

Journal of **Nutrition and Food Security**

Shahid Sadoughi University of Medical Sciences School of Public Health Department of Nutrition Nutrition & Food Security Research Center



eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2023; 8(2): 325-339 Website: jnfs.ssu.ac.ir

Vitamin D Supplementation in Adults with Spinal Cord Injury: A Systematic Review

Hamed Mohammadi; PhD¹, Karim Parastouei; PhD^{*1}, Hosein Rostami; PhD¹, Maryam Miraghajani; PhD^{2,3,5} Masoumeh Rafiee; PhD⁴, Abed Ghavami; PhD⁴ & Anastasia-Viktoria Lazaridi; PhD⁵

¹ Health Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran; ² Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; ³ Nottingham Digestive Disease Centre and Biomedical Research Centre, School of Medicine, University of Nottingham, Nottingham, UK; ⁴ Student Research Committee, Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran; ⁵ The Early Life Research Unit, Division of Child Health, Obstetrics and gynecology, School of Medicine, University of Nottingham, Nottingham, UK.

ARTICLE INFO

REVIEW ARTICLE

Article history:

Received: 16 Sep 2021 Revised: 10 Jan 2022 Accepted: 10 Feb 2022

*Corresponding author

parastouei@gmail.com Health Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran.

Postal code: 9597118948 **Tel**: +98 21 88600062

ABSTRACT

Background: The current systematic review was conducted to investigate the effects of vitamin D supplementation on vitamin D levels, bone health, and physical performance indices in adults with spinal cord injury (SCI). Methods: The PubMed, Scopus, Web of Science, and Embase databases were searched for studies published up to June 2020, with no language limits. To determine the risk of bias, the Academy of Nutrition and Dietetics Quality criteria checklist was used. Results: Eight studies that met all of the inclusion criteria were identified. All of the eligible studies had a high level of heterogeneity regarding outcome measures, study design, and the dose of vitamin D. The majority of the trials showed beneficial effects of vitamin D supplementation on serum vitamin D levels and other outcome measures in patients with SCI. Three randomized controlled trials revealed a low risk of bias, whilst other studies were rated as the either neutral or negative risk of bias. Conclusion: This review suggests that vitamin D supplementation could improve vitamin D levels, bone health, and physical performance indices in individuals with SCI. However, due to the high level of heterogeneity, the results should be interpreted with caution. Further studies on this population should be performed to have sufficient power and a robust design to give definitive conclusions.

Keywords: Spinal cord injury; Vitamin D; Systematic review.

Introduction

Spinal cord injury (SCI) as a traumatic event has a profound, alarming effect on the sensory, motor, autonomic and bowel function (Singh *et al.*, 2014). This impairment of neural elements, dependent on the lesion level and extend, profoundly affects a patient's physical, social, and

emotional well-being and can result in a substantial cost and burden on the families, healthcare providers, and communities (Singh *et al.*, 2014). Apart from the apparent health injuries, it is seen that patients with SCI have a greater risk to develop several health problems such as

This paper should be cited as: Mohammadi H, Parastouei K, Rostami H, Miraghajani M, Rafiee M, Ghavami A, et al. Vitamin D Supplementation in Adults with Spinal Cord Injury: A Systematic Review. Journal of Nutrition and Food Security (JNFS), 2023; 8(2): 325-339.

cardiovascular disease (Groah *et al.*, 2009), muscle atrophy, osteoporosis, cognitive deficits, neurogenic bladder/bowel, and reduced levels of some hormones, and nutrients deficiency (Navarrete-Opazo *et al.*, 2017).

Nutritional support has been suggested to be a practical approach to manage some of the SCI complications (Groah et al., 2009). Nutritional deficiencies have been previously reported in most patients with SCI (Javidan et al., 2014, Oleson et al., 2010a). These deficiencies are multi-factorial and include the metabolic effects of SCI, medical history, reduced dietary intake, and increased excretion of nutrients (Dionyssiotis, Additional factors including diarrhea, eating disorders, prolonged colon transition time, early dysgeusia, depression, satiety, swallowing disorder, age, medications, and socio-economic level can also develop the risk of nutritional deficiencies (Dionyssiotis, 2012, Wong et al., 2011).

Among deficiency of a variety of nutrients (Dionyssiotis, 2012, Wong et al., 2011), low vitamin D levels have been reported in most patients with SCI (Oleson et al., 2010b). Vitamin D deficiency is associated with several health issues such as neuromuscular, musculoskeletal, and cardiovascular disease (Gordon et al., 2007, Lamarche and Mailhot, 2016, Nasri, 2017, Nasri et al., 2014). Patients with SCI, who are already at significant risk of musculoskeletal and cardiometabolic disorders, could escalate the rate of these conditions with vitamin D insufficiency or deficiency (Flueck and Perret, 2017). Apart from the oral intake of vitamin D, patients with SCI could develop lower levels or even deficiency in vitamin D levels as a consequence of the limited mobility, skin sensitivity due to low blood flow, and thermoregulatory issues in the paralyzed extremities (Flueck and Perret, 2017).

adequate seems that vitamin D supplementation among SCI patients with recognition of vitamin D deficiency could be crucial. However. little research has been conducted on the effects of vitamin supplementation in SCI patients. For this reason,

the current review was conducted to investigate the effects of vitamin D supplementation on vitamin D levels, bone health, and physical performance indices in adults with SCI through a systematic review. The study aims to include all the interventional studies on this topic. This study can enable healthcare providers to properly recommend vitamin D supplementation to improve SCI patients' health conditions and quality of life.

