Effects of vitamin D on muscle function and performance: a review of evidence from randomized controlled trials

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***Abstract*:** Vitamin D insufficiency is frequent in the general population. Meta-analyses of randomized controlled trials (RCTs) have shown a decreased risk of falls in elderly treated with vitamin D supplements, which may be due to an improved neuromuscular function in vitamin D-replete subjects. In most observational studies, vitamin D status correlates positively with muscle strength and postural stability. However, as physical activity is associated with vitamin D status as well as muscle strength, effects of vitamin D status on muscular health can only be assessed properly in RCTs. A systematic search was performed and 16 RCTs on the effects of treatment with vitamin D on muscle function were identified. All except one of the studies were performed in subjects above 50 years of age. Baseline 25-hydroxyvitmin D (25OHD) levels were below 50 nmol/l in 11 studies. Plasma 25OHD levels increased significantly in all studies. In seven studies, a beneficial effect of vitamin D treatment was documented on muscle strength of the lower legs, body sway, and/or physical performance. Identified studies were heterogeneous with regard to most aspects including indices measured. No obvious characteristics delineated studies showing beneficial effects from studies showing no effects. Only a few investigators reported the statistical power of measurements performed. In conclusion, evidence from RCTs do support an effect of vitamin D supplements on muscle strength and function in the elderly, but more studies showing a lack of an effect have been published than studies showing beneficial effects. There is a major lack of data on possible effects in younger subjects.

***Keywords*:** elderly, muscle strength, vitamin D

Introduction

For many years, vitamin D has been known to be of importance to musculoskeletal health [Pfeifer *et al.* 2002]. It is well known that severe deficiency causes rickets (in children) and osteomalacia ('softening of the bones') in adults. Symptoms include paresthesia in hands and feet as well as aching muscles and bones [Ahmed *et al.* 2009; Pfeifer *et al.* 2002; Glerup and Eriksen, 1999]. Findings include muscle weakness with particularly proximal myopathy causing difficulty getting up from a chair without using arms and by walking on stairs [Schott and Wills, 1976; Skaria *et al.* 1975]. Gait disturbance occur and gait is often characterized as waddling ('penguin gait') [Glerup *et al.* 2000; Boland, 1986; Skaria *et al.* 1975]. The clinical feature of the myopathy associated with severe vitamin D deficiency is supported by findings from *in vivo* and *in vitro* experimental studies showing histological and electrophysiological changes in severe vitamin D deficiency [Sato *et al.* 2005; Boland, 1986; Sorensen *et al.* 1979; Skaria *et al.* 1975]. The vitamin D receptor (VDR) is expressed in the cell nuclei of muscle cells [Bischoff-Ferrari *et al.* 2004a; Bischoff *et al.* 2001; Simpson *et al.* 1985] and vitamin D has been shown to affect muscle cell contractility [Marcinkowska, 2001; Bellido and Boland, 1991; Rodman and Baker, 1978]. The number of VDRs decreases with age, which supposedly is a contributing factor to reduced muscle strength in the elderly [Bischoff-Ferrari *et al.* 2004a]. In addition to a direct effect of vitamin D on muscle cells, vitamin D deficiency causes secondary hyperparathyroidism (SHPT) which may also impair muscle function [Baczynski *et al.* 1985].

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Vitamin D is either ingested from food or synthesized in the skin during sun exposure. In most subjects, sun exposure is the primary determinant of vitamin D status, accounting for 80–90% of the vitamin D body stores. Cholecalciferol (vitamin D3) is synthesized in the skin and found in fatty fish and mammals, whereas ergocalciferol (vitamin D2) comes from yeasts and plants. Vitamin D supplements may contain either vitamin D2 or D3. Previously, the two vitamin D metabolites were considered to have an equal potency, but recent studies have suggested that vitamin D2 may be inferior to vitamin D3 in the treatment of vitamin D insufficiency [Romagnoli *et al.* 2008]. Vitamin D2 and D3 are both hydroxylated primarily in the liver to 25-hydroxyvitamin D (25OHD) and subsequently in the kidneys (and different peripheral cells) to become the active vitamin D metabolite, 1,25-dihydroxyvitamin D (calcitriol), which acts on the VDR [Hewison *et al.* 2000].

Vitamin D status is usually assessed by measuring plasma 25OHD levels. Plasma 25OHD levels below 50 nmol/l are considered as a state of insufficiency, although an increasing number of studies suggest that levels above 80 nmol/l are needed to ensure an optimal vitamin D status [Dawson-Hughes *et al.* 2005]. Vitamin D deficiency is defined as plasma 25OHD levels below 25 nmol/l, and levels below 12 nmol/l are considered as a state of severe deficiency which may cause frank osteomalacia and severe proximal myopathy.

