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Relationship of vitamin D deficiency and generalized bone pain

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Abstract— Hypovitaminosis D can result from a disruption in any part of the vitamin D metabolism and can occur at any age. Common manifestations of vitamin D deficiency are symmetric low back pain, muscle weakness, muscle pain, and throbbing bone pain. Reduced bone mass combined with muscle weakness can lead to falls and fractures. The biologically active form of vitamin D, 1,25 dihydroxycholecalciferol, exerts its effect on calcium and phosphate metabolism via specific nuclear receptors. One of the diverse biological roles of vitamin D is its effect on pain sensitivity. The nociceptive, neuropathic, and psychological components of pain are regulated by both the central and peripheral nervous systems. The immune system also has a role in pain through its effects on inflammatory processes. Studies have postulated an important role of vitamin D in the regulatory mechanisms of both central and peripheral components of pain sensitivity by its action on central pain sensitization and immune modulation. Vitamin D supplementation has been proven to be beneficial in the prevention and treatment of chronic pain conditions on several occasions. A host of new and more focused research involving large RCTs is necessary for this field.

Keywords: Vitamin D deficiency, generalized bone pain, hypovitaminosis, calciferol, chronic pain.

Introduction

Vitamin D deficiency can occur due to an abnormality in any part of the metabolic pathway of vitamin D. The deficiency of this vitamin causes bone pain, muscle weakness, and reduced bone density. These may lead to pathological fractures from trivial injury and falls [1]. In recent times, there has been an exponential rise in the number of Vitamin D testing [2], although the relevance of testing and defining criteria of vitamin D deficiency is still unclear [3]. Studies in this field revealed that there is a high prevalence of hypovitaminosis D in the general population. Patients presenting to rheumatology clinics with musculoskeletal diseases have especially high rates of vitamin D deficiency among them [4]. The prevalence rates of hypovitaminosis D range from 30%–90% in developing countries irrespective of geographic region, and in Middle Eastern countries, the prevalence is almost 33% to 50% of the population [5]. A systematic review of 195 studies covering more than 168 000 subjects and 44 countries revealed that the serum vitamin D levels were less than 50 nmol/L among 33.7% of the study population (mean values ranging from 4.9 to 136.2 nmol/L) [6]. A study in 2016 showed that vitamin D deficiency is present in nearly 40% of Europeans and 13% have a severe deficiency [3].

People with chronic pain have a high prevalence of vitamin D deficiency among them, indicating that there may be a causal association [1]. Sometimes, vitamin D deficiency may coexist with other common causes of chronic pain such as fibromyalgia, resulting in significant diagnostic confusion [7]. The fact that symptoms like muscle ache, bone pain, fatigue, and weakness are common to both conditions only adds to this confusion. Moreover, both are characterized by hypersensitization to pain, lower pain threshold, poor exercise recovery, and increased soreness of the muscle [1]. In this review, I will discuss the relationship between vitamin D and its deficiency in generalized chronic bone pain.

Methods

Articles were searched in PubMed (MEDLINE). Relevant articles published in the English language up to 31 December 2021 were retrieved. The number of vitamin D-related research publications has exponentially increased in recent times. Due to this reason, only the most significant, relevant, and recent studies were considered for this review.

