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Independent and Combined Effects of Calcium-Vitamin D_3 and Exercise on Bone Structure and Strength in Older Men: An 18-Month Factorial Design Randomized Controlled Trial

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Context: Exercise and calcium-vitamin D are independently recognized as important strategies to prevent osteoporosis, but their combined effects on bone strength and its determinants remain uncertain.

Objective: To assess whether calcium-vitamin D_3 fortified milk could enhance the effects of exercise on bone strength, structure, and mineral density in middle-aged and older men.

Design, Setting, Participants: An 18-month factorial design randomized controlled trial in which 180 men aged 50–79 years were randomized to the following: exercise + fortified milk; exercise; fortified milk; or controls. Exercise consisted of progressive resistance training with weight-bearing impact activities performed 3 d/week. Men assigned to fortified milk consumed 400 ml/d of 1% fat milk containing 1000 mg/d calcium and 800 IU/d vitamin D_3.

Main Outcome Measures: Changes in bone mineral density (BMD), bone structure, and strength at the lumbar spine (LS), proximal femur, mid-femur, and mid-tibia measured by dual energy x-ray absorptiometry and/or quantitative computed tomography.

Results: There were no exercise-by-fortified milk interactions at any skeletal site. Main effect analysis showed that exercise led to a 2.1% (95% confidence interval, 0.5–3.6) net gain in femoral neck section modulus, which was associated with an approximately 1.9% gain in areal BMD and cross-sectional area. Exercise also improved LS trabecular BMD [net gain 2.2% (95% confidence interval, 0.2–4.1)], but had no effect on mid-femur or mid-tibia BMD, structure, or strength. There were no main effects of the fortified milk at any skeletal site.

Conclusion: A community-based multi-component exercise program successfully improved LS and femoral neck BMD and strength in healthy older men, but providing additional calcium-vitamin D_3 to these replete men did not enhance the osteogenic response. **(*J Clin Endocrinol Metab* 96: 0000–0000, 2011)**

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Abbreviations: 1-RM, One repetition maximum; 25(OH)D, 25-hydroxyvitamin D; aBMD, areal bone mineral density; BMD, bone mineral density; CI, confidence interval; CSA, cross-sectional area; CV, coefficient of variation; DXA, dual energy x-ray absorptiometry; PTH, parathyroid hormone; QCT, quantitative computed tomography; RCT, randomized controlled trial; vBMD, volumetric bone mineral density.

The mechanical strength of bone and its resistance to fracture is dependent on its size, shape, and microarchitecture, and the material properties of bone, including the porosity and degree of mineralization (1). Bone strength is compromised with advancing age due to an imbalance in bone remodeling, where more bone is resorbed than formed (1, 2). This leads to a reduction in bone mineral density (BMD) and cortical thickness, due to continued net endocortical resorption (2). Concurrent periosteal apposition is reported to partially maintain the cross-sectional area of bone, offsetting the negative effect that endocortical surface bone erosion has on bone strength (2). Thus, any factor that influences bone remodeling, including disease, drugs, or lifestyle factors, has the potential to affect whole bone strength and fracture risk (1).

Regular weight-bearing exercise and calcium and/or vitamin D supplementation have been independently shown to have beneficial effects on bone strength and its determinants in older men (3–5) and women (6–8). However, their mechanisms of action are different; exercise has a site-specific modifying effect that may enhance periosteal apposition and/or reduce endocortical resorption, whereas calcium appears to have a generalized, permissive effect that acts to slow endocortical bone loss (9). Despite these differing mechanisms of action, there are some reports in older women that the skeletal benefits of exercise may be dependent on dietary calcium intakes of around 1000 mg/d (10). Therefore, the aim of this 18-month, factorial 2 × 2 design randomized controlled trial (RCT) in community-dwelling men aged >50 yr was to investigate whether calcium and vitamin D_3 fortified milk combined with a multi-component, targeted bone loading program could enhance bone strength and its determinants at loaded sites, more than the sum of each factor alone.

Materials and Methods

Study design

In this 18-month factorial 2 × 2 RCT, participants (n = 180) were randomized in equal numbers to one of four groups: 1) exercise + fortified milk (n = 45); 2) exercise alone (n = 46); 3) fortified milk alone (n = 45); or 4) a control group (n = 44). Before randomization, participants were stratified according to age (<65 or ≥65 yr) and dietary calcium intake (<800 or ≥800 mg/d). The study recruitment and intervention was conducted from February 2003 to February 2006.

Participants

We recruited healthy community dwelling Caucasian men aged 50–79 yr from Geelong, a major regional city in southeastern Australia (38 degrees south latitude), with a population of around 220,000 people and surrounding areas in Victoria, Australia. Participants were excluded for the following reasons: 1) use of calcium-vitamin D supplementation within the past 12 months; 2) participation in resistance training in the past 12 months and/or high-impact weight bearing activities for >30 min three times per week in the preceding 6 months; 3) body mass index (BMI) of >35 kg/m^2; 4) a history of osteoporotic fracture or any medical condition or medication use known to affect bone metabolism; 5) lactose intolerance; 6) consumption of more than four standard alcoholic drinks per day; 7) current smokers; and 8) any chronic condition that might limit participation in the trials.

