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Review Article

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Hypovitaminosis D in Painful Peripheral Neuropathy

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Abstract

Vitamin D is an essential vitamin necessary for maintaining proper bone structure by regulating calcium-phosphorus metabolism in the body. Vitamin D, as a hormone, also has effects on the nervous system. Peripheral neuropathy (PN) comprises a group of disorders involving the peripheral nervous system, which includes sensory, motor, and autonomic nerves. PN manifests as various symptoms, such as pain, numbness, and muscle weakness, alone or in combination. PN is caused by a wide variety of etiologies. Accumulating evidence from clinical and laboratory studies shows that hypovitaminosis-D may be a potentially independent risk factor for painful PN. Administering vitamin D to patients with hypovitaminosis-D alleviates their neuropathic symptoms. In this article, we review up-to-date clinical observations on hypovitaminosis-D and painful PN.

Keywords

25-hydroxyvitamin D_3, Hypovitaminosis-D, Painful neuropathy, Paresthesia, Peripheral neuropathy, Vitamin D deficiency

Vitamin D is essentail for bone metabolism and growth. Recent studies have implicated vitamin D, as a hormone, contributing to various important cellular activities, such as regulating intestinal absorption of calcium in normal bone metabolism, sustaining normal modulatory functions of the immune and cardiovascular systems. Vitamin D has effects on the pancreas, muscles, brain, and cell cycles [1, 2]. Accumulating evidence from clinical and laboratory studies suggested that hypovitaminosis-D may serve as a potentially independent risk factor exacerbating painful diabetic PN. Administering vitamin D to patients with hypovitaminosis-D alleviates their neuropathic symptoms [3, 4]. In this article, we brielfly review up-to-date clinical observations on the relationship between hypovitaminosis-D and painful PN.

What is Vitamin D?

Vitamin D is a lipophilic vitamin containing a group of secosteroids [1, 2]. Vitamin D was first discovered in 1932 and was isolated from an irradiated mixture of ergosterol, while vitamin D_1 was an artefact of an adduct between vitamin D_2 and lumisterol [5]. Vitamin D_3, which is a naturally existing species of vitamin D, can be made in the skin during exposure to sunshine. Vitamin D_3 was initially identified in 1937 after a substance, 7-dehydrocholesterol, received Ultraviolet (UV) irradiation, however, it was not proven until 1978 [1]. A normal vitamin D level can be maintained by adequate absorption from food or supplements in the gastrointestinal tract, and synthesis from cholesterol in the skin epi-

dermis upon exposure to UVB. UV is a segmental spectrum of the light ranging from 100 - 400 nm in wavelength, which is invisible by humans. UV has been categorized into three subgroups according to the wavelength: UVA in the range of 315 - 400 nm, UVB in 280 - 315 nm, and UVC in 100 - 280 nm. UVA is not absorbed by the ozone layer and atmosphere, and it can be visible by some animals. UVB can be utilized for medical therapeutic purposes, such as treatment of psoriasis or vitamin D production in the skin. UVC is a germicidal because UVC disrupts the synthesis of DNA of bacteria, virus and other pathogens and deprives of their abilities to proliferate and cause diseases. It is estimated that, in humans under normal physiologic circumstances, approximately 20% of vitamin D are absorbed from the intestine while 80% synthesized in the skin (Figure 1).

Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are the most important subtypes of vitamin D. D_3 is a naturally existing species of vitamin D; which can be made by the skin upon sun exposure and exists in foods and as a supplement. D_2 is synthesized in the laboratory by radiating fungus and not naturally occurring in humans. D_3 undergoes two hydroxylations for activation [6]. It is initally hydroxylized in the liver under the enzyme 25-hydroxylase to convert to calcidiol (25-hydroxyvitamin D_3, or $25(OH)D_3$), which is the main species of vitamin D circulating in the bloodstream with low biologic activity. Calcidiol is then hydroxylated, or avtivated, in the kidneys by the enzyme 1-alpha-hydroxylase, to convert to calcitriol (1,25-dihydroxyvitamin D_3, or $1,25(OH)_2D_3$), which is the biologically active form. The second hydroxylization is restrictly regulated by parathyroid hormone. In the kidneys, calcidiol and calcitriol are further hydroxylated and metabolized by the enzyme 24-hydroxylase to the deactivated forms of 24,25-dihydroxyvitamin D_3, or $24,25\ (OH)_2D_3$, and 1,24,25-trihydroxyvitamin D_3, or $1,24,25(OH)_3D_3$, respectively, before they are excreted from the body via kidneys [6]. The half-life is approximately 15 hours for calcitriol, or $1,25(OH)_2D_3$, and 15 days for calcidiol, or $25(OH)D_3$ [2]. Vitamin D is also a hormone. Vitamin D binds to its receptors located throughout the body and plays different roles via various processes under the physiologic condition, such as regulating bone metabolism, controlling absorption of calcium, magnesium, and phosphate in the garstointestinal tract; safeguarding normal meataboism for cell survuial, growth and maturation; maintaining normal immune function; synerging blood glucose metabolism by affecting pancreatic secretion of insulin; strengthening muscle contraction; and sustaining normal heart and brain activities.

Hypovitaminosis-D occurs when vitamin D level is lower than normal. Vitamin D levels are measured in the concentration of serum 25-hydroxyvitamin D_3 as "normal" in the range of 30 - 50 ng/ml or 75 - 125 nmol/L, "insufficient" in 20 - 29 ng/ml or 50 - 75 nmol/L, "deficiency" <20 ng/ml or <50 nmol/L, or "severe deficiency" <12 ng/ml or <30 nmol/L (Figure 2) [7, 8]. The percentages of the US population with hypovitaminosis-D are estimated to be 69.5% - 77% as the 25-hydroxyvitamin D_3 levels less than 30 ng/ml [9, 10] and

