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Author

Harding, Amy T, Weeks, Benjamin K, Lambert, Conor, Watson, Steven L, Weis, Lisa J, Beck, Belinda R

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Title:

Effects of supervised high-intensity resistance and impact training or machine-based isometric training on regional bone geometry and strength in middle-aged and older men with low bone mass: The LIFTMOR-M semi-randomised controlled trial

Authors:

Amy T Harding, BExSc (Hons) [a, b]

Benjamin K Weeks, PhD [a, b]

Conor Lambert, PhD [a, b]

Steven L Watson, PhD [a, b]

Lisa J Weis, MBA [c]

Belinda R Beck, PhD [a, b, c]

Affiliations:

[a] Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia

[b] School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia

[c] The Bone Clinic, Brisbane, Queensland, Australia

Corresponding author contact details:

Professor Belinda R. Beck, PhD

School of Allied Health Sciences, Griffith University, Gold Coast, QLD, AUSTRALIA, 4222

Phone: +61 (07) 5552 8793 Email: b.beck@griffith.edu.au

ABSTRACT

Introduction: Few data exist on the effects of bone-targeted exercise on geometric and biomechanical indices of bone strength in men. The Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men (LIFTMOR-M) trial was designed to compare the efficacy and safety of two novel, supervised, twice-weekly, high-intensity exercise programs in middle-aged and older men with osteopenia and osteoporosis on musculoskeletal health and risk factors related to falls and fractures. The current report includes secondary outcomes of the LIFTMOR-M exercise intervention trial.

Purpose: Our goal was to determine the effects of two supervised, twice-weekly, high-intensity exercise programs on bone geometry and strength of the proximal femur, and distal and proximal sites of the tibia and radius in middle-aged and older men with osteopenia and osteoporosis.

Methods: Generally-healthy men (≥ 45 years), with low lumbar spine (LS) and/or proximal femur areal bone mineral density (aBMD), were recruited from the community. Eligible participants were randomised to either eight months of twice-weekly supervised high-intensity progressive resistance and impact training (HiRIT) or supervised machine-based isometric axial compression (IAC) exercise training. Intervention group outcomes were compared at baseline and eight months with a matched but non-randomised control group (CON) who self-selected to usual activities. DXA scans (Medix DR, Medilink, France) of the skeletally non-dominant proximal femur were analysed using 3D hip software (DMS Group, France) to derive femoral neck (FN) and total hip (TH) bone mineral content (BMC), volume, and volumetric bone mineral density (vBMD) for total, trabecular and cortical bone compartments. Total FN cortical thickness was determined as well as anterior, posterior, lateral and medial subregions. pQCT scans (XCT-3000, Stratec, Germany) of the 4 and 38% sites of the tibia, and 4 and 66% sites of the radius were conducted to determine a range of geometric and bone structural strength indices. Intervention effects were examined using univariate ANCOVA of percent change, and repeated measures ANCOVA of raw baseline and follow-up data, controlling for initial values, using intention-to-treat and per-protocol approaches.

Results: Ninety-three men (67.1 ± 7.5yrs, 175.2 ± 6.7cm, 82.1 ± 11.6kg, 26.7 ± 3.5kg/m^2) with lower than average aBMD (LS T-score -0.06 ± 1.04 , FN T-score -1.58 ± 0.58, TH T-score -1.00 ± 0.58) were recruited, and designated CON (n = 26) or randomised to HiRIT (n = 34) or IAC (n = 33). Compliance to the supervised exercise programs did not differ (HiRIT, 77.8 ± 16.6% versus IAC, 78.5 ± 14.8%, p = 0.872). HiRIT improved medial FN cortical thickness compared with CON (5.6 ± 1.7% versus -0.1 ± 1.9%, p = 0.028) and IAC (5.6 ± 1.7% versus 0.7 ± 1.7%, p = 0.044). Distal tibia total BMC, vBMD, area and bone strength index, and trabecular BMC and bone strength index all declined for CON compared with maintenance for both HiRIT and IAC (all p < 0.05). HiRIT maintained distal tibia trabecular area compared with a loss in CON (0.2 ± 0.5% versus -1.6 ± 0.5%, p = 0.013). HiRIT and IAC maintained distal radius total BMC compared with loss in CON (-0.1 ± 0.7% versus -3.7 ± 0.8%, p = 0.001; 1.3 ± 0.7% versus -3.7 ± 0.8%, p < 0.001, respectively). HiRIT and IAC maintained distal radius total bone strength index compared with loss in CON (1.4 ± 1.4% versus -6.0 ± 1.6%, p = 0.001; 0.2 ± 1.3% versus -6.0 ± 1.6%, p = 0.004, respectively). HiRIT reduced proximal radius cortical area compared with CON (-3.1 ± 1.0% versus 1.1 ± 1.2%, p = 0.011) and IAC (-3.1 ± 1.0% versus -0.2 ± 1.0%, p = 0.042). No between-group differences were detected in any pQCT-derived bone outcome at the diaphyseal tibia 38% site.