Screening and randomization

We prescreened 451 men (via telephone), of whom 296 were invited to have a dual energy x-ray absorptiometry (DXA) hip areal BMD (aBMD) scan (Fig. 1). Men with normal to below average aBMD (*i.e.*, total hip or femoral neck T-score between +0.4 and −2.4 SD) were included in the study (n = 180) and randomized to one of the four groups according to our statistician's computer generated randomization of study numbers. All eligible men were required to obtain medical clearance from their local physician to ensure that they were free of any contra-indicated medical conditions to exercise, based on the American College of Sports Medicine (ACSM) guidelines (11). The study was approved by the Deakin University Human Ethics Committee and Barwon Health Human Research Ethics Committee, and written consent was obtained from all participants.

Interventions

Exercise program

Supervised exercise training was performed on three nonconsecutive days per week for 18 months in one of four community leisure facilities under the supervision of qualified exercise trainers. Each session lasted 60–75 min and consisted of the following three types of activities: 1) a 5- to 10-min warm-up and cool-down involving stationary cycling and stretching; 2) six to eight moderate- to high-intensity progressive resistance training exercises; and 3) three moderate impact weight-bearing exercises. For the first 12 weeks, participants completed three sets of 15–20 repetitions at 50–60% of their one repetition maximum (1-RM) strength for each resistance exercise. Thereafter, training volume was prescribed at two sets of 8–12 repetitions, as follows: 1) a warm-up set at 60–65% 1-RM; and 2) a single training set at 60–70% 1-RM for the first 4 weeks of each 12-week training cycle and 80–85% 1-RM for the remaining 8 weeks. The high-intensity progressive resistance training involved combining upper and lower body machine and free weights with core strength exercises. The key hip and spine exercises used included squats (or leg press), lunges, hip abduction/adduction, latissimus dorsi pull down (or seated row), back extension, and a combination of abdominal and core stability exercises. For the first 12 months, all participants performed exercises in a slow, controlled manner. For the final 6 months, the program switched from maximal strength to high-velocity power-based training (rapid concentric muscle contractions). The moderate-impact weight-bearing exercises consisted of three impact exercises interspersed between the resistance training exercises. Participants were initially required to complete three sets of 10 repetitions for each exercise, which increased progressively to a maximum of 20 repetitions that varied in magnitude, rate, and distribution (direction) by

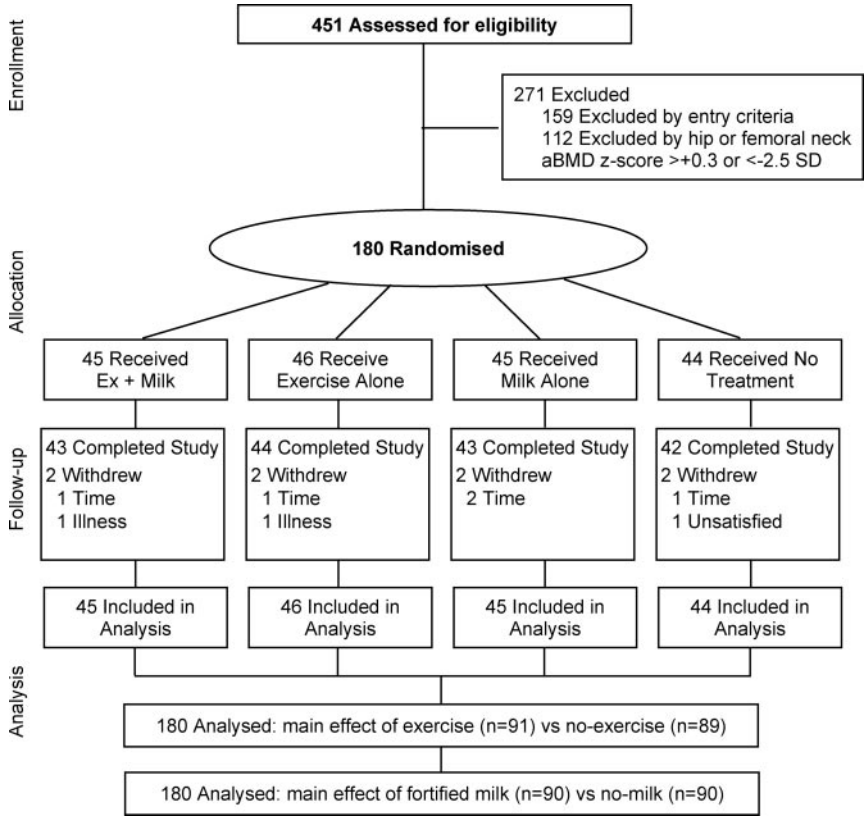

FIG. 1. Flowchart of participants through the GENTS Osteoporosis Prevention Study.

either increasing the height of jumps and/or by introducing more complex movement patterns. The exercises included single and double foot landings, bench stepping, and jumping off 15- and 30-cm benches. Peak vertical ground reaction forces (GRFs) for these exercises varied from 1.5 to 9.7 times body weight (BW) (5). Exercise compliance was computed from daily exercise cards completed by the men at the gymnasium and checked by records completed daily by the trainers that were returned to the research staff every month. The personal trainers also recorded any adverse events or injuries associated with the program.

