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ORIGINAL ARTICLE

Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis

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Abstract
Summary This systematic review demonstrates that vitamin D supplementation does not have a significant effect on muscle strength in vitamin D replete adults. However, a limited number of studies demonstrate an increase in proximal muscle strength in adults with vitamin D deficiency.
Introduction The purpose of this study is to systematically review the evidence on the effect of vitamin D supplementation on muscle strength in adults.
Methods A comprehensive systematic database search was performed. Inclusion criteria included randomised controlled trials (RCTs) involving adult human participants. All forms and doses of vitamin D supplementation with or without calcium supplementation were included compared with placebo or standard care. Outcome measures included evaluation of strength. Outcomes were compared by calculating standardised mean difference (SMD) and 95% confidence intervals.
Results Of 52 identified studies, 17 RCTs involving 5,072 participants met the inclusion criteria. Meta-analysis showed no significant effect of vitamin D supplementation on grip strength (SMD −0.02, 95%CI −0.15,0.11) or proximal lower limb strength (SMD 0.1, 95%CI −0.01,0.22) in adults with 25(OH)D levels >25 nmol/L. Pooled data from two studies in vitamin D deficient participants (25(OH)D <25 nmol/L) demonstrated a large effect of vitamin D supplementation on hip muscle strength (SMD 3.52, 95%CI 2.18, 4.85).
Conclusion Based on studies included in this systematic review, vitamin D supplementation does not have a significant effect on muscle strength in adults with baseline 25(OH)D >25 nmol/L. However, a limited number of studies demonstrate an increase in proximal muscle strength in adults with vitamin D deficiency.

Keywords Muscle · Muscle fibre · Strength · Vitamin D

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Introduction

It is estimated that more than a billion people worldwide are deficient in vitamin D [1]. Those most at risk include older people in residential care [2], darker-skinned women [3] (particularly if veiled) and people with medical conditions that require sun avoidance or cause malabsorption [4]. The prime source of vitamin D is the conversion of 7-dehydrocholesterol to previtamin D_3 in the skin by solar ultraviolet B radiation. Very little vitamin D is obtained from the diet.

It is well established that vitamin D is an integral part of calcium and phosphate homeostasis and thus essential to bone health. In addition, vitamin D receptors have been identified on many other tissues including skeletal muscle [5, 6]. Severe vitamin D deficiency causes rickets in

children and osteomalacia in adults resulting in proximal muscle weakness. Muscle atrophy, particularly of type 2 fibres in vitamin D deficiency has been described histopathologically [7, 8]. There is conflicting evidence as to whether Vitamin D deficiency contributes to proximal muscle weakness. Some studies demonstrating an association [9–12], others finding no relationship between vitamin D levels and weakness [13–15]. A recent study investigating the relationship between quadriceps strength and vitamin D levels [16] found a significant association with univariate analysis. However, there were no statistically significant relationship once potential confounders such as physical activity, age, and comorbidities were controlled for. Thus, the effect of vitamin D supplementation on muscle strength has not been clearly established.

A systematic review conducted in 2003 [17] concluded that Vitamin D alone cannot be recommended for use in clinical practice where the primary aim is to improve muscle strength or physical function or reduce the risk of falling in frail elderly people. This review [17] investigated the effect of vitamin D supplementation on muscle strength, physical function, and falls in the elderly. However, there was no rating regarding the methodological quality of the included studies. In addition, effect sizes and confidence intervals were only calculated for the outcome "falls". Further randomised controlled trials (RCTs) have been published since 2003. In addition, the last few years has seen an increase in articles reporting the benefits of vitamin D on muscle strength in both peer-reviewed journals [18] and public health literature. The aim of this current systematic review was to critically review the evidence on the effect of vitamin D supplementation on outcome measures specifically relating to muscle strength including all adults, not just the elderly. Thus, the research question is: Does vitamin D supplementation result in improved strength in adults?

Materials and methods

A systematic review of the published literature on the effect of vitamin D supplementation on muscle strength was conducted. Table 1 outlines the inclusion criteria.

Data sources and study selection

The databases, searched with language restrictions (English only), included: MEDLINE, CINAHL, EMBASE, Pubmed, Cochrane Controlled Trials Register, Sportdiscus, Scopus and Full text clinicians' health journals @ Ovid from the earliest time to May 2010. These databases were searched using the terms vitamin D OR vitamin D_2 OR vitamin D_3 OR 1-alpha hydroxyvitamin D3 OR 1-alpha hydroxycalciferol OR 1,25-dihydroxyvitamin D_3 OR 1,25 dihydroxycholecalciferol OR 25-hydroxycholecalciferol OR 25 hydroxyvitamin D OR calcitriol OR vitamin D OR ergocalciferol OR cholecalciferol calcifediol OR alfacalcidol OR calcidiol OR "calciferol" AND "muscle". A detailed search strategy is presented in Appendix 1.

