

Vitamin D supplementation improves neuromuscular function in older people who fall

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Abstract

Background: vitamin D supplementation reduces the incidence of fractures in older adults. This may be partly mediated by effects of vitamin D on neuromuscular function.

Objective: to determine the effects of vitamin D supplementation on aspects of neuromuscular function known to be risk factors for falls and fractures.

Design: randomised, double-blind, placebo-controlled study.

Setting: falls clinic taking referrals from general practitioners and accident and emergency department.

Subjects: 139 ambulatory subjects (≥ 65 years) with a history of falls and 25-hydroxyvitamin D (25OHD) ≤ 12 $\mu\text{g/l}$.

Intervention: patients were randomised to receive a single intramuscular injection of 600,000 i.u. ergocalciferol or placebo.

Outcome measures: assessments including biochemistry, postural sway, choice reaction time (CRT), aggregate functional performance time (AFPT), and quadriceps strength were carried out at baseline and 6 months post-intervention.

Results: baseline characteristics were comparable between both groups. 25OHD in the treatment group increased significantly at 6 months. AFPT deteriorated in the control group and improved in the intervention group, representing a significant difference between groups (+6.6 s versus -2.0 s, $t=2.80$, $P<0.05$). Similar changes were observed for CRT (-0.06 s versus $+0.41$ s, $t=-2.52$, $P<0.01$) and postural sway ($+0.0025$ versus -0.0138 , $t=2.35$, $P<0.02$). There was no significant difference in muscle strength change between groups (-10 N versus -2 N, $t=-1.26$, ns). A significant correlation between change in AFPT and change in 25OHD levels was observed ($r=0.19$, $P=0.03$). There was no significant difference in the number of falls (0.39 versus 0.24, $t=1.08$, $P=0.28$) or fallers (14 versus 11, $P=0.52$) between two groups.

Conclusions: vitamin D supplementation, in fallers with vitamin D insufficiency, has a significant beneficial effect on functional performance, reaction time and balance, but not muscle strength. This suggests that vitamin D supplementation improves neuromuscular or neuroprotective function, which may in part explain the mechanism whereby vitamin D reduces falls and fractures.

Keywords: vitamin D, muscle, accidental falls, aged, 25-hydroxyvitamin D3, elderly

Introduction

Vitamin D insufficiency is common in later life [1], not only in frail housebound older people [2] but also in those living independently and going out frequently [3]. It is a major

contributor to fracture risk [4] and a recent study demonstrated that vitamin D supplementation reduces the fracture rate in older adults [5]. The modest changes in bone mineral density observed with vitamin D supplements are unlikely to be the sole explanation for the reduced fracture rate. In

the elderly most non-vertebral fractures occur as a result of falls [6] and it is noted that in this population age-related factors other than bone mineral density are important determinants of fracture risk [7].

Cross-sectional studies show that serum 25-hydroxy-vitamin D (25OHD) levels are associated with quadriceps strength [8, 9] and balance [10, 11], both being predictors of falls and non-vertebral fracture [12, 13]. Furthermore, older adults with higher vitamin D levels have less frequent falls [14] and both short-term vitamin D and calcium supplementation in healthy older adults [11] and longer term supplementation in long-stay geriatric care appear to reduce falls, with recurrent fallers appearing to benefit most from treatment [15]. In contrast, vitamin D supplementation in older community-dwelling men (with normal 25OHD levels) did not improve muscle strength, physical performance or health perception [16], suggesting that future investigations should focus on individuals with low vitamin D levels.

In a randomised, double-blind, placebo-controlled study we focused on a falls clinic population; a group known to be at increased risk of falls and fracture and also a group with a high prevalence of vitamin D insufficiency [3]. We examined the effects of vitamin D supplementation on neuromuscular parameters known to be risk factors for falls and fractures.

Patients and methods

Study design

Prospective, randomised, double-blind, placebo-controlled study.

Participants

All patients attending a falls clinic between May 1999 and May 2001 were screened. As recruitment continued over 2 years, the effects of fluctuations in vitamin D levels due to seasonal variation were minimised. All patients were aged 65 and over, lived in their own homes, and had had at least one fall in the preceding 8 weeks. A fall was defined as inadvertently coming to rest on the ground or other lower level with or without loss of consciousness and other than as a consequence of sudden onset of paralysis, epileptic seizure, excess alcohol intake, or overwhelming external force [17]. Patients with 25OHD levels $\leq 12 \mu\text{g/l}$ and normal bone biochemistry (calcium, phosphate, alkaline phosphatase) were recruited. This level of 25OHD was chosen as patients fulfilling these criteria have previously been shown to have significantly impaired neuromuscular function compared with those with 25OHD levels $> 12 \mu\text{g/l}$ [10]. It was therefore postulated that they would benefit most.

