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# Vitamin D and muscle function

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In 1922, at Johns Hopkins University in Baltimore, Professor McCollum discovered a factor, which has since been referred to as vitamin D, following the alphabetical order of the other vitamins identified up to that time. It is capable of curing rickets in children and osteomalacia in adults. Diseases in which, as we know from the first scientific descriptions published in London in the mid-seventeenth century, muscle involvement consisting of weakness and generalized hypotonia is associated with bone involvement, its main characteristic. Therefore, since the discovery of vitamin D, it has been associated not only with bone health but also with muscle health[1]. Paradoxically, at present, there is no consensus on the potential beneficial effects of vitamin D supplementation on muscle function, balance and risk of falls, a situation highlighted in the last meta-analysis published by Bolland et al.[2], who review in 81 randomized clinical trials (RCTs) that include 53,537 participants the effect of vitamin D on fractures and falls as a primary outcome. The pooled analyses showed that vitamin D supplementation had no effect on falls (37 RCTs, n=34,144, RR=0.97, 95% confidence interval -0.93 to 1.02), what the authors concluded that "vitamin D supplementation does not exert significant effects in falls", affirming that "potential future trials will probably not alter those conclusions, and that, therefore, there is little justification for the use of vitamin D supplements. to maintain or improve musculoskeletal health, indicating that clinical guidelines should reflect these findings"[2]. From this publication, many physicians and patients could mistakenly conclude that they can stop prescribing or taking vitamin D supplements, which is a potentially dangerous message, given the high prevalence of vitamin D deficiency in Spain[3].

Loss of muscle strength and/or function, severe invalidating myopathy predominantly proximal with diffuse muscular or skeletal pain in adults, generalized muscle atrophy and electromyographic abnormalities, such as polyphasic motor unit, potentials with shortened duration and decreased range, involvement of Type II muscle fiber atrophy (of rapid contraction) and marked fatty infiltration are findings in severe and sustained vitamin D deficiency, in severe renal insufficiency, or in the congenital absence of the CYP27B1 gene due to inability to adequately synthesize 1,25 dihydroxyvitamin D (1,25 DHCC), hormonally active metabolite of the endocrine system of vitamin D, with rapid improvement of muscle function after vitamin D or 1,25 DHC supplementation in these patients. More subtle changes in muscle function can be observed in subjects with less severe and perhaps less chronic vitamin D deficiency[4].

In our current issue, Gómez Alonso et al.[5], present an article in which they observe that in patients of both sexes of the cohort EVOS (European Study of Vertebral Osteoporosis) that maintain serum levels of calcidiol higher than 20 ng/mL present greater grip strength in the hands, maintenance of daily activities and lower losses of bone mineral density in the hip, measured by densitometry in the proximal extremity of the femur[5], proven beneficial effects that constitute the novelty of this study. The mechanisms of action of vitamin D in muscle biology and the impact of its deficiency show that a possible link between muscle and vitamin D is plausible[6].

In fact, observational studies show a correlation between poor vitamin D status and frailty, muscle weakness or fatigue and falls. While a meta-analysis of 15 intervention studies performed on a total of 2,866 participants did not reveal a significant improvement in hand grip strength or walking tests[7], other meta-analyzes showed a discrete beneficial effect on muscle strength and the balance[8], or only showed benefits in people with the levels of 25 hydroxyvitamin D (25OHD) lower (<10 ng/mL)[9]. Beaudart et al. they also found no effect on muscle mass, but observed a small positive effect on muscle strength in patients older than 65 years with vitamin D deficiency (<12 ng/mL)[10]. These data are supported by studies in patients with severe vitamin D deficiency in which the administration of vitamin D improves the symptoms of fatigue, fatigue and pain, and energy recovery after physical exercise demonstrated *in vivo* by resonance spectrometry techniques. nuclear magnetic[11]. Some intervention studies show that administration of 800-1,000 IU of vitamin $D_3$ per day, or slightly more than its weekly equivalent, improves strength and balance in the elderly with vitamin D deficiency[12-14].

