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Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial

Pamela S. Hinton, Ph.D.[a], **Peggy Nigh**[a], and **John Thyfault, Ph.D.**[a,b]

[a]Department of Nutrition and Exercise Physiology, University of Missouri, Columbia MO 65211

[b]Internal Medicine – Division of GI and Hepatology, University of Missouri, Columbia MO 65211

Abstract

Purpose—To examine the effects of 12 mo of resistance training (RT, 2x/wk, N= 19) or jump training (JUMP, 3x/wk, N= 19) on bone mineral density (BMD) and bone turnover markers (BTM) in physically active (≥4 hr/wk) men (mean age: 44 ± 2 y; median: 44 y) with osteopenia of the hip or spine.

Methods—Participants rated pain and fatigue following each RT or JUMP session. All participants received supplemental calcium (1200 mg/d) and vitamin D (10 μg/d). BMD was measured at 0, 6, and 12 mo using DXA scans of the whole body (WB), total hip (TH) and lumbar spine (LS). BTM and 25 OHD were measured by ELISA. The effects of RT or JUMP on BMD and BTM were evaluated using 3×2 repeated measures ANOVA (time, group). This study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Missouri IRB.

Results—At baseline, 36 of 38 participants were vitamin D sufficient (25OHD>50 nmol/L); at 12 mo, all participants were 25OHD sufficient. 25OHD did not differ between groups. WB and LS BMD significantly increased after 6 months of RT or JUMP and this increase was maintained at 12 mo; TH BMD increased only in RT. Osteocalcin increased significantly after 12 mo of RT or JUMP; CTx decreased significantly after 6 mo and returned to baseline concentrations at 12 mo in both RT and JUMP. Pain and fatigue ratings after RT or JUMP sessions were very low at 0, 6, and 12 mo.

Conclusion—RT or JUMP, which appeared safe and feasible, increased BMD of the whole body and lumbar spine, while RT also increased hip BMD, in moderately active, osteopenic men.

Address correspondence to: Dr. Pamela S. Hinton, 204 Gwynn Hall, Department of Nutrition and Exercise Physiology, Columbia, MO 65211, hintonp@missouri.edu, Phone: (573) 882-4137, FAX: (573) 884-4885.

Conflict of Interest and Source of Funding

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Keywords

exercise intervention; bone turnover markers; male osteopenia; bone formation; bone resorption

1. Introduction

1.1. Male osteoporosis

Osteoporosis affects more than 2 million men in the United States today and nearly 16 million more have low bone mass [1]. Men account for approximately 40% of the 9 million new osteoporotic fractures that occur annually [2] and the lifetime fracture risk in men aged ≥60 years is estimated to be as high as 25% [3]. Compared with women, men have a significantly greater risk for complications after a hip fracture, including increased morbidity, mortality, loss of independence, and rate of institutionalization [4, 5], yet treatment rates are much lower in males than females [6]. Recent estimates indicate that one-third of Caucasian males over 65 years and greater than one-half over 75 years would be recommended pharmacologic treatment for osteoporosis based on National Osteoporosis Foundation guidelines [7]. Yet, even after suffering an osteoporosis-related fracture, >90% of men remain undiagnosed and untreated [8, 9]. Post-fracture, men are less likely to receive follow-up care than women [10], including calcium and vitamin D supplementation[11] and prescription of anti-resorptive pharmacotherapy [6].

Although anti-resorptive medications are an FDA-approved treatment for osteoporosis in males [12], less than 10% of men with osteoporotic fractures are treated with bisphosphonates. Enthusiasm for use of these medications in men appears to be limited by the relative lack of long-term safety and efficacy studies in men, the especially poor treatment compliance in males [13], and data suggesting poor cost effectiveness of bisphosphonate treatment in men [14]. Drug treatments for osteoporosis have low rates of compliance and persistence, and most patients who stop taking their osteoporosis medication do not restart [15].

1.2. Exercise interventions to improve bone outcomes

Exercise-based interventions are an attractive alternative to medication due to the reduced cost, fewer serious side effects, and additional health benefits, including improved balance and fall reduction [16, 17]. Moreover, because osteoporotic fractures occur most frequently at the hip and spine, site-specific interventions to increase bone mineral density are highly desirable. Physical activity allows for targeted strengthening of the hip and spine because sufficient skeletal loading stimulates net bone formation at the stressed skeletal sites [18]. A recent meta-analysis and review by an expert panel strongly recommends multi-component exercise for individuals with osteoporosis to improve bone health outcomes [16].

Most of the data that support this recommendation are from exercise intervention trials in women. Exercise that exerts in high muscle-contraction or ground-reaction forces on the skeleton, such as resistance training [19] or structured jump-training, respectively, increase BMD in pre- and post-menopausal women [20–22]. Consistent with controlled studies of high-impact exercise and resistance training in women, voluntary long-term participation in

running or weight-lifting was associated with greater BMD compared with participation in cycling, a weight-supported activity, in adult men [23, 24]. However, there are very few controlled trials that examine the effects of resistance training or high-impact exercise on bone mass in men [25–32]. Unfortunately, most of these studies have included men and women, elderly men, or a mixed study population of men who had either normal or low BMD. Thus, intervention trials that test the efficacy of exercise-based interventions to increase BMD in *adult males with low bone mass* are needed.

1.3. Study objectives and hypotheses

Thus, the objective of this randomized clinical trial was to determine the effects of 12 months of resistance training (RT) or jump training (JUMP) on whole body (WB), total hip (TH), and lumbar spine (LS) BMD and on markers of bone formation and resorption in apparently healthy men with low TH or LS bone mass. We hypothesized that both the RT and JUMP interventions would significantly increase BMD of the TH and LS, and that bone formation would increase relative to resorption based on changes in serum markers.

2. Materials and Methods

2.1. Trial Design

This was a 12-month randomized, parallel intervention clinical trial with a 1:1 allocation ratio of participants to either resistance training or high-intensity jump training. We did not include a no-exercise control group, as we did not feel it was ethical to do so in men with clinically significant low bone mass [33, 34]. This study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Missouri IRB. Informed written consent was obtained from each study participant.

2.2. Participants

2.2.1. Inclusion and exclusion criteria and screening—Apparently healthy, physically active (≥4 hours of leisure time physical activity/week for the past 24 months) men aged 25–60 years with low BMD of the lumbar spine or hip (>−2.5 SD T-score ≤ −1.0 SD) were eligible to participate in this study. Exclusion criteria were as follows: use of medications or supplements that affect bone metabolism or prevent exercise; previous or current medical condition affecting bone health; osteoporosis of the lumbar spine and/or hip (T score < −2.5 SD); cardiovascular disease; metal implants; current smoker (i.e., within the past 6 months); current regular participation in high-intensity resistance training and/or plyometrics; reversed sleep/wake cycle, i.e., sleep during the day, work at night; and drink excessive amounts of alcohol (more than 3 drinks per day).

