Physical Performance, Muscle Strength, Falls, and Vitamin D

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Abstract

Vitamin D status is associated with muscle strength, physical performance, and falls as has been observed in many epidemiological studies. When serum 25-hydroxyvitamin D increases from very low levels to 50 nmol/l, physical performance increases and plateaus with higher levels of serum 25(OH)D. Randomized controlled clinical trials were performed with vitamin D alone or with vitamin D and calcium with the endpoint falls. Eight of thirteen studies showed a significant decrease of fall incidence, and in six of seven significant double-blind studies, vitamin D was combined with calcium and compared with double placebo. The decrease of fall incidence ranged from −19 to −70 %. One study with vitamin D3 dose of 500,000 IU once per year showed an increased fall incidence in the vitamin D group compared with the placebo group. The increased fall incidence was observed in the first 3 months after the high vitamin D dose. Eight meta-analyses have been performed on the effects of vitamin D on fall incidence. One may conclude from these that vitamin D3 is effective in doses of 800 IU/day or more and preferably combined with calcium. Vitamin D may influence muscle strength through genomic and non-genomic pathways. The active metabolite 1,25-dihydroxyvitamin D binds to the nuclear vitamin D receptor and can activate more than 300 genes, and it may also bind to a membrane receptor thus activating second messengers leading to fast calcium influx. Vitamin D may influence muscle

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P. Burckhardt et al. (eds.), *Nutritional Influences on Bone Health*,
DOI 10.1007/978-1-4471-2769-7_19, © Springer-Verlag London 2013

fiber proliferation and differentiation, and calcium influx and calcium transport to the sarcoplasmic reticulum. There is still some debate on the presence of the vitamin D receptor in human muscle tissue because it was demonstrated by some but not by other investigators.

In conclusion, vitamin D can influence muscle strength, balance, and prevent falls.

Keywords

Physical performance • Muscle strength • Falls • Vitamin D • Vitamin D receptor • Genomic and non-genomic pathways • Meta-analyses • Prevention of falls

Introduction

Vitamin D is necessary for calcium absorption and mineralization of new bone matrix, the osteoid. Vitamin D deficiency results in rickets in children and osteomalacia in adults. Long-term less severe vitamin D deficiency leads to secondary hyperparathyroidism and bone loss and contributes to osteoporosis. More recently, a relationship has been observed between vitamin D status, muscle strength, physical performance, and falls. Vitamin D and calcium supplementation can decrease the incidence of hip fractures and other non-vertebral fractures as was shown by Chapuy et al. [1]. The effect of supplementation on the incidence of other non-vertebral fractures was already visible within 6 months, leading to the suggestion that vitamin D and calcium might prevent falls. In this chapter, the relationship between vitamin D and physical performance, muscle strength, and falls will be discussed. Subsequently, the effects of supplementation in randomized clinical trials on fall prevention will be described. These trials have led to several meta-analyses on the effects of vitamin D on the incidence of falls. Finally, the mechanistic basis of the described relationships will be reviewed with an emphasis on genomic and non-genomic pathways. The chapter will end with a conclusion and research agenda.

Epidemiological Association Studies

A relationship between physical performance tests and vitamin D status was observed in the National Health and Nutrition Examination Survey (NHANES III). The timed walking test and the timed chair stands (five chair stands without using hands) showed a fast improvement when serum 25 hydroxyvitamin D increased from below 20 to 50 nmol/l. With higher levels, the needed time tended to plateau [2]. Similar data were obtained in the Longitudinal Aging Study Amsterdam, an epidemiological study in a representative sample of the Dutch population. Almost 50 % of the participants of 65 years and older were vitamin D deficient or insufficient (serum 25(OH)D < 25 or 25–50 nmol/l, respectively). In this study physical performance tests and a fall follow-up were done. The physical performance score consisting of a walking test, five chair stands, and tandem stand was scored on a scale from 0 to 12. When serum 25(OH)D increased from below 10 to 50 nmol/l, physical performance increased 5 points, and following adjustment for age, sex, chronic diseases, and BMI, the increase with improving vitamin D status still was more than 2 points on the scale of 12 [3]. A plateau of the physical performance score vs. vitamin D status was seen above 50 nmol/l. In the LASA study vitamin D deficiency could predict the loss of muscle strength and muscle mass during 3 years of follow-up. Loss of muscle strength was more than twice as frequent when serum 25(OH)D was below 25 nmol/l than with higher values [4]. In the LASA study, a fall follow-up was done every 3 months during 3 years with a fall calendar. When serum 25(OH)D was lower than 25 nmol/l, the risk ratio for two falls or three falls was more than five in comparison with the participants with a serum 25(OH)D higher than 25 nmol/l. This was apparent below 75 years of age, but above

