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Muscle strength and muscle mass in elderly women after cholecalciferol supplementation in Southern Brazil

Força muscular e massa muscular em mulheres idosas após suplementação com colecalciferol no sul do Brasil

Fuerza muscular y masa muscular en mujeres mayores después de suplementación con colecalciferol en el sur de Brasil

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ABSTRACT

AIMS: Vitamin D is known to be vital in sustaining musculoskeletal functions, with its deficiency may cause muscle weakness and decreased bone mineral density. Vitamin D inadequacy is highly prevalent and its deficiency or insufficiency estimated to affect one billion people worldwide. It causes secondary hyperparathyroidism, bone loss, fractures and it has been associated with a number of other conditions, such as impaired muscle function (1), we decided to verify if there is an association between 25(OH)D status and handgrip strength and with lean muscle mass after cholecalciferol supplementation in elderly women.

METHODS: We studied fifty-four postmenopausal women with serum 25(OH)D below 30 ng/mL during three months. Cholecalciferol supplementation was divided into two levels according to classification: deficient (10000 units/day) and insufficient (2000 units/day). Changes in biochemical response and in body composition were assessed using dual-x-ray energy absormetry, handgrip strength and blood tests before and after supplementation.

RESULTS: The majority of the sample were vitamin D deficient. There was no difference in the deficient group for handgrip strength after the supplementation ($p=0,489$), but PTH had a statistically significant reduction ($p=0.001$). Besides, the deficient group had a decrease in lean mass even after the intervention ($p=0.006$). The results were similar when comparing within results of the insufficient group, however lean mass remained stable ($p=0.423$).

CONCLUSION: Three-month cholecalciferol supplementation alone in elderly women with doses according to 25(OH)D serum was insufficient to change handgrip strength and total lean muscle mass, however secondary hyperparathyroidism was corrected.

KEYWORDS: Cholecalciferol; Muscle strength; Elderly.

RESUMO

OBJETIVOS: A vitamina D é conhecida por ser vital na manutenção das funções musculoesqueléticas, sua deficiência pode causar fraqueza muscular e diminuição da densidade mineral óssea. A inadequação da vitamina D é altamente prevalente e sua deficiência ou insuficiência estimada afeta um bilhão de pessoas em todo o mundo. Causa hiperparatireoidismo secundário, perda óssea, fraturas e tem sido associada a uma série de outras condições, como função muscular prejudicada, por isso decidimos verificar se há associação entre 25(OH)D e força de preensão manual e com massa muscular magra após suplementação com colecalciferol em mulheres idosas.

MÉTODOS: Foram estudadas 55 mulheres na pós-menopausa com 25(OH)D sérica abaixo de 30 ng/mL durante três meses. A suplementação de colecalciferol foi dividida em dois níveis de acordo com a classificação: deficiente (10000 unidades/dia) e insuficiente (2000 unidades/dia). Alterações na resposta bioquímica e na composição corporal foram avaliadas usando a absorciometria de raios-x de dupla energia, força de preensão manual e exames de sangue antes e após a suplementação.

RESULTADOS: A maioria da amostra era deficiente em vitamina D. Não houve diferença no grupo com deficiência para força de preensão manual após a suplementação (*p*=0,489), mas o PTH teve redução estatisticamente significativa (*p*=0,001). Além disso, o grupo deficiente apresentou diminuição da massa magra mesmo após a intervenção (*p*=0,006). Os resultados foram semelhantes quando comparados com resultados de grupo insuficiente, porém a massa magra permaneceu estável (*p*=0,423).

CONCLUSÃO: A suplementação isolada de colecalciferol por três meses em mulheres idosas com doses de acordo com níveis sérico de 25(OH)D foi insuficiente para alterar a força de preensão manual e a massa muscular total, porém o hiperparatireoidismo secundário foi corrigido.

Palavras-chave: Colecalciferol; Força muscular; Idoso.