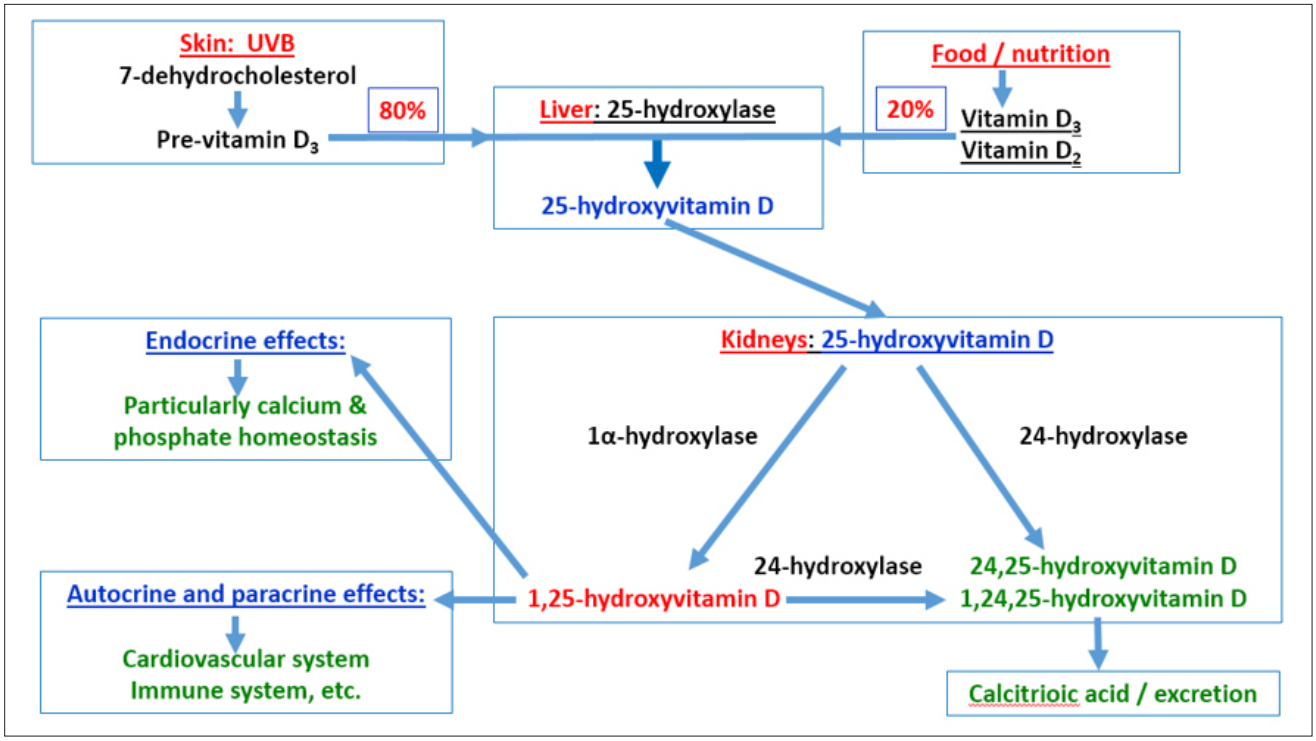

Figure 1: Human metabolism of vitamin D.

Endogenous vitamin D synthesis takes place in the skin (80%): 7-dehydrocholesterol is converted to pre-vitamin D_3 in exposure to UVB, or exogenous is taken from dietary or nutrition supplement of vitamin D_2/D_3 (20%). They bind to the vitamin D-binding protein and are transported to the liver where vitamin D is hydroxylated to 25-hydroxyvitamin D before transported to kidney, In the kidney, 25-hydroxyvitamin D is hydroxylated to the active form of 1,25-dihydroxyvitamin D upon 1α-hydroxylation and exerts various physiologic actions via endocrine or autocrine and paracrine routes. Vitamin D is then deactivated to 24,25-hydroxyvitamin D or 1,24,25-dihydroxyvitamin D under the 24-hydroxylase and subsequently metabolized to calcitrioic acid before it is excreted by the kidney.

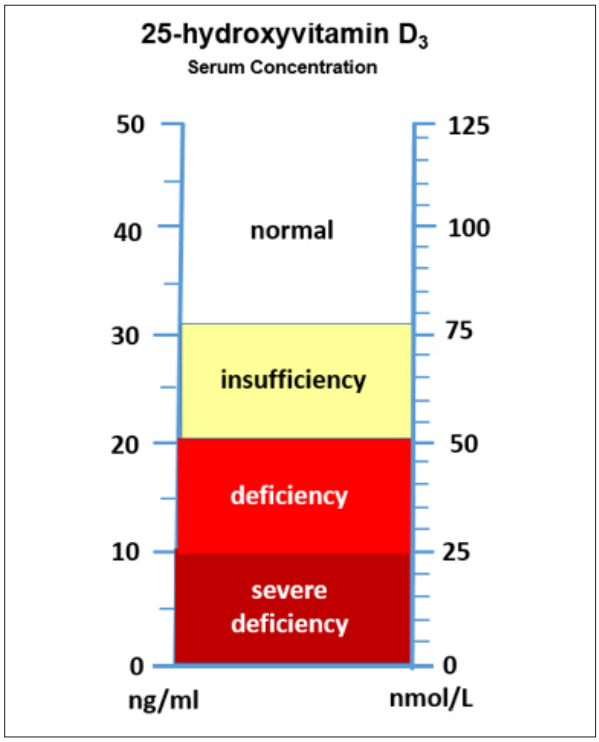

Figure 2: Classification of vitamin D levels.

36% as less than 20 ng/ml [10].

What is Peripheral Neuropathy?

PN is a collective name of a group of disorders involving the peripheral nervous system causing sensory, motor, and autonomic dysfunctions. PN exhibits various symptoms such as pain, numbness and muscle weakness, separately or in combination, usually involving the hands and feet. It can also affect autonomic dysfunction such as digestion, urination, and circulation.