Exclusion criteria included over-the-counter or prescribed vitamin D or calcium supplements. Patients were also excluded if they had a history of chronic renal failure, alcohol abuse, or conditions likely to impair postural stability (cerebellar disease, vestibular disease), or those on medications likely to interfere with postural stability or

vitamin D metabolism and those with an abbreviated mental test score of $\leq 7/10$. Verbal and written informed consent was obtained. The study was approved by the local research ethics committee. The progress of patients throughout the trial is shown in Figure 1.

Baseline assessment

An existing falls clinic proforma was used to record medical history and physical examination [18]. Medical staff trained in falls assessment saw all patients. An abbreviated mental test score (AMT) and the number of times the patient went outdoors per week were recorded. The SF-36 Health Survey was undertaken. Body mass index was calculated using the formula $\text{weight}/\text{height}^2$ (kg/m^2). Patients were given a falls diary to record any falls over the trial period, as verbal recall is known to be poor. The diary was reviewed with the patient by the first author at the follow-up assessment.

Neuromuscular parameters

All patients received standardised instructions from trained staff (first and third authors) for the following neuromuscular tests, which are well validated.

Functional performance—aggregate functional performance time

Objective assessment of lower limb functional performance was determined by the time taken to perform four common activities of daily living (50 ft walk, rising from a 42 cm high chair and walking 50 ft, ascent and descent of 13 steps). The sum of the time (in seconds) taken to perform these activities was calculated to determine the Aggregate Functional Performance Time (AFPT) [19]. Patients were requested to use their normal walking aids.

Psychomotor function—choice reaction time

Psychomotor performance was assessed by the four-choice reaction time (CRT), using an automated computer program. Patients took part in a familiarisation session to minimise learning effects. Once a plateau was reached, the patients completed the test three times. The mean CRT was calculated (seconds) and taken as an estimate of CRT [20].

Postural stability

Postural sway was assessed during a bipedal stance with eyes open. Patients were asked to stand as still as possible on a custom-built platform with arms by their sides, looking at a stationary target for 15 s. The degree of body sway was estimated using software, which adjusted for each patient's height, weight and gender [21, 22].

Quadriceps strength

Quadriceps strength was assessed using a strain gauge system attached to a specially constructed chair upon which the patients were seated with their hips and knees flexed to

