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SHORT SCIENTIFIC COMMUNICATION

Physical activity modifies the effect of calcium supplements on bone loss in perimenopausal and postmenopausal women: subgroup analysis of a randomized controlled trial

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Abstract

Summary We aimed to determine whether the effect of calcium supplements on bone metabolism is modified by physical activity (PA) through a subgroup analysis of an RCT. PA may be a favorable effect modifier of the association between calcium intake and bone loss in perimenopausal and postmenopausal women.

Purpose Physical exercise can potentially modify bone metabolism. Here we aimed to determine whether the effect of calcium supplements on bone metabolism is modified by physical activity (PA) through a subgroup analysis of a randomized, double-blind, placebo-controlled trial.

Methods The trial was conducted over the course of 2 years, and participants were 450 healthy women between 50 and 75 years of age who were randomly assigned to three equally-sized ($N = 150$ each) groups (500 mg calcium, 250 mg calcium, and placebo). Levels of PA at baseline were evaluated by quantifying moderate (4 METs) and vigorous (6 METs) activities based on a 7-day activity recall, and the total MET-hours per week was calculated. Follow-up BMD examinations were conducted 2 years later. Two-year changes in BMD were compared between the intention-to-treat higher PA subgroup (≥ 10 MET-hours/week) and the lower PA subgroup (< 10 MET-hours/week).

Results Of the 450 participants, 418 underwent follow-up BMD measurements. Regarding the lower PA subgroup, spinal BMD in the 500 mg/day calcium supplement group decreased significantly less (− 0.029 g/cm^2, $P = 0.042$) than in the placebo group (− 0.045 g/cm^2), and femoral neck BMD in the 500 mg/day calcium supplement group decreased significantly less (− 0.027 g/cm^2, $P = 0.049$) than in the placebo group (− 0.038 g/cm^2). In contrast, changes in neither spinal nor femoral neck BMD significantly differed between the three treatment groups in the higher PA subgroup.

Conclusions PA is a favorable effect modifier of the association between calcium intake and bone loss in perimenopausal and postmenopausal women with low calcium intake.

Clinical trials registry number UMIN000001176

Keywords Bone density · Calcium · Postmenopause · Physical activity · Randomized controlled trial

Introduction

Physical activity (PA) has beneficial effects on bone health, and physical exercise can potentially modify bone metabolism [1]. Studies in humans have shown an interaction between PA and calcium intake. During growth, PA plays an important role in bone acquisition and development, particularly in individuals with sufficient calcium intake [2]. A similar interaction was reported in a review of intervention trials targeting older populations showing that the beneficial effects of physical exercise on bone may be more apparent in those with higher calcium intake (> 1000 mg/day) than in those with lower intake [3]. Although most previous studies have

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focused on the importance of PA based on various levels of calcium intake, few studies have focused on reverse, i.e., effects of calcium intake in relation to PA levels [4, 5]. Murphy and Carroll [6] suggested a hypothesis that high levels of daily PA permit the adaptation to low calcium intake; however, this hypothesis has not been tested in empirical studies, much less controlled trials. We previously conducted a randomized controlled trial (RCT) in which a low calcium intake population took low-dose calcium supplements [7]. In this framework, we aimed to determine whether the effects of calcium supplements are modified by PA through a subgroup analysis of the RCT.

Methods

The present study involved a subgroup analysis of a randomized, double-blind, placebo-controlled trial over the course of 2 years. Participants of the trial were 450 healthy women aged 50–75 years who were randomly assigned to three equally-sized ($N = 150$ each) groups (i.e., 500 mg/day calcium, 250 mg/day calcium, or placebo) using the permuted-block design. Written informed consent was obtained from all participants, and the Ethics Committee of Niigata University School of Medicine approved the study protocol. Details of the study protocol were published previously (Clinical Trials Registry, UMIN000001176) [6].