In vitamin D insufficiency, muscle function and physical function may be impaired before clinical or biochemical signs of bone disease are evident [Glerup *et al.* 2000]. An increased risk of falls in elderly subjects with low vitamin D levels have been documented in several studies and randomized controlled trials (RCTs), and meta-analyses of RCTs have shown a reduced risk of falls in elderly treated with vitamin D supplements [Bischoff-Ferrari *et al.* 2009; Jackson *et al.* 2007; Bischoff *et al.* 2003]. Most likely, this is due to an improved neuromuscular function in response to vitamin D supplementation. Similarly, associations between vitamin D status and muscle strength, body sway and physical performance have been investigated in a large number of cohort and cross-sectional studies with most [Kuchuk *et al.* 2009; Stewart *et al.* 2009; Ward *et al.* 2009; Houston *et al.* 2007; Rinaldi *et al.* 2007; Wicherts *et al.* 2007; Bischoff-Ferrari *et al.* 2004b; Dhesi *et al.* 2002; Bischoff *et al.* 2000, 1999; Mowe *et al.* 1999; Skaria *et al.* 1975], but not all [Annweiler *et al.* 2009a, 2009b; Verreault *et al.* 2002], studies showing the beneficial effect of vitamin D status on measured indices. However, interpretation of results from observational studies is difficult, as plasma 25OHD levels, physical activity and muscle strength are closely interrelated. In several studies, physical activity has been shown to correlate positively with vitamin D status which most likely is due to the fact that physically active subjects spend more time outdoors in the sun and accordingly have a higher endogenous vitamin D synthesis than physically inactive subjects [Scragg and Camargo, 2008; Scragg *et al.* 1995]. In addition, physical activity improves muscle strength. Although most observational studies have adjusted statistically for potential interactions of physical activity and vitamin D status on muscular strength, residual confounding may exist and accordingly results from RCTs are imperative in order to draw valid conclusions on the effects of vitamin D status on muscle function.

The aim of the present paper is to review systematically the current state of knowledge on the effects of vitamin D on muscle strength and performance, based on results from individual RCTs.

Methods

By systematically searching the electronic databases MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews, studies published in the English language up to March 2010 on vitamin D, muscle strength, function and performance were identified. This was supplemented by searching the reference lists of the retrieved articles, textbooks and reviews.

Selection criteria

Only randomized trials of vitamin D supplementation in terms of either ergo- or cholecalciferol compared with placebo or with active comparators were included. Studies on the effects of treatment with active vitamin D (alfacalcidol, calcitriol) were excluded. Data on quality of life (QoL) from questionnaires were included if the study aim was to assess the effects on musculoskeletal function, but the search did not include data from studies including questionnaires on QoL without assessing muscle function.

Types of outcome measures

Data on the place of study and participant characteristics were collected (age, sex, residential status in terms of community-dwelling or patients and the condition to be treated) together with the following:

- treatment regime (type and dose of vitamin D administrated, concomitant administration of calcium and duration of treatment);
- type of outcome measures used in the individual studies, including the methods used to assess muscle strength, body sway, physical performance and questionnaires used;
- effects of vitamin D treatment compared with placebo/active comparator on the individual outcome measures;
- plasma 25OHD and parathyroid hormone (PTH) levels at baseline and end of study (when reported).

Results

A total of 18 RCTs were identified [Janssen *et al.* 2010; Lips *et al.* 2010; Witham *et al.* 2010; Kukuljan *et al.* 2009; Moreira-Pfrimer *et al.* 2009; Brunner *et al.* 2008; Bunout *et al.* 2006; Hajj Fuleihan *et al.* 2006; Sato *et al.* 2005; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Kenny *et al.* 2003; Latham *et al.* 2003; Pfeifer *et al.* 2009, 2000; Cordless *et al.* 1985; Johnson *et al.* 1980], among which two were omitted from further analysis as one of the papers reported duplicate data [Bischoff-Ferrari *et al.* 2006] and the other paper lacked detailed information on muscle measurements preformed [Johnson *et al.* 1980]. A summary of included studies is presented in Table 1. Only 1 of the 16 studies was not performed as a double-blinded trial [Lips *et al.* 2010]. The 16 RCTs included a total of 35,283 subjects. The trial from the Women's Health Initiative (WHI) study was substantially larger than any of the other trials, reporting physical functioning questionnaires data on 33,067 women, and clinical physical function measures in a subsample of 3137 women [Brunner *et al.* 2008]. The other 15 studies included a total of 2216 subjects with 65 to 363 subjects included in each of the individual trials (Table 1). All except one study [Hajj Fuleihan *et al.* 2006] included only subjects aged >50 years, and the mean age of included subjects was ≥74 years in 13 of the studies (Table 1). Solely females were included in five studies [Janssen *et al.* 2010; Brunner *et al.* 2008; Sato *et al.* 2005; Bischoff *et al.* 2003; Pfeifer *et al.* 2000], whereas two studies included only males [Kukuljan *et al.* 2009; Kenny *et al.* 2003]. Eight studies had frailty as a criteria for inclusion, as only subjects from geriatric care units [Janssen *et al.* 2010; Moreira-Pfrimer *et al.* 2009; Bischoff *et al.* 2003; Latham *et al.* 2003; Cordless *et al.* 1985], subjects with poststroke hemiplegia [Sato *et al.* 2005], heart failure [Witham *et al.* 2010] or a history of falls [Dhesi *et al.* 2004] were included (Table 1).