The Physical Activity Readiness Questionnaire (PAR-Q) and a medical history questionnaire were used to screen for exclusion criteria. Study personnel reviewed each subject's responses on the medical history questionnaire and PAR-Q to verify completeness of the written responses. In addition, DXA scans of the whole body, total hip and lumbar spine to screen for eligibility based on BMD of the hip or lumbar spine (i.e., low bone mass, which was defined as −2.5 SD<T-score ≤−1.0 SD) [35].

2.2.2. Recruitment—Potential subjects were recruited from the university and local community via email to university employees and fliers posted on campus, at local sporting goods stores, parks and recreation areas and at community events. Because most potential participants would not know their BMD status (i.e., would not have had a BMD assessment as part of routine healthcare), recruitment was targeted to moderately active, apparently health men aged 25–60 years.

2.3. Exercise Interventions

2.3.1. Intervention design—The RT and JUMP exercise interventions tested in this study were designed to optimize the osteogenic response. Unlike cardiovascular and metabolic adaptations to exercise, which depend on exercise volume (quantity and intensity, i.e., rate of energy expenditure), the bone response does not increase with exercise volume [36]. Therefore, we did not attempt to equalize exercise time or energy expenditure between the RT and JUMP interventions; rather, each intervention was independently designed to result in the greatest increases in BMD of the TH and LS. The frequency of the RT and JUMP interventions (2 and 3 times per week, respectively) was determined by the recovery period required for RT (48 hours) and JUMP (24 hours).

2.3.2 Exercise intervention training sessions—All training sessions were supervised by study personnel and were performed in McKee Gym Fitness Center. Participants were required to complete all training sessions. If a participant missed a scheduled training session (e.g., due to illness), he was required to make up the missed session. Make-up of missed sessions was feasible because RT trained twice per week with a minimum of 48 hours between sessions and JUMP three times per week with at least 24 hours between training. Because the training sessions were supervised and participants were required to complete all sessions, the “compliance” with the RT or JUMP training was 100%.

Study personnel recorded information for each RT or JUMP training set (i.e., resistance exercise or jump type, weight lifted and % of 1-repetition maximum (RM) for RT, and number of repetitions) in each participant’s exercise intervention log book. Before and after each training session, participants were asked to rate their pain and fatigue on a visual analog scale from 0 to 100 with 100 being the worst pain or fatigue imaginable. These data, which were collected to evaluate the pain and fatigue associated with the JUMP and RT interventions and to monitor the participants’ pain and reduce risk of injury during each training session, were also recorded by the study personnel in the participant’s exercise intervention log book.

2.3.3 Supplemental calcium and vitamin D—All participants were provided supplemental calcium (1200 mg calcium carbonate/d) and vitamin D (10 μg vitamin D_3/d) (Nature Made, Mission Hills, CA, USA) to ensure adequate intake of these nutrients by all participants. Participants were instructed to take one calcium and vitamin D supplement (each supplement contained 500 mg calcium and 5 μg vitamin D_3) in the morning and the other in the evening. Every 6 weeks, participants were provided a 6-week supply of supplements. Participants were required to return unconsumed supplements for determination of compliance with the calcium and vitamin D supplementation.

2.3.4. Jump training—Subjects randomized to the JUMP intervention were required to attend 3 training sessions per week with a minimum of 24 hours between sessions. The JUMP intervention was designed based on data from experimental animals showing that an "ideal" exercise prescription for bone health should include the following: load the skeletal sites of interest, high-impact activity, result in dynamic strain, be "unusual" and include rest between loading cycles (10–15 seconds), sessions (8 hours), and blocks (several days) [18, 37, 38]. Because bone becomes refractory to additional loading after 40–100 loading cycles [36], no more than 100 jumps were performed in a single training session. Therefore, the JUMP intervention included different jump exercises that varied in intensity, direction, single- or double-leg: squat jumps, forward hops, split-squat jumps, lateral box push-offs, bounding, bounding with rings (lateral), box drill with rings, lateral hurdle jumps, zigzag hops, single-leg lateral hops, progressive depth jumps (10–100 cm), and jumps off a box.

To minimize risk of injury and maximize efficacy of the intervention, the JUMP training used a progressive intensity design based on a 6-week cycle followed by a rest week; a total of 8 cycles were completed. The number of jumps and intensity of the jumps increased during the 6-week cycle. Intensity was determined by the estimated ground reaction forces associated with the jumps (e.g., jump off box more "intense" than squat jump) and by the complexity of the movement (e.g., single-leg jump more intense than double-leg jump). Weeks 1–2 were comprised of low-intensity jumps (10 repetitions of squat jump, forward hop, split squat and lateral box push-off jumps); weeks 3–4 also included moderate-intensity jumps (10 repetitions of 6–8 different jumps, which included bounding, lateral bounding, box jump, lateral hurdle, zig-zag jumps, or single-leg lateral hurdle and 2 randomly selected low-intensity jumps); and, high-intensity jumps (depth jumps and jumps off a box) were introduced during weeks 5–6 (10 repetitions of 10–12 different jumps, which included depth jumps and jumps off a box and 8–10 randomly selected low- and moderate-intensity jumps). Participants were instructed to perform the jumps "explosively", and they were required to rest for 10 seconds between each jump. The order in which the different types of jumps were performed varied between sessions. The intensity of the jumps for each 6-week cycle was constant throughout the intervention (i.e., the height for the jumps off a box did not change).

Maximal vertical height was measured after each 6-week cycle using a vertical-jump measuring device (Vertec, JumpUSA; Sunnyvale, CA, USA). After a light cardiovascular warm-up (5–10 min), subjects made 3 attempts at their maximal vertical jump, and the highest value was recorded as their maximum. Changes in vertical jump height after 6 and 12 months were used to evaluate improvements in maximal jump height due to the intervention.

2.3.5. Resistance Training—Subjects randomized to the resistance training (RT) intervention were required to complete 2 training sessions per week. The RT intervention included exercises that load the hip and spine: squats, bent-over-row, modified dead lift, military press, lunges, and calf raises. To minimize risk of injury and to account for strength adaptations as a result of strength training improvements, the RT intervention also used a progressive intensity design based on a 6-week cycle followed by a rest week; a total of 8 cycles were completed.