Calcium-vitamin D_3 fortified milk

Participants assigned to the fortified milk were asked to consume 400ml/d (2 × 200 ml tetra packs) of reduced-fat (~1%) ultra-high temperature milk (Murray Goulburn Cooperative, Brunswick, Australia). Each 200-ml milk tetra pack contained approximately 500 mg calcium and 400 IU vitamin D_3, 418 kJ energy, 6.6 g protein, 2.2 g fat, 11 g lactose, 100 mg sodium, and 250 mg phosphorous. The average (±SD) calcium and vitamin D_3 levels per 100 ml for six batches produced throughout the study were 247 ± 17 mg and 190 ± 26 IU, respectively. Participants recorded the number of tetra packs consumed per day on compliance calendars. Compliance was calculated as a percentage by dividing the number of tetra packs consumed by the expected consumption each month and multiplied by 100.

Measurements

Anthropometry, diet, and physical activity measurements

Height was assessed using a stadiometer, and weight was measured on a digital scale. Nutrient intakes were assessed at baseline and 12 and 18 months using a 3-d food diary (two weekdays and one weekend day) and analyzed using the Foodworks nutrient analysis software program (Xyris Software, Brisbane, Queensland, Australia). Weight-bearing habitual activity outside of the exercise intervention (hours/week) was assessed at each visit using the CHAMPS Activity Questionnaire, developed, and validated for use with older adults (12). Information on medication use (including calcium-vitamin D supplementation) was determined by questionnaire and confirmed by interview at each visit.

Bone mineral density, bone structure, and strength

Lumbar spine (L_1–L_4) and proximal femur aBMD were assessed by DXA (Prodigy, GE Lunar Corp., Madison, WI), with analysis software version 8.10.027. The short-term coefficient of variation (CV) for these measures ranged from 0.6–1.0%. The Lunar Advanced Hip Analysis (AHA) program was used to calculate femoral neck bone geometry [diameter (mm) and cross-sectional area (cm^2)], tissue distribution [cross-sectional moment of inertia (CSMI, mm^4)], and bone strength [section modulus (Z, cm^3)] from the planar DXA scan as described previously (13).

Quantitative computed tomography (QCT) scans of the mid-femur, mid-tibia and lumbar spine (L_1-L_3) were obtained using a Philips Mx8000 CT scanner (Philips Mx8000 Quad CT scanner, Philips Medical Systems, The Netherlands). The scan parameters were 120 kVp and 50–100 mAs. A series of four 2.5-mm slices were obtained through the mid-portion of L_1–L_3 and the left femoral and tibial mid-shafts, with the middle two slices at each site analyzed and averaged. All participants were scanned simultaneously with a fluid dipotassium hydrogen phosphate (K_2HPO_4) bone equivalent calibration phantom containing differing concentrations of K_2HPO_4 (50, 100, 150, 250 mg/cm^3). Mid-femur and mid-tibia total, cortical and medullary area (cm^2), cortical volumetric BMD (vBMD, g/cm^3), and the density-weighted polar moment of area (I_{polar} mg/cm) and lumbar spine (L_1–L_3) total and trabecular vBMD (g/cm^3) were assessed using the Geanie 2.1 software program (BonAlyse Oy, Jyvakyla, Finland). The thresholds used to quantify each of the above measures have been described previously (3). Vertebral compressive strength index (vCSI) was calculated according to the method described by Sievanen *et al.* (14) where vCSI = vertebral cross-sectional area multiplied by the total $vBMD^2$.