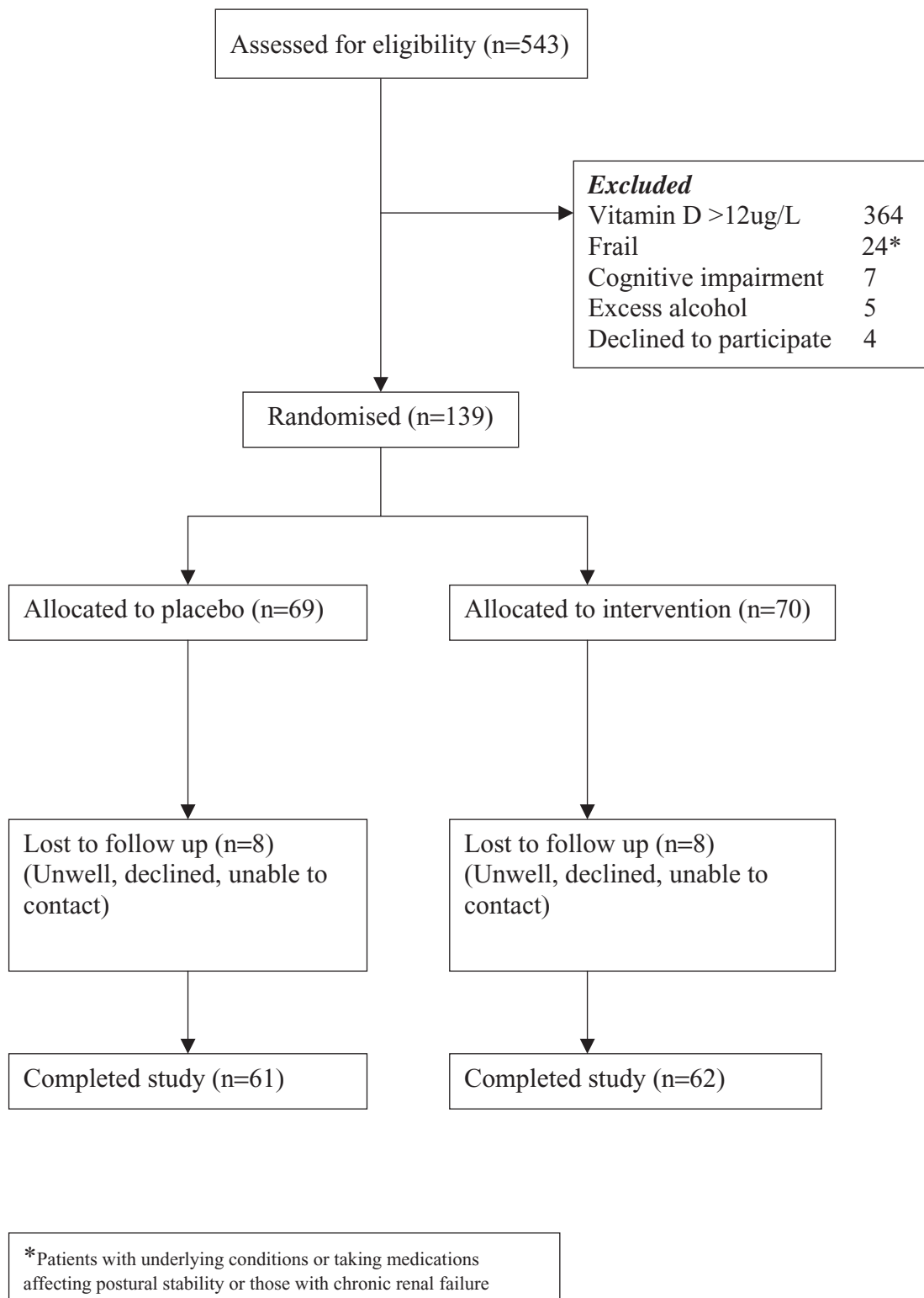


Figure 1. Flow diagram for the study.

approximately 90°. In this position, three maximal voluntary contractions (MVC) were recorded and analysed off-line. The strongest MVC (newtons) of the dominant leg was used in data analysis [23].

Laboratory analyses

Calcium, phosphate, alkaline phosphatase and albumin were measured by standard automated chemistries on DAX (Bayer, UK). Intact parathyroid hormone (PTH) was measured by

ELISA (Nichols Inst. Diagnostics Ltd, Newport, UK). Serum 25OHD was measured using an IDS Gamma-B 25-OH immunoassay with [¹²⁵I]25-OH vitamin D label and a highly specific sheep anti-25-OH polyclonal antibody (IDS, Tyne & Wear, UK).

Intervention

At the end of the first assessment, patients were randomised (in blocks of 20, by computer program, independently of the investigators) to receive either active treatment or placebo as a single intramuscular injection. Active treatment comprised 600,000 i.u. of ergocalciferol and the placebo was an equivalent volume (2ml) of normal saline, administered by a senior nurse not involved in assessments. An intramuscular injection was chosen for the active treatment as it is a cheap, simple and reliable method for administration and ensures compliance. The dose was based on previous work demonstrating sustained 25OHD levels at 6 months [24]. Patients in both groups received usual care through the falls clinic.

Follow-up

All baseline assessments of the patients who agreed to take part were repeated at 6 months following intervention. One week prior to the second assessment, the patients were reminded of their appointment. Patients who did not wish to attend for the second assessment were advised to discuss the need for vitamin D replacement with their general practitioners. The reason for non-attendance was recorded.

Statistical analyses

It was decided, a priori, that CRT and AFPT would be the primary outcome measures. These measures are predictors of falls and fractures, and were previously shown by our group to be reliable, reproducible and amenable to intervention. Secondary outcome measures were muscle strength, postural stability, biochemical measures and number of falls. Data were analysed on an intention to treat basis using the Stata Intercooled computer package (Timberlake, London, UK). Results with *P* values <0.05 were considered statistically significant. Results for baseline characteristics and for biochemical measures were expressed as means with standard deviations. Neuromuscular parameters were log transformed and the results expressed as geometric means with 95% confidence intervals. Within-group changes over the 6 months in the placebo and intervention groups were compared using paired *t*-tests.