Prior to and every 6 weeks during the RT intervention, maximal strength testing was performed [39]. 1-RMs were conducted for squat, modified dead lift, and military press exercises and modified maximums (10-RMs) were calculated for exercises for which 1RM are not commonly performed. Briefly, subjects performed a warm-up set of 5–10 repetitions, equal to 40–60% of their perceived maximum for each exercise. After a brief rest period, a second set of 3–5 repetitions at an intensity of 60–80% of perceived maximum was performed. Subsequent attempts were conducted using incremental increases in weight until a failed attempt, typically within 3 to 5 maximal attempts. During the 6-week cycle, the intensity progressively increased every 2 weeks based on the RMs measured at the end of each 6-week cycle: weeks 1–2 were light intensity, consisting of one warm-up set of 10 repetitions at 20% 1RM and 3 sets of 10 repetitions at 50% 1RM; weeks 3–4 were moderate intensity with one warm-up set of 10 repetitions at 20% 1RM, two sets of 10 repetitions at 60% 1RM, and one set of 6–8 repetitions at 70–75% 1RM; and weeks 5–6 were high-intensity, starting with one warm-up set of 10 repetitions at 20% 1RM, followed by 2 sets of 10 repetitions at 60% 1RM, and one set of 3–5 repetitions at 80–90% 1RM. Participants were instructed to perform the eccentric phase of each lift in 2–3 seconds and to perform the concentric contraction “explosively.” Changes in 1RMs after 6 and 12 months were determined to evaluate changes in muscular strength due to the RT intervention.

2.3.6. Data safety monitoring plan—The RT and JUMP interventions posed minimal risk with musculoskeletal injury the most likely adverse consequence. In addition, there was the potential for participants to experience continued loss of bone mass over the study period. The data safety monitoring plan for this clinical trial focused on close monitoring by the principal investigator (PI) in conjunction with a safety officer, along with prompt reporting of excessive adverse events and any serious adverse events to the NIH and to the IRB at the University of Missouri. Adverse events were monitored bi-monthly and BMD semi-annually. If a participant’s TH or LS BMD T-score at 6 months was ≤ −2.5 SD (i.e., osteoporosis), then the participant would be removed from the study and referred to his physician for follow-up care. There were no adverse events reported during the study, and no participant became osteoporotic.

2.4. Outcomes

Primary outcomes included WB, TH, and LS BMD and markers of bone formation (OC and BAP) and resorption (CTx and TRAP5b); primary outcomes were measured prior to the intervention (0 months) and after 6 and 12 months of the intervention. Secondary outcomes included measures to evaluate the safety and efficacy of the intervention (pain and fatigue ratings of the RT and JUMP interventions, and 1RMs and vertical jump) and potential confounders (changes in 25OHD, body weight and composition, nutrient intake and physical activity level). Secondary outcomes were measured at 0, 6, and 12 months with the exception of 25OHD that was measured only at 0 and 12 months.

2.4.1. Anthropometry and BMD—Body weight was measured to the nearest 0.05 kg and height to 0.5 cm, and height and weight were used to calculate body mass index (BMI, kg/m^2). Dual-energy X-ray absorptiometry (DXA) (Hologic Delphi W; Shelby Township, MI, USA) scans of the WB, TH and LS (L1–L4) were performed for determination of areal

BMD (g/cm^2) BMD. Body composition (fat mass, fat-free mass, and percent body fat) was determined from the whole body scan. All DXA scans were performed and analyzed by one investigator (PN). CVs for BMD in our laboratory are <1%. Low bone mass was defined as a TH or LS BMD T-score >−2.5 SD and ≤−1.0 SD and osteoporosis as ≤ 2.5 SD.

2.4.2. Bone marker and 25OH Vitamin D assays—Blood samples (15 mL) were collected from subjects at 0, 6, and 12 months at the same time between 06:00 and 08:00 AM after an overnight fast and a 24-hour period of no exercise. All samples were allowed to clot at room temperature and then were centrifuged at 4°C for 15 min at 2000g in a Marathon 21000R centrifuge (Fisher Scientific, Pittsburgh, PA) for isolation of serum. The separated serum was transferred to cryogenic vials and stored at −80°C for subsequent analysis. All assays were performed in duplicate measurements and in a single run to eliminate inter-assay variability. Commercially available ELISA analysis kits were used to determine the serum concentrations of OC, BAP, TRAP5b, CTx, and 25OHD. The OC, BAP, TRAP5b ELISA kits were purchased from Quidel (San Diego, CA, USA) and had CVs of 4.7, 4.0, and 5.5%, respectively; the CTx and 25OHD kits were purchased from Immunodiagnostic Systems (Scottsdale, AZ, USA) and had CVs of 3.7 and 2.5%, respectively.

2.4.3. Nutrient intake and physical activity—At baseline and after 6 and 12 months of the RT or JUMP intervention, participants completed a prospective 7-day diet record and physical activity log. Participants recorded food/beverage type, portion size, and time of day consumed, and nutrient intake was estimated from the diet record (Food Processor 8.0, esha, Salem, OR, USA). Participants recorded purposeful exercise in the activity log, including activity type, duration, and intensity. The Compendium of Physical Activities was used to estimate daily energy expended during purposeful exercise [40].

2.5. Randomization and Blinding

Allocation of study participants to either RT or JUMP was random. One member of the research team (i.e., the “randomization officer”) who was not involved in the day-to-day management of the study was responsible for the randomization process, which was accomplished using numbered sealed envelopes each containing a random allocation. The randomization officer recorded the participant’s name, unique identifier, treatment, and date of randomization in the “treatment allocation code”. This treatment allocation code was kept in a locked file cabinet in a location separate from the participants’ data folders. The PI, who was responsible for assessing outcomes and statistical analyses, was blind to the assignment of interventions. The intervention was conducted by the study coordinator (PN) and graduate research assistants; the PI did not attend or directly oversee any of the training sessions.

2.6. Statistical Analysis

2.6.1. Sample size—The primary objective of this study was to determine the effectiveness of 12 months of RT or JUMP to increase TH and LS BMD. We previously found that prevalence of osteopenia of the LS was much higher than osteopenia of the hip in apparently healthy, moderately active men [24]. Thus, estimates of sample size were based on: 1) preliminary data on lumbar spine BMD (0.998 ± 0.019 g/cm^2) of apparently healthy,

physically active men (n=27) [24]; and, 2) an expected 2.0–2.5% difference in BMD as a result of the RT or JUMP intervention based on a RT intervention study in men [25], and jump-training intervention studies in pre- and postmenopausal women [20–22]. At the time the study was designed, there were no published reports of the effects of jump training in male subjects, nor were there any published studies that compared the effects of resistance training to jump training in men. To detect a significant change of 2.5% in lumbar spine or hip BMD, with the level of significance set at $\alpha = 0.05$ and the power of the test at 0.80, the estimated sample size was approximately 40 subjects (20 in each of 2 groups).

