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ORIGINAL ARTICLE

Calcifediol versus vitamin D_3 effects on gait speed and trunk sway in young postmenopausal women: a double-blind randomized controlled trial

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Abstract
Summary In this double-blind RCT, 4-month treatment with calcifediol compared with vitamin D_3 improved gait speed by 18 % among young postmenopausal women. Consistently, change in 25(OH)D blood levels over time were significantly correlated with improvement in gait speed in these women. No effect could be demonstrated for trunk sway.

Introduction The aim of this study is to test the effect of calcifediol compared with vitamin D_3 on gait speed and trunk sway.
Methods Twenty healthy postmenopausal women with an average 25(OH)D level of 13.2 ng/ml (SD=±3.9) and a mean age of 61.5 years (SD=±7.2) were randomized to either 20 μg of calcifediol or 20 μg (800 IU) of vitamin D_3 per day in a double-blind manner. At baseline and at 4 months of follow-up, the same physiotherapist blinded to treatment allocation tested 8-m gait speed and a body sway test battery (Sway star pitch and roll angle plus velocity while walking 8 m, and standing on both legs on a hard and soft surface). All analyses adjusted for baseline measurement, age, and body mass index.
Results Mean 25(OH)D levels increased to 69.3 ng/ml (SD=±9.5) in the calcifediol group and to 30.5 ng/ml (SD=±5.0) in the vitamin D_3 group ($p<0.0001$). Women receiving calcifediol compared with vitamin D_3 had an 18 % greater improvement in gait speed at 4-month follow-up ($p=0.046$) adjusting for baseline gait speed, age, and body mass index. Also, change in gait speed was significantly correlated with change in serum 25(OH)D concentrations ($r=0.5$; $p=0.04$). Across three tests of trunk sway, there were no consistent differences between groups and no significant correlation between change in 25(OH)D serum concentrations and change in trunk sway.
Conclusions Calcifediol improved gait speed in early postmenopausal women compared with vitamin D_3 and change in 25(OH)D level was moderately correlated with improvement in gait speed. A benefit on trunk sway could not be demonstrated.

Keywords 25(OH)D · Gait speed · Postmenopausal women · RCT · Trunk sway · Vitamin D

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Introduction

Gait speed assessment among older patients has been proposed as a key diagnostic tool [1] for the prediction of disability [2] and loss of autonomy [3] and its association with accelerated progression of several age-related chronic diseases, such as falls and fractures, as well mortality risk [4].

Several cross-sectional studies found an association between higher 25(OH)D level and greater gait speed [5–10]. However, a recent trial-level meta-analysis of clinical trials could not confirm this association based on limited data from three trials that tested gait speed as an endpoint [11]. Of the three trials pooled by Muir and Montero-Odasso, one provided 300,000 IU vitamin D_3 [12], one 20 IU calcitriol [13], and one 400 IU vitamin D_3 in combination with 800 mg calcium [14], and only the latter demonstrated a significant benefit on gait speed. The same meta-analysis demonstrated a significant reduction of postural sway across three trials, which individually showed a nonsignificant benefit (standardized mean difference of −0.20; 95 % confidence interval (CI)=−0.39 to −0.01): one provided 400 IU vitamin D_3 in combination with 800 mg calcium daily [14], one 600,000 IU vitamin D_2 once per year [15], and one 800 IU vitamin D_3 plus 1000 mg of calcium daily [16]. With respect to their analyses by dose, the authors concluded that optimal benefits are achieved with daily doses of 800 to 1000 IU, while lower doses or a large annual dose of vitamin D were less effective with respect to muscle strength and balance [11].

Mechanistically, several lines of evidence support a possible role of vitamin D supplementation in gait speed and trunk sway among individuals at risk of vitamin D deficiency. First, the vitamin D receptor (VDR) is expressed in human muscle tissue [17, 18], although this was questioned recently [19]. Second, VDR activation may promote de novo protein synthesis in muscle [20], as recently confirmed in a controlled clinical trial among 21 mobility-limited women aged 65 and older [21]. Third, Mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [22, 23]. Fourth, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [24]. Clinical findings in vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [25].

To our knowledge, no trial to date has tested whether shifting individuals to a higher 25(OH)D serum concentration beyond what would be achieved with the current standard of 800 IU vitamin D per day has an effect on gait speed or balance. Therefore, the goal of this trial was to assess the effect of calcifediol, known to be two to three times more potent than vitamin D_3 [26, 27], compared with 800 IU vitamin D_3 per day on gait speed and trunk sway in early postmenopausal women.