Hormonal measurements

At baseline and 12- and 18-months fasting, morning (0800–1000 h) venous blood samples (10 ml) were obtained from each participant's antecubital vein. All serum samples were subaliquoted and stored at −80 C until assayed. All assays were performed in duplicate, and each participant's samples across the time points were assessed in a single batch. Serum intact parathyroid hormone (PTH) (1-84) was measured by an immunoradiometric assay

TABLE 1. Baseline characteristics of the study participants

Characteristic	Ex + milk (n = 45)	Exercise (n = 46)	Milk (n = 45)	Control (n = 44)
Age, yr	61.7 ± 7.6	60.7 ± 7.1	61.7 ± 7.7	59.9 ± 7.4
Height, cm	174.3 ± 6.3	174.2 ± 6.6	174.4 ± 5.8	175.0 ± 6.6
Weight, kg	83.2 ± 11.9	85.2 ± 10.9	84.1 ± 9.8	81.9 ± 10.7
BMI, kg/m^2	27.4 ± 3.7	28.1 ± 3.3	27.7 ± 3.3	26.7 ± 2.9
Diet				
Energy intake, kJ/d	9694 ± 2149	9884 ± 1948	9761 ± 1717	10199 ± 2201
Protein intake, g/kg/d	1.26 ± 0.32	1.32 ± 0.32	1.23 ± 0.28	1.33 ± 0.31
Calcium intake, mg/d	911 ± 360	1064 ± 449	1039 ± 455	996 ± 293
Vitamin D intake, μg/d	1.2 ± 2.1	0.8 ± 1.1	1.4 ± 3.0	0.7 ± 1.0
Physical activity				
Weight-bearing activity, h/wk	3.7 ± 3.9	3.6 ± 3.4	3.3 ± 3.8	3.4 ± 4.1
DXA and AHA				
L1-L4, g/cm^2	1.231 ± 0.163	1.247 ± 0.140	1.206 ± 0.146	1.238 ± 0.169
Total hip, g/cm^2	1.026 ± 0.079	1.022 ± 0.092	1.004 ± 0.085	1.010 ± 0.115
Femoral neck, g/cm^2	0.922 ± 0.072	0.938 ± 0.080	0.919 ± 0.076	0.933 ± 0.084
Neck diameter, mm	37.4 ± 2.4	37.8 ± 2.9	38.2 ± 2.6	38.0 ± 2.0
Neck CSA, mm^2	162.8 ± 15.7	165.9 ± 17.2	164.4 ± 17.4	167.5 ± 16.0
Neck Z, mm^3	781 ± 116	809 ± 148	803 ± 136	821 ± 112

All values are mean ± SD. BMI, body mass index; AHA, advanced hip analysis; Z, section modulus.

(IRMA) using the DiaSorin N-tact PTH IRMA kit (DiaSorin Inc, Stillwater, MN). The mean intra- and interassay CV was 9.4% and 18.9%, respectively. Serum 25-hydroxyvitamin D [25(OH)D] was measured using a DiaSorin immunoassay (RIA; Stillwater, MN). The mean interassay CV ranged from 3.9–5.8%.

Statistical analysis

Statistical analyses were conducted using Stata Statistical Software release 8.0 (Stata, College Station, TX). Baseline characteristics between the groups were compared using ANOVA. Pooled time series regression analysis for longitudinal data was used to test for an interaction between exercise and calcium-vitamin D_3. If no significant interactions were detected, the main effects of exercise (exercise + fortified milk and exercise alone *vs.* fortified milk and control) and calcium-vitamin D_3 fortified milk (exercise + fortified milk and fortified milk *vs.* exercise and controls) were examined. All data were analyzed based on an intention-to-treat. Serum 25(OH)D and PTH were log transformed before analyses. Between group differences were calculated by subtracting within-group changes from the baseline values in each group for each parameter. Separate models were used to assess the within group changes, which were expressed either as absolute changes or as a percentage changes from baseline. Percentage changes in log transformed serum 25(OH)D and PTH represents the absolute differences from baseline multiplied by 100. All data are presented as means ± SD or 95% confidence interval (CI) unless otherwise stated.

Results

Baseline characteristics

As shown in Table 1, the baseline characteristics did not differ among the four groups. The average dietary calcium intakes of the men in each group ranged from 911 to 1064 mg/d, but 58% had a calcium intake below the Australian recommended dietary intake (RDI) of 1000 mg/d for men aged 50 to 70 yr (15). Mean baseline serum 25(OH)D levels averaged 34.5 ± 14.4 ng/ml across the groups; no participants had severe vitamin D deficiency [25(OH)D <5 ng/ml]; one participant had moderate deficiency [25(OH)D 5–10 ng/ml] and 17 participants (9.4%) had mild deficiency [25(OH)D 10–20 ng/ml].

Study attrition and adherence

Eight (4.4%) of the 180 men (two from each group) withdrew from the study (Fig. 1). The mean adherence with the exercise program and fortified milk was 63% (95% CI: 57, 69) and 90% (95% CI, 87, 93), respectively, and there were no differences in adherence between the two exercise or two fortified milk groups. There were no serious injuries or adverse events associated with the exercise program.

