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The role of Vitamin D in muscle strength, neuromuscular function and risk of fall in the elderly

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Dedicatória

Dedico esta monografia aos meus pais, avós e irmã por todo o apoio e suporte que me deram ao longo de todo o curso.

Dedico também aos meus amigos que tornaram esta caminhada mais fácil.

The role of Vitamin D in muscle strength, neuromuscular function and risk of fall in the elderly

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Short title: Vitamin D and neuromuscular function and falls

Abstract

Aims: Vitamin D deficiency is very common in elderly populations throughout the world and seems to be related with poorer muscle strength, function and risk of falls. This review aims to summarize the available data about the vitamin D role in this matter.

Methods: A search was conducted in the Pubmed database for articles with the following terms: “muscle strength”, “body sway”, “balance”, “risk of fall”, “vitamin D”, “elderly”, “cholecalciferol” and “ergocalciferol”. Further articles were obtained thru reference lists.

Results: Observational studies point to a relationship between serum 25-hydroxyvitamin D levels and muscle strength, neuromuscular function and falls. Concentrations ≥ 40 nmol/L or ≥ 25 nmol/L were associated with better short physical performance battery test and ≥ 50 nmol/L with handgrip strength. Levels below 25 nmol/L had worst stride-to-stride variability of stride test and diminished handgrip strength overtime. One study found an association with falls while two studies found no association.

Randomized controlled trials convey contradictory results. Muscle strength was only seen to be related with treatment in women with 25-hydroxyvitamin D levels below 60 nmol/L and with lowest strength. Associations were found with body sway, timed up and go test and preferred walking speed. In terms of falls a reduction from 19% to 49% was seen in studies but others didn’t achieve statistical significance and one even showed adverse effect when very high doses were used.

A systematic review concluded that randomized trials with low 25-hydroxyvitamin D baseline levels showed a positive effect on muscle function. Several meta-analysis attribute a positive effect of vitamin D supplementation on falls and one showed a tendency without statistical significance.

Conclusions: Vitamin D, especially when combined with calcium and in vitamin D deficient elderly, provides some fall prevention. Its effects on muscle strength and function are less consistent.

Keywords: vitamin d, muscle strength, neuromuscular function, falls

List of abbreviations

25(OH)D – 25-hydroxyvitamin D
LASA – Longitudinal Aging Study Amesterdam
OR – Odds Ratio
OPRA – Malmo Osteoporosis Prospective Risk Assessment
OPUS – Osteoporosis and Ultrasound Cohort
RCT – Randomized controlled trial
RR – Relative Risk
SPPB – Short Physical Performance Battery
STV – Stride-to-Stride variability of stride time
TCS – Timed Chair Stand
TUG – Timed Up and Go test
UVB – Ultraviolet B light
VDR – Vitamin D Receptor

Introduction

Vitamin D is a generic term used to describe the molecules ergocalciferol (also known as vitamin D_2) and cholecalciferol (or vitamin D_3). [1] The main source of vitamin D is believed to be the sunlight (thru UVB radiation) but if it is enough for optimal levels to be achieved in human beings, is still a controversial subject.[2] A large number of studies concluded that vitamin D deficiency is highly prevalent in North America[3] and Europe[4,5]. Prevalence is higher in elderly populations[6] and in housebound[7] or institutionalized[8] older individuals.

The incidence of falls in the elderly population is approximately 30% per year[9,10] and within this group, the falls result in a fracture in 7,7%[10]. With the aging of the world population, the prevention of this type of falls should be addressed to diminish these numbers.

Vitamin D receptor (VDR) KO mice are associated with type I and type II muscle fibers atrophy, poor musculoskeletal performance and changes in gait. Rats in which vitamin D deficiency was induced also showed altered muscle function.[11]

In humans, vitamin D deficiency is characterized by muscle weakness, muscle pain and impaired gait[12,13], so the relationship between vitamin D serum levels and muscle function seems to exist. Several studies address this relationship and will be discussed in this paper.

The aim of this study is to give a global perspective on the available data regarding vitamin D serum levels and its association with muscle strength, coordination and risk of fall in the elderly population.