About Vitamin D

Vitamin D is a fat-soluble vitamin. Chemically, it is a secosteroid, which means it has a broken bond in the steroid ring structure. Vitamin D, which is also called calciferol, most commonly exists in two forms, vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [8]. Vitamin D has an important role in the regulation of calcium and phosphorus homeostasis. It is essential for bone mineralization. The active form of vitamin D is 1,25-dihydroxy vitamin D. It has specific nuclear receptors, through which it increases calcium absorption from the gastrointestinal tract and regulates bone metabolism [9]. Besides dietary sources, vitamin D can also be synthesized in the skin under the appropriate exposure to ultraviolet radiation [10]. Vitamin D is biologically inactive in its non-hydroxylated form. The active form, 1,25 dihydroxy cholecalciferol, is synthesized after two successive hydroxylations of the first and the twenty-fifth carbons of the ring structure occurring in the liver and kidney respectively [11]. The second hydroxylation in the kidneys happens under the influence of a cytochrome P450 enzyme, 25-hydroxyvitamin D-1α hydroxylase (CYP27B1). The amount of 1,25-dihydroxy vitamin D synthesized in the kidneys is inversely controlled by the circulation level of parathyroid hormone, calcium, and phosphorus. Fibroblast growth factor, which is secreted from bone, also suppresses 1,25-dihydroxy vitamin D synthesis in the kidneys. This factor also suppresses the renal and intestinal absorption of phosphorus. On the contrary, 1,25-dihydroxy vitamin D increases the absorption of calcium and phosphorus in the intestine and kidneys. It also upregulates another cytochrome P450 enzyme, named 25-hydroxyvitamin D-24-hydroxylase (CYP24). This enzyme is involved in the metabolism of 25-hydroxyvitamin D and 1,25-dihydroxy vitamin D, producing a biologically inert end product, calcitroic acid, which is water-soluble and easily excreted [12].

Deficiency can result from any interfering factors in the intake, absorption, synthesis, or metabolism of vitamin D. Known risk factors for vitamin D deficiency include old age, darker skin complexion, dietary deficiency, high body mass index (BMI), inadequate sun exposure, higher latitude, and intake of certain medications that impair vitamin D activation or increase clearance from the body [13]. However, the vitamin D status of a person cannot always be predicted from these standard risk factors.

The effects of Vitamin D result from gene expression modulation due to the binding of vitamin D to its receptor (VDR). There are many genetic polymorphisms in the key genes associated with vitamin D-related pathways. These can result in variations in the bioavailability, transport, distribution, storage, metabolism, and action of vitamin D [14].

Vitamin D deficiency

Vitamin D deficiency results from inappropriate dietary intake or inadequate exposure to ultraviolet B rays. The 25-hydroxyvitamin D is the main form of vitamin D in the circulation and has a longer half-life (2 to 3 weeks) compared to 1,25 dihydroxy vitamin D (about 2 days) and only a fraction of the former is converted to the later active form [15,16]. The circulating level of 25 hydroxyvitamin D is also easy to measure, and the level correlates with clinical disease states quite well. Because of these facts, in universal clinical practice, the level of 25-hydroxyvitamin D is taken as a proxy indicator of

Vitamin D status in the body [17]although 1,25-(OH)2D is the functional form of vitamin D. However, an optimal vitamin D level is yet to be established that is acceptable to a wide population.

Most authors prefer to classify a 25-OH D level of less than 20 ng/mL as 'vitamin D deficiency' while a level of 20–29 ng/mL is designated as 'vitamin D insufficiency. A level of more than 30 ng/mL is considered 'sufficient' vitamin D status [16,18-20]. Vitamin D insufficiency status can be regarded as a milder form of hypovitaminosis D with effects including hypocalcemia, reduced bone mass, and secondary hyperparathyroidism. However, in current practice, the vitamin D insufficiency status is considered as a condition where the patient might benefit from vitamin D supplementation, particularly with optimal extra skeletal health, regardless of parathyroid hormone status [16,18,-20].

The reported prevalence rates of severe vitamin D deficiency are 5.9% in the United States [21], 7.4% in Canada [22], and 13% in Europe [3]. Severe vitamin D deficiency is defined as serum 25 hydroxyvitamin D level less than 12 ng/ml. Levels of less than 20 ng/ml have been reported in 24%, 37%, and 40% of the population of the United States, Canada, and Europe, respectively [3,21-23]. The prevalence rates may vary by age and ethnicity. Populations of both extreme ages have lower levels of vitamin D [23]. European Caucasians have a lower prevalence of vitamin D deficiency than nonwhite individuals [3,23]. Worldwide, many countries have a very high prevalence of severe vitamin D deficiency. In India, an estimated 490 million individuals are severely vitamin D deficient, amounting to >20% of the population of India. Such high levels of severe vitamin a deficiency are also seen in Tunisia, Pakistan, and Afghanistan [3,23].