Changes in diet, physical activity, and hormonal measures

On average, total dietary calcium and vitamin D intakes were 688 to 721 mg/d and 17 to 18 μg/d greater in the fortified milk compared with the nonfortified milk groups (all $P < 0.001$). Serum 25(OH)D concentrations increased by an average 8.4 ng/ml in the fortified milk compared with nonfortified milk groups after 12 months ($P < 0.001$), with no further increases observed after 18 months (Table 2). There were no main effects of exercise or the fortified milk on serum PTH after 12 months, but a significant decrease in PTH was observed in the exercise relative to nonexercise groups after 18 months ($P < 0.05$). There were no other main effects of exercise on any of the hormonal measures, and habitual activity levels did not

TABLE 2. Mean baseline, 12- and 18-month values (±SD), and the percentage changes (95% CI) from baseline for serum 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH), respectively, within each group, and the mean differences (95% CI) between the exercise and calcium-vitamin D_3 fortified milk groups (main effects)

Characteristic	Ex + milk (n = 45)	Exercise (n = 46)	Milk (n = 45)	Control (n = 44)	Main effects	
					Exercise	Milk
25(OH)D, ng/ml						
Baseline	36.3 ± 12.0	34.0 ± 16.3	33.5 ± 13.1	34.3 ± 16.1		
12 months	39.3 ± 13.3	28.7 ± 9.6	39.2 ± 15.3	30.6 ± 11.3		
18 months	40.7 ± 14.9	33.8 ± 11.4	36.9 ± 12.5	35.9 ± 15.0		
Change at 12 months[a]	7 (−4, 18)	−16 (−28, −4)[b]	15 (6, 25)[c]	−7 (−14, 0)[b]	−8 (−19, 2)	23 (13, 33)[d]
Change at 18 months[a]	11 (−1, 24)	2 (−13, 16)	11 (−2, 24)	5 (−8, 18)	−2 (−14, 11)	8 (−5, 20)
PTH, pg/ml						
Baseline	26.1 ± 12.2	27.7 ± 13.3	27.1 ± 10.2	25.3 ± 9.8		
12 months	25.3 ± 11.5	26.3 ± 15.9	26.2 ± 10.9	25.1 ± 9.6		
18 months	23.2 ± 10.2	27.2 ± 22.1	26.0 ± 10.0	25.4 ± 8.2		
Change at 12 months[a]	−5 (−13, 3)	−7 (−17, 3)	−4 (−15, 7)	0.1 (−9, 11)	−4 (−14, 5)	−1 (−11, 8)
Change at 18 months[a]	−13 (−26, −1)[b]	−8 (−18, 2)	−2 (−10, 5)	3 (−7, 13)	−11 (−21, 0)[b]	−5 (−15, 5)

[a] Percent changes for serum 25(OH)D and PTH represent the absolute difference from baseline in the log-transformed data multiplied by 100.

[b] $P \leq 0.05$, [c] $P < 0.01$, [d] $P < 0.001$ within group change from baseline or between group differences. To convert serum 25(OH)D from ng/ml to nmol/liter, multiply by 2.496.

change in any of the four groups throughout the intervention.

Changes in BMD, bone structure, and strength

There was no significant exercise-by-calcium-vitamin D_3 interaction for any DXA or QCT bone measurement. Thus, the main effects of exercise and fortified milk are reported (Table 3 and Fig. 2). After 18 months, exercise resulted in significant net gains in femoral neck aBMD [1.9% (95% CI, 1.2, 2.5)], cross-sectional area (CSA) [1.8% (95% CI, 0.8, 2.7)], and section modulus [2.1% (95% CI, 0.5, 3.6)] as well as lumbar spine trabecular vBMD [2.2% (95% CI, 0.2, 4.1)] relative to no-exercise. There were no other beneficial effects of exercise on any DXA or QCT bone measurement (Table 3 and Fig. 2). Lumbar spine aBMD increased to a similar extent in all treatment groups relative to controls (all $P < 0.01$). However, main effects analysis revealed that supplementation with the fortified milk had no significant effect on any bone measurement relative to those assigned to the non-supplemented group. Adjusting for changes in weight did not alter any of the above results.

Discussion

The findings from this 18-month, factorial design RCT show that a multi-component resistance and weight-bearing impact exercise program was safe and effective for improving femoral neck BMD, CSA, and strength, and lumbar spine trabecular BMD in healthy community dwelling middle-aged and older men. However, supplementing the diet of these men with an additional 1000 mg calcium and 800IU vitamin D_3 per day did not enhance the skeletal effects of exercise. These results suggest that the baseline calcium intakes (~1000 mg/d) and vitamin D status (~35 ng/ml) of our men were already sufficient to permit a positive skeletal response to the training. Furthermore, these findings support previous research in older women which has shown that the benefits of exercise on BMD can be achieved with calcium intakes of at least 1000 mg/d (10).

