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CASE SERIES

A Review of Clinical Trials about Vitamin D Supplementation's Effect on Physical Performance of Community Dwelling Oldest-Olds

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Abstract

Background: Although observational studies with community dwelling older adults demonstrate that low serum 25(OH)D (vitD) negatively impacts on the health, the effects of its supplementation are still controversial. The aim of this study is to review clinical trials that evaluated the effect of vitD supplementation on physical performance in community dwelling oldest old.

Methods: A comprehensive search on electronic databases, including Pubmed, Medline, LILACS and Scielo was conducted. Eligible studies were clinical trials published between January 2015 and June 2021 in Portuguese, English and Spanish. The selected articles should meet the following inclusion criteria: Included elderlies aged 80 and over, independent, community-dwelling and of both sexes. Experimental studies with dependent elderly, institutionalized, hospitalized, diagnosed with dementia, acute and/or severe diseases were excluded.

Results: Out of the 11533 articles from the literature search, 21 studies met the inclusion criteria. The results suggest that vitD supplementation alone in most studies does not improve physical performance, even in populations at higher risk (elderly people with insufficiency or deficiency of this vitamin, pre-frailty and frailty, functional impairment and advanced age). When combined with resistance exercise and with other nutrients that are also important for muscle health, there seems to be an improvement in physical tests. However, the heterogeneity of the studies carried out so far contribute to still contradictory results.

Conclusion: Although vitD supplementation corresponds to a potential therapy to prevent physical decline in the elderly, studies with the Brazilian population will be needed to better clarify these effects in community dwelling oldest old.

Keywords

Vitamin D, Aged, Aged 80 and over, Physical functional performance, Aging

Introduction

Worldwide low vitamin D status is emerging as a very common condition. It is estimated that more than one billion people are affected by this vitamin deficiency with a prevalence of 5.9% in the United States, 7.4% in Canada and 13% in Europe [1]. Even though Brazil has and elevated ultraviolet radiation vitamin D deficiency, which is defined as serum 25(OH)D (vitD) levels < 30 nmol/L or 12 ng/m, is still very prevalent. In São Paulo low serum concentrations range from 42% to 63% in the elderly [2,3].

Older adults are a risk group for vitD deficiency due to decreased skin capacity for pre-Vitamin D3 synthesis, reduced exposure to sunlight, increased adiposity, reduced consumption of major food sources, reduced intestinal absorption capacity and presence of comorbidities such as chronic kidney disease [4].

Vitamin D receptor (VDR) is expressed in different human tissues, which strengthens the hypothesis that VitD acts beyond its classical function of bone metabolism and calcium homeostasis, playing an important role in various systems [5]. In the central nervous system, for example, vitD seems to be associated

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with neurotransmitter synthesis and cell differentiation [6]. Vitamin D metabolites stimulate the proliferation and differentiation of muscle cells and influence the skeletal muscle contraction through calcium influx. In the elderly, this vitamin deficiency seems to be related to increased oxidative stress, negatively impacting on strength, balance and mobility [7-9].

Observational studies with community dwelling older adults have reported associations between vitD lower serum levels and poorer physical performance. Although vitD supplementation is proposed as a possible strategy to prevent or delay physical decline through its direct action on muscle fibers, the results of clinical trials that evaluated the effect of the supplementation in improving physical performance in elderlies are still inconsistent and controversial [1,10,11].

Objective

The aim of this study is to review clinical trials that evaluated the effect of vitD supplementation on physical performance in community dwelling oldest old.

Methods

A comprehensive search on electronic databases, including Pubmed, Medline, LILACS and Scielo was conducted. Eligible studies were clinical trials published between January 2015 and June 2021 in Portuguese, English and Spanish. The following Mesh terms were used: Vitamina D and Idosos de 80 anos ou mais, Vitamina D and Idoso, Vitamina D and Anciano de 80 o más años, Vitamina D and Anciano, Vitamin D and aged, 80 and over, Vitamin D and aged.

