Journal of Steroid Biochemistry and Molecular Biology 173 (2017) 313–316

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Vitamin D and muscle function

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ARTICLE INFO

Keywords:
Vitamin D
Muscle mass
Muscle performance
Falls

ABSTRACT

Muscle weakness is a hallmark of severe vitamin D deficiency, but the effect of milder vitamin D deficiency or insufficiency on muscle mass and performance and risk of falling is uncertain. In this presentation, I review the evidence that vitamin D influences muscle mass and performance, balance, and risk of falling in older adults. Special consideration is given to the impact of both the starting 25-hydroxyvitamin D [25(OH)D] level and the dose administered on the clinical response to supplemental vitamin D in older men and women. Based on available evidence, older adults with serum 25(OH)D levels < 40 nmol/L appear most likely to improve their muscle performance with supplementation. The vitamin D dose range of 800–1000 IU per day has been effective in many studies; lower doses have generally been ineffective and several doses above this range have increased the risk of falls. In conclusion, older adults with serum 25(OH)D levels < 40 nmol/L are likely to have fewer falls if supplemented with 800–1000 IU per day of vitamin D.

1. Introduction

The declines in muscle mass and function that occur with aging have significant clinical consequences, including frailty, increased risk of falling with the associated fractures and other injuries, and death. Exercise is highly effective in retarding muscle wasting and loss of function, but many older adults do not exercise enough to prevent these changes. The diet is important for preserving muscle mass and function. Most notably dietary protein provides the substrate for muscle building and it also stimulates the anabolic process by stimulating the production of IGF-1. Vitamin D is also important, as evidenced by the profound muscle weakness that accompanies frank vitamin D deficiency. The role of vitamin D insufficiency on muscle is less certain. The purpose of this paper is to review the changes in muscle that occur with aging, the similarities of these changes to the changes observed in vitamin D deficiency, and the impact of vitamin D supplementation on muscle mass and function, on balance, and on risk of falling.

2. Muscle changes with aging

2.1. Tissue level changes

Type I fibers have a slow contraction time and low force generation but a long duration of use (hours) and are often described as ‘endurance’ fibers. In contrast, Type II fibers have a rapid contraction time and high force generation but relatively short endurance (minutes). Type II fibers are ‘first responders’ to prevent falling.

With aging, there is a general decline in muscle fibers [1], but the loss of the Type II fibers is greater than the loss of Type I fibers. The preferential loss of Type II fibers appears to result from the decline in Type II stem cells with aging [1]. The fractional synthesis rate (FSR) of mixed muscle proteins has been assessed in young, middle aged and older adults [2]. In both the middle-aged and older adults, the FSR was half that of the young adults [2]. An age-related decrease in mitochondrial ATP production likely contributes to the decrease in FSR [3]. Finally, motor neurons enervating muscle decline with aging. Brown et al. documented a significant inverse association of thenar muscle neurons with age in 44 healthy subjects aged 13–89 years [4].

2.2. Clinical consequences

With aging there is loss of muscle mass (approximately 2 kg per decade after age 50 years), a greater loss in muscle strength, and an even greater loss of muscle power [5]. Goodpaster et al. have documented 3-yr changes in leg lean mass and knee extensor strength in adults in age 70 years and older in participants in the Health ABC study. They found that lean mass declined by an average of 1% per year whereas knee extensor strength declined by a higher rate of 3% per year [6]. These rates of decline were similar in men and women and in African-Americans and whites [6].

Age-related declines in muscle mass and strength ultimately lead to increased risk of falling. One in three adults age 65 years and older and one in 2 age 80 years and older will fall [7]. Falls have dire consequences including fractures, other injuries, and self-imposed

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http://dx.doi.org/10.1016/j.jsbmb.2017.03.018
Received 19 July 2016; Received in revised form 17 March 2017; Accepted 20 March 2017
Available online 22 March 2017
0960-0760/

inactivity and isolation as a consequence of fear of falling. Of the 10 most common risk factors for falls, muscle weakness, gait deficit, and balance deficit rank in the top four, the fourth being a history of falls [8]. Reducing the rates of decline in muscle mass and function therefore has great potential to reduce the risk of falls and to allow seniors to live independently for longer.

3. Vitamin D and muscle

3.1. Physiology

It is well known that profound vitamin D deficiency is associated with muscle pain and extreme weakness. In adults with profound vitamin D deficiency, muscle biopsies show atrophy of type II muscle fibers, a pattern similar to that seen with aging. Vitamin D receptors (VDRs) have been identified in muscle tissue [9]. The number of VDRs in muscle appears to decline with aging [10]. A recent small study suggests that vitamin D supplementation increases the number of VDRs in muscle. In this study of 21 elderly women with a low mean starting serum 25(OH)D level of 46 nmol/L, treatment with 4000 IU per day of vitamin D_3, when compared with placebo, significantly increased intramyonuclear VDRs in type II muscle fibers whereas changes in type I fibers did not reach significance [9]. In this study, the cross-sectional area of muscle fibers also increased significantly in response to the treatment [9].

