International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 4; April 2018; Page No. 128-131

Is vitamin D deficiency an independent risk factor for fracture risk?

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Abstract
Objective: The purpose of this systematic review was to evaluate the role of and importance of Vitamin D deficiency as an independent risk factor for fracture.
Methods: A search of the current literature was performed, leading to the inclusion of 15 suitable papers for analysis. A search on EMbase conducted using the search items "Vitamin D deficiency" and "fracture" was performed. The outcomes of these papers were used to outline a better understanding of the role of Vitamin D deficiency as an independent risk factor for fracture.
Results/Discussions: Often implicated in the pathophysiology of osteoporosis, Vitamin D deficiency is often described as a risk factor for the development of fractures in both adults and children.
Conclusion: While sufficient intake and metabolism of Vitamin D is important for proper bone health, the true impact of Vitamin D insufficiency and deficiency varies across different populations. Overall, large, long-term and prospective studies must be completed to further our current understanding of this important area of musculoskeletal medicine.

Keywords: vitamin D deficiency, fracture, risk profile, pathophysiology, paediatric

Introduction
Fractures are a common presentation to general practitioners, emergency medicine physicians, sports physicians and orthopaedic surgeons. The trauma resulting from a fracture leads to pain, immobility and loss of function of the affected limb. Fractures are not exclusive to any age group, but different patterns and variations are observed in different patient groups. The aim of management is anatomical or functional restoration of the limb and its component bones through operative or non-operative methods. Independent risk factors exist for fractures that include osteoporosis, advanced age, a history of maternal hip fracture, low body mass index (BMI), poor health, and metabolic disorders, among others [1]. One factor of increasingly recognised importance is Vitamin D deficiency (hypovitaminosis D), which is advocated to be an independent risk factor in fracture aetiology. This systematic review aims to evaluate the recent literature and determine whether any causation exists in this key area of clinical interest.

Methods
In order to review Vitamin D levels and fracture risk, a literature search was performed on EMBase. The search terms used were "Vitamin D" and "Fracture", these were combined using the "And" option. The results were limited to English, "Human" and "Last 10 years" which subsequently produced 125 results. All conference abstracts were immediately excluded, of which there were 98. One individual (RS) reviewed the remaining studies and after review of title and content, a further twelve were excluded as they were clinically inappropriate or of low-level evidence, leaving the total of included studies at 15. A further six studies were found using reference sources and searches and these studies were deemed to be of clinical importance.

Critical Analysis and Discussion
Often implicated in the pathophysiology of osteoporosis, Vitamin D deficiency (VDD) is often described as a risk factor without having its relationship with fracture quantified. It is often subclinical, however it can present in different groups in myriad ways. Several reviews have been performed in an attempt to delineate the effect of Vitamin D on fracture risk. Khaw, Luben and Wareham (2014) reviewed the effect of Vitamin D on osteoporosis and fracture over a 13-year population study. This UK study reviewed 14,641 adults between 42-82 years of age in 1997-2000 and followed up in 2012. Participants were separated into five groups according to baseline serum concentration of Vitamin D (Vitamin D <30, 30 - <50, 50 - <70, 70 - <90, >90 nmol/L) The mean serum Vitamin D found throughout the groups was 56.6 nmol/L and while other factors were measured, a 20 nmol/L increase in Vitamin D had a hazard ratio of 0.89 for fractures (563 total events).
Furthermore, concentrations of Vitamin D were also inversely associated with incidental fractures and hip fractures, although this was less apparently linear with the lower risk ratio flattening at VDL greater than 50 nmol/L. Plasma VDL were also found to predict 13-year total mortality, incident cardiovascular disease, respiratory disease and fracture [2]. A recent review by O. Sahota (2015) suggested that the literature, including systematic reviews, was still extremely contentious, however there is evidence that VDD is associated with proximal muscle weakness and that appropriate supplementation may result in a reduction of non-vertebral

fracture risk [3].

