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A comparison of bone-targeted exercise strategies to reduce fracture risk in middle-aged and older men with osteopenia and osteoporosis: LIFTMOR-M semi-randomized controlled trial

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ABSTRACT

Investigations into the effects of bone-targeted exercise programs on musculoskeletal health and function in men are limited. The purpose of the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men (LIFTMOR-M) trial was to examine the efficacy and safety of two novel, supervised, eight-month, twice-weekly exercise programs in middle-aged and older men with low BMD. Men with low proximal femur and/or LS BMD were recruited and randomized to high-intensity progressive resistance and impact training (HiRIT) or machine-based isometric axial compression (IAC). Intervention responses were compared with those of a non-randomized matched control group (CON). Outcomes included: proximal femur and LS BMD; calcaneal ultrasound parameters; anthropometry; body composition; physical function (timed up-and-go [TUG], five-times sit-to-stand [FTSTS]); muscle strength (back [BES] and leg extensor strength [LES]); compliance and adverse events. Ninety-three men (67.1±7.5yrs; 82.1±11.6kg; 175.2±6.7cm; FN T-score -1.6±0.6) were recruited, and randomized to HiRIT (n=34) or IAC (n=33), or allocated to CON (n=26). HiRIT effects were superior to CON for trochanteric BMD (2.8±0.8%; -0.1±0.9%, p=0.024), LS BMD (4.1±0.7%; 0.9±0.8%, p=0.003), broadband ultrasound attenuation (2.2±0.7%; -0.8±0.9%, p=0.009), stiffness index (1.6±0.9%; -2.0±1.1%, p=0.011), lean mass (1.5±0.8%; -2.4±0.9%, p=0.002), TUG, FTSTS, BES and LES ($p<0.05$). IAC improved lean mass (0.8±0.8%; -2.4±0.9%, p=0.013) and FTSTS (-4.5±1.6%; 7.5±2.0%, $p<0.001$) compared with CON. HiRIT was superior to IAC for LS BMD (4.1±0.7%; 2.0±0.7%, p=0.039), stiffness index (1.6±0.9%; -1.3±0.9%, p=0.025), and FTSTS (-10.7±1.6%; -4.5±1.7%, p=0.010). Compliance was high in both exercise groups (HiRIT 77.8±16.6%; IAC 78.5±14.8%, p=0.872). There were five instances of minor musculoskeletal discomfort (HiRIT n=2; IAC n=3). Findings suggest HiRIT was well tolerated, and provides a more positive stimulus to bone and functional indices of falls and fracture risk compared

with CON and IAC. High compliance suggests HiRIT is acceptable and feasible. Findings will facilitate development of an optimal exercise prescription for men with low BMD.

Keywords: AGING, CLINICAL TRIALS, EXERCISE, FRACTURE PREVENTION, OSTEOPOROSIS

Introduction

Osteoporosis is a growing public health problem for men. Considerable growth in the number of Australian men over the age of 50 with osteoporosis is predicted by 2022, with 285,000 currently afflicted and a further 2.48 million living with osteopenia [(1)]. The economic impact of low bone mass in Australia is substantial; the estimated total direct cost of osteopenia, osteoporosis, and fractures in 2017 was $3.44 billion (US$2.77 billion) [(2)], of which, men accounted for almost 30%. Corresponding figures for the United States indicate 18.1 million men over 50 years of age have osteopenia and osteoporosis [(3)], accounting for almost 30% of incident fractures, and one quarter of the total cost burden (equating to US$4.1 billion) [(4)]. Although osteoporotic fracture incidence is one in five for men over the age of 50 years, compared with the higher incidence of one in three for women of the same age, fragility fractures in men are associated with higher morbidity and mortality than in women [(5,6)].

Although an updated Cochrane review reported exercise reduced the rate of falls in older adults by 23%, and the number of individuals experiencing fractures by 27% [(7)], exercise remains somewhat contentious as a strategy for the prevention and management of osteoporosis. Some continue to argue that the effect of exercise on BMD is less than pharmacological interventions and that bone-targeted exercise is hazardous for osteoporotic bone. Nevertheless, there is growing recognition that high intensity exercise can be a potent stimulus for bone even in older age, with the added benefit of reducing the risk of falls by virtue of enhanced muscle strength and balance. Recently, we reported findings of the LIFTMOR trial (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation) in postmenopausal women with osteopenia and osteoporosis. Specifically, we observed that an eight-month supervised high-intensity progressive resistance and impact training (HiRIT) program improved FN and LS BMD, muscle strength and physical function in postmenopausal women with low to very low bone mass [(8)].

Furthermore, the HiRIT program did not increase risk of vertebral fracture [9], and no serious adverse events occurred.

Simultaneous to the rollout of the LIFTMOR trial, an exercise device was developed to facilitate a set of four near-maximal isometric contractions (the bioDensity™ system, Performance Health Systems, USA), theoretically to create axial compressive forces on the skeleton with a goal to improve bone mass, hereafter referred to as isometric axial compression (IAC). The technology is currently marketed for individuals with osteoporosis, however, a quality evidence base is lacking. To our knowledge, the sole published study of sufficient duration to examine the efficacy of the IAC device on bone outcomes examined nine postmenopausal women with osteopenia and osteoporosis who improved bone mass following six months of supervised, isometric training (one repetition of each of the four movements for five seconds duration, once per week) [10]. The study was confounded by a lack of control group, and the DXA subgroup included a small number of participants, thus findings must be interpreted with considerable caution.

Thus, the primary aim of the LIFTMOR for Men (LIFTMOR-M) trial was to determine the effects of eight months of supervised HiRIT or IAC exercise on determinants of osteoporotic fracture risk in middle-aged and older men with low BMD, and compare intervention group responses with those of a matched but non-randomized control group of men who self-selected to follow their usual lifestyle activities for eight months in parallel. The secondary aim was to determine compliance and adverse events of each exercise protocol.

Materials and Methods

Study design

The study protocol has been published [11]. We conducted a single-center, three-arm, eight-month, semi-randomized controlled exercise intervention trial. Testing was performed at baseline and eight months. All assessments and training took place in the School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia. Although it is not possible to blind exercise from non-exercise groups, no expectations of superiority of either exercise protocol were held by investigators, or conveyed to participants, thus the intervention arm was in essence blind to a treatment hypothesis. Analyses of all DXA and pQCT scans were verified by an investigator blind to group allocation. All research activities were conducted in accordance with the *Declaration of Helsinki*. The trial was approved by the Griffith University Human Research Ethics Committee (AHS/07/14/HREC), and registered on the Australian New Zealand Clinical Trials Registry (ANZCTR12616000344493). All participants provided written informed consent.

Participants

Apparently-healthy, middle-aged and older men were recruited from the Gold Coast and surrounding community in south-east Queensland, Australia. Recruitment ran from May 2016 to July 2018, and all participants completed the intervention by April 2019. Following trial registration, the originally stipulated minimum age of eligibility (being 50 years) was reduced to 45 years. Participants were required to exhibit osteopenia or osteoporosis at the lumbar spine and/or proximal femur, determined as a DXA-derived T-score ≤ -1.0. Exclusion criteria included: presence of musculoskeletal, neurological, respiratory or unstable cardiovascular conditions likely to affect the ability to exercise, conditions or medications (apart from calcium, vitamin D, and osteoporosis medications) known to affect bone metabolism, metal implants, notable recent radiation exposure, cancer, recent fracture or lower extremity

surgery (in the preceding six months), or current participation in high-intensity resistance and/or impact training. Further exclusion to the exercise arms was based on inability or unwillingness to attend twice-weekly supervised training for the stipulated eight-month period.

