Effects of Ibuprofen and Resistance Training on Bone and Muscle: A Randomized Controlled Trial in Older Women

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ABSTRACT

DUFF, W. R. D., P. D. CHILIBECK, D. G. CANDOW, J. J. GORDON, R. S. MASON, R. TAYLOR-GJEVRE, B. NAIR, M. SZAFRON, A. BAXTER-JONES, G. A. ZELLO, and S. A. KONTULAINEN. Effects of Ibuprofen and Resistance Training on Bone and Muscle: A Randomized Controlled Trial in Older Women. *Med. Sci. Sports Exerc.*, Vol. 49, No. 4, pp. 633–640, 2017. **Introduction/Purpose**: Resistance training with ibuprofen supplementation may improve musculoskeletal health in postmenopausal women. The study purpose was to determine the efficacy of resistance training and ibuprofen supplementation on bone and muscle properties in postmenopausal women. **Methods**: Participants (n = 90, 65.3 ± 4.9 yr) were randomly assigned to: supervised resistance training or stretching (placebo-exercise) with postexercise ibuprofen (400 mg) or placebo supplementation for 3 $d \cdot wk^{-1}$ (9 months). Baseline and postintervention measurements included distal and shaft scans of the forearm and lower leg using peripheral quantitative computed tomography. Distal site outcomes included cross-sectional area, content, and density for total and trabecular bone, as well as estimated bone strength in compression. Shaft site outcomes included total bone area; cortical bone area, content, and density; estimated bone strength in torsion; and muscle area and density. **Results**: Exercise–supplement–time interactions for total bone content at the distal radius (P = 0.009) and cortical density at the radius shaft (P = 0.038) were significant. Resistance training with ibuprofen decreased total bone content (−1.5%) at the distal radius in comparison to the resistance training (0.6%; P = 0.032) and ibuprofen alone (0.5%; P = 0.050). Change in cortical density at the radius shaft differed between the stretching with placebo and ibuprofen supplementation groups (−1.8% vs 1.1%; P = 0.050). Resistance training preserved muscle density in the lower leg more so than stretching (−3.1% vs −5.4%; P = 0.015). **Conclusions**: Ibuprofen consumed immediately after resistance training had a deleterious effect on bone mineral content at the distal radius, whereas resistance training or ibuprofen supplementation individually prevented bone loss. Resistance training prevented muscle density decline in the lower leg. **Key Words:** EXERCISE, BONE STRENGTH, PQCT, POSTMENOPAUSAL

Chronic inflammation may be a contributing factor to the loss of bone and muscle mass and strength with aging (2,9,15,22). Resistance training is a proven strategy for decreasing inflammation and increasing muscle mass and preserving bone mineral (2,4,42). Anti-inflammatory therapies, such as nonsteroidal anti-inflammatory drugs (NSAID), are theorized to have beneficial effects on aging bone and muscle (19,26,40). Therefore, the combination of resistance training and ibuprofen, a popular NSAID, may be an effective lifestyle intervention to improve musculoskeletal health when aging.

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Submitted for publication July 2016.
Accepted for publication November 2016.

0195-9131/17/4904-0633/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000001172

Epidemiological and experimental evidence of the combined therapy of resistance training with ibuprofen on bone and muscle properties is limited. One epidemiological study demonstrated associations between regular NSAID use and 13% to 34% greater cortical and trabecular density at the lumbar spine, whereas areal bone mineral density (aBMD) in the total body and at the hip were 4% to 5% greater (7). Randomized controlled trials in humans (although limited in number) have shown benefits for aBMD, at clinically relevant sites, in *premenopausal* women who supplemented resistance training with low-dose ibuprofen (400 mg, 3 $d \cdot wk^{-1}$, 9 months) (25,26); however, recent findings from our group and others indicate no benefits for aBMD in *postmenopausal* women after a similar intervention (13,23). Further, no benefits for fat-free mass in premenopausal or postmenopausal women were evident (13,23), in contrast to findings in animal models (36) or in older participants on higher doses of ibuprofen (i.e. 1200 $mg \cdot d^{-1}$) (40).

To date, no study has assessed the musculoskeletal effects of combined resistance training and ibuprofen on bone structure and strength. This is important because changes in bone

structure and strength can often be overlooked if measurements rely on DXA-derived aBMD only (24,34). Measuring bone structure and volumetric density via peripheral quantitative computed tomography (pQCT) enables assessment of possible redistribution of bone mineral and estimation of the intervention effect on bone strength (1,20,24,31,41).