RESUMEN

OBJETIVOS: La vitamina D es conocida por ser vital en el mantenimiento de las funciones musculoesqueléticas, su deficiencia puede causar debilidad muscular y disminución de la densidad mineral ósea. La inadecuación de la vitamina D es altamente prevalente y su deficiencia o insuficiencia afecta a mil millones de personas en todo el mundo. Causa hiperparatiroidismo secundario, pérdida ósea, fracturas y viene siendo asociada a una serie de otras condiciones, como la función muscular perjudicada, por eso decidimos verificar si hay una asociación entre 25(OH)D y la fuerza de prensión manual y con masa muscular magra después de suplementación con colecalciferol en mujeres mayores.

MÉTODOS: Se estudiaron 55 mujeres en la post menopausia con 25(OH)D sérica debajo de 30 ng/mL durante tres meses. La suplementación de colecalciferol fue dividida en dos niveles según la clasificación: deficiente (1000 unidades/día) e insuficiente (2000 unidades/día). Alteraciones en la respuesta bioquímica y en la composición corporal fueron evaluadas usando la absorciometría de rayos-x de doble energía, fuerza de prensión manual y análisis de sangre antes y después de la suplementación.

RESULTADOS: La mayoría de la muestra era deficiente en vitamina D. No hubo diferencia en el grupo con deficiencia para la fuerza de prensión manual después de la suplementación (*p*=0,489), pero la PTH tuvo reducción estadísticamente significativa (p=0,001). Además, el grupo deficiente presentó disminución de la masa magra aun después de la intervención (p=0,006). Los resultados fueron similares cuando comparados con los resultados del grupo insuficiente, sin embargo la masa magra permaneció estable (*p*=0,423).

CONCLUSIÓN: La suplementación aislada de colecalciferol por tres meses en mujeres mayores con dosis según los niveles sérico de 25(OH)D fue insuficiente para alterar la fuerza de prensión manual y la masa muscular total, pero el hiperparatiroidismo secundario fue corregido.

Palabras clave: Colecalciferol; Fuerza muscular; Anciano

INTRODUCTION

Vitamin D is known to be vital in sustaining musculoskeletal functions, with vitamin D deficiency causing muscle weakness and decreased bone mineral density[1]. Vitamin D inadequacy is highly prevalent, with vitamin D deficiency or insufficiency estimated to affect one billion people worldwide[1,2]. Hypovitaminosis D is a public health problem worldwide[3] and it is extremely common among elderly subjects[1]. It causes secondary hyperparathyroidism, bone loss, fractures and it has been associated with a number of other conditions, such as impaired muscle function[1].

Low vitamin D status, reduced renal function and low dietary intake of calcium can result in mild secondary hyperparathyroidism in which may be associated with low muscle mass in elderly populations[4]. Changes in concentrations of both 25-hydroxyvitamin-D (25(OH)D) and parathyroid hormone (PTH) may play a role in muscle mass and strength[5]. Inadequate levels of vitamin D stimulate PTH release which may have direct effects on skeletal muscle since the administration of PTH in animals can impair energy production, transfer, and utilization in skeletal muscle and also influences skeletal muscle protein and amino acid metabolism[6,7].

Serum vitamin D levels have been reported to be associated with individual components of body composition. Previous studies have indicated a significant association between low serum vitamin D and components of abnormal body composition, manifesting as osteoporosis, sarcopenia and obesity[8-12]. Observational studies found serum 25(OH)D associated with different anthropometric measures and body composition measures[13-15]. A recent study found that an increase in serum 25(OH)D was associated with 0.23 higher lean mass percentage[16]. However, it is still unclear whether vitamin D status is associated with alterations in body composition, especially in the elderly.

Studies about the effect of vitamin D in skeletal muscle are still controversial. One of the problems to deal with is about what to consider the optimal range of circulating vitamin D levels. According to the Institute of Medicine, the optimal range 25(OH)D levels in the blood should be between ≥20 ng/mL-40 ng/mL. However, The Endocrine Society recommendations are different, considering as normal blood levels between 30 ng/mL-50 ng/mL. The decision of what to consider normal, insufficient and deficient is still an ongoing debate. Moreover, these values are established considering the bone-related outcomes and so cholecalciferol supplementation doses are indicated taking into consideration the needs of bone metabolism.