Conclusion: Findings indicate that supervised HiRIT provides a positive stimulus to cortical bone at the medial FN compared with supervised IAC exercise, and both HiRIT and IAC preserve bone strength at the distal tibia and distal radius. These effects may translate into a reduced risk of lower and upper extremity fracture in middle-aged and older men with low bone mass.

Keywords:

Bone geometry; Exercise training; Fracture prevention; Older men; Osteoporosis; Peripheral Quantitative Computed Tomography

Abbreviations:

1RM, one repetition maximum; 3D, three-dimensional; aBMD, areal bone mineral density; BMC, bone mineral content; BMI, body mass index; BPAQ, Bone-specific Physical Activity Questionnaire; BSI, bone strength index; BW, body weight; CI, confidence interval; DXA, Dual-energy X-ray Absorptiometry; FN, femoral neck; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; LIFTMOR-M, Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men; LS, lumbar spine; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography; QCT, Quantitative Computed Tomography; SND, skeletally non-dominant; SSIp, polar strength strain index; TH, total hip; vBMD, volumetric bone mineral density; vGRF, vertical ground reaction force.

1 Introduction

For every one standard deviation decrease in areal bone mineral density (aBMD) the incidence of fracture increases two-fold [1], thus individuals with osteoporotic aBMD have the highest risk of incident fracture. Nevertheless, most fragility fractures occur in individuals who are not classified as osteoporotic from DXA-derived aBMD. For instance, data from a large population-based study of postmenopausal Australian women over the age of 60 indicated around 70% of all low trauma fractures occurred in women who did not meet the ≤ -2.5 aBMD T-score definition of osteoporosis. In fact, 56.5% of fractures occurred in women with osteopenia and 16.6% in women with normal aBMD [2]. The Dubbo Osteoporosis Epidemiology Study of community-dwelling men and women aged over 60 similarly reported over half of fractures occur when aBMD is in the osteopenic (42%) or normal (12%) range [3].

While the mineral density of bone provides primarily a surrogate estimate of whole bone mass and strength, bone morphology (size, spatial distribution and shape) contributes directly to the ability of a bone to resist fracture [4]. Imaging modalities beyond areal DXA such as Quantitative Computed Tomography (QCT) and peripheral Quantitative Computed Tomography (pQCT) are required to quantify geometric parameters of bone strength, and to differentiate cortical and trabecular compartments. Bone strength indices estimated from these 3D imaging technologies are able to predict fragility fracture, sometimes with greater accuracy than aBMD alone. The Osteoporotic Fractures in Men Study found that pQCT-derived bone geometry and strength parameters at the radius and tibia were negatively associated with risk of incident osteoporotic fracture, even after adjusting for DXA-derived femoral neck (FN) aBMD [5]. For example, each standard deviation reduction in diaphyseal bone geometric parameters (total and cortical cross-sectional area, and periosteal circumference) at the 33% site of the radius and tibia was associated with a 40-70% increased risk of non-vertebral fragility fracture after adjusting for age, body mass index and FN aBMD [5].