This proof-of-concept study was conducted among postmenopausal women who participated in a randomized controlled trial (13). The overall goal of the study was to assess the effects of long-term (9 months) low-dose ibuprofen (400 mg) and exercise training on muscle and bone mass, with primary outcomes identified as aBMD of the proximal femur and lumbar spine (13). The purpose of the current study was to investigate the effects of the intervention on pQCT-derived properties of bone and muscle in postmenopausal women, with secondary outcomes identified as bone properties and strength at the distal radius. It was hypothesized that the combined effects of progressive resistance training and ibuprofen supplementation would be additive for improving bone properties, estimated bone strength, muscle cross-sectional area, and density compared with placebo exercise (flexibility) and supplement.

MATERIALS AND METHODS

Study Design

The study design has been described in detail elsewhere (13). Briefly, participants were randomized on a 1:1:1:1 basis to one of four groups after exclusion criteria were applied. Randomization was completed using a computer-generated allocation schedule with a block size of four by one of the investigators who was not involved in the measurement of outcome variables or the analysis. The four groups were: 1) resistance training combined with ibuprofen supplementation (ExIbu), 2) resistance training combined with placebo supplementation (Ex), 3) flexibility training (i.e. stretching, placebo-exercise) combined with ibuprofen supplementation (Ibu), and 4) flexibility training combined with placebo supplementation (control). A relatively safe and well tolerated ibuprofen dosage of 400 mg was administered immediately after exercise training only (maximum, three times per week) for 9 months (6,35). The supplement, or identical placebo, was prepackaged into sequentially numbered containers according to the randomization schedule. The allocation sequence was blinded from the study personnel enrolling and assessing the participants. All participants were provided supplements of calcium and vitamin D (600 $mg \cdot d^{-1}$ and 400 $IU \cdot d^{-1}$, respectively), the corresponding exercise training program, and an exercise/supplement tracking log. All study personnel involved in the outcome assessment and analysis were blinded to the group assignment, including the study statistician via coding of the groups. The study was approved by the Biomedical Research Ethics Board of the University of Saskatchewan. Reporting of this study adhered to the Consolidated Standards of Reporting Trials guidelines for randomized clinical trials. This trial was registered with clinicaltrials.gov (NCT01886196) with primary outcome identified as change from baseline in aBMD of the proximal femur and lumbar spine at 9 months.

Participants

Participant recruitment and flow through the study have been described thoroughly elsewhere (13). In short, participants were assessed for eligibility using a modified version of the Mediterranean Osteoporosis Study Questionnaire (11,34). Participants were not eligible if they had a high risk of fracture (38). Grounds for further exclusion included: comorbidities or concurrent medication usage that were known to affect bone mineral metabolism, having contraindications to administration of ibuprofen (13), cigarette smoking, or current (within past 6 months) engagement in a strength training regimen.

The proof-of-concept study sample size was based on adaptive response of femoral neck aBMD via NSAID supplementation after exercise in 54 younger adults (25) and increased based on greater aBMD variability in older adults (5,13). After applying the exclusion criteria, 144 women were eligible to take part in the study, of which 90 agreed to participate. The participants signed informed consents and completed the Physical Activity Readiness Questionnaire and Physical Activity Readiness Medical Examination (39) before baseline testing to ensure there was no contra-indication to exercise participation.

Interventions

Interventions have been described in detail elsewhere (13). Briefly, ibuprofen (Saskatoon Medical Arts Pharmacy, Saskatoon, SK) and placebo capsules (indistinguishable in taste and appearance) were ingested immediately after exercise training (3 $d \cdot wk^{-1}$ for 9 months). All participants further received a supplement of 600 mg of calcium and 10 μg (400 IU) of vitamin D (Jamieson Laboratories, Toronto, ON) (38).

After orientations, whole-body resistance and flexibility exercise training was performed 3 $d \cdot wk^{-1}$, on nonconsecutive days, to reduce the risk of injury and minimize fatigue. Resistance training exercise sessions were completed at our research facility under the direct supervision of study personnel while flexibility training was performed at home. The resistance training program consisted of two sets of 8 to 12 repetitions (to fatigue) for 12 machine and dumbbell exercises. Participants also performed a medicine ball toss and catch against a wall. The resistance training program was progressive in nature, with load increased when no longer challenging (i.e., once participants were able to achieve 12 repetitions per set with good form), and designed to provide training stimulus to the entire body. However, intervention exercises were chosen to benefit both primary outcomes of the proof-of-concept study (13) and secondary outcomes presented in the current study. Thus, focus was on providing training stimulus to the clinically relevant sites (hip, lumbar spine, distal radius, and tibia). The exercise training placebo was a home-based flexibility program consisting of two sets of static stretches (held for 20–30 s) designed to improve flexibility of the major muscle groups (3). Flexibility participants were advised not to

perform any resistance training exercise for the duration of the intervention. Further, flexibility participants were advised to consume supplement after training sessions 3 $d \cdot wk^{-1}$. Compliance was assessed via tracking logs and through pill counting of the leftover supplement. Outcome measurements were performed at baseline and after the 9-month intervention. Postintervention participants were instructed to not perform any exercise training the day before outcome measurements being performed; therefore, there was typically at least 48 h between the final exercise session and postintervention measurements.