Table 1 Inclusion criteria

Design	Randomised controlled trials
Participants	Adults >18 years of age
	All baseline 25(OH)D levels
	Humans
Intervention	Vitamin D supplementation—all forms and all doses
Comparisons	Vitamin D or vitamin D metabolite with or without calcium compared with placebo treatment or standard care
Outcome measure	Measure of muscle strength

The search was supplemented by citation tracking, reference checking, and key author searches. The two reviewers (KS and KB) independently assessed the titles and abstracts of articles identified by the initial search strategy for the inclusion criteria. Differences of opinion regarding selection of articles were resolved between the two investigators through discussion and consensus. Full-text versions of relevant articles were obtained and assessed by the two independent reviewers.

Assessment of methodological quality of studies

Empirical studies were rated using the Physiotherapy Evidence Database (PEDro) scale (http://www.pedro.org.au) which is an 11-item checklist suitable for RCTs [19]. High interobserver reliability has been found for this scale [20]. Differences of opinion regarding scoring of articles were resolved between the two investigators through discussion and consensus, and authors were contacted to clarify important points.

Data extraction and analysis

Data extraction was completed for all included studies by one reviewer (KS) and cross-checked by a second reviewer (KB). Data extraction included number of participants, gender and age of participants, baseline 25(OH)D level, length of intervention, and outcome measures. To provide a comparison between outcomes reported by the studies, effect sizes (standardised mean difference, SMD) with 95% confidence intervals (CI) were calculated using software package Comprehensive Meta Analysis, Biostat v2. Effect

sizes provide a measure of the impact of an intervention. Conventionally, the effect size is reported as: 0.8, large; 0.5, moderate; and 0.2, small [21]. A meta-analysis using a random effects model was applied to investigate specific muscle groups. Between-study heterogeneity was assessed firstly by visually inspecting the forest plots. In addition, Cochran's X^2 test ($p<0.05$ indicating significance) and the I^2 index (values of 25%, 50%, and 75% representative of low, moderate, and high heterogeneity, respectively) were calculated; it is noted that visual inspection may be more informative than I^2 values for a small number of trials [22]. All statistical analyses were independently cross-checked by a statistician (KM).

Results

Figure 1 details the flow of studies included in the review. A final library of 17 RCTs remained involving 5,072 participants [23–39].

Study quality assessment

Table 2 provides a summary of the assessment of each study with respect to the criteria in the PEDro scale. A median score of 8 out of 10 (range 4–10; mode 8) on the PEDro scale [19] was found. Fifteen of the 17 studies reported random allocation [23–27, 29–36, 38, 39], with six studies also reporting concealment of treatment allocation [23, 27, 32, 35, 38, 39]. Twelve of the included studies reported blinding of the assessors to group allocation [23–27, 30, 32–36, 39] and 13 reported blinding of participants [23, 24, 26, 27, 29, 30, 32–35, 37–39]. Intention-to-treat analysis occurred in 13 studies [23–25, 27, 30–36, 38, 39]. Missing data meant that effect sizes could not be calculated for two papers [29, 33].

The key features of the studies are summarised in Tables 3 and 4.

Intervention

The trials used a variety of vitamin D supplementation regimes. Six trials compared vitamin D alone with placebo [26, 27, 29, 32, 35, 37], four of which used ergocalciferol (D_2) [26, 27, 29, 35], and two cholecalciferol (D_3) [32, 37]. One study compared vitamin D metabolite (calcitriol) with placebo [28]. Treatment with a combination of vitamin D_3 and calcium supplements was used in nine studies [23–25, 30, 31, 33, 34, 38, 39]. Five studies compared vitamin D and calcium with calcium alone [23, 25, 30, 33, 34], three studies investigated calcium and vitamin D versus placebo [24, 38, 39] and one study calcium and vitamin D versus nothing [31]. Finally, one study investigated vitamin D via sunlight exposure (with clearly defined exposed region and documented daily exposure time) to usual care [36]. Timeframes of the intervention period ranged from 12 weeks to 5 years with the mode being 6 months in duration. Two studies did not state baseline 25(OH)D level [24, 29], participants in four studies had baseline 25(OH)D >50 nmol/L [28, 30, 31, 34], the mean baseline 25(OH)D level was 25–50 nmol/L in seven studies [23, 25, 27, 32, 33, 37, 39], and <25 nmol/L in four studies [26, 35, 36, 38]. Baseline $1,25(OH)_2D$ was within normal range in the study that used calcitriol as a supplement [28].

Outcome measures

Grip strength was an outcome in eight studies [23–25, 28, 30, 37–39] and was measured via hand held dynamometry (HHD) in seven studies [24, 25, 28, 30, 37–39] and using a vigorimeter in one study [23]. Pinch strength was measured in one study by a pinch gauge [38]. Knee