Methods

Participants

Twenty white postmenopausal women 50–70 years of age and in good general health were recruited through newspaper advertisements for this clinical trial and randomized to receive oral supplementation of either 20 μg of calcifediol or 20 μg (800 IU) of vitamin D_3 per day. Other inclusion criteria were serum 25 (OH)D level between 8 and 24 ng/ml (20 to 60 nmol/l), body mass index between 18 and 29 kg/m^2, and ability to give informed consent. Exclusion criteria consisted of medical contraindications to vitamin D supplements, medical conditions, or medication use that would alter pharmacokinetics of study products or otherwise interfere with the study. All subjects were recruited at the Centre on Aging and Mobility, University Hospital Zurich, Switzerland. This study was approved by the Zurich Cantonal Ethical Committee and Swiss Medic. Written informed consent was obtained from all study participants. The trial has been registered at the international trial registry (NCT00718276). The primary trial findings with respect to pharmacokinetics, lower extremity strength, blood pressure, and markers of innate immunity are published elsewhere [28, 29].

Treatment arms

The original study design envisioned two regimens for calcifediol (n=10) and vitamin D_3 treatment (n=10). For each treatment strategy, five participants took 20 μg (800 IU) daily and another five participants took 140 μg (5600 IU) once a week. As in the earlier analysis, effects of daily and weekly treatment regimens were similar [28], and we combined daily and weekly data for each of the two treatment groups: calcifediol (daily or weekly) and vitamin D_3 (daily or weekly).

Outcome measures

Study participants attended a screening visit and 14 clinical visits during a 4-month follow-up period with laboratory measures of 25(OH)D taken at each visit as described earlier [28, 29]. Gait speed (normal pace) and trunk sway measurements were made at baseline (visit 2) and at 4-month follow-up visit (visit 15). For trunk sway testing, we used the SwayStar™ system [30] which consists of two angular velocity transducers fixed on a belt strapped around the waist at the level of the lumbar spine [31]. For trunk sway testing, each participant performed an 8-m walk, a two-legged stance on a firm surface, and a two-legged stance on a soft surface. For each of the three trunk sway tests, we documented pitch and roll trunk angular displacement and pitch and roll angular velocity. The time that participants took to complete their 8-m walk was used to calculate gait speed (meter per seconds).

Subjects, investigators, study physician, and nurses were aware of treatment regimen (daily or weekly), but blinded with regard to type of treatment (calcifediol or vitamin D_3). The physiotherapist who assessed gait speed and trunk sway was blinded to both regimen and type of treatment. Two participants of the calcifediol group did not have trunk sway and gait speed measured at baseline and follow-up, which is why our endpoint analyses compares 10 women in the vitamin D_3 group to 8 women in the calcifediol group. All other functional measures (Timed up and go, knee extensor and flexor strength, repeated sit-to-stand) and laboratory values were available in all 20 women and are reported elsewhere [28]. In brief, serum 25(OH)D concentration was assessed by means of a sensitive and selective assay based on liquid chromatography coupled to tandem mass spectrometry detection (HPLC-MS/MS), which selectively measures 25(OH)D_3 and was validated in an international NIST comparison (www.nist.gov; available from the authors). 1,25-hydroxyvitamin D was assessed by a radioimmunoassay. Intact PTH was measured in EDTA blood by means of an electrochemiluminescence immune assay [32]. Serum calcium levels and urinary calcium excretion (calcium/creatinine ration in spot urine) were assessed with automated assays at the Institute for Clinical Chemistry at the University Hospital in Zurich. For all laboratory analyses, we used the two measurements (at baseline and 4 months of follow-up) that coincide with the gait speed and trunk sway measurements.

Statistical analyses

All statistical analyses were based on intent to treat. Comparability of the treatment groups with respect to important demographic characteristics, baseline serum levels of 25(OH)D, gait speed, and trunk sway characteristics was assessed by a two-sample *t* test. Variables whose distributions grossly deviated from normal were log-transformed to comply with assumptions of the *t* test. To evaluate association between gait speed and balance measurements and serum 25(OH)D levels, differences between follow-up and baseline measurements were calculated for gait speed and each of the balance measurements. Then, Pearson's correlations between each of these differences and a similarly calculated difference between the follow-up and baseline concentrations of 25(OH)D were evaluated. Linear regression models were run to evaluate the effects of vitamin D_3 and calcifediol supplementation on gait speed and trunk sway. Each model adjusted for age, BMI, and baseline values of the respective outcome variables. Since angular displacement and angular velocity measurements had highly skewed distributions, these variables were log-transformed to improve their normality and fulfill modeling assumptions. The modeling was done on the logarithmic scale, and the results were converted back to their original scale. Since the functional endpoints were considered secondary endpoints, we did not adjust for multiple testing. However, caution is appropriate when interpreting the *p* values for our secondary outcomes.