3.2. Muscle performance

The amount of vitamin D and the associated serum 25(OH)D level required for maximal muscle performance is a matter of ongoing investigation. It is beyond the scope of this presentation to review all of the evidence, but I will cite a couple of examples of cross-sectional and observational studies, two meta-analyses of randomized clinical trials (RCTs), and more recently published trials. In the cross-sectional National Health and Nutrition Examination Survey (NHANES) in the US, there was an inverse association of serum 25(OH)D with the timed walk and the sit-to-stand tests, with the steepest part of the curve seen at low and low-normal serum 25(OH)D levels [11]. Consistent with this was the observation by Wicherts et al. that older men and women with serum 25(OH)D levels below 25 nmol/L performed less well on the 3-m walk, the sit-to-stand test, and tandem stands than those with serum 25(OH)D levels > 75 nmol/L [12]. These studies by design are not able to establish causality.

A number of high quality vitamin D intervention trials examining muscle outcomes have been performed and they have had rather mixed results. We will examine some of these trials giving particular attention to the mean starting serum 25(OH)D levels of the participants and to the serum 25(OH)D levels achieved during treatment. In 2009, Stockton et al. published a meta-analysis of 17 RCTs examining the effect of vitamin D on muscle performance [13]. Their conclusion was that "vitamin D supplementation does not have a significant effect on muscle strength in adults with baseline serum 25(OH)D levels > 25 nmol/L". Two trials in participants with low mean starting serum 25(OH)D levels < 15 nmol/L did show improvement in muscle strength when supplemented with 1000 IU of vitamin D_2 [14] and when exposed to regular sunshine [15]. A more recent meta-analysis published in 2014 by Beaudart et al. included 30 RCTs and 5615 participants with a mean age of 61 years [16]. They found a small significant improvement in muscle strength with vitamin D supplementation, but no effect of vitamin D on muscle mass or power [16]. Several large trials have been published since the 2014 meta-analysis. Hansen et al. found no effect of either 800 IU of vitamin D daily or 50,000 IU every two weeks on the sit-to-stand or timed walk tests in postmenopausal women mean age 61 years [17]. Their mean starting 25(OH)D level was 52.5 nmol/L. Similarly, Bischoff-Ferrari et al. tested 3 vitamin D treatment regimens in 200 men and women age 70 years and older: 24,000 IU of vitamin D_3 per month (equivalent to 800 IU per day), 60,000 IU of vitamin D_3 per month, and 24,000 IU of vitamin D_3 plus 300 μg of calcifidiol per month [18]. There were no significant differences in the Short Physical Performance Battery (SPPB) scores in the three groups after one year of treatment. The mean starting serum 25(OH)D levels were similar at about 47 nmol/L in the three groups and they increased to 80 nmol/L, 100 nmol/L and 112 nmol/L, respectively, after one year of treatment.

Despite a voluminous amount of evidence, the role of vitamin D on muscle strength, mass and power in older adults is not fully defined largely because few trials have been done in vitamin D insufficient subjects. Current evidence, although limited, suggests that supplementation may benefit muscle in older adults with 25(OH)D levels < 25 or 30 nmol/L. Further evidence is needed.

3.3. Balance

A few studies have assessed the effect of vitamin D on balance. Pfeifer et al. [19] found that treatment with 800 IU of vitamin D_3 per day when compared with placebo reduced body sway in 242 seniors, mean age 77 years. The participants had a mean starting serum 25(OH)D level of 55 nmol/L. Both the vitamin D and placebo groups received a calcium supplement. It is theoretically possible that the calcium supplement affected balance in this trial. Similarly, Cangussu et al. found that supplementation with 1000 IU of vitamin D_3 when compared with a true placebo, significantly reduced body sway in 160 Brazilian women who had a starting serum 25(OH)D level of 37.5 nmol/L [20]. While far fewer in number, these two trials showed similar favorable effects of vitamin D supplementation on balance.

3.4. Falls

Given the potential effects of vitamin D on muscle strength and balance described above, it is reasonable to expect that vitamin D supplementation may also reduce risk of falling in vitamin D insufficient elders. In 2009, Bischoff-Ferrari et al. reported a meta-analysis of published trials assessing the effect of vitamin D on risk of falling [21]. The team assessed the effect of both the administered dose of vitamin D and the received dose (calculated as the administered dose x the proportion taken, as estimated from compliance records). Several trials were included in this analysis [19,22–27]. The relative risk of falling as a function of dose administered is shown in Fig. 1 [28]. The Broe et al. trial appears several times in the figure because it tested several doses of vitamin D [22]. Overall there was a significant 27% reduction in risk of falling with vitamin D treatment [28]. There was a significant 34% reduction in trials giving 700–1000 IU of vitamin D per day, but no significant reduction in trials administering lower doses in the range of

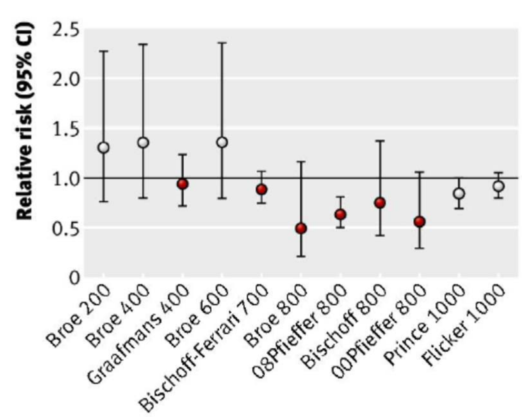

Fig. 1. Relative risk of falling with vitamin D supplementation. Filled circles are trials with oral vitamin D_3 and open circles trials with oral vitamin D_2. Numbers after author names are doses administered to the treatment group. From Bischoff-Ferrari et al. [28], with permission.