The impact of cholecalciferol supplementation in the muscle mass and strength in older persons is not a consensus in the literature and, besides, the availability of works with this aim is scarce. Recently, a systematic review and meta-analysis[17] about vitamin D with or without calcium supplementation and its influence on muscle strength and mobility in community-dwelling observed no improvement in muscle strength after the administration of vitamin D. However, this study was limited on a number of research and participants.

Regarding the findings above, another systematic review and meta-analysis[18] about the effects of vitamin D supplementation on muscle function showed a small positive impact on muscle strength, especially being more effective on people aged 65 years or older compared to younger.

Many other researchers[19-22] have been investigating the effects of vitamin D supplementation on muscle function but results remain controversial.

Due to the explanations above, we decided to verify if there is an association between 25(OH)D status and handgrip strength and with total lean muscle mass after cholecalciferol supplementation in elderly women. Based on the previously mentioned works, the scope of this work is to compare the impact of cholecalciferol supplementation between two groups, considering deficient and insufficient elderly women.

METHODS

Participants and Sample Size

Women aged over 60 years were screened from March 2016 to December 2016. The study was conducted in South Brazil at a big city, Porto Alegre (30°01'S). Fifty-four subjects who had low vitamin D levels (below 30 ng/mL) were split into two groups (between 30 ng/mL-20 ng/mL 25(OH)D and below 20 ng/mL). History of chronic renal failure, arthritis, Alzheimer's disease, osteoporosis, others bone diseases, diagnosis of cancer, primary hyperparathyroidism or use of calcium, bisphosphonates, cholecalciferol or corticoid were exclusion criteria. The study was approved by the local research ethics committee and all participants gave their informed consent prior to inclusion in the study (CAAE 255294113.9.0000.5336). Deficient vitamin D group had 28 subjects and insufficient vitamin D group had 26 subjects.

Sample size (n) was calculated using the statistical software SPSS version 18.0, based on the mean of handgrip strength difference and PTH among elderly women with normal levels of vitamin D compared with low levels of vitamin D in elderly women. A significance level (p) of 5%, 80% power was considered, according to Marantes' study[20]. The variation means was 3.73 N for handgrip strength and 1.5 pmol/L for PTH. The sample size was 45, considering losses 20%, 54 participants in total.

Biochemical tests

For each participant, fasting blood samples were collected in the morning. Total calcium (Ca), creatinine (Cr), urea (Ur), intact PTH (PTH) and 25(OH)D were measured by automated standard laboratory methods. Creatinine, calcium, and urea were measured by colorimetric assay. Serum intact PTH concentrations were measured using electrochemiluminescence immunoassay; the normal range in adults is 15-68.3 pg/mL. Serum 25(OH)D concentration was measured using high-performance liquid chromatography. The range of the test for serum 25(OH)D concentrations was 3 ng/mL to 120 ng/mL. Vitamin D deficiency was defined as 25(OH)D concentration <20 ng/mL and insufficiency <30 ng/mL-20 ng/mL[23]. Blood tests were measured in the beginning and at the end of the study.

Measure of body composition

Body composition was assessed using Dual-energy X-ray absorptiometry (DXA) after laboratory tests in the beginning and in the end of the study. For the whole body DXA scans, we used Hologic™ General Electric. Total body weight was divided into bone mineral content, lean mass, fat mass, and fat percentage.

Other covariates

At the baseline visit, subjects were interviewed by investigators and all provided data regarding health conditions using a structured questionnaire which included age, weight, height, level of education, medications, preview diseases, personal antecedents of fractures in adulthood, tobacco use, physical exercise, and sun exposure.

Intervention

After laboratory and DXA tests, participants with 25(OH)D <20 ng/mL received 10000 U per day of cholecalciferol in drops during twelve weeks plus calcium carbonate 1 g/day. Participants with 25(OH)D <30 ng/mL-20 ng/mL received 2000 U per day of cholecalciferol in drops during twelve weeks plus calcium carbonate 1 g/day. All participants were oriented to maintain the same lifestyle as before the study. Every four weeks of treatment, they were recalled at the hospital to withdraw medication and bring back empty bottles. After finishing supplementation, they collected 25(OH)D, PTH, Ca and DXA.