Materials and Methods

Search strategy: This systematic review was performed based on the Preferred Reporting Item Systematic Review and meta-analysis (PRISMA) guidelines. A literature search was performed using ISI Web of Science, Scopus, PubMed, and Embase as search engines until 21 June 2020. There was not any limitation in searching regarding the language. We used ("spinal cord injury" OR "spinal cord injuries" OR "spinal cord" OR "Spinal Cord Trauma" OR paraplegi* OR quadriplegi* OR tetraplegi* OR " neurotrauma " OR "spinal trauma") AND ("Ergocalciferols" OR "vitamin D" OR "cholecalciferol") as search terms. The first selection was made based on the review of abstract contents, titles, or even full text, and also the included literature was searched to identify more relevant studies. After eliminating the duplicates, the remained manuscripts reviewed by two of the authors (Mohammadi H and Parastouei K) separately.

Inclusion and exclusion criteria: The titles and abstracts of all the papers were scanned in the primary search separately by two reviewers (Mohammadi H and Parastouei K). The eligible trials the following criteria: (1) applied interventional design (pre-post, cross-over or parallel), (2) administered vitamin D as an intervention, and (3) conducted on adults with SCI (aged \geq 18 years). Studies were excluded if they had at least one of the following characteristics: (1) used non-nutritional supplements, (2) reported duplicate data, and (3) reviews, letters, editorial articles, study protocol or case reports.

Data extraction: From the eligible studies, the following information was extracted from articles

and recorded: publication information (first author's last name, publication date, and study location), participants' characteristics (total sample size, target population, mean age, and mean duration post-injury), details of study design, study duration, dose and type of interventions in intervention and placebo groups, outcome measures, and significant findings.

Quality assessment: Reviewers (Ghavami A and Mohammadi H) independently evaluated the quality of the relevant studies using the Academy of Nutrition and Dietetics Quality Criteria Checklist (QCC) for Primary Research (Academy of Nutrition and Dietetics, 2016), which includes ten validity questions as follows: research question, sample selection/bias, control and confounders, intervention assignment and outcome measures reliability, statistical relevance, and analyses. Eligible studies were rated positive if the validity questions and at least one additional question were answered as "YES", negative if 6 questions or more were answered as "No", or neutral if answers to validity questions were not clearly described.

Results

Search results and study selection: Initially, 1594 articles were identified, after removing duplicates, 1150 articles remained. After screening of the titles and abstracts, 50 articles remained. Then, based on the full-text review, 42 papers were excluded for the following reasons: non-interventional studies (*n*=39), conference paper (n=1), and duplicate publication (n=2). Finally, 8 articles with nine arms were included in this systematic review (Aminmansour *et al.*, 2016b, Amorim *et al.*, 2018b, Bauman *et al.*, 2011a, Bauman *et al.*, 2005b, Bauman *et al.*, 2018b, Pritchett *et al.*, 2019b). The study selection process is presented in **Figure 1**.

Characteristics of included studies: The main characteristics of the eligible studies are summarized in **Table 1**. The included studies were published between 2005 and 2018. The design of three studies was a randomized controlled trial (Aminmansour *et al.*, 2016b, Amorim *et al.*,

2018b, Bauman *et al.*, 2005d), four studies reported pre/post measurement and did not have any data about control group (Bauman *et al.*, 2011a, Bauman *et al.*, 2005b, Mailhot *et al.*, 2018b, Pritchett *et al.*, 2019b), and one study had a double-blinded non-randomized design (Flueck *et al.*, 2016b). These studies were conducted in the USA (n=4) (Bauman *et al.*, 2011a, Bauman *et al.*, 2005b, Bauman *et al.*, 2005d, Pritchett *et al.*, 2019b), Iran (n=1) (Aminmansour *et al.*, 2016b), Switzerland (n=1) (Flueck *et al.*, 2016b), Portugal (n=1) (Amorim *et al.*, 2018b), and Canada (n=1) (Mailhot *et al.*, 2018b). Also, the time of intervention ranged between 5 weeks to 24 months.

Risk of bias and quality of included studies: Three randomized controlled trials (Aminmansour et al., 2016b, Amorim et al., 2018b, Bauman et al., 2005d) showed a low risk of bias with a positive score, while the other studies were rated as either neutral (n= 4) (Bauman et al., 2011a, Bauman et al., 2005b, Mailhot et al., 2018b, Pritchett et al., 2019b) or negative (n=1) (Flueck et al., 2016b) (Table 2). A non-randomized controlled study, pre-post design, lack of power calculation and adjustment factors, incomplete outcome data, and selection bias were the primary reasons for low quality and high risk of bias.

Main results: Eight articles with 9 arms investigated the effects vitamin supplementation in SCI patients with various outcome measures. Bauman et al. conducted a drug-intervention study in seven vitamin D deficient patients with chronic SCI paraplegia, and three had tetraplegia). For 3 months, daily administration of 2000 IU vitamin D3 (cholecalciferol) and 1.3 g calcium carbonate was provided. After supplementation with 25hydroxyvitamin D (25(OH) D3), there was a significant increase in the serum compared to the baseline. After this period, the intact parathyroid and hormone (PTH) N-telopeptide significantly decreased; however, serum and urinary calcium remained within the normal ranges (Bauman et al., 2011a).

Bauman et al. conducted another study

investigating the effects of vitamin D supplementation in patients with SCI. In phase 1, ten participants with chronic SCI and vitamin D deficient received 50µg of hydroxyvitamin D3 twice a week and 1.5 g/d elemental calcium for 14 days. In the second phase, 40 participants with chronic SCI were administrated with 20µg of 25(OH)D, for 12 months without considering the vitamin D status. After 14 days, in phase 1, there was a significant increase in vitamin D levels $(8.7\pm2.1 \text{ vs } 14.7\pm3.6 \text{ mg/dl}, P<0.005)$ and PTH levels (35±26 vs 17±12 pg/ml, P<0.01). Although serum calcium levels were not significantly different, there was a change in the urinary calcium $(103\pm81 \text{ vs } 184\pm145 \text{ mg/dl}, P=0.01)$. In phase 2, after 12 months of vitamin D administration, the number of patients with absolute and relatively vitamin D deficiency decreased from 33 and 6 patients to 23 and 9 patients, respectively. Also, an increase in the 25(OH)D and a significant drop in PTH levels were observed. Although 25(OH)D levels increased in both studies, the results from these two different phases showed that a higher dose of 25(OH)D and/or administration for a longer period of time is needed (Bauman et al., 2005b).