Type and duration of interventions

In most studies, vitamin D3 has been administrated orally as either a daily [Janssen *et al.* 2010; Kukuljan *et al.* 2009; Pfeifer *et al.* 2009, 2000; Brunner *et al.* 2008; Bunout *et al.* 2006; Bischoff *et al.* 2003; Kenny *et al.* 2003], weekly [Lips *et al.* 2010; Hajj Fuleihan *et al.* 2006] or monthly [Moreira-Pfrimer *et al.* 2009] dose. In most studies, an average daily dose of between 400 and 1200 IU of vitamin D3 was studied, whereas two studies used substantially higher average doses administrated either weekly (2000 IU/day) [Hajj Fuleihan *et al.* 2006] or monthly (3700 IU/day) [Moreira-Pfrimer *et al.* 2009]. In five studies, vitamin D2 has been administrated as either a single intramuscular [Dhesi *et al.* 2004] or oral [Latham *et al.* 2003] dose, as two doses administrated 10 weeks apart [Witham *et al.* 2010], or as a daily oral dose [Sato *et al.* 2005; Cordless *et al.* 1985]. As shown in Table 1, the doses of vitamin D2 used have varied widely. In nine studies, vitamin D3 has been administrated in combination with a daily calcium supplement [Janssen *et al.* 2010; Kukuljan *et al.* 2009; Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009, 2000; Brunner *et al.* 2008; Bunout *et al.* 2006; Bischoff *et al.* 2003; Kenny *et al.* 2003] and in these studies calcium alone (without vitamin D) has been used as a comparator (Table 1).

In the WHI study, follow up was performed after an average of 7.1 years [Brunner *et al.* 2008], whereas time to follow up has varied from 2 to 24 (average 8) months in the other 15 studies (Table 1).

Effects of interventions on plasma 25OHD and PTH levels

In all but one study [Brunner *et al.* 2008], the effect of treatment on plasma 25OHD levels has been reported, showing a significant increase in 25OHD levels in vitamin D treated subjects compared with controls (Table 1).

Table 1. Randomized controlled trials on effects of vitamin D on muscle function.

Reference	Study population; age; mean (range); place of study	Intervention; duration of treatment; design	Effects on plasma 25OHD and PTH levels in the control (C) and vitamin D intervention (I) group		Effects on muscle function
			Start of study	End of study	
Cordless *et al.* [1985]	65 male and female in-patients from a geriatric ward. All with P-25OHD <40 nmol/l; age 82 y; England	Daily oral 9000 IU of D_2 *vs.* identical placebo tablets; 6 months; double-blind design	P-25OHD: C: 17 nmol/l I: 18 nmol/l P-PTH: NA	P-25OHD: C: 15 nmol/l I: 120 nmol/l#	Using Northwick Park ADL system, the intervention did not affect 'Muscle strength score' or 'activity of daily living score'. Neither did treatment affect 'mental assessment scores' as assessed by a short questionnaire followed by a simple practical test of cognitive functions.
Pfeifer *et al.* [2000]	148 healthy free-living women with P-25OHD < 50 nmol/l; age 74 (70–86) y; Germany	Daily oral 800 IU D_3 + 1200 mg calcium *vs.* 1200 mg calcium alone; 2 months; double-blind design	P-25OHD: C: 25 nmol/l I: 26 nmol/l P-PTH: C: 6.1 pmol/l I: 6.1 pmol/l	'P-25OHD: C: 43 nmol/l I: 67 nmol/l# P-PTH: C: 5.2 pmol/l I: 4.4 pmol/l#	Compared with calcium alone, treatment with calcium plus vitamin D significantly reduced body sway (measured by the use of a sway meter).
Bischoff *et al.* [2003]	122 institutionalized women from a long-stay geriatric care unit; age 85 (63–99) y; Switzerland	Daily oral 800 IU D_3 + 1200 mg calcium *vs.* 1200 mg calcium alone; 3 months; double-blind design	P-25OHD: C: 29 nmol/l I: 31 nmol/l P-PTH: C: 3.7 pmol/l I: 3.9 pmol/l	P-25OHD: C: 29 nmol/l I: 66 nmol/l# P-PTH:C: 3.7 pmol/l I: 2.8 pmol/l#	No effects on individual measurement of isometric muscle strength at knee flexion and extension, grip strength or the TUG test. Combining the four individual measures into an overall 'musculoskeletal function index' showed significantly improvement in the vitamin D + calcium group compared with calcium alone.
Kenny *et al.* [2003]	65 healthy, community-dwelling males; age: 76 (65–87) y; Connecticut, USA	Daily oral 1000 IU D_3 + 500 mg calcium *vs.* 500 mg calcium alone; 6 months; double-blind design	P-25OHD: C: 59 nmol/l I: 65 nmol/l P-PTH: C: 6.6 pmol/l I: 6.4 pmol/l	P-25OHD: C: 57 nmol/l I: 87 nmol/l# P-PTH: C: 6.4 pmol/l I: 4.0 pmol/l ¤)	No effect on leg extension strength, handgrip strength (dynamometer), physical performance (including ability to rise from a chair, static balance, 6-foot walk time and TUG test), Physical Activity Scale for the Elderly (PASE) questionnaire, or the Medical Outcome Survey Short-form 8.
Latham *et al.* [2003]	243 frail males and females (53%) admitted to a geriatric rehabilitation unit (inpatient or day ward); age: 79 (77–81) y; New Zealand and Australia	Single oral dose of 300,000 IU D_2 *vs.* placebo tablets; 6 months follow up; double-blind design	P-25OHD: C: 48 nmol/l I: 38 nmol/l P-PTH: NA	P-25OHD: C: 48 nmol/l I: 60 nmol/l#	No effects on isometric knee extensor strength (dynamometer), the Berg Balance Test, TUG test, the time taken to walk 4 meters or the Short Form 36-item (SF36) questionnaire. Neither did treatment with vitamin D alter any of the physical performance measures in the subgroup of subjects with baseline 25OHD levels <30 nmol/l.
Dhesi *et al.* [2004]	139 males and females (75%) with a history of falls and P-25OHD < 30 nmol/l; age: 77 y (All > 65 y); England	Single intramuscular injection of 600,000 IU D_2 *vs.* placebo injection; 6 months follow-up; double-blind design	P-25OHD: C: 25 nmol/l I: 27 nmol/l P-PTH: C: 6.5 pmol/l I: 5.7 pmol/l	P-25OHD: C: 27 nmol/l I: 44 nmol/l# P-PTH: C: 6.6 pmol/l I: 5.5 pmol/l	Compared with placebo, vitamin D improved significantly postural sway (bipedal stance with eyes open. on a platform), aggregate functional performance time (the time taken to perform four common activities of daily living), and four-choice reaction time. No effect on maximal voluntary