Allocation

Allocation of eligible participants to the exercise arms was achieved via block randomization, stratified on previous 12 month presence or absence of osteoporosis pharmacotherapy (1:1 allocation ratio, block size 8). Block randomization was undertaken in order to achieve equal sample sizes within each exercise intervention group during the study period. We defined the 'presence' of osteoporosis therapy as a current minimum of 12 months of continuous treatment with an antiresorptive agent and an expectation to remain on the same medication for the duration of the trial. The 'absence' of osteoporosis therapy was defined as an individual who was treatment naïve (i.e. never been administered osteoporosis medication) or an individual who had discontinued osteoporosis treatment a minimum of 12 months prior to enrolment. The latter condition applied to only one participant. A researcher external to the trial prepared the computer-generated randomization sequence, and group allocation was concealed from the tester and participant until completion of baseline testing. The allocation sequence was filed in sequentially numbered, opaque, sealed, envelopes.

Exercise interventions

A detailed description of the content and progression of the training programs has been published in the study protocol [(11)]. All exercise participants attended twice-weekly (non-consecutive days), 30-minute, supervised sessions for eight months. During the initial two-week familiarization period, the HiRIT group performed low-load variants of each resistance exercise focusing on technique development in order to ensure a safe transition to the three fundamental barbell-based, resistance exercises. The barbell-based, resistance-training component of each HiRIT session comprised three compound movement

exercises (deadlift, squat and overhead press) with five sets of five repetitions, corresponding to an intensity of ≥ 80-85% of one repetition maximum (1RM) performed for each exercise. The Rating of Perceived Exertion (RPE) scale (6-20 point Borg scale) was used to subjectively select exercise intensity and guide weight progression, aiming for an RPE ≥ 16. Load was progressed in increments of 2.5 kg when a participant was able to perform seven repetitions at their current weight with good form. Determination of 1RM was performed for the deadlift and squat at weeks 12 and 24 to guide load progression. The impact-training component consisted of five sets of five repetitions of jumping chin-ups per session, with intensity progressed by encouraging participants to increase jump height and land 'heavier' as tolerated. During the initial familiarization period heel drops were performed to ensure safe transition to high-impact loading. HiRIT participants trained in a group under the supervision of a qualified exercise scientist (maximum ratio of participants to trainer 8:1). Each IAC exercise session also included four exercises: chest press, leg press, core pull, and vertical lift on the bioDensity device. During the initial two-week familiarization period, low intensity repetitions (at approximately 50% of 1RM) of each exercise were performed focusing on technique. For the remainder of the trial period one self-initiated near-maximal five-second isometric contraction was performed for each exercise at an intensity corresponding to ≥ 80-85% of 1RM (RPE of ≥ 16 on the 6-20 point Borg scale). IAC participants trained individually with the same qualified exercise scientist (participant to trainer ratio 1:1).

Control group activities

The control group comprised a sample of middle-aged and older men, recruited in the same manner and screened using identical criteria to the exercise arms, but who were unwilling to commit to attendance at twice-weekly training sessions for eight months, thereby allocated to 'no intervention' (parallel control group; CON). Our decision to apply this strategy for CON recruitment stemmed from experience in a

pilot trial run immediately prior to LIFTMOR-M that middle-aged and older men volunteering for an exercise trial but randomized to control are unlikely to comply with control group instructions to refrain from initiating exercise training during the trial period. Self-selected CON participants were instructed to continue with their usual daily routines and refrain from taking up either of the exercise modalities of the intervention groups for a period of eight months between testing sessions. CON participants recorded alterations in physical activity, diet, medications, and medical conditions as well as falls or injuries (including fractures) during the trial period using a purpose-designed lifestyle diary issued at baseline and returned at follow-up. CON participants were instructed to telephone the investigators in the event of a fall or fracture so that full details could be recorded.

Anthropometrics and lifestyle characteristics

Age and race were obtained by self-report at baseline. Height and weight were measured using a wall-mounted stadiometer (Model 216, Seca, Germany) and mechanical beam scale (Model 700, Seca, Germany), respectively, from which BMI was calculated. Waist circumference was measured using an anthropometric steel tape (Model W606PM, Lufkin Executive Thinline, USA) at the level of the iliac crests. Lifetime physical activity of relevance to bone was quantified using the Bone-specific Physical Activity Questionnaire (BPAQ) [12]. Daily calcium intake, including supplementation, was estimated from the AusCal food frequency questionnaire [13], and responses were analyzed using Australian-specific dietary analysis software (FoodWorks, Xyris Software, Australia).

Bone and body composition

DXA scans of the LS and skeletally non-dominant proximal femur (FN, TH and trochanter ROIs) were performed to estimate BMD (Medix DR, Medilink, France). The skeletally non-dominant lower extremity corresponded to the functionally dominant limb [14]. LS, FN and TH T-scores were calculated using host software and the Geelong Osteoporosis Study reference database, an Australian-specific

population-based sample of Caucasian men [15]. Lean mass (LM), fat mass (FM), appendicular lean mass (ALM; sum of upper and lower extremity lean mass) and body fat percentage were determined from WB DXA scans. The short-term coefficients of variation (CV) for repeated measurements of LS, FN and TH BMD measurements in a sample of older men in our laboratory were 0.91%, 1.52% and 0.86%, respectively. The CVs for LM and FM were 0.62% and 2.33%, respectively. Peripheral QCT (pQCT; Stratec XCT-3000, Medizintechnik GmbH, Germany) of the skeletally non-dominant leg and forearm were performed to obtain muscle cross-sectional area (MCSA) and muscle density at the 66% sites; a detailed description of acquisition and analyses has been published elsewhere [11]. CVs for pQCT-derived MCSA and muscle density were 0.66% and 0.75% at the leg and 1.02% and 0.44% at the forearm, respectively. Skeletally non-dominant calcaneal broadband ultrasound attenuation (BUA), speed of sound (SOS) and stiffness index (SI) were obtained using QUS (Lunar Achilles InSight, GE Healthcare, USA). CVs for BUA, SOS and SI from a subsample of LIFTMOR-M participants were 0.98%, 0.35% and 1.71%, respectively. All devices underwent daily calibration and quality control procedures, and all scans were performed by the same certified technician.

Physical function, muscle strength and muscle power

A series of common physical function tests related to risk of falling were performed to examine mobility and dynamic balance, including: timed up-and-go (TUG) [16], five-times sit-to-stand (FTSTS) [17], and functional reach test (FRT) [18]. Maximal isometric leg extensor strength (LES) was determined using a leg strength platform dynamometer (TTM Muscle Meter, Japan) [19] and maximal isometric back extensor muscle strength (BES) was measured using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA) [20]. Muscle power was assessed by calculating peak impulse (N·s) and peak impulse relative to body weight (N·s/kg) from vertical ground reaction forces during a maximal

countermovement vertical jump on a force plate (Advanced Mechanical Technology Inc., USA). The specifics of all measures have been previously described [11].