Another randomized, double-blind controlled trial on 40 patients with SCI from Bauman et al., investigated the effects of daily intake of vitamin D analog (4µg) (1-alpha-hydroxyvitamin D2) on the bone mineral density of leg. After 24 months of the analog administration, the leg's bone mineral density significantly increased in the treatment group, and the urinary NTx, a marker of bone resorption, reduced during the analog treatment (Bauman et al., 2005d). Flueck et al. based on the idea that vitamin D seems to have a direct impact on the neuromuscular function by docking on vitamin D receptors in the muscle tissue, tested the effectiveness of daily intake of 6000 IU/day vitamin D over a 12-weeks period on 25 (OH) D status and performance in 22 indoor wheelchairs athletes. All subjects had baseline vitamin D level below 75 nmol/l and reached optimal levels after 12 weeks. Although calcium concentration did not significantly change during the intervention, no differences in peak power, fatigue index, maximal heart rate and maximal lactate concentrations were found in three measurements of the study intervention. However, isokinetic strength significantly increased in the no-dominant arm after 12 weeks (Flueck *et al.*, 2016b).

Amorim et al. conducted a trial to determine whether creatine or vitamin D supplementation can improve muscle strength in individuals with SCI who undergo resistance training. The participants were randomly divided into three groups including (1) 3g/day creatine, (2) 25000 IU vitamin D every two weeks, and (3) placebo. The levels of 25(OH)D3 increased in the vitamin D group. Also, corrected arm muscle area, seated medicine ball throw, handgrip strength, and 1-RM chest press improved in the vitamin D group. However, there were no changes in the muscle strength indicators between the vitamin D and placebo groups (Amorim et al., 2018b). Pritchett et al. conducted a pre-post study on 34 elite athletes with SCI. Participants were assigned to vitamin D3 supplementation protocol based on their initial 25(OH)D concentrations. The participants who were deficient in 25(OH)D (<50nmol/l) received 50,000IU/week for 8 weeks. Also, the participants with insufficient 25(OH)D status (50-75nmol/l) were administrated with 35,000 IU/week for 4 weeks, and both of these groups received a maintenance dose of 15,000 IU/week. On the other hand, the participants who had a sufficient status (>75nmol/l) received just the maintenance dose of 15,000 IU/week. After 12-16 weeks of 25(OH)D supplementation, the concentration increased $(66.3\pm24.3 \text{nmol/l}; 111.3\pm30.8 \text{nmol/l}; P < 0.001).$ Twenty-six percent of athletes had sufficient 25(OH)D concentrations before supplementation, whereas this number increased to 91% after the supplementation. The handgrip strength significantly increased by 62% percent participants after the treatment, but no change was observed regarding 20-meter wheelchair sprint performance (Pritchett et al., 2019b).

Mailhot *et al.* assessed the effectiveness and safety of two vitamin D_3 repletion protocols in adults with recent SCI (Mailhot *et al.*, 2018b).

Nine participants with serum $25\text{OHD} \leq 30\text{nmol/l}$ were assigned to the higher dose group and given 10,000 IU/week plus 1000 IU/day of vitamin D_3 for 36.8 ± 11.9 days. Fourteen participants with serum 25(OH)D > 30 nmol/l were assigned to the lower dose group and received 1000 IU/day vitamin D_3 for 38.2 ± 11.6 days. Although both protocols significantly improved the serum 25(OH)D levels, the effect on the higher dose protocol (12.56 ng/ml, 95% CI: 6.68, 18.4) was greater than the lower dose protocol (4.68 ng/ml, 95% CI: 0.88, 8.48). However, only 3 out of 23 achieved vitamin D

sufficiency (25(OH)D>30 ng/ml). In another study, Aminmansour et al. evaluated the effects of progesterone and vitamin D on the functional outcome of patients with acute traumatic SCI (Aminmansour et al., 2016b). The participants allocated were randomly to receive intramuscular injection of 0.5mg/kg progesterone twice daily and 5µg/kg oral vitamin D twice daily for 5 days or placebo. Compared to the placebo group, those who received progesterone and vitamin D had significantly higher motor scores in left and right upper extremities, assessed according to the American Spinal Injury Association score.

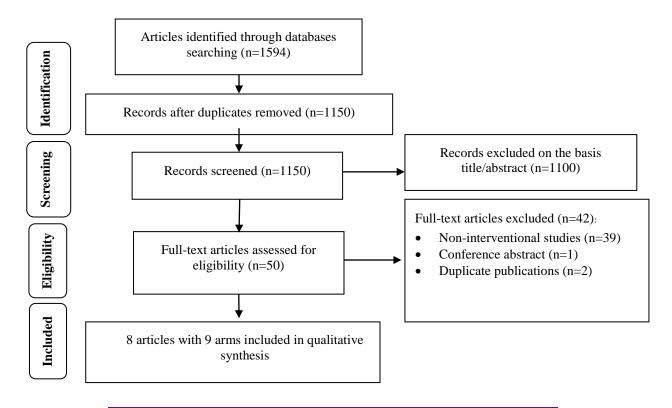


Figure 1. Literature search and review flow chart for selecting studies

Table 1. Characteristics of included trials.