Outcomes

Primary DXA outcomes were reported in our previous publication (13). Secondary pQCT-derived outcome measures in the current study at the distal radius and tibia were total and trabecular bone area, content, and density and bone strength index and at the shaft sites were total bone area and cortical bone area, content, and density, and bone strength index (12). Additional pQCT-derived outcome measures included muscle cross-sectional area and density of the forearm and lower leg (18). Anthropometric measurements were taken before pQCT measurements.

Anthropometric measurements. Height was measured using a wall-mounted stadiometer (Holtain Limited, Britain) to the nearest 0.1 cm. The nondominant radius and tibia lengths were measured with an anthropometric sliding caliper (segmometer; Rosscraft Innovations, Canada) three times, with the median value recorded. For the radius, the proximal lateral radial head and the most distal point of the styloid process were palpated and the distance measured with the participant standing (14). For the tibia, the superior margin of the medial epicondyle and the base of the medial malleolus were palpated and the distance measured while the participant assumed a cross-legged position (14).

Peripheral pQCT. Bone and muscle properties and estimated bone strength of the nondominant forearm and lower leg were assessed via pQCT (Stratec Medizintechnik GmbH, Pforzheim, Germany). Participants were positioned with the forearm and lower leg centered in the gantry with consideration for the comfort level of the participant (12,17). A scout view was performed, and a reference line was placed at the medial tip of the distal endplate for both the radius and tibia. Cross-sectional slices, proximal from the reference line, were then obtained at the distal (4% of radius and tibia length) and shaft (65% of radius and 66% tibia lengths, respectively) sites with scanning parameters set at 0.4 mm pixel size and 20 $mm \cdot s^{-1}$ scanning speed (12,17). We used manufacturer software (Stratec, version 6, Pforzheim, Germany) and our standard protocols to analyze bone and muscle outcomes (12,18). Outcomes for the distal sites included total area (ToA; mm^2), total content (ToC; $mg \cdot mm^{-1}$), and total density (ToD; $mg \cdot cm^3$); trabecular area (TrA; mm^2), trabecular content (TrC; $mg \cdot mm^{-1}$), and trabecular density (TrD; $mg \cdot cm^{-3}$); and bone strength index against compressions (BSIc; $mg^2 \cdot mm^{-4}$). BSIc was calculated as the product of ToA and squared ToD ($BSIc = ToA \times ToD^2$; mm^4) (27). At the distal sites, ToA and ToD were defined using contour mode 1 (outer threshold of 169 $mg \cdot cm^{-3}$), whereas TrA, TrC, and TrD were defined using peel mode 2 (threshold of 480 $mg \cdot cm^{-3}$). Outcomes for the shaft sites included total area (ToA; mm^2); cortical area (CoA; mm^2), cortical content (CoC; $mg \cdot mm^{-1}$), and CoD ($mg \cdot cm^{-3}$); stress–strain indices during torsion (mm^3); and muscle cross-sectional area (mm^2) and density ($mg \cdot cm^{-3}$). At the shaft sites, ToA was defined using contour mode 1 (outer threshold of 280 $mg \cdot cm^{-3}$), whereas CoA, CoC, and CoD were defined using separation mode 4 (threshold of 480 $mg \cdot cm^{-3}$) (12); muscle area and density of the cross-section of the forearm and lower leg (including all muscles) was defined using threshold of 40 $mg \cdot cm^{-3}$ (17). Precision errors ($CV\%_{rms}$) for the bone and muscle parameters in postmenopausal women measured in our laboratory range between 0.7% and 6.1%, with the largest error observed in the distal radius BSIc (12,18).

Descriptive outcomes. Participants completed a food frequency questionnaire (Block 98256318-2, Block Dietary Data Systems, Berkeley, CA) to assess the changes from baseline to intervention completion for total energy, macronutrients, and dietary calcium and vitamin D levels. Participants were further asked to report any adverse events that occurred throughout the duration of the study, these were recorded on adverse event forms.

Statistical Analysis

Data were analyzed on an intent-to-treat basis using IBM SPSS Statistics for Windows (Version 21.0; IBM Corp, Armonk, NY). Baseline descriptives for all variables between groups were compared using Student's *t* tests. Variables were analyzed via a 3-factor analysis of variance, with time as a within-group factor (baseline vs 9 months postintervention) and drug (ibuprofen versus placebo) and exercise (resistance training vs flexibility (placebo)) as between-group factors. Tetrad contrast hypothesis tests were used for the *post hoc* analyses. We report partial eta-squared (η_p^2) as an estimate of effect size. All descriptive results were expressed as either means and standard deviations or mean absolute changes and 95% confidence intervals. P values ≤ 0.05 were deemed statistically significant.

