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BASIC SCIENCE

The contribution of Vitamin D on the Rehabilitation of patients with Chronic Spinal Cord Injury. Newer Data

Vlachos C, Vlamis J, Pneumaticos SG

3rd Department of Orthopaedic Surgery, University of Athens Medical School, KAT Hospital, Athens, Greece

ABSTRACT

The metabolism and actions of vitamin D in human body are nowadays under intensive investigation. Even if a lot are known about its role in the general population, a few are acquainted as for vitamin's D effects on people who have sustained a spinal cord injury (SCI). Low mobility, poor nutritional supply and the accompanied coherences of SCI individuals makes them predominant for vitamin D deficiency in comparison to able-bodied people. The so far available studies suggest that the decreased vitamin's D status probably have a negative action mainly on musculoskeletal system but also on cardiovascular, respiratory and endocrine system, leading to difficulties on patients attempt for rehabilitation and return to everyday activities.

KEY WORDS: Spinal Cord injury (SCI), chronic SCI, Vitamin D, 25(OH)Vit D, SCI Rehabilitation

Introduction

Vitamin D is a hormone produced from sterols in the body. Sources of vitamin D include biosynthesis through the actions of ultraviolet light in the skin and through the diet as ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3).

Both isoforms are available in foods and supplements, whereas vitamin D3 can be synthesized in the skin from ultraviolet-B (UVB) radiation. Vitamin D is then transported in the circulation, where binds to the D-binding protein (DBP) and can be stored in the adipose tissue. Actually, it is considered a prohormone since it requires further hydroxylations before becoming biological active. The first hydroxylation step occurs in liver where 25OHD is produced, the universally accepted metabolite for vitamin D status, while the second takes place in the kidneys and extra-renal tissues, leading to the formation of bioactive 1,25-dihydroxyvitamin D (1,25(OH)2D). The hormone binds to the nuclear vitamin D receptor (VDR) regulating the transcription of a wide range of genes (1).

Individuals with a spinal cord injury (SCI) demonstrate higher risk for serious complications in almost all human systems (2). SCI patients may suffer from pulmonary atelectasis and high inci-

CORRESPONDING AUTHOR, GUARANTOR

Vlachos Christos: Third Department of Orthopedic Surgery, University of Athens Medical School, KAT Hospital, Nikis Avenue 2, 14651, Athens, Greece
E-mail address: christosorto@gmail.com
Phone number: +30 6947005235
Christos Vlachos: christosorto@gmail.com
Evangelopoulos DS: ds.evangelopoulos@gmail.com
John Vlamis: jvlamis@email.com
Spyros G. Pneumaticos: pansec@kat-hosp.gr

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dence of pneumonia due to their incompetence to mobilize lung secretions (3). As for the cardiovascular system, these patients present hypertension, dysreflexia and high thromboembolism rate (4,5,6). Moreover, SCI individuals undergo increased bone loss and deterioration of the skeletal microarchitecture (7), resulting frequently in low impact fractures (8). The metabolic and endocrine profile of this population is also disturbed. They often develop glucose intolerance (9) and dyslipidemia (10) or they put up with obesity (11).These problems have a further negative impact not only on patient's functional independence and quality of life, but also on families and SCI specialists. Therefore, prevention and early treatment are of crucial importance. Vitamin D deficiency is identified in the majority of SCI population and may be related with the severity of these conditions and poor outcomes. In addition, there are no clear guidelines on the ideal vitamin D supplementation strategy for these patients.

Low serum Vitamin D levels have multifactorial causes. Among them is the insufficient Vitamin D from food as well as the inadequate exposure to sunlight, mainly due to patient's impaired mobility and independence. Moreover, weather conditions and skin color contribute to low Vitamin D synthesis (12). These factors have to be taken under consideration when assessing Vitamin D levels in SCI population.

Therefore, vitamin D deficiency is a significant issue for SCI individuals, undergoing rehabilitation programs **(**13). Especially, athletes with a SCI might be impaired from such a deficiency, due to decrease in neuromuscular performance and having a higher rate of injuries (14). The purpose of this review is to investigate vitamin D status and accompanying effects in spinal cord injured individuals, detect various factors leading to vitamin D deficiency and evolve potential guidelines.