It has been estimated that more than 20 million Americans suffer PN [11]. Etiologies for PN are widely distributed. The common medical conditions that predispose to the development of PN include metabolic, toxic, malnutritive, infectious, inherited, traumatic, inflammatory or autoimmune-mediated mechanisms, and obesity as well [12]. The most common cause of PN is diabetes mellitus (DM) [12, 13]. However, some patients with PN have no identifiable etiologies after routine laboratory investigations. These patients are labelled as having idiopathic neuropathy. When the underlying etiologies are suboptimally investigated, potentially treatable causes for PN may be undiscovered, unrecognized, or missed, which may lead to prematurely labeling a patient with the diagnosis of "idiopathic neuropathy" and, therefore, delaying or deferring effective treatment on the causative etiology [14]. Notably, the prevalence of PN has been reported to be approximately 7% in the elderly, 40% of whom are "idiopathic" [15].

Recent studies showed that PN in many patients labelled as "idiopathic" PN is caused by treatable etiologies [14]. Clinical observations disclosed a causal association of hypovitaminosis-D with the development of PN [16]. Indeed, hypovitaminosis-D was recognized as the second most likely abnormality on the top list among the laboratory findings in neuromuscular consultation for patients with PN [12]. However, there is a gap in recognition of hypovitaminosis-D as a treatable etiology for PN.

Is There a Relationship Between Hypovitaminosis-D and Peripheral Neuropathy?

An increasing body of clinical studies suggests a plausible association between hypovitaminosis-D and PN [16-18]. In a study enrolled 240 subjects including 120 DM-patients and 120 healthy controls, vitamin D deficiency was observed in 64.2% and 36.6%, vitamin D insufficiency 25% and 38.4%, and normal vitamin D levels 10.3% and 25% in DM-patients and healthy controls, respectively [19]. The findings disclosed that hypovitaminosis-D was significantly prevalent in DM-patients ($p = 0.002$) than in the healthy individuals. The findings were supported by additional clinical observations showing that 40.5 - 89% patients with DM-PN had evidence of hypovitaminosis-D [20, 21]. A well-designed but small scale, retrospective study enrolled 43 patients [22] with type 1 diabetes: PN without pain (DM-PN-no-pain) ($n = 20$), PN with pain (DM-PN-pain) ($n = 23$) and normal healthy control subjects without DM ($n = 14$). Subjects were assessed on neurologic deficits based on the evaluations of a battery of clinical tests, including quantitative sensory testing (QST), neurophysiology, corneal confocal microscopy, skin biopsy, and serum 25-hydroxyvitamin D_3 levels. Their findings showed a significant decrease in the levels of 25-hydroxyvitamin D_3 in the group of DM-PN-pain (24.0 ± 14.1 ng/ml) versus the groups of DM-PN-no-pain (34.6 ± 15.0; $p = 0.01$) or healthy controls (34.1 ± 8.6; $p = 0.03$), suggesting an association of vitamin D deficiency (OR, 9.8; 95% CI, 2.2 - 76.4; $p = 0.003$) or insufficiency (OR, 4.4; 95% CI, 1.1 - 19.8; $p = 0.03$) with an elevated risk for DM-PN-pain. Significantly higher rates of both positive ($p = 0.009$) and negative ($p = 0.02$) symptoms were seen in the group of DM-PN-pain than those in the group of DM-PN-no-pain. McGill pain score, visual analogue score, and neuropathy symptom profile were significantly higher in DM-PN-pain ($p < 0.0001$, $p < 0.0005$, and $p < 0.0001$, respectively) versus DM-PN-no-pain and controls [22]. These findings confirmed the notion that hypovitaminosis-D is highly prevalent in people with painful DM-PN [23-27]. Indeed, an abnormal laboratory finding of hypovitaminosis-D is the secondly most often encountered in people with PN with acral paresthesia [12]. Notably, there is an association in the severity between hypovitaminosis-D and DM-PN [4, 28] with the evidence of both large [29] and small [12, 29] nerve fiber dysfunction.

