

Vitamin D in neurological and neurodegenerative patients: Current knowledge and future perspectives

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ABSTRACT

Effective pharmacological treatments for neurological and neurodegenerative patients have not yet been identified. Previous studies show that vitamin D may be involved in neurodevelopment adult brain. Reduced status of vitamin D have been reported in various neurological and neurodegenerative disorders. Insufficient levels of vitamin D in neurological and neurodegenerative have been confirmed. The neuroprotective effect of vitamin D is associated with its effects on neurotrophin synthesis and prevention of oxidative or inflammation damage to nervous tissue. We here review the role of vitamin D in the pathogenesis disease, such as seizure, Pain, depression and anxiety, sleep, sexual dysfunction, addiction, alzheimer's, parkinson's. Adequate administrate of vitamin D in the lifetime seems to be crucial in terms of prevention of these diseases. The aim of this review is to assess the current knowledge related to the role of vitamin D supplementation on the pathogenesis and disease course of neurological and neurodegenerative.

Key words: Vitamin D, Neurological, Neurodegenerative

INTRODUCTION

Vitamin D

Vitamin D is a pro-hormone and not actually a vitamin [1]. The main source of vitamin D is from disposal to sunlight. Ultraviolet irradiation from sunlight change 7-dehydrocholesterol to vitamin D₃, which is biologically primrose. The classical synthetic vitamin D₃ is metabolized to 25-hydroxyvitamin D and 1 α , 25-hydroxyvitamin D in the liver and kidney, which is the active metabolite that functions via an intracellular receptor, which is present in many different bodily tissues [1, 2]. Epidemiological studies suggest that in many countries world, vitamin D insufficiency levels are prevalent across all age groups, irrespective of the geographical location or seasonal changes, as well as in healthy populations [3-5].

The major role of vitamin D in the human body is commonly associated with calcium (Ca) homeostasis and bone structure [1, 6]. An active metabolite of vitamin D, 1,25-(OH)₂D₃, impacts target cell function related to regulating gene expression and biochemical profiles. The effects non genomic 1,25-(OH)₂D₃ involves membrane-associated rapid response steroid binding receptors [7].

The impacts of vitamin D administration have been evidence in neurodegenerative diseases [8] and, neurological symptoms [9-11]. This is not surprising as the receptors of vitamin D and the enzyme (α 1-hydroxylase) needed for its activation are located in many neuromuscular, internal organs, immune cells, and brain [12].

Neurological patients

Seizure

Epilepsy is one of the most common and serious brain disorders in the world. It affects at least 50 million people worldwide. Approximately 100 million people will have at least one epileptic seizure during their lifetime. It causes serious physical, psychological, social, and economic consequences [13]. The median prevalence of lifetime epilepsy for developed countries is 5.8 per 1,000 and 10.3 per 1,000 for developing countries [14]. There is evidence that epilepsy is associated with immune system dysfunction [15], increased inflammatory markers [16] and metabolic abnormalities [17, 18]. Also, patients with epilepsy had increased markers of oxidative stress, which might cause cell apoptosis, lipid peroxidation, and DNA damage [19, 20].

The most epileptic patient requires long-term therapy with antiepileptic drugs (AEDs). Many classical AEDs are inducers of hepatic P450 system and may cause vitamin D deficiency [21, 22]. However, non-enzyme-inducing AEDs may also be associated with hypovitaminosis D. Several studies indicate increased risk for bone loss in patients on antiepileptic medication as well as low levels of serum 25(OH) D, the major circulating form of vitamin D₃ [23-25]. In contrast to the above-mentioned antiepileptic drug-related studies, fewer studies have addressed the relation between vitamin D and epilepsy itself. There is one study addressing the effect of vitamin D supplementation on seizures in a group of patients with pharmacoresistant epilepsy. A few case studies suggested a link between

maternal vitamin D deficiency and newborn seizures eliminated by vitamin D treatment [26, 27]. Also, since animal studies support an anticonvulsant effect of vitamin D [26, 28, 29]. Current evidence supports the therapeutic benefits of vitamin D in the treatment of seizures. Clinical trials and more studies are regained to evaluate the therapeutic potential of vitamin D in the treatment of patients with seizures.