Materials and Methods

A search was conducted in the Pubmed database for publications in the English, Spanish and Portuguese languages, with abstracts available and containing the following search terms: “muscle strength”, “body sway”, “balance”, “risk of fall”, “vitamin D”, “elderly”, “cholecalciferol” and “ergocalciferol”. Additional studies were identified searching reference lists. The studies with populations below 60 years of age, focusing on animals, related with fractures and with unavailable full article access were excluded.

Results

A total of 26 articles were used in this review, of which one was a systematic review and four were meta-analysis.

In a study conducted with 4100 ambulatory subjects aged ≥ 65 years, 49% woman, higher serum concentrations of 25-hydroxyvitamin D (25(OH)D) were associated with better results in musculoskeletal function. The higher quintile showed an average improvement of 5.6% in the 8-foot walk test and 3.9% in the sit-to-stand test, when compared with the lowest quintile.[14]

A cross-sectional study, using data from the InCHIANTI study, including 976 subjects aged ≥ 65 years, assessed physical performance using a short physical performance battery (SPPB), consisting of walking speed, ability to stand from a chair and ability to maintain balance in progressively more challenging positions. Handgrip strength was measured with a handheld dynamometer. Serum levels of 25(OH)D <25 nmol/L were associated with lower SPPB scores and values below 50 nmol/L were associated with lower handgrip strength.[15]

Another cross-sectional study examined the association between stride-to-stride variability of stride time (STV) and the serum levels of 25(OH)D in 411 subjects above 65 years of age. 25(OH)D levels below 10 ng/mL (25 nmol/L) were significantly associated with higher STV and low lower limb proprioception score. No changes were observed in handgrip strength.[16]

In the OPRA study, 986 women aged 75 years old, were examined for balance, muscle strength and gait speed. The results showed inferior gait speed, poorer balance and lower knee extension strength for subjects with 25(OH)D levels below 30 ng/mL (75 nmol/L).[17]

In a cohort of 109 men and 131 women aged 65 years of age or older and community dwelling, no significant associations were found between the levels of serum 25(OH)D and muscle strength in men. In women, after adjustment for confounders, low levels were associated with higher handgrip force.[18]

Using data from the LASA study, Visser et al. concluded that low 25(OH)D levels (<25 nmol/L) were associated with higher prevalence of loss of grip strength in the elderly (OR 2.57, 95% CI 1.40-4.70).[19]

In a cross-sectional and longitudinal analysis, Dam and co-workers concluded that women with lower 25(OH)D levels had poorer results in the Timed up and Go (TUG) and Timed Chair Stand (TCS) tests. In the prospective analysis, women with levels ≤ 80 nmol/L, had a mean percentage reduction of 20% in the TUG and TCS tests when compared with women with levels ≥ 115 nmol/L. No association was found for males.[20]

A sample of 1234 individuals aged 65 years or older, of which 600 are men and 634 women, were assessed by three performance tests during a three year follow up: walking test, chair stands and tandem stand. These three tests were combined in a performance score.

Participants with serum 25(OH)D levels below 10 ng/mL scored lower on all tests when compared with subjects with levels ≥ 30 ng/mL. Participants with levels below 20 ng/mL had significantly lower scores for physical performance and higher odds for decline in physical performance.[21]

A 16 week, double-blind study examined the effects of a weekly dose of 8400 IU vitamin D_3 on postural stability, muscle strength and safety compared with placebo, in a sample population aged ≥ 70 years old, ambulatory and with serum 25(OH)D concentrations between 6 ng/mL and 20 ng/mL. Even though 25(OH)D levels increased significantly in the treatment group, no differences were found in body sway and in the SPPB score between the two groups. However, in a post hoc analysis, those individuals with mediolateral sway ≥ 0.46 cm showed a significant reduction in the treatment group when compared with the placebo group.[22]

In a prospective, randomized, double-blind, placebo controlled study, patients attending a falls clinic, aged over 65 years and with 25(OH)D levels ≤ 12μg/L were assessed with the following neuromuscular tests: aggregate functional performance time, chain reaction time, postural stability and quadriceps strength. Then they were randomized to receive 600000 IU of ergocalciferol or placebo. After six months the treatment group improved aggregate functional performance time by 2s versus the 6.6s decrease in the placebo group. In the chain reaction time the results were 15% improvement versus 3% decrease in the placebo group. Postural sway improved 13% in the treatment group and decreased 3% in the placebo. Muscle strength difference was not statistically different but with a tendency for less loss of strength in the treatment group.[23]