2.6.2. Descriptive and hypothesis-testing statistics—Descriptive statistics were performed on demographic and anthropometric variables. Differences between RT and JUMP at baseline were evaluated using independent t-tests (2-tailed). A 3×2 repeated measures ANOVA (3 timepoints and 2 treatment groups) was employed to compare the effects of RT versus JUMP on WB, TH, and LS BMD and serum markers of bone turnover. In the case of a significant interaction ($p<0.1$), a repeated measures one-way ANOVA within group was used to locate the interaction; within group changes over time were not examined unless the interaction was significant. Potential covariates (e.g., age, height, body mass, body mass change, baseline 25OHD, 25OHD change) were screened for inclusion in the RMANOVA using bivariate correlations with primary outcome variables (% changes); none of the potential covariates screened were significant. A 3×2 repeated measures ANOVA was also used to examine changes in pain and fatigue ratings and to verify that nutrient intake and physical activity did not change during the 12-month study. A one-factor repeated measures ANOVA was used to evaluate changes in muscular strength and vertical jump within group. Group means and least squared means were considered statistically different at $p < 0.05$, as determined by the protected least significant difference (LSD) technique. All statistical analyses were performed using the SPSS statistical package (SPSS/22.0, SPSS, Chicago, IL, USA). Data are presented as means (SD) and 95% CI.

3. Results

3.1. Participant enrollment

Because DXA scans were required to determine eligibility, informed consent was obtained prior to screening. Of the 210 individuals who were screened for study participation, 135 were determined to be ineligible, as follows: normal BMD (n=118), osteoporosis (n=5), less 4 hours/week of physical activity (n=3), current participation in RT or plyometrics (n=2), medications/disease (n=2; inhaled steroid for asthma/allergies and Crohn's disease treated with prednisone), irregular sleep schedule (n=1), smoking (n=1), implanted metal (n=1), excessive alcohol consumption (n=1), and age <25 years (n=1).

Of the 75 participants who met the eligibility criteria, 17 decided not to participate after learning they were eligible based on their BMD; thus 58 participants started the study. Of these, 15 voluntarily withdrew consent after being active in the study (5 from RT and 10 from JUMP). The reasons the participants gave for withdrawing consent did not suggest that they found the RT or JUMP intervention painful. The reasons for withdrawing from the study were: the time required to participate (n=10); did not want to take calcium/vitamin D supplement (n=1); restriction on physical activity outside of the study (n=1); change in

employment that precluded participation (n=1); and relocation (n=1). Participants who withdrew from the study did not differ in age, height, weight, BMI, or baseline BMD from those who completed the study. Participation of five individuals was terminated by the principal investigator due to physical or mental health issues that developed during the study that were unrelated to the RT or JUMP intervention (3 from RT and 2 from JUMP). Thirty-eight participants completed the 12-month intervention and were included in the primary statistical analysis. In addition, an intention-to-treat analysis (i.e., 2×2 repeated measures ANOVA) on BMD outcomes was performed on the participants for whom baseline and 6-month BMD data were available (n=44).

3.2. Participant baseline characteristics

Participants ranged in age from 25–60 y (median: 43.5 y; mean ± SD: 43.7 ± 10.1 y). There were no differences in age, anthropometric characteristics, nutrient intakes or physical activity between RT and JUMP at baseline (Table 1). Of the participants who completed the JUMP intervention, 17 of 19 were white; 18 of 19 participants who completed RT were white. There were no differences in WB, TH, or LS BMD (Table 1) or in TH or LS T-scores between groups [TH T-scores: RT= −0.9 (0.5); JUMP= −0.8 (0.8); LS T-scores: RT= −1.4 (0.7); JUMP= −1.5 (0.5)]. At baseline, there were no differences in 25OHD between groups [RT: 90.8 (23.2) nmol/L; JUMP: 90.4 (22.2) nmol/L]; 36 of the 38 participants were vitamin D sufficient based on their serum 25OH vitamin D concentration (i.e., >50 nmol/L) and 2 participants (1 in RT and JUMP) were vitamin D “insufficient” (28 nmol/L>25OHD<50 nmol/L [41].

3.3. Pre- to post-intervention changes

3.3.1. Anthropometrics, nutrient intake and physical activity—Participants in RT exhibited small, but statistically significant, increases in total and lean body mass over the course of the study, and participants, regardless of group, had significantly lower percent body fat at 12 months compared with baseline (Table 2). Nutrient intakes and physical activity remained unchanged from pre- to post-intervention (Table 3).

3.3.2. Vertical jump and muscular strength—Participants in the JUMP intervention increased their vertical jump height (Table 4) by 11% on average. Participants in the RT intervention increased their RM for the squat, lunge, modified deadlift, calf raise, military press and bent-over row (Table 4) by 79, 114, 64, 79, 52, 44%, respectively.

3.3.3. Pain and fatigue associated with RT and JUMP interventions—Participants’ ratings of pain and fatigue immediately after an RT or JUMP training session were low, and they did not differ between groups (Table 4). In addition, participants in JUMP and RT reported lower pain at 6 and 12 months compared with pain at 0 months (Table 4).

3.3.4. Bone mineral density—There was a significant time main effect whole body BMD (Figure 1, Supplemental Table 1), such that BMD increased by 0.6% after 6 months of RT or JUMP relative to pre-treatment and this increase was maintained at 12 months [mean (SD), 95% CI. 0 mo: 1.123[b] (0.076), 1.098–1.148; 6 mo: 1.130[a] (0.078), 1.104–1.155; 12

mo: 1.128[a] (0.078), 1.102–1.154 g/cm^2]. There was also a significant time main effect for LS BMD (Figure 1; Supplemental Table 1), which was significantly increased by 1.3% after 6 months of RT or JUMP compared with 0 months, and this increase was maintained at 12 months [mean (SD) 95% CI. 0 mo: 0.929[b] (0.069), 0.906–0.952; 6 mo: 0.942[a] (0.074), 0.917–0.966; 12 mo: 0.941[a] (0.072), 0.918–0.965 g/cm^2]. Changes in WB and LS BMD did not differ between groups (i.e., no significant time × group interactions); therefore, post hoc within group comparisons were not performed. There was a significant time × group interaction, such that TH BMD was significantly increased only by RT and not by JUMP (Figure 1; Supplemental Table 1). In RT, TH BMD at 6 and 12 months was increased by 0.8% compared with 0 months [mean (SD) 95% CI. RT 0 mo: 0.898[b] (0.082), 0.851–0.945 g/cm^2; 6 mo: 0.905[a] (0.087), 0.857–0.954 g/cm^2; 12 mo: 0.906[a] (0.089), 0.860–0.953 g/cm^2].