Pain and Neuropathic pain

Vitamin D deficiency related to musculoskeletal and nervous system disorders [30], including muscle weakness, balance problems, and increase in the frequency of falls. It has been recognized as an independent risk factor for diabetic peripheral neuropathy, retinopathy, and nephropathy [31-33]. Long-term vitamin D deficiency may lead to decreased immune response and chronic inflammation, which may cause disabling pain [34]. Individuals with vitamin D deficiency often report increased pain perception, which has been ascribed to hyperinnervation and hypersensitivity in nerve fibers [35]. Vitamin D supplementation is an essential therapeutic approach for the prevention of many health problems related to its deficiency [36, 37]. For example, short-term oral vitamin D supplementation improved clinical symptoms of diabetic peripheral neuropathy [38]. Peripheral neuropathy was reversed with calcium and vitamin D supplementation in a case of idiopathic hypoparathyroidism [39]. In a rat model of peripheral nerve injury, vitamin D2 treatment significantly increased axonogenesis and axon diameter [40], whereas vitamin D3 treatment improved myelination and recovery after nerve injury, increased the number of preserved or newly formed axons in the proximal end, and increased the mean axon diameter in the distal end [41]. The current study showed that vitamin D supplementation may decrease the severity of pain and increase the overall Quality of life, as well as some specific domains of health-related Quality of life. Moreover, the changes in severity pain were moderately correlated with the changes in some domains and the overall Quality of life [42, 43]. Vitamin D supplementation may reduce pain and improve Quality of life in individuals with pain and vitamin D deficiency, albeit without improving peripheral nerve conduction. Long-term randomized placebo-controlled trials are needed to confirm these preliminary results.

Depression and Anxiety

Major depressive and anxiety disorder are defined as a mental disturbance characterized by a pervasive and persistent low mood that is accompanied by a loss of pleasure in normally activities [44]. Fifteen years ago it was demonstrated that vitamin D status was the forgotten neurosteroid. Vitamin D deficiency, diagnosed when the serum vitamin D level are less than 20 ng/ml, is highly prevalent worldwide and thought to potentiate a variety of chronic patients, including Seizure, chronic pain, neurological and neurodegenerative diseases, diabetes, addiction, cancer [45]. The overall estimation of current prevalence of depression and anxiety is 5.1% in Iran [46].

Several factors, including psychological, hereditary, evolutionary, and biological, might contribute to the risk of depression and anxiety [47]. This disorder may result in considerable morbidity, mortality, and enhanced quality of life [48]. Several finding have indirectly evaluated the impact of vitamin D intake on reduce of depression and anxiety score. Results a recent meta-analysis demonstrated that subjects with clinically significant depression had a reduction in depressive scores after vitamin D intake [49]. We have previously reported that vitamin D supplementation at a dosage of 50000 IU for 12 weeks improved depression and anxiety in subjects under methadone maintenance treatment [50]. In the study by Sepehrmanesh et al. [51], it was seen observed that the administration of vitamin D had the beneficial effects on depression score in major depressive disorder (MDD). Furthermore, some studies have demonstrated a favorable effect from vitamin D administration on score of depression in overweight population [52] and subjects with MDD [53]. However, vitamin D supplementation at a dosage of 50000 IU for 12 years may not impact on mood in older women [54]. The accurate mechanism of function of vitamin D in the brain and its impacts on depression and anxiety parameters is not completely understood. Increased expression of the tyrosine hydroxylase gene and enhancement of the bioavailability of some neurotransmitters such as dopamine, norepinephrine, and epinephrine might describe some of the beneficial effects of consuming vitamin D supplements on anxiety and depression [53, 55]. Overall, taking vitamin D had beneficial effects on depression and anxiety score.