The initial screening was carried out by the review of the title and abstract of each study. After identifying the ones of interest, they were independently analyzed by two researchers. The selected clinical trials should meet the following inclusion criteria: performed with elderlies aged 80 and over, even if not exclusively, independent, community-dwelling and of both sexes. We also reviewed the references of the selected articles for the identification of relevant studies.

Experimental studies with dependent elderly, institutionalized, hospitalized, diagnosed with dementia, acute and/or severe diseases were excluded. The selected studies were read in full and reviewed in detail by the researchers. Any disagreement between the authors was resolved by consensus.

Results

A total of 11533 articles were identified through the database search. Of the 158 clinical trials originally identified 139 were excluded after full-text review because the intervention was performed with animals, the outcome evaluated was not related to the subject of interest, did not include individuals aged 80 years or over, participants were institutionalized, dependent, hospitalized, diagnosed with a specific health condition (dementia, acute or severe illnesses) and were in the immediate pre or postoperative period. Two articles analyzed different outcomes, but in the same population and with the same intervention, thus, they were considered as a single study.

The additional search of bibliographic references resulted in one clinical trial and two systematic reviews with only clinical trials published until 2016. Although one of the systematic reviews included a study with women who lived in nursing homes, all other clinical trials were carried out with community-dwelling elderly, therefore it was selected. These 3 studies added to the previous ones, resulted in 22 articles included in the current review (Table 1) [12-33].

Regarding the methodology and objective, all studies used cholecalciferol or vitamin D3 as main intervention and had as one of the aims evaluated the effect of this supplementation on physical performance. Ten clinical trials assessed the impact of cholecalciferol alone and nine mixed it with physical exercise and/or other nutrients. Rosendahl-Riise, et al. [16], in a systematic review of 15 clinical trials with healthy community dwelling older adults, demonstrated that vitamin D supplementation (different forms and dosages) with or without calcium did not result in improvement in muscle strength and mobility. Similarly, in the systematic review by Antoniak and Greig [18], an improvement in muscle strength assessed by handgrip strength occurred only when vitD supplementation was performed together with resistance exercise.

Cholecalciferol supplementation in vitamin D deficiency or insufficiency individuals had no beneficial effects on muscle mass [30] or strength and on Short Physical Performance Battery (SPPB) test [17,25,29]. While Ranathunga, et al. [25] at baseline found an association between low plasma VitD concentrations and poorer hand grip strength, after the supplementation this association was not significant, suggesting no effect of the intervention. In the study by Bislev, et al. [20], contrary to expectations, there was a significant 4% reduction in handgrip strength. On the other hand, at Rathmacher, et al.'s [33] clinical trial, supplementation with cholecalciferol, calcium and β-hydroxy-β-methylbutyrate (HMB) improved muscle strength and physical functionality even in participants not engaged in the exercise program. In Lee, et al.'s [27] study, cholecalciferol supplementation and resistance training enhanced muscle mass and reduced time to walk a standard course.

In sedentary elderly the combination of home-based resistance band training with daily intake of a supplement containing whey, dairy proteins, creatine, omega-3 fatty acids and cholecalciferol significantly improved maximal strength and appendicular and total lean mass [32]. In the study by Aoki, et al. [24] both

Table 1: Studies included in the review.