An intention-to-treat analysis was performed using data from the 44 participants for whom baseline and 6-month BMD data were available (RT, n=21; JUMP, n=23). The results were similar to those observed for changes in BMD from baseline to 12 months. There was a significant time × group interaction for TH BMD (p=0.027), such that TH BMD was increased only by RT. In RT, TH BMD at 6 months was significantly increased compared with 0 months [mean (SD) 95% CI. RT 0 mo: 0.901[b] (0.082), 0.858–0.944 g/cm^2; 6 mo: 0.909[a] (0.086), 0.866–0.953 g/cm^2]. In JUMP, TH BMD did not change [mean (SD) 95% CI. JUMP 0 mo: 0.924 (0.109), 0.883–0.964 g/cm^2; 6 mo: 0.919 (0.109), 0.878–0.961 g/cm^2]. There was a significant time main effect for LS BMD, which was significantly after 6 months of RT or JUMP compared with 0 months [mean (SD) 95% CI. 0 mo: 0.934[b] (0.065), 0.914–0.954; 6 mo: 0.947[a] (0.068), 0.927–0.968 g/cm^2]. WB BMD tended to increase from baseline to 6 months [mean (SD) 95% CI. 0 mo: 1.125 (0.072), 1.103–1.147; 6 mo: 1.139 (0.083), 1.107–1.152 g/cm^2], but the time main effect did not reach statistical significance (p=0.137).

3.3.5. 25OHD and bone turnover markers—Serum 25OHD increased in RT and JUMP after 12 months of daily vitamin D supplementation (Supplemental Table 1), and all study participants were vitamin D sufficient at 12 months [mean (SD), 95% CI. 0 mo: 90.6[b] (3.7), 83.1–98.1 nmol/L; 12 mo: 97.8[a] (3.2), 91.1–104.6 nmol/L]. There were no differences in bone formation (OC, BAP) or resorption (TRAP5b, CTx) markers between groups at baseline (Figure 2; Supplemental Table 1). There was a significant time main effect for OC and CTx (Figure 2; Supplemental Table 1), such that OC was significantly increased at 12 months compared to baseline and 6 months [mean (SD), 95% CI. 0 mo: 10.8[b] (5.1) 9.1–12.5; 6 mo: 10.4[b] (4.7), 8.8–12.0; 12 mo: 12.3[a] (4.4), 10.9–13.7 μg/L]. CTx was significantly reduced at 6 months and then returned to baseline concentrations at 12 months [mean (SD), 95% CI. 0 mo: 0.321[a] (0.202), 0.254–0.388; 6 mo: 0.274[b] (0.158), 0.221–0.326; 12 mo: 0.351[a] (0.192), 0.288–0.414 μg/L]. Post hoc within group comparisons were not performed for OC or CTx as there were no significant time-by-group interactions. BAP and TRAP5b remained unchanged over the course of the study (Figure 2; Supplemental Table 1).

4. Discussion

4.1. Synopsis of study results

In this 12-month randomized clinical trial of men with low bone mass of the hip or spine, we found that RT or JUMP increased whole body and lumbar spine BMD, while only RT increased BMD of the total hip. It is unclear why both the RT and JUMP intervention had a greater effect on LS BMD than on TH BMD. One possible explanation is that the participants tended to have lower BMD of LS than TH prior to the study and, thus, may have had a greater potential to respond to the intervention at the LS compared to the TH. The increases in BMD observed in the present study were associated with altered bone turnover; specifically, a reduction in bone resorption and an increase in bone formation. This study is novel because it is the first to demonstrate the efficacy of exercise-based interventions to increase BMD in middle-aged men with low bone mass who are otherwise healthy. The biological and clinical significance of these results can be appreciated only if one considers that bone loss occurs with normal aging. Young adult and middle-aged men lose BMD at rates of ~0.4–1.5% per year [42–44]. The results are also important because they suggest that a time-efficient (2–3 days per week) intervention of either RT or JUMP can improve BMD in otherwise healthy men.

4.2. Exercise interventions and bone in men

4.2.1. Effects of exercise on BMD—Generally, other intervention studies that examined the effects of RT or impact exercise on changes in BMD and/or BTM in older men reported results similar to those of the present study. Kukuljan found that 12 mo of progressive RT and impact exercise (3 d/wk) increased BMD of the femoral neck and LS by 1.8 and 1.5%, respectively, in men aged 50–79 years with normal to below average BMD [29]. A 12-mo, unilateral, high-impact exercise intervention (hopping) increased FN BMD (the only skeletal site examined) by 0.7% in men aged 65–80 years [32]. Ryan also reported a 2.8% increase in FN BMD after 4 months of RT in men aged ~60 years [26], and Menkes observed significant increases LS (2.0%) and FN (3.8%) BMD in men 55–60 years of age [25].

4.2.2. Biological and clinical significance of increased BMD in men—We did not include a no-exercise control group in the present study as we did not feel it was ethical to do so in men with low bone mass [34, 45]. However, we previously observed that physically active, adult men with osteopenia, similar to those in the present study, lost hip BMD at a rate of 0.8% per year [46], consistent with the literature consensus that bone loss occurs with aging. Therefore, the increases in BMD observed in this and previous exercise-intervention studies, although relatively small (0.6–1.3%), are biologically significant, in that exercise reversed the bone loss that occurs with normal aging.

The increases in BMD observed following exercise interventions likely have clinical significance, as small increases in BMD result in much larger gains in bone strength. For example, increasing BMD by 5% increased bone strength by 65% [37], and in women with postmenopausal osteoporosis, a 1% increase in spine BMD reduced the risk of fracture by 8% [47]. Finally, it is worth noting that BMD, along with BTM, is the primary outcome by which the efficacy of pharmacologic interventions is currently evaluated [48].

4.2.3. Bone formation and resorption markers: clinical and research utility— Clinically, bone turnover markers are used to monitor treatment efficacy. Although BMD is primary the therapeutic target of osteoporosis medications, measurable changes in BMD can be detected only after 12 months of treatment. BTM are clinically useful because they respond much more quickly than BMD to interventions and also predict long-term changes in BMD and fracture risk [49]. From a research perspective, BTM are also useful in understanding the effects of an intervention on bone resorption versus bone formation.

4.2.4. Effects of RT or JUMP on BTM—In the present study, CTx was significantly reduced at 6 months compared with baseline and then returned to pre-treatment concentrations at 12 months; TRAP5b did not change over the course of the study. Because CTx is a byproduct of breakdown of bone collagen and TRAP5b is an indicator of osteoclast number [50], these results suggest that bone resorption was reduced after 6 months of the RT or JUMP intervention due to a reduction in osteoclast activity rather than a reduction in osteoclast number. Regarding bone formation markers, we observed a significant increase in OC after 12 months of RT or JUMP, while BAP did not change. BAP and OC expression occur at different times in osteoblast differentiation. BAP expression occurs post-proliferation during maturation of the extracellular matrix prior to mineralization and OC is expressed by mature osteoblasts during mineralization of the extracellular matrix [51]. Therefore, the discrepant response between OC and BAP suggests that there was an increase in the number of mature osteoblasts or in secretion of OC by mature osteoblasts after 12 months of RT or JUMP.