In addition to function, we have multiple observational studies that relate vitamin D deficiency with frailty and the incidence of falls. Thus, an analysis of 18 studies revealed an odds ratio (OR) of falls significantly greater than 1.23-1.44 for subjects with 25OHD concentrations below 10-20 ng/mL[15].

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Muscle strength (especially proximal) can be modestly improved with vitamin D supplementation in the elderly with serum levels of 25OHD <12 ng/mL[16]. According to this concept, supplementation for 9 months with 1,000 IU of vitamin $D_3$ daily significantly decreased the first falls and the total of them in more than 50% of patients[13].

Several trials have examined the effect of vitamin D supplementation on fall rates. A meta-analysis of 9 RCTs showed that daily supplementation of less than 600 IU of vitamin D was not effective, while administration of between 700 and 1,000 IU significantly decreased the risk of falls[17].

In a Cochrane review, vitamin D supplementation reportedly reduced the risk of falls in institutionalized patients (RR=0.63, 95% CI: 0.46-0.85)[18]. In outpatients, supplementation with vitamin D did not reduce the risk of falls in a meta-analysis of all RCTs combined (RR=0.57, 95% CI 0.37-0.89), but it reduced the risk of falls in four studies that selected patients with lower levels of vitamin D (all four studies had cutoffs of <12, <20, <24 and <31 and ng/mL, risk index=0.70, 95% CI %: 0.56 to 0.87). The 30% reduction in the risk of falls in these studies (risk index=0.70, 95% CI 0.56 to 0.87) was significantly lower than in the other 9 studies evaluated in the meta-analysis that did not select participants according to vitamin D status (risk index=1.00, 95% CI 0.93-1.07, interaction p<0.01)[19].

Supporting these data, a more recent meta-analysis of RCTs found that supplementation with vitamin D reduced the rate of fall only in subjects with an initial serum concentration of 25OHD below 20 ng/mL[20].

Megadoses employ intermittent supplementation regimens with long and variable dosing intervals of 100,000 IU of colecalciferol orally, every four months[21], or a month[22]; 30,000 IU of vitamin $D_2$ intramuscularly once a year[21,23] or 500,000 IU per year[24], of which its absence of effects or, even, the negative effects are known, increasing the risk of fractures and falls. They are, therefore, not recommended in guidelines or in usual practice because they are associated with oscillations in serum 25OHD concentrations (which means that serum concentrations do not remain above the normal threshold throughout the treatment period), and they have become obsolete and ineffective or harmful. Therefore, these designs with this posology should not be included in the meta-analyzes[25-27] and, however and surprisingly, have a weight of 50% of the meta-analysis proposed by Bolland et al.

In a study of elderly women with baseline vitamin D deficiency, falls occurred in 48% of the group treated with 24,000 IU of vitamin $D_3$, in 67% of the group treated with 60,000 IU of vitamin $D_3$, and in 66% of the group treated with vitamin $D_3$ group that received 24,000 IU of vitamin $D_3$ or more than 300 µg of calcifediol; the authors concluded from a post hoc analysis that 25OHD concentrations greater than 45 ng/mL may be associated with an increased risk of falls[28]. Along the same lines, Smith et al.[29], in a study conducted in women with vitamin D deficiency (<15 ng/dL) treated with a full range of daily doses of vitamin $D_3$ (400-4,800 IU) vs. placebo for 1 year, they found a U-shaped association in falls, whose nadir occurred in the dose range of 1,600 to 3,200 IU per day; a greater number of falls were observed in the patients who received the highest doses of vitamin D.

Thus, in our usual practice we must be clear that the available evidence consistently indicates that vitamin D has important physiological effects on skeletal and cardiac muscle, that these effects are observed consistently when patients included in the studies have 25OHD levels. with cut-off points at least below 30 ng/mL. That the administration between 800 and 1,000 IU daily of vitamin $D_3$ are recommended, except in obese patients or in treatments that increase the catabolism of vitamin $D_3$[30], to obtain the proposed benefits; that higher doses may be harmful and that massive doses that become ineffective or harmful should not be administered, increasing the risk of falls and, potentially, the rate of fractures. So, maintaining adequate levels of 25OHD in patients should be a constant public health aim.