Generalized chronic pain and Vitamin D

Chronic pain is defined by The International Association for the Study of Pain (IASP) as "pain that persists or recurs for longer than three months. Such pain often becomes the sole or predominant clinical problem in some patients" [24]. In some instances of chronic pain disorders, like trigeminal neuralgia and rheumatoid arthritis, the characteristic feature is recurrent episodes of acute exacerbations [8]. A chronic inflammatory condition, tissue destruction, neural damage, and alteration of neural function all can lead to chronic pain. Similarly, chronic long-standing pain can cause the central and peripheral nervous system to undergo chemical, functional, and anatomical changes [8].

The potential impact of vitamin D on the causation and exacerbation of chronic pain has been shown in many research. Vitamin D has an influence on the anatomic, hormonal, neurological, and immunological factors of pain [25-28]. The active form of vitamin D, 1,25 dihydroxy vitamin D, plays a major role in bone metabolism and muscle function [29]. Deficiency of this vitamin leads to pain and weakness of muscle in both young and adults [30,31]. It has been reported many times in publications that deficiency of vitamin D is highly prevalent in different types of pain [32-39]. Patients with cystic fibrosis also suffer from chronic pain, which is related to low vitamin D levels [40,41]. In 2020, a study by Heidari et al. demonstrated that women have a relation between vitamin D deficiency and nonspecific pain throughout the skeletal system. Tibial bone pain had the strongest association, followed by generalized joint pain, pain over the sternum and ribs. These associations were only found in women and the average vitamin D level was significantly lower in symptomatic patients than the asymptomatic control population. A higher fraction of patients suffering from chronic skeletal pain had associated serum vitamin D deficiency compared to controls in their study [42]. This statement is also supported by a study conducted by Hicks et al. [43].

Gloth et al. in 1991 showed that Vitamin D supplementation helps in increasing bone density and alleviating specific or nonspecific musculoskeletal pain [44]. Several other studies have indicated the

same [45-48]. In a 2016 meta-analysis on the effect of vitamin D supplementation on hospitalized patients with pain-related ailments, it was found that vitamin D given for an average 3 months duration reduced pain in conditions such as myalgia, arthritis, and chronic musculoskeletal pain [49]. Nevertheless, an association between musculoskeletal pain and high serum 25 hydroxyvitamin D has also been reported in some studies. However, the underlying mechanism of this negative association is not clearly understood [50,51].

Vitamin D deficiency is frequently seen in regions where the burqa is commonly worn by women due to cultural reasons. Batty et al. observed this in fibromyalgia and nonspecific musculoskeletal pain patients in a study conducted in Pakistan [7]. Wepner et al. studied the impact of Vitamin D supplementation on reducing pain by the use of the visual analog scale (VAS) for pain assessment. They used 2,400 or 1,200 IU/day doses of vitamin D supplement to raise the serum 25-hydroxyvitamin D levels in the range of 32 to 48 ng/mL in fibromyalgia patients. According to this study, the pain score was significantly reduced in the patients after supplementation [52]. A potential source of confusion leading to misdiagnosis maybe that osteomalacia caused by vitamin D deficiency and fibromyalgia both are painful conditions [25,26].

Vitamin D also has demonstrable immunomodulatory effects. It induces immune tolerance by suppressing the pro-inflammatory response (Th1) and stimulating the anti-inflammatory response (Th2) [53]. It is thought that this immunomodulatory effect may be the main reason for pain-relieving effect of vitamin D, as seen in many autoimmune diseases like rheumatoid arthritis, rather than the direct action on the pain modulation pathway [54-57]. A prospective study by Skaaby et al. in 2015 conducted on a population of a wide age groups (18 to 71 years) of both sexes showed that even a rise of 10 nmol/L of serum 25 hydroxyvitamin D was significantly associated with a reduced incidence of many autoimmune-related diseases like multiple sclerosis, type 1 diabetes, Crohn's disease, and thyrotoxicosis [58].