Because BMD was the primary outcome of interest, our sample size was based on sufficient statistical power to detect changes in BMD with RT or JUMP and not in the BTM, which were secondary outcomes. Nevertheless, the observed power for the changes in CTx and OC with RT or JUMP was 0.886 and 0.867, respectively, suggesting these findings are quite robust. Taken together, the changes CTx and OC suggest that the RT or JUMP interventions have both anti-resorptive and anabolic effects on bone. Given the timecourse of the changes in CTx and OC relative to the increases in BMD, as well as the length of a remodeling cycle, it appears that increases in WB, LS, and TH (in RT) BMD observed after 6 months were due to the anti-resorptive effects of the RT or JUMP intervention. It is less clear whether the maintenance of increased BMD observed at 12 months was due to decreased resorption, increased formation or a combination, as we cannot determine when between 6 and 12 months of the intervention OC increased above baseline concentrations. Likewise, given the delay between changes in BTM and changes in BMD, we cannot determine the effects of the increase in OC relative to CTx after 12 months on BMD. But, presumably, if OC is elevated, mineralization of new matrix is taking place.

Similar to the increase in OC and decrease in CTx observed in the present study, others have reported increases in bone formation markers relative to resorption following high-intensity resistance training in older men [30, 52, 53]. These data suggest that exercise might counteract age-related bone loss in men, which has been attributed primarily to a deficit in bone formation relative to bone resorption [54]. Future studies are needed to determine the mechanisms by which chronic RT or JUMP signals changes in osteoclast and osteoblast activity, e.g., mechanotransduction and/or endocrine effects, in men with low bone mass.

4.3. Safety and feasibility of RT and JUMP interventions

In addition to proving to be effective, our 12-month clinical trial of RT or JUMP in men with low bone mass also demonstrated that the RT and JUMP interventions were safe. To evaluate safety, we assessed the pain and fatigue associated with the exercise at each RT or JUMP training session. On average, the participants rated the intensity of the pain caused by the RT or JUMP as a score of 10 or less, on a scale of 0–100 with 100 being the most intense pain imaginable. In addition, the pain ratings decreased from the baseline assessment at the 6- and 12-month timepoints. Participants also rated the fatigue associated with the interventions as less than 30 at all timepoints, on a scale of 0 to 100 with 100 being the most intense fatigue imaginable. In addition, there were no injuries reported during any of the ~1800 supervised RT training sessions or ~2700 JUMP training sessions. Thus, both the RT and JUMP interventions were well tolerated by the participants and appear to have minimal risk of injury or discomfort, which predicts both good compliance and practical application. From a practical perspective, it is worth noting that time required to complete the RT or JUMP training each week was minimal, ranging from 60 minutes during a “light” week to 120 minutes for a “heavy” week. In addition, the RT or JUMP interventions could be done at home and require only minimal exercise equipment. These observations coupled with evidence of long-term compliance with voluntary, unsupervised high-impact exercise interventions in pre-menopausal women [55] suggests that exercise-based interventions might be effective in the “real world.”

Our study included apparently healthy men with low bone mass who were relatively physically active. It is not clear how the participants’ habitual physical activity affected their response to the interventions. Although the participants in the present study were active, we excluded men who were currently participating in resistance- or jump-training. Therefore, the RT or JUMP intervention presented a novel training stimulus to the participants. It is possible that being accustomed to exercise facilitated the participants’ ability to become proficient at the RT or JUMP exercises. Whether the RT and JUMP interventions would also be safe and effective in populations with more severe bone loss or who are not as physically active is not known. However, other studies have reported that older adults with low bone mass can safely perform maximal strength training (squats) [56] or jumping [57, 58]. Morever, a recent review by a panel of experts strongly recommends multi-component exercise that includes resistance training for individuals with osteoporosis. Results of this expert review also indicate that the evidence regarding harms associated with exercise is very low quality, and that the possible harms do not outweigh the potential benefits [16]. Moreover, evidence from observational and intervention exercise trials suggest that increased risk of fracture with exercise occurs under preventable conditions, e.g., walking in slippery conditions. Osteoporosis Canada, the National Osteoporosis Foundation, and Osteoporosis Australia’s Medical and Scientific Advisory Committee endorsed the recommendation that individuals with osteoporosis engage in resistance training that targets all major muscle groups at least twice per week [16].

4.4. Study strengths and limitations

4.4.1. Study strengths—A strength of this study is that the RT and JUMP interventions were designed based on the existing literature to maximize the osteogenic response.

Moreover, because all exercise sessions were supervised and because participants were required to complete all training sessions, compliance with the exercise was not a limitation. Another strength of the study is that all participants were provided supplemental calcium and vitamin D, ensuring that differences in calcium or vitamin D status did not confound the response to RT or JUMP. In addition, because all but two participants were vitamin D sufficient at baseline and because there is a threshold effect for calcium and vitamin D on bone (i.e., at intakes above the threshold, additional calcium or vitamin D does not further improve bone outcomes; IOM, 2011), the effects of the interventions on BMD and BTM were likely due to the exercise component of the treatment and not the supplemental vitamin D. We also verified that participants' nutrient intake and physical activity level did not change over the course of the study.

4.4.3. Study limitations—The primary limitation of this study is that, because we studied only healthy men who volunteered to participate in the study, the results cannot be generalized to other populations who might benefit, such as men with more severe bone loss (i.e., osteoporosis) or those with low bone mass due to other conditions such as diabetes or glucocorticoid therapy. The lack of a placebo control group also could be considered a limitation. Whether the use of placebo-controlled studies of treatments to reduce fracture risk in participants with osteoporosis is ethical has been the focus of debate for the past decade [33, 59]. While the present study did not include osteoporotic patients or have fracture as an endpoint, we determined inclusion of a placebo control group or a no intervention group to be unethical in a study population at risk for osteoporosis and related fractures. Our decision was guided by the Declaration of Helsinki, which cautions against exposing participants "to additional risk of serious or irreversible harm" by use of a placebo or no intervention [34]. Regardless, the impact of this limitation on the conclusions of the present study is diminished by our previously published data, showing that in apparently healthy, moderately active men with low bone mass, who declined to participate in an intervention, lumbar spine BMD decreased by 0.8% per year [46].

5. Conclusions

In summary, the results of the present study suggest that RT or JUMP interventions are safe and effectively increase BMD, particularly of the lumbar spine, in men with low bone mass. These results have clinical implications, as exercise may be the appropriate "prescription" for some individuals with low bone mass. Which intervention should be prescribed to improve bone health depends on the individual patient's current hip and lumbar spine BMD, activity patterns, exercise preference, as well as time and equipment constraints. From a basic science perspective, next questions to be answered relate to identification of whole-animal- and cell-level mechanisms for the osteogenic effects of exercise in men with low bone mass for possible refinement of exercise-based interventions and identification of other therapeutic approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Whole body and lumbar spine BMD increased after 6 months of resistance training or jump training.
- Total hip BMD increased only after resistance training.
- Osteocalcin increased significantly after 12 mo of resistance training or jump training.
- CTx decreased significantly after 6 months of resistance training or jump training.
- Pain and fatigue ratings after resistance training or jump training sessions were very low at 0, 6, and 12 months.