To obtain results, treatment must be maintained long-term both individually and in the design of clinical trials. Administration to patients with normal 25OHD serum levels will not help the patient, will not improve muscle health, nor will it prevent falls and, probably, not achieve other health objectives.

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## Bibliography

1. O'Riordan JLH, Bijvoet OLM. Rickets before the discovery of vitamin D. Bonekey Rep. 2014;3:478.
2. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018;6:847-58.
3. Quesada-Gómez JM, Díaz-Curiel M, Sosa-Henríquez M, Malouf-Sierra J, Nogues-Solan X, Gómez-Alonso C, et al. Low calcium intake and inadequate vitamin D status in postmenopausal osteoporotic women. J Steroid Biochem Mol Biol. 2013;136:175-7.
4. Bouillon R. Extra-skeletal effects of vitamin D. Front Horm Res. 2018,50:72-88.
5. Gómez Alonso C, Díaz López JB, Rodríguez Rebollar A, Martínez Arias L, Martín Vírgala J, Martín Carro B, et al. Niveles de calcidiol y mantenimiento de la función muscular, capacidad funcional y densidad mineral ósea en población española no seleccionada. Rev Osteoporos Metab Miner. 2019;11(1): 6-11.
6. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev. 2013;34:33-83.
7. Rosendahl-Riise H, Spielau U, Ranhoff AH, Gudbrandsen OA, Dierkes J. Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis. J Hum Nutr Diet. 2017; 30:3-15.
8. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and metaanalysis. J Am Geriatr Soc. 2011;59: 2291-300.
9. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int. 2011;22:859-71.
10. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014; 99(11):4336-45.
11. Sinha A, Hollingsworth KG, Ball S, Cheetham T. Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. J Clin Endocrinol Metab. 2013; 98(3):E509-13.
12. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20(2):315-22.
13. Cangussu LM, Nahas-Neto J, Orsatti CL, Poloni PF, Schmitt EB, Almeida-Filho B, et al. Effect of isolated vitamin D supplementation on the rate of falls and postural balance in postmenopausal women fallers: a randomized, double-blind, placebo-controlled trial. Menopause. 2016;23(3):267-74.
14. Lips P, Binkley N, Pfeifer M, Recker R, Samanta S, Cohn DA, et al. Once-weekly dose of 8400 IU vitamin D3 compared with placebo: effectson neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am J Clin Nutr. 2010;91 (4):985-91.
15. Annweiler C, Beauchet O. Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a 'forgotten step'. J Intern Med. 2015; 277(1):16-44.
16. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014; 99(11):4336-45.
17. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomized controlled trials. BMJ. 2009;339:b3692.
18. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;12:CD005465.
19. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012(9):CD007146.
20. LeBlanc ES, Chou R. Vitamin D and falls-fitting new data with current guidelines. JAMA Intern Med. 2015;175 (5):712-3.
21. Lyons RA, Johansen A, Brophy S, Newcombe RG, Phillips CJ, Lervy B, et al. Preventing fractures among older people living in institutional care: a pragmatic randomized double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007;18(6):811-8.
22. Khaw KT, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo CA Jr, et al. Effect of monthly high-dose vitamin D supplementation on falls and nonvertebral fractures: secondary and post-hoc outcomes from the randomized, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017 Jun;5(6):438-47.
23. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women-a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007;46 (12):1852-7.
24. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303(18):1815-22.
25. Bolland MJ, Grey A, Avenell A. Assessment of research waste part 2: wrong study populations- an exemplar of baseline vitamin D status of participants in trials of vitamin D supplementation. BMC Med Res Methodol. 2018;18(1):101.
26. Bolland MJ, Grey A, Avenell A. Assessment of research waste part 1: an exemplar from examining study design, surrogate and clinical endpoints in studies of calcium intake and vitamin D supplementation. BMC Med Res Methodol. 2018;18(1):103.
27. Scragg R. Emerging evidence of thresholds for beneficial effects from vitamin D supplementation. Nutrients. 2018;10(5). pii: E561.
28. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med. 2016;176(2):175-83.
29. Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Mol Biol. 2017;173:317-22.
30. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int. 2010;21(7):1121-32.