Evidence From Clinical Observations and Laboratory Findings in Hypovitaminosis-D and Peripheral Neuropathy

The correlation between hypovitaminosis-D and neuropathic pain can be quantitatively assessed in patients with DM-PN using Neuropathy Disability Score (NDS) [18], Short Form McGill Pain Questionnaire (SFMPQ) score or total Mc-

Gill pain score, Douleur Neuropathique 4 (DN4) score [20]. Decreased levels of 25-hydroxyvitamin D are correlated well with the prevalence of DM-sensory neuropathy and the severity of PN [28]. Intramuscular injection of one dose of 600,000 international units (IU) vitamin D promptly improved both the vitamin D level and positive symptoms measured with SFMPQ, total pain score, and DN4 [20] suggesting a potential therapeutic approach for painful DM-PN [26]. Effective treatment for vitamin D deficiency reversed PN-symptoms in a DM-patient [30]. The therapeutic effects were confirmed in an open-label clinical trial by weekly administering vitamin D_3 at 50,000 IU for 12 weeks resulting in remarkable improvement in both serum vitamin D level and symptoms and signs of DM-PN [31]. Clinical trials in randomized and placebo-controlled using either topical or oral administration of vitamin D_3 in patients with DM-PN showed favorably therapeutic benefits [4]. Importantly, in a randomized, placebo-controlled study on vitamin D replacement therapy in painful DM-PN patients with balance disequilibrium, with concurrent hypovitaminosis-D and performance of an electromyography, administration of an one-time injection of 300,000 IU vitamin D significantly alleviated neuropathic pain, improved balance test scores. Furthermore, improved scores were observed by measuring using electric shock and burning sensations against a 12-week study protocol, suggesting improvement in small nerve fiber function with DN4 sensory assessment and large nerve fibers with Berg balance scale assessments [29]. Additionally, decreased levels of circulating 25-hydroxyvitamin D_3 may contribute to an increased risk in developing large fiber neuropathy shown in neuroelectrophysiologic studies. An increase in 1 ng/ml of serum 25-hydroxyvitamin D_3 was estimated to be correlated with 2.2% and 3.4 % decrease in the occurence and severity, respectively, of neuropathy-impairment measured by neurophysiological studies in DM-patients with vitamin D supplementary therapy [32]. However, this result requires validation as other neurophysiologic studies failed to show a significant association with vitamin D status on the sensory and motor fibers [19, 26]. Moreover, effects of vitamin D on muscles and CNS related to disequilibrium in patients with PN were also proposed [33].

Possible Mechanisms of Vitamin D Supplementation in Patients with Peripheral Neuropathy

The underlying mechanisms relevant to hypovitaminosis-D potentiating DM-PN symptoms are currently not well understood. Hypovitaminosis-D is frequently observed in people with insulin resistance and obesity [12, 34]. Accumulating evidence suggests that vitamin D exerts preventative function in pancreatice islet cell death and may be beneficial in improving the viability of islet cell grafts [35], suggesting a potetial therapeutic target for DM. Therefore, hypovitaminosis-D may result in losing its protective effects on the vialbility and functional status of pancreatic beta cells, decreaseing sensitivity to insulin and/or increasing insulin resistance [36]. Many studies have shown that lower levels of 25-hydroxyvitamin D_3 were frequently encountered in patients with DM, particularly in whom were treated with insulin than those were treated with oral hypoglycemic agents and healthy controls; while patients with DM receiving a long-term insulin therapy demonstrated much higher prevalence of DM-PN [37-39]. These observation could be, at least partly, due to the ineffective treatment in diet control and oral hypoglycemic therapies alone or in combination to control DM prior to the development of PN before starting insulin therapy [19]. The pathogenesis of DM-PN has been postulated to be an multifactorial processes and multiple hypotheses have been proposed. Viewed in this context, an abnormal interplay among several factors including vitamin D, vitamin D-binding protein, and its receptors [40] may affect the blood supply to peripheral nerves. Further, abnormally disarrayed functions in sodium and calcium channels may cause membrane structural and functional deviations leading to proinflammatory cell activation that may also affect blood vessel pathology. Vitamin D appears to influence a broad array of metabolic jointpoints through complex signaling pathways [4]. Hypovitaminosis-D may potentiate DM-PN sensory symptoms by disordering nociceptor function. Thus, patients with DM-PN may become hypersensitive to pain at a threshold requesting a higher level of serum 25-hydroxyvitamin D_3 than that of nondiabetic individuals [41]. Clinical studies demonstrated an inverse correlation between the levels of serum 25-hydroxyvitamin D_3 and HbA1c [42, 43]. However, glycemic controls failed to distinguish between diabetic patients with hypovitaminosis-D when compared to those with normal levels of vitamin D [44], suggesting that the mechanism underlying by vitamin D in mitigating DM-PN symptoms may be different than the mechanism underlying by glycemic control. Administering one-time intramuscular injection of vitamin D at 600,000 IU prompted remarkable increase in the level of vitamin D and favorable improvement of neuropathic symptoms measured with SFMPQ, total pain score, and DN4 [20], suggesting that vitamin D may modify pain threshold through modulating nociceptor function [40]. Additionally, the possibility that vitamin D may modulate central pain mechanisms can not be overlooked [45].