First author (country, year)	Study design/ Follow-up/ Participants characteristics	Intervention/ Control	Outcome measures and findings		
Bauman (USA,2005)-a	Pre-post/12 months/ 40 subjects with SCI (17 had paraplegia and 23 had tetraplegia), mean age was 43±13 years, the mean duration of injury was 12±10 years	400 IU (10 $\mu g)$ vitamin D3 and a multivitamin with 400 IU (10 micrograms) vitamin D3 daily, for a total of 800 IU vitamin D3 (20 $\mu g)$ for 12 months	9 subjects had an absolute and 23 had a relative vitamin D deficiency, compared with 33 and 6 subjects, respectively, at baseline. By 12 months, the 25(OH)D level increased (10.7 ± 7.1 to 22.5 ± 7.5 ng/ml; P <0.0001) and the serum PTH level decreased (37 ± 16 vs 25 ± 11 pg/ml; P <0.0001		
Bauman (USA,2005)	RCT, double-blind/ 24 months/ 40 subjects with chronic complete motor SCI, 17 with tetraplegia and 23 with paraplegia, 39 male and 1 female, mean age 43±13 years, the mean duration of injury was 12±10 years	Either 1α -D2 (4 $\mu g/day$, n=19) or a placebo (n=21) was administered daily for 24 months. Both groups received calcium (1.3 g/d) and vitamin D (800 IU/d; 20 $\mu g/d$) supplementation.	BMD in the leg and percent change from baseline significantly increased at 6 (percent change only), 12, 18, and 24 months in the treatment group, but not in the placebo group. Urinary NTx, a marker of bone resorption significantly reduced during treatment with 1-alpha D2, but markers of bone formation did not change.		
Bauman (USA, 2011)	Pre-post/3 months/ Seven subjects with SCI (6 men, one women), mean age was 35±7 years, four subjects with paraplegia and three with tetraplegia, mean duration of injury was 15±7 years.	Oral vitamin D3 (2000 IU daily) and elemental calcium (1.3 g daily) were prescribed for 90 days	Serum 25(OH)D levels were greater at months 1 and 3 than at baseline. Serum iPTH levels were significantly decreased at month 1 and month 3. Serum NTx levels were significantly lower at month 3 than at baseline. Serum and urinary calcium levels remained within the normal range.		

Table 1. Characteristics of included trials.

First author (country, year)	Study design/ Follow-up/	Intervention/ Control	Outcome measures and findings		
First author (country	Participants characteristics	-			
Aminmansour (Iran, 2016	RCT/6 months/64 adult patients with acute traumatic SCI admitted within 8 hours of injury, age range 18-65 years	intramuscular injection of 0.5 mg/kg progesterone twice daily and $5\mu g/kg$ oral vitamin D3 twice daily for 5 days or placebo.	The motor powers and sensory function increased significantly after 6 months in both study groups. Those who received progesterone and vitamin D had significantly higher motor powers and sensory function after 6 months. Those who received the therapy within 4 hours of injury, had significantly higher motor powers and sensory function 6 months after treatment in progesterone and vitamin D group. Therapy lag was negatively associated with 6-month motor powers and sensory function in progesterone and vitamin D group.		
Flueck (Switzerland,2016	double-blind, non-randomized intervention study/12 weeks/ 20 male elite wheelchair athletes, age 21-65 years	Subjects were supplemented with 6000 IU of vitamin D daily over 12 weeks.	Vitamin D status, as well as a Wingate test and an isokinetic dynamometer test, were performed at baseline and after six and 12 weeks. All athletes increased vitamin D status significantly over 12 weeks and reached an optimal level. Wingate performance was not significantly increased. Isokinetic dynamometer strength was significantly increased but only in the non-dominant arm in isometric and concentric elbow flexion. No significant differences in peak power were found during the intervention study. No significant differences were found in fatigue index, maximal heart rate and maximal lactate concentration.		

Table 1. Characteristics of included trials.

First author (country, year)	Study design/ Follow-up/ Participants characteristics	Intervention/ Control	Outcome measures and findings		
Amorim, (Portugal, 2017)	RCT, double-blind/ 8 weeks/ Fourteen SCI subjects, thirteen males and one female, mean age 47 ± 10.6 years, duration post injury (3-122 months)	Subjects were randomized to three groups while participating in a progressive resistance training. Group1 (n=5): 3 g of dextrose daily (placebo powder) with 250 mL of water after lunch and one vitamin D ampoule (25 000 IU) every two weeks. Group2 (n=5): 3 g of creatine monohydrate powder daily with 250 mL of water after lunch and 5mg of vitamin E (placebo ampoule) every two weeks. Group3 (n=4): 3 g of dextrose daily (placebo powder) with 250 mL of water after lunch and 5 mg of vitamin E (placebo ampoule) every two weeks.	Mean values of 25(OH)D improved significantly in the vitamin D group and compared to control group. In the vitamin D group, improvements were also observed in which concerns the corrected arm muscle area, seated medicine ball throw, Handgrip strength and 1-RM Chest press.		
Pritchett (USA, 2018)	Pre-post/ 12-16 weeks/ 34 adults with SCI (30 males, and 5 females; age: 33 + 15 years, 4 Asian, 1 African American, and 30 Caucasian)	Participants were assigned a sliding scale vitamin D3 supplementation protocol (from winter to spring) based on initial 25(OH)D concentrations. Participants with deficient 25(OH)D (<50 nmol/l) status received 50,000 IU/wk for 8 wks, and participants with insufficient status (50-75 nmol/l) received 35,000 IU/wk for 4 wks, after which both received a maintenance dose of 15,000 IU/wk. Participants with sufficient status (>75nmol/l) received the maintenance dose of 15,000 IU/wk.	25(OH)D concentrations and performance measures (handgrip strength, and 20M wheelchair sprint) were assessed pre and post supplementation (winter and spring). 25(OH)D concentrations increased significantly after supplementation (<i>P</i> <0.001; 66.3 + 24.3 nmol/l; 111.3 + 30.8 nmol/l) for winter and spring, respectively. 26% of athletes had sufficient 25(OH)D concentrations before supplementation, and 91% had sufficient concentrations post supplementation. 62% of participants improved handgrip strength post supplementation with no change in 20-meter wheelchair sprint performance time.		
Mailhot (Canada, 2018)	Two arm pre-post/ 5-6 weeks/ Thirty adults with recent SCI complete or incomplete sensorimotor impairments,	Participants with serum $25(OH)D \le 30$ nmol/l were given $10,000$ IU of weekly and 1000 IU of daily vitamin D3+ 500 mg calcium for 36.8 ± 11.9 days (higher dose: HD). Subjects with serum $25(OH)D > 30$ nmol/l received 1000 IU of daily vitamin D3+ 500 mg calcium for 38.2 ± 11.6 days (lower dose: LD).	25(OH)D with a greater increase in the HD vs. LD regimen		

RCT: Randomized controlled trial; SCI: Spinal cord injury; iPTH: Intact parathyroid hormone; NTx: N-telopeptide; BMD: bone mineral density.