RESULTS

Baseline data for the intervention groups are presented in Table 1. There were no significant differences between groups for any variables at baseline. Of the 90 participants randomized, 69 were included in the final analysis, 21 (23%) were lost to follow-up. Researchers were able to contact 14 of the 21 lost to follow-up, with reasons for withdrawal cited as exclusion after randomization, unhappiness with randomization, personal health reasons, relocation out of province, or no desire to return. Compliance to the interventions was similar ($P > 0.05$) between groups: ExIbu, 89%; Ex, 84%; Ibu, 88%; and control, 87%. Reported compliance corresponds to both exercise and supplement because the supplement was only

TABLE 1. Baseline data by intervention group.

	ExIbu (n = 23)	Ex (n = 22)	Ibu (n = 23)	Control (n = 22)
Age (yr)	65.4 (3.5)	65.3 (4.6)	65.5 (6.7)	65.0 (4.7)
Height (cm)	160.5 (4.7)	162.4 (5.7)	162.5 (6.6)	160.0 (6.6)
Total Mass (kg)	74.0 (12.9)	71.02 (11.7)	76.1 (13.7)	75.5 (15.0)
Distal radius				
ToA (mm^2)	371.2 (52.9)	383.2 (53.6)	405.7 (56.8)	381.1 (52.9)
ToC ($mg \cdot mm^{-1}$)	99.6 (16.4)	98.9 (19.9)	100.1 (15.1)	101.9 (19.3)
ToD ($mg \cdot cm^{-3}$)	270.1 (38.0)	260.4 (47.1)	250.0 (44.3)	267.7 (38.9)
TrA (mm^2)	327.4 (55.3)	344.3 (59.8)	369.6 (64.6)	339.1 (56.8)
TrC ($mg \cdot mm^{-1}$)	69.4 (14.6)	71.7 (16.2)	75.9 (13.4)	72.7 (16.9)
TrD ($mg \cdot cm^{-3}$)	212.6 (28.5)	209.0 (30.2)	206.7 (23.8)	213.3 (28.0)
BSIc ($mg^2 \cdot mm^{-4}$)	27.2 (6.9)	26.3 (9.2)	25.4 (7.0)	27.8 (8.5)
Radial shaft				
ToA (mm^2)	129.5 (14.7)	129.8 (25.1)	137.9 (18.2)	130.2 (23.2)
CoA (mm^2)	82.9 (10.0)	78.5 (11.0)	87.6 (11.1)	82.4 (13.7)
CoC ($mg \cdot mm$)	87.8 (11.3)	82.8 (13.3)	90.8 (13.1)	88.2 (16.1)
CoD ($mg \cdot cm^{-3}$)	1058.6 (45.7)	1054.1 (71.0)	1035.9 (64.1)	1067.8 (60.2)
SSIp (mm^3)	259.5 (41.5)	250.7 (55.2)	275.5 (58.6)	264.4 (59.2)
Distal tibia				
ToA (mm^2)	1089.4 (114.9)	1106.5 (125.1)	1141.6 (109.9)	1073.7 (133.0)
ToC ($mg \cdot mm^{-1}$)	288.3 (34.7)	287.3 (37.7)	297.7 (39.3)	287.9 (57.6)
ToD ($mg \cdot cm^{-3}$)	266.1 (31.4)	260.2 (24.4)	262.2 (35.4)	272.9 (42.7)
TrA (mm^2)	1024.1 (122.7)	1042.8 (123.5)	1079.0 (126.6)	1005.8 (139.2)
TrC ($mg \cdot mm^{-1}$)	245.6 (31.8)	246.1 (33.5)	256.9 (34.3)	246.2 (53.1)
TrD ($mg \cdot cm^{-3}$)	241.1 (27.1)	236.5 (22.0)	239.4 (28.3)	244.1 (37.9)
BSIc ($mg^2 \cdot mm^{-4}$)	77.4 (16.1)	75.2 (15.4)	79.0 (18.8)	82.2 (28.2)
Tibial shaft				
ToA (mm^2)	579.0 (64.8)	595.2 (87.1)	604.2 (94.8)	580.6 (63.0)
CoA (mm^2)	301.8 (32.1)	288.4 (37.5)	294.5 (45.1)	295.4 (40.2)
CoC ($mg \cdot mm$)	313.2 (36.0)	296.9 (49.5)	305.7 (51.1)	308.7 (47.4)
CoD ($mg \cdot cm^{-3}$)	1038.0 (45.4)	1025.8 (65.6)	1035.8 (45.2)	1043.4 (46.7)
SSIp (mm^3)	2196.7 (303.7)	2128.3 (396.5)	2160.5 (366.4)	2164.2 (354.7)

All values are means (SD).
SSIp, strength strain index against torsion.