					isometric quadriceps strength (using a strain gauge system) or QoL as assessed by SF35 questionnaire.
Sato *et al.* [2005]	96 women with post-stroke hemiplegia; age 74 y; Japan	Daily oral 1000 IU D_2 *vs.* placebo; 24 months; double-blind design	P-25OHD: C: 55 nmol/l I: 55 nmol/l P-PTH: C: 2.0 pmol/l I: 2.0 pmol/l	P-25OHD: C: 50 nmol/l I: 81 nmol/l[#] P-PTH: C: 2.4 pmol/l I: 2.4 pmol/l	Muscle strength was evaluated on the gluteus maximus and iliopsoas muscles on the nonhemiplegic side by a physical therapist using the British Medical Research Council scale. After 2 years of treatment, muscle strength on intact side had improved significantly in the vitamin D_2 group ($57 \pm 41\%$) compared with the changes in the placebo group ($-28 \pm 12\%$; $p < 0.01$). Muscle biopsies showed a significantly increased diameter of Type II fibres, and an increased percentages of Type II fibres.
Hajj Fuleihan *et al.* [2006]	363 healthy boys and girls (49%) Recruited from 4 schools in the greater Beirut area; age 13 (10–17) y; Lebanon	Weekly oral 1400 IU D_3 *vs.* weekly oral 14000 IU D_3 *vs.* placebo; 12 months; double-blind design	P-25OHD: C: 35 nmol/l I_{low}: 35 nmol/l I_{High}: 35 nmol/l PTH: NA	P-25OHD: C: 40 nmol/l I_{low}: 43 nmol/l I_{High}: 95 nmol/l[#]	Compared with placebo, both doses of vitamin D caused a significant increase in lean tissue mass In pre- but not in postmenarcheal girls. No dose–response effect. No effect on grip strength, as measured by a pneumatic squeeze dynamometer. In boys, there was no consistent positive effect of vitamin D.
Bunout *et al.* [2006]	96 elderly healthy free-living males and females (90%) with P-25OHD < 40 nmol/l; age: 77 y; Chile	Daily oral 400 IU D_3 + 800 mg calcium *vs.* 800 mg calcium alone; 9 months; double-blind design, full factorial design, i.e. in addition to supplements subjects were randomized to either physical training or no training.	P-25OHD: C: 33 nmol/l I: 31 nmol/l	P-25OHD: C: 36 nmol/l I: 65 nmol/l[#] P-PTH: did not change in any of the studied groups	TUG, 12 minute gait speed, and body sway (using a computerized posturograph) improved significantly in the vitamin D + calcium group compared with the calcium alone group. No effect on handgrip (dynamometer) or isometric quadriceps maximum voluntary strength, as assessed by using a quadriceps table.
Brunner *et al.* [2008]	33,067 free-living women; age 62 (50–79) y; USA	Daily oral 400 IU D_3 + 1000 mg calcium *vs.* placebo; 7 y follow up; double-blind design, substudy within the Women's health initiative (WHI) study. Women were additionally randomized to hormone therapy and dietary modification trials	P-25OHD: NA		Physical functioning was assessed in questionnaires incl. the SF36, showing no effects. A random subsample ($n = 3137$) of subjects had three objective physical function measures made at WHI baseline and 2- and 5-years after calcium/vitamin D trial enrolments. No effects of treatment were found on grip strength (dynamometer), chair–stand test, or 6-m timed walk test.

(continued)

Table 1. Continued.