Table 2. Quality assessment of included studies ^a

Validity questions	Bauman (USA,2005)	Bauman (USA, 2011)	Aminmansour (Iran, 2016)	Flueck (Switzerland, 2016)	Amorim, (Portugal, 2017)	Pritchett (USA, 2018)	Mailhot (Canada, 2018)
1. Was the research question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the selection of study subjects/patients free from bias?	No	No	Yes	No	Yes	No	No
3. Were study groups comparable?	No	No	Yes	No	Yes	No	No
4. Was method of handling withdrawals described?	No	No	Yes	No	No	No	No
5. Was blinding used to prevent introduction of bias?	No	No	Yes	No	Yes	No	No
6. Were intervention/exposure factor or procedure and any comparison(s) described in detail?	Yes	No	Yes	Yes	Yes	Yes	Yes
7. Were outcomes clearly defined and the measurements valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes	Yes	Yes	No	Yes	Yes	Yes
9. Were conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	Yes	No	Yes	Yes	Yes
10. Is bias due to study funding or sponsorship unlikely?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall rating	Neutral	Neutral	Positive	Negative	Positive	Neutral	Neutral

Discussion

Several studies have acknowledged that vitamin D deficiency has been a burden on most patients with chronic and acute SCI (Javidan et al., 2014, Oleson et al., 2010a). There have been a few studies investigating the effects of the administration of various doses of vitamin D in patients with SCI. The majority of the clinical trials included in the present systematic review have spotted the need to improve the serum vitamin D concentrations in patients with SCI (Bauman et al., 2011b, Bauman et al., 2005a, Bauman et al., 2005c, Flueck et al., 2016c, Mailhot et al., 2018a, Pritchett et al., 2019a).

Other biochemical marks have been reported, such as reduced concentration of the PTH and high level of serum calcium in patients with SCI (Oleson et al., 2010a). Some studies have suggested that the PTH levels reduce linearly during the administration of vitamin D at any basal serum 25(OH)D concentration (Gallagher et al., 2012, Kroll et al., 2015). The study results show that the serum NTx, a useful marker in evaluating the long-term BMD changes (Hong et al., 2020), decrease following any supplementation. In contrast with the present study, a study by Smith et al. did not reveal any effect of the vitamin D supplementation with daily doses ranging 400-4800 IU on the serum NTx in elderly women (Smith et al., 2018).

A common outcome in patients with SCI was bone fractures (Grassner et al., 2018). Active patients have a higher intake of vitamin D and calcium than inactive ones. Therefore, increasing attention to the BMD and its indirect biomarkers could prevent the patients from falling and fractures (Flueck et al., 2016a). Thus, the most crucial nutritional therapy in preventing fractures in SCI patients is to maintain normal levels of 25(OH)D (Farkas et al., 2019). Having this in mind, Pritchett et al. discovered that a 15,000 IU/week supplementation of vitamin D could maintain its levels in patients with SCI (Pritchett et al., 2019b). However, in the general population, current literature suggests different long-term oral maintenance doses of vitamin D (50,000 IU/month or 2,000 IU/day) (Hassan et al., 2018).

It has been presented that hypercalciuria, deriving from the vitamin D administration, could increase the risk of kidney stone in patients with SCI (Oleson *et al.*, 2010a). For this reason, a high dose of vitamin D supplementation should be avoided (Malihi *et al.*, 2016). Thus, proper monitoring of the baseline serum vitamin D levels before to administration of vitamin D supplementation in patients with SCI is vital.

This systematic review presented that vitamin D supplementation may have a beneficial impact on the isokinetic, muscle strength, and hand grip strength in patients with SCI (Amorim et al., 2018a, Pritchett et al., 2019a). However, in these studies, no significant difference was observed in peak power, fatigue index, maximal heart rate, and maximal lactate concentrations after vitamin D (Flueck al., supplementation Interestingly, low strength is a physical index exam for weak mobility and one of the most important clinical signs of low muscle mass (Latham et al., 2003). For high muscle strength and health, some dietary factors can contribute. The most important one is vitamin D, which has received attention in the present decade due to its positive effects on all aspects of health (Muir and Montero-Odasso, 2011).

In plenty of animal and human studies, the vitamin D receptor (VDR) has been identified, as located in human skeletal muscle, and substantially affects muscle metabolism (Bischoff- Ferrari et al., 2004). Possible mechanisms involved include both genomic and non-genomic models (Christakos et al., 2013). In the genomic model, vitamin D by nuclear VDR-mediated gene results in growth, proliferation, and differentiation of the muscle fibers (Pfeifer et al., 2002, Sanders et al., 2014). In the non-classical pathway (nonegenomic), vitamin D may be affected by calcium homeostasis and the growth-related transduction pathway (Dirks-Naylor and Lennon-Edwards, 2011). These mechanisms have been demonstrated in experimental studies, but in humans, findings are still unknown due to controversy in clinical trials (Kim et al., 2019). In

line with the present study findings, a systematic review and meta-analysis reported that supplemental vitamin D has beneficial effects on muscle strength and balance (Muir and Montero-Odasso, 2011). On the other hand, another systematic review reported no improvement in muscle strength after vitamin D administration (Latham *et al.*, 2003).