A high prevalence of vitamin D deficiency has also been observed in patients suffering from sickle cell disease. There is a seasonal variation in the prevalence rate seen in these cases and sometimes the prevalence rate can reach as high as 65–100% [59-63]. Patients with sickle cell disease develop chronic pain from vascular complications, like ischemic infarction of bone and injury to a peripheral nerve. Prolonged use of opioids in these patients is also responsible for central pain sensitization, and hyperalgesia syndrome. An increase in the number of bone pain and bone fragility has been observed by Osunkwo et al. in young patients suffering from sickle cell disease who are also simultaneously deficient in 25-hydroxyvitamin D (serum level less than 20 ng/mL) [64]. This study also found that vitamin D supplementation in high doses is greatly helpful in reducing the number of episodes of pain in sickle cell disease patients [65]. A study conducted on cancer patients requiring opioids for pain management showed that patients with less than 20 ng/ml of serum 25-hydroxyvitamin D needed a higher dose opioid for the same effect than patients with normal vitamin D levels. A high level of 25-hydroxyvitamin D was also found to be a good predictor of longevity in cancer patients in the same study [66].

The underlying mechanism of chronic pain due to Vitamin D deficiency

As mentioned earlier, the influence of vitamin D on the modulation of pain is not merely an effect on the neurological pathway of pain but encompasses the anatomic, hormonal, and immunological factors of pain [25-28]. Studies on mechanical pain stimulation in chronic pain patients found that decreased vitamin D level in the circulation is associated with hypersensitivity of the central pain axis by hyperactivity of pain processing mechanisms [67]. This effect is particularly seen in the case of

migraine and fibromyalgia [68,69]. The central hypersensitivity state in chronic pain is potentially maintained by a host of neuroexcitatory substances released by activated glial and microglial cells of the central nervous system. These substances include nitric oxide, varieties of excitatory amino acids, proinflammatory cytokines, and other chemical modulators [68]. Vitamin D, being a central neuroactive steroid, can potentially modulate the activity of these cells as well as the excitability of central neurons. Vitamin D exerts these neuromodulatory effects by influencing the intrinsic excitability of neurons and duration of the action potential, thereby inducing spontaneous regular firing of neurons. Vitamin D also affects the sensitivity of a neuron to different neurotransmitters, like gonadotropin-releasing hormone, endogenous opioids, etc. as well as the activity of different neurotransmitter receptors such as gamma-aminobutyric acid and N-methyl-D-aspartate receptors [70-72].

Astrocytes are the main cell for the cytochrome P450 dependent detoxification of the central nervous system. Vitamin D plays an important role in this system [73]. Astrocytes and microglial cells are also responsible for the secretion of tumor necrosis factor-alpha (TNFa), macrophage colony-stimulating factor (M-CSF), and inducible nitric oxide synthase in response to various inflammatory conditions and cytokine stimuli [74]. TNFa has a proven role in pain sensitization at both peripheral and central levels [75]. On the other hand, the cytokine M-CSF is essential in the various stages of maturation of monocytes macrophages lineage. Macrophages, in turn, produce a host of inflammatory mediators, including TNFa, interleukin-1 beta (IL-1b), nerve growth factor (NGF), nitric oxide (NO), prostaglandins, and prostacyclins [76]. Vitamin D has been convincingly shown to suppress the secretion of TNFa, M-CSF, and nitric oxide synthase from glial cells, thereby proving its potential role in the inhibition of central pain pathways.

Many important mediators associated with vitamin D pathway like vitamin D receptor (VDR), 1a hydroxylase enzyme, and vitamin D binding protein (DBP) all have been detected in the hypothalamus. This may suggest the potential role of vitamin D deficiency in the pathophysiology of many primary headache disorders [77]. The synthesis ofmany neurotrophins such as nerve growth factor (NGF), neurotrophin 3, and glial cell line-derived neurotrophic factor are increased under the influence of Vitamin D, whereas the synthesis of neurotrophin 4 is decreased [73,74]. This proves how vitamin D fundamentally affects the development and survival of neurons [76].