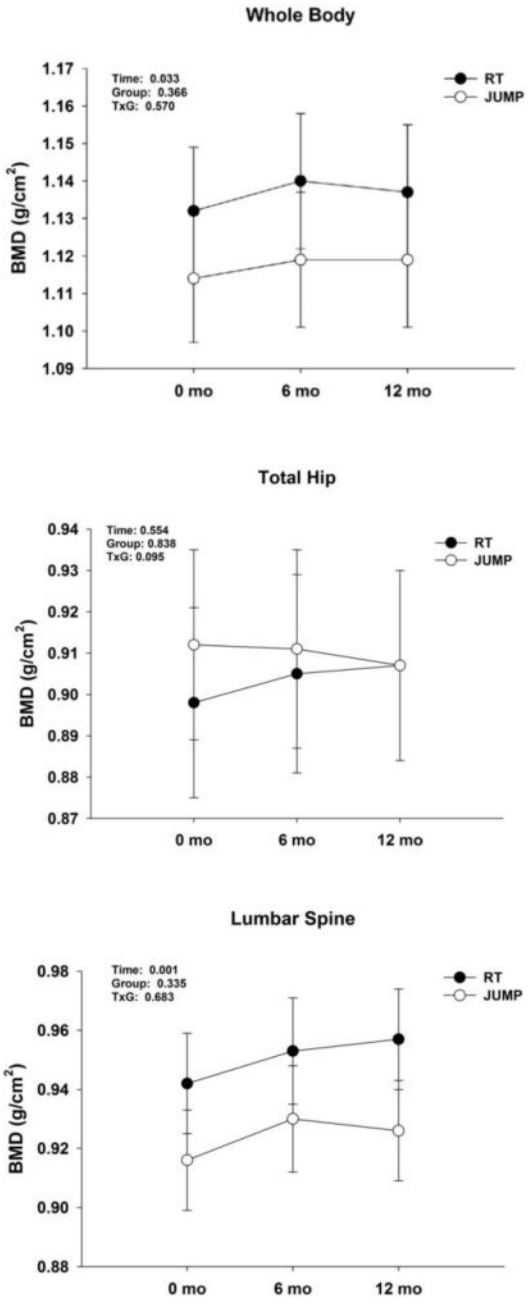

Figure 1.

BMD (means ± SEM) of the whole body, total hip and lumbar spine after 0, 6, or 12 months of RT or JUMP. Significant time main effect for WB BMD [mean (SD), 95% CI. 0 mo: 1.123[b] (0.076), 1.098–1.148; 6 mo: 1.130[a] (0.078), 1.104–1.155; 12 mo: 1.128[a] (0.078), 1.102–1.154 g/cm^2] and LS BMD [0 mo: 0.929[b] (0.069), 0.906–0.952; 6 mo: 0.942[a] (0.074), 0.917–0.966; 12 mo: 0.941[a] (0.072), 0.918–0.965 g/cm^2); post hoc within group comparisons were not performed for WB or LS BMD as there were no significant time-by-group interactions. Significant time-by-group interaction for TH BMD [mean (SD), 95% CI. RT 0 mo: 0.898[b] (0.082), 0.851–0.945; 6 mo: 0.905[a] (0.087), 0.857–0.954; 12 mo: 0.906[a]

(0.089), 0.860–0.953 g/cm^2]. Means with different letter superscripts are significantly different.

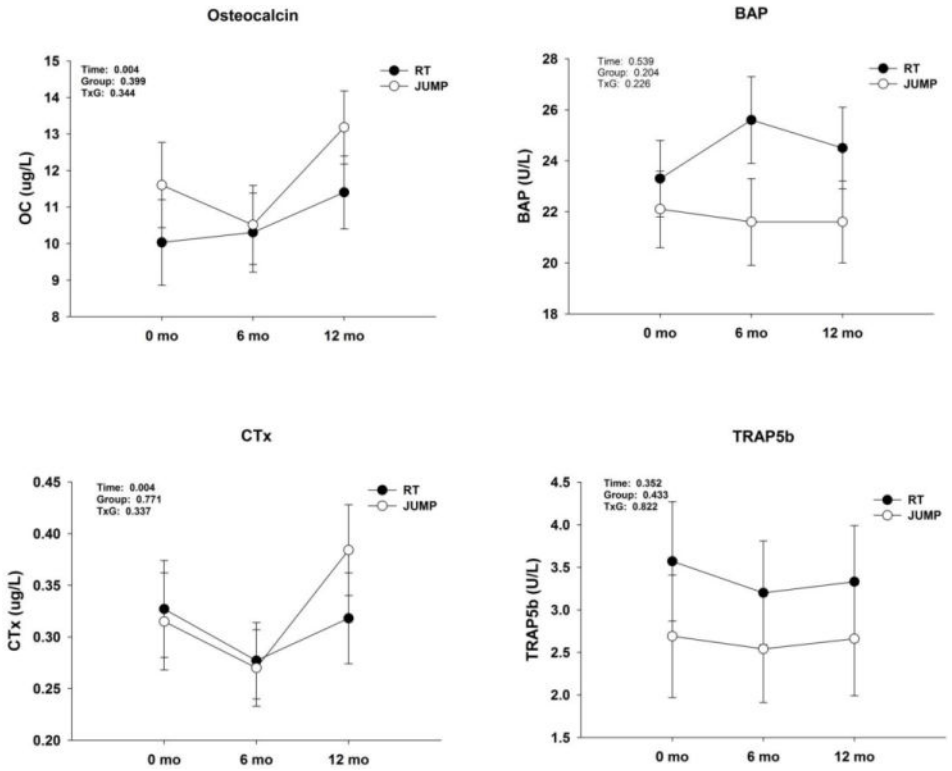

Figure 2.

Concentrations of bone formation (osteocalcin, OC; bone-specific alkaline phosphatase, BAP) and resorption (carboxy-terminal cross-linking telopeptide of type I collagen CTx; tartrate-resistance acid phosphatase isoform 5b, TRAP5b) markers (means ± SEM) after 0, 6, and 12 months of RT or JUMP. Significant time main effect for OC [mean (SD), 95% CI. 0 mo: 10.8^{b} (5.1) 9.1–12.5; 6 mo: 10.4^{b} (4.7), 8.8–12.0; 12 mo: 12.3^{a} (4.4), 10.9–13.7 μg/L) and CTx [mean (SD), 95% CI. 0 mo: 0.321^{a} (0.202), 0.254–0.388; 6 mo: 0.274^{b} (0.158), 0.221–0.326; 12 mo: 0.351^{a} (0.192), 0.288–0.414 μg/L]; post hoc within group comparisons were not performed as there were no significant time-by-group interactions. Means with different letter superscripts are significantly different.