Authors	Study participants	Objective	Design and Methodology	Results and Conclusions
Li-hong Gao, et al. 2015 [12]	Community-dwelling postmenopausal women, capable of independently completing the tests involved in the study and with normal blood counts, normal results on liver and kidney function tests and normal serum levels of calcium, phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) (n = 461)	To investigate the effects of calcium and vitamin D supplementation on bone turnover marker levels, muscle strength and quality of life in postmenopausal Chinese women.	Open-label trial. The participants were divided into group A, B, C, which were treated with calcium (600 mg/d) alone, calcium (600 mg/d) and cholecalciferol (800 IU/d) or calcium (600 mg/d) and calcitriol (0.25 μg/d), respectively, for 2 years.	The participants in group C (calcium (600 mg/d) and calcitriol (0.25 μg/d)) maintained the grip strength, while those in groups A (calcium (600 mg/d) alone) and B (calcium (600 mg/d) and cholecalciferol (800 IU/d)) exhibited decreased grip strength at 24-month follow-up.
Pirotta S, Kidgell DJ, Daly RM. 2015 [13]	Older adults (≥ 60 years) recruited from the local community in Melbourne, Australia and with 25(OH) D concentrations between 25-60 nmol/L (n = 26)	To examine the effects of vitamin D supplementation on neuroplasticity, serum brain-derived neurotrophic factor (BDNF) and muscle strength and function in older adults.	Double-blinded, placebo-controlled randomized trial. The participants were randomized to receive 2,000 IU/day of vitamin D3 or matched placebo for 10 weeks.	There was no effect of vitamin D on muscle power and function (Muscle strength, stair climbing power, TUG/Dynamic balance)
Bauer, et al. 2015 [14]	Participants (≥ 65 anos) were recruited from 18 study centers in 6 European countries. They were diagnosed with sarcopenic according to the following criteria: SPPB scores between 4 and 9, and low skeletal muscle index muscle mass index (≤ 37% for men and ≤ 28% for women) (n = 380)	To test the hypothesis that a specific oral nutritional supplement can result in improvements in measures of sarcopenia.	Randomized, Double-Blind, Placebo-Controlled Trial The active group received a vitamin D and leucine-enriched whey protein nutritional supplement to consume twice daily for 13 weeks. The control group received an iso-caloric control product to consume twice daily for the same period.	This 13-week intervention of a vitamin D and leucine-enriched whey protein oral nutritional supplement resulted in improvements in appendicular muscle mass and in the chair-stand test. However handgrip strength and SPPB improved in both groups without significant between-group differences.
Bischoff-Ferrari, et al. 2016 [15]	Home-dwelling men and women 70 years and older with a low-trauma fall in the previous 12 months	To determine the effectiveness of high-dose vitamin D in lowering the risk of functional decline.	Randomized, double-blind, clinical trial. The participants were randomized in three groups: low-dose control group receiving 24,000 IU of vitamin D3; a group receiving 60,000 IU of vitamin D3 and a group receiving 24,000 IU of vitamin D3 plus 300 μg of calcifediol. All participants were treated monthly	Although higher monthly doses of vitamin D were effective in reaching a threshold of at least 30 ng/mL of 25-hydroxyvitamin D, they had no benefit on lower extremity function (SPPB) and were associated with increased risk of falls compared with 24,000 IU.