There is a sound physiological rationale for the existence of an interaction between exercise and calcium on bone; exercise is needed to stimulate bone modeling and remodeling, and calcium is an important substrate for bone mineralization (9, 16). However, there is no reason to suggest that calcium in excess of requirements or circulating 25(OH)D levels higher than a particular threshold will enhance BMD, bone structure, or strength in response to a given dose of loading. In adults, increased calcium and vitamin D have acute antiresorptive effects on bone that act synergistically to down-regulate bone remodeling. As a result, BMD is maintained by reducing endocortical resorption and preserving cortical thickness (3, 4, 17). There is no evidence that additional calcium or vitamin D administration can promote periosteal apposition. In our study, the mean baseline calcium intakes and serum 25(OH)D levels of the men ranged from 911-1064 mg/d and 34–36 ng/ml, respectively, across the four groups. Because these levels were equivalent to the current recommended calcium intake of 1000 mg/d for Australian men aged 51 to 70 yr (15) and exceeded the proposed 'optimal' musculoskeletal benefit threshold of around 30 ng/ml for serum 25(OH)D (18), it was not surprising that we failed to detect a significant exercise by calcium–vitamin D interaction. It is likely that if an exercise-by-calci-

TABLE 3. Mean baseline QCT bone values (±SD) and percentage unadjusted changes (95% CI) from baseline within each group and the mean differences (95% CI) between the exercise and calcium-vitamin D_3 fortified milk groups (main effects)

Characteristic	Ex + milk (n = 45)	Exercise (n = 46)	Milk (n = 45)	Control (n = 44)	Main effects	
					Exercise	Milk
Lumbar spine (L_1–L_3)						
Total vBMD, mg/cm^3						
Baseline	172 ± 35	172 ± 30	164 ± 25	171 ± 34		
Change at 18 months	0.0 (−1.4, 1.4)	0.7 (−1.2, 2.6)	−0.6 (−2.1, 0.8)	−0.05 (−1.5, 1.4)	0.7 (−0.8, 2.2)	−0.7 (−2.2,0.8)
Trabecular vBMD, mg/cm^3						
Baseline	119 ± 30	120 ± 26	115 ± 22	120 ± 34		
Change at 18 months	0.8 (−0.8, 2.5)	1.1 (−1.4, 3.6)	−1.5 (−3.1, 0.9)	0.8 (−2.9, 1.2)	2.2 (0.2, 4.1)[a]	−0.5 (−2.5, 1.5)
vCSI, g^2/cm^4						
Baseline	0.411 ± 0.158	0.428 ± 0.143	0.381 ± 0.101	0.417 ± 0.155		
Change at 18 months	0.8 (−2.1, 3.8)	2.2 (−1.6, 6.0)	−0.7 (−3.5, 2.1)	0.1 (−2.7, 3.0)	1.8 (−1.3, 4.9)	−1.2 (−4.2, 1.9)
Mid−femur						
Total area, mm^2						
Baseline	686 ± 81	689 ± 71	673 ± 69	688 ± 70		
Change at 18 months	0.1 (−0.03, 0.3)	0.1 (−0.1, 0.2)	−0.03 (−0.2, 0.1)	0.03 (−0.1, 0.2)	0.1 (−0.05, 0.2)	0.0 (−0.1, 0.1)
Cortical area, mm^2						
Baseline	503 ± 53	510 ± 54	499 ± 46	509 ± 44		
Change at 18 months	−0.3 (−0.6, 0.0)	−0.3 (−0.6, 0.0)[a]	−0.4 (−0.8, −0.1)[b]	−0.3 (−0.6, 0.0)[a]	0.1 (−0.2, 0.4)	−0.1 (−0.4, 0.3)
Medullary area, mm^2						
Baseline	183 ± 50	179 ± 53	147 ± 45	178 ± 46		
Change at 18 months	1.2 (0.7, 1.8)[c]	1.0 (0.5, 1.5)[c]	0.6 (0.3, 1.6)[c]	1.0 (0.5, 1.5)[c]	0.2 (−0.4, 0.7)	0.1 (−0.5, 0.6)
Cortical vBMD, g/cm^3						
Baseline	1119 ± 31	1120 ± 34	1104 ± 39	1108 ± 38		
Change at 18 months	−1.1 (−1.6, −0.6)[c]	−0.9 (−1.4, −0.3)[c]	−1.0 (−1.4, −0.6)[c]	−0.7 (−1.3, −0.2)[b]	−0.1 (−0.6, 0.4)	−0.2 (−0.7, 0.3)
I_{polar}, mg/cm						
Baseline	8078 ± 1901	8135 ± 1637	7714 ± 1609	8095 ± 1536		
Change at 18 months	−1.0 (−1.7, −0.3)[b]	−0.9 (−1.6, −0.4)[a]	−1.1 (−1.8, −0.6)[c]	−0.8 (−1.6, 0.0)[a]	0.05 (−0.6, 0.7)	−0.3 (−0.7, 0.3)
Mid−tibia						
Total area, mm^2						
Baseline	519 ± 68	529 ± 59	506 ± 54	528 ± 66		
Change at 18 months	−0.3 (−0.6, 0.0)[b]	−0.3 (−0.6, −0.1)[a]	−0.1(−0.4, 0.1)	−0.3 (−0.6, 0.0)	−0.1 (−0.4, 0.1)	0.1 (−0.2, 0.4)
Cortical area, mm^2						
Baseline	380 ± 45	389 ± 45	366 ± 37	387 ± 44		
Change at 18 months	−0.3 (−0.7, 0.0)[a]	−0.3 (−0.6, −0.1)[b]	−0.4 (−0.7, −0.1)[b]	−0.4 (−0.8, −0.1)[a]	0.1 (−0.2, 0.4)	0.02 (−0.3, 0.3)
Medullary area, mm^2						
Baseline	140 ± 39	141 ± 38	140 ± 37	141 ± 49		
Change at 18 months	−0.1 (−0.9, 0.7)	−0.4 (−1.2, 0.3)	0.6 (−0.2, 1.3)	0.1 (−0.5, 0.7)	−0.6 (−1.4, 0.1)	1.3 (0.2, 2.4)
Cortical vBMD, g/cm^3						
Baseline	1116 ± 28	1118 ± 41	1105 ± 43	1113 ± 49		
Change at 18 months	−0.8 (−1.3, −0.3)[b]	−0.8 (−1.3, −0.3)[c]	−1.2 (−1.7, −0.7)[c]	−1.1 (−1.6, −0.5)[c]	0.3 (−0.2, 0.8)	−0.05 (−0.6, 0.5)
I_{polar}, mg/cm						
Baseline	5171 ± 1235	5298 ± 1104	4841 ± 1054	5262 ± 1187		
Change at 18 months	−1.4 (−2.3, −0.5)[b]	−1.5 (−2.2, −0.7)[c]	−1.5 (−2.3, −0.6)[b]	−1.7 (−2.7, −0.7)[c]	0.1 (−0.7, 1.0)	0.1 (−0.7, 1.0)