Sleep

Sleep good, much like diet and physical activity, is a critical indicator of mental health in the life time [56, 57]. The national sleep research and education recommends that adult health should get 7 hour sleep in one every day, albeit sleep demands may vary in age and gender. The healthy sleep is necessary for maintaining physical and psychological health. In recent years, sleep disturbance have become an epidemic in the world [57-60]. Previous studies demonstrated that excessive sleep or sleep disorder were related to enhanced risk of adverse health events, including psychiatric disorder, diabetes, hypertension, cancers, and mortality [61, 62]. Recent studies reported that low Vitamin D levels was related to an enhanced risk of metabolic disorder, overweight, diabetes mellitus, and mental health problems [63-65]. The evidence studies have demonstrated the relationship between vitamin D deficiency and sleep disturbance [66-69]. In the study, after vitamin D intake at a dosage of 50,000 IU/week for 3 months significantly improved Pittsburgh Sleep Quality Index (PSQI) score in patients under methadone maintenance treatment (MMT) [50]. In another study, Huang et al. [70], showed that vitamin D supplementation at a dosage of 1200 IU daily and 50,000 IU weekly significantly improved pain status, sleep, and various aspects in veterans with multiple areas. However, other evidence presented that vitamin D level was not related to sleep duration [71, 72]. The accurate mechanism of vitamin D in the brain and its effects on sleep is not

completely understood. There may be some possible reasons for Describing the relationship between vitamin D levels and sleep latency. For example, lower vitamin D status might lead to sleep disturbance via affecting sleep regulating substance, such as melatonin hormone, tumor necrosis factor alpha, interleukin-1 and prostaglandin D2 [63-65, 73]. Another mechanism possible explanation is that vitamin D receptors have been showed in specific regions in the CNS involved in regulating sleep, which include the anterior and posterior hypothalamus, the raphe nuclei, the midbrain central gray, and the nucleus reticularis pontis caudalis and oralis [74, 75]. However, sleep disorder may be link to changes in dietary habits and daily activity patterns, which could affect vitamin D status [76-78]. Therefore, further cohort evidence and well-designed clinical trial are needed to verify this relationship and to determine the beneficial effect of vitamin D intake.

Sexual dysfunction

The epidemiological studies reported the prevalence sexual disturbance rates were 7% for those 40–49 years of age, 22% for 50–59 years of age, 49% for 60–70 years of age and 37.5% for the entire group of 40- to 70-year olds in world. Asian evidence demonstrated a 7–15% rate of erectile dysfunction for ages 40–49 years and 39–49% for ages 60–70 years [79]. The previous evidence have been demonstrated that low vitamin D status increases the risk of neurological and neurodegenerative disease, psychiatric disorder, stroke, myocardial infarction, hypertension, diabetes, and autoimmune diseases [80-83]. Several evidence conducted in the last few years showed the association between vitamin D status and sexual function. Low vitamin D status was related to the presence of sexual dysfunction in dialysis patients [84]. In the study by Farag et al. [85], it was seen observed that men with vitamin D deficiency had a higher prevalence of erectile dysfunction. Also, reported that severity of male sexual dysfunction associated with the degree of hypovitaminosis D [86]. However, in the clinical trial demonstrated vitamin D intake may not effect on sexual dysfunction in subjects under hemodialysis [87]. Low vitamin D status may be to have an unfavorable effect of blood vessels and is regarded as a risk factor for cardiovascular diseases, including hypertension, atherosclerosis, coronary artery disease, stroke, heart failure [81, 88]. Also, it is associated with impaired production of nitric oxide [89]. Vitamin D induces a significant enhance in nitric oxide production [90]. In conclusion, in states of its deficiency blood flow through genital organs during the sexual intercourse may be disrupted. On the other hand, vitamin D deficiency may affect the production of hormones implicated, particularly of testosterone. Loss of sexual desire, also the remaining disturbances of female sexual functioning occurs more frequently in women with low testosterone hormones [91, 92]