consumed after exercise. Of the participants that adhered to the ibuprofen–placebo intervention, the percent able to correctly identify the supplement were: ExIbu, 47% (n = 17); Ex, 63% (n = 19); Ibu, 47% (n = 15); and control, 79% (n = 14). Compliance to calcium and vitamin D supplementation was similar between groups ($P > 0.05$): ExIbu, 83%; Ex, 72%; Ibu, 76%; and control, 84%. Finally, the number of participants analyzed per outcome varied as follows. Two radius shaft scans were excluded from the analysis from two intent-to-treat participants due to significant movement artefacts: ExIbu (n = 1) and Ex (n = 1). Two tibia scans (distal and shaft) were excluded from one intent-to-treat participant due to improper placement of the reference line: Ibu (n = 2). Five intent-to-treat participants were unable to complete scanning of the lower leg due to a large leg girth and the limiting size of the gantry: Ex (n = 1), Ibu (n = 3), and control (n = 1).

Bone properties and strength. There was a significant exercise–supplement–time interaction for total bone content at the distal radius ($P = 0.009$; $\eta_p^2 = 0.082$) (Table 2; Fig. 1). ExIbu decreased the average total bone content in comparison to the Ex ($P = 0.032$) and Ibu ($P = 0.050$) groups (Table 2; Fig. 1). There was a significant exercise–supplement–time interaction for total area at the radial shaft ($P = 0.048$; $\eta_p^2 = 0.062$) (Table 2). *Post hoc* analyses failed to find significance when comparing changes between groups. There was a significant exercise–supplement–time interaction for CoD at the radial shaft ($P = 0.038$; $\eta_p^2 = 0.067$) (Table 2). When comparing changes between groups, Ibu maintained the average CoD at the radial shaft when compared with control ($P = 0.050$) (Table 2). No significant interactions were apparent for the other remaining variables at the distal radius and tibia or at the radius and tibia shaft (Table 2).

Muscle properties. Interactions (exercise–supplement–time) for muscle properties at the forearm were not significant. There was a significant exercise–time interaction for lower leg muscle density ($P = 0.015$; $\eta_p^2 = 0.099$) (Table 3). Resistance training preserved the average lower leg muscle density more so than flexibility training.

Diet. There was a significant exercise–supplement–time interaction for average *dietary* vitamin D intake ($P = 0.024$; $\eta_p^2 = 0.081$). *Post hoc* analyses failed to find significance when comparing average changes between groups. Interactions for the average *dietary* calcium intake were not significant. Further, there was a significant exercise–time interaction for the average total energy ($P = 0.046$; $\eta_p^2 = 0.068$) and fat intake ($P = 0.039$; $\eta_p^2 = 0.073$). The stretching group decreased average total energy intake ($-225 \pm$ SD 347 calories per day) via reduced average fat intake (-10 ± 18 $g \cdot d^{-1}$) compared with the resistance training group. Baseline to postintervention averages for remaining macronutrients (carbohydrates, protein) and activity outcomes were not different between groups. All groups met the recommended dietary allowances (RDA) of 0.8 $g \cdot kg^{-1}$ of protein and 130 $g \cdot d^{-1}$ of carbohydrates, as well as the acceptable macronutrient distribution range of 20% to 35% for total fat (the RDA for total fat is not determinable).

TABLE 2. Mean absolute changes (95% CI) from baseline to 9 months for bone properties and strength within groups.