vCSI, vertebral compressive strength index; I_{polar}, density−weighted polar moment of inertia.

[a] $P \leq 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ within group change from baseline or between group differences.

um-vitamin D interaction does exist, it may be limited to situations where groups move from an inadequate calcium and vitamin D status to adequacy. In support of this notion, a 10-month trial in Chinese postmenopausal women who had habitually low calcium intakes (<275 mg/d) reported that supplementation with 800 mg/d of calcium for 10 months enhanced the effects of load bearing exercise on femoral neck aBMD (19).

To our knowledge, this is the first long-term (>12 months) RCT to demonstrate that a multi-component exercise program is safe and effective for enhancing BMD, bone structure, and strength at the femoral neck in middle-aged and older men. The 1.9% net exercise-induced gain in femoral neck areal BMD in our study is consistent with the findings from a similar 18-month multi-component exercise trial in women aged 65 yr and older, which reported an ~2% net benefit at the femoral neck (20). A novel aspect of our study was that we assessed the structural basis underlying the exercise-induced gains in femoral neck BMD. We found that exercise led to a significant 1.8% net gain in femoral neck CSA and a 2.1% net increase in section modulus or bending strength but had no effects on femoral neck diameter, a surrogate estimate of bone size (periosteal apposition). This suggests that the exercise-induced gain in BMD and strength were related to endosteal apposition (or reduced resorption) rather than periosteal expansion. Contrary to these findings, the results from cross-sectional studies in older adults have generally shown that a higher level of physical activity or athletic participation is associated with greater cortical area and bone strength at loaded sites, largely attributable to an increase in bone size (periosteal apposition) (21, 22).