In a 6 months randomized controlled trial (RCT), 113 institutionalized women over 70 years of age received calcium and vitamin D supplementation and 56 also received whole body vibration. The preferred speed of 10 m walk and the TUG tests obtained significantly better performances in both groups. Fall risk did not change significantly in any group. However, results were better in the whole body vibration group.[24]

In a RCT, 302 women aged between 70 and 90 years of age, with a plasma 25(OH)D concentration below 24 ng/mL, and with a history of at least one fall in the previous 12 months were randomized to receive 1000 IU ergocalciferol per day or placebo during one year. All participants received 1000 mg/d calcium. Muscle strength was measured with a strain gauge and mobility with the TUG test. The vitamin D group showed significantly improved hip muscle strength in the subjects within the lower tertile of strength, and 17,5% improved TUG time in the participants with time longer than 12s.[25]

A systematic review including 16 RCTs concerning muscle function and performance, concluded that almost all studies observed an increase in 25(OH)D levels with treatment. A little less than half showed an improvement in muscle strength, reduced body sway, improved TUG test, increase in gait speed and improved aggregated measures of physical abilities. However, no beneficial effects were found for hand grip strength. The author also points out that all studies showing a beneficial effect included only participants with low vitamin D concentrations at baseline and that the studies are very heterogeneous in many aspects.[26]

A study analyzing the association between vitamin D receptor gene polymorphisms and falls in the OPUS cohort concluded that no statistical difference existed between the serum levels of 25(OH)D and the incidence of falls.[27]

An observational study including 9526 community-dwelling women aged 65 years and older examined the relationship between supplementation with vitamin D and neuromuscular function and falls incidence in a 4 year period. Grip strength, quadriceps strength, chair-stand time, gait speed and balance walk time were examined. Participants were asked if they had fallen in the last 4 months, every four months. They found no association between vitamin D supplement users and all neuromuscular function tests used. Higher concentrations of 25(OH)D (≥26 ng/mL) were associated with poorer grip strength. No association was found between 25(OH)D concentrations and falls.[28]

However, another observational study concluded that serum 25(OH) levels <10 ng/mL in a population aged ≥ 65 years, were associated with an increase in the incidence of recurrent falls. This association was particularly accentuated in the ≥ 65 - < 75 age range.[29]

A RTC with a sample comprised by 112 women aged 60 years or older and in a long-stay geriatric unit in Switzerland, compared treatment with vitamin D (800 IU/d) + calcium (1200 mg/d) vs calcium alone for 12 weeks. 50% of the women had baseline 25(OH)D levels below 30 nmol/L. The results showed a reduction of 49% in the number of falls per person in the treatment group. There was no statistically significant difference in the number of fallers. Musculoskeletal function was a secondary endpoint and also improved in the treatment group (knee flexor strength, knee extensor strength, grip strength, TUG test).[30]

Another RCT with a sample of 302 community-dwelling women aged 70 to 90 years living in Australia, tested the effects of treatment with 1000 IU/d ergocalciferol + 1000 mg/d calcium vs placebo + 1000 mg/d calcium on the risk of falls. Only patients with 25(OH)D levels below 24 ng/mL and at least one fall in the previous year were included. The ergocalciferol group showed a 19% decrease in the risk of falling. This decrease was particularly accentuated in winter/spring. No effects were found in multiple fallers.[31]

Two hundred and five patients aging 65 years or older and admitted to a geriatric medical unit were randomized to receive 800 IU vitamin D_3 + 1200 mg calcium or just 1200 mg calcium in a RCT. Falls and fractures were registered until discharge. 85% of the patients had a previous history of falls and the median length of stay in the unit was 30 days. No statistically significant changes were detected in terms of risk of fall, total falls or fractures comparing the treatment group and the control group. The serum levels of 25(OH)D didn't increase in a significant manner in the treatment group.[32]

M. Law et al., in a RCT conducted in 118 Britain care homes and with 3717 participants, determined the effects of supplementation with 2.5 mg ergocalciferol every 3 months. No placebo was given to the control group. Falls were recorded by the care home staff. No reduction in falls was found with this supplementation, even thou 25(OH)D levels increased.[33]