Rosendahl-Riise H, et al. 2017 [16]	Community-dwelling older subjects with 65 years old or more (n = 2866, 15 clinical trials)	To investigate the effects of vitamin D supplementation (with or without calcium) in community-dwelling older subjects on muscle strength and mobility	Systematic review A systematic search of the literature (PubMed, Embase, Medline, Web of Science e Cochrane) was performed in April of 2016. The systematic review includes studies that used vitamin D with or without calcium supplementation as the exposure variable and various measurements of muscle strength and mobility.	In the majority of studies, no improvement in muscle strength and mobility was observed after administration of vitamin D with or without calcium supplements. In the meta-analysis, it was observed a small, a small, significant increase in the TUG test after vitamin D supplementation
Levis S, Gómez-Marín O. 2017 [17]	Sedentary men (n = 130) with baseline 25(OH)D levels of less than 30 ng/mL and SPPB scores of 9 or less.	To determine the effectiveness of vitamin D supplementation in preventing decline in physical function in older men.	Randomized, double-blind, placebo-controlled clinical trial. Participants were daily supplemented with 4,000 IU of cholecalciferol or placebo for 9 months	Daily supplementation resulted in significant increases in 25(OH)D concentrations, but achieving these higher levels did not result in improvements in SPPB score or gait speed.
Antoniak AE, Greig CA. 2017 [18]	Men and women aged ≥ 65 years or mean age ≥ 65 years (n = 792) from the community or *nursing homes* (only one study with 113 women)	To evaluate the effectiveness of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health in older adults	Systematic review A systematic search of the literature (Science Direct, Medline, PubMed, Google Scholar and Cochrane Central Register of Controlled Trials) was conducted. Eligible studies were randomized controlled trials published until March 2016 that evaluated resistance exercise training and vitamin D3 supplementation	Muscle strength of the lower limb was significantly improved within the intervention group (vitamin D and resistance exercise training group). Nevertheless for other functional variables, such as SPPB and TUG, no additional benefit beyond exercise was shown.
Vaes, et al. 2018 [19]	Prefrail or frail (according to the Fried criteria), community-dwelling older adults (n = 78) aged ≥ 65 years, with a baseline 25(OH)D concentration between 20 and 50 nmol/L.	To investigate the effect of daily supplementation with 25(OH)D3 or cholecalciferol on muscle strength and physical performance in older adults.	Randomized, double-blind, placebo-controlled clinical trial. Participants were supplemented daily with 10 µg 25(OH)D3, 20 µg cholecalciferol, or a placebo capsule.	Increasing the serum 25(OH)D concentration over a period of 6 months did not significantly change muscle strength and physical performance in pre frail and frail older adults
Bislev, et al. 2018 [20]	Healthy community-dwelling postmenopausal women (n = 81) with plasma levels of 25(OH)D < 50 nmol/l and high parathyroid hormone (PTH) levels	To investigate effects of vitamin D3 supplementation on muscle strength, physical performance, postural stability, well-being, and quality of life in healthy community-dwelling postmenopausal women	Randomized Placebo-Controlled Trial. Participants were 1:1 treated with vitamin D3, 70 µg (2800 IU)/day or identical placebo for three months during wintertime	Compared with placebo, a daily supplement with a relatively high dose of vitamin D3 had no beneficial effects on muscle strength and TUG. In some measures of muscle strength and physical performance, it was observed a small unfavorable effect
Bray NW, Doherty TJ, Montero-Odasso M. 2018 [21]	Older adults 75 years of age or more with frail or pre-frail (according to the modified Frailty Phenotype), able to ambulate 10 meters with or without a mobility aid and proficiency in English (n = 40)	To determine if 4000 IU per day of vitamin D3 is safe for frail older adults, and to establish the efficacy of this dose to improve physical performance outcomes in this population.	Open-label, feasibility study Intervention: 4000 IU of vitamin D3 and 1200 mcg of calcium carbonate daily for four months	Vitamin D supplementation using 4000 IU/daily is safe and has a modest beneficial effect on physical performance (SPPB, grip strength and gait speed) for frail individuals and those with insufficient vitamin D levels. Participants with vitamin D insufficiency (≤ 75 nmol/L) showed greater benefits.