All statistical analyses were performed using SAS v.9.3 statistical software (Copyright© SAS Institute, Cary, NC, USA) at α=0.05 (two-sided) level of statistical significance. Randomization was computer generated by an independent statistician.

Results

Table 1 summarizes baseline characteristics of the study population. Groups randomized for treatment with vitamin D_3 and calcifediol were comparable with respect to all investigated characteristics. Mean age, 25(OH)D level, and BMI were slightly lower in the calcifediol group; however, none of the group differences reached statistical significance (Table 1).

Serum 25(OH)D_3 levels, serum 1,25-dihydroxyvitamin D, serum intact PTH

Mean 25(OH)D_3 levels increased from 12.3 to 69.3 ng/ml (SD=±9.5) in the calcifediol group and from 14.2 to 30.5 ng/ml (SD=±5.0) in the vitamin D_3 group ($p<0.0001$). Serum 25(OH)D levels shifted to above 30 ng/ml in all participants of the calcifediol group, while in the vitamin D_3 group, about 50 % of participants remained below this threshold at 4 months of follow-up. Both treatments resulted in an increase in 1,25$(OH)_2$D levels, but this increase was more pronounced with calcifediol. Average circulating 1,25$(OH)_2$D rose by 19.5 pg/ml in the calcifediol group and by 2.5 pg/ml in the vitamin D_3 group (p=0.004). Circulating concentrations of intact PTH declined in both groups, but the decreases in the two groups did not differ significantly. Average circulating intact PTH declined by 20.2 pg/ml in the calcifediol group and by 3.2 pg/ml in the vitamin D_3 group (p=0.09).

Mean serum calcium levels did not differ by group at 4 months of follow-up (2.27 for vitamin D_3 and 2.27 for calcifediol; p value=0.97; reference range 2.19 to 2.60 mmol/l) [28]. Similarly, at 4-month follow-up, there was no significant difference in urinary calcium excretion between groups assessed as the calcium/creatinine ratio in spot urine (0.33 for vitamin D_3 and 0.33 for calcifediol; p value=0.98; reference range 0.1–0.5 mmol/mmol) [28].

Gait speed

Women receiving calcifediol compared with vitamin D_3 had a 16 % greater improvement in gait speed at 4-month follow-up

Table 1 Baseline characteristics of the study population

Characteristic	Treatment group		*p* value
	Vitamin D_3 (N=10)	Calcifediol (N=10)	
Age (years)	63.5 (7.8)	59.5 (6.3)	0.22
BMI (kg/m$^{2)}$	25.5 (3.4)	23.2 (3.2)	0.15
25(OH)D (ng/ml)	14.2 (3.6)	12.3 (4.1)	0.20
1,25(OH)2D (pg/ml)	38.6 (12.1)	33.0 (13.6)	0.36
Intact PTH (pg/ml)	54.9 (10.7)	63.2 (16.4)	0.19
Serum calcium (mmol/l)	2.27 (0.08)	2.26 (0.07)	0.71
Urinary calcium excretion (calcium/creatinine ratio)	0.25 (0.15)	0.28 (0.18)	0.28
Gait speed—8-m walk (m/s)	1.11 (0.22)	1.08 (0.08)	0.83
Trunk sway 8-m walk			
Roll angular displacement (deg)	1.16 (0.98)	0.98 (0.94)	0.91
Roll angular velocity (deg/s)	0.82 (0.34)	0.64 (0.51)	0.18
Pitch angular displacement (deg)	3.33 (1.47)	4.99 (4.39)	0.60
Pitch angular velocity, (deg/s)	1.01 (0.79)	0.96 (0.99)	0.36
Standing on two legs on firm surface			
Roll angular displacement (deg)	0.13 (0.13)	0.11 (0.05)	0.57
Roll angular velocity (deg/s)	0.008 (0.005)	0.009 (0.006)	0.66
Pitch angular displacement (deg)	0.45 (0.39)	0.43 (0.35)	0.76
Pitch angular velocity (deg/s)	0.04 (0.03)	0.02 (0.01)	0.98
Standing on two legs on soft surface			
Roll angular displacement (deg)	0.28 (0.13)	0.33 (0.31)	0.46
Roll angular velocity (deg/s)	0.02 (0.01)	0.03 (0.04)	0.70
Pitch angular displacement (deg)	0.71 (0.61)	0.67 (0.64)	0.80
Pitch angular velocity (deg/s)	0.05 (0.03)	0.04 (0.04)	0.27