Results

Demographic characteristics

Subjects were elderly, cognitively intact and comparatively fit, as demonstrated by the low number of medications and the frequent days out per week (Table 1). The majority were female and Caucasian, and all lived in their own homes. There were no significant differences in baseline demographic characteristics between the placebo or intervention group.

Table 1. Baseline characteristics of patients randomised to receive placebo (P) or 600,000 i.u. of ergocalciferol (I) (mean with SD)

	P	I
Age (years)	76.6 (6.1)	77.0 (6.3)
Sex		
Male (<i>n</i>)	14	16
Female (<i>n</i>)	55	53
Ethnicity		
Caucasian (<i>n</i>)	53	61
Afro-Caribbean (<i>n</i>)	9	6
Middle Eastern (<i>n</i>)	7	2
BMI	27.0 (4.5)	27.3 (5.6)
No. of times out per week	3.8 (2.3)	4.2 (2.4)
No. of drugs	2.5 (2.2)	2.2 (1.7)
AMT	9.4 (0.8)	9.5 (0.8)

Biochemical assessment

At baseline there were no significant differences in any biochemical test between the placebo and intervention groups (Table 2). There were no significant changes in corrected calcium, phosphate, alkaline phosphatase or albumin levels in either group over the 6 months.

As expected, there was a significant increase in 25OHD levels in the intervention group (10.4 µg/l versus 17.5 µg/l, *t*=−13.2, *P*<0.01). There was a small but statistically significant increase in 25OHD in the placebo group (10.0 µg/l versus 12.6 µg/l, *t*=−4.2, *P*<0.01). This is in keeping with seasonal fluctuation and values in this range still reflect severe deficiency.

25OHD and PTH were negatively correlated at baseline (*r*=−0.234, *P*<0.05) and at 6 months (*r*=−0.229, *P*<0.01). PTH decreased more in the intervention group than the placebo group, although these changes were not significant (−3.7 versus −1.6, *t*=0.55, ns).

Baseline neuromuscular function

There was no significant difference in baseline neuromuscular parameters between the placebo and intervention groups (Table 2).

Functional performance

The placebo group showed a 6.6 s deterioration in AFPT over the trial period, whereas the treatment group improved by 2.0 s, resulting in a significant difference in the change over 6 months between the two groups (+6.6 s versus −2.0 s, *t*=2.80, *P*<0.01) (Table 2).

Choice reaction time

The placebo group demonstrated a non-significant reduction in CRT, whereas the intervention group became faster by 0.41 s, resulting in significant differences in the change over 6 months between the two groups (+0.06 s versus −0.41 s, *t*=−2.52, *P*=0.01) (Table 2).

Postural stability

The placebo group showed a slight deterioration (3%), whereas the intervention group improved by 13%, with a significant

Table 2. Biochemistry and neuromuscular function of placebo (P) and intervention (I) groups at baseline and at 6 months

		Baseline	6 months	Change over 6 months
25OHD (µg/l)	P	10.0 (9.5–10.5)	12.6 (11.4–13.8)	2.7 (1.6–3.8)
	I	10.7 (10.2–11.2)	17.5 (16.5–18.5)	6.9 (5.9–8.0)
PTH (i.u.)	P	59.1 (51.7–66.5)	60.1 (50.0–70.3)	1.2 (–8.6–11.1)
	I	52.1 (44.8–59.5)	49.8 (44.0–55.7)	–2.1 (–7.8–3.6)
AFPT (s)	P	72.9 (63.0–82.8)	76.8 (65.4–88.1)	+6.6 (0.8–12.4)
	I	65.8 (55.6–76.0)	65.5 (54.9–76.1)	–2.0 (–4.4–0.3)
CRT (s)	P	2.29 (1.82–2.76)	2.32 (1.80–2.84)	+0.06 (–0.35–+0.23)
	I	2.67 (2.13–3.21)	2.30 (1.82–2.78)	–0.41 (+0.17–+0.66)
Postural sway	P	0.0978 (0.0850–0.1105)	0.0999 (0.0857–0.1140)	+0.0025 (–0.0089–+0.0139)
	I	0.1044 (0.909–0.1178)	0.0899 (0.0784–0.1015)	–0.0138 (–0.0218––0.0059)
MVC (Newtons)	P	205 (187–223)	198 (178–218)	–10 (–19––2)
	I	203 (182–225)	204 (181–227)	–2 (–11––8)

difference in the change over 6 months between the two groups (+0.0024 versus –0.0138, $t=2.35$, $P=0.02$) (Table 2).