Exercise program compliance, adverse events and injuries

Exercise compliance was recorded in training diaries, with 100% compliance defined as completion of 70 sessions over the eight-month trial period. Prior to each training session, participants rated muscle soreness on a 10-point visual analog scale (VAS), any falls, fractures or injuries, and any changes in physical activity, diet, medications or medical conditions since the last training session in the training diary. We included retrospective and prospective fall and fracture data collection methods. In order to increase the likelihood of capturing all data and minimize the effect of recall bias, self-administered questionnaires were also completed at baseline and follow-up assessments to document falls and fractures. A fall was defined as "unintentionally coming to rest on the ground, floor or other lower level after an unexpected loss of balance which was not the result of a violent blow, loss of consciousness, sudden onset of paralysis or an epileptic seizure, and can include a slip or trip" [21].

Sample size

FN areal BMD was selected as the primary outcome for reasons of clinical relevance due to elevated mortality following fragility fracture at the femoral neck in middle-aged and older men with low bone mass, and for the purposes of comparison across trials. An *a priori* sample size calculation was conducted based on the coefficient of variation for FN BMD (1.5%) to determine least significant change (4.2%), and FN BMD data from the aforementioned pilot trial of 0.790 ± 0.061 g/cm^2. A sample size of 64 participants per group was thereby predicted to be required to detect the minimum change difference of 0.033 g/cm^2 from a two-tailed test with a power of 80% and level of significance set at $\alpha = .05$, accounting for a dropout rate of 20%.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc, USA). Between-group comparisons of baseline characteristics were examined using one-way ANOVA for normally distributed continuous data, non-parametric equivalents for non-normally distributed data, and Chi-Square for categorical data. Between-group comparisons for outcome measures were examined using repeated measures Analysis of Covariance (RMANCOVA) for group, time and group-by-time interaction effects using raw baseline and follow-up data, adjusting for initial values if there was a significant difference identified between-groups at baseline. Mean change ± SE (calculated as final value minus initial value) and 95% CI are reported. Fisher's LSD method was applied to adjust for multiple comparisons. All randomized participants were included in intention-to-treat (ITT) analyses, with imputation of the mean percentage change value for the specific group employed in the case of missing follow-up data. Per-protocol (PP) exploratory analyses were undertaken including HiRIT and IAC participants who achieved ≥ 70% training program compliance. Univariate ANCOVA of percent change for primary and secondary outcomes was performed, adjusting for initial values if a significant difference was detected between-groups at baseline. Those results are presented in figures. Statistical significance was set at $p \leq 0.05$.

Results

Recruitment and allocation outcomes

Study recruitment, allocation, and follow-up are reported according to CONSORT guidelines in Supplemental Figure 1. Over the two-year period, 565 volunteers expressed interest in the study and were screened for eligibility by telephone. A total of 437 volunteers were ineligible to participate. One hundred and twenty-eight men underwent BMD assessments to confirm eligibility. Of those found to be ineligible at baseline assessments (n = 35), reasons were: LS, FN, and/or TH T-score > -1.0 (n = 23),

belatedly disclosed exclusion criteria (n = 10), and withdrawal of consent (n = 2). Ninety-three men either self-selected to CON (n = 26), or were randomized to HiRIT (n = 34) or IAC exercise (n = 33). Five CON participants were lost to follow-up. Three withdrew from HiRIT due to: medical condition or injury unrelated to the intervention (n = 2), and lack of interest (n = 1). One HiRIT participant was lost to follow-up due to death in a motor vehicle accident. Three withdrew from IAC due to: travel and family commitments (n = 2), and medical condition unrelated to the intervention (n = 1).

Participant physical and behavioural characteristics at baseline

Participant characteristics at baseline are presented in Table 1. There were no significant differences between groups in race, age, anthropometric characteristics, daily calcium, bone-relevant physical activity, current osteoporosis medication usage, and LS and TH BMD or T-scores. FN BMD and T-scores were higher for CON in comparison to both exercise intervention groups, while trochanteric BMD was higher for CON than HiRIT. QUS-derived calcaneal characteristics were similar between-groups. ALM was higher in CON than IAC. Physical function, muscle strength and muscle power were similar across groups, however, CON performed FTSTS more quickly than either exercise group at baseline. Overall, 3.8% of CON, 14.7% of HiRIT, and 21.2% of IAC were classified as osteoporotic based on DXA-derived T-score for at least one of the LS, FN or TH sites. Durations of osteoporosis medication use for the two participants in the HiRIT group were six years and 18 months. Durations of use for the two participants on osteoporosis medication in the IAC group were 9 years and 14 months. All were taking antiresorptive medication and had received continuous treatment without a drug holiday. There were no significant within-group changes in amount of external physical activity from BPAQ across the trial period. There were statistically significant, but arguably clinically insignificant, within-group increases in daily calcium in CON (206.3 ± 63.1 mg/day, p = 0.002; 95% CI: 80.9 to 331.8 mg/day) and HiRIT (166.3 ± 55.2 mg/day, p = 0.003; 95% CI: 56.6 to 276.0 mg/day) but no between-

group difference for change was observed. No participant commenced calcium supplementation or reported any significant change to daily calcium intake.

Exercise program compliance and progression

Not including dropouts, compliance was 77.8 ± 16.6% (range 35.7 to 95.7%) for HiRIT (n = 30) and 78.5 ± 14.8% (range 32.9 to 97.2%) for IAC (n = 30), and did not differ between groups (p = 0.872). Overall, 76.7% of HiRIT and 80.0% of IAC participants achieved ≥ 70% compliance. Including only participants who achieved ≥ 70% training compliance, there was no difference between HiRIT (85.9 ± 7.2%, range 72.2 to 95.7%; n = 23) and IAC compliance (84.5 ± 7.4%, range 70.8 to 97.2%; n = 24) (p = 0.466). For the HiRIT group, a significant time effect was observed for weight lifted for the deadlift, squat and overhead press at weeks 4, 8 and 35 (all $p < 0.05$). From week 4 to week 35 of the HiRIT intervention, weight lifted during the deadlift, squat and overhead press increased by 185.4 ± 84.2%, 242.0 ± 176.6% and 89.7 ± 37.7%, respectively. Deadlift 1RM increased from 68.0 ± 14.8 kg at week 12 to 80.8 ± 18.2 kg at week 24, and squat 1RM increased from 56.5 ± 15.5 kg at week 12 to 67.8 ± 21.2 kg at week 24. For the IAC group, peak force attained during the chest press, leg press, core pull and vertical lift increased from week 4 to 35 by 63.2 ± 67.2%, 77.3 ± 81.0%, 28.9 ± 31.5%, and 35.9 ± 43.6%, respectively. There was a significant time effect for peak force attained during all four IAC exercises at weeks 4, 8 and 35 (all $p < 0.001$).

