly, Fu *et al*^[37] found vitamin D to favor fracture healing, bone content, and bone strength, and the transformation of woven bone into lamellar bone, results generally consistent with results by Goodman *et al*^[38] who suggested vitamin D promotes osteoid maturation and mineralization in vitamin D-deficient rats.

However, while more of the available related studies on this topic do in fact support some form of vitamin D-fracture linkage, no conclusions can yet be drawn, in light of the limited numbers of comparable studies, potential publication biases, and weak study designs that may heighten the risk for spurious conclusions. Osteoblast responses in animals may also not replicate those in humans^[39], and modes of fracture induction may not parallel those found in the clinic. Yet, several mechanisms that are consistent with a number of prior cellular and some clinical studies can potentially explain some of the more supportive findings.

Table 3 Sample of clinically oriented studies examining the association of vitamin D and fracture healing showing thematic variations and diverse approaches and categorized as either supportive or non supportive of a positive role for supplementation

Researchers	Study Focus
Support for supplementation	
Alkalay <i>et al</i> [78]	Assessed vitamin D metabolite levels postfracture/surgery
Briggs <i>et al.</i> [69]	Examined vitamin D levels in 28 fracture cases
Brinker <i>et al</i> [79]	Patients with nonunions
Behrouzi <i>et al</i> [80]	Hip fracture patients
Clutton <i>et al</i> [23]	Patients with 5th metatarsal fractures
Dawson-Hughes <i>et al</i> [81]	Community-based adults 65 yrs and older
Degli Espositi <i>et al</i> [77]	3475 patients with fragility fractures
Doetsch <i>et al</i> [68]	Quantified impact vitamin D3 + CA on osteoporitic fractures
Ettehad <i>et al</i> [74]	Measured vitamin D in 73 fracture patients
Fentaw <i>et al</i> [6]	118 fracture patients followed up prospectively
Gigante <i>et al</i> [41]	Examined effect vitamin D on fracture site mesenchymal stem cells
Gorter <i>et al</i> [66]	Adults with upper or lower extremity fractures
Harwood <i>et al</i> [83]	150 hip fracture cases-surgical
Inklebarger <i>et al</i> [84]	Case study
Kurado <i>et al</i> [85]	899 post-menopausal women foll. for 6 yr
Lips <i>et al</i> [86]	Meta-analysis
Parchi <i>et al</i> [26]	Case report of child post-fracture
Ruohalo <i>et al</i> [87]	756 young men with stress fractures
Tauber <i>et al</i> [88]	Determined active metabolites of vitamin D in 7 fracture cases
Counter evidence	
Bernstein <i>et al</i> [89]	1030 hip fracture surgical cases
Bodendorfer <i>et al</i> [90]	201 orthopedic trauma cases foll. 20 months
Bosszczyk <i>et al</i> [73]	35 patients with inexplicable fracture healing problems
Hoikka <i>et al</i> [82]	Supplementation study of 37 osteoporotic fracture cases
Kolb <i>et al</i> [91]	94 postmenopausal women with wrist fractures
Meller <i>et al</i> [92]	Prospectivve study of 13 young fracture patients
Moosavi <i>et al</i> [28]	46 cases with closed tibial fractures foll. 6m
Tanaka <i>et al</i> [93]	107 patients with vertebral fractures received vitamin D
Wasnik <i>et al</i> [54]	Adult stem cells
Wolf <i>et al</i> [76]	30 patients with wrist, shoulder, hip fractures

For example, Liu *et al.*^[40] 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, did show that the bone-implant contact ratio and bone volume around the implant can possibly be increased in response to vitamin D supplementation. This result was consistent with that of Gigante *et al.*^[41] who demonstrated vitamin D stimulated osteoblast differentiation of fracture site-derived mesenchymal stem cells, as well as observations that the post-fracture administration of vitamin D can improve the fractured bone's mechanical strength, as well as its degree of healing^[36]. Early observations by Kato *et al.*^[42,43] did reveal the presence of vitamin D receptor/binding proteins in callus membrane fractions of a chick tibial fracture, thereby suggesting a role for active vitamin D, as well as vitamin D metabolites as highly plausible physiological and biological substrates in the context of fracture healing.