Reference	Study population; age; mean (range); place of study	Intervention; duration of treatment; design	Effects on plasma 25OHD and PTH levels in the control (C) and vitamin D intervention (I) group		Effects on muscle function
			Start of study	End of study	
Pfeifer *et al.* [2009]	242 elderly community-dwelling males and females (75%) with P-25OHD < 78 nmol/l; age: 77 (all > 70) y; Germany and Austria	Daily oral 800 IU D_3 + 1000 mg calcium *vs.* 1000 mg calcium alone; 12 months followed by a treatment-free but still blinded 8 months observation period; double-blind design	P-25OHD: C: 54 nmol/l I: 55 nmol/l P-PTH: C: 5.8 pmol/l I: 5.3 pmol/l	P-25OHD: C: 57 nmol/l I: 84 nmol/l[#] P-PTH: C: 4.3 pmol/l I: 3.9 pmol/l [¤])	Compared with calcium alone, calcium plus vitamin D increased significantly quadriceps strength by 8% (using a dynamometer), and decreased significantly TUG by 11%. These changes remained significant at months 20. In addition at months 20, body sway (using a sway meter) was decreased significantly by 28% in the calcium + vitamin D group compared with the calcium alone group.
Kukuljan *et al.* [2009]	180 healthy community-dwelling White men; age: 61 (50–79) y; Australia	Daily fortified milk with 800 IU D_3 + 1000 mg calcium *vs.* no consumption of fortified milk; 18 months; randomized but not blinded, full factorial design, i.e. in addition to supplements subjects were randomized to either physical training or no training	P-25OHD: C: 85 nmol/l I: 87 nmol/l P-PTH: C: 2.9 pmol/l I: 3.0 pmol/l	P-25OHD: C: 75 nmol/l I: 97 nmol/l[#] P-PTH: did not change significantly	No effects on muscle strength (assessed as leg press, latissimus dorsi pull down and bench press) or postural sway (using a sway meter).
Moreira-Pfrimer *et al.* [2009]	56 males and females (79%) living in long-stay geriatric care units; age 78 (62–94) y; Brazil	Calcium 1000 mg/d + oral D_3 150,000 IU once a month during the first 2 months, followed by 90,000 IU D_3 once a month for the next 4 months *vs.* calcium 1000 mg/d; 6 months; double-blind design	P-25OHD: C: 40 nmol/l I: 46 nmol/l P-PTH: C: 5.0 pmol/l I: 5.3 pmol/l	P-25OHD: C: 52 nmol/l I: 87 nmol/l[#] P-PTH: C: 5.2 pmol/l I: 4.6 pmol/l	Vitamin D caused a significant improvement in maximal isometric strength of hip flexors and knee extensors (dynamometer).
Witham *et al.* [2010]	105 males and females (34%) with systolic heart failure and P-25OHD < 50 nmol/l; age 79 (all ≥ 70) y; Scotland	Oral 100,000 IU D_2 at baseline and 10 weeks later *vs.* similar placebo; 5 months follow-up; double-blind design	P-25OHD: C: 24 nmol/l I: 21 nmol/l P-PTH: C: 8.5 pmol/l I: 8.7 pmol/l	P-25OHD: C: 25 nmol/l I: 40 nmol/l[#] P-PTH: C: 8.5 pmol/l I: 8.1 pmol/l	No effects on 6-minute walk distance, TUG test, or Functional Limitations Profile. QoL as measured by the Minnesota Living With Heart Failure score worsened slightly, but significant in the treatment- compared with the placebo-group.
Lips *et al.* [2010]	226 ambulatory males and females with P-25OHD between 15 and 50 nmol/l; age: 78 (all ≥ 70) y; medical centres in North America and Europe	Weekly oral 8400 IU D_3 *vs.* placebo; 4 months; double-blind design	P-25OHD: C: 35 nmol/l I: 34 nmol/l P-PTH: C: 6.2 pmol/l I: 6.4 pmol/l	P-25OHD: C: 35 nmol/l I: 66 nmol/l[#] P-PTH: C: 6.7 pmol/l I: 6.1 pmol/l[#]	No effects of treatment on mediolateral body sway with eyes open (assessed using an AccuSway[PLUS] platform), gait speed test, or on a *short* physical performance battery (combined measures of balance, gait speed, and ability to rise from a chair). No significant treatment differences in mediolateral sway were seen in either of two prespecified subgroups on the basis of the baseline 25(OH)D concentration (≤15 or > 15 ng/ml).

Janssen *et al.* [2010]	70 female geriatric outpatients with P-25OHD between 20 and 50 nmol/l; age: 81 (all > 65) y; The Netherlands	Daily oral 400 IU D_3 + 500 mg calcium *vs.* 500 mg calcium; 6 months; double-blind design	P-25OHD: C: 34 nmol/l I: 33 nmol/l P-PTH: C: 9.1 pmol/l I: 10.6 pmol/l	P-25OHD: C: 42 nmol/l I: 77 nmol/l[#] P-PTH: C: 7.4 pmol/l I: 7.1 pmol/l	No effects on handgrip strength (dynamometer), isometric knee extension strength (dynamometry), explosive leg extension power (Nottingham Power Rig), TUG test, maximum walking distance achieved in 2 minutes, or habitual physical activity as measured with a physical activity questionnaire for the elderly.

[#] $p < 0.05$ between treatment groups.
P-25OHD, plasma 25-hydroxyvitamin D; P-PTH, plasma parathyroid hormone; TUG, timed up-and-go test; QoL, quality of life.