Bone mineral density

Results of the univariate ANCOVA for eight-month percent change in BMD are presented in Figure 1A (ITT). HiRIT improved LS BMD more than CON (4.1 ± 0.7% versus 0.9 ± 0.8%, p = 0.003; 95% CI: 2.7 to 5.5% versus -0.7 to 2.5%) and IAC (4.1 ± 0.7% versus 2.0 ± 0.7%, p = 0.039; 95% CI: 2.7 to 5.5% versus 0.6 to 3.4%). HiRIT improved trochanteric BMD more than CON (2.8 ± 0.8% versus -0.1 ±

0.9%, p = 0.024; 95% CI: 1.2 to 4.4% versus -2.0 to 1.8%). There were no significant between-group differences in eight-month percent change for TH and FN BMD.

Results of the ITT analyses of intervention effects on LS and proximal femur BMD are presented in Supplemental Table 1. From RMANCOVA (adjusting for initial trochanteric BMD), eight-month change in trochanteric BMD was greater for HiRIT than CON (p = 0.026), but no other significant between-group differences were detected for BMD. Within-group analyses indicated HiRIT improved LS BMD (p < 0.001), FN BMD (p = 0.004), TH BMD (p = 0.045) and trochanteric BMD (p = 0.001), while IAC increased LS BMD (p = 0.006).

Results of PP analyses of eight-month change in DXA-derived BMD at the LS and proximal femur are presented in Supplemental Table 2. PP analysis of participants with ≥ 70% compliance indicate there were no significant between-group differences in change for DXA-derived BMD at the LS or proximal femur. Significant within-group improvements for HiRIT in LS BMD (0.038 ± 0.008 g/cm^2, p < 0.001) and trochanter BMD (0.019 ± 0.008 g/cm^2, p = 0.024), and LS BMD (0.025 ± 0.008 g/cm^2, p = 0.003) for IAC, were detected in PP analysis.

Calcaneal ultrasound parameters

Percent change in calcaneal ultrasound parameters, with between-group differences from univariate ANCOVA, are presented in Figure 1C (ITT). HiRIT improved BUA (2.2 ± 0.7% versus -0.8 ± 0.9%, p = 0.009; 95% CI: 0.8 to 3.6% versus -2.5 to 0.9%) and SI (1.6 ± 0.9% versus -2.0 ± 1.1%, p = 0.011; 95% CI: -0.2 to 3.4% versus -4.1 to 0.1%) more than CON. HiRIT also improved SI more than IAC (1.6 ± 0.9% versus -1.3 ± 0.9%, p = 0.025; 95% CI: -0.2 to 3.4% versus -3.2 to 0.5%).

QUS-derived calcaneal data from ITT analyses of intervention effects are presented in Supplemental Table 3. From RMANCOVA, there was a significant difference between HiRIT and CON in SOS (p = 0.048). Within-group analysis showed HiRIT significantly improved BUA (p = 0.003), whereas CON

lost SI (p = 0.019). IAC also lost SOS (p = 0.018). Results of the PP analyses of calcaneal parameters (including participants with ≥ 70% compliance, n = 71) are presented in Supplemental Table 4. While there were no between-group differences in absolute change for calcaneal parameters, HiRIT improved BUA (p = 0.020), and IAC lost SOS (p = 0.021) based on within-group analyses.

Anthropometrics and body composition

Percent change in DXA-derived body composition, with between-group differences from univariate ANCOVA (adjusting for initial values for appendicular lean mass analysis), are presented in Figure 1B (ITT). HiRIT (1.5 ± 0.8% versus -2.4 ± 0.9%, p = 0.002; 95% CI: -0.1 to 3.1% versus -4.2 to -0.5%) and IAC (0.8 ± 0.8% versus -2.4 ± 0.9%, p = 0.013; 95% CI: -0.9 to 2.4% versus -4.2 to -0.5%) improved lean mass in comparison to CON. There were no between-group differences in percent change for anthropometrics, appendicular lean mass, fat mass and body fat percent. HiRIT improved tibia (0.7 ± 0.3% versus -0.4 ± 0.3%, p = 0.014; 95% CI: 0.2 to 1.3% versus -1.1 to 0.3%) and radius (0.9 ± 0.3% versus -0.9 ± 0.3%, p < 0.001; 95% CI: 0.3 to 1.4% versus -1.5 to -0.2%) muscle density, as well as radius MCSA (2.6 ± 0.7% versus -0.2 ± 0.8%, p = 0.011; 95% CI: 1.2 to 4.0% versus -1.8 to 1.5%) compared with CON. HiRIT also improved radius MCSA more than IAC (2.6 ± 0.7% versus 0.4 ± 0.7%, p = 0.028; 95% CI: 1.2 to 4.0% versus -0.9 to 1.8%). IAC improved radius muscle density more than CON (0.4 ± 0.3% versus -0.9 ± 0.3%, p = 0.003; 95% CI: -0.1 to 1.0% versus -1.5 to -0.2%). The results of the ITT analyses of intervention effects on anthropometrics and body composition are presented in Supplemental Table 5. From RMANCOVA, no between-group differences in change for any anthropometric measure or DXA-derived body composition parameter were detected. HiRIT improved pQCT-derived forearm MCSA more than IAC (p = 0.038) and forearm muscle density more than CON (p = 0.030). Within-group analyses revealed HiRIT increased weight (p = 0.039) and BMI (p = 0.039), and reduced fat mass (p = 0.044) and body fat percentage (p = 0.036). HiRIT also improved

forearm MCSA ($p < 0.001$), forearm muscle density ($p = 0.002$), and leg muscle density ($p = 0.014$). IAC reduced DXA-derived FM ($p = 0.020$) and body fat percentage ($p = 0.050$). CON lost waist circumference ($p = 0.016$), ALM ($p = 0.003$), LM ($p = 0.010$), and forearm muscle density ($p = 0.008$) but gained FM ($p = 0.004$), body fat percentage ($p = 0.001$) and leg MCSA ($p = 0.010$). Results of PP analyses of eight-month change in anthropometrics and body composition outcomes are presented in Supplemental Table 6 and largely reflect findings from the ITT analyses.

Physical function, muscle strength and muscle power

Percent change in physical function, muscle strength and muscle power, with between-group differences from univariate ANCOVA (adjusting for initial values for sit-to-stand analysis), are presented in Figure 2. Compared with CON, HiRIT improved TUG (-5.3 ± 1.3% versus 0.2 ± 1.5%, $p = 0.007$; 95% CI: -7.9 to -2.7% versus -2.8 to 3.2%), FTSTS (-10.7 ± 1.6% versus 7.5 ± 2.0%, $p < 0.001$; 95% CI: -14.0 to -7.4% versus 3.7 to 11.4%), BES (26.0 ± 5.1% versus 4.0 ± 5.8%, $p = 0.006$; 95% CI: 15.9 to 36.2% versus -7.5 to 15.6%), LES (25.1 ± 3.8% versus 9.2 ± 4.4%, $p = 0.008$; 95% CI: 17.5 to 32.8% versus 0.5 to 18.0%) and peak impulse (3.2 ± 2.0% versus -4.2 ± 2.3%, $p = 0.017$; 95% CI: -0.8 to 7.2% versus -8.7 to 0.3%). Improvement in FTSTS was greater in HiRIT than IAC (-10.7 ± 1.6% versus -4.5 ± 1.7%, $p = 0.010$; 95% CI: -14.0 to -7.4% versus -7.9 to -1.1%). IAC improved FTSTS more than CON (-4.5 ± 1.7% versus 7.5 ± 2.0%, $p < 0.001$; 95% CI: -7.9 to -1.1% versus 3.6 to 11.4%). No significant between-group differences were observed in FRT and relative peak impulse.