Table 1

Baseline characteristics of participants in the RT and JUMP interventions

Group	RT (n=19)	JUMP (n=19)	p-value
Age (y)	45.5 (9.6)	42.1 (10.6)	0.325
Anthropometrics			
Height (m)	1.79 (0.08)	1.76 (0.05)	0.229
Body mass (kg)	82.6 (14.2)	77.1 (9.7)	0.252
BMI (kg/m^2)	25.7 (4.0)	24.0 (3.9)	0.716
LBM (kg)	60.9 (8.8)	58.9 (5.5)	0.415
Fat mass (kg)	19.5 (7.3)	16.0 (5.4)	0.212
% Body fat	22.8 (6.1)	20.2 (4.8)	0.337
BMD (g/cm^2)			
WB	1.132 (0.081)	1.114 (0.071)	0.482
TH	0.898 (0.082)	0.912 (0.116)	0.675
LS	0.939 (0.069)	0.919 (0.056)	0.425
Nutrient intake per day			
Energy (kcal)	2537 (693)	2343 (616)	0.158
Calcium (mg)	1151 (143)	944 (459)	0.070
Vitamin D (μg)	5.4 (5.2)	3.9 (3.1)	0.777
Physical activity per day			
Time (hr)	0.6 (0.3)	0.9 (1.7)	0.449
Energy (kcal)	338 (243)	439 (610)	0.593

Data are means (SD). P-values are for independent t-test (2-tailed) comparison of RT and JUMP means.

Table 2

Anthropometric outcomes in apparently health men at baseline and after 6 and 12 months of RT or JUMP

Group	RT (n=19)			JUMP (n=19)			RMANOVA		
Time (mo)	0	6	12	0	6	12	Time	Group	T x G
Anthropometrics									
Body mass (kg)	82.6 (14.2)^{b}	83.4 (14.8)^{ab}	84.2 (14.9)^{a}	77.9 (9.9)	77.5 (9.8)	77.1 (9.7)	0.547	0.152	0.010
BMI (kg/m^2)	25.7 (4.0)	26.1 (4.2)	26.3 (4.1)	25.3 (3.3)	25.0 (3.3)	24.0 (3.9)	0.539	0.288	0.047
LBM (kg)	60.9 (8.8)^{b}	61.2 (9.3)^{ab}	62.2 (9.2)^{a}	59.0 (5.5)	59.2 (5.7)	58.9 (5.5)	0.144	0.322	0.037
Fat mass (kg)	19.5 (7.3)	19.0 (7.5)	19.2 (7.5)	16.8 (5.4)	15.8 (5.9)	16.0 (5.4)	0.065	0.159	0.640
% Body fat	22.8 (6.1)	22.3 (6.1)	22.2 (6.1)	21.1 (5.0)	20.4 (4.5)	20.2 (4.8)	0.041	0.285	0.905

Data are means (SD). Means with different letter superscripts are significantly different within group. Significant time main effect for % body fat [mean (SD), 95%CI. 0 mo: 22.0^{a} (5.6), 20.1–23.8; 6 mo: 21.4^{a} (5.4), 19.6–23.1; 12 mo: 21.2^{b} (5.5), 19.4–23.0%].

Table 3

Daily nutrient intake and physical activity in apparently healthy men at baseline and after 6 and 12 months of RT or JUMP

Group	RT			JUMP			RMANOVA		
Time (months)	**0**	**6**	**12**	**0**	**6**	**12**	**Time**	**Group**	**T x G**
Nutrient intake									
Energy (kcal)	2537 (693)	2529 (593)	2440 (420)	2343 (616)	2323 (486)	2430 (725)	0.927	0.607	0.462
Carbohydrate (g)	309 (66)	311 (91)	314 (104)	288 (89)	296 (65)	297 (89)	0.824	0.683	0.809
Fat (g)	100 (42)	96 (28)	89 (21)	90 (29)	83 (22)	87 (36)	0.894	0.447	0.424
Protein (g)	98 (23)	105 (32)	97 (27)	93 (26)	93 (22)	93 (19)	0.709	0.625	0.629
Calcium (mg)	1151 (143)	1094 (255)	877 (106)	944 (459)	900 (337)	952 (341)	0.232	0.347	0.086
Vitamin D (μg)	5.4 (5.2)	6.5 (4.7)	4.8 (5.8)	3.9 (3.1)	4.5 (3.4)	3.8 (3.3)	0.594	0.313	0.837
Physical Activity									
Time (hr/d)	0.6 (0.3)	0.6 (0.5)	0.8 (0.8)	0.9 (1.7)	1.3 (2.7)	0.6 (0.6)	0.742	0.515	0.262
Energy (kcal/d)	338 (243)	341 (285)	474 (474)	439 (610)	449 (601)	317 (296)	0.982	0.843	0.270

Data are means (SD).

Table 4

Physical performance and post-exercise ratings of pain and fatigue in apparently healthy men at baseline and after 6 and 12 months of RT or JUMP

Group	RT			JUMP		
Time (mo)	**0**	**6**	**12**	**0**	**6**	**12**
1-RM or Vertical Jump						
Squat (kg)	86.8 (19.5)[c]	132.7 (27.9)[b]	156.8 (30.0)[a]	–	–	–
Deadlift (kg)	38.9 (10.0)[c]	61.9 (10.3)[b]	79.3 (13.5)[a]	–	–	–
Lunge (kg)	83.6 (25.8)[c]	118.7 (31.3)[b]	132.4 (35.6)[a]	–	–	–
Calf raise (kg)	78.9 (22.7)[c]	115.5 (26.0)[b]	136.5 (30.0)[a]	–	–	–
Military press (kg)	45.0 (12.9)[c]	58.5 (16.9)[b]	64.7 (20.4)[a]	–	–	–
Bent-over row (kg)	49.0 (13.9)[c]	66.5 (17.6)[b]	73.3 (19.8)[a]	–	–	–
Vertical jump (m)	–	–	–	0.486 (0.105)[c]	0.497 (0.084)[b]	0.524 (0.099)[a]
Post-exercise Pain or Fatigue						
Pain (0–100)	9 (10)	4 (6)	5 (10)	5 (6)	3 (4)	1 (4)
Fatigue (0–100)	29 (19)	19 (15)	22 (17)	18 (19)	16 (19)	16 (16)

Data are means (SD). Significant time main effect (p=0.015) for Pain [mean (SD), 95% CI. 0 mo: 7[a] (9), 4–10; 6 mo: 4[b] (5), 2–6; 12 mo: 3[b] (8), 1–6]. Means with different letter superscripts are significantly different].