Vitamin D supplementation in chronic pain

Measurement of serum vitamin D levels should be considered in any patient presenting with either frank symptoms of hypovitaminosis D, like reduced bone density, fractures due to trivial injury, bone or muscle pain, weakness etc. or there is a risk factor associated with vitamin D deficiency, like inadequate sun exposure, advanced age, darker skin complexion, etc [1]. Vitamin D supplementation may be beneficial in these patients if hypovitaminosis is found [78].

Vitamin D supplements can be given in a variety of dosing regimens, such as daily, weekly, monthly, or longer intervals. The selection of a dosing regimen is important as it may affect serum vitamin D levels. A daily dose of vitamin D will result in a gradual increase in the serum level of 25-hydroxyvitamin D and will take a duration of 3 to 6 months to reach a steady level [79]. However, this regimen will ensure a stable circulating serum level of both vitamin D and 25-hydroxyvitamin D. On the other hand, weekly doses cause unstable serum levels of circulating vitamin D. However, the levels of 25-hydroxyvitamin D remain stable even after a weekly dose [80-82]. Large bolus dosing usually produces a very unpredictable and unstable serum level of 25-hydroxyvitamin D [79]. While selecting a dose of vitamin D supplementation, a target serum level of 75 nmol/L is considered

optimum. A large variety of vitamin D dose regimens have been used in various trials (Table 1) [83-90], however, most studies have shown that a dose of less than 1000 IU of vitamin D per day is usually inadequate for achieving the target level [91,92].

Table 1: Dosing schedules of vitamin D [83-90]

Dose schedule	Dose range (IU)
Daily	400–4000
Weekly	8400–50,000
Monthly	50,000–120,000
Four-monthly	100,000
Yearly	300,000–600,000

Different varieties of vitamin D formulations can be used for treatment (Table 2). A commonly used regimen is to administer a weekly dose of 50,000 IU of vitamin D for 8 weeks. This can quickly normalize the serum level of 25-hydroxyvitamin D. This should be followed by 400 to 1000 IU every day or 50,000 IU every 2 to 4 weeks to maintain the normal level achieved by the loading dose. One important thing to remember is that patients having fat malabsorption or disorders of vitamin D metabolism need higher doses of vitamin D. Sometimes, UV-B therapy is needed for continuing symptom alleviation in these patients [1,92].

Table 2: Treatment options for patients with vitamin D deficiency.

Name	Formulation	Description
Ergocalciferol	Vitamin D2	A plant source of vitamin D available only by prescription at 50,000 IU per capsule
Cholecalciferol	Vitamin D3	Represents the vitamin D found in dairy products, fatty fish, and over-the-counter supplements in doses of 400 – 1000 IU per tablet
Calcitriol	1.25(OH)2D	Represents the biologically active form of vitamin D; used in patients with chronic kidney disease who are unable to convert 25(OH)D to 1.25(OH)2D
Suntanning bed	UV-B	Induces skin synthesis of vitamin D precursor; long-term safety with risk of skin cancer is unknown
*25(OH)D, 25-hydroxyvitamin D; 1.25(OH)2D, 1.25-dihydroxy vitamin D.		

Conclusion

The deficiency of Vitamin D is a worldwide prevalent disease. Vitamin D deficiency is frequently seen in patients diagnosed with nonspecific musculoskeletal pain and fibromyalgia. Studies using visual analog scale (VAS) pain scores as the primary or solitary outcome measure have shown mixed

results in chronic pain patients when evaluating the impact of vitamin D supplementation in this condition [35,93-96]. Significant improvements in the assessment of sleep, mood, pain levels, wellbeing, and various aspects of quality of life with vitamin D supplementation have been shown [93,97-100]. While there is a growing body of both clinical and laboratory evidence pointing to a potential relationship between low levels of 25(OH)D and chronic pain, it is not possible to state conclusively that vitamin D deficiency is directly linked to the etiology or maintenance of chronic pain states. The scientific evidence for the use of vitamin D as a treatment option for chronic pain is limited at present due to low-quality designs and the lack of RCTs.

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