Baseline plasma 25OHD levels were below 50 nmol/l in 11 of the included studies. In 13 studies, the effects of treatment on plasma PTH levels was reported showing either significantly decreased levels [Lips *et al.* 2010; Pfeifer *et al.* 2009, 2000; Bischoff *et al.* 2003; Kenny *et al.* 2003] or no effects [Janssen *et al.* 2010; Lips *et al.* 2010; Witham *et al.* 2010; Kukuljan *et al.* 2009; Moreira-Pfrimer *et al.* 2009; Bunout *et al.* 2006; Sato *et al.* 2005; Dhesi *et al.* 2004] compared with the controls (Table 1). Vitamin D3 has been co-administrated with calcium in four of the five studies showing decreased PTH levels [Pfeifer *et al.* 2009, 2000; Bischoff *et al.* 2003; Kenny *et al.* 2003], as well as in four of the studies showing no effects on PTH levels [Janssen *et al.* 2010; Kukuljan *et al.* 2009; Moreira-Pfrimer *et al.* 2009; Bunout *et al.* 2006]. No apparent differences exist between studies showing or not showing effects on plasma PTH levels regarding dose of vitamin D administrated or baseline plasma 25OHD levels (Table 1). However, none of the studies using vitamin D2 showed effects on plasma PTH levels [Witham *et al.* 2010; Sato *et al.* 2005; Dhesi *et al.* 2004].

Effects on muscle function

Overall, seven studies showed a positive effect of vitamin D treatment on muscle strength, postural sway and/or physical performance [Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009, 2000; Bunout *et al.* 2006; Sato *et al.* 2005; Dhesi *et al.* 2004; Bischoff *et al.* 2003], whereas nine studies found no evidence of effects on measured indices [Janssen *et al.* 2010; Lips *et al.* 2010; Witham *et al.* 2010; Kukuljan *et al.* 2009; Brunner *et al.* 2008; Hajj Fuleihan *et al.* 2006; Kenny *et al.* 2003; Latham *et al.* 2003; Cordless *et al.* 1985].

Effect on muscle strength

Effects of vitamin D on muscle strength was evaluated in 12 studies [Janssen *et al.* 2010; Kukuljan *et al.* 2009; Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009; Brunner *et al.* 2008; Bunout *et al.* 2006; Hajj Fuleihan *et al.* 2006; Sato *et al.* 2005; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Kenny *et al.* 2003; Latham *et al.* 2003]. In most studies, a dynamometer/strain gauge system was used to measure maximal voluntary isometric muscle strength [Janssen *et al.* 2010; Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009; Brunner *et al.* 2008; Bunout *et al.* 2006; Fuleihan *et al.* 2006; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Hajj Kenny *et al.* 2003; Latham *et al.* 2003].

Lower legs isometric muscle strength, as assessed by using a strain gauge system, was evaluated in eight studies [Janssen *et al.* 2010; Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009; Bunout *et al.* 2006; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Kenny *et al.* 2003; Latham *et al.* 2003]. Two studies showed an improved isometric muscle strength in response to treatment [Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009]. Accordingly, in response to 6 months of treatment with 800 IU/day vitamin D3, Pfeifer and colleagues found significantly increased quadriceps strength compared with placebo [Pfeifer *et al.* 2009]. Similarly, Moreira-Pfrimer and colleagues found significantly improved maximal isometric strength of hip flexors and knee extensors in vitamin D3-treated subjects compared with placebo [Moreira-Pfrimer *et al.* 2009].

In addition to using a strain gauge system, effects of vitamin D treatment have been evaluated in a Japanese study in terms of a physical therapist (blinded to treatment allocation) assessing muscle strength using the British Medical Research Council scale. The study included women with poststroke hemiplegia and showed that compared with placebo, 2 years of treatment with 1000 IU/day vitamin D2 caused a significantly improved strength of the gluteus maximus and iliopsoas muscles on the intact side [Sato *et al.* 2005].

Effects of vitamin D treatment on hand grip strength have been evaluated in five studies, none of them showing significant effects [Janssen *et al.* 2010; Brunner *et al.* 2008; Bunout *et al.* 2006; Hajj Fuleihan *et al.* 2006; Kenny *et al.* 2003].

As shown in Table 1, no obvious differences exist between the studies showing or not showing effects in terms of characteristics of included subjects or effects of treatment on plasma 25OHD or PTH levels.

Body sway

Effects of vitamin D on postural balance have been evaluated in eight RCTs [Lips *et al.* 2010; Kukuljan *et al.* 2009; Pfeifer *et al.* 2009, 2000; Bunout *et al.* 2006; Dhesi *et al.* 2004; Kenny *et al.* 2003; Latham *et al.* 2003]. In four studies treatment with vitamin D decreased body sway as assessed by the use of either a sway meter [Pfeifer *et al.* 2009, 2000] or a balance platform [Bunout *et al.* 2006; Dhesi *et al.* 2004], whereas no effect was found in another four studies assessing postural balance by the use of either a sway meter [Kukuljan *et al.* 2009], a balance platform [Lips *et al.* 2010], single leg stance (seconds) [Kenny *et al.* 2003], or Berg Balance Test [Latham *et al.* 2003]. All of the four studies showing an effect included only subjects who had low vitamin D levels at baseline, whereas only one of the three studies showing no effect had low plasma 25OHD levels as inclusion criteria. In terms of other characteristics, no obvious differences exist between studies showing or not showing an effect (Table 1).