The aged population form a significant portion of individuals with VDD. Increased age is a risk factor for fractures, as well as further health problems that develop with age. Lips *et al* attempted to quantify the reduction of fracture risk with calcium and Vitamin D supplementation. It categorised abnormal Vitamin D levels (VDL) into insufficiency (25-50nmol/L or 10-20ng/mL), deficiency, (<25nmol/L or <10 ng/mL) and severe deficiency (<12.5nmol/L or <5ng/ml). The study also reviewed 14 previous studies and compared the changes in hip and non-vertebral fractures with Vitamin D and calcium supplementation. Of these, one study with 800 IU/day of Vitamin D and 1200mg/day of calcium caused a 43% reduction in hip fracture risk, as well as 32% reduction in non-vertebral fracture risk in 3270 patients [4, 5]. Another group used 700 IU/day of Vitamin D and 500 mg/day of calcium dosing found a relative risk reduction of 0.5 in the supplementation group vs. the control group [6].

Moreover, the only study that found a significant reduction in non-vertebral fracture (22%), without calcium supplementation, was one where the subjects had 100,000IU/4 monthly [7]. All but five of the included studies found non-significant results in regards to Vitamin D supplementation and reduction of fracture risk. However, in Lips' review, it did not state whether each study further performed subgroup analysis between levels of Vitamin D and fracture risk. It did recommend a supplementation of 800 IU/day as this did have the most successful outcome reported [4]. One hundred patients were chosen who presented with fractures from a population of 1246. Following their treatment for the fracture, they were voluntarily enrolled and underwent DEXA scanning and those with osteoporosis and recorded VDL were recruited. This study aimed to identify contributors to fracture risk and determine whether they were reversible or not. The study concluded that approximately one in two patients who present with clinical vertebral or non-vertebral fractures have secondary risk factors, of which most are reversible. Despite this, it made no comment on the risk reduction or change in incidence following correction of these contributors [8].

Other studies reviewing specific populations have also been performed. Chan *et al* reviewed Vitamin D status, BMD and non-vertebral fracture risk in community-based men in Hong Kong and found no change in fracture risk over four years. This conclusion was drawn from a cross-sectional analysis and longitudinal analysis of 939 and 712 men older than 65 years. The study used a value of 50 nmol/L or below as having VDD and found the 94.1% of the patients were not in this group. Following adjustment for confounders, higher VDL was associated with higher baseline BMD, however there was no association between VDD and non-vertebral or hip fracture risk [9]. A further study by Zhifeng *et al* (2013) reviewed 609 healthy postmenopausal Chinese women. This study found that 72.6% of the women had VDD with a level <50 nmol/L. By using the FRAX risk calculator, it found that Vitamin D reduced 10-year hip fracture risk by 0.100 and reduced 10-year major osteoporotic fracture by 0.111, which yielded statistical significance. This study therefore supported the suggestion that Vitamin D deficiency increased risk of fracture (as an independent risk factor), albeit only in the population under review [10]. In practical terms, this can be compared to elderly nursing home and community dwelling individuals. The case control study by De Konig *et al* (2012) clearly supported this notion, however their findings only stated that this relationship was non-linear and that VDL was inversely associated with hip fracture below 70 nmol/L (Odds ratio = 0.81 per 10 nmol/L increase) [11].

Building on this work, Shinkov *et al* (2016) undertook a cross-sectional study of 66 nursing home patients and 139 matched community based older subjects to assess their general fracture risk, as well as hip fracture risk specifically. While the nursing home residents reported a higher proportion of VDD (65.2% vs. 22.3%), fractures were distributed equally amongst the two groups and were of comparable rates between deficient and sufficient groups. Hip fracture rate was slightly higher in the nursing home patient group (8% vs. 2%), however this was associated with elevated PTH levels and not with VDL or residency status [12]. One must also consider the alterations that systemic disease has on fracture risk when added to VDD; these confounding factors need to be appreciated in this particular patient population. Renal impairment requiring maintenance haemodialysis has been found to be associated with increase bone fragility. Ambrose *et al* had demonstrated low VDL and decreased bone mineral density (BMD) in haemodialysis patients, as well as abnormal bony microstructure potentially associated with increased fracture risk. Indeed, 144 patients who had been on maintenance haemodialysis for greater than six months were approached, with 130 enrolled. The patients were surveyed about previous bone fracture, as well as medical charts examined. Weekly laboratory tests were completed, as well as DEXA scanning to assess BMD. Indeed, of those reviewed, 21 had previous fractures, with 109 remaining fracture-free. The former group had a mean VDL of 15.8 nmol/L and the latter had one of 30 nmol/L. Overall, the prevalence of deficiency (<20 nmol/L) was 41% and insufficiency (20-30 nmol/L) was 13.3%.