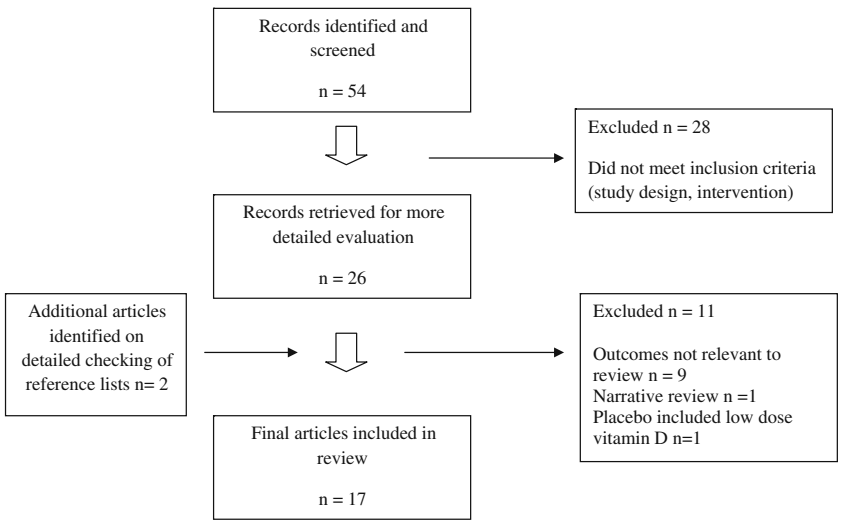

Fig. 1 Flow of studies through the review

Table 2 Quality scores for eligible studies

Author (ref)	PEDro scale item											Total
	1[a]	2	3	4	5	6	7	8	9	10	11	
Bischoff [23]	+	+	+	+	+	+	+		+	+	+	9
Brunner [24]	+	+		+	+		+	+	+	+	+	8
Bunout [25]	+	+		+			+	+	+	+	+	7
Corless [26]	+	+		+	+	+	+			+	+	7
Dhesi [27]	+	+	+	+	+		+	+	+	+	+	9
Grady [28]	+			+				+		+	+	4
Gupta [38]	+	+	+	+	+			+	+	+	+	8
Janssen [39]	+	+	+	+	+	+	+		+	+	+	9
Johnson [29]		+			+			+		+		4
Kenny [30]	+	+			+	+	+	+	+	+	+	8
Kukuljan [31]	+	+						+	+	+	+	5
Latham [32]	+	+	+	+	+	+	+	+	+	+	+	10
Moreira [33]	+	+		+	+	+	+		+	+	+	8
Pfeifer [34]	+	+		+	+		+	+	+	+	+	8
Sato [35]	+	+	+	+	+	+	+	+	+	+	+	10
Sato [36]	+	+		+			+	+	+	+	+	7
Smedshaug [37]	+			+	+					+	+	4
Total	14	15	6	14	13	6	12	12	13	17	16	Median 8

PEDro Physiotherapy Evidence Database, + the item was clearly satisfied

The PEDro scale is based on the Delphi list developed by Verhage et al. at the Department of Epidemiology, University of Maastricht [53]. Only criterion 2–11 are scored giving a total out of 10: *1* eligibility criteria, *2* randomisation, *3* concealed allocation, *4* groups similar at baseline, *5* blinding subjects, *6* blinding therapists, *7* blinding assessors, *8* Measures obtained for >85%, *9* intention to treat, *10* between-groups statistical comparison, *11* point measures and measures of variability

[a] Column 1 not used in the calculation of the scores

extension strength was measured in eight studies [23, 25, 27, 28, 32–34, 39] by a variety of techniques. HHD was utilised in two studies [32, 33], four studies used a strain gauge [23, 27, 34, 39], one study employed a one repetition maximum (1RM) using a quadriceps table [25] and one used an isokinetic dynamometer [28]. Two studies measured leg press by 1RM [30, 31]. Two studies examined knee flexion, one via strain gauge [23] and one with an isokinetic dynamometer [28]. One study measured calf strength using isokinetic dynamometry [38]. Four studies measured a combination of proximal muscles: Moreira-Pfrimer et al. [33] measured hip flexion via HHD, Kukulijan et al. [31] measured bench press and latissimus dorsi pull down via 1RM, Sato et al. [36] computed a combined score of hip external and internal rotators and knee flexion and extension via manual muscle test (MMT). In the second study by this group a combined score of hip extension and flexion strength measured via MMT was utilised [35]. Finally, two studies derived a strength score from functional activities [26, 29]. It is questionable whether a derived score truly reflects strength; however, the studies have been included in this review for completeness.

Effect of vitamin D supplementation on muscle strength

End of trial 25(OH)D level—response to intervention

All but one study [27] achieved mean 25(OH)D levels >50 nmol/L in the vitamin D-treated group post-intervention (Table 4).

End of trial 1,25(OH)$_2$D

Calcitriol was the supplement used in one study [28] with the treatment group achieving an increase in 1,25(OH)$_2$D from 85.6 (33.7) to 95.4 pmol/L (baseline and post-supplementation within accepted normal range). However, seven of 50 patients in the treatment group required a reduction in dosage due to elevated serum or urinary calcium levels.

Muscle strength

The Q test for heterogeneity was nonsignificant ($p < 0.05$) with I^2 index ≤15% for all pooled studies when grouped according to baseline 25(OH)D level i.e. ≤25 and >25 nmol/L.