Although according to the existing evidence, the majority of studies in other populations are in line with the present study (Hanley et al., 2010, Montero-Odasso and Duque, 2005), some studies failed to demonstrate this effect (Sanders et al., 2010). It is important to note that an administration of a single oral bolus of 300,000 IU of vitamin D is an affirmative therapy protocol to fight its deficiency; levels are reconsidered to be safe (Rossini et al., 2012). Some studies have revealed that higher dose, e.g. more than 500,000 IU, can cause some side effects such as a greater risk of falls and fractures (Sanders et al., 2010). Aminmansour et al. reported a beneficial effect on motor powers and sensory function in patients with SCI after vitamin D administration (Aminmansour et al., 2016a).

There is considerable controversy on the association between vitamin D concentration and motor and sensory performance. The majority of the studies on this topic have focused on the physical functions and muscle strength in the general population, especially the elderly, which is consistent with the current study (Dhanwal et al., 2013, Lee et al., 2013, Von Hurst et al., 2013), while others failed (Ceglia et al., 2011). Interestingly, several prospective studies have demonstrated controversial findings related to vitamin D's baseline level and mobility, physical, and sensorial function (Dam et al., 2009, Faulkner et al., 2006, Houston et al., 2011, Wicherts et al., 2007). The co-existence of vitamin D deficiency and limitation in the motor and sensory capability in patients with SCI could represent a synergist effect on the physical functions. Patients with SCI have lower outdoor activity and sunlight exposure because of mobility disorders, which can induce adverse effects on skeletal muscle health and serum level of vitamin D (Ceglia, 2008). Furthermore, in addition to the SCI effect on the strength and mass muscle, the mobility and power motor are involved (Hicks *et al.*, 2011). The main finding of the quantitative meta-analysis in an older adults showed no improvement in muscle strength after supplement therapy with vitamin D; however, there was a slight and significant improvement in mobility (Rosendahl- Riise *et al.*, 2017).

Vitamin D supplementation has improved physical function and mobility significantly in different populations, which is in line with the preen study (Bischoff-Ferrari et al., 2009, Bischoff-Ferrari et al., 2004, Boonen et al., 2006, Ceglia et al., 2013, Pfeifer et al., 2009, Songpatanasilp et al., 2011). However, some studies have not shown any association between vitamin D deficiency and mobility (Brunner et al., 2008, Lips et al., 2010, Wood et al., 2014). Therefore, the administration of vitamin D supplements should be aimed at maintaining muscle, motor and sensory strength. inconsistency in results may be related to differences in studies design, type, and duration of the intervention, different methods of outcomes and different commercial kits for serum vitamin D assessment. All these factors may affect the findings and play a substantial role as a heterogeneity factor.

The present systematic review has several limitations. The included studies in the present review have a high level of heterogeneity, including variations in vitamin D dosage, setting, outcome measures and intervention duration. Also, most of the included records were uncontrolled studies with negative or neutral quality. Although most of the studies were conducted on SCI patients, some studies were performed on elite athletes with SCI. Therefore, diverse muscle build could affect any nutrition intervention in SCI patients. Besides, different outcome measures in included the studies make the results incomparable.

The present systematic review suggests that vitamin D supplements for SCI patients and SCI

athletes could have beneficial effects on vitamin D concentrations and some physical performance indices. However, we are still far from applying definitive practice recommendations in patients and athletes with SCI due to the high variability and lack of sufficient well-planned, high-quality trials.

Conclusion

This review suggests that vitamin D concentrations could improve vitamin D levels, bone health, and physical performance indices in SCI patients. Based on current evidence, it seems that 15,000 IU/week of vitamin D supplementation could maintain vitamin D levels in SCI patients. These findings should be interpreted with caution due to the high heterogeneity and low-quality evidence of the included studies. recommended that future research focusing on the evaluation of the efficacy of vitamin supplementation in such populations should have sufficient power and robust design to give definitive conclusions. Thus, further well-planned randomized controlled trials examining the effects of different vitamin D supplementation strategies in this population are necessary to reach practice recommendations.

Authors' Contributions

Mohammadi H, Parastouei K, Rostami H, Lazaridi AV and Miraghajani M designed, screened, and selected the studies; Rafiee M designed the figures. Ghavami G analyzed data. All the authors drafted, modified, and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflicts of interest.

References

- Academy of Nutrition and Dietetics 2016. Evidence Analysis Manual: Steps in the Academy Evidence Analysis Process.
- **Aminmansour B, et al.** 2016b. Effects of progesterone and vitamin D on outcome of

- patients with acute traumatic spinal cord injury; a randomized, double-blind, placebo controlled study. *Journal of spinal cord medicine*. **39** (3): 272-280.
- **Amorim S, et al.** 2018b. Creatine or vitamin D supplementation in individuals with a spinal cord injury undergoing resistance training: A double-blinded, randomized pilot trial. *Journal of spinal cord medicine.* **41 (4)**: 471-478.
- Bauman WA, Emmons RR, Cirnigliaro CM, Kirshblum SC & Spungen AM 2011a. An effective oral vitamin D replacement therapy in persons with spinal cord injury. *Journal of spinal cord medicine*. **34** (**5**): 455-460.
- Bauman WA, Emmons RR, Cirnigliaro CM, Kirshblum SC & Spungen AM 2011b. An effective oral vitamin D replacement therapy in persons with spinal cord injury. *The Journal of Spinal Cord Medicine*. **34** (5): 455-460.
- Bauman WA, Morrison NG & Spungen AM 2005b. Vitamin D replacement therapy in persons with spinal cord injury. *Journal of spinal cord medicine*. **28** (3): 203-207.
- **Bauman WA, Spungen AM, Morrison N, Zhang R-L & Schwartz E** 2005c. Effect of a vitamin D analog on leg bone mineral density in patients with chronic spinal cord injury. *Journal of rehabilitation research & development.* **42** (5).
- **Bauman WA, Spungen AM, Morrison N, Zhang RL & Schwartz E** 2005d. Effect of a vitamin D analog on leg bone mineral density in patients with chronic spinal cord injury. *Journal of rehabilitation research and development.* **42** (5): 625-633.
- **Bischoff-Ferrari HA, et al.** 2009. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *British medical journal.* **339**: b3692.
- **Bischoff-Ferrari HA, et al.** 2004. Effect of vitamin D on falls: a meta-analysis. *Journal of the American medical association.* **291** (16): 1999-2006.
- **Bischoff- Ferrari H, et al.** 2004. Vitamin D receptor expression in human muscle tissue decreases with age. *Journal of bone and mineral research.* **19 (2)**: 265-269.