Contrary to other studies, there was no difference between the fractured and non-fractured groups in PTH levels. On multivariate analysis, there was a significant odds ratio of 11.215 (P = 0.026) between fracture in those with VDL <20 nmol/L. Furthermore, it was demonstrated that Vitamin D insufficiency, as well as other factors such as radial bone density and relative hypoparathyroidism are independently associated with fractures in those on haemodialysis [13]. Another study reviewed bone and calcium metabolism in relation to fracture incidence in those with spinocerebellar degeneration (SCD). Sato *et al* (2016) prospectively reviewed 110 patients with SCD who were age-matched to healthy controls. Over the ten-year study period, the SCD mean VDL decreased to < 5ng/mL, as well as BMD in men (15.2%) and women (24.6%). Additionally, the fracture rate was significantly higher in the SCD group for both men (8/49 vs. 1/42) and women (16/49 vs. 2/48). While there was no analysis to review for confounding variables, the study authors hypothesised that severe Vitamin D deficiency contributed to the frequency of fracture and increased fracture risk due to sunlight deprivation, increased bone resorption due to immobilisation and frequent falls [14].

Kim *et al* further investigated systemic disease in 2013 in individuals with an ever more common syndrome. Kim

reviewed serum Vitamin D levels and vertebral fractures in postmenopausal women and men > 50 years of age who visited diabetes clinics in May to September 2010. This study aimed to determine whether low VDL was associated with vertebral fractures. The study found women had on average lower VDL than men (31.3 vs. 41.3 ng/mL), with vertebral fractures being found in 16% of all patients. Men with higher VDL showed a reduced prevalence of vertebral fractures (9.4% vs. 17.9% vs. 21.7%, >30 vs. 20-29.9 vs. <20 ng/mL respectively), however this was not reproduced in the female subjects. Once further factors were excluded, men with serum VDL of less than 20 ng/mL was associated with an increased risk of vertebral fracture in those with type 2 diabetes [15].

A 2013 study by Busse *et al* reviewed iliac bone cores taken from 15 Vitamin D deficient and 15 non-Vitamin D deficient subjects at autopsy (within 48 hours of death), with 20 ng/mL being the cut-off. These samples then underwent significant laboratory testing with a further 10 being used to investigate toughness, strength and mode of failure. All the samples in this study underwent 2D and 3D histomorphometry, Raman and FTIR spectroscopy and in situ fracture testing. The latter test involved removing a sample of cortical bone from the crest. Following preparation samples underwent Gatan Microtest mechanical testing with serial images being taken during different phases. These found initiation and propagation were increased by VDD by 22 to 31%. Additionally, the other tests found that the bone with VDD had more uncalcified osteoid surrounding bone with higher mineral content, mature collagen and mineral constituents; the latter three features being a feature of older tissue. As a result, the study demonstrated that normal Vitamin D levels are essential in maintaining bone's structure and function and that VDD worsens fracture risk and progression [16].

In the paediatric population, Contreras *et al* aimed to determine whether children with fractures from minor trauma had a raised prevalence of VDD compared to children without fractures [17]. The study compared the VDL of two groups of 100 children, one with fractures and one without, with VDD being defined as VDL <20ng/mL and Vitamin D insufficiency being 20-30ng/mL. Despite this, no relationship was found between VDD and fracture risk in the two groups. Paterson attempted to review several case reports with young children with rickets secondary to VDD [18]. This group identified 35 patients between 0-23 months of age with 18 of them having multiple fractures in case reports from 1918-2012. A significant number of rib fractures (>40) were documented with femoral fractures, the most common diaphyseal injury. Indeed, VDL were only recorded in 17 patients, with 16 of them having VDL <10ng/mL. No statistical analysis was performed in this study, as well as no control or comparative group provided. Radiographic features of rickets diagnosed the cases in this study; however, this does mean that fractures occur in the absence of the radiographic signs. Of the 58 diaphyseal fractures, 40 of them were spontaneous, with a further 11 not having a known mechanism of injury. This study draws importance to the recognition of potentially multiple fractures in those children with rickets [19]. It may also draw attention to the need for testing of Vitamin D levels in children with unknown or spontaneous fractures, with an otherwise unknown or undetermined etiology.