Addiction

The reported that 230 million people have used illicit drugs at least once during the year 2010 and 27 million

people have had problems. Substance abuse is a serious public health problem, leading to increased rates of mortality, HIV, hepatitis B and hepatitis C infection [93]. In Iran, the prevalence of opioid use is rising and was nearly three times higher than the prevalence worldwide. About 1.2 millions of Iranians have opioid dependency with opium is the most commonly used opioid (82%), followed by opium ashes (28%), methadone for non-medical usages (16.6%), heroin and heroin/cracked (16%), and morphine (2.6%) [94]. Effective pharmacological treatments for substance abuse and drug addiction have not yet been identified [95]. Many evidence demonstrated that vitamin D plays an important role in brain function [96]. Low vitamin D levels, which we use to refer to either vitamin D deficiency, have been recognized in a variety of peoples with medical conditions. It has received little attention in drug abuse populations. Previous studies have shown that low vitamin D status and low bone mineral density were present in a majority of patients under MMT program [97, 98]. Low levels of vitamin D may relate to nonspecific musculoskeletal pain [99], periodontal disease [100], and higher risk of fracture by exacerbating osteoporosis [101]. It has been shown that substance abuse stimulate neurons in nucleus accumbens and VTA. However, all of them share a final action in which they increase dopamine status in the brain [102]. In the animal studies have been demonstrated vitamin D administration significant attenuated methamphetamine-induced reductions in dopamine and metabolites. Also, indicating that vitamin D intake provides protection for the dopaminergic system against methamphetamine abuse [103]. In the study by ghaderi et al. [50], it was demonstrated that vitamin D supplementation at a dosage of 50000 IU for 12 weeks had the beneficial effects on clinical and metabolite profiles in patients under MMT. The protective effects of 1,25-(OH)₂D₃ may be due to a mechanism of upregulation of glial cell line derived neurotrophic factor [103]. It was demonstrate that when glial cell line derived neurotrophic factor (GDNF) is injected directly into the striatum before methamphetamine treatment, complete protection against the dopaminergic toxicity of methamphetamine, such as reductions in striatal dopamine release, could be observed [104]. In addition, vitamin D enhances glutathione status and inhibits nitric oxide production, which could decrease methamphetamine toxicity to the dopamine system [103]. Over all, advances in addiction research may be contributed towards new choices in substance abuse treatment, although several studies need further investigation.

Neurodegenerative patients

Alzheimer's

The epidemiological reported that 24 million people suffer from the disease, and this number is expected to double by 2040 [105]. Alzheimer's disease is a neurodegenerative disturbance affecting mostly elderly persons resulting in cognitive deficits, dementia, Memory impairment, and behavioral alterations [106, 107]. In pathology of Alzheimer's disease, a major hallmark of the disease is the accumulation of amyloid-beta (A β) plaques,

neurofibrillary tangles (NFTs), synapse loss in brain [108]. Strong risk factors for Alzheimer's disease include environmental, genetic, gender, family history [109]. Vitamin D has promising clinical applications in the prevention and treatment of various diseases [110, 111]. In recent studies has shown that patients with Alzheimer's have lower status of vitamin D relative to healthy controls. Also, vitamin D deficiency has been reported to be linked to Alzheimer's disease [80, 112-114]. In the animal studies have been demonstrated vitamin D administration (10,000 IU/Kg/day) for 5 to 6 months significant performed better learning and memory task in the Morris water maze test and cognitive disturbance worsened when vitamin D injection was removed from the diet of animals models [115]. A randomized controlled double-blind placebo trial demonstrated the beneficial effect of vitamin D administration on cognitive performance in healthy elderly subjects compared to the control group [116]. In addition, vitamin D intake at a dosage of 2336.41 IU weekly for 7 years had the beneficial effects on cognition parameters and reduced risk of Alzheimer's disease in older women [117]. However, in the clinical trial by Stein et al. [118], it was demonstrated high dose vitamin D provides no benefit effects for cognition or disability over low-dose vitamin D in mild-moderate Alzheimer's disease. The exact mechanism of function of vitamin D in the brain and its impacts on Alzheimer's disease is not completely understood. Vitamin D administration reduces oxidative stress and preventing neurons from dying through the activation of macrophages which help A β plaques clearance as shown [119]. However, in Alzheimer's disease, the presence of A β activates low-voltage calcium channels leading to disorders of calcium homeostasis. Also, in animal studies vitamin D intake enhanced Ca homeostasis and protected neuronal death [120]. In other hand, vitamin D supplementation had reduced nerve growth factor and GDNF [121]. In summary, vitamin D intake should be encouraged in the elderly subjects and Alzheimer's disease patients to combat the possible detrimental sequelae of low serum vitamin D status.