Statistical analysis

The descriptive data were expressed by mean ± SD or the median. Statistical comparisons between groups (before and after intervention) were performed using Student's test for patients with a normal distribution. If the data were not normally distributed, comparisons between groups were made using the Mann-Whitney test. For correlations, we used Pearson's correlation test for normal distribution and Spearman's for not normally distributed. P values lower than 0.05 were considered to be statistically significant.

The percentage difference was defined by the expression below:

$$\Delta\% = 100\,\frac{var(\mathrm{T1}) - var(\mathrm{T0})}{var(\mathrm{T0})}$$

T1 = after intervention
T0 = before intervention
var = variable

RESULTS

After the beginning, one died during the study due to other cause not related to the intervention and the other gave up. Thus 52 patients with age of 72±9 years were included in the analysis. The majority of patients were non-smokers (92,6%), non-users of sunscreen (85%) and without regular sun exposure (95%). The mean BMI was 28.8±6 kg/m².

The deficient group was the majority of the sample size, 54% participants.

General characteristics variables are given in **Table 1**. There were no significant differences between subgroups with regard to the urea, creatinine, PTH, BMI. As expected difference between groups (deficient *versus* insufficient) of 25(OH)D level before supplementation was significant (13.55±3.4 ng/mL versus 25.1±3 ng/mL $p<0.000$)

Considering the deficient and the insufficient groups, 68% and 58% had secondary hyperparathyroidism, respectively. Handgrip strength and serum 25(OH)D were correlated before the intervention in the deficient

Table 1. General characteristics variables before the intervention.

Variables	Deficient (n=28)	Insufficient (n=24)	*p**
Age (years)	70±7	68±6	0.2
Serum 25(OH)D (ng/mL)	13.55±3.4	25.1±3	0.000
PTH (pg/mL)	79.2**	82.5**	0.84
Urea (mg/dL)	43±15.5	40.1±8.5	0.40
Creatinine (mg/dL)	1.02±0.21	0.97±0.1	0.34
BMI (kg/m²)	27.6±6.3	30.1±5.22	0.13
Total lean mass (kg)	37.62±5.2	39.9±5.8	0.15

* *p* significance <0.05; ** non-normal distribution

Table 2. Variables results before and after intervention for each group.

Variables	T0 Mean±SD	T1 Mean±SD	*p**
Deficient group			
PTH (pg/mL)	79.2 (18.8-217.2)**	58.24±24.25	0.001
Lean mass (g)	37630±5492	36131±5486	0.006
25(OH)D (ng/mL)	13.60±3,5	53.35 (24.4-126.2)**	0.000
Handgrip strength (lb)	36.70±14.08	37.75±11.88	0.489
Insufficient group			
PTH (pg/mL)	82.5 (49.2-176.7)**	76.45±33.54	0.018
Lean mass (g)	39874±5815	40272±6270	0.423
25(OH)D (ng/mL)	25.13±3.01	35.95 (27.6-47.5)**	0.000
Handgrip strength (lb)	48.42±11.92	47.95±11.74	0.707

* *p* significance <0.05; ** non-normal distribution.

Table 3. Comparison means of percentage variation between groups

Variables	Deficient (Δ%)	Insufficient (Δ%)	*p**
25(OH)D	328±209	45±29	0,000
Handgrip strength**	0±30	0±15	0,565
PTH	-27±23	-11±24	0,028
Lean mass	-3,8±6	0,9±5	0,006

* *p* significance <0.05; ** non-normal distribution.

group (r=0.35 *p*=0.05). This correlation was not found in the insufficient group. There was an inverse linear correlation between hyperparathyroidism (PTH >68 pg/mL) and handgrip strength lower than 20 kg in deficient subgroup (r=-0.65 *p*=0.009). **Table 2** shows the comparison between means before and after intervention for each group. During a 3-month intervention, there was no difference in the deficient group for handgrip strength after the supplementation (*p*=0,489), but PTH had a statistically significant reduction (*p*=0.001). Besides, the deficient group had a decrease in lean mass even after the intervention (*p*=0.006). The results were similar when comparing within results of the insufficient group, however lean mass remained stable (*p*=0.423). When comparing the percentage difference between groups, PTH and lean mass had lower variation in the insufficient group as showed in **Table 3**.