Verlaan, et al. 2018 [22]	Community-dwelling adults over 65 years were recruited from 18 study centers in Europe. Participants were eligible when presenting mild to moderate limitations in physical function (SPPB score 4-9) and low skeletal muscle mass (37% men and 28% women) (n = 380)	To test if baseline serum 25(OH)D concentrations and dietary protein intake influenced changes in muscle mass and function in older adults who received nutritional intervention.	Randomized, double-blind, placebo-controlled clinical trial. Participants were randomized to receive either the intervention or an iso-caloric control product twice daily during 13 weeks. The intervention product contained per serving 20 g whey protein, 3 g total leucine, 9 g carbohydrates, 3 g fat, 800 IU vitamin D and a mixture of vitamins, minerals and fibers, and the iso-caloric control drink contained only carbohydrates, fat and some trace elements.	Participants with higher baseline 25(OH) D concentrations and dietary protein intake had, independent of other determinants, greater gain in appendicular muscle mass, skeletal muscle index, and relative appendicular muscle mass in response to the nutritional intervention. There was no effect modification of baseline 25(OH)D status or protein intake on change in chair-stand test.
Seino S, et al. 2018 [23]	Community-dwelling older adults (n = 82) who were aged 65 to 80 years and did not exercise regularly	To investigate whether supplementation with low-dose dairy protein plus micronutrients augments the effects of resistance exercise (RE) on muscle mass and physical performance compared with RE alone among older adults.	Randomized, controlled trial The RE plus supplementation group participants ingested supplements with dairy protein (10.5 g/day) and micronutrients (8.0 mg zinc, 12 µg vitamin B12, 200 µg folic acid, 200 IU vitamin D, and others/day). Both groups performed the same twice-weekly RE program for 12 weeks.	Low-dose dairy protein plus micronutrient supplementation during resistance exercise significantly increased muscle mass in older adults but did not further improve physical performance.
Aoki K, Sakuma M, Endo N. 2018 [24]	Community-dwelling elderly individuals (aged ≥ 60 years) who were not taking osteoporosis medications (n = 130)	To investigate the impact of exercise and vitamin D supplementation on physical function and locomotor dysfunction in community-dwelling elderly individuals	Randomized trial. The participants were randomly divided into an exercise group, vitamin D group, and exercise and vitamin D group. Exercise comprised three daily sets each of single-leg standing and squatting and vitamin D supplementation was 1000 IU/day.	Both exercise and vitamin D supplementation independently improved physical function and increased muscle mass in community-dwelling elderly individuals.
Ranathunga, et al. 2019 [25]	Community dwelling men and women (≥ 70 years) (n = 379)	To determine the effect of monthly supplemental vitamin D3 on muscle function in older adults	Randomized double-blind interventional trial. Participants were randomized to receive one of these three doses of vitamind D3: 12,000 IU, 24,000 IU or 48,000 IU, monthly for one year.	Baseline plasma 25(OH) D concentration < 25 nmol/L was associated with lower Hand Grip Strength. Although, after supplementation the change in Hand Grip Strength and TUG was not different between treatment groups, suggesting no effect of the intervention.
Koning, et al. 2019 [26]	Community-dwelling persons aged 60-80 years who had clinically relevant depressive symptoms, ≥ 1 functional limitations, and serum 25(OH)D concentrations of 15-50/70 nmol/L (n = 155)	To investigate the effect of vitamin D supplementation on depressive symptoms, functional limitations, and physical performance in a high-risk older population with low vitamin D status	Randomized placebo-controlled trial Participants received 1200 IU/day vitamin D3 or placebo tablets for 12 months	No relevant differences between the treatment groups were observed regarding depressive symptoms, functional limitations, physical performance, or any of the secondary outcomes.