Jinguisha *et al.*^[44] too, who found that the active form of vitamin D does accumulate in the fracture callous during fracture healing, indicated this process might possibly help to regulate selected stages associated with fracture healing in some way, a finding similar to that of Seo *et al.*^[45,46], Blahos *et al.*^[47], and Omeroglu *et al.*^[48,49]. A more recent investigation by Han *et al.*^[50] also tended to support this view of a possible critical role of vitamin D in the formation of normal trabeculae and strong callus at fracture repair sites as outlined by McCabe *et al.*^[51].

Here again, however, contrary results include those of Sun *et al.*^[52] who found vitamin D binding protein had no effect on enhancing healing in rat bone defects. Vitamin D can also increase the state of bone resorption, or raise the risk for further fractures or negative healing outcomes^[22], may not foster better implant healing^[53], and may well hamper the initial pro-inflammatory state that occurs post-fracture as indicated by Wasnik *et al.*^[54].

Overview of clinical studies

Although a good account of the variety of available clinical studies examining the role of vitamin D in fracture healing has been provided by Gorter *et al.*^[30,66] and Sprague *et al.*^[67], as in animal model studies little advanced work in this realm prevails. There is also very little systematic work on any of the most common fracture sites known to occur clinically, almost no double blind randomized controlled trials in the context of supplementation studies, highly diverse fracture sites are studied, modes of fracture fixation are not always forthcoming, and bone status varies from healthy bone to osteoporotic bone to bone non union situations. Some researchers studied young patients, others older patients, some measured inactive metabolites, some active vitamin D, and some measured both, and levels of vitamin D sufficiency, or deficiency if stated, were not consistently defined.

Among these studies, most surprisingly, very few strove to assess fracture healing or relevant correlates of this, although that by Doetsch *et al.*^[68] who 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 1g calcium or placebo in a double blinded prospective study stands out. The treatment which included vitamin D and calcium supplementation improved healing as determined by the mechanical properties of the bone, as well as radiographs. Bone mineral density was comparable among groups at baseline, and both increased over the 12 week period. The authors found positive benefits of vitamin D3 and calcium over the first 6 weeks of the fracture for the active group, which may have

been beneficial, but this was a very small sample, the sample were osteopenic or osteoporotic women only though, and fracture healing and the actual role of vitamin D per se was not easy to verify. Why bone mineral density increased in both groups was also hard to comprehend.

There does however seem to be some decline in levels of active vitamin D over time after a fracture, as observed by Briggs *et al.*^[69] who sought to examine the extent of bioavailable levels of vitamin D metabolites among 28 long bone cross-shaft fracture patients over a 6 week period. These changes were paralleled by concomitant related changes in calcium levels that were maintained over 6 weeks and seemed associated to the observed 21% decline in the patients' active vitamin D levels. Since the real effect of vitamin D on fracture healing may be due to its effect on calcium metabolism^[70], it is clear a role for vitamin D in fracture healing cannot be ruled out.

By contrast, the presence of deficient vitamin D may produce a state of inadequate fracture healing that is reversible with the application of vitamin D supplementation^[26]. Fracture nonunion situations have also been attributed to the presence of a vitamin D deficiency^[71]. This latter finding, which generally supported the observations of Van Denmark *et al.*^[72] of a relationship between non union of a distal tibial stress fracture and a vitamin D deficiency, was contrary however, to that reported by Boszczyk *et al.*^[73] who compared vitamin D concentrations in patients with normal and impaired bone union. Although a vitamin D deficiency was reportedly found in 86% of 35 patients examined by Boszczyk *et al.*, no deficiency difference was noted among those with normal or impaired bone healing.

However, Ettehad *et al.*^[74] who recently examined changes in the serum vitamin D levels during fracture healing of the tibial and femoral shafts did find levels of vitamin D to decline by the end of the third week post fracture that suggested a possible role for vitamin D during the formation and mineralization stages of callus formation. This group also discussed the possibility of the importance of applying supplements of vitamin D during the fracture healing process since vitamin D might need be extracted from remote skeletal sites to foster optimal post-fracture healing.