All variables are presented as mean (SD); *p* values are based on two-sample *t* test. For the *t* tests age, BMIs were compared on their natural scales, and the rest of the variables were log-transformed to bring their distributions closer to normality. In the vitamin D_3 group, all measurements are based on 10 participants. In the calcifediol group, gait speed and trunk sway are based on eight participants only. Both treatment groups are comparable with respect to all baseline assessments

(p=0.03) adjusting for baseline gait speed (minimally adjusted model). This difference was maintained at 18 % (p=0.046) after adjustment for age and body mass index in addition to baseline gait speed (Table 2, Fig. 1). Further, change in gait speed was correlated with change in serum 25-hydroxyvitamin D concentrations (r=0.50; p=0.04, Table 3, Fig. 2a) and inversely correlated with change in intact PTH levels (r=−0.42; p=0.08, Fig. 2b), significant for change in 25(OH)D and approaching significance for change in intact PTH level . Change in gait speed was not correlated with change in 1,25(OH)2D (r=0.19; p=0.46).tgrouptgroup

Notably, for change in 25(OH)D serum concentration, there was no overlap between the two treatment groups in Fig. 2a. Also, in the calcifediol group alone the line was flat, suggesting that all participants were above the threshold needed for gait speed performance. For the correlation plot on change in gait speed with change in serum intact PTH concentrations (Fig. 2b), there was an overlap between treatment groups with a suggestion that overall and within treatment groups a greater suppression of intact PTH levels was associated with better gait speed performance.

As an exploratory analysis due to the small sample size, we added change in 25(OH)D level and change in PTH level to our minimally adjusted model of the effect of treatment (calcifediol versus vitamin D_3) on gait speed at 4-month follow-up to assess which of the two changes attenuates the treatment effect. In the minimally adjusted model, controlling for baseline gait speed only, women receiving calcifediol compared with vitamin D_3 had a 16 % greater improvement in gait speed at 4-month follow-up (p=0.03). Adding change in 25(OH)D level (follow-up minus baseline) to this model, the treatment effect was not attenuated and change in 25(OH)D level had no independent effect on gait speed at 4-month follow-up (p=0.99). Adding change in intact PTH level (follow-up minus baseline) to the model, the treatment effect was attenuated from 16 to 10.9 % and change in PTH level approached significance (p=0.11). These exploratory findings, taking the limitation of a small sample size into account, support parathyroid hormone response as a mediator of the treatment effect, rather than change in 25(OH)D level.

Trunk sway test battery

Across three tests of trunk sway (walking 8 m, standing on two legs on firm surface, standing on two legs on soft surface), there were no consistent differences between groups in the

Table 2 Effect of treatment (calcifediol versus vitamin D_3) on gait speed and trunk sway

Tests	Least square means by treatment at 4 month		Difference (calcifediol–vitamin D_3)	*p* value
	Vitamin D_3	Calcifediol		
Gait speed—8-m walk				
Gait speed (m/s)	1.02 (0.91–1.13)	1.20 (1.08–1.33)	0.18 (18 %)	0.046
Trunk sway test battery				
8-m walk				
Roll angular displacement (deg)	0.72 (0.26–1.99)	0.31 (0.10–1.00)	−0.41 (56 %)	0.30
Roll angular velocity (deg/s)	0.39 (0.24–0.63)	0.69 (0.40–1.19)	0.30 (77 %)	0.13
Pitch angular displacement (deg)	2.43 (1.22–4.86)	3.84 (1.75–8.39)	1.40 (58 %)	0.39
Pitch angular velocity, deg./s.	0.62 (0.21–1.85)	0.35 (0.10–1.20)	−0.27 (44 %)	0.49
Standing on two legs on firm surface				
Roll angular displacement (deg)	0.07 (0.03–0.15)	0.07 (0.03–0.16)	0.0 (0 %)	0.99
Roll angular velocity (deg/s)	0.005 (0.003–0.008)	0.012 (0.007–0.021)	0.007 (132 %)	0.04
Pitch angular displacement (deg)	0.27 (0.12–0.57)	0.45 (0.19–1.07)	0.18 (69 %)	0.40
Pitch angular velocity (deg/s)	0.03 (0.01–0.07)	0.04 (0.02–0.09)	0.01 (19 %)	0.77
Standing on two legs on soft surface				
Roll angular displacement (deg)	0.16 (0.04–0.58)	0.09 (0.02–0.41)	−0.06 (40 %)	0.60
Roll angular velocity (deg/s)	0.013 (0.004–0.042)	0.008 (0.002–0.031)	−0.005 (38 %)	0.60
Pitch angular displacement (deg)	0.44 (0.31–0.62)	0.31 (0.21–0.46)	−0.12 (29 %)	0.21
Pitch angular velocity (deg/s)	0.02 (0.01–0.05)	0.03 (0.01–0.10)	0.01 (72 %)	0.45