Few investigations of therapeutic exercise for bone have included bone morphology outcomes, and male studies are rare. Only three trials including middle-aged and older men [6-8] and one mixed sex trial [9] have been conducted with the goal to reduce risk of fragility fracture by modifying geometric parameters of bone strength. The exercise protocols implemented in those studies varied by mode, intensity, frequency and duration, and participant heterogeneity, and an absence of upper limb involvement further limited the ability to translate findings into exercise recommendations to optimise bone structure and strength in men. Thus, further examination of the response of bone strength parameters to targeted exercise training in this demographic was required.

We have previously reported beneficial effects of high-intensity progressive resistance and impact training (HiRIT) and machine-based isometric axial compression (IAC) training in the LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) semi-randomised controlled trial preliminary findings on aBMD [10]. The aim of the present work was to determine the effects of HiRIT or IAC exercise on geometric and biomechanical indices of strength at the proximal femur, tibia and radius in middle-aged and older men with osteopenia and osteoporosis, in comparison with a matched but self-selected control group who followed their usual lifestyle activities during the trial. It was hypothesised that middle-aged and older men with osteopenia and osteoporosis participating in supervised HiRIT would have greater improvements in parameters of bone geometry and indices of bone biomechanical strength at the proximal femur, tibia and radius than machine-based IAC training or control.

2 Materials and Methods

2.1 Study design

The LIFTMOR-M trial was a single-centre, three-arm, eight-month, semi-randomised controlled exercise intervention trial. The study protocol has been published [11]. Study recruitment ran from May 2016 to July 2018, and the intervention was completed by April 2019. Primary and secondary outcomes of the LIFTMOR-M trial, including anthropometrics, aBMD, body composition, muscle cross sectional area and density, functional performance, muscle strength, compliance and adverse events (injuries, falls and fractures) have been reported [10] and are currently under review elsewhere. The sample size was calculated based on the primary outcome DXA-derived femoral neck aBMD. A total of 64 participants per group were required to detect 80% power, with $\alpha = 0.05$, and accounting for a 20% dropout rate. The current report comprises the findings of analyses of secondary outcomes including geometric and biomechanical indices of bone strength of the proximal femur, and distal and proximal tibia and radius.

2.2 Ethical approval

All research activities were conducted in accordance with the *Declaration of Helsinki*. The trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR12616000344493), and approved by the Griffith University Human Research Ethics Committee (AHS/07/14/HREC). Written informed consent was obtained from all participants.

2.3 Participants and allocation

Participant recruitment and flow through the trial have been comprehensively described elsewhere (manuscript under review). In brief, we recruited community-dwelling, middle-aged and older men ($\geq$ 45 years of age) with osteopenia (T-score -1.0 to -2.5) or osteoporosis (T-score below -2.5) at the lumbar spine, FN and/or total hip (TH) from the Gold Coast and surrounding locale in Queensland, Australia. Following trial registration, the originally stipulated minimum age of eligibility (being 50 years) was reduced to 45 years. Exclusion criteria were as follows: musculoskeletal or neurological conditions affecting the ability to participate in high-intensity exercise, unstable cardiovascular or respiratory disease, medical conditions or medications known to affect bone metabolism (with the exception of calcium and vitamin D supplementation, and/or ≥ 12 months of stable dose osteoporosis pharmacotherapy), metal implants, excessive radiation exposure, cancer, recent fracture or lower extremity surgery, or current engagement in high-intensity resistance training and/or high-impact-type exercise. High-impact exercise was defined as current, regular participation in organised or structured high-intensity activity including impact such as plyometric-type training, sprint training, fight sports and martial arts or Master's level competitive training. Eligible participants were block randomised, stratified by the presence (≥ 12 months exposure) or absence (lack of exposure) of osteoporosis pharmacotherapy with a 1:1 allocation ratio (block size of eight), to either HiRIT or IAC using sequentially numbered, opaque, sealed, envelopes. The computer-generated randomisation sequence was created by a researcher external to the trial, and the allocation sequence was concealed from both the tester and participant until completion of the initial testing session. It is not possible to blind participants to an exercise intervention, however, neither study hypotheses nor an expectation of superiority of either exercise protocol was conveyed to participants.