	ExIbu (n = 18)		Ex (n = 19)		Ibu (n = 17)		Control (n = 15)	
	Change	95% CI	Change	95% CI	Change	95% CI	Change	95% CI
Distal radius								
ToA (mm^2)	−2.3	(−13.1 to 8.4)	−0.2	(−17.8 to 17.5)	5.0	(−15.7 to 25.6)	2.4	(−8.9 to 13.7)
ToC ($mg \cdot mm$)	−1.5	(−3.0 to −0.1)[a,b]	0.6	(−0.7 to 1.9)[a]	0.5	(−1.5 to 2.5)[b]	−1.3	(−2.6 to 0.0)
ToD ($mg \cdot cm^{-3}$)	−0.9	(−10.2 to 8.3)	2.3	(−10.1 to 14.7)	−1.4	(−11.6 to 8.8)	−4.9	(−13.2 to 3.4)
TrA (mm^2)	−1.2	(−15.2 to 12.8)	−0.6	(−22.0 to 20.8)	5.6	(−20.4 to 31.5)	3.9	(−10.7 to 18.4)
TrC ($mg \cdot mm^{-1}$)	−1.1	(−4.2 to 2.0)	0.8	(−3.0 to 4.5)	0.8	(−4.8 to 6.5)	0.2	(−2.6 to 3.1)
TrD ($mg \cdot cm^{-3}$)	−2.0	(−5.7 to 1.8)	2.7	(−2.2 to 7.5)	−1.2	(−6.0 to 3.6)	−2.1	(−3.6 to −0.6)
BSIc ($mg^2 \cdot mm^{-4}$)	−0.5	(−1.6 to 0.6)	0.2	(−0.9 to 1.4)	−0.1	(−1.1 to 0.8)	−0.9	(−2.0 to 0.2)
Radial shaft								
ToA (mm^2)	2.5	(−0.3 to 5.3)	−0.3	(−3.9 to 3.4)	−0.6	(−4.6 to 3.4)	1.7	(−1.0 to 4.4)
CoA (mm^2)	1.3	(−1.2 to 3.9)	0.4	(−1.4 to 2.1)	−1.0	(−4.1 to 2.1)	1.1	(−0.4 to 2.7)
CoC ($mg \cdot mm^{-1}$)	−0.1	(−1.4 to 1.3)	0.2	(−0.9 to 1.4)	−0.4	(−2.3 to 1.6)	−0.2	(−1.6 to 1.2)
CoD ($mg \cdot cm^{-3}$)	−16.8	(−42.9 to 9.2)	−2.6	(−29.1 to 24.0)	9.2	(−9.9 to 28.2)[c]	−19.8	(−33.0 to −6.5)[c]
SSIp (mm^3)	1.8	(−11.1 to 14.8)	−1.0	(−11.9 to 9.8)	5.9	(−3.4 to 15.1)	−2.8	(−12.3 to 6.7)
Distal tibia								
ToA (mm^2)	6.2	(−11.2 to 23.7)	9.6	(−2.5 to 21.8)	4.5	(−17.8 to 26.7)	8.9	(−15.6 to 33.4)
ToC ($mg \cdot mm^{-1}$)	−0.3	(−3.1 to 2.4)	1.9	(−0.1 to 3.9)	0.3	(−4.7 to 5.4)	4.5	(−5.2 to 14.1)
ToD ($mg \cdot cm^{-3}$)	−1.8	(−4.1 to 0.6)	−0.6	(−3.0 to 1.8)	−0.8	(−3.7 to 2.1)	−5.6	(−12.8 to 1.6)
TrA (mm^2)	8.9	(−11.6 to 29.3)	12.8	(−3.5 to 29.0)	12.6	(−14.8 to 40.0)	12.6	(−15.5 to 40.7)
TrC ($mg \cdot mm^{-1}$)	1.6	(−3.4 to 6.5)	4.3	(0.3 to 8.2)	1.2	(−4.9 to 7.2)	3.8	(−4.3 to 11.9)
TrD ($mg \cdot cm^{-3}$)	−0.4	(−1.8 to 1.1)	1.1	(−0.3 to 2.5)	−0.3	(−1.5 to 0.8)	0.5	(−2.3 to 3.3)
BSIc ($mg^2 \cdot mm^{-4}$)	−0.5	(−1.2 to 0.2)	0.3	(−0.6 to 1.2)	−0.2	(−1.2 to 0.7)	−2.9	(−8.5 to 2.7)
Tibial shaft								
ToA (mm^2)	−1.4	(−10.1 to 7.3)	0.7	(−6.2 to 7.5)	−6.6	(−13.2 to 0.1)	1.2	(−7.1 to 9.4)
CoA (mm^2)	−0.5	(−2.5 to 1.6)	−0.9	(−4.7 to 2.8)	1.9	(−0.9 to 4.6)	0.4	(−1.4 to 2.1)
CoC ($mg \cdot mm^{-1}$)	−0.7	(−2.9 to 1.6)	−0.8	(−2.2 to 0.7)	1.6	(−1.5 to 4.7)	−2.1	(−4.2 to −0.1)
CoD ($mg \cdot cm^{-3}$)	−0.6	(−6.9 to 5.8)	0.9	(−9.8 to 11.6)	−1.6	(−7.9 to 4.7)	−7.9	(−14.4 to −1.4)
SSIp (mm^3)	−9.3	(−37.8 to 19.3)	−14.8	(−46.9 to 17.4)	−12.8	(−44.6 to 19.0)	−20.4	(−46.2 to 5.3)

[a]ExIbu different from Ex (*post hoc*; P = 0.032).
[b]ExIbu different from Ibu (*post hoc*; P = 0.050).
[c]Ibu different from control (*post hoc*; P = 0.050).
CI, confidence interval.

Adverse events. Throughout the duration of the intervention, there were two serious adverse events reported. These included a transient ischemic attack (ExIbu) and a fractured pelvis from a fall on ice (control). Although both serious adverse events were deemed "not related" to the intervention, both participants discontinued the study.

DISCUSSION

To our knowledge, this is the first study to examine the efficacy and interactions of resistance training and ibuprofen supplementation on pQCT-derived bone properties, estimated bone strength, and muscle properties in postmenopausal women. Results showed that the combination of resistance training and ibuprofen had a negative effect on distal radius bone mineral content; however, ibuprofen maintained cortical bone density and resistance training preserved muscle density compared with stretching alone. Resistance training and ibuprofen therefore independently maintained bone or muscle in postmenopausal women.