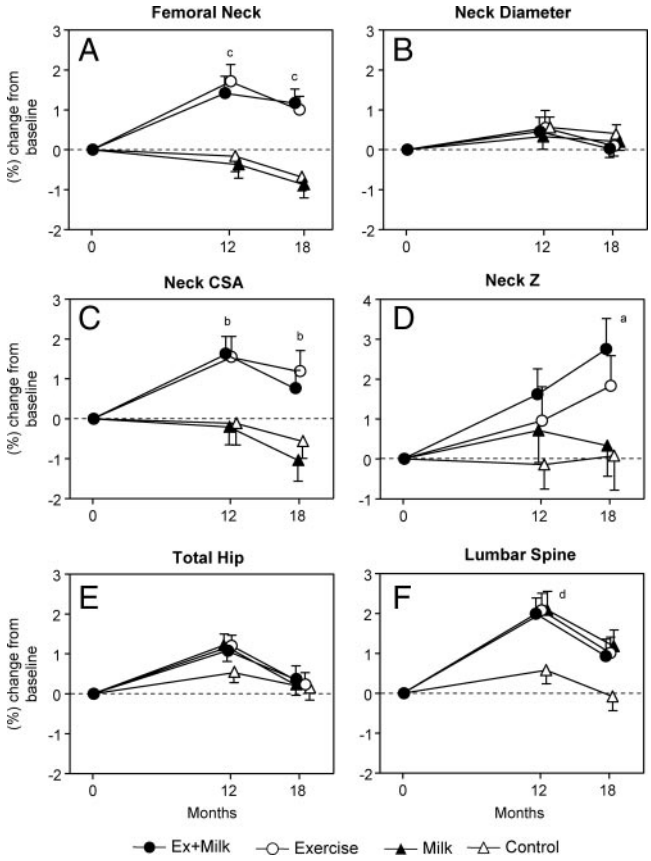

FIG. 2. Mean unadjusted percentage changes (±SE) from baseline in femoral neck aBMD (A), diameter (B), cross-sectional area (CSA) (C), and section modulus (D), and total hip (E) and lumbar spine (L1–L4) aBMD (F) according to treatment group. No exercise-by-calcium-vitamin D_3 interactions were detected. [a], $P < 0.05$; [b], $P < 0.01$; [c], $P < 0.001$ for main effect of exercise *vs.* no exercise. [d], $P < 0.01$ ex + milk, exercise, milk > controls.

In a recent review and meta-analysis, we reported that there was little evidence from intervention trials in older adults that exercise training can promote periosteal apposition (9, 23). In fact, our findings are consistent with the results from a 12-month multi-directional jumping intervention in postmenopausal women which found that exercise improved pQCT-derived bone strength at the distal tibia by increasing the ratio of cortical to total area, but had no effect on total bone area, indicating that exercise reduced endocortical bone loss (24).

Because changes that occur on the periosteal surface throughout adult life are reportedly very small (2–5 μm/yr) (2), it is likely that the use of the DXA hip structural analysis program to assess bone structural changes (periosteal apposition) limited our ability to detect any potential subtle exercise-related changes that may have occurred on the three-dimensional periosteal surface of the femoral neck. However, previous intervention studies in older adults that have examined the effects of resistance training and/or weight-bearing impact exercise on cortical bone geometry and strength at the tibial and radial diaphysis using pQCT have reported either no effect (25, 26) or a modest, site-specific effect on cortical bone geometry (24). Our QCT results showed that there was no significant effect of exercise on bone size or any other cortical bone structural or strength measure at either the mid-femur or mid-tibia. Notably, however, there was a trend for exercise to attenuate bone loss from the endosteal surface at the mid-tibia. This is consistent with our femoral neck findings, indicating that the benefits of exercise on cortical bone in older adults may be limited to attenuating endocortical bone loss.

Another clinically important finding from our study relates to the positive effects of our exercise program on lumbar spine trabecular vBMD. Previous intervention trials in older women have shown that exercise training can stop lumbar spine trabecular BMD loss (27), but we found that exercise increased trabecular BMD. For trabecular vBMD to increase, there must be an increase in either the thickness and/or the number of trabecular elements within the vertebral bodies. In young adult men, a positive association was reported between weight-bearing physical activity and trabecular bone volume fraction (BV/TV) at the distal tibia, which was attributable to an increase in trabecular number but not altered trabecular thickness (28). These findings are important because a loss in trabeculae has been associated with a greater reduction in bone strength than reduced trabecular thickness. Whether exercise has a greater effect on trabecular number or thickness in older men is not known, but the finding that trabecular BMD increased in our study, without a significant gain in vertebral bone area, suggests that there may be a compensatory skeletal adaptation in trabecular bone microarchitecture to maintain or increase vertebral bone strength.

The strengths of our study include the factorial randomized controlled trial design, the relatively long-term follow-up, the high participant retention and adherence to the intervention, and the comprehensive assessment of BMD, bone geometry, and strength at both axial and appendicular skeletal sites. In addition, as previously reported, the periodized exercise program was also effective for improving leg muscle strength by an average of 25%, total body lean mass by 0.6 kg, and mid-femur muscle cross-sectional area by 1.8%, and reduced fat mass by 1.1 kg (29). Importantly, there were no major injuries or adverse events associated with the program. However, there are several limitations. Our final sample size may have limited our ability to detect a significant exercise-by-calcium-vitamin D_3 interaction; initial power calculations indicated that we required 58 men per group (total target n = 232) (5). Furthermore, the men enrolled in the study were relatively healthy community-dwelling men without os-

teoporosis or low dietary calcium or serum 25(OH)D levels. Further factorial design trials are needed to evaluate the combined effects of exercise and nutrition on bone strength and its determinants in adults at greater risk of fracture.

In conclusion, our results demonstrate that a community-based exercise program incorporating a combination of progressive resistance training and weight-bearing impact exercise was safe, feasible, and effective for improving bone health at the femoral neck and lumbar spine as well as muscle strength, mass, and size in healthy middle-aged and older men. However, daily consumption of 400 ml of low-fat (1%) calcium-vitamin D_3 fortified milk did not enhance the effects of exercise on bone in this group of ambulatory community-dwelling men who had adequate dietary calcium intakes and sufficient circulating 25 (OH)D levels at baseline.

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