- **Boonen S, et al.** 2006. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcified tissue international.* **78** (5): 257-270.
- **Brunner RL, et al.** 2008. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. *Journal of the American dietetic association*. **108** (9): 1472-1479.
- Ceglia L 2008. Vitamin D and skeletal muscle tissue and function. *Molecular aspects of medicine*. **29** (6): 407-414.
- Ceglia L, Chiu GR, Harris SS & Araujo AB 2011. Serum 25- hydroxyvitamin D concentration and physical function in adult men. *Clinical endocrinology.* **74** (3): 370-376.
- Ceglia L, et al. 2013. A randomized study on the effect of vitamin D3 supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *Journal of clinical endocrinology & metabolism.* 98 (12): E1927-E1935.
- Christakos S, et al. 2013. Vitamin D: beyond bone. Annals of the New York academy of sciences. 1287 (1): 45.
- **Dam T-T, von Mühlen D & Barrett-Connor EL** 2009. Sex-specific association of serum vitamin D levels with physical function in older adults. *Osteoporosis international.* **20** (5): 751-760.
- Dhanwal DK, Dharmshaktu P, Gautam V, Gupta N & Saxena A 2013. Hand grip strength and its correlation with vitamin D in Indian patients with hip fracture. *Archives of osteoporosis*. 8 (1-2): 158.
- **Dionyssiotis Y** 2012. Malnutrition in spinal cord injury: more than nutritional deficiency. *Journal of clinical medicine research.* **4 (4)**: 227.
- Dirks-Naylor AJ & Lennon-Edwards S 2011.

 The effects of vitamin D on skeletal muscle function and cellular signaling. *Journal of steroid biochemistry and molecular biology.* 125 (3-5): 159-168.
- Farkas GJ, Pitot MA, Berg AS & Gater DR 2019. Nutritional status in chronic spinal cord injury: a systematic review and meta-analysis. *Spinal cord.* **57** (1): 3-17.

- Faulkner K, et al. 2006. Higher 1, 25-dihydroxyvitamin D 3 concentrations associated with lower fall rates in older community-dwelling women. *Osteoporosis international*. 17 (9): 1318-1328.
- **Flueck J & Perret C** 2017. Vitamin D deficiency in individuals with a spinal cord injury: a literature review. *Spinal Cord.* **55** (**5**): 428-434.
- Flueck JL, Hartmann K, Strupler M & Perret C 2016a. Vitamin D deficiency in Swiss elite wheelchair athletes. *Spinal cord.* **54** (11): 991-995.
- Flueck JL, Schlaepfer M & Perret C 2016b. Effect of 12-Week Vitamin D Supplementation on 25 OH D Status and Performance in Athletes with a Spinal Cord Injury. *Nutrients.* 8 (10).
- Flueck JL, Schlaepfer MW & Perret C 2016c. Effect of 12-week vitamin D supplementation on 25 [OH] D status and performance in athletes with a spinal cord injury. *Nutrients*. **8 (10)**: 586.
- Gallagher JC, Sai A, Templin T & Smith L 2012. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. *Annals of internal medicine*. **156** (6): 425-437.
- **Gordon PL, Sakkas GK, Doyle JW, Shubert T** & **Johansen KL** 2007. Relationship between vitamin D and muscle size and strength in patients on hemodialysis. *Journal of renal nutrition.* **17 (6)**: 397-407.
- Grassner L, Klein B, Maier D, Bühren V & Vogel M 2018. Lower extremity fractures in patients with spinal cord injury characteristics, outcome and risk factors for non-unions. *The Journal of Spinal Cord Medicine*. **41** (**6**): 676-683.
- **Groah SL, et al.** 2009. Nutrient intake and body habitus after spinal cord injury: an analysis by sex and level of injury. *The journal of spinal cord medicine.* **32** (1): 25-33.
- **Hanley DA, et al.** 2010. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *Cmaj.* **182** (12): E610-E618.
- Hassan AB, Hozayen RF, Alotaibi RA & Tayem YI 2018. Therapeutic and maintenance regimens

- of vitamin D3 supplementation in healthy adults: A systematic review. *Cellular and molecular biology (Noisy-le-Grand, France).* **64 (14)**: 8-14.
- **Hicks A, et al.** 2011. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. *Spinal cord.* **49 (11)**: 1103-1127.
- Hong L, et al. 2020. Correlation between Bone Turnover Markers and Bone Mineral Density in Patients Undergoing Long-Term Anti-Osteoporosis Treatment: A Systematic Review and Meta-Analysis. *Applied Sciences*. 10 (3): 832.
- Houston DK, et al. 2011. Serum 25-hydroxyvitamin D and physical function in older adults: the Cardiovascular Health Study All Stars. *Journal of the American Geriatrics Society.* **59** (10): 1793-1801.
- Javidan AN, et al. 2014. Calcium and vitamin D plasma concentration and nutritional intake status in patients with chronic spinal cord injury: A referral center report. *Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences.* 19 (9): 881.
- Kim B-J, Kwak MK, Lee SH & Koh J-M 2019. Lack of association between vitamin d and hand grip strength in asians: A nationwide population-based study. *Calcified tissue international.* **104** (2): 152-159.
- **Kroll MH, et al.** 2015. Temporal relationship between vitamin D status and parathyroid hormone in the United States. *PloS one.* **10** (3): e0118108.
- **Lamarche J & Mailhot G** 2016. Vitamin D and spinal cord injury: should we care? *Spinal cord.* **54 (12)**: 1060-1075.
- Latham NK, Anderson CS & Reid IR 2003. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. *Journal of the American geriatrics society.* **51** (9): 1219-1226.
- **Lee HJ, et al.** 2013. Evaluation of vitamin D level and grip strength recovery in women with a distal radius fracture. *Journal of hand surgery*. **38** (3): 519-525.