Between-group differences in absolute change in physical function, muscle strength and muscle power from ITT RMANCOVA are presented in Supplemental Table 7. Compared with CON, HiRIT improved FTSTS ($p < 0.001$), LES ($p = 0.008$), peak impulse ($p = 0.008$) and peak relative impulse ($p = 0.022$). IAC reduced FRT and improved FTSTS compared to CON ($p = 0.042$ and $p < 0.001$, respectively). Compared to IAC, HiRIT improved FTSTS ($p = 0.005$), FRT ($p = 0.011$), peak impulse ($p = 0.001$), and

peak relative impulse (p = 0.003). Within-group analysis revealed HiRIT improved TUG (p < 0.001), FTSTS (p < 0.010), BES (p < 0.001) and LES (p < 0.001), and that IAC improved TUG (p = 0.011), FTSTS (p = 0.004), BES (p = 0.008) and LES (p < 0.001). CON improved LES (p = 0.014), but slowed on the FTSTS task (p = 0.003). Results of PP analyses (participants with ≥ 70% compliance) for physical function, muscle strength and muscle power are presented in Supplemental Table 8 and largely reflect those of the ITT analyses, although within-group change in TUG and FTSTS was no longer significant for IAC and within-group change in peak impulse reached significance for HiRIT.

Falls and fractures

Three participants (3.2%) (HiRIT n = 2; IAC n = 1) reported a fall within the previous 12 months, at baseline, and there was no between-group difference in falls history. During the trial period, CON reported two falls resulting in minor bruising. In HiRIT, one participant reported two falls, and two participants fell once. In IAC, two participants fell once across the trial period. No fall necessitated a visit to a healthcare provider, nor resulted in fracture or hospital admission; none occurred during study-related training or testing. There were no between-group differences in the number of falls (p = 0.878), number of fallers (p = 0.887), number sustaining at least 1 fall (p = 0.756) or number of recurrent fallers (p = 0.423). Nine participants (9.7%) (CON n = 2; HiRIT n = 2; IAC n = 5) reported 12 previous fragility fractures, with no differences between groups (p = 0.377). Of those reporting multiple previous fragility fractures at baseline (n = 2), one IAC participant reported three radiographically-confirmed osteoporotic vertebral wedge fractures, and one IAC participant reported two previous fragility fractures (tibial plateau and talus, both conservatively managed). Both had a previous diagnosis of osteoporosis and prolonged use of osteoporosis medications (> 12 months). No participant sustained a fragility fracture during the trial period (PP data, n = 81), nor did any participant who was lost to follow-up report any falls or fractures during the period they were active in the trial.

Adverse events and injuries

Three participants withdrew from the exercise groups due to unrelated medical conditions, which included: cerebrovascular event (HiRIT n = 1), age-related disc degeneration advised by their medical practitioner to discontinue all exercise and physical activity (IAC n = 1), and an inguinal hernia requiring surgical repair which occurred when lifting heavy luggage on holidays (HiRIT n = 1). There were five minor adverse events directly associated with delivery of the exercise program, all including minor musculoskeletal discomfort reported during training; HiRIT n = 2 (mild low back muscle strain on the first repetition of squat at week 26, right knee soreness during the squat at week 19 [two sessions missed]; IAC n = 3 (right knee discomfort during leg press, left shoulder muscle discomfort during the chest press [three weeks missed], low back discomfort after completing the vertical lift [continued training but refused to perform the vertical lift for four subsequent sessions]. Pre-training session ratings of muscle soreness from the 10-point VAS, were 0.89 ± 1.03 for HiRIT (n = 30) and 0.22 ± 0.34 for IAC (n = 30), with a significant difference between groups (p = 0.001). Muscle soreness, however, was reportedly primarily associated with activity engaged in outside of the exercise intervention, for instance lower extremity muscle soreness from bushwalking and generalized muscle soreness attributed to gardening or occupational activity.

Discussion

The aim of the LIFTMOR-M trial was to determine the effects of eight months supervised HiRIT or machine-based IAC exercise on determinants of fracture risk in middle-aged and older men with low BMD, and to compare with 'usual lifestyle' control (CON). In general, HiRIT improved parameters of bone strength, physical function and muscle strength compared with CON and IAC. HiRIT was well accepted and tolerated, as evidenced by strong compliance and retention, and minimal adverse events.

The outcomes reflect those of the LIFTMOR trial and thus demonstrate similar HiRIT efficacy in men and women [8] in terms of reducing risk factors for osteoporotic fracture.

High compliance for HiRIT and IAC suggests both programs were feasible and sufficiently appealing to this demographic, comparing favorably to previous bone-targeted exercise interventions for men [22-29]. Our short-duration, low-volume exercise protocols address a predominant barrier to exercise engagement – lack of time [30]. Opportunity for social interaction is a known facilitator and cost has been identified as a barrier to exercise engagement [30], thus, supervised HiRIT performed in a group setting may be more engaging and economically viable than one-on-one IAC training. An identical HiRIT program achieved higher compliance in postmenopausal women [8], an observation that corresponds to findings of a meta-analysis demonstrating that women are more compliant to exercise for BMD than men [31].

Differences in BMD change were detected between HiRIT and CON at the LS and trochanter, and between HiRIT and IAC at the LS. No differences were observed between IAC and CON. While HiRIT increased LS, FN, TH and trochanteric BMD in within-group analyses, only LS BMD increased for IAC, and by roughly half the amount of HiRIT.

In other studies designed to improve bone mass in men, a small number have detected a LS BMD improvement of 1.4-1.9% [24,28], but more frequently no difference has been observed [22,23,27,29,32]. In 50-60 year old men with unknown bone status at baseline, six months of thrice-weekly moderate- to high-intensity resistance training (70 to > 90% 1RM) increased LS BMD by 1.9%, compared to no change for low- to moderate-intensity resistance training (40-60% 1RM) [28]. The single remaining male exercise trial observing an effect at the LS, reported a smaller response (≈1.5%) than we did, despite greater training frequency (thrice-weekly) and intervention duration (12 months) [24].

Few male studies have reported trochanteric BMD, however, the majority of those that do have failed to observe a between-group difference [24,27,28], and one study detected a difference between exercise groups, but no difference compared to control [23]. Nine months of moderate-dose impact (40 jumps) plus upper body resistance training reduced trochanteric BMD relative to no change for the high-dose impact (80 jumps) plus upper body resistance training group [23], showing even high-dose impact exercise alone was insufficient to increase trochanteric BMD (although it likely prevented loss). We detected an increase in trochanteric BMD for HiRIT in comparison to CON but not IAC. The two remaining studies that failed to detect an exercise effect at the trochanter despite greater session frequency (thrice-weekly) and longer study duration (12 months) than ours, had lower training intensities and incorporated machine-based, single-joint movements [24,27]. By contrast, our HiRIT program incorporated high intensity, free-weight, compound movement exercises targeting the hip. Although HiRIT increased FN and TH BMD from baseline, we did not detect between-group differences. We note that only 12-month trials have reported improvements at the FN [24]. Shorter duration trials (six to nine months), including ours, have failed to detect differences between groups [23,28]. Similarly, no exercise effect is reported at the TH for most intervention studies of men [24,27,28], with the exception of two [22,23]. A 12-month trial in osteopenic men compared exercise modes (resistance versus impact) and observed a superior effect for twice-weekly resistance training compared to the thrice-weekly impact-loading [22], however, training frequency differed.