75 years the relationship was no longer significant [5]. An Australian study [6] showed similar risk factors for falling. Higher serum 25(OH)D levels and higher weight were protective for falling, while antipsychotic treatment, cognitive decline, a past Colles fracture, and being a wanderer all increased the risk for falling.

Randomized Clinical Trials

An intervention study [7] in 148 older women with vitamin D3 800 IU/day vs. placebo for 8 weeks reduced sway by 9 % and reduced the fall incidence. This group repeated this study in 242 community-dwelling seniors, and the fall incidence decreased 39 % ($p<0.01$) in the vitamin D group in comparison to the placebo group [8]. An Australian study comparing vitamin D 1,000 IU/day vs. placebo in 540 older persons in residential care showed a decrease of fall incidence ($p<0.05$) and a lower fracture incidence in the vitamin D group, but the latter was not significant [9]. Altogether at least 13 studies have been performed, and 8 of these showed a significant decrease of fall incidence [10–18, 20] (Table 19.1). In six of seven double-blind studies, vitamin D was combined with calcium and compared with double placebo. The decrease of fall incidence ranged from −19 to −70 %. In four studies the change was not significant, and one Australian study with a large dose of 500,000 IU once per year showed an increased fall incidence in the vitamin D group compared with the placebo group. In this study [18], the fall incidence was 15 % higher in the vitamin D group, and the fracture incidence was higher, but this was only borderline significant. It turned out that the increase in fall and fracture incidence was visible in the first 3 months after the high vitamin D dose. During these 3 months mean serum 25(OH)D increased to levels higher than 120 nmol/l. This led to the conclusion that a high dose once per year is not the way to administer vitamin D, and the high peak levels of serum 25(OH)D may be deleterious. We performed a multicenter study comparing the effect of 8,400 IU/week vs. placebo, but there was no effect on the physical performance tests and sway. However, when baseline sway was high, a decrease of sway was seen in the vitamin D group [19]. Recently, a short-term intervention study with protein and vitamin D in malnourished older adults showed a decrease of fall incidence in the intervention group compared with the control group [20]. It is difficult to deduct a threshold serum 25(OH)D necessary for fall

Table 19.1 The effect of vitamin D on fall incidence: results of randomized clinical trials

Reference	Pat N	Vit D dose	Calcium	Baseline 25(OH)D[a]	Posttreatment 25(OH)D[a]	Outcome *n* of fallers
Graafmans et al. [10]	330	400 IU/day	–	27	55	NS
Pfeifer et al. [7]	148	800 IU/day	1,200 mg/day	26	66	−40 %
Latham et al. [11]	243	300,000 IU	–	38	61	NS
Harwood et al. [12]	150	800 IU/day	1,000 mg/day	29	50	−52 %
Flicker et al. [9]	625	1,000 IU/day	600 mg/day	<40		−27 %
Bischoff-Ferrari et al. [13]	445	700 IU/day	500 mg/day	70	104	−46 %(women)
Law et al. [14]	223	100,000 IU/3 m	–	47	82	NS (men)
Broe et al. [15]	124	800 IU/day	–	53	75	−72 %
Prince et al. [16]	302	1,000 IU/day	1,000 mg/day	45	60	−19 %
Pfeifer et al. [8]	242	800 IU/day	1,000 mg/day	55	84	−27 %
Kärkkäinen et al. [17]	1,645	800 IU/day	1,000 mg/day	50	75	NS[b]
Sanders et al. [18]	2,256	500,000 IU/year	–	49	120[c]	+15 %
Neelemaat et al. [20]	210	576 IU/day	500 mg/day[d]	40	65	−59 %