Briefly, in 2008, we conducted a baseline medical examination, in which demographic characteristics, medical history, and lifestyle information, including calcium intake and PA, were obtained in an interview. Current calcium intake was assessed with a validated food frequency questionnaire [8]. Levels of exercise-based PA were evaluated by quantifying moderate (4 metabolic equivalents [METs]) and vigorous (6 METs) activities based on a 7-day activity recall [9]. Total MET-hours per week of moderate and vigorous activities were calculated for each participant. Bone mineral density (BMD) of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry (DXA) using the Hologic QDR 4500a scanner (Hologic Inc., Bedford, MA, USA). Serum 25-hydroxyvitamin D was measured using the Liaison® 25OH vitamin D total assay (DiaSorin Inc., Stillwater MN, USA). Intact parathyroid hormone (PTH) was measured using a two-site immunoradiometric assay (Nichols Institute Diagnostics, Inc., San Clemente, CA, USA), Osteocalcin (OC) was measured using an immunoradiometric assay (Mitsubishi Kagaku Medical, Inc., Tokyo, Japan), and type I collagen cross-linked N-telopeptide (NTX) was measured using an enzyme-linked immunosorbent assay (Osteomark NTX Serum; Ostex International, Inc., Seattle, WA, USA). Follow-up BMD examinations were conducted in 2009 and 2010. Compliance was determined by counting left-over tablets.

Intention-to-treat analyses were carried out. Two-year changes in BMD were compared between the intention-to-treat higher PA subgroup (≥ 10 MET-hours/week, median) and the lower PA subgroup (< 10 MET-hours/week). One-factor repeated measures analysis of variance (ANOVA) was used to analyze differences in mean changes of BMD (follow-up minus baseline examination values). Dunnett's multiple comparison was used to compare mean values between the calcium supplement and placebo groups. SAS software (release 9.13, SAS Institute Inc., Cary, NC, USA) was used for statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Of the 450 participants, 32 did not undergo follow-up examinations. This left a final study population of 418 participants, including 142 in the 500 mg/day calcium supplement group, 139 in the 250 mg/day calcium supplement group, and 137 in the placebo group. The average compliance rate was 83.4% for the 500 mg/day calcium supplement group, 84.6% for the 250 mg/day calcium supplement group, and 86.8% for the placebo group. Baseline characteristics of participants by PA levels and treatment are shown in Table 1. There were no significant differences in any variable at baseline among the three groups in both PA subgroups. Baseline calcium intake ($P = 0.010$) and PA ($P < 0.001$) significantly differed between the low and high PA subgroups. Of the 198 participants in the low PA group, 105 did not perform moderate or vigorous PA.

Two-year changes in BMD were compared between the intention-to-treat lower PA subgroup (< 10 MET-hours/week) and the higher PA subgroup (≥ 10 MET-hours/week). For the lower PA subgroup, spinal BMD in the 500 mg/day calcium supplement group decreased significantly less (− 0.029 g/cm^2 or − 3.0%, $P = 0.042$) than in the placebo group (− 0.045 g/cm^2 or − 4.7%) (Fig. 1, upper left). Moreover, femoral neck BMD in the 500 mg/day calcium supplement group decreased significantly less (− 0.027 g/cm^2 or − 3.8%, $P = 0.049$) than in the placebo group (− 0.038 g/cm^2 or − 5.4%) (Fig. 1, upper right). In contrast, in the higher PA subgroup, changes in neither spinal nor femoral neck BMD significantly differed between the three treatment groups (Fig. 1, lower left and right).

Discussion

We found that calcium supplementation significantly slowed both spinal and femoral neck bone loss in the low PA subgroup, but not in the high PA subgroup, suggesting that PA may modify the association between calcium intake and bone

Table 1 Baseline characteristics of participants who underwent follow-up examinations by calcium (Ca) treatment and physical activity ($n = 418$)

