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

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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

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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, 2012). Additional factors including diarrhea, eating disorders, prolonged colon transition time, early satiety, dysgeusia, depression, 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 cardio-metabolic 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).

It seems that adequate 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 D 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 for 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 were 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 met 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 ≥ 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

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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.*, 2005d, Flueck *et al.*, 2016b, Mailhot *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 of vitamin D 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 (had 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 25-hydroxyvitamin D (25(OH) D3), there was a significant increase in the serum compared to the baseline. After this period, the intact parathyroid hormone (PTH) and N-telopeptide (NTx) significantly decreased; however, serum and urinary calcium remained within the normal ranges (Bauman *et al.*, 2011a).

Bauman *et al.* conducted another study

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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±2.1 vs 14.7±3.6 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±81 vs 184±145 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±24.3nmol/l; 111.3±30.8 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 of 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).

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Nine participants with serum 25OHD ≤ 30nmol/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 were randomly allocated to receive an 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.

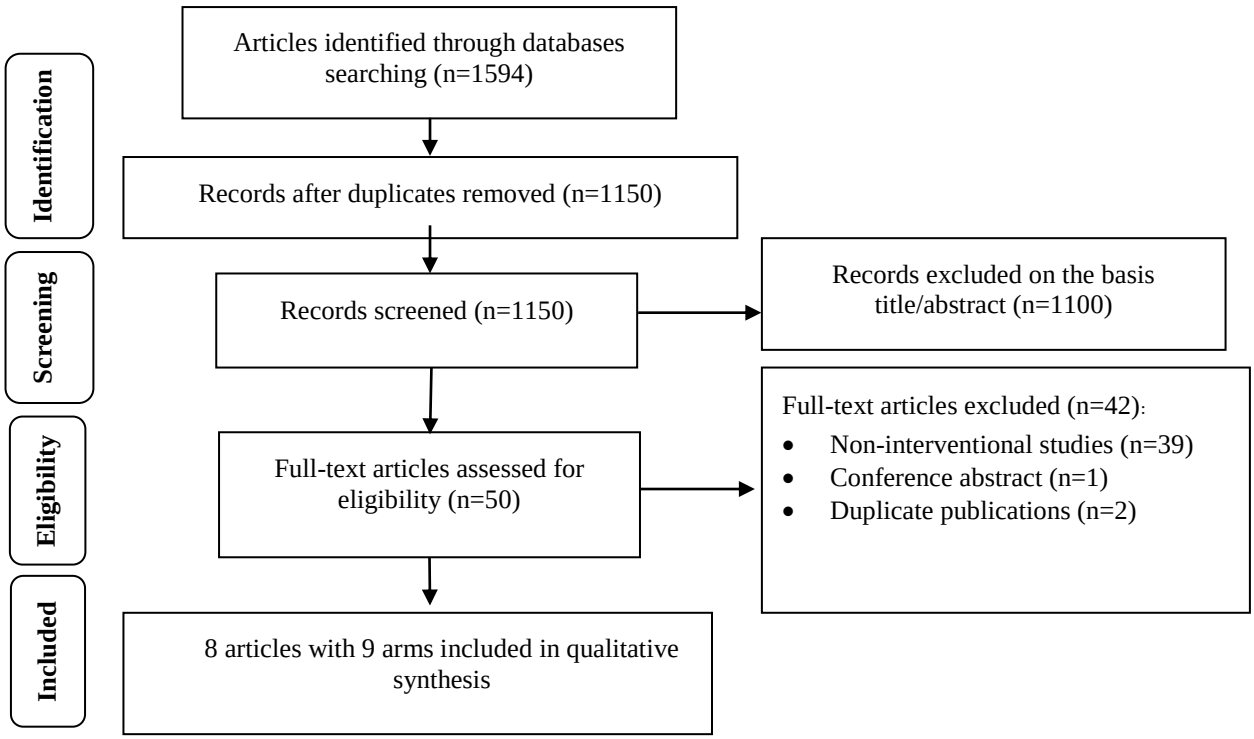

Figure 1. Literature search and review flow chart for selecting studies

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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 μg) vitamin D3 and a multivitamin with 400 IU (10 micrograms) vitamin D3 daily, for a total of 800 IU vitamin D3 (20 μg) 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 μg/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 μg/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.

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Table 1. Characteristics of included trials.

First author (country, year)	Study design/ Follow-up/ Participants characteristics	Intervention/ Control	Outcome measures and findings
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 5µg/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.

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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 (*P* <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 ≤ 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).	At baseline, 34 and 66% of participants had serum 25(OH)D < 30 and >30 nmol/l. Both protocols induced a rise in serum 25(OH)D with a greater increase in the HD vs. LD regimen (31.4, 95% CI: 16.7, 46.0 vs. 11.7 nmol/l, 95% CI: 2.2, 21.2). None of the participants given the HD remained vitamin D deficient, but only one achieved vitamin D sufficiency. Nearly all individuals on the LD regimen remained vitamin D insufficient with only two reaching vitamin D sufficiency.

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

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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

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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), could decrease following any vitamin D 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 supplementation (Flueck *et al.*, 2016c). 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 (none-genomic), vitamin D may be affected by calcium homeostasis and the growth-related signal 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

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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. The 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 the included studies make the results incomparable.

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

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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. It is recommended that future research focusing on the evaluation of the efficacy of vitamin D 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.

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Conflict of interest

The authors declare no conflicts of interest.

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