Table 2 presents least square means (95 % confidence interval) by treatment group and the difference between treatment groups as a mean difference and percent difference. Women receiving calcifediol compared with vitamin D_3 had an 18 % greater improvement in gait speed at 4-month follow-up (p= 0.046) adjusting for baseline gait speed, age, and body mass index. Across three tests of trunk sway, there were no consistent differences between groups; only roll angular velocity standing on two legs on a firm surface was 132% greater in the calcifediol group compared with the vitamin D_3 group (p=0.04).

analyses that adjusted for baseline sway only (data not shown). In the fully adjusted analyses presented in Table 2, only roll angular velocity standing on two legs on a firm surface was 132 % greater in the calcifediol group compared with the vitamin D_3 group (p=0.04).

Consistent with the overall lack of between treatment group differences for trunk sway, we did not find a correlation between change in 25(OH)D level and change in any of the trunk sway measures (Table 3). Similarly, there was no correlation significant correlation between change in 1,25(OH)2D level and change in any of the trunk sway measures (data not shown).

Change in PTH was significantly and inversely correlated with change in pitch angular displacement during 8-m walk

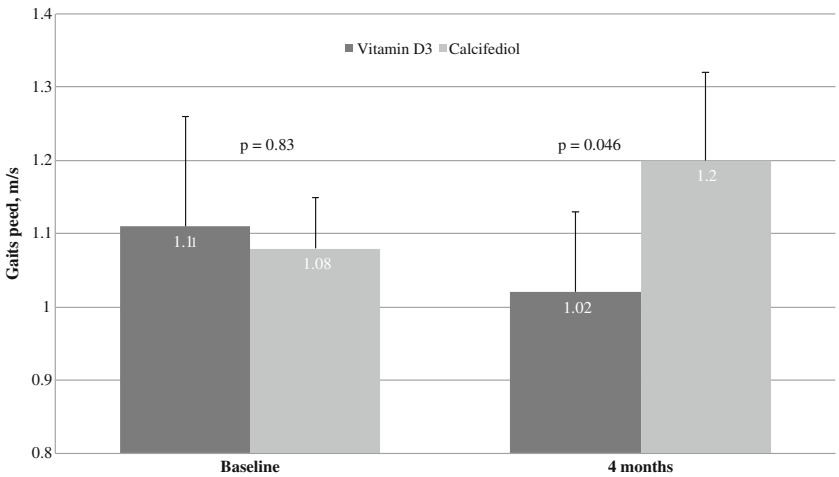

Fig. 1 Gait speed by treatment group at baseline and at 4-month follow-up. Baseline *box plots* show the unadjusted means for gait speed. The 4-months follow-up *box plots* show the least square means of gait speed adjusted for baseline gait speed, age, and BMI. *Whiskers* show standard errors. At baseline, mean gait speed did not differ significantly between groups (p=0.83). At 4-month follow-up, calcifediol treatment contributed to an 18 % increase in gait speed compared with vitamin D_3 (p=0.046)

Table 3 Correlations between change in serum 25(OH)D concentration—and change in gait speed/trunk sway over 4-month follow-up