	Low physical activity subgroup (< 10 MET-hours/wk)					High physical activity subgroup (≥ 10 MET-hours/wk)				
	Ca 500 mg/d ($N = 71$)	Ca 250 mg/d ($N = 58$)	Placebo ($N = 69$)	*P* value[a]	Total ($N = 198$)	Ca 500 mg/d (N = 71)	Ca 250 mg/d ($N = 81$)	Placebo ($N = 68$)	*P* value[a]	Total ($N = 220$)
Age (years)	57.3 (5.5)	60.5 (6.3)	57.3 (4.8)	0.959	58.2 (5.7)	61.1 (5.8)	60.1 (6.0)	61.7 (5.5)	0.558	60.9 (5.8)
Height (cm)	154.1 (5.6)	153.1 (4.5)	154.8 (6.0)	0.473	154.1 (5.5)	152.8 (5.4)	153.9 (5.1)	153.0 (5.0)	0.744	153.3 (5.2)
Weight (kg)	52.5 (7.4)	53.8 (6.9)	54.0 (8.1)	0.226	53.4 (7.5)	52.5 (7.0)	53.7 (8.0)	54.0 (6.9)	0.236	53.4 (7.4)
Body mass index (kg/m^2)	22.1 (2.9)	23.0 (3.1)	22.6 (3.2)	0.382	22.5 (3.1)	22.5 (2.7)	22.7 (3.5)	23.1 (2.7)	0.274	22.7 (3.0)
BMD of LS (g/cm^2)	0.916 (0.135)	0.872 (0.124)	0.954 (0.164)	0.128	0.916 (0.146)	0.888 (0.155)	0.913 (0.155)	0.911 (0.156)	0.360	0.904 (0.155)
BMD of FN (g/cm^2)	0.699 (0.091)	0.676 (0.086)	0.708 (0.104)	0.581	0.695 (0.095)	0.684 (0.098)	0.689 (0.104)	0.699 (0.100)	0.392	0.691 (0.100)
Calcium intake (mg/d)	479 (125)	486 (116)	464 (118)	0.445	476 (120)[b]	506 (126)	508 (135)	512 (153)	0.794	509 (138)[b]
Physical activity[c]	2.4 (3.2)	3.0 (3.4)	2.7 (3.2)	0.640	2.7 (3.3)[b]	39.4 (36.2)	38.8 (37.2)	34.0 (32.6)	0.374	37.5 (35.4)[b]
Serum 25(OH)D (nmol/L)	42.3 (13.1)	46.2 (15.6)	44.8 (15.1)	0.311	44.3 (14.6)	43.6 (13.5)	45.7 (17.6)	43.6 (13.1)	1.000	44.4 (15.0)
Serum iPTH (pmol/L)	4.5 (1.2)	4.6 (1.3)	4.5 (1.5)	0.805	4.5 (1.3)	4.8 (2.3)	4.6 (1.5)	4.2 (1.3)	0.076	4.5 (1.8)
Serum osteocalcin (mg/dL)	8.2 (2.0)	7.9 (1.7)	8.1 (2.5)	0.733	8.1 (2.1)	8.1 (2.1)	8.1 (2.6)	8.2 (2.2)	0.736	8.1 (2.3)
Serum NTX (nmol BCE/L)	17.7 (4.8)	16.6 (4.6)	17.0 (4.5)	0.349	17.1 (4.6)	17.5 (7.0)	17.3 (4.2)	18.5 (6.7)	0.317	17.8 (6.0)
Smokers (proportion)	4/69 (5.8%)	1/58 (1.7%)	3/71 (4.2%)	0.644	8/198 (4.0%)	2/68 (2.9%)	1/81 (1.2%)	3/71 (4.2%)	0.633	6/220 (2.7%)
Drinkers (proportion)	24/69 (34.8%)	20/58 (34.5%)	30/71 (42.3%)	0.360	74/198 (37.4%)	27/68 (39.7%)	31/81 (38.3%)	24/71 (33.8%)	0.471	82/220 (37.3%)

BMD bone mineral density, *LS* lumbar spine, *FN* femoral neck, *25(OH)D* 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *NTX* type I collagen cross-linked N-telopeptide

Standard deviation values are indicated in parentheses

[a] Difference among the three treatments tested by one-factor analysis of variance or Kruskal-Wallis test

[b] Significantly different between low and high physical activity subgroups

[c] Total MET-hours per week of moderate and vigorous activities during the previous 7 days