Table 3 Demographics

Study (ref)	*N*	Participant description	Baseline 25(OH)D nmol/L Mean (sd) unless otherwise stated[a]	Gender M:F (%)	Age Mean years (sd) unless otherwise stated	Length of intervention
Bischoff [23]	122	Long stay geriatric unit	30 (23,55) Mean (IQR)	0:100	85.3 (range 63–99)	12 weeks
Brunner [24]	3,137	Community dwelling Post-menopausal	Baseline 25OHD not given—but stated patients not selected for low vitamin D levels	0:100	50–79 (range)	5 years
Bunout [25]	96	Community dwelling	31.9 (6.1)	10:90	76 (4)	9 months
Corless [26]	65	Geriatric inpatient	17.1 (2.1)	22:78	Mean 82.5	40 weeks
Dhesi [27]	139	Community dwelling referred from falls clinic.	25.9 (24.6,27.1) Mean (95%CI)	22:78	76.8 (6.2)	6 months
Grady [28]	98	Community dwelling Calcium intake at or below 1,000 mg/day	>60 (1,25-$(OH)_2D_3$ within normal range)	50:50	79.2 (5.4)	6 months
Gupta [38]	40	Healthy volunteers	23.25 (9.7)	60:40	31.6 (4.8)	6 months
Janssen [39]	70	Community dwelling women	33.5 (11.6)	0:100	80.5 (6.6)	6 months
Johnson [29]	109	Community dwelling 14% weren't ambulant	Not stated	Not stated - mix	Females >60 Males >65	6 months
Kenny [30]	65	Community dwelling—healthy	62 (17.75)	100:0	76 (4)	6 months
Kukuljan [31]	180	Community dwelling—healthy	>80	100:0	60.8 (7.6)	1 year
Latham [32]	243	Frail in geriatric rehabilitation unit	42.5 (37.5,49) Median (95% CI)	47:53	Mean (95%CI) 79.5 (78–81)	6 months
Moreira [33]	46	Institutionalised elderly	42.7 (20.3,76.8) Median (range)	27:73	Mean (95%CI) 78 (62–94)	6 months
Pfeifer [34]	242	Community seniors	55 (19)	25:75	Range 70–94	1 year
Sato [35]	96	Institutionalised stroke	24.5 (3.2)	0:100	74.2 (4.0)	2 years
Sato [36]	264	Institutionalised with Alzheimers	24 (6.4)	0:100	72.3 (5.4)	1 year
Smedshaug [37]	60	Nursing home residents	49.6 (30.7)	35:65	82.4 (7.3)	1 year

[a] Baseline 25(OH)D mean of control and treatment groups

1,25(OH)$_2$D$_3$ 1,25-dihydroxyvitamin D$_3$ a biologically active form of vitamin D, 25(OH)D 25 hydroxyvitamin D, Rx treatment; *95%CI* 95% confidence interval; *IQR* interquartile range

Table 4 Interventions and outcome measures

Study (ref)	Intervention		End of trial 25(OH)D nmol/L mean (SD) unless otherwise stated		Strength Outcome measures (units)	Individual study
	Control Group	Treatment Group	Control	Treatment	Measurement technique	Effect size (95%CI)
Bischoff [23]	Calcium	800 IU D_3 and 1,200 mg calcium	28.5 (24.5,41.5)	65.5 (49.8,82.8)	Knee flexion (kiloponds)	0.19 (−0.31,0.69)
					Knee extension (kiloponds)	0.2 (−0.29,0.69)
			Median (IQR)	Median (IQR)	*Strain gauge*	
					Grip strength (bars)	0.12 (−0.38,0.62)
					HHD	–[a]
Brunner [24]	Placebo	400 IU D_3 with 1,000 mg calcium	Not stated		Grip strength (kg)	2 years
						0.01 (−0.06,0.09)
					HHD	5 years
						0.03 (−0.05,0.11)
Bunout [25]	400 IU D3 and 800 mg calcium or calcium alone 4 groups: • Exercise • No exercise • Vitamin D • Placebo		36.3 (11.5)	64.5 (16.3)	Pooled right and left knee extension (kg) *1RM*	−0.29 (−0.86, 0.28)
					Pooled right and left grip strength (kg) *HHD*	0.30 (−0.27, 0.87)
Corless [26]	Placebo	9,000 IU D_2 daily (oral)	18 (2)	110 (30)	Derived muscle strength score from functional tasks 40 weeks	Derived score, thus effect sizes not calculated. Authors found no statistically significant difference between groups.
Dhesi [27]	Placebo of saline injection	600,000 D_2 by injection	31.5 (28.5,34.5) Mean (95%CI)	43.8 (41.3,46.3) Mean (95%CI)	Knee extension (N) *strain gauge*	0.23 (−0.13, 0.58)
Grady [28]	Placebo	0.25 mcg calcitriol ($1,25(OH)_2D_3$) twice daily	Not stated		Knee extension	
					90 dps (*n–m*)	0.09 (−0.3, 0.49)
					120 dps (*n–m*)	0.12 (−0.28, 0.52)
					180 dps (*n–m*)	0.17 (−0.22, 0.57)
					Work 120 dps (joules)	0.19 (−0.21,0.59)
					Knee Flexion	
					90 dps (*n–m*)	0.04 (−0.36,0.43)
					120 dps (*n–m*)	−0.02 (−0.41,0.38)
					180 dps (*n–m*)	−0.03 (−0.42,0.37)
					Work 120 dps (joules)	−0.07 (−0.46,0.33)
					Isokinetic	
					Grip	−0.4 (−0.8,0)
					HHD	
Gupta [38]	Placebo	60,000 IU D3/week for 8 weeks followed by 60,000 IU D3 per week for 4 months. Calcium 1,000 mg daily	29.7 (15)	56 (17)	Grip strength (kg)	–[b]
					HHD	2.4 (1.2,3.6)
					Calf strength	3.0 (0.1,5.9)
					180 dps	
					Isokinetic	
					Pinch grip	0.2 (−0.01,0.4)
					Pinch gauge	
Janssen [39]	Placebo and 500 mg calcium	400 IU D3 and 500 mg calcium daily	41.6 (19)	77.2 (19.4)	Knee extension (*N*)	0.2 (−0.27,0.67)
					Strain gauge	
					Grip strength (kg)	0.13 (−0.34,0.6)