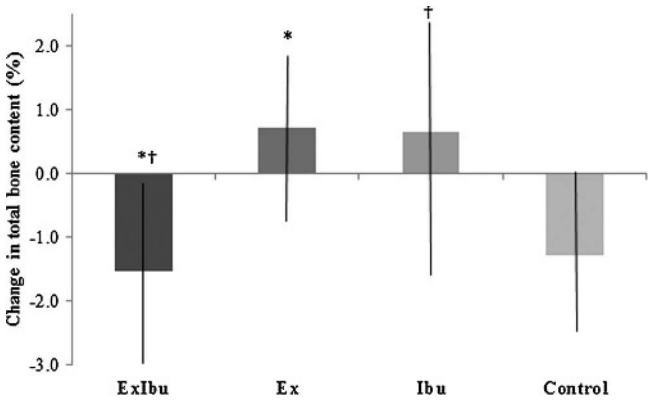

FIGURE 1—Mean %-change in total bone mineral content at the distal radius across the groups over the 9-month intervention. Error bars indicate 95% confidence intervals. *ExIbu different from Ex (*post hoc*; P = 0.032). †ExIbu different from Ibu (*post hoc*; P = 0.050).

Our results add to the limited evidence on the effects of resistance training combined with ibuprofen supplementation on properties of bone and muscle in postmenopausal women. Two previous studies performed by the same research group (23,25) demonstrated conflicting results in premenopausal compared with postmenopausal women. Resistance training supplemented with 400 mg of ibuprofen (immediately after exercise, 3 $d \cdot wk^{-1}$) improved aBMD of the hip in *premenopausal* women over 9 months of training, but not in *postmenopausal* women (23,25). In these studies, menopausal status may have been a contributing factor as the cessation of estrogen likely influences bone and muscle biology (21). We previously reported small, independent benefits of ibuprofen on aBMD of Ward's region at the proximal femur (13). Here we provide evidence that the independent benefits and deleterious interactions manifest to a greater extent in measures of bone properties (vs areal bone density) at clinically relevant sites (i.e., wrist), other than the hip in postmenopausal women. Collectively, these findings justify the need for further clinical studies.

Our findings are in contrast to studies involving premenopausal women and rodents. Research in premenopausal women suggests

TABLE 3. Mean absolute changes (95% CI) from baseline to 9 months for muscle properties within groups.

	ExIbu (n = 18)		Ex (n = 19)		Ibu (n = 17)		Control (n = 15)	
	Change	95% CI	Change	95% CI	Change	95% CI	Change	95% CI
Forearm muscle								
Area (mm^2)	43.9	(−13.8 to 101.6)	78.2	(31.6 to 124.8)	−4.97	(−63.0 to 53.0)	−2.6	(−54.2 to 49.0)
Density ($mg \cdot cm^{-3}$)	−3.5	(−6.0 to −1.0)	−3.4	(−5.3 to −1.5)	−4.37	(−6.3 to −2.5)	−3.2	(−4.9 to −1.6)
Lower leg muscle								
Area (mm^2)	116.0	(−271.3 to 39.3)	−22.0	(−174.9 to 130.8)	−93.45	(−360.6 to 173.7)	−88.8	(−333.2 to 155.6)
Density ($mg \cdot cm^{-3}$)	−2.5	(−3.9 to −1.2)	−2.5	(−4.2 to −0.8)	−4.16	(−5.7 to −2.6)	−3.8	(−5.2 to −2.4)

Lower leg muscle density change differed between resistance training and flexibility groups (P = 0.015).

a *beneficial* effect when ibuprofen is consumed immediately after loading (25). Production of proinflammatory prostanoids, derived from reactions catalyzed by the cyclooxygenase (COX-1 and COX-2) enzymes, is inhibited by NSAID (35). Animal experiments suggest that the loading-induced osteogenic response and consequential bone formation process is not *suppressed* when COX-2 inhibitors are consumed immediately after loading versus before loading in mature rats (8,29). Literature to date (human or animal) has yet to suggest a *deleterious* effect. As such, one has to be cautious when applying results from younger adults or animals to older adults. For example, the osteogenic response in older adults may be delayed (compared to younger adults), so that consuming ibuprofen postexercise may prevent both the inflammatory and osteogenic responses to loading. Further, ibuprofen is a nonselective COX-1 and COX-2 inhibitor, with a time of maximal concentration in adult serum of 1 to 2 h (400 mg) (35), whereas the metabolic response to the exercise is nearly constant during training. Muscle protein synthesis and the metabolic response in bone (i.e., increased formation, reduced resorption) are elevated at least 24 h after loading (30,32). This suggests that only some of the metabolic responses to exercise in muscle and bone were likely altered with the 400-mg ibuprofen and probably only to a fraction of the total response. Thus, it is evident not all metabolic responses to exercise were altered, nor to a full extent.