DISCUSSION

This study demonstrated that 54% of the participants had vitamin D deficiency. This number stands out when compared to data from Brazilian literature that are scarce. According to the literature[24], the estimates are around 41.9% of insufficiency and 15.4% of vitamin D deficiency. This difference can be attributed to the fact that most of the Brazilian studies on 25(OH) D levels occur in São Paulo with the geographical position 23º34'S, while Porto Alegre presents latitude 30°01'S. The southern position of the city may favor the lower incidence of ultraviolet rays and, therefore, lower serum 25(OH)D. Participants had a handgrip strength of less than 44 lbs (<20 kg) (**Table 2**). According to Cruz-Jentoft et al.[25] one of the determinants of sarcopenia is handgrip strength lower than 20 kg. Therefore, this direct correlation between serum 25(OH)D levels and handgrip strength prior to intervention corroborates that hypovitaminosis D increases the risk of sarcopenia. In our study, the same correlation was met in the deficient group between handgrip strength and 25(OH)D. Besides, a recent study[5] demonstrated that vitamin D deficiency was present in 41% of a sample of elderly women with sarcopenia. Another prospective, population-based study[4] found that low serum 25(OH)D levels and high PTH levels increase the risk of sarcopenia in individuals over 65 years of age. In addition, these studies showed that the risk of sarcopenia was higher in subjects with baseline 25(OH)D levels below 20 ng/mL based on handgrip strength.

Although there are some studies[19,26,27] associating muscle strength with vitamin D, this issue still shows conflicting results. Marantes et al.[20] found no consistent association between 25 (OH) D or PTH levels with muscle mass or strength in the population aged over 50 years. In the same line, a study with older elderly did not confirm the association between serum 25(OH)D and handgrip strength[21].

In this study, there was no significant variation in either lean muscle mass or handgrip strength after vitamin D supplementation. These results are in accordance with some literature that demonstrated that vitamin D supplementation had no significant effect on muscle mass[20,21,28]. However, these findings are still conflicting. Recently, a study[29] demonstrated that treatment with vitamin D showed beneficial effects on appendicular muscle mass in pre-sarcopenic older Lebanese men and women. Although, it had no effect on muscle strength relative to placebo. Another study[30] with prefrail and frail older adults and cholecalciferol supplementation in different doses during six months also demonstrated that there were no significant change in muscle strength and physical performance. In this search, it was used different doses of cholecalciferol supplementation as Lebanese study above. The different protocols of doses (2000 and 10000 U) does not affect results, because the doses are defined according to serum levels of 25(OH)D (insufficient >20 ng/mL-29.9 ng/mL and deficient <20 ng/mL) based on the physiological needs already described in the literature[2] to reach vitamin D levels of normality.

Although vitamin D supplementation in this study was not associated with an increase in handgrip strength nor in lean muscle mass, there was a significant reduction in PTH after supplementation and a significant inverse correlation between serum 25(OH)D and PTH after the intervention. These results are in agreement with the literature[31], which an inverse correlation between 25(OH)D and PTH is presented. Evidence indicates that the use of vitamin D or calcium in combination with vitamin D supplementation might be an effective strategy for suppressing hyperparathyroidism and minimizing the possible negative effects on muscle mass[32].

With regard to the limitations of the present study, the small sample size, the study design, short duration and lack of other variables that influence muscle strength, it can only observe associations, therefore a longitudinal and prospective study with control group should be conducted to determine differences in cause and effect. It is possible that only cholecalciferol supplementation is insufficient to have a positive impact on increasing lean muscle mass. Modulation of muscle strength is a complex process. Vitamin D is one of several factors involved such as diet, hormones response, exercise. A long term study associated with other variables needs to be explored.

In conclusion, our results suggest that cholecalciferol supplementation affects PTH levels and it's associated with secondary hyperparathyroidism, especially in deficient vitamin D participants. However, even after hyperparathyroidism treatment it, was insufficient to change handgrip strength and total lean muscle mass with 12-week treatment.

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