Table 4 (continued)

Study (ref)	Intervention		End of trial 25(OH)D nmol/L mean (SD) unless otherwise stated		Strength Outcome measures (units)	Individual study
	Control Group	Treatment Group	Control	Treatment	Measurement technique	Effect size (95%CI)
					HHD	
					Leg extension power (W)	
					Nottingham Power Rig	
Johnson [29]	Placebo	2,000 IU D_2 in arachis oil	Not stated		Actual muscle test used not given in detail. A derived score given	Effect sizes unable to be calculated due to incomplete data.
					One group had arms tested, another legs	No difference between treatment and control groups
Kenny [30]	Calcium	D_3 1,000 IU/day and 500 mg calcium	56.5 (17)	87.3 (13.8)	Leg press (*N*)	−0.03 (−0.48, 0.53)
					Leg press (watts)	
					1RM	
					Grip strength (kg)	−0.04 (−0.54, 0.47)
					HHD	
Kukuljan [31]	400 ml milk daily (1,000 mg calcium and 800 IU D_3)		>80	>80	Leg press (kg)	0.09 (−0.34, 0.51)
	Four groups:				Latissimus dorsi pull down (kg)	−0.32 (−0.75, 0.10)
	• Exercise				Bench press (kg)	−0.23 (−0.66,0.19)
	• No exercise				*1RM*	–[c]
	• Milk					
	• No milk					
Latham [32]	300,000 IU D_3 once (oral)		47.5 (40–52.5)	60 (52.5,77.5)	Knee extension (kg)	0 (−0.25,0.25)
	Four groups:		Median (95%CI)	Median (95%CI)	*HHD*	
	• Exercise					
	• No exercise					
	• Vitamin D					
	• Placebo					
Moreira [33]	Calcium	150 000 IU D_3 once a month for first 2 months followed by 90 000 IU per month for next 4 months and 1,000 mg calcium	51.8 (23.5,107.8)	86.6 (52.3,106.5)	Knee extension (kg) *HHD*	Effect sizes unable to be calculated due to incomplete data.
			Median (range)	Median (range)	Hip flexion (kg) *HHD*	No change in strength in control group. Hip flexion strength improved by 16.4% and knee extension strength by 24.7% in treatment group.
Pfeifer [34]	Calcium	800 IU D_3 daily and 1,000 mg calcium	57 (20)	84 (18)	Knee extension (*N*) *Strain gauge*	0.21 (−0.05, 0.47)
Sato [35]	Placebo	1,000 IU D_2 daily	13.3 (2.8)	83.5 (8.3)	Hip extension and hip flexion Scale 0–5 on right *Manual muscle test*	2.82 (2.22, 3.42)
Sato [36]	Calcium	Sunlight 15 min per day and 1,200 mg calcium	10.7 (5.2)	52.2 (9.7)	Hip rotation, knee flexion and extension Scale 0–5 on right *Manual muscle test*	4.18 (3.73, 4.63)
Smedshaug [37]	Placebo	400 IU D_3 in cod liver	Actual figure not given but stated no change from baseline	Actual mean not given but estimated to increase by 21.1 nmol/L	Grip strength *HHD* All patients	−0.31 (−0.82, 0.20)

Table 4 (continued)

Study (ref)	Intervention		End of trial 25(OH)D nmol/L mean (SD) unless otherwise stated		Strength Outcome measures (units)	Individual study
	Control Group	Treatment Group	Control	Treatment	Measurement technique	Effect size (95%CI)
			49.9 (34.8)	thus mean approx 70.3	25OHD <30 nmol/L (control n=10, Rx n=9)	−0.24 (−1.43, 0.67)

[a] standard deviation (SD), derived from interquartile range (IQR) using formula 1/2IQR=SD×0.675

[b] Difference in means after adjustment for age, gender, and baseline value

[c] Authors contacted and provided raw data for effect size calculation

25OHD 25 hydroxyvitamin D; *HHD* hand-held dynamometer; *1RM* one repetition maximum; *IU* international units; *CI* confidence interval; D_3 cholecalciferol; D_2 ergocalciferol

Baseline 25(OH)D level ≥25 nmol/L

Twelve studies with a total of 4,498 participants [23–25, 27, 28, 30–34, 37, 39].