Lower limb muscle strength

Both groups showed a loss of strength over the trial period. Although this was greater in the placebo compared with the intervention group (–10 N versus –2 N), the difference between groups was not significantly different ($t=-1.26$, ns) (Table 2).

SF-36

There were no significant differences between the intervention and placebo group in any parameter of the SF-36 at baseline. There was a significant improvement in emotional role and social functioning in the placebo group over the 6 months. However, there were no other significant changes in any of the other parameters in either the placebo or treatment group (Table 3).

Falls

In the placebo group, 14 patients had 24 falls, in comparison to 11 patients having 15 falls in the intervention group. There was no significant difference in the mean number of falls (0.39 versus 0.24, $t=1.08$, $P=0.28$) or fallers (14 versus 11, $P=0.52$) between the placebo and intervention group.

Table 3. SF-36 Health Survey of placebo (P) and intervention (I) groups at baseline and at 6 months (mean with SD)

		Baseline	6 months	<i>P</i>
Physical functioning	P	49.6 (28.7)	51.0 (27.8)	0.47
	I	56.7 (31.0)	54.7 (29.3)	0.36
Role – physical	P	44.2 (40.2)	56.2 (42.4)	0.05
	I	56.2 (42.2)	61.6 (41.8)	0.31
Bodily pain	P	62.3 (26.8)	67.4 (25.7)	0.15
	I	61.7 (28.0)	62.8 (23.9)	0.74
General health	P	61.0 (10.9)	60.2 (11.0)	0.68
	I	60.0 (13.3)	60.7 (10.6)	0.63
Vitality	P	48.6 (21.9)	47.0 (19.4)	0.41
	I	46.5 (23.5)	47.5 (19.3)	0.67
Social functioning	P	66.3 (28.3)	76.8 (27.6)	0.03
	I	68.8 (26.8)	75.0 (26.3)	0.10
Role – emotional	P	78.6 (36.8)	89.3 (25.5)	0.04
	I	86.6 (28.9)	89.9 (33.0)	0.59
Mental health	P	69.3 (24.4)	71.1 (19.9)	0.24
	I	71.1 (21.4)	73.6 (14.5)	0.28

Correlation between changes in vitamin D and changes in neuromuscular parameters

A significant correlation was noted between change in vitamin D and change in AFPT across both groups ($r=0.19$, $P=0.03$). However, there was no relationship between change in 25OHD and change in MVC ($r=0.05$, $P=0.58$), CRT ($r=0.02$, $P=0.83$) or postural sway ($r=-0.11$, $P=0.22$).

Interpretation

This study demonstrates that vitamin D supplementation has clinically beneficial effects on neuromuscular function in older adults with vitamin D insufficiency who have fallen.

The intervention used, intramuscular ergocalciferol, ensured treatment adherence and a clinically meaningful increase in 25OHD levels in the intervention group. The dose used was similar to that used in studies of vitamin D supplementation and fracture rate [5]; however, some patients had serum 25OHD levels in the deficient range at 6 months. This may reflect a variation in response or, alternatively, levels may have peaked earlier and been in decline at 6 months.

Functional performance, although related to quadriceps strength, is an objective measure of coordinative neuromuscular function. Cross-sectional studies have demonstrated correlation between serum 25OHD and both functional performance [10] and exercise capacity [25]. In our randomised controlled trial, physical performance deteriorated in the placebo group by 9%, whereas the intervention group showed improvements of 3%. We also observed a correlation between change in AFPT and change in 25OHD levels. One previous randomised study conducted in long-stay geriatric patients did not observe an improvement in functional abilities; however, these patients had significant comorbidities which were likely to affect performance [26]. Similarly, vitamin D supplementation in healthy older community-dwelling men did not improve functional abilities [16]. Our findings are contrary to those studies and suggest that a specific group of patients, those with vitamin D insufficiency attending a falls clinic, is a group likely to benefit from supplementation. Gloth *et al.* have approached this question using different methodology, a questionnaire designed specifically to assess function in homebound elderly subjects. A relationship between an

increase in vitamin D and an improvement in questionnaire score was observed [27].