This latter argument seems reasonable, in light of similar conclusions by Fischer *et al.*^[1], Fentaw *et al.*^[6], and Gomberg *et al.*^[75]. However, given that Wolf *et al.*^[76] who examined the time course of vitamin D levels during fracture healing in persons with fractures of healthy bone versus osteoporotic bone over an eight-week period found no intergroup differences, caution is advised in arriving at any conclusion as to whether vitamin D status at the time of fracture can affect fracture healing, or whether vitamin D supplementation is desirable. Although Degli Espositi *et al.*^[77] found osteoporosis drug treatment, especially when consistently applied in combination with calcium/vitamin D correlated with a lower risk of both re-fracture and all-cause mortality they do not definitively support a role for vitamin D supplementation in the fracture healing processes^[1,67].

DISCUSSION

Fractures are often highly common debilitating occurrences among older individuals especially those with prevailing chronic health conditions, as well as in cases where bone healing is delayed or inhibited, or a state of non-union, pseudo-arthritis, or healing in an unfavorable anatomical position occurs^[94,95]. Their prevention as well as their treatment, along with research to uncover how to optimize fracture healing are thus topics of high clinical importance. In this regard, given the documented role of vitamin D in mediating

bone health, a number of researchers have sought to examine the question of whether vitamin D deficiencies lead to fractures, and whether vitamin D supplementation is beneficial or not for fostering fracture healing. Although several investigative reports on this topic have been generated in both animal and human models, no report to date has provided any strong support either for regarding vitamin D levels as predictive of fractures or fracture healing processes or for negating this possible role. In this regard, the aim was to examine and summarize the most up to date literature to establish if any progress has been made in this realm.

As per findings of Gorter *et al.*^[30,66], plus those of Sprague *et al.*^[67], and van Driel and van Leeuwen^[39], this remains an unresolved topic, albeit one of high potential import.

Indeed, despite a number of animal model and clinical research efforts regarding the role of vitamin D and its possible association with fracture healing/prevention, it seems impossible at present to arrive at any definitive answer as to the need to consider vitamin D supplementation in the context of either fracture prevention or healing, whether supportive or non-supportive. Promising unpublished studies^[67] also remain inconclusive.

As a result, claims for or against vitamin D supplementation in the context of fracture prevention or healing must remain in question, even if the vitamin has been deemed inconsequential in fracture contexts^[15]. In addition, substantive numbers of cellular and basic studies conducted over the years do not negate a role for vitamin D in bone remodeling, fracture healing or prevention or both, although there seems to be a possible bi phasic dose-related response, differing rates of Vitamin D2 and D3 clearance^[96], differing vitamin D supplementation needs^[96] and inter-species differences. As well, vitamin D may not only be osteo-protective in some cases^[97,98], but potentially relevant in exerting optimal fracture repair^[94], direct effects on both osteoblasts as well as osteoclasts^[99], and bone formation^[96], as well helpful for purposes of fracture prevention^[100], falls prevention^[96], and attenuating new fracture occurrence rates^[101].

Moreover, many clinical studies not only suffer from one or more serious design problems, potentially inadequate or poorly timed or no follow-up observations, varied definitions and modes of measuring vitamin D, some of which are less accurate than others^[102], but also a great mix of trials among other attributes^[103]. The type of movement that occurs during healing-which can help or hinder healing^{-[95]} is also seldom discussed-thus precluding any fracture healing consensus in vitamin D supplementation studies. In addition, not only is the nature of any prevailing vitamin D interactions with differing fracture healing stages, either not examined, or impossible to accurately unravel in most studies, but failure to establish the potential influences of age, medication intake, health status, fracture type, site and causative mechanism, levels of daily activity, compliance with supplementation, along with its dosage and mode of delivery, among other possible fracture healing determinants, further weakens the ability to tease out whether vitamin D supplementation is useful, or not in relation to the varied pathways through which bone can heal.

Furthermore, although more studies than not support possible linkages (Tables 2 and 3), it is not possible to state conclusively whether low vitamin D found in fracture cases is a consequence, rather than a cause of the condition, or a spurious finding related to health status and metabolic health factors^[104].