[a]25(OH)D nmol/l
[b]30 % less multiple falls
[c]After 1 month 120 nmol/l, after 3 months 90 nmol/l
[d]The intervention group received a protein-rich diet in addition

Table 19.2 The effect of vitamin D on fall incidence: results of meta-analyses

Reference	*N*	RR	Remarks
Latham et al. [23]	4	0.99 (0.89–1.11)	
Bischoff-Ferrari et al. [24]	5	0.78 (0.64–0.92)	incl 2 alphacal[b]
Jackson et al. [25]	5	0.88 (0.78–1.00)	
Richy et al. [26]	11	0.92 (0.86–0.99)	incl 2 alphacal[b]
Cochrane, community [27]		0.96 (0.92–1.01)	
Cochrane, nursing care [27]		0.98 (0.89–1.09)[a]	
Bischoff-Ferrari et al. [28]	8	0.87 (0.77–0.99)	Dose split (high/low)
Kalyani et al. [29]	10	0.86 (0.79–0.93)	Dose 800 (IU/day)

[a]Rate of falls 0.72 (0.55–0.95)
[b]These meta-analyses include two studies done with the active vitamin D metabolite alphacalcidol

prevention. It may be around 50 or 60 nmol/l, near the recommendation of the Institute of Medicine [21]. A vitamin D dose of 800 IU/day will increase serum 25(OH)D to above 50 nmol/l in most older persons.

Meta-analysis

A meta-analysis of studies on the effect of vitamin D on muscle strength, gait, and balance showed a significant improvement of sway and the timed up and go test. An increase of lower extremity strength or improvement of distance walked (gait) was not obtained [22]. At least eight meta-analyses have been performed on the effect of vitamin D on fall incidence. The outcomes of the meta-analyses were different. Two meta-analyses contained studies with an active vitamin D metabolite (alphacalcidol), and one meta-analysis of Bischoff-Ferrari compared lower and higher doses showing a decreased fall incidence only with the higher dose. Another meta-analysis only included studies with vitamin D3 800 IU or more [23–29] (Table 19.2). One may conclude from these meta-analyses that vitamin D3 only is effective in higher doses of 800 IU/day or more and particularly in combination with calcium.

Mechanistic Studies

Vitamin D may influence muscle strength through genomic and non-genomic pathways [30]. The active vitamin D metabolite, 1,25-dihydroxyvitamin D, binds to the nuclear vitamin D receptor after entering the cell and can activate more than 300 genes. The alternative is binding to a membrane receptor, thus activating second messengers leading to a fast calcium influx. The active vitamin D metabolite, 1,25-dihydroxyvitamin D, may influence muscle fiber proliferation and differentiation. It may influence calcium influx and phosphate transport and especially calcium transport to the sarcoplasmic reticulum. On the other side, 1,25-dihydroxyvitamin D may also influence the metabolism of neurotransmitters or stimulate neural growth factor in the nervous system and thus indirectly influence muscle activity. Abnormal skeletal muscle development has been shown in the vitamin D receptor null mouse, and the mean size of muscle fibers was smaller in this mouse than in the wild-type mouse [31].

The vitamin D receptor was demonstrated in human muscle tissue by immunologic methods, and it turned out that the number decreased with aging [32]. However, the debate on the vitamin D receptor in muscle tissue continues with positive and negative studies showing vitamin D receptor in muscle tissue or not [33, 34].

Conclusion

Clinical and epidemiological studies suggest that vitamin D influences muscle strength and balance. Clinical trials show that vitamin D with calcium (and maybe without) can improve balance and prevent falls. Clinical trials and meta-analyses suggest that vitamin D is more effective in frail or institutionalized elderly; however, a high once yearly dose of vitamin D

may increase the fall incidence. There are several explanations why vitamin D could influence muscle function.

Research Agenda

The mechanism why vitamin D can prevent falls should be further clarified. It is not known which dose of vitamin D is optimal to prevent falls and whether calcium always should be added. It is not known which groups should most likely profit from vitamin D to prevent falls. Polymorphisms of vitamin D-related genes may influence fall incidence and the effect of vitamin D treatment.

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