A double-blind, placebo-controlled trial including 2256 community-dwelling women with age above 70 years were randomized to receive 500000 IU of cholecalciferol or placebo, once a year for a period of 3 to 5 years. The study aimed to improve patient's adherence to vitamin D supplementation and reduce falls and fractures. The cumulative incidence of first fall was higher in the vitamin D group, with a hazard ratio of 1.16, p=0.003. A post-hoc analysis found a higher incidence of falls in the vitamin D group in the first 3 months following the annual dose. The median 25(OH)D level at baseline was 49 nmol/L whereas at 1 month after the dose was 120 nmol/L, with 82% above 100 nmol/L.[34]

Glendenning et al. tested the effects of treatment with 150000 IU of cholecalciferol administered every three months combined with lifestyle advices vs placebo and lifestyle advices, on falls, mobility and muscle strength in 686 community dwelling women aged above 70 years. Falls were self-registered in a diary. During the 9 months period of the study, the OR for the treatment group compared with the placebo group was 1.11 (95% CI 0.80-1.56) for at least one fall and 1.58 (95% CI 0.83-2.99) for multiple falls. Hand grip strength and TUG test, which were a secondary endpoint, didn't differ significantly in any of the groups.[35]

A meta-analysis comprising only double-blind RCTs assessing vitamin D treatment and falls (as a primary or secondary outcome) and with a fall definition well defined, compiled data from 5 studies. The corrected odds ratio was 0.78 (95% CI, 0.64-0.92), suggesting a reduced risk of falls by 22%. When 5 other studies that didn't meet the initial criteria were added the reduction was attenuated, suggesting a reduction in the risk of fall with vitamin D supplementation of 13%.[36]

Another meta-analysis including 9 studies (8 RCTs and one prospective study) pooled data relative to vitamin D_3 treatment (with or without calcium) and the risk of fall. Vitamin D_3 daily doses ranged from 300 to 800 IU. The pooled RR was 0.88 (95% CI 0.78-1.00), showing a trend to the prevention of falls.[37]

Bischoff-Ferrari et al. conducted another meta-analysis including 10 RCTs regarding treatment with oral vitamin D (vitamin D_2, vitamin D_3 and active forms) and the prevention of falls in individuals of at least 65 years of age and a 3 months minimum follow-up. The results showed a pooled RR of 0.87 (95% CI 0.77 to 0.99) but with heterogeneity detected. After stratifying the studies into a low dose (200-600 IU) and high dose (700-1000 IU) vitamin D supplementation, heterogeneity was solved and the pooled RR was 1.10 (95% CI 0.89 to 1.35) and 0.81 (95% CI 0.71 to 0.92), respectively. Moreover, 25(OH)D concentrations above 60 nmol/L resulted in a 23% fall reduction and levels below 60 nmol/L had no effect on fall rate. Also, in a subgroup analysis of the high dose vitamin D studies, relative risk reduction was 12% in vitamin D2 trials and 26% in vitamin D3, although this observation was not statistically significant (p=0.28).[38]

A recent meta-analysis concerning vitamin D and its effect on falls, included 26 randomized trials comparing vitamin D supplementation with no supplementation. Trials with calcitriol were excluded from the analysis. The results showed a statistically significant reduction in the risk of falls in the vitamin D treated group (OR 0.86 with a 95% CI of 0.77-0.96). However, the I^2 test detected substantial heterogeneity in the studies. In a subgroup analysis, a statistically significant relationship was found between vitamin D deficient and not deficient and between risk of fall and calcium co-administration. No relationship was found when the subgroups were tested for dose of vitamin D (at least 800 IU or greater than 600 IU).[39]

Discussion

In the recent years a lot of literature involving vitamin D and its possible applications has been published. On the subject of muscle strength and neuromuscular coordination, the available studies show conflicting results.