Grip strength Seven studies [23–25, 28, 30, 37, 39] on 3,648 participants with 25(OH)D >25 nmol/L measured grip strength. Vitamin D supplementation had no significant effect on grip strength (SMD −0.02, 95% CI −0.15, 0.11; Fig. 2).

Proximal trunk and upper limb strength One study [31] on 180 community dwelling men with baseline 25(OH)D >25 nmol/L measured proximal upper limb muscles. There was no significant effect of vitamin D supplementation on bench press (SMD −0.23, 95% CI −0.66, 0.19) or lateral pull downs (SMD −0.32, 95% CI −0.75, 0.10).

Knee strength Of the eight studies that measured knee extension strength in participants with 25(OH)D >25 nmol/L, one study [33] did not provide enough data to calculate effect sizes. This study on 46 institutionalised elderly participants with insufficient 25(OH)D levels found that supplementation with vitamin D improved knee extension strength by 24.7% whilst there was no statistically significant difference between baseline and end of study strength in the control group. Vitamin D supplementation had no significant effect on knee extension strength when data from the remaining seven studies (n=1,010) was pooled (SMD 0.10, 95%CI −0.02, 0.29) [23, 25, 27, 28, 32, 34, 39]. Vitamin D supplementation had no significant effect on knee flexion strength when data was pooled from two studies [23, 28], total n=220, (SMD 0.10, 95%CI −0.21, 0.41).

Leg press There was no statistically significant difference between placebo and vitamin D groups in the two studies on 245 community dwelling vitamin D-sufficient men that measured leg press [30, 31] SMD 0.06 (95% CI −0.26, 0.39).

Hip strength One study [33] measured hip strength but did not provide enough data to calculate effect sizes. This

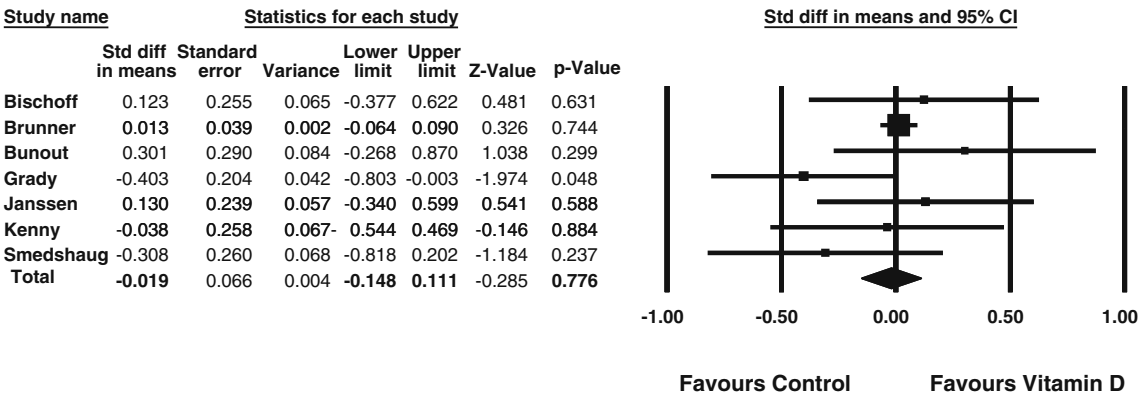

Fig. 2 Standardised mean difference, SMD and (95% confidence intervals) of effect of vitamin D supplementation on grip strength: SMD −0.02 (95% CI −0.15, 0.11) in studies with baseline 25(OH)D >25 nmol/L

study [33] on 46 institutionalised elderly patients with 25 (OH)D >25 nmol/L found that vitamin D supplementation improved hip flexion strength compared to control group in those participants with baseline 25(OH)D levels <50 nmol/L (p=0.003). There was no statistically significant improvement in hip flexion strength in those patients with baseline 25(OH)D levels >50 nmol/L (p=0.21).

Overall proximal lower limb strength The results from knee extension, knee flexion, leg press, and hip strength in studies with 25(OH)D >25 nmol/L were combined to give an overall SMD of proximal lower limb strength from eight studies with a total of 1,255 adults. There was no significant effect of vitamin D supplementation on proximal lower limb strength (SMD 0.1, 95%CI −0.01, 0.22) in this pooled group of studies (Fig. 3).

Baseline 25(OH)D level ≤25 nmol/L

Four studies with a total of 465 participants with baseline 25(OH)D <25 nmol/L were identified [26, 35, 36, 38]. Three of the studies included participants from geriatric inpatient settings [26, 35, 36], the remaining study was on healthy young adults [38]. One study on inpatient geriatric participants derived a strength score from functional activities and found no significant difference between groups. A recent study on healthy, young adults demonstrated a statistically significant difference between treatment and control groups in grip strength (p<0.001) and calf strength (p=0.04), but not in pinch grip strength (p=0.07).

Finally, two studies on a total of 360 institutionalised adults [35, 36] demonstrated a significant effect of vitamin D supplementation on proximal lower limb muscle strength (SMD 3.52, 95%CI 2.18, 4.85).