Calcaneal QUS has been used as a surrogate for DXA-derived bone mass in prospective studies of postmenopausal women, but rarely for men, to the extent that no exercise trial of men could be located for comparison of QUS-derived bone response. The increase in BUA following HiRIT was of a similar magnitude to that reported following 12 months of daily Alendronate and calcium treatment in osteoporotic men [33]. By contrast, SI decreased for CON, and IAC was insufficient to prevent loss of

SOS. The positive effects of HiRIT at the calcaneus is important given findings of the prospective Osteoporotic Fractures in Men Study which indicate that each SD reduction in BUA was associated with a doubling of the risk of hip fracture and a 60% increase in risk of any non-spine fracture [34]. The efficacy of our HiRIT program on BUA is therefore very encouraging.

Findings of a recent population-based study in community-dwelling older men indicate maintenance of appendicular lean mass (ALM) with an accompanying reduction in fat mass (FM) is associated with reduced incidence of falls [35]. While the CON group lost lean mass and gained fat mass, HiRIT improved body composition with an increase in weight but reduction in fat suggesting increased lean mass, and IAC reduced fat. Within-group effects notwithstanding, only whole body LM differed between groups, with HiRIT and IAC effects being superior to CON. Similarly, others have shown resistance training or resistance training combined with impact exercise increased LM compared to no-exercise [24] or walking (active control) [27]. Six months of moderate- to high-intensity resistance exercises, similar to our HiRIT protocol, increased LM but no difference in change from low- to moderate-intensity machine-based resistance training was detected [28]. Our lack of between-group effects for anthropometry and a number of DXA-derived body composition parameters mirror the findings of other resistance training and/or impact loading studies in similar populations [22,23,26]. In some cases, brevity of loading [26] and poor compliance [23] appear to have tempered body composition changes, but power may also have been a problem. Furthermore, DXA estimates of LM are confounded by other soft tissues of similar density.

As force-generating capacity is related to muscle size and density (the latter being an index of intramuscular fat and muscle quality), our observed improvements in forearm MCSA and density, and leg muscle density suggest HiRIT is an effective countermeasure to age-related declines in muscle size and quality. Indeed, higher leg muscle density is associated with a reduced likelihood of falls

independent of functional mobility in community-dwelling older adults [36]. Our non-intuitive observation of an absence of change in leg MCSA following HiRIT may be related to moderate statistical power (i.e. 53.3%) and low sensitivity of pQCT for subtle changes. Similarly non-intuitive was the modest increase in leg MCSA in CON, suggesting participants engaged in non-trivial amounts of lower extremity loading during the course of the trial, despite assurances to the contrary. It is likely the lack of effect of IAC on any pQCT-derived soft tissue parameters is attributable to the very low training load exposure (a single repetition of the four exercises each training session, per manufacturer recommendations).

HiRIT improved numerous functional outcomes related to risk for falls and fracture, while IAC improved only FTSTS, compared with CON. HiRIT improved FTSTS compared with IAC, although there were no differences between exercise groups in the remaining measures of function or strength. In middle-aged and older men, moderate-intensity upper body resistance training in combination with either moderate- or high-dose impact exercise was insufficient to improve lower body muscle strength or functional fitness related to risk of falling compared to control [23], suggesting impact exercise alone is insufficient stimulus to improve function of the lower extremity. By contrast, our whole body HiRIT program improved physical function, muscle strength and muscle power compared with CON. Overall, the observed improvements in function and strength for HiRIT in men were consistent with the changes reported for the identical program implemented in postmenopausal women [8], showing similar effectiveness for improving characteristics associated with risk of falling.

The supervised HiRIT exercises and training loads were well tolerated, and associated with only two minor musculoskeletal adverse events. Similarly, IAC was largely well tolerated, being associated with only three adverse events, slightly more serious than for HiRIT. There were no incident fractures during the trial period. Our adverse event observations reflect the experiences of others who report no major

adverse events or injuries [22,28], or minor discomfort requiring less than two weeks rest [32] during supervised resistance training interventions, albeit lower intensity than ours. By contrast, impact-only interventions or combined resistance and impact-loading have been more problematic, with only two out of five trials reporting an absence of training-related adverse events [22,23]. In the Hip Hop study there were eight impact intervention-related musculoskeletal adverse events, and three participants withdrew due to 'discomfort during exercise' [26]. In a 12-month multimodal exercise trial there were six instances of exacerbation or aggravation of existing injuries that required program modification or rest, and one withdrawal due to low back injury [24]. The Osteo-cise study, that combined high-velocity resistance training and impact exercise, reported the highest number of adverse events. In that study, approximately 42% of participants reported an adverse event, including one wrist fracture and 40 musculoskeletal complaints or injuries by 34 participants, with six injuries leading to study discontinuation [25]. As Osteo-cise results were presented for both sexes combined it is unknown how many adverse events were sustained by male participants. An important difference between the latter two multimodal interventions and the current trial is lack of full supervision. The fact that our HiRIT and IAC interventions were well tolerated is likely a function of an initial familiarization period focusing on technique and ongoing supervision. Training on non-consecutive days to allow sufficient recovery between sessions is also likely to be key (per traditional resistance training protocols [37]), particularly for older 'untrained' adults unaccustomed to high-intensity resistance and high-impact training. While intuitive that supervision reduces the likelihood of improper technique and therefore injury, full supervision is traditionally considered to be impractical in the older adult exercise space, despite no evidence to suggest that is the case and some to suggest it is not [38]. Application of the HiRIT protocol should focus on monitoring of individual performance through 1RM testing and RPE, which allows for adjustments in load to maintain the desired intensity of ≥ 80-85% of 1RM.

Strengths and limitations

The strength of our study lies in the application of theoretically sound principles of effective bone loading in our exercise protocol and the inclusion of men with osteopenia and osteoporosis, some with a history of fragility fracture. The latter are an underrepresented group, having been excluded from previous exercise trials in men [22-25]. LIFTMOR-M is the first trial to examine the effects of HiRIT in comparison to machine-based IAC training on parameters of bone mass and strength, along with risk factors for falls and fractures, in middle-aged and older men. There are, however, a number of limitations that warrant acknowledgement. First, despite an extensive recruitment strategy over two years, we did not meet our target sample size. The final sample of 93 men limited statistical power for some analyses, including the primary outcome, FN BMD, however, numbers were sufficient to examine many other important outcomes. Instead, we were able to demonstrate significant within-group improvements following HiRIT (LS BMD, TH BMD, FN BMD, and BUA) and IAC (LS BMD), by employing least significant change analysis which accounts for measurement error. For those recruited, the intervention was feasible and enjoyable, with a low dropout rate for both exercise arms. We also note that few participants were taking osteoporosis medications (n = 4), however, analyses for bone outcomes excluding those individuals did not change our findings (data not presented). Second, we acknowledge the engagement of a parallel matched but non-randomized control group who elected to continue with their customary lifestyle patterns was not ideal, nor in line with the gold standard of randomized controlled trial design. As previously described, the strategy was implemented to maximize the likelihood that CON would not initiate a novel exercise program external to the study activities, as had been our experience in piloting the trial. Furthermore, we felt that randomizing men who are at increased risk of fragility fracture to a no-exercise group when volunteering under the expectation of receiving a potentially beneficial exercise program would be ethically unacceptable. Our semi-randomized