Cross-sectional studies[14-17] present a positive interaction between serum 25(OH)D levels and better muscular function, assessed by various methods. This association was also apparent in both sexes[14,15] and concentrations $\geq$ 40 nmol/L[14] or $\geq$ 25 nmol/L for SPPB and $\geq$ 50 nmol/L for handgrip strength[15]. On the other hand, a study[16] only found an association between levels below 10 ng/mL (25 nmol/L) and STV. Only one study[18] reported no

association in men and an inverse association for handgrip strength and low levels of 25(OH)D in women, although the sample was small and the prevalence of vitamin D deficiency in the sample wasn't know, only for the total cohort which included ages ranging from 21 to 93 years.

Longitudinal studies supported this association when loss of grip strength was observed to be more pronounced in individuals with 25(OH)D levels below 25 nmol/L[19,21] and levels ≤ 80 nmol/L were associated with 20% reduction in TUG and TCS tests compared with levels ≥ 115 nmol/L in women[20]. Similarly with the study from Marantes et al, Faulkner and colleagues[28] concluded that 25(OH)D levels had no relationship with neuromuscular function. However, dosage of supplementation was unknown and the population had higher levels at baseline.

Randomized controlled trials also support these findings, however in a partial manner. Some find that body sway is improved but only when above 0.46 cm[22] and no effect on muscle strength. Another[23] positively relates vitamin D treatment and aggregate functional performance time, chain reaction time and body sway but failed to achieve statistically significant results in muscle strength. Other[24] shows a positive relation with TUG test and preferred walking speed, but failed to achieve significance in terms of body sway. Concerning muscle strength, a statistically significant positive result was seen in women with 25(OH)D levels below 24 ng/mL (60 nmol/L) and lowest strength.[25]

A systematic review[26] concluded that almost half the included RCT had positive effects and that those were the ones with low baseline 25(OH)D levels, but also points that studies were heterogeneous. This review also included trials with populations below 60 years of age.

Observational studies and the relation between vitamin D levels and falls have conflicting data. Some are positive[29], others negative[27,28]. The positive one was aimed to a vitamin D deficient population and falls were assessed weekly. In the negatives falls were assessed yearly and every 4 months.

RCT data, like observational, also conveys contradictory results. There are positive studies, reporting a positive relation ranging from 19% to as much as 49% decrease in falls per person[30,31]. There are also many tests showing no relation[32,33,35] or even an adverse effect when very high doses of cholecalciferol were used[34].

This topic was highly reviewed in meta-analysis and those results tend to attribute a positive effect of vitamin D on fall risk. Some didn't reach statistical significance but all

studies that targeted vitamin D deficient populations or/and high daily dose reached a positive association.

Study heterogeneity is a major issue when analyzing the role of vitamin D and muscle strength, function and falls. Studies use different measuring methods for body sway and muscular function. Baseline 25(OH)D concentrations in the sample population also differ from study to study. To this matter also contribute the controversy around the vitamin D deficiency definition. Several different values for vitamin D deficiency have been proposed using different methods.[40,41] Other confounding factor is 25(OH)D serum concentrations and its variability inter-laboratories.[42] Some studies include males and females whereas others only females. Doses of vitamin D treatment are also different and even the type administered (vitamin D_2 or vitamin D_3). Different types of vitamin D might imply different results in 25(OH)D concentration[43]. The study durations are also very different, ranging from 30 days to years. Falls assessing methods also vary, with some studies using self-report methods while others are reported by nursing home staff.

A recent review[11] arrived to very similar conclusions to those of this work.

Conclusion

Despite the heterogeneity in studies and the difficulty to compile data, vitamin D supplementation associated with calcium appears to be beneficial to older individuals, especially if vitamin D deficient and at doses above 800 IU/d, to prevent falls.

In terms of muscle strength and function, there's also a suggestion that supplementation might be beneficial, but larger and more standardized studies are necessary for safer conclusions to be made.

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ANEXOS

AIMS AND SCOPE

Acta Reumatólogica Portuguesa (ARP) is an international scientific peer reviewed journal covering clinical and experimental aspects of rheumatic diseases. The journal publishes Original Articles, Reviews, Case Reports, Images in Rheumatology, Letters to the Editor and special articles intended to improve Clinical Practice (e.g. guidelines and clinical protocols).

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- **Article published online (insert DOI)**

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Ex: Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde – Divisão de Doenças Transmissíveis, Março de 2005. http://www.dgsaude.pt/upload/membro.id/ ficheiros/ i006875.pdf. Accessed in January 25th 2008.

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