Discussion

The aim of this systematic review was to evaluate the effect of vitamin D supplementation on muscle strength in adults. The majority of studies were of medium to high methodological quality as assessed on the PEDro scale. This systematic review demonstrates no significant effect of vitamin D supplementation on grip strength, knee extension strength, and knee flexion strength in participants with 25(OH)D levels >25 nmol/L. However, a limited number of studies demonstrate a positive effect of vitamin D supplementation on proximal muscle [35, 36], calf [38], and grip strength [38] in participants with 25(OH)D levels ≤25 nmol/L. Studies investigating vitamin D supplementation in falls and fracture reduction have recommended that a minimum of 800 IU daily is required. This recommendation is in the absence of baseline (and often post-treatment) 25(OH)D levels. The majority of studies included in this current systematic review provided baseline and post-treatment 25(OH)D serum levels. With all but one study achieving 25(OH)D levels of >50 nmol/L regardless of type or dose of supplementation. Baseline 25 (OH)D levels in the study that did not achieve >50 nmol/L of vitamin D in the supplemented group [27] were bordering on deficiency (median 26 nmol/L). The treatment group received 600,000 IU D_2 once by injection with outcome measures taken at 6 months. It has been suggested that D_2 is more rapidly metabolised than D_3, thus a large once off dose may be inadequate at 6 months given the baseline 25(OH)D status [40, 41]. The role of calcium in combination with vitamin D on muscle function is not clear and warrants further investigation given the recent meta-analyses demonstrating that to reduce fractures, vitamin D must be given in conjunction with calcium [42, 43].

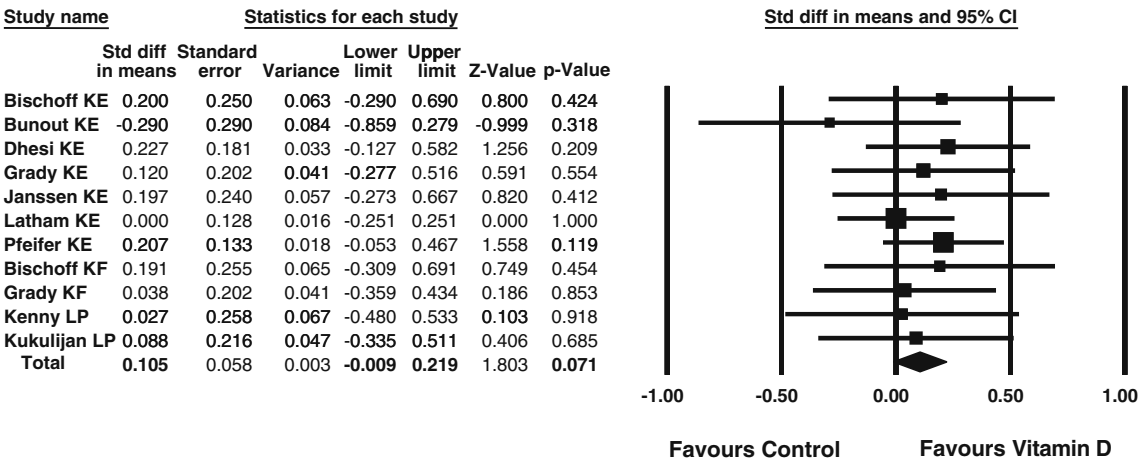

Fig. 3 Standardised mean difference, SMD and (95% confidence intervals) of effect of vitamin D supplementation on proximal lower limb strength in adults with 25(OH)D levels >25 nmol/L: SMD 0.1 (95% CI −0.01,0.22). *KE* knee extension, *KF* knee flexion, *LP* leg press

Calcitriol ($1,25(OH)_2D$ vitamin D) was the supplement of choice in one of the included studies [28]. However, due to its expense and the risk of hypercalcaemia, it is only recommended as a supplement in those patients who cannot convert standard vitamin D supplement to activated vitamin D, such as severe renal disease.

Vitamin D receptors have been identified in muscle cells [5, 6] which supports the concept of a direct effect of vitamin D on muscle tissue. However, very few studies have explored this. Vitamin D deficiency is reported to cause proximal muscle weakness with a reduction in type 2 muscle fibres [44]. Type 2 fibres are fast twitch and are recruited in activities of high intensity but short duration. An uncontrolled study [45] on elderly women demonstrated an increase in cross-sectional area and number of type 2A muscle fibres in vastus lateralis following 3–6 months supplementation with 1α hydroxyvitamin D. Only one study in this current review [35] incorporated muscle fibre analysis and this was in patients with deficient 25(OH)D whereby a significant increase in strength and type 2 fibre cross-sectional area and percentage of vastus lateralis muscle was found. Type 2 muscle fibres are the first to be recruited in balance and preventing a fall which may explain the inverse association between 25(OH)D levels and falls [46, 47]. In addition, a recent study on healthy young women [48] demonstrated an inverse relationship between skeletal muscle fat and 25(OH)D levels. The effect of this relationship on muscle strength and/or function has not been established. Future studies investigating the effect of vitamin D supplementation on muscle should incorporate analysis of muscle composition.