Lee Y, Sohng K. 2019 [27]	Community-dwelling individuals living alone and with vitamin D levels < 20 ng/mL (n = 94)	To examine the effects of vitamin D on depression, cognitive function, and physical function in elderly individuals	Nonequivalent control group and pre-test–post-test design In the experimental group exercise programs were prescribed and participants received 1,000 IU vitamin D daily. In the control group only exercise programs were prescribed. Treatment duration was 12 weeks.	Vitamin D supplementation was associated with improved vitamin D levels, muscle mass, and time to walk a standard course
Hangelbroek, et al. 2019 [28]	Frail older adults according to the Fried criteria aged above 65 years and blood 25(OH) D concentrations between 20 and 50 nmol/L (n = 22)	To investigate the effect of calcifediol on whole genome gene expression in skeletal muscle of vitamin D deficient frail older adults.	Double-blind placebo-controlled trial Subjects were randomized across the placebo group and the calcifediol group (10 µg per day). Muscle biopsies were obtained before and after 6 months	No significant difference between treatment groups was observed on strength outcomes.
Grimnes G, Kubiak J, Jorde R. 2019 [29]	Men and women with low serum vitamin D status (< 42 nmol/L) aged 40 years and older (n = 417)	To study whether vitamin D supplementation improves muscle strength in men and women with low serum vitamin D status	Randomized, double-blind, placebo-controlled clinical trial. All participants were randomized to receive a loading dose of 100,000 IU vitamin D3 followed by 20,000 IU/week, or placebo. Muscle strength was tested by dynamometers at baseline and after four months.	Muscle strength (hip flexion, biceps flexion, pectorals and handgrip strength) did not change in any of the groups. The results were the same in analyses stratified on sex, 25(OH)D above/below 25 nmol/L (10 ng/ml), smoking status and BMI above/below 27 kg/m^2
Shea MK, Roger AF, Dawson-Hughes B. 2019 [30]	Healthy community-dwelling men and postmenopausal women ≥ 60 years old who had serum 25(OH)D ≤ 20 ng/mL at screening (n = 100)	To to test the effect of 12 months of vitamin D supplementation on lower-extremity power and function in older community-dwelling adults	Double-blind, randomized, placebo-controlled trial. Participants were randomly assigned to 800 IU vitamin D3/day or placebo. Those in the intervention group whose serum 25(OH)D was < 28 ng/mL after 4 months were given an additional 800 IU vitamin D3/d, whereas all other participants received placebo as an additional pill.	Increasing serum 25(OH)D to > 32 ng/mL (on average) over 12 months did not affect lower-extremity power, strength, or lean mass in older community-dwelling adults.
Bischoff-Ferrari HA, et al. 2020 [31]	Adults aged 70 years or older who had no major health events in the 5 years prior to enrollment and had sufficient mobility and good cognitive status (Mini-Mental State Examination score of at least 24) (n = 2157)	To test whether vitamin D, omega-3 and a strength-training exercise program, alone or in combination, improved 6 health outcomes among older adults	Double-blind, placebo-controlled, 2 × 2 × 2 factorial randomized clinical trial. Participants were randomized to 3 years of intervention in 1 of the following 8 groups: 2000 IU/day of vitamin D3, 1 g/day of omega-3s, and a strength-training exercise program; vitamin D3 and omega-3s; vitamin D3 and exercise; vitamin D3 alone; omega-3s and exercise; omega-3s alone; exercise alone; or placebo	Treatment with vitamin D3, omega-3s or a strength-training exercise program did not result in statistically significant differences in physical performance (SPPB). Thus, the results do not support the effectiveness of these three interventions in improving physical performance.

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Nilsson MI, et al. 2020 [32]	Male cohort (≥ 65 years) representative of the North American aging community in general: individuals with low physical activity levels (sedentary), normal-to-high BMIs, and varying degrees of age-related muscle loss (n = 32)	To test the utility of a five-ingredient protein-based (Muscle5) in combination with low-intensity training for maintenance of skeletal muscle mass, strength, performance and muscle quality in sedentary, free-living elderly	Double-blind, randomized, placebo-controlled trial. Participants underwent twelve weeks of home-based resistance band training (3 d/week), in combination with daily intake of a five-nutrient supplement containing whey, micellar casein, creatine, vitamin D and omega-3 fatty acids or an isocaloric/isonitrogenous placebo containing collagen and sunflower oil	In the intervention group appendicular and total lean mass, lean mass to fat ratios, maximal strength (handgrip and leg press), function (5-Times Sit-to-Stand time) and fast-twitch muscle fiber cross-sectional areas of the quadriceps muscle were significantly improved.
Rathmacher JA, et al. 2020 [33]	Older adults (n = 117) over 60 years of age with insufficient circulating 25(OH)D levels (15-30 ng/mL)	To determine whether supplementation with calcium, HMB and vitamin D3 would enhance muscle function and strength in older adults	Double-blind, randomized, placebo-controlled trial. Participants were randomly assigned to treatments consisting of: (a) control + no exercise, (b) HMB+ Vitamin D3 + no exercise, (c) Control + exercise, and (d) HMB+Vitamin D3+ exercise. The study evaluated the participants via multiple measurements over the 12 months that included body composition, strength, functionality, and questionnaires.	At 3, 6 and 12 months after the intervention, the group who received only the supplementation with HMB and vitamin D3 had a significant increase in the functional index compared to the control group without exercise. Supplementation with HMB+Vitamin D3 did not further improve the functional index within the exercising group.