- **Lips P, et al.** 2010. Once-weekly dose of 8400 IU vitamin D3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. *American journal of clinical nutrition.* **91 (4)**: 985-991.
- Mailhot G, Lamarche J & Gagnon DH 2018a. Effectiveness of two vitamin D 3 repletion protocols on the vitamin D status of adults with a recent spinal cord injury undergoing inpatient rehabilitation: a prospective case series. *Spinal cord series and cases.* 4 (1): 1-8.
- Mailhot G, Lamarche J & Gagnon DH 2018b. Effectiveness of two vitamin D(3) repletion protocols on the vitamin D status of adults with a recent spinal cord injury undergoing inpatient rehabilitation: a prospective case series. *Spinal cord series and cases.* 4: 96.
- Malihi Z, Wu Z, Stewart AW, Lawes CM & Scragg R 2016. Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: a systematic review and meta-analysis. *American journal of clinical nutrition.* **104** (4): 1039-1051.
- Montero-Odasso M & Duque G 2005. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. *Molecular aspects of medicine*. **26** (3): 203-219.
- Muir SW & Montero- Odasso M 2011. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta- analysis. *Journal of the American geriatrics society.* **59** (12): 2291-2300.
- Nasri H 2017. The adverse effects of vitamin D deficiency on health. *Journal of renal endocrinology*. **3** (1): e03-e03.
- **Nasri H, et al.** 2014. Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. *Journal of renal injury prevention.* **3 (1)**: 31.
- Navarrete-Opazo A, Cuitiño P & Salas I 2017. Effectiveness of dietary supplements in spinal cord injury subjects. *Disability and health journal.* **10** (2): 183-197.
- Oleson CV, Patel PH & Wuermser L-A 2010a. Influence of season, ethnicity, and chronicity on

- vitamin D deficiency in traumatic spinal cord injury. *journal of spinal cord medicine*. **33** (3): 202-213.
- Oleson CV, Patel PH & Wuermser LA 2010b. Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury. *Journal of spinal cord medicine*. **33** (3): 202-213.
- Pfeifer M, Begerow B & Minne H 2002. Vitamin D and muscle function. *Osteoporosis international.* **13 (3)**: 187-194.
- **Pfeifer M, et al.** 2009. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis international.* **20** (2): 315-322.
- Pritchett K, Pritchett RC, Stark L, Broad E & LaCroix M 2019a. Effect of vitamin D supplementation on 25 (OH) D status in elite athletes with spinal cord injury. International journal of sport nutrition and exercise metabolism. 29 (1): 18-23.
- Pritchett K, Pritchett RC, Stark L, Broad E & LaCroix M 2019b. Effect of Vitamin D supplementation on 25(OH)D Status in elite athletes with spinal cord injury. *International journal of sport nutrition and exercise metabolism.* 29 (1): 18-23.
- Rosendahl- Riise H, Spielau U, Ranhoff AH, Gudbrandsen OA & Dierkes J 2017. Vitamin D supplementation and its influence on muscle strength and mobility in community- dwelling older persons: a systematic review and meta-analysis. *Journal of human nutrition and dietetics.* 30 (1): 3-15.
- **Rossini M, et al.** 2012. Short-term effects on bone turnover markers of a single high dose of oral vitamin D3. *Journal of clinical endocrinology & metabolism.* **97 (4)**: E622-E626.
- Sanders KM, Scott D & Ebeling PR 2014. Vitamin D deficiency and its role in muscle-bone interactions in the elderly. *Current osteoporosis reports.* **12** (1): 74-81.

- Sanders KM, et al. 2010. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *Journal of the American medical association*. **303** (18): 1815-1822.
- **Singh A, Tetreault L, Kalsi-Ryan S, Nouri A & Fehlings MG** 2014. Global prevalence and incidence of traumatic spinal cord injury. *Clinical epidemiology*. **6**: 309-331.
- Smith LM, Gallagher J, Kaufmann M & Jones G 2018. Effect of increasing doses of vitamin D on bone mineral density and serum N- terminal telopeptide in elderly women: a randomized controlled trial. *Journal of internal medicine*. **284** (6): 685-693.
- Songpatanasilp T, Chailurkit L-o, Nichachotsalid A & Chantarasorn M 2011. Combination of alfacalcidol with calcium can improve quadriceps muscle strength in elderly ambulatory Thai women who have hypovitaminosis D: a randomized controlled trial. Journal of the medical Association of thailand. 92 (9): 30.
- Von Hurst P, Conlon C & Foskett A 2013. Vitamin D status predicts hand-grip strength in young adult women living in Auckland, New Zealand. *Journal of steroid biochemistry and molecular biology.* **136**: 330-332.
- Wicherts IS, et al. 2007. Vitamin D status predicts physical performance and its decline in older persons. *Journal of clinical endocrinology & metabolism.* **92** (6): 2058-2065.
- Wong S, et al. 2011. The prevalence of malnutrition in spinal cord injuries patients: a UK multicentre study. *British journal of nutrition*. **108** (5): 918-923.
- **Wood A, et al.** 2014. A parallel group double-blind RCT of vitamin D 3 assessing physical function: is the biochemical response to treatment affected by overweight and obesity? *Osteoporosis international.* **25 (1)**: 305-315.