A literature search was performed using Pubmed, Medline, Embase, and Google Scholar databases, as search engines. Our analysis included studies published until June 2020 in English language, assessing 25-hydroxy vitamin D status (ergocalciferol). The literature search was performed using the keywords outlined below and combined as follows: ('vitamin D OR ergocalciferol OR 25-hydroxy vitamin D') AND ('SCI OR Chronic SCI) (Figure1). As inclusion criteria we defined: (i) the presence of SCI with at least one year follow-up, and (ii) the absence of comorbidities.

Patients with either teraplegia or hemiplegia were enrolled in the search. A concentration of 20 ng ml^{-1} (50nmol l^{-1}) was proposed as a threshold for vitamin D deficiency. Review articles, letters to the editor and studies including animals or children were excluded from data analysis. In addition, studies assessing vitamin D status following a period of supplementation were also excluded.

Discussion

Insufficient sun exposure and limited intake from the daily diet

The easiest way to imrove vitamin D status is a short, daily and unprotected sun exposure however no clear data and guidelines exist as for the level of this sun exposure. Summarily, UVB radiation converts the precursor 7-dehydrocholesterol, which can be found in the cell membrane of skin fibroblasts and keratinocytes, to previtamin D3. In turn, it is metabolized to vitamin D3 (cholecalciferol), which is then transported into the bloodstream and is pinioned to D-binding protein (DBP) (1). Many factors limit the time and the quality of sun exposure of SCI individuals. Thermoregulatory disorders, particularly in individuals with above T6 injuries causing high sensitivity to heat or cold, the use of clothes to protect against sunburns and the use of a sunscreen with high index are only a few of them (15). Moreover, people with SCI often homebound and experience long lasting periods of hospitalization, due to reduced mobility and independence.

The other method of receiving enough vitamin D is through oral intake. However, vitamin D2 (ergocalciferol) input, particularly through dairy products, is yet low in SCI population. This occurs due to wrong perceptions and poor compliance of these people (15). More specific, SCI individuals incorrectly believe that products that are rich in vitamin D and calcium can cause kidney stones. In addition, use of medications that are mainly metabolized by the P450 cytochrome CYP3A4, such as anticonvul-

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sants and antibiotics, usually administered to SCI patients, further reduce Vitamin D levels (16).

Koutrakis et al. (17) applying specific questionnaires as for vitamin D and calcium intake, food habits, alcohol use, smoking, medical history and physical activity of SCI individuals. Concluded that neurological level and mobility, AIS score and duration from injury do not have any important effect on vitamin D levels. On the other hand, way of life, nutritional habits and physical activity demonstrate a positive impact on vitamin D. Especially, the author reported that levels of vitamin D from daily nutrition are limited in comparison to vitamin D supplements. In addition, Oleson et al. (15) reported that even in summer, vitamin D levels remain insufficient and only slightly higher than in winter for SCI population. Moreover, age had no influence on vitamin D levels and that the most patients were advised to follow a low-calcium diet to minimize of kidney stones risk. Consequently, it is important vitamin D and calcium levels to be closely monitored in SCI population to achieve optimum rehabilitation results.

Respiratory

SCI Individuals have impaired pulmonary function, resulting inhigh morbidity and mortality rates (18**).** In able-bodied persons, respiratory symptoms, such as chronic phlegm, chronic cough, and wheeze, are related to future chest illness, by means of COPD, asthma, decreased pulmonary function and high infection rate, leading to long lasting hospitalization (19,20). Bronchial epithelium and immune cells have the ability of converting 25(OH) D to active 1,25(OH)D. This metabolite decreases the release of inflammatory cytokines from the epithelial cells which in turn, quaintly, maintains the antimicrobial response (21). Furthermore, Vitamin D urges immune responses needed for protection against pathogens and promotes autophagy (22,23), which is essential in clearing intracellular microbes that may cause pneumonia. Clark et al. (24) reported that there is a suggestive association between vitamin D deficiency and future chest illness, while duration from injury, higher neurologic level and completeness of the spinal cord injury seems to have no effect. On the other hand, Garshic et al. (25) stated that there is no significant relation between vitamin D levels and FEV_1, FVC and FEV_1/ FVC respiratory parameters. Accordingly, Walia et al. (26) mentioned that increased body fat and not vitamin D status is associated with wheeze in chronic SCI. Further studies are warranted to evaluate the protective role of vitamin D on the respiratory system of SCI patients.