controlled study design was therefore adopted for pragmatic and ethical reasons. Third, our sample was limited to 'otherwise healthy', community-dwelling men. As individuals with uncontrolled cardiovascular or debilitating musculoskeletal co-morbidities were excluded, our results may not be generalizable to the broader population of men with osteoporosis, some of whom are likely to be frailer, less physically active and less motivated to exercise. And finally, our twice-weekly machine-based IAC training protocol varied from manufacturer recommendations which stipulate only once-weekly training. It was important to match treatment exposure (i.e. number of sessions per week) in order to make a valid comparison between exercise groups. As it is unlikely that doubling the extremely small dose of the IAC stimulus would reduce its effect, we are confident that our modification in IAC protocol did not detract from the ability of the device to apply an osteogenic stimulus.

Conclusion

In conclusion, our novel, eight-month exercise intervention of twice-weekly HiRIT improved BMD at the proximal femur and LS, calcaneal ultrasound characteristics, body composition, physical function and muscle strength in middle-aged and older men with osteopenia and osteoporosis. Furthermore, the supervised HiRIT program was well tolerated, with no incident fractures or major adverse events across the intervention period. High compliance suggests the regime is acceptable and feasible. By contrast, machine-based IAC provides a largely insufficient stimulus for musculoskeletal or functional benefits in this demographic. Given a 1-2% BMD increase translates to a 5-10% reduction in fracture risk [39], the observed BMD improvements for HiRIT, particularly at the spine, may confer fracture prevention benefits. On a backdrop of previously limited evidence for the effect of targeted exercise on BMD in older men, the novel findings of the current trial suggest that twice-weekly HiRIT is strongly indicated to reduce risk of fragility fracture in older men with low bone mass.

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References

1. Watts JJ, Abimanyi-Ochom J, Sanders KM. Osteoporosis costing all Australians: A new burden of disease analysis 2012 to 2022. In: Australia O, editor. 1 ed. Osteoporosis Australia, Melbourne, VIC, Australia: Osteoporosis Australia; 2013. p. 75.
2. Tatangelo G, Watts J, Lim K, Connaughton C, Aibmanyi-Ochom J, Borgstrom F, et al. The cost of osteoporosis, osteopenia, and associated fractures in Australia in 2017. J Bone Miner Res. 7 January 2019 2019;34(4):616-25.
3. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. Nov 2014;29(11):2520-6.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. Mar 2007;22(3):465-75.
5. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. Feb 4 2009;301(5):513-21.
6. Ström O, Borgström F, Kanis JA, Compston J, Cooper C, McCloskey EV, et al. Osteoporosis: Burden, health care provision and opportunities in the EU. Arch Osteoporos. 2011;6(1-2):59-155.
7. Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community. Cochrane Database Syst Rev. 31 Jan 2019 2019;1(1):CD012424.
8. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR. High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: The LIFTMOR randomized controlled trial. J Bone Miner Res. Oct 4 2018;33(2):211-20.
9. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR. High-intensity exercise did not cause vertebral fractures and improves thoracic kyphosis in postmenopausal women with low to very low bone mass: The LIFTMOR trial. Osteoporos Int. 05 January 2019 2019;30(5):957-64.
10. Hunte B, Jaquish J, Huck C. Axial bone osteogenic loading-type resistance training therapy showing BMD and functional bone performance musculoskeletal adaptations over 24 weeks with postmenopausal female subjects. J Osteopor Phys Act. June 2015;3(3).
11. Harding AT, Weeks BK, Watson SL, Beck BR. The LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semirandomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass. BMJ Open. Jun 12 2017;7(6):e014951. Epub 2017/06/15.
12. Weeks BK, Beck BR. The BPAQ: A bone-specific physical activity assessment instrument. Osteoporos Int. Nov 2008;19(11):1567-77.
13. Beck BR, Weeks BK, Norling TL. A novel Australian calcium-specific diet questionnaire: Validity and reliability. Osteoporos Int. Sep 2011;22:S626-S7.
14. Beck BR, Weeks BK. Which limb to scan? Revisiting the relationship between funcitonal and skeletal limb dominance. J Bone Miner Res. 2010;25(S306).

15. Henry MJ, Pasco JA, Korn S, Gibson JE, Kotowicz MA, Nicholson GC. Bone mineral density reference ranges for Australian men: Geelong Osteoporosis Study. Osteoporos Int. Jun 2010;21(6):909-17.
16. Podsiadlo D, Richardson S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. Feb 1991;39(2):142-8. Epub 27 April 2015.
17. Bohannon RW. Measurement of sit-to-stand among older adults. Top Geriatr Rehabil. Jan-Mar 2012;28(1):11-6.
18. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: A new clinical measure of balance. J Gerontol. Nov 1990;45(6):192-7.
19. Scott D, Blizzard L, Fell J, Jones G. Statin therapy, muscle function and falls risk in community-dwelling older adults. Q J Med. Sep 2009;102(9):625-33.
20. Harding AT, Weeks BK, Horan SA, Little A, Watson SL, Beck BR. Validity and test-retest reliability of a novel simple back extensor muscle strength test. SAGE Open Med. 2017;5:2050312116688842.
21. Hauer K, Lamb SE, Jorstad EC, Todd C, Becker C. Systematic review of definitions and methods of measuring falls in randomised controlled fall prevention trials. Age Ageing. Jan 2006;35(1):5-10.
22. Hinton PS, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: A 12-month randomized, clinical trial. Bone. Oct 2015;79:203-12.
23. Bolam KA, Skinner TL, Jenkins DG, Galvão DA, Taaffe DR. The osteogenic effect of impact-loading and resistance exercise on bone mineral density in middle-aged and older men: A pilot study. Gerontology. 2016;62(1):22-32.
24. Kukuljan S, Nowson CA, Bass SL, Sanders K, Nicholson GC, Seibel MJ, et al. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: A randomised controlled trial. Osteoporos Int. Jul 2009;20(7):1241-51.
25. Gianoudis J, Bailey CA, Ebeling PR, Nowson CA, Sanders KM, Hill K, et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: A community-based randomized controlled trial. J Bone Miner Res. Jan 2014;29(1):182-91.
26. Allison SJ, Folland JP, Rennie WJ, Summers GD, Brooke-Wavell K. High impact exercise increased femoral neck bone mineral density in older men: A randomised unilateral intervention. Bone. Apr 2013;53(2):321-8. Epub 2013 Jan 3.
27. Whiteford J, Ackland TR, Dhaliwal SS, James AP, Woodhouse JJ, Price R, et al. Effects of a 1-year randomized controlled trial of resistance training on lower limb bone and muscle structure and function in older men. Osteoporos Int. Sep 2010;21(9):1529-36.
28. Maddalozzo GF, Snow CM. High intensity resistance training: Effects on bone in older men and women. Calcif Tissue Int. Jun 2000;66(6):399-404. Epub 22 March 2014.
29. Menkes A, Mazel S, Redmond RA, Koffler K, Libanati CR, Gundberg CM, et al. Strength training increases regional bone mineral density and bone remodeling in middle-aged and older men. J Appl Physiol. May 1993;74(5):2478-84.
30. Rodrigues IB, Armstrong JJ, Adachi JD, MacDermid JC. Facilitators and barriers to exercise adherence in patients with osteopenia and osteoporosis: A systematic review. Osteoporos Int. Mar 2016;28(3):735-45.