Moreover, even though Briggs *et al.*^[69] found no changes in measures of vitamin D2 metabolites in their prospective 6 week study of fractures that would warrant concern, the finding that serum 1,25(OH)2D3 levels declined 21% over 6 weeks relative to

baseline, may yet speak to an unmet need bolster any potentially declining levels of vitamin D post fracture even though this idea was not discussed. As outlined by Yoshida and Stern^[22], and Fisher *et al.*^[105] controlled levels of vitamin D supplementation may yet be warranted in efforts to attenuate post-fracture declines in bone density, as well as efforts to help to accelerate wound healing, shorten the immobilization period, and increase muscle strength^[106-108]. In addition, based on findings by Ettehad *et al.*^[74] even if baseline vitamin D levels are deemed sufficient, over time, vitamin D levels may not only decline during the healing process, due to an increased fracture healing need, but because of the patient's decreased exposure to sunlight or nutrients or both, comorbid illnesses, as well as certain prescribed medications, non-prescription drugs, smoking, and alcohol use^[95].

Consequently, careful assessment, surveillance, and early and appropriate supplementation of vitamin D or a vitamin D metabolite as indicated, may yet yield more successful formation and mineralization of the fracture callus than not, or prevent future fractures more readily or both^[95]. On the other hand, since Johnson *et al.*^[13] did find the majority of 448 hip fracture patients to exhibit vitamin D insufficiencies, and a causal relationship between osteomalacia and fractures of the hip can be assumed in the elderly^[109], those patients who fail to receive vitamin D supplements may not only develop rickets, but may also exhibit evidence of prolonged or suboptimal fracture healing^[57]. Dawson-Hughes *et al.*^[110,111], also identified that a desirable level of vitamin D for older men and women may still place these vulnerable adults at a lower risk of fracture than not. As well, as they noted, this vitamin D serum level may not have been achieved or used as a benchmark to guide supplementation interventions in all prevailing studies. Indeed, while actual levels of 800 to 1,000 IU of vitamin D per day appear to be required to maintain bone health, this level of supplementation was not necessarily delivered to this required degree or complied with over time in related studies, and even then may be unlikely to correct vitamin D deficiency in the obese individual, those with dark complexions, limited exposure to sunlight, or malabsorption^[96]. Using hospital based controls to determine vitamin D trends over time and concurrent calcium supplementation may also have lead to questionable conclusions about vitamin D specifically in some cases.

However, the odds of sustaining a stress fracture, plus non-union of a human fracture may yet implicate a vitamin D deficiency among other factors^[51,112] even if discrepant results prevail. Indeed, research conducted by Fentaw *et al.*^[6] led this group to conclude that it may be vital to improve serum levels of vitamin D-where required early on in the healing process-to promote post-fracture bone healing, as well as to maximize health, despite the negation of this need by others. Hence, while it seems vitamin D-sufficient conditions may not require supplementation or treatment, and might be detrimental, if provided during the pro-inflammatory phase of fracture healing^[54], or in excess^[22], vitamin D baseline deficiencies, as well as vitamin D depletion due to the consequences of injury may be highly relevant clinically in the context of fractures, due to its effect of increasing calcium absorption, bone mineral density, and reducing the risk of falls^[96]. Vitamin D deficiencies among fracture cases and those at risk should at least be sought, in our view, rather than overlooked, and if identified, treated accordingly because this deficiency may yet impact outcomes of fracture surgery^[113], as well as conservative treatments, and the risk of second fractures^[114].

Clearly, given the multitude of physiological actions that require or involve vitamin D, including calcium and phosphate metabolism, osteoblast and osteoclast functions^[58,115] bone collagen synthesis, and

resorption^[22], the role of vitamin D in influencing bone metabolism in health and injury situations is surely a topic of considerable import and one that merits more comprehensive study, before discarding it out of hand. In particular, controlled prospective studies of well-defined samples that consider the state of prevailing calcium metabolism, as well as vitamin D serum and intraosseus levels over carefully considered time frames along with careful monitoring of the fracture healing process^[76] may be helpful in efforts to examine any specific role vitamin D may have in optimizing fracture repair, as well as in preventing adverse fracture outcomes. In addition, use of carefully construed fracture and bone repair models that emulate human physiological processes quite closely, plus efforts to examine the role of vitamin D at all stages of the fracture healing process using advanced technologies^[86], plus attempts to discriminate the impact of vitamin D2 measures and supplements from D3 measures and supplements, which are three times more effective^[102] may help to advance this present body of contention and ambiguity. As well, why some find vitamin D is of value to bone health and fracture healing, and others not, might prove revealing.