TUG: Time Up and Go test; SPPB: Short Physical Performance Battery test; RE: Resistance Exercise; BMI: Body Mass Index; HMB: β-hydroxy-β-methylbutyrate

exercise and vitamin D supplementation independently improved physical function and increased muscle mass in community-dwelling elderly individuals, with no differences between the groups. Although Seino, et al. [23] had demonstrated that resistance exercise (RE) plus dairy protein and micronutrient supplementation (200 IU/day cholecalciferol) resulted in muscle mass gain, this did not further improve balance, gait speed (GS), Time Up and Go (TUG) and strength tests.

In pre-frail or frail elderly people, two studies [19,28] with cholecalciferol supplementation did not show a significant change in muscle strength and physical performance. Bray, et al. [21] combined calcium carbonate and vitamin D3 supplement and instead of the previous ones it showed a modest beneficial effect on SPPB and GS in frail individuals and those with insufficient vitamin D levels at baseline.

One study with sarcopenic older adults reported results of treatment combining vitamin D and leucine-enriched whey protein supplement. Muscle mass and lower extremity function evaluated by the chair-stand test improved, but handgrip strength and SPPB improved in both groups without significant between-group differences. Still, those with higher baseline VitD values and dietary protein intake had better results of appendicular muscle mass in response to the intervention [14,22].

Two clinical trials enrolled community-dwelling men and women 70 years and older with a prior fall and measured the impact of different concentrations of vitamin D3 supplement alone [15] or associated with omega-3 fatty acids and RE [31] in lowering the risk of functional decline. In both there was no difference on SPPB results after the intervention.

Physical performance also did not significantly improved with vitD supplement in older adults with 25(OH)D serum concentrations between 25-60 nmol/L [13] and in community-dwelling persons aged 60-80 years who had clinically relevant depressive symptoms and one or more functional limitations [26].

Gao, et al. [12] assessed in healthy postmenopausal women the effects of calcium, calcitriol and cholecalciferol supplementation on muscle strength. The participants that received calcitriol and calcium maintained the grip strength, while those supplemented with calcium alone or combined with cholecalciferol exhibited decreased grip strength at follow-up.

Discussion

Although evidence from cross-sectional and cohort studies suggests a negative correlation between serum VitD concentrations and physical performance in higher-risk populations, that is, elderly people with vitamin D insufficiency or deficiency, pre-frailty and frailty, functional impairment and 80 years or more,

[34] the clinical trials included in our review did not identify an improvement at physical performance with cholecalciferol supplementation alone. A systematic review conducted by Rosendahl-Riise, et al. [16] found that in addition to no beneficial results on muscle strength, in some cases the TUG results worsened. Antoniak & Greig, et al. [18] at a systematic review showed that despite the RE combined with cholecalciferol supplement resulted in an increased muscle strength, when performance was assessed using the SPPB and TUG there was no additional benefit beyond that attributed to physical training. Studies following these systematic reviews, also described in this article, confirmed that isolated calcitriol supplementation does not seem to improve physical performance, requiring its association with other interventions.

Functional limitations related with greater dependence to perform activities of daily living (ADL), increased mortality and health care costs can be assessed through physical performance [35-37]. The tests used by the articles included in this review were gait speed, sit to sit to stand, handgrip... handgrip strength, Time Up and Go (TUG) and the Short Physical Performance Battery (SPPB). These tests assess muscle strength and balance, with gait speed being directly correlated with morbidity and mortality; [8] the sit to stand test measures in addition to lower limb strength, balance and risk of falls; [38] the handgrip strength, although evaluates the strength of the upper limbs, has a good correlation with functional capacity and health outcomes; [36,39] the TUG corresponds to an important predictor of functional limitations as it assesses muscle strength and gait speed, [40] as well as the SPPB, which has a high level of sensitivity and reliability to measure changes in physical performance in older adults in the community [41].

The studies included in this review show that although there are several clinical trials with the aim of evaluating in community-dwelling elderly people the effect of cholecalciferol supplementation on physical performance, this correlation is yet to be proven. Questions about the type of supplementation (associated or not with other nutrients and with resistance exercise), dose, period and who in the older population would benefit from this intervention are still controversial. The heterogeneity of the studies carried out so far, with differences in designs, populations, duration and dose of the supplement, tests and thresholds for assessing physical performance have made it difficult to draw conclusions.