Bone metabolism

Osteoporosis is characterized by disruption of bone's micro-architecture, which results in increased bone fragility and predisposition for fracture. The maximum bone loss occurs the first 4 to 6 months and until up to one year from SCI (27). In contradiction with classic forms of osteoporosis that influence the whole skeleton, in SCI population the primarily affected sites are the weight-bearing areas or those who are rich in trabecular bone, such as the distal site of the femur and the proximal site of the tibia. For that reason, SCI individuals have a high risk of suffering from insufficiency fractures of the lower extremities, either spontaneous or traumatic (28), which will dramatically change their independence and quality of life.

It is so far unknown whether vitamin D affects the bone directly or indirectly, via regulation of the intestinal absorption of calcium and phosphate. In vitro studies suggest that the metabolic active 1,25-dihydroxyvitamin-D (1,25(OH)D) acts directly on the bone via the VDR and induces osteoclasts and osteoblasts to get differentiated. Additionally, osteoblasts have the enzymatic ability of converting the circulating 25-hydroxyvitamin-D (25(OH) D) to bioactive 1.25(OH)D, which in turn not only regulates the differentiation of osteoblasts but also the secretion of various proteins, such as collagen type I, osteocalcin and RANKL (2). Moreover, vitamin D deficiency results in deregulation of calcium homeostasis and secondary hyperparathyroidism, leading to increased bone resorption (29,30). More specific, high bone loss during the first months leads to increased serum calcium levels and a subsequent decrease in PTH, which by its turn reduces renal production of bioactive 1.25(OH)D. However, after the first year, PTH seems to return in normal levels.

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Karapolat et al. (31) reported that although the axis of PTH and vitamin D is under suspension during the first months, their levels are increased at 12months, while calcium and phosphate levels remain stable. They also showed that bone mass density (BMD) decrease is strongly related with time from SCI and duration of immobilization. Vaziri et al. (32) mentioned that PTH and calcium statuses remain low in SCI group, while vitamin D status is identical in SCI and able-bodied individuals. Likewise, Morse et al. (33) referred that bone loss has nothing to do with the traditional risk factors, such as vitamin D, age, gender and body composition. Furthermore, Jørgensen (34) cited that increased bone turnover markers, such as carboxy terminal collagen (CTX) are related with high incidence of fracture, while deficiency of vitamin D has no association. Finally, Bauman et al. (35) suggested that vitamin D2 supplement, as monotherapy for osteoporosis in SCI individuals, has only a small and not significant effect on BMD. These findings lead to the conclusion that there are a lot yet to be found in regard not only to vitamin D mechanisms but also to potential therapies for osteoporosis.

Muscle strength

A deficient Vitamin D status is related with loss of muscle strength and myalgia, herby suggesting that it has a key role in muscle health (36). Muscle cells are expressing the VDR and also dispose 1-a hydroxylase, which makes them able of converting 25(OH) D to active 1.25(OH)D. The presence of these two muscle cell properties is confirmed only in animals, while in humans is still debatable (37,38). Over and above, in animal studies, vitamin D can urge both genomic and non-genomic mechanisms (39). The first ones regulate the expression of genes, such as VDR, myogenin and myostatin, that are involved in differentiation and proliferation of myoblasts (40). Through the second mechanisms, vitamin D induces muscle cellular responses that are not mediated by genes. These include for example an influx of calcium into muscle cells relevant to contraction strength and an increase of glucose transporter 4 (GLUT4), which provides the needed energy for the muscles actions (36,41).

Several studies were retrieved, examining the association between Vitamin D levels and status of physical performance and function. Barbonetti et al. (42) used special questionnaires to approach the theme, taking into consideration the neurological level of SCI individuals. The results indicated that vitamin D is an independent predictor of potential poor physical function. Moreover, in another study, Barbonetti et al, taking into account vitamin D, BMI, patient's morphological characteristics and ASIA score, ended up in the same conclusion (43).

Metabolic profile

Dyslipidemia: Although it is not clear how vitamin D and lipids are linked, several studies report that either vitamin D affects directly or indirectly lipid profile via homeostasis of PTH and calcium. Studies on VDR knockout mice showed that vitamin D may reduce triglycerides (TG) and cholesterol levels, by inducing lipolysis (44). Indirectly, vitamin D modulates lipid status either through regulation of calcium absorption; nevertheless, calcium seems to have only a minor effect in serum lipid levels (45), or through PTH axis. Maintenance of serum calcium leads to reduced secretion of PTH, which in turn modulates lipolysis (46,47). Beal et al. (48) reported that increased vitamin D levels decreases total cholesterol levels; however only a limited positive effect was observed on HDL, while no effect was observed on LDL and TG levels.