Severity of the neurological deficits resulting from the peripheral or central nervous system may be influenced by hypovitaminosis-D. Individuals with multiple sclerosis (MS) frequently showed decreased levels of vitamin D than those with no MS. A study from Turkey showed that approximately two thirds of patients with MS were concurrent with hypovitaminosis, osteoporosis, and pain [46]. A study in a long-term care facility on patients with MS in the USA demonstrated a high prevalence of osteoporosis, chronic pain, and hypovitaminosis-D [47]. While administering vitamin D modified the risk for MS by 40% of reduction, even at a very low dose [48].

Sensation and the convey of pain signals firstly occur at the dorsal root ganglional sensory neurons. Vitamin D, together with its receptors, may interact with module-specific pain signaling molecules such as opioid receptors, epidermal growth factor receptor, glial-derived neurotrophic factor, and nerve growth factor (NGF) [49]. Administering vitamin D promotes expression of NGF in an animal model for diabetes. Understandably, NGF plays a crtical role in the survival, growth and differentiation of sensory and sympathetic neurons [50], which are categorized to small nerve fibers. The

occurrence of regeneration and remyelination promoted by vitamin D treatment following nerve injury may be partly due to the increased production of neurotrophins, such as NGF, which targets on sensory and sympathetic neurons [51]. Vitamin D-associated improvements have been observed in neurologic symptoms and in axon regeneration with myelination following nerve injury [52], which may have resulted from an increase in NGF synthesis and reduction in neuronal degeneration [53].

Additionally, hypovitaminosis-D in painful DM-PN is associated with increased expression of inflammatory cytokines [54], such as tumor necrosis factor-alpha and/or interleukin-6 in both large and small sensory fibers as well as the nerve endings, which may play a role in causing painful symptoms. A neurophysiologic study showed that treatment with vitamin D improved nerve conduction velocity and alleviated DM-PN symptoms [32]. A double-blind, randomized, placebo-controlled clinical trial has demostrated beneficial effects of vitamin D in clinic paralled with laboratory findings of improved cytokine profiles in patients with congestive heart failure [55]. Additionally, an inverse correlation of hypovitaminosis-D with inflammatory cytokines was demonstrated in a 12-month follow-up study [56]. Indeed, vitamin D exerts an anti-inflammatory effect by reducing inflammatory cytokines [57]. However, a correlation between vitamin D and inflammatory cytokines in painful PN remains to be firmly established [26, 54].

Populations Susceptible to Hypovitaminosis-D

Vitamin D deficiency prevails worldwide. It is estimated that more than 1 billion individuals suffer vitamin D deficiency and 50% of the people suffer vitamin D insufficiency [58], particularly in seniors, long-term care inhabitants, hospitalized persons, and obese people [59]. A prevalence of hypovitaminosis-D was observed 35% hgher in obese people regardless to latitude and age [60]. In the USA, an estimated 50% to 60% of residents in long-term care facilities have vitamin D deficiency [59, 61, 62]. Hypovitaminosis-D may be more prone to the individuals who clothe in extensive skin coverage and who have higher skin melanin content.