Postural stability is a major determinant of falls and fracture risk in older adults [12, 13], and is related to 25OHD status [10, 28]. We observed a 13% improvement in postural stability with vitamin D supplementation in comparison with a 3% deterioration in the placebo group. This is similar to the improvements seen by Pfeifer *et al.* with short-term (8 weeks) vitamin D supplementation in healthy, community-dwelling, vitamin D-deficient women. They observed a 9% reduction in total body sway [11]. Our population may have benefited more from supplementation as they had a history of falls and lower baseline vitamin D levels.

Reaction times deteriorate with age [29] and play an important role in neuroprotective responses [30]. In cross-sectional work we identified a correlation between vitamin D status and reaction times, suggesting a role in neuroprotection [10]. We now demonstrate that supplementation in vitamin D-insufficient older adults results in a 15% improvement in reaction time, in comparison with mild deterioration in the placebo group (3%).

Despite the observed relationship between declining vitamin D status and decline in muscle strength [8, 9, 31], previous studies have been unable to show improvements with vitamin D replacement. Grady *et al.* did not show any change in knee flexion or extension in a randomised study; however, the majority of subjects were vitamin D replete at baseline [32]. However, one small case-controlled study in vitamin D-deficient elderly women has observed improvement in strength following 6 months treatment with α -calcidiol [33]. Our data suggest that vitamin D does not improve muscle strength in older adults with vitamin D insufficiency attending a falls clinic. However, strength does seem to decline if vitamin D insufficiency is untreated, in accordance with Grady's findings, and it is possible that vitamin D could mitigate this decline. The second assessment at 6 months may have been too early, particularly as the histological changes secondary to vitamin D deficiency [34, 35] take 6–12 months treatment to recover [36]. Alternatively, vitamin D may affect power or endurance more than strength.

In order to assess well-being we utilised the SF36. The placebo group improved significantly in emotional role and social functioning over 6 months. No significant change was observed in the intervention group, whereas previous work has demonstrated an improvement in seasonal affective disorder with vitamin D supplementation [37].

A significant correlation between 25OHD levels and the occurrence of falls has been reported [8, 14]. In a randomised trial of treatment for 8 weeks with vitamin D and calcium in healthy older women, fewer falls per subject over 1 year were observed [11]. However, long-term treatment in the healthy elderly in Holland (vitamin D monotherapy over 2 years) [38] and in Boston (vitamin D and calcium over 3 years) did not significantly lower the incidence of falls [39]. We did not find a significant reduction in falls; however, our study was not powered to assess such an effect. Interestingly, PTH has been identified as an independent predictor of both falls [14] and muscle strength [10]. Vitamin D supplementation in our study did not significantly alter

PTH levels. In order to see beneficial effects on muscle strength and falls, it may be necessary to observe a significant change in PTH, suggesting that a higher dose of vitamin D may be necessary.

Our study identified a trend, albeit non-significant, for deterioration in the measured parameters in the placebo group over a relatively short time period. This suggests that the falls clinic population is at high risk of functional decline, highlighting the need to identify and treat such a population as early as possible. Furthermore, we have demonstrated that a subgroup of this population benefits from vitamin D supplementation. In particular, improvements in postural sway and reaction times were observed and supplementation mitigated the deterioration in functional performance, suggesting beneficial effects on neuromuscular or neuroprotective functions more so than muscle strength *per se*. Review of our work in the context of previous studies suggests that specific older populations benefit from supplementation. Although our study was confined to those with vitamin D levels $\leq 12 \mu\text{g/l}$, it is possible that all falls clinic patients would benefit from supplementation in terms of neuromuscular function and further research is needed to address this subject.

Key points

- Impaired neuromuscular function is related to an increased risk of falls and fractures in the older population.
 - Previous cross-sectional work suggests that neuromuscular function is related to vitamin D status.
 - Our study demonstrates that vitamin D supplementation has beneficial effects on functional performance, balance and reaction time but not on muscle strength.
 - Vitamin D supplementation improves neuromuscular co-ordination, rather than muscle strength *per se*, and may reduce falls and thereby fractures.
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