31. Kelley GA, Kelley KS. Dropouts and compliance in exercise interventions targeting bone mineral density in adults: A meta-analysis of randomized controlled trials. J Osteoporos. 2013;2013:250423.
32. Vincent KR, Braith RW. Resistance exercise and bone turnover in elderly men and women. Med Sci Sports Exerc. Jan 2002;34(1):17-23.
33. Gonnelli S, Cepollaro C, Montagnani A, Bruni D, Caffarelli C, Breschi M, et al. Alendronate treatment in men with primary osteoporosis: A three-year longitudinal study. Calcif Tissue Int. Aug 2003;73(2):133-9.
34. Bauer DC, Ewing SK, Cauley JA, Ensrud KE, Cummings SR, Orwoll ES. Quantitative ultrasound predicts hip and non-spine fracture in men: The MrOS study. Osteoporos Int. Jun 2007;18(6):771-7.
35. Scott D, Seibel MJ, Cumming R, Naganathan V, Blyth F, Le Couteur DG, et al. Associations of body composition trajectories with bone mineral density, muscle function, falls and fractures in older men: The Concord Health and Ageing in Men project. J Gerontol A Biol Sci Med Sci. Aug 13 2019.
36. Frank-Wilson AW, Farthing JP, Chilibeck PD, Arnold CM, Davison KS, Olszynski WP, et al. Lower leg muscle density is independently associated with fall status in community-dwelling older adults. Osteoporos Int. Jul 2016;27(7):2231-40.
37. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. 'American College of Sports Medicine' position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med Sci Sports Exerc. Jul 2011;43(7):1334-59.
38. Beck BR, Weis LJ. Effective exercise for osteoporosis in the real world: Three year observations from The Bone Clinic. J Bone Miner Res. Nov 2018;33(Suppl 1):400.
39. Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: Systematic review and meta-analysis. BMJ. Sep 29 2015;351:h4183.

Figure legends

Figure 1. Box and whisker plot of eight-month percent change (median ± interquartile range) in (A) DXA-derived bone mineral density, (B) DXA-derived body composition parameters, and (C) QUS-derived bone characteristics at the skeletally non-dominant calcaneus. Data points that are more than 1.5 × interquartile range are presented by 'O' (Tukey's outlier detection method). (DXA and body composition ITT data n = 93; Control n = 26, HiRIT n = 34, IAC n = 33; QUS ITT data n = 90; Control n = 24, HiRIT n = 34, IAC n = 32). Abbreviations: ALM, appendicular lean mass; BUA, broadband ultrasound attenuation; FM, fat mass; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; LM, lean mass; SI, stiffness index; SOS, speed of sound; Troc, trochanteric. P values indicate between-group difference in percent change from univariate ANCOVA. Note: FN BMD and trochanteric BMD were adjusted for initial values as a difference between groups at baseline was detected with one-way ANOVA.

Figure 2. Box and whisker plot of eight-month percent change (median ± interquartile range) in (A) physical function, and (B) isometric muscle strength and muscle power. Data points that are more than 1.5 × interquartile range are presented by 'O' (Tukey's outlier detection method). (ITT data n = 93; Control n = 26, HiRIT n = 34, IAC n = 33). Abbreviations: BES, back extensor strength; FRT, functional reach test; FTSTS, five-times sit-to-stand; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; LES, leg extensor strength; TUG, timed up-and-go. P values indicate between-group difference in percent change from univariate ANCOVA. Note: FTSTS adjusted for initial values as a difference between groups at baseline was detected with one-way ANOVA. Peak impulse calculated from maximal CMVJ (ITT data n = 92; Control n = 26, HiRIT n = 33, IAC n = 33).

Table 1. Participant characteristics at baseline (ITT data, n = 93)

Parameter	Control (n = 26)	HiRIT (n = 34)	IAC (n = 33)	p-value
Age, years	67.4 ± 6.3	64.9 ± 8.6	69.0 ± 6.8	0.072
Weight, kg	81.6 ± 10.0	83.4 ± 11.7	81.2 ± 12.9	0.720
Height, cm	176.0 ± 7.3	175.2 ± 7.0	174.6 ± 6.1	0.712
BMI, kg/m^2	26.3 ± 2.8	27.2 ± 3.5	26.6 ± 4.0	0.636
Osteoporosis medication, n (%)	0 (0.0%)	2 (5.9%)	2 (6.1%)	
Alendronate	0 (0.0%)	1 (2.9%)	1 (3.0%)	0.444 [a]
Denosumab	0 (0.0%)	1 (2.9%)	1 (3.0%)	
T-score, unitless				
Lumbar spine	0.27 ± 1.15	-0.22 ± 0.95	-0.17 ± 1.03	0.149
Femoral neck	-1.28 ± 0.57	-1.62 ± 0.56†	-1.77 ± 0.54‡	0.004
Total hip	-0.80 ± 0.58	-1.08 ± 0.62	-1.07 ± 0.51	0.125
BMD, g/cm^2				
Lumbar spine	1.153 ± 0.190	1.072 ± 0.154	1.082 ± 0.171	0.158
Femoral neck	0.832 ± 0.085	0.781 ± 0.083†	0.758 ± 0.080‡	0.004
Total hip	0.996 ± 0.100	0.947 ± 0.107	0.948 ± 0.088	0.105
Trochanter	0.830 ± 0.094	0.761 ± 0.102†	0.784 ± 0.096	0.027
ALM, kg	30.1 ± 3.9	28.6 ± 3.8	27.5 ± 3.5‡	0.032
Body fat percent, %	21.2 ± 4.8	23.8 ± 5.1	23.0 ± 6.9	0.215
PAQ, unitless	39.9 ± 21.4	27.2 ± 20.1	34.3 ± 21.9	0.073
Calcium intake, mg/day	743.1 ± 426.3	897.1 ± 411.5	1018.5 ± 602.7	0.108
Ethnicity, n (%)				
Caucasian	26 (100.0%)	33 (97.1%)	31 (93.9%)	0.618 [a]
Asian	0 (0.0%)	1 (2.9%)	1 (3.0%)	
Eurasian	0 (0.0%)	0 (0.0%)	1 (3.0%)	

Abbreviations: HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; tBPAQ, total Bone-specific Physical Activity Questionnaire score.

Data are mean ± SD unless otherwise indicated. [a] X^2 test.

Between-group difference $p < 0.05$: † HiRIT vs Control, ‡ IAC vs Control, # HiRIT vs IAC.