Isokinetic dynamometry provides an objective, reproducible evaluation of strength more closely aligned to activities of daily living than isometric evaluation. However, only two studies in this review [28, 38] utilised isokinetic dynamometry. Methods used for evaluation of strength in the other studies carry an increased risk of error. Accurate measures from HHD and strain gauge rely on ensuring that the force transducer is placed in exactly the same position on the limb at each measurement time point and that there is adequate stabilisation of the body part being tested [49] both of which were not mentioned in most studies [23, 27, 32, 34]. In addition, with HHD, the tester must be able to exert a force greater than the muscle being tested [50]. Measurement error of 1RM is high and relies on adequate familiarisation of the participant and experience of the investigator [51]. MMT as measured by two studies [35, 36] has been found to be inaccurate at higher grades. However, the baseline strength of the participants in both studies was very low, thus MMT would be less prone to error and possibly a suitable measure for this population.

All studies included in this systematic review investigated maximal muscle strength which is only one component of muscle function. In activities of daily living, maximal force is rarely required. Rate of force development (RFD) may be more appropriate to test given the evidence regarding preferential atrophy of type 2 muscle fibres with vitamin D insufficiency. RFD can be measured using isokinetic/isometric contraction with electromyography or functionally such as use of jumping mechanography. Jumping mechanography has been used in a cross-sectional study of 99 post-menarchal 12–14-year-old girls demonstrating a relationship between 25 (OH)D level, jump velocity, and power. Due to the cross-sectional design, causality cannot be determined; however, the outcome measure utilised may be preferable to measuring maximal strength alone when investigating the effect of vitamin D supplementation on muscle function.

Limitations

A positive effect of vitamin D supplementation on muscle if higher than 25(OH)D levels are achieved cannot be excluded. Recently, the International Osteoporosis Foundation Position Statement on Vitamin D has been published [52]. The majority of the working party members felt that based on RCTs in falls and fracture reduction, the optimal level for serum 25(OH)D is 75 nmol/L. The optimal level of 25(OH)D for muscle is not known. This review found no evidence that vitamin D supplementation improved muscle strength in patients with levels >25 nmol/L. Measuring proximal hip muscle strength may yield a different outcome given that Moreira-Pfrimer et al. [33] found positive effect of vitamin D supplementation on hip flexion strength in participants with baseline 25(OH)D 25–50 nmol/L. It is difficult to draw conclusions regarding this as Moreira-Pfrimer et al. was the only study included in this review that measured hip muscle strength in participants with baseline 25(OH)D >25 nmol/L and effect sizes could not be calculated due to insufficient data.

Population studied

Despite inclusion criteria aiming to include adults >18 years of age only one study included participants <60 years of age [38].

A further limitation of this review is the possible effect of publication bias. An attempt was made to decrease the likelihood of this occurring by searching for registered trials in the area and contacting key researchers in the field where appropriate. Only English-language studies were included; however, as only two non-English language RCTs were identified, this is unlikely to have biassed the outcomes.

Conclusion

Based on studies included in this systematic review; while vitamin D supplementation may not be effective at improving muscle strength in vitamin D replete adults, there is evidence that supplementation may increase muscle strength in adults with 25(OH)D ≤25 nmol/L. It would be difficult to ethically justify randomised placebo-controlled trials of vitamin D supplementation in patients with clearly established deficiency (<25 nmol/L) due to the implications on calcium and phosphate homeostasis and thus bone health. Further, well-designed randomised controlled trials using appropriate outcome measures need to be conducted investigating the effect of vitamin D supplementation on muscle fibre composition and its relationship to proximal muscle power and physical function in patients with insufficient levels of vitamin D (25–50/75 nmol/L). In addition, there is a distinct lack of randomised controlled trials investigating vitamin D supplementation in disease-specific populations where Vitamin D deficiency is common.

Conflicts of interest None.

Appendix 1—search strategy

The databases, searched with language restrictions (English only) included: MEDLINE, CINAHL, EMBASE, Pubmed, Cochrane Controlled Trials Register, Sportdiscus, Scopus and Full text clinicians' health journals @ Ovid from the earliest time to May 2010.

Database*

1. Muscle	725,556
2. Vitamin D	46,203
3. Vitamin D2	3,330
4. Vitamin D3	21,590
5. 1-alpha hydroxyvitamin D3	924
6. 1-alpha hydroxycalciferol	6
7. 1,25 dihydroxyvitamin D3	15,436
8. 1,25 dihydroxycholecalciferol	14,828
9. 25 hydroxycholecalciferol	2,901
10. 25 hydroxyvitamin D	3,660
11. Calcitriol	14,347
12. Ergocalciferol	2,791
13. Cholecalciferol	19,270
14. Calcifediol	2,319
15. Alfacalcidiol	871
16. Calcidiol	2,438
17. Calciferol	2,931
18. 2 to 17 "OR"	48,722
19. 1. "AND" 18	1,611
20. 19 limits RCT, clinical trial, meta-analysis, review	315
21. eliminate review	53
22. 21 "AND" English	51

*Medline

Search format repeated for Cinahl, Sportdiscus, Cochrane library, Pubmed and Embase.

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