An agreement about what constitutes adequate vitamin D supplementation and fostering compliance with any desired supplementary regimen also appears paramount in light of prior failures in this regard^[51,118]. As discussed by Sprague *et al*^[67], high quality basic studies to better understand the role of the VDR sites on osteogenic cells along with the role of vitamin D analogs^[104] in the context of fracture healing and prevention also warrants attention by those seeking to advance this body of knowledge. Moreover, documentation of fracture healing outcomes or indicators other than bone mineral density should not be neglected.

As outlined by Binkley *et al*^[119] adopting more consistent laboratory measurements of serum total 25-hydroxyvitamin D[25(OH)D] may reduce confusion that prevails due to the multiple definitions of vitamin D, and unresolved debates about the optimal level of any form of vitamin D on bone formation and healing^[96]. More intense study of possible confounding factors that might be examined in negative studies include age, gender, health status, the nature of the fracture injury and its severity, the injury site, the presence of past fractures as well as additional the presence of multiple, plus mode of vitamin D intake or treatment. Other factors include skin color, prevailing degree of outdoor activity, clothing and cultural issues, calcium levels, seasonal, and geographic factors^[6].

In those patients receiving supplementation who continue to exhibit a vitamin D deficiency, examination of the corresponding VDR binding sites and CYP24A1 enzyme system, which has not been studied may warrant attention as implied by Anderson^[116]. As well, tests to identify any possible problems in processing or absorbing supplementary forms of vitamin D may be worthy of study, as might the nature of any vitamin D need in cases with second or multiple fractures as discussed by Degli Espositi *et al*^[77] and Chiodinni and Chinari^[117]. What the optimal levels of vitamin D should be in the context of fracture healing and in light of the many cofactors that influence this process should also be more intensely studied.

In the meantime, since very few safety issues have been uncovered^[96], and adequate vitamin D does seem to impact pain, muscle function, and possible fracture risk^[96,102], it seems prudent to suggest persons at risk for vitamin D deficiencies, including those who appear healthy, but sustain first and/or second fractures, might be duly assessed, especially in winter, and followed up accordingly to prevent any potential suboptimal outcomes of either conservative or operative interventions applied to reduce fractures

in the event they are vitamin D deficient or become deficient. In addition, for those fracture vitamin D deficient fracture cases who undergo internal fixation surgery, vitamin D supplementation may yet improve the bone-implant contact ratio and surrounding bone volume as well as implantation resistance as reported by Liu *et al*^[40]. Those presenting with non-union of past fractures as well as stress fractures might also benefit from being closely monitored to avert further disability as discussed by Lips *et al*^[6].

CONCLUSION

As outlined by Bernard^[120], articles in the current realm are not only limited in number, and oftentimes challenging to follow, but continue to be challenging to aggregate. It is also hard to differentiate specific vitamin D effects when this compound has been delivered alongside calcium and other bone building agents in selected treatment groups, and possibly control groups. The additional unexplored role of competing therapies, illnesses that may impact vitamin D metabolism, plus studies that do not differentiate active vitamin D from its inactive metabolites that may have different half lives, and modes of impact, plus the variations in attempts to measure vitamin D status that are not all comparable and that may be misleading^[102], clearly precludes attainment of any universal claim or resolution for or against a role for vitamin D in fracture healing, or indeed what constitutes a vitamin D deficient state. In addition, even though some case reports appear promising, the ambiguity of these results, along with inconsistent findings from animal studies and cellular investigations suggests a need for more comprehensive higher level research, and novel study designs. At the same time, recommendations for what vitamin D intakes should be for both therapeutic fracture healing as well as what levels are unsafe for fracture repair should be especially examined, along with prospective changes in bone turnover markers to ensure that a viable treatment for some is not overlooked as outlined by Bryson *et al*^[113], Maier^[121], Bouillion *et al*^[122], Stewart *et al*^[123] and Larsen and Shmal^[124].

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