Other paediatric studies have revealed minimal information regarding fracture risk in relation to VDD. A 2012 study by Perez-Rossello *et al* reviewed 40 children with diagnosed VDD from a parent study. These children had high quality wrist and knee x-rays taken and reviewed for rachitic changes. Two patients had rachitic changes and another two had demineralization changes, however none had fractures present. While this study estimated that fracture risk for those with Vitamin D deficiency, it could not formally calculate or draw conclusions from its findings [19]. Marana attempted to establish whether bone biopsy findings correlated with clinical, radiological and biochemical parameters in children with fractures. Twenty-four children referred for primary osteoporosis with no clinical diagnosis of osteogenesis imperfect or other known cause of bone fragility. This study divided patients into various groups using multi-variate analysis, however when it came to vitamin D levels, three subgroups were found. A total of 67 non-vertebral fractures were found with the median age for first long-bone fracture was 7.5 years. Also there were nine vertebral compression fractures prior to referral and five found on radiographic screening. The most common injury was fracture of the forearm and/or distal radius and ulna (n=28) and all but three fractures were cause by low-to-moderate energy trauma. The subgroups by VDL were <37.5nmol/L, 37.5-50nmol/L and >50nmol/L with nine, five and ten patients in each group respectively. The study made no attempt to identify a link between Vitamin D levels and childhood fractures, but did state that VDD was associated with high bone turnover, as well as correlated to osteoid surface and volume on biopsy. Subsequently it stated that hypovitaminosis D may be associated with suboptimal bone quality and decreased bone strength [20]. The final paediatric publication assessed whether there were any differences either in behaviour, physically or biochemically between children > 2 low-energy fractures (68) and those without (57). The study found 20% of case cases and 23% of control subjects had idiopathic hypercalcuria (IH). In the controls, the presence of this did not affect bone mineral density, whereas in the cases almost all of the patients with IH also had decreased bone mineral density. Further analysis of VDL showed that there was no significant difference in the levels between each group, but that there was with those with fractures [21].

When reviewing these studies it must be noted that while they all used extremely similar classifications for decreased levels of Vitamin D, some used the classification of insufficiency, deficiency and severe deficiency and had an associated value range, where others attempted to use the range of values obtained to form their range. Additionally, the use of both ng/mL and nmol/L in standard testing for VDL created some difficulty when comparing studies and thus it may be of benefit both having a standard criteria and unit of measurement. Each study used a varying form of statistical analysis and used different methodology and results grouping, creating heterogeneity between the studies in general.

Conclusion

There has been significant literature reviewing Vitamin D deficiency and its impact on fractures. While sufficient intake and metabolism of Vitamin D is important for proper bone

health, the true impact of Vitamin D insufficiency and deficiency is varies across different populations. Although much literature supports the view that there is a clear increased risk of both vertebral and fragility fractures with Vitamin D deficiency, there are also an equal number of studies that oppose this conclusion. Of note, the studies suggested that in those with concomitant disease, there was a notable association with VDD and fracture risk, whereas certain populations across different continents, sexes and residential status all produced different results, likely due to different sun exposure, diet and activity level. In the paediatric population, more studies are required for delineation, however results suggest that there is no associated increase in fracture risk in of itself. Overall, large, long-term and prospective studies must be completed to further our current understanding of this important area of musculoskeletal medicine.