Glucose intolerance: Previous studies on animals (11) have shown that insulin secretion may be regulated through vitamin D repletion, in various ways. Calcium serum concentration is crucial to achive insulin exocytosis (49). Vitamin D indirectly participates in this process through modulating extracellular calcium homeostasis. Additionally, vitamin D affects glucose intolerance via VDR and 1-a hydroxylases in pancreas islets and beta cells (50). On the other hand, increased PTH, due to vitamin D deficiency has been shown to cause decreased sensitivity in insulin (51). Moreover, vitamin D has the ability of controlling the transcription of insulin receptor through of a vitamin D response element consensus sequence on its promoter region (52). Beal et al. (48) found a small but important improvement in glucose homeostasis, independent of body composition

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changes in SCI individuals.

Obesity: Several studies have proved that obesity is more frequent among SCI individuals, in comparison to able-bodies persons (53), as well as that this population seems to have high percentage of body fat (54), especially below the level of injury (55). Nevertheless, it is still undefined why obese individuals present insufficient vitamin D levels. It has been suggested that this is caused due to increased fat tissue storage, leading to high vitamin D clearance (56). However, it is not clear if the great fat concentration influences serum levels, pharmacokinetics and body distribution of vitamin D. Koutrakis et al. (17)found no association between vitamin D levels and BMI. Oppositely, Barbonetti et al. (43) reported that patients who were presenting vitamin D insufficiency had a significant higher BMI. As a consequence, there is a great need of further investigation to reach definite conclusions for SCI individuals.

Cardiovascular health: There is a brand new field under investigation as for the role of vitamin D in cardiovascular disease. Its deficiency is hypothesized to contribute in hypertension through: (i) the rennin-angiotensin-aldeosterone axis (57), possibly via VDR functions, (ii) hyperparathyroidism inhibition (58), PTH acts directly on vessel's smooth muscle cells of the, causing increased arterial stiffness and (iii) oxidative stress, leading to vessel wall damage (59). Smooth muscle and endothelial cells of the vessels dispose VDR and 1-a hydroxylase. In smooth muscle cells, 25(OH)D deficiency causes vasoconstriction and mediates cell differentiation and proliferation, leading to atherosclerosis. Vitamin D deficiency decrease the efficiency of nitric oxide synthase and increase the expression of adhesion molecules in endothelial cells, causing inflammation and consequent atherosclerosis.

Heterotopic ossification (HO):

HO, the pathological bone formation in soft tissues, is more usual in the acute rather than chronic SCI phase. Injury induced local hypoxia, inflammatory cytokines, autonomic dysfunction and electrolytic derangements provoque the release of several factors that prompt the local and circulating progenitor cells to differentiate into osteoblasts, thus leading to ectopic bone formation . (60,61). HO results in intense pain and a dramatical loss of joints' range of motion (ROM), reducing mobility of SCI individuals and limiting their quality of life. Oleson et al. (15) found no direct association between HO and vitamin D. However, low vitamin D levels may affect indirectly through increase in PTH levels and secondary hyperparathyroidism. Thereafter is essential monitoring vitamin D level, as well as initiating early treatment, so as to prevent formation of HO.

Vitamin D replacement therapy: 25OHD has a half-life of about 21 days, which makes it appropriate for intermittent dosing regimens (62). Several protocols have been used and evaluated, however there are no official guidelines as for vitamin D and calcium supplements.. Since vitamins D2 and D3 demonstrate high chemical affinity, it is hypothesized that they have the same effect on human body. Nevertheless, it is yet debatable whether D3 and D2 equivalently raise vitamin D levels (63,64). Bauman et al. (65) mentioned that daily doses of cholecalciferol (D3) for 3 months can safely reach vitamin D normal levels in chronic SCI individuals receiving calcium supplementation. In another study from the same author (66), administration of D3 in two different protocols resulted in non-significant raise of vitamin D levels. Literature data support that D3 supplementation represents a preferable treatment for vitamin D deficiency, since it can achieve high serum levels due to the higher affinity of 25-hydroxylase of D3 to DBP, compared to D2 (2).

Conclusion

In conclusion, the constantly new studies reveal that vitamin D plays a crucial role in almost all systems of the human organism. Particularly there is a whole scientific field, which is occupied with the effects of vitamin D in SCI population and how can it improve their way of life. Even if there is a lot yet to be discovered, the literature proves that vitamin D is the future in rehabilitation of SCI patients.

Conflicts of Interest

The authors declared no conflicts of interest

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