Resistance exercise training corresponds to one of the most effective non-pharmacological treatments to improve physical performance, nevertheless when this practice is associated with VitD supplementation, muscle synthesis and regeneration seem to be enhanced [42]. VitD seems to play an important role in myogenesis and muscle regeneration by modulating the differentiation of satellite cells into muscle cells. Furthermore, it was recently shown that through specific signaling pathways, VitD would also be involved in glucose metabolism, in mitochondrial activity and in the production of energy needed to maintain muscle health [42,43]. In the post-exercise period, vitD as well seems to act helping muscle recovery through its anti inflammatory properties, reducing the synthesis of pro-inflammatory cytokines such as IL-2 and TNF-α that occur in response to physical activity [44].

Likewise, vitD might act synergistically with other nutrients, stimulating muscle synthesis, probably through anabolic pathways induced by insulin and leucine. According to the results of the clinical trials included in this review, interventions vitD supplement combined with other nutrients that are also important for muscle health, such as amino acids, creatine and omega-3 fatty acids, may be an important strategy to maintain and improve physical performance [45].

The mechanisms through which VitD can influence muscle function are still unclear, however two pathways are considered of the most importance: the genomic and the nongenomic pathway. and the nongenomic pathway. In the genomic pathway, the binding of calcitriol to the VDR receptor on muscle cells would trigger a nuclear response resulting in the *de novo* protein synthesis. This protein appears to determine calcium absorption, phospholipid metabolism and muscle cell proliferation and differentiation [45]. The non-genomic effects of VitD are also mediated by VDR receptors. Through the activation of cell signaling pathways, there is a rapid influx of calcium from the sarcoplasmic reticulum, resulting in the prolongation of the relaxation phase of muscle contraction [36]. Another non-genomic action of vitD includes the release of arachidonic acid which modifies the fluidity and permeability of the cell membrane [45]. Furthermore, recent studies have shown that vitD deficiency appears to be associated with increased oxidative stress with consequent skeletal muscle atrophy [36].

Although observational studies show an inverse association between serum 25(OH)D levels and the risk of falls possibly due to reduced type II muscle fibers and proximal muscle atrophy observed in vitamin D deficiency's elderlies, LeBoff, et al. [46] in a clinical trial with 25871 healthy community older adults demonstrated that vitamin D3 supplementation (2000 IU/day) for 5.3 years did not result in a reduced risk of falls, even in participants with baseline 25(OH)D levels < 30 nmol/L. Studies on the effects of vitamin D supplementation on falls in this population are still conflicting.

The present review showed that vitamin D supplementation alone is not associated with improved physical performance even in populations at higher risk, however, when combined with resistance exercise and other nutrients also important for muscle health, this intervention can result in beneficial effects. It should be noted that all clinical trials included in our study are international, carried out with elderly people aged 80 years or more in a non-exclusive way and that most participants had basal concentrations of 25(OH)D corresponding to insufficiency.

In conclusion, to clarify the issues surrounding the role of vitamin D in improve physical performance in community dwelling oldest old, further Brazilian randomized controlled trials with community-independent elderly with frailty, sarcopenia, age over 80 years and serum 25(OH)D concentrations below < 25 nmol/l will be needed. In addition, well-designed and well conducted studies assessing the short, medium and long term results of different forms of supplementation combined with resistance exercise and nutrients such as whey protein, casein, creatine, leucine and omega-3 on these populations should be implemented. Finally, it is important to emphasize that the method chosen to measure physical performance must enable an early screening of physical decline, resulting in the prevention of negative outcomes.

Conclusions

Vitamin D supplementation corresponds to a potential economic and safe adjuvant therapy to maintain the elderly's independence and autonomy, nevertheless, studies with the Brazilian population will be needed to clarify its effects on community dwelling oldest-olds.

Sources of Support

None.

Statement of Equal Authors' Contribution

All authors contributed significantly and are in agreement with the content of the manuscript. We have no conflicts of interest to disclose.

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