References

1. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The Assessment of Fracture Risk. The Journal of Bone and Joint Surgery, 2010, 743-753.
2. Khaw Kt, Luben R, Wareham N. Serum 25-hydroxyvitamin D, mortality, and incident cardiovascular disease, respiratory disease, cancers, and fractures: a 13-y prospective population study, 2014; 1361-1370.
3. Sahota O.. Vitamin D: effects on muscle function, falls and fractures. Bone & Joint. 2015; 4(3): 360.
4. Lips P, Bouillon R, van Schoor NM, Vanderschueren D, Verschueren S, Kuchuk N. *et al*. Reducing fracture risk with calcium and vitamin D. Clinical Endocrinology, 2010, 277-285.
5. Chapuy MC, Arlot MME, Duboeuf F, Brun J, Crouzet B, Arnaud S, *et al*. (n.d.). Vitamin D3 and calcium to prevent hip fractures in the elderly women. New England Journal of Medicine, 1637-1642.
6. Dawson-Hughes B, Harris S, Krall E, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. New England Journal of Medicine, 1997, 670-676.
7. Trivedi D, Doll R, Khaw K. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. British Medical Journal, 2003, 469-474.
8. Dumitrescu B, van Helden S, ten Broeke R, Nieuwenhuijzen-Kruseman A, Wyers C, Udrea G, *et al*. Evaluation of patients with a recent clinical fracture and osteoporosis, a multidisciplinary approach. *BMC* Musculoskeletal Disorders, 2009, 1-11.
9. Chan R, Chan CC, Woo J, Ohlsson C, Mellstrom D, Kwok T, *et al*. Serum 25-hydroxyvitamin D, bone mineral density, and non-vertebral fracture risk in community-dwelling older men: results from Mr. Os, Hong Kong. Archives of Osteoporosis, 2011; 21-30.
10. Zhifeng S, Shuang L, Yangna O. Vitamin D status and its relationship with body composition, bone mineral density and fracture risk in postmenopausal Central South Chinese women. Annals of Nutrition and Metabolism, 2014, 9-13.
11. de Konig L, Henne D, Hemmelgarn BR, Woods P, Naugler C. Non-linear relationship between serum 25-hydroxyvitamin D concentration and subsequent hip fracture. Osteoporosis International, 2013, 2061-2065.
12. Shinkov A, Borissova AD, Vlahov J, Kassabova L, Svinarov D, Krivoshiev S. Differences in the prevalence of vitamin D deficiency and hip fractures in nursing home residents and independently living elderly. The Archives of Endocrinology and Metabolism, 2016.
13. Ambrus C, Almasi C, Berta K, Deak, G, Marton A, Molnar MZ, *et al*. Vitamin D insufficiency and bone fractures in patients on maintenance hemodialysis. International Urology and Nephrology, 2011, 475-482.
14. Sato Y, Honda Y, Asoh T, Iwamoto J. Longitudinal Study of Bone and Calcium Metabolism and Fracture Incidence in Spinocerebellar Degeneration. European Neurology, 2006, 155-161.
15. Kim YJ, Park SO, Kim TH, Lee JH, & Kim SH. The association of serum 25-hydroxyvitamin D and vertebral fractures in patients with type 2 diabetes. Endocrine Journal, 2013, 179-184.
16. Busse B, Bale HA, Zimmermann EA, Panganiban B, Barth HD. Carriero A, *et al*. Vitamin D Deficiency Induces Early Signs of Aging in Human Bone, Increasing the Risk of Fracture. Science Translational Medicine, 2013, 1-11.
17. Contreras JJ, Hiestand B, O'Neill JC, Schwartz R, Nadkarni M. Vitamin D Deficiency in Children With Fractures. Paediatric Emergency Care, 2013, 777-781.
18. Paterson CR. Fractures in rickets due to vitamin D deficiency. Current Orthopaedic Practice, 2015, 261-264.
19. Perez-Rossello JM, Feldman HA, Kleinman PK, Connolly SA, Fair RA, Myers RM, *et al*. Rachitic Changes, Demineralization, and Fracture Risk in Healthy Infants and Toddlers with Vitamin D Deficiency. Paediatric Imaging, 2012, 234-241.
20. Mayranpaa MK, Tamminen IS, Kroger H, Makitie O. Bone Biopsy Findings and Correlation With Clinical, Radiological, and Biochemical Parameters in Children With Fractures. Journal of Bone and Mineral Research, 2011, 1748-1758.
21. Olney RC, Mazur JM, Pike LM, Froyen MK, Ramirez-Garnica G, Loveless EA, *et al*. Healthy Children With Frequent Fractures: How Much Evaluation Is Needed? Paediatrics, 2008, 890-897.