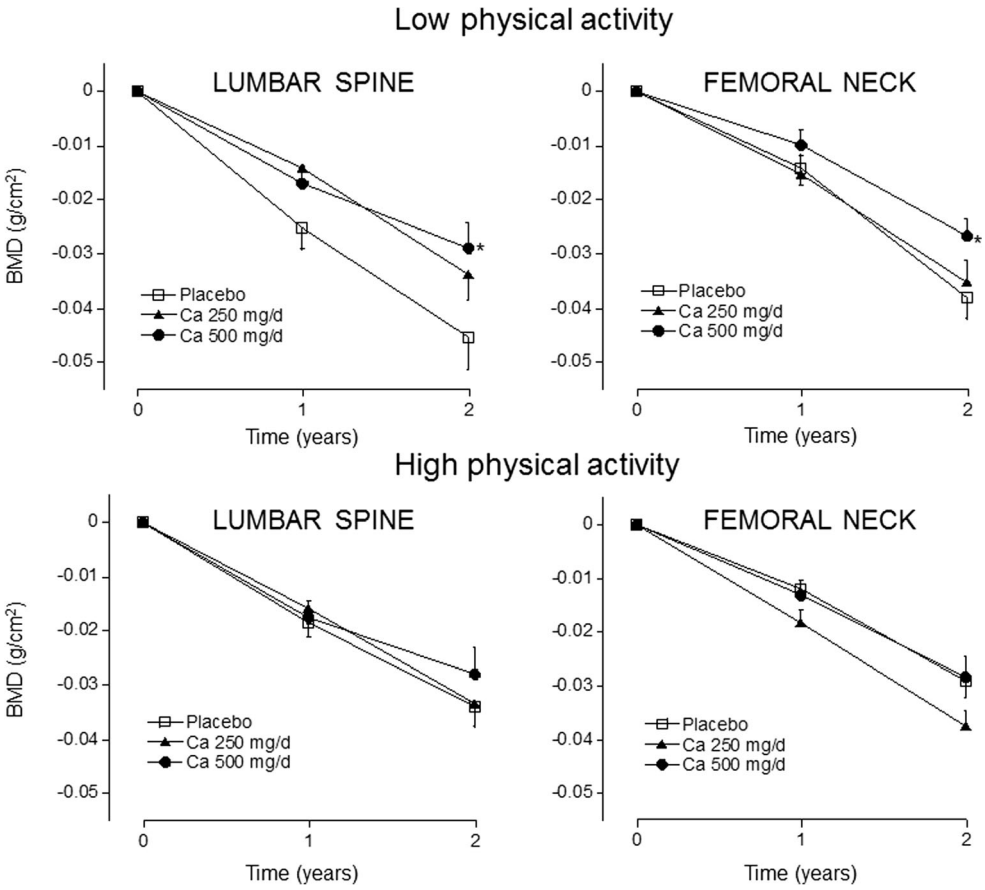

Fig. 1 Intention-to-treat analysis of changes (follow-up minus baseline examination values) in bone mineral density (BMD) of the lumbar spine in low (upper left) and high (upper right) physical activity subgroups, and BMD of femoral neck in low (lower left) and high (lower right) physical activity subgroups for the three calcium supplement treatment groups. Bars indicate standard errors. An asterisk (*) indicates a statistically significant difference ($P < 0.05$) in mean BMD changes in calcium supplement groups compared to the placebo group, tested by one-factor repeated measures ANOVA with Dunnett's multiple comparison

loss in women. One interpretation of our findings is that the effects of high PA levels can be reproduced by increased calcium intake in those with low PA levels. The possibility that PA increases calcium absorption efficiency was previously suggested [4], and our findings support this hypothesis. Alternatively, there may be unknown mechanisms by which the association between calcium intake and bone loss is influenced by PA levels.

Baseline calcium intake in the high PA group was slightly, but significantly, higher than in the low PA group (difference, 33 mg/day), which may have influenced the association between calcium supplementation and bone loss toward null in the high PA group. It should be noted, however, that our previous subgroup analysis revealed that a higher calcium intake at baseline did not attenuate this association, i.e., calcium supplement treatment was effective in the high baseline calcium intake group, but not in the low intake group at baseline [7]. Therefore, it is unlikely that the difference in baseline calcium intake between the low and high PA subgroups influenced the association between calcium supplementation and bone loss.

Although we used an RCT design, subgroup analyses do not necessarily warrant strict randomization for each subgroup. We used a previously validated 7-day activity recall method to assess physical activity levels; however, we did not confirm the reliability or validity of this method for use in the present study. This is a limitation of our study.

This is the first longitudinal study to show that physical activity may be a favorable effect modifier of the association between calcium intake and bone loss in perimenopausal and postmenopausal women.

Author contribution Study design: KN. Acquisition of data: KN, RK, RO, and KK. Interpretation of data: KN, TS, KK, and YW. Drafting of the manuscript: KN. Critical revision of the manuscript for important intellectual content: KN, KK, and YW. Statistical analysis: KN.

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Compliance with ethical standards

Ethical statement The study was conducted in accordance with the Declaration of Helsinki, written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Niigata University School of Medicine.

Conflict of interest None.

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