Women in pregnancy and/or in lactation are potential risks for hypovitaminosis-D [63]. Additionally, women usually exert less outdoor exposures than do men as per cultural or religious traditions [64]. Vitamin D levels may be related to circulating sex hormones as per gender difference because a correlation was observed in the levels between vitamin D and testosterone, which circulates at lower levels in women [65].

Elderly are more vulnerable to hypovitaminosis-D because of several factors including decline in the numbers of vitamin D receptors, intestinal resistance to respond $1,25(OH)_2D_3$, decreased production of vitamin D_3 in the aging-skin and comropmised activation of $1,25(OH)_2D_3$ in the aging-kidney [66]. Comparably, sensory neuropathy observed in women and elderly may be more likely related to the status of hypovitaminosis-D. A significantly reduced serum 25-hydroxyvitamin D_3 level in diabetic patients is observed across ethnic populations and geographic locations in the world, particularly women and elderly are more prone to hypovitaminosis-D with PN [59].

Treatment for Hypovitaminosis-D

Currently, there is no guideline or consensus for treating patients with hypovitaminosis-D in painful PN. Vitamin D is commonly used to treat and prevent bone disorders, such osteoporosis or rickets. A healthy man consumes vitamin D at approximately 3,000 to 5,000 IU a day [67]. Foods rich with Vitamin D include salmon, herring, fish liver oil, and fortified milk. The Food and Nutrition Board of the Institute of Medicine recommended daily dose of vitamin D intakes: 200 IU for men and women aged 19 to 50 years; 400 IU for men and women aged 51 to 70; and 600 IU for men and women 71 and older. D_3, as the natural form, is recommended as it is made in the skin in exposure to sunlight and is more effective than D_2 in treating hypovitaminosis-D [68, 69]. Although an one-time dose of 50,000 IU of D_2 or D_3 or a daily dose of 1000 IU of D_2 or D_3 showed no difference in vitamin D levels [25(OH)D_2, 25(OH)D_3, or total 25(OH)D] [70], D_3 had a longer half-life [68]. Notably, the intracellular signal transduction pathway may be differently activated by D_3 than D_2 [71].

Under normal physiologic circumstances, adequate amount of D_3 can be produced in the skin when expose to UVB from sunlight. All UV light goes through water while ordinary glass absorbs UVB but letting UVA through. An individual staying in a glass-room could not manufacture vitamin D. Swimming for 10 to 15 minutes/day may be sufficient on a standard UV index [72]. It is estimated that approximately 10,000 IU to 15,000 IU of D_3 can be made in the whole body when exposed to sunlight. However, proploned exposure in the sunlight doesn't produce more D_3 but may raise risks for skin cancer. Exposure of a small skin territory of the body to sunlight for prolonged periods wouldn't produce more vitmanin D because once the amount of D_3 is maximally manufactured in a limited skin area (approximately in 15 minutes), no more D_3 can be made until, roughly, next day [72]. Toxicity is rare but may occur if more than 40,000 IU a day are intaken in the form of supplements [72], which may manifest as hypercalcemia, gallbladder and kidney stones, and tissue calcifications.

Summary

Hypovitaminosis-D may be a potentially independent risk factor for painful PN. Recognition of an underlying etiology agent for PN, such as hypovitaminosis-D, is more impressive than merely treating neuropathic symptoms. Administering vitamin D to patients with hypovitaminosis-D may mitigate their neuropathic manifestatons and may have the potential to reverse or arrest the progression of hypovitaminosis-D related painful PN . Notably, higher levels of vitamin D are correlated to improved longevity [73, 74]. A large ramdomized, double-blind and placebo-controlled prospective trial is needed to validate the effects of hypovitaminosis-D and vitamin D in patients with painful PN.

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Conflict of Interest

Authors declare no conflict of interest.

Credit Author Statement

Dr. Luo generated and designed the idea and critical thinking, drafted and revised the manuscript.

Dr. Dun conducted critical thinking, drafted and revised the manuscript.

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