Parkinson's

Parkinson's disease is the very common form of neurodegeneration disease among the elderly people. Disturbance of the dopaminergic neurons in the substantia nigra, resulting in clinical finding such as tremors, rigidity, slowness of movement, and postural imbalance [122]. Parkinson's disease is the result of complex of genetic, environmental, nutritional, and aging factors. Among nutritional factors, studies demonstrate that vitamin D may be implicated in the development of Parkinson's disease [123-125]. Vitamin D receptors are widespread in the body, including muscle, spinal cord, and brain, supporting the notion that vitamin D is necessary for normal functioning of the peripheral and central nervous systems [126, 127]. Vitamin D could play a key role in neurological disorders such as PD and dementia [12, 128]. It has been demonstrated that serum vitamin D levels is significantly lower in subjects with Parkinson's disease, and serum 25(OH)D status progressively reduce with enhancing severity of Parkinson's disease [129-131].

There are very few evidence studies that have been undertaken to investigate a potentially the favorable effect of vitamin D in patients with Parkinson's disease. These studies have been shown some of the clinical presentations of Parkinson's disease such as falls, fractures, and balance disturbance related to low status of circulating vitamin D [132-134]. In the study by Suzuki et al. [133], it was demonstrated that vitamin D intake at a dosage of 1200 IU per day for 12 months had the beneficial effects on disease progression in patients with Parkinson's disease. However, short term, high dose vitamin D supplementation at a dosage of 10,000 IU/day for 16 weeks appears safe, but did not significantly improve in subjects with Parkinson's disease [135]. Favorable effects vitamin D supplementation has been demonstrated by potential neuroprotective effects, stimulates the synthesis of the antioxidants, neuronal calcium regulation, inhibit the synthesis of nitric oxide and free radical, immunomodulation, and detoxification mechanisms [12, 136-138]. In addition, vitamin D may act as a neurotrophic effects, via the stimulation of nerve growth factor, GDNF and neurotrophin [139, 140]. In other hand, Animal studies have demonstrated the effects of vitamin D receptor gene transcription in neuronal cells, and have shown that vitamin D receptor and vitamin D are key molecules to brain development, the prevention of Parkinson disease, the through induction of GDNF, and nerve growth factor synthesis [141, 142]. Over all, subjects with lower vitamin D levels were related to high risk of Parkinson's disease. Many randomized controlled clinical trials (RCT) of vitamin D intake for the prevention of Parkinson's disease are needed to be conducted to determine the risks and the favorable effects.

Conclusions

Evidence studies demonstrated that vitamin D acts like a neurosteroid and is required for bone health, cognitive function and normal brain development. Adequate taking of vitamin D in the lifetime seems to be crucial in terms of prevention of neurological and neurodegenerative patients. Prospective studies are needed to evaluate the eligibility of vitamin D-related parameters in neurological and neurodegenerative patients. Prospective studies are needed to evaluate the eligibility of vitamin D-related parameters in neurological and neurodegenerative patients.

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