Change gait speed and change in trunk sway (follow-up—baseline)	Change in serum concentration of 25(OH)D (follow-up—baseline)		Change in serum concentration of intact PTH (follow-up—baseline)	
	r	*p*	*r*	*p*
Gait speed (m/s)	0.50	0.04	− 0.42	0.08
Trunk sway				
8-m walk				
Roll angular displacement (deg)	0.23	0.36	−0.14	0.57
Roll angular velocity (deg/s)	0.19	0.45	−0.41	0.09
Pitch angular displacement (deg)	0.11	0.67	−0.51	0.03
Pitch angular velocity (deg/s)	−0.05	0.85	0.02	0.93
Standing on two legs on firm surface				
Roll angular displacement (deg)	−0.05	0.84	0.48	0.04
Roll angular velocity (deg/s)	0.08	0.76	0.06	0.81
Pitch angular displacement (deg)	−0.01	0.97	−0.12	0.63
Pitch angular velocity (deg/s)	0.34	0.17	−0.15	0.54
Standing on two legs on soft surface				
Roll angular displacement (deg)	−0.20	0.42	0.17	0.51
Roll angular velocity (deg/s)	−0.24	0.34	0.27	0.29
Pitch angular displacement (deg)	−0.11	0.68	0.05	0.83
Pitch angular velocity (deg/s)	0.11	0.66	−0.10	0.69

Changes are calculated based on difference between the 4-month follow-up value minus baseline value. All correlations listed for gait speed and trunk sway measurements refer to the same change in the serum 25(OH)D concentrations/intact PTH concentrations. Only change in gait speed was significantly correlated with change in serum 25-hydroxyvitamin D concentrations (r=0.50; p=0.04), and otherwise, none of the trunk sway measures reached or approached significance for the correlation with change in 25(OH)D concentrations. Individual measurements for change in gait speed by change in 25(OH)D serum concentrations are shown in Fig. 2a. Change in PTH concentration was inversely correlated with change in gait speed and approached significance (r=−0.42; p=0.08; see Fig. 2b). Change in PTH was significantly and inversely correlated with change in pitch angular displacement during 8-m walk (r=−0.51, p=0.03) and moderately positively correlated with roll angular displacement when standing on firm surface (r=0.48, p=0.04). Another negative correlation between PTH change and change in roll angular velocity during 8-m walk approached significance (r=−0.41, p=0.09)

(r=−0.51, p=0.03) and moderately positively correlated with roll angular displacement when standing on firm surface (r=0.48, p=0.04). Another negative correlation between PTH change and change in roll angular velocity during 8-m walk approached significance (r=−0.41, p=0.09).

Discussion

In this clinical trial, calcifediol improved gait speed by 18 % in young postmenopausal women compared with 800 IU vitamin D_3 and within 4 months of treatment. Notably, we also documented a significant positive correlation between change in 25(OH)D level and change in gait speed, as well as an inverse correlation between change in intact PTH level and change in gait speed approaching significance. In contrast, our detailed assessment of trunk sway while walking or standing did not change differentially with treatment or with a greater change in 25(OH)D status over time. Our study supports the concept that calcifediol may be more potent than standard vitamin D_3 not only with respect to change in 25(OH)D status but also with respect to gait speed improvement in young postmenopausal women.

In this study, calcifediol treatment shifted all participants to a mean of 69.3 ng/ml at 4-month follow-up compared with a mean of 30.5 ng/ml in women receiving 800 IU vitamin D_3 per day. The change over time assessed in 14 visits among all participants has been reported earlier showing that already at day 35, all participants in the calcifediol group reached the threshold of 30 ng/ml [28]. Notably, within the range of change in 25(OH)D achieved in the calcifediol group, the response to change in gait speed was flat suggesting that gait speed improvement had leveled off in the higher 25(OH)D level—reached by all participant of the calcifediol group. Our findings are supported by several large cross-sectional studies, where gait speed continued to increase to the upper end of the respective reference range in 25(OH)D concentrations of the individual studies. In a large population-based study including the ambulatory US population aged 60 to ≥90 years of age