Physical performance

Effects on physical performance have been assessed using a variety of different measures (Table 1), including the timed up-and-go (TUG) test [Janssen *et al.* 2010; Witham *et al.* 2010; Pfeifer *et al.* 2009; Bunout *et al.* 2006; Bischoff *et al.* 2003; Kenny *et al.* 2003; Latham *et al.* 2003], gait speed tests [Janssen *et al.* 2010; Lips *et al.* 2010; Witham *et al.* 2010; Brunner *et al.* 2008; Bunout *et al.* 2006; Kenny *et al.* 2003; Latham *et al.* 2003], chair–stand tests [Brunner *et al.* 2008; Kenny *et al.* 2003], as well as by the use of aggregated measures of physical abilities [Lips *et al.* 2010; Witham *et al.* 2010; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Kenny *et al.* 2003; Cordless *et al.* 1985] and different questionnaires [Witham *et al.* 2010; Brunner *et al.* 2008; Dhesi *et al.* 2004; Kenny *et al.* 2003; Latham *et al.* 2003; Cordless *et al.* 1985].

In seven studies, the effect of vitamin D on the TUG test has been investigated [Janssen *et al.* 2010; Witham *et al.* 2010; Pfeifer *et al.* 2009; Bunout *et al.* 2006; Bischoff *et al.* 2003; Kenny *et al.* 2003; Latham *et al.* 2003]. In two studies, a beneficial effect was shown [Pfeifer *et al.* 2009; Bunout *et al.* 2006]. Both studies include only study subjects with low vitamin D levels at baseline, whereas low baseline vitamin D levels were a predefined criteria for inclusion in two [Janssen *et al.* 2010; Witham *et al.* 2010] of the five studies showing no effect. In two studies, no effect of vitamin D was shown on the ability to rise from a chair (chair–stand test) [Brunner *et al.* 2008; Kenny *et al.* 2003].

Whether vitamin D affects gait speed has been tested in seven trials [Lips *et al.* 2010; Janssen *et al.* 2010; Witham *et al.* 2010; Brunner *et al.* 2008; Bunout *et al.* 2006; Kenny *et al.* 2003; Latham *et al.* 2003] assessing time taken to

walk either 6 feet [Kenny *et al.* 2003], 4 meters [Lips *et al.* 2010; Latham *et al.* 2003] or 6 meters [Brunner *et al.* 2008]. In addition, the maximum walking distance achieved in either 2 [Janssen *et al.* 2010], 6 [Brunner *et al.* 2008] or 12 minutes [Bunout *et al.* 2006] have been measured. Only one of the studies showed a significant effect of vitamin D treatment. Accordingly, in a group of 96 elderly, community-dwelling males and females with plasma 25OHD <40 nmol/l, Bunout and colleagues found an increased 12-minute gait speed in response to 9 months of treatment with a daily dose of 400 IU vitamin D3 + 800 mg calcium compared with 800 mg calcium alone (Table 1) [Bunout *et al.* 2006].

As shown in Table 1, the effects of vitamin D on physical performance have been investigated in terms of different aggregated measures of physical abilities in six studies [Lips *et al.* 2010; Witham *et al.* 2010; Dhesi *et al.* 2004; Bischoff *et al.* 2003; Kenny *et al.* 2003; Cordless *et al.* 1985]. In two studies, a beneficial effect of vitamin D was shown [Dhesi *et al.* 2004; Bischoff *et al.* 2003]. Both studies included rather frail study subjects, i.e. in the study by Bischoff and colleagues only institutionalized elderly women (mean age 85 years) from a long-stay geriatric care unit participated [Bischoff *et al.* 2003], and in the study by Dhesi and colleagues only subjects with a history of falls and plasma 25OHD levels <30 nmol/l were included [Dhesi *et al.* 2004]. In the study by Bischoff and colleagues no significant effects of individual muscle measurements were shown, but a positive effect was demonstrated by combining four individual measures of muscle strength (isometric muscle strength at knee flexion and extension, grip strength and the TUG test) into an overall *musculoskeletal function index* [Bischoff *et al.* 2003]. Similarly, Dhesi and colleagues showed no effect on individual measures of muscle strength but a beneficial effect of vitamin D was shown by combining the time taken to perform four common activities of daily living (50-foot walk, rising from a 42-cm high chair and walking 50 feet, ascent and descent of 13 steps) into an aggregate functional performance time [Dhesi *et al.* 2004]. In the studies showing no effects, different measures of physical performance have been combined (Table 1). So far, all published studies have used their 'own' combined measures of physical performance, i.e. no two studies have assessed the same measure.

No effects of vitamin D treatment on musculoskeletal function have been demonstrated by the use of different types of questionnaires [Witham *et al.* 2010; Brunner *et al.* 2008; Dhesi *et al.* 2004; Kenny *et al.* 2003; Latham *et al.* 2003; Cordless *et al.* 1985], including the Short Form 36 (SF36) questionnaire [Brunner *et al.* 2008; Dhesi *et al.* 2004; Latham *et al.* 2003].