2.4 Exercise interventions

Detailed information on the exercise training protocols has been published elsewhere [11]. Sessions were undertaken twice weekly, on non-consecutive days, for eight months in the School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia and supervised by a qualified Exercise Scientist. Compliance with the allocated exercise program was recorded and expressed as the percentage of the maximum possible 70 supervised training sessions over the eight-month intervention period.

2.4.1 High-intensity progressive resistance and impact training program

The compound movement, barbell-based resistance training component consisted of five sets of five repetitions (≥ 80-85% of one repetition maximum) of the three fundamental exercises, the deadlift, squat and overhead press. Exercises were performed at a moderate contraction velocity (one second concentric, two second eccentric), at a 2-0-1 tempo. Sets were interspersed with a one-minute rest. During the initial two-week familiarisation period, low-load variants of the fundamental exercises were performed, with a focus on technique development and spine sparing movement patterns (i.e. learning the hip hinge and avoiding spine flexion). One repetition maximum (1RM) testing for the deadlift and squat exercises were performed at weeks 12 and 24 to guide weight progression. Prior to determination of 1RM, participants subjectively rated exercise intensity using the 6-20 point Borg Rating of Perceived Exertion (RPE) Scale, aiming for an RPE of ≥ 16 which corresponds to the high-intensity domain. The impact component consisted of five sets of five repetitions of jumping chin-ups with a firm, flat-footed landing. Impact intensity was progressed by increasing jump height and moving towards a more straight-legged landing with heel contact. Exercise order was as follows: deadlifts, alternating sets of overhead press and impact, and lastly squats. Peak vertical ground reaction force (vGRF) during landing for the jumping chin-up exercise was determined in a random subgroup of HiRIT participants using a Leonardo Mechanograph Ground Reaction Force Plate (Novotec Medical GmbH, Pforzheim, Germany). A transient increase in vGRF with jumping chin-ups during landing approaching 7.27 ± 1.36 kN was observed, corresponding to 10.43 ± 2.10 times body weight (BW) when normalised. Witzke and Snow [12] provide guidelines for impact loading intensity domains using vGRF, with high-intensity impact loading being ≥ four times BW, moderate-intensity two to four times BW, and low intensity ≤ two times BW. Thus, jumping chin-up landings were within the high-intensity loading domain.

2.4.2 Isometric axial compression exercise program

One self-initiated near-maximal five-second isometric contraction (≥ 80-85% of 1RM) was performed for the seated chest press, seated leg press, core and arm pull, and vertical lift on the bioDensity™ (Performance Health Systems, Chicago, USA) machine. During the initial two-week familiarisation period, low intensity repetitions were performed focusing on technique (at approximately 50% of 1RM). Participants subjectively rated exercise intensity using the 6-20 point RPE scale and were instructed to achieve an RPE of $\geq$ 16 in order to achieve a high-intensity equivalent for each five-second isometric contraction. Integrated monitors provide real-time force production feedback from load cells integrated in the machine, allowing modulation of the force applied by the participant against fixed external resistance. Although the twice-weekly training protocol implemented differs from the bioDensity™ manufacturer once-weekly recommendation, in order to match treatment exposure (i.e. number of training sessions per week) with the HiRIT group, we implemented twice-weekly supervised sessions.

2.5 Control group activities

A sample of age-matched men, recruited and screened using identical criteria to the two exercise arms, but self-selecting to 'no intervention', formed a non-randomised parallel control group (CON). CON participants were instructed to continue with their usual daily routines and not to alter their physical activity levels during the eight-month trial period. In order to track alterations to physical activity engagement and diet across the trial period, lifestyle diaries were issued in which any relevant changes were documented.

2.6 Outcomes

All outcomes were assessed at baseline and eight months in the Bone Densitometry Research Laboratory at Griffith University, Gold Coast, Queensland, Australia. The same investigator performed and analysed all outcome measures. Analyses of pQCT and DXA scans were verified by a blinded investigator.