A decline in total bone content at the distal radius after resistance training with ibuprofen supplementation may lead to bone fragility at the wrist. Total bone content provides a surrogate measure for bone's resistance to axial compressive forces (27) and discriminates between fractured and nonfractured women (37). Both resistance training and ibuprofen alone *maintained* total content at the distal radius over the 9-month intervention. Further investigation with a longer duration and altered timing of ibuprofen supplementation are warranted to assess the potential for resistance training or ibuprofen to *increase* bone content and other properties at the fracture-prone distal radius.

Resistance training preserved lower leg muscle density (−3.5%) to a greater extent than stretching (−5.5%). This finding may have clinical relevance related to fall and fracture prevention. Our group demonstrated lower calf muscle density in postmenopausal women with recent wrist fracture compared with nonfractured peers (10) and lower muscle density of the lower leg in women who were fallers versus nonfallers (16). Also, thigh muscle density has shown to predict hip fracture risk in older men and women (28). Lower leg muscles vary in design, fiber type, and function, and cannot be separated in computed tomography muscle analyses. However, because power in the lower body is affected by aging, it could be speculated that muscles of the lower leg with higher percentage of powerful type II fibers, such as the gastrocnemius, may respond better to the resistance training (5). The current study indicates the efficacy of resistance training to preserve muscle density in the lower leg. Maintained muscle density in postmenopausal women may help reduce the risk of falls and related injuries, including fractures.

Our experiment had several strengths. The four group design of our study allowed assessment of both additive effects and possible interactions between ibuprofen and exercise training. Further, our measurements included pQCT-imaged data of bone mineral distribution and muscle density which may predict clinically relevant wrist fracture and may serve as early indicators of future fracture risk (10). However, limitations in our experiment need to be addressed. Although able to indicate hip fracture risk, pQCT cannot directly assess the clinically relevant hip (or spine). The stretching group decreased average total energy intake via reduced fat intake. This could potentially have a negative impact on muscle and bone; however, because the stretching group met the RDA for protein and carbohydrate and the acceptable macronutrient distribution range for fat throughout the study, and had no change in body mass, we believe this impact was minimal. The lower dosage of ibuprofen used (400 mg, 3 $d \cdot wk^{-1}$) may not have been great enough to elicit independent or additive improvements in the muscle, as previously demonstrated in older adults and old rats, respectively (36,40). Our study was most likely underpowered to detect small differences in bone changes within the 9 months of training. Our findings support the recommendation for a minimum of 2 yr for exercise interventions assessing bone structure and strength adaptation (33).

In summary, our results indicated a deleterious interaction between resistance training and ibuprofen (−1.5%) on bone mass at the distal radius in comparison to resistance training (0.6%) or ibuprofen (0.5%) alone. Ibuprofen alone also maintained CoD (1.1%) when compared with the control group (−1.8%) at the radial shaft. Collectively, these results suggested that resistance training or ibuprofen provides independent benefits for maintaining bone properties at the forearm, but contrary to our original hypothesis, when ibuprofen was consumed immediately after resistance training, these benefits were

negated, rather than *enhanced*. Resistance training and/or ibuprofen supplementation had no effect on bone properties or strength at the tibia. Although further interventions of this nature in postmenopausal women and older men are warranted, the study design could be adjusted to accommodate cumulating evidence. Based on our findings, future study design could include increasing to daily dosages of ibuprofen, provide the ibuprofen supplementation several hours beyond the resistance training, increase duration of the intervention to 2 yr, increase the sample size, and include men in the study sample.

CONCLUSIONS

Ibuprofen supplementation immediately after resistance training sessions did not have an additive effect on bone and muscle properties or estimated bone strength. In contrast, our findings suggest that ibuprofen consumed immediately after resistance training had a deleterious effect on bone mineral mass at the distal radius, whereas resistance training or ibuprofen supplementation alone prevented bone loss.

No conflicts of interest for all authors. The results of the present study do not constitute endorsement by American College of Sports Medicine. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Funding from Canadian Institutes of Health Research (grant 264196). We thank study participants and summer student Anthony M. Kehrig for his assistance.

P. C., D. C., A. B., G. Z., and S. K. participated in the study design. W. D., P. C., J. G., R. T., B. N., R. M., and S. K. participated in the study conduct. W. D., J. G., and S. K. participated in data collection and analysis. M. S. participated in Statistical analysis. W. D., P. C., M. S., and S. K. participated in data interpretation. W. D. participated in drafting the article. W. D., P. C., D. C., R. T., M. S., A. B., G. Z., and S. K. participated in revising the article content. All authors approved the final version of the article. S. K. and W. D. take responsibility for the integrity of the data analysis.

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