Discussion

For the present review, 16 RCTs on the effects of vitamin D supplements on muscle function were identified. Except for one study, all studies included solely subjects older than 50 years of age indicating a major lack of data on the effects of vitamin D on muscle function in younger subjects.

In general, the studies identified all showed significant effects of vitamin D supplementation on plasma 25OHD levels, whereas only 5 of 13 studies reported decreased plasma PTH levels in response to treatment. A little less than half of the studies showed beneficial effects of vitamin D treatment on muscle function in terms of an improved muscle strength [Moreira-Pfrimer *et al.* 2009; Pfeifer *et al.* 2009; Sato *et al.* 2005], a reduced body sway [Pfeifer *et al.* 2009, 2000; Bunout *et al.* 2006; Dhesi *et al.* 2004], an improved TUG test [Pfeifer *et al.* 2009; Bunout *et al.* 2006], an increased 12-minute gait speed [Bunout *et al.* 2006] or an improved aggregated measure of physical abilities [Dhesi *et al.* 2004; Bischoff *et al.* 2003]. Accordingly, the findings from observational studies on the effects of vitamin D on muscle function is to a certain degree supported by the finding from RCTs, although the beneficial effects of vitamin D are less consistently present. In contrast to the findings from observational studies on beneficial effects of vitamin D status on grip strength in adolescent girls [Foo *et al.* 2009] and postmenopausal women [Stewart *et al.* 2009], no RCTs have shown effects of vitamin D supplements on grip strength. This agrees with the notion that vitamin D primarily affects the proximal muscles causing proximal myopathy in the state of severe deficiency. As all studies showing beneficial effects of vitamin D supplements on body sway [Pfeifer *et al.* 2009, 2000; Bunout *et al.* 2006; Dhesi *et al.* 2004] and the TUG test [Pfeifer *et al.* 2009; Bunout *et al.* 2006] had low baseline plasma 25OHD levels as a predefined criteria for inclusion, it seems likely that a beneficial effect is more prone to be shown in the setting of low

vitamin D levels. However, it should be noted that several of the studies with a lack of an effect also included solely study subjects with plasma 25OHD levels below a certain limit [Kukuljan *et al.* 2009; Brunner *et al.* 2008; Hajj Fuleihan *et al.* 2006; Kenny *et al.* 2003; Latham *et al.* 2003], making it difficult to draw any definite conclusions on this matter (Table 1).

Overall, no major differences are apparent between the seven studies showing a beneficial effect and the nine studies with a lack of an effect of vitamin D treatment on measured indices (Table 1). Nevertheless, conclusions should only be drawn with caution on whether the characteristics of studied subjects or dose of vitamin D used are of importance, as the studies identified were heterogeneous with regard to most aspects. Different outcome measures have been reported by different investigators and even in the case of measurements of similar characteristics, different methods have been applied making it difficult to compare studies directly. Moreover, although measured indices have been investigated in the setting of RCTs, the effects on muscle function have been investigated as secondary endpoints in most studies and only few investigators have reported sample size calculations of measurements performed [Lips *et al.* 2010]. It cannot be ruled out that the lack of effect in some of the studies may be due to a low statistical power (Type II error).

Several *in vivo* and *in vitro* experimental studies have shown physiological, histological and electrophysiological changes in severe vitamin D deficiency, supporting an effect of vitamin D on muscle health. Binding of vitamin D to its receptors stimulates uptake of inorganic phosphate used for the formation of energy-rich phosphate compounds necessary for muscle cell contractility [Marcinkowska, 2001; Bellido and Boland, 1991; Rodman and Baker, 1978]. In addition, low vitamin D levels may cause secondary hyperparathyroidism and excess PTH had been shown to enhance the degradation of muscle proteins [Baczynski *et al.* 1985]. An effect of vitamin D on muscle cell function is further supported by studies on muscle biopsies and electrophysiological examinations. Atrophy of type II muscle fibres as well as nonspecific histological abnormalities such as fatty infiltration, interstitial fibrosis and sarcolemmal nuclear proliferation have been shown in muscle biopsies from subjects with vitamin D deficiency and treatment with vitamin D has been shown to reverse these changes, including an increased number and cross-sectional area of type II fibres [Sato *et al.* 2005; Boland, 1986; Sorensen *et al.* 1979]. In electrophysiological studies, low vitamin D levels have been shown to cause an abnormal pattern with a reduced motor unit potential duration and amplitude and an increased percentage of polyphasicity without concomitant signs of denervation [Boland, 1986; Skaria *et al.* 1975].

In conclusion, several lines of evidence support an effect of vitamin D on muscle function and findings from RCTs have shown beneficial effects of vitamin D supplementation in the elderly. However, an effect is not universally present as more papers showing a lack of an effect have been published than papers showing beneficial effects. Explanations for the discrepant results are not obvious, as no general characteristics seem to separate studies showing beneficial effects from studies showing no effect of an improved vitamin D status. Further studies should try to replicate findings from the studies showing beneficial effects with predefined sample size calculations in order to assure a proper statistical power. Moreover, as low vitamin D levels are common in the general population, more studies are needed in younger subjects in order to assess potential harmful effects of vitamin D insufficiency on neuromuscular health in subjects below the age of 50 years.

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Conflict of interest statement

The author reports no conflict of interest in preparing this manuscript.

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