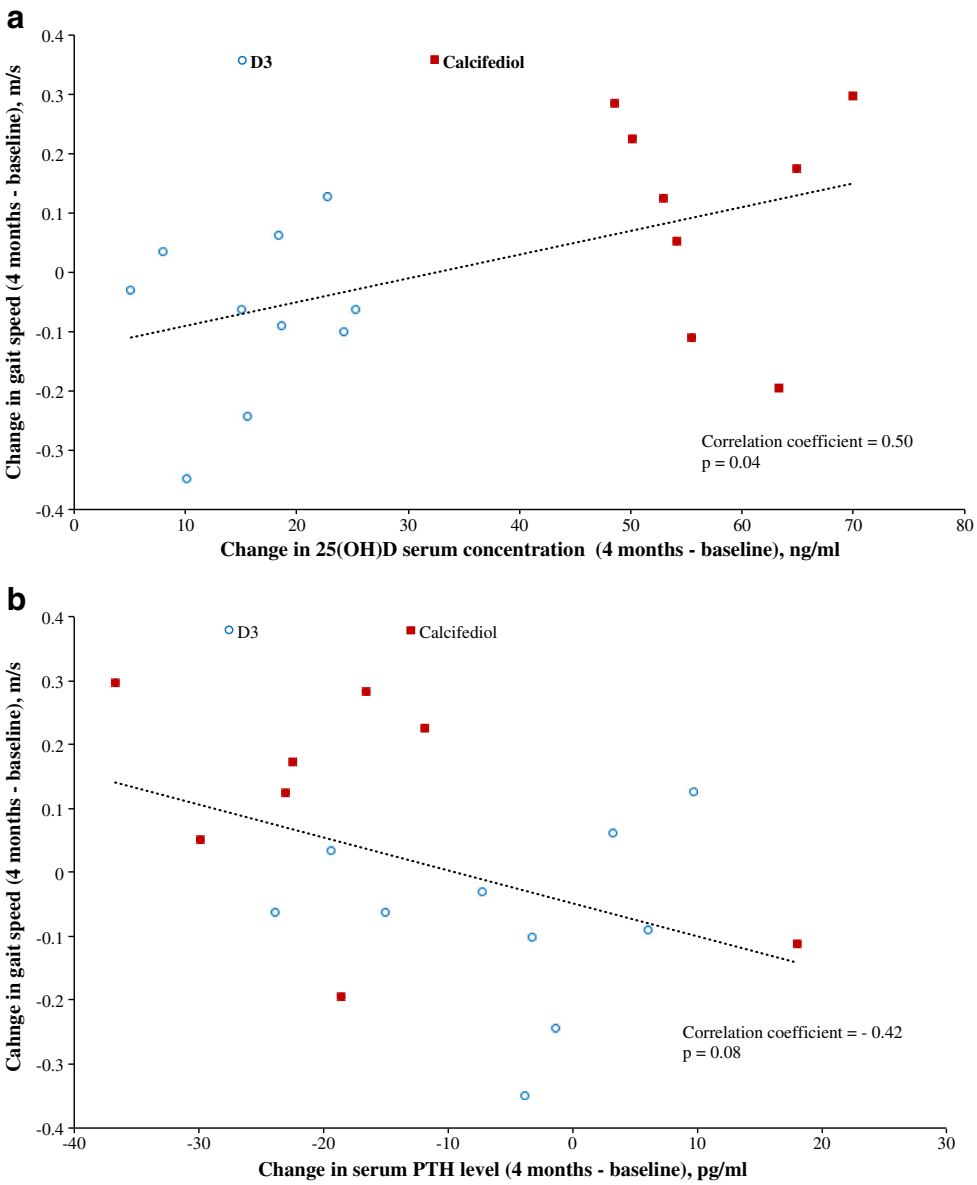

Fig. 2 Correlation between change in gait speed and change in 25(OH)D and change in intact PTH level. **a** Correlation between change in 25(OH)D serum concentration and change in gait speed (baseline—month 4). Change in gait speed was significantly correlated with change in serum 25-hydroxyvitamin D concentrations (r=0.50; p=0.04). Correlation coefficient is based on Pearson correlation. There was no overlap between the two treatment groups (indicated with different symbols: *open circle* = vitamin D_3 group; *filled square* = calcifediol). Notably, within the range of change in 25(OH)D achieved in the calcifediol group, the response to change in gait speed was flat suggesting that gait speed improvement had leveled off in the higher 25(OH)D level—reached by all participant of the calcifediol group. **b** Correlation between change in intact PTH concentrations and change in gait speed (baseline—month 4). Change in gait speed was significantly correlated with change in serum intact PTH concentrations (r=−0.42; p=0.08). Correlation coefficient is based on Pearson correlation. For the correlation plot on change in gait speed with change in serum intact PTH concentrations, there was an overlap between treatment groups (indicated with different symbols: *open circle* = vitamin D_3 group; *filled square* = calcifediol)