2.6.1 *Anthropometrics and lifestyle characteristics*

Height was assessed without shoes using the stretch stature method with a wall-mounted stadiometer (Model 216, Seca, Hamburg, Germany). Weight in light clothing was measured using a calibrated mechanical beam scale (Model 700, Seca, Hamburg, Germany). Body mass index (BMI) was calculated as mass divided by height squared. Physical activity participation and daily calcium intake were estimated using validated questionnaires. Lifetime exposure to osteogenic physical activity was quantified with the Bone-specific Physical Activity Questionnaire (BPAQ), as previously described [13]. Responses were scored using a custom-designed online program (http://www.fithdysign.com/BPAQ/) to generate a total BPAQ score (tBPAQ) reflecting bone-relevant exercise history. Daily calcium intake was estimated from a calcium-focused food frequency questionnaire, the AusCal [14]. AusCal questionnaire responses were analysed using Australian-specific dietary analysis software (FoodWorks Version 7, Xyris Software, Brisbane, Australia).

2.6.2 *Dual-energy X-ray Absorptiometry*

Standard DXA scans of the skeletally non-dominant proximal femur were performed (Medix DR, Medilink, Mauguio, France). As previous findings have identified the *functionally* dominant lower extremity is *skeletally* non-dominant (normally has lowest bone mass) [15], the functionally dominant leg was examined. Daily scans of the manufacturer supplied phantom were undertaken throughout the course of the study to maintain quality control.

Standard DXA scans of the proximal femur were analysed using three-dimensional (3D) hip analysis software (DMS Imaging Group, Mauguio, France) to estimate parameters of content, geometry and vBMD of the trabecular, cortical and total (trabecular plus cortical) bone compartments for the FN and TH regions of interest. Parameters at the FN and TH included: total, trabecular and cortical bone mineral content (BMC), volume and vBMD, along with mean total, anterior, posterior, medial and lateral FN cortical thickness. The 3D hip software analysis algorithm uses a statistical shape and density model of the proximal femur developed from a database of QCT scans of Caucasian men and women (n = 111) to produce a subject-specific model of proximal femur shape and density distribution, providing estimates of trabecular and cortical vBMD, and cortical thickness [16]. The modelling pipeline is fully automated following the semi-automated placement of three anatomical landmarks that are positioned on the standard DXA image of the proximal femur. All analyses were performed in accordance with manufacturer guidelines. Technical software details have been described elsewhere [16]. Correlation coefficients between 3D hip software analysis and QCT of FN and TH trabecular vBMD (r = 0.80-0.86), cortical vBMD (r = 0.85-0.93), and mean cortical thickness (r = 0.66-0.91) were high (n = 157) [16]. In our laboratory, the coefficients of variation for 3D hip outcomes range from 1.03% to 1.99% at the TH, 0.83% to 2.11% for the FN, and 1.55% to 2.71% for FN cortical thickness in a sample of men.