(NHANES III) [6], gait speed continued to increase throughout the NHANES III reference range of 25(OH)D (9 to 37.6 ng/ml) with most of the improvement occurring in 25(OH)D levels going from 9 to approximately 16 ng/ml. Compared with the lowest quintile of 25(OH)D, the highest quintile showed an average improvement by 5.6 % in gait speed (test for trend: p<0.001). A similar association was seen in 2694 community-dwelling seniors age 65 and older from Italy. Compared to the lowest quintile of 25(OH)D, the highest quintile showed an average improvement in gait speed by 21 % in both men and women (test for trend: p<0.0001) [7]. Similarly, in the EPIDOS study, both usual and fast walking speed was associated with 25(OH)D status. Compared with seniors reaching a 25(OH)D serum level of greater than 30 ng/ml, any lower 25(OH)D range (20 to 30 ng/ml; 10 to 20 ng/ml; <10 ng/ml) was associated with a significant 2.8 to 7.0-fold increased odds of being in the worst quintile of walking speed for both usual and fast walking speed, with the most extreme risk observed among seniors with 25(OH)D levels <10 ng/ml [8]. Also, in the Health ABC study, adjusting for demographic factors, site, and season, baseline 25(OH)D was associated with 20 and 400 m gait speed at baseline and 2 and 4 years later, and participants with baseline 25(OH)D <20 ng/ml had slower gait speed at each time point compared with seniors who had 25(OH)D ≥30 ng/ml (p<0.01) [33].

In our detailed assessment of trunk sway while walking or standing (firm and soft surface), calcifediol versus standard vitamin D_3 did not improve trunk sway. Also, we did not find a significant correlation between change in 25(OH)D level and change of any trunk sway measure while walking or standing over time. There are several possible speculations regarding our differential finding compared with the meta-

analysis of Muir and Montero-Odasso [11]. One speculation could be that we selected a relatively healthy and young group of postmenopausal women with a mean age below 65 years where trunk sway may not have been impaired to a degree where vitamin D supplementation mattered enough to be detected within the 4-month follow-up or the small study sample we investigated. The pooled analysis of Muir included seniors at higher age and, in part, pre-frail with a history of a fall [11]. Using the same SwayStar technology in an earlier trial among 64 institutionalized elderly women treated with 800 IU vitamin D plus 1200 mg of calcium versus calcium alone, we observed a 60 % reduction in the rate of falls in the vitamin D group, and up to 22 % of the treatment effect was explained by a change in postural balance and up to 14 % by dynamic balance [34]. Alternatively, there could be different 25(OH)D thresholds for different aspects of function as suggested by Houston and colleagues in the Health ABC study [9]. Within this concept, the 25(OH)D threshold for optimal trunk sway may be lower than that for gait speed [11], which allowed us to detect a groups difference for gait speed but not for trunk sway as the control group received 800 IU vitamin D_3, which may be a sufficient dose for trunk sway improvement. Finally, our sample may have been too small to detect small changes in trunk sway.

Despite its small sample size, our exploratory analysis provides some support to the concept that parathyroid hormone suppression may improve gait speed independent of a rise in 25(OH)D level, as described by Sambrook and colleagues for fall risk [35]. A possible independent role of parathyroid hormone is also suggested in a small study of 18 asymptomatic patients (mean age 66 years) with primary hyperparathyroidism who were found to have a 52 % lower gait speed compared with healthy age-matched normative values despite their replete vitamin D status (mean 25(OH)D serum concentrations were 44 ng/ml) [36]. Further, our trial found that parathyroid hormone response is a correlate with gait speed improvement (r=−0.42; p=0.08) and few trunk sway measures.

Our trial has several strengths despite its small size. The trial was sufficiently powered to detect a treatment effect for gait speed. Further, the improvement in gait speed by calcifediol is consistent with and is an extension of the findings of the earlier paper from the same trial, where we documented a significant 17 % improvement for knee extensor strength with calcifediol versus vitamin D_3 and nonsignificant improvements for knee flexor strength (4 %), for functional mobility (timed up and go test; 8 %), and for reaction time (repeated sit-to-stand test; 12 %) [28].

In conclusion, our results support calcifediol over standard vitamin D as a potential strategy in improving gait speed in young postmenopausal women at risk for vitamin D deficiency. Given the small size of our trial, our data need confirmation in a larger clinical trial and more research is needed to identify the desirable 25(OH)D threshold for gait speed versus trunk sway in healthy postmenopausal women.

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Conflicts of interest Heike Bischoff-Ferrari has been an invited speaker/advisory boards by Nestlé, MSD, Roche, Amgen, WILD, Sanofi, and DSM Nutritional Products. The original trial has been supported by an investigator-initiated grant by DSM Nutritional Products. DSM Nutritional Products had no influence on the analysis presented in this paper, had no access to the data, and did not contribute to this manuscript in any way. Otto Meyer, Bess Dawson-Hughes, Eduard Sidelnikov, Andreas Egli, Daniel Grob, Hannes B Staehelin, Gudrun Theiler, Reto Kressig, Hans-Peter Simmen, and Robert Theiler declare that they have no conflict of interest.

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