2.6.3 Peripheral Quantitative Computed Tomography

Scans of the skeletally non-dominant leg and forearm were performed using pQCT (Stratec XCT-3000, Medizintechnik GmbH, Pforzheim, Germany) to obtain geometric, volumetric and biomechanical indices of bone strength; a detailed description of acquisition and analyses has been published elsewhere [11]. Skeletal dominance was determined from functional dominance, with the functionally dominant lower extremity being the skeletally non-dominant lower limb and the functionally non-dominant upper extremity being the skeletally non-dominant upper limb [15]. Tibia and forearm length were measured to the nearest millimetre with an anthropometric ruler. Tibial length was measured as the distance from the medial tibial plateau to the tip of the medial malleolus. Forearm length was measured as the distance from the tip of the olecranon process to the tip of the ulnar styloid process. Briefly, we acquired two image slices of the tibia (4 and 38% of tibial length proximal to the distal endplate) and two image slices of the radius (4 and 66% of radius length proximal to the distal endplate). The scan parameters were voxel size, slice thickness and scan speed of 0.5 mm, 2.3 mm, and 25 mm/sec, respectively. A planar scout view over the joint line was acquired in order to place the anatomic reference line. Analyses were conducted using host software (Version 6.20, Stratec Medizintechnik GmbH, Pforzheim, Germany). For the distal tibia and distal radius (4% site; trabecular bone dominant) bone outcomes were: total BMC, vBMD and area; trabecular BMC, vBMD and area; and total and trabecular bone strength index (BSI). Total and trabecular BSI were determined from measures of density and area where BSI = total density^2 × total area, reflecting bone resistance to compression [17]. For the diaphyseal tibia (38% site; cortical bone dominant) and proximal radius (66% site; cortical bone dominant) bone outcomes were: cortical BMC, vBMD, area and thickness; periosteal and endocortical circumference; polar section modulus; and polar strength strain index (SSIp). SSIp reflects diaphyseal resistance to bending and torsional bone strength [17]. In our lab, the coefficients of variation for pQCT measures of the tibia range from 0.21% to 2.71%, and from 0.62% to 4.65% for the radius. Quality control was maintained with daily scanning of the manufacturer provided phantom across the intervention period, and all scans were performed by a single certified technician. Scans were reviewed for motion artefact and repeated if significant movement was detected for bone and soft tissue analysis in line with the qualitative grading scale developed by Blew and colleagues [18]. If artefact was present in the second scan (i.e. images graded four or five with movement streaking and/or disruption of cortical shell evident) the participant was excluded from undergoing a third pQCT scan in line with radiation exposure guidelines. Scans graded less than three were considered valid for inclusion. Overall, one radius scan at baseline for HiRIT and one follow-up radius scan for IAC were excluded due to motion artefact occurring during the first and second pQCT scans resulting in poor scan quality (i.e. graded four and five, respectively). We were unable to obtain baseline tibia and radius scans on five participants (CON n = 3, HiIRT n = 2) due to pQCT device maintenance at the time of testing. A comparison between those who did and those who did not undergo baseline pQCT revealed no differences in characteristics (data not reported). Thus, a total of 88 tibial scans (CON n = 23, HiRIT n = 32, IAC n = 33) and 87 radius scans (CON n = 23, HiRIT n = 31, IAC n = 33) are included in the intention-to-treat analyses.

2.7 Statistical analysis

Statistical analyses were undertaken using SPSS statistical software version 25.0 (SPSS Inc., USA). Descriptive statistics were generated for participant characteristics, biometrics and all dependent variables. Between-group differences at baseline were compared using one-way analysis of variance (ANOVA) for normally distributed continuous data, and Chi-Square (X^2) for categorical data. Repeated measures analysis of covariance (ANCOVA) was used to determine main effects using raw baseline and follow-up data, and univariate ANCOVA was conducted to analyse percent change. Initial values were applied as a covariate if a significant difference was detected between-groups at baseline. To adjust for multiple comparisons, Fisher's LSD method was applied. For intention-to-treat (ITT) analyses all randomised participants were included regardless of withdrawal or compliance, 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 also undertaken including HiRIT and IAC participants who achieved $\geq 70\%$ training program compliance. Statistical significance was set at $p < 0.05$.

3 Results

3.1 Participant characteristics at baseline

Participant flow through the study is presented in Figure 1. In total, 93 eligible participants underwent the full suite of testing at baseline; 26 were designated CON, or randomly assigned to HiRIT (n = 34) or IAC (n = 33). At baseline, the combined sample averaged 67.1 ± 7.5 years, weighed 82.1 ± 11.6 kg, and was 175.2 ± 6.7 cm tall. Five participants designated CON were lost to follow-up (could not be contacted at the time of follow-up testing [n = 4], or withdrew due to musculoskeletal injury [n = 1]). A total of 60 participants (HiRIT n = 30, IAC n = 30) completed the supervised exercise training arms of the LIFTMOR-M trial. 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 IAC participants withdrew (travel and family commitments [n = 2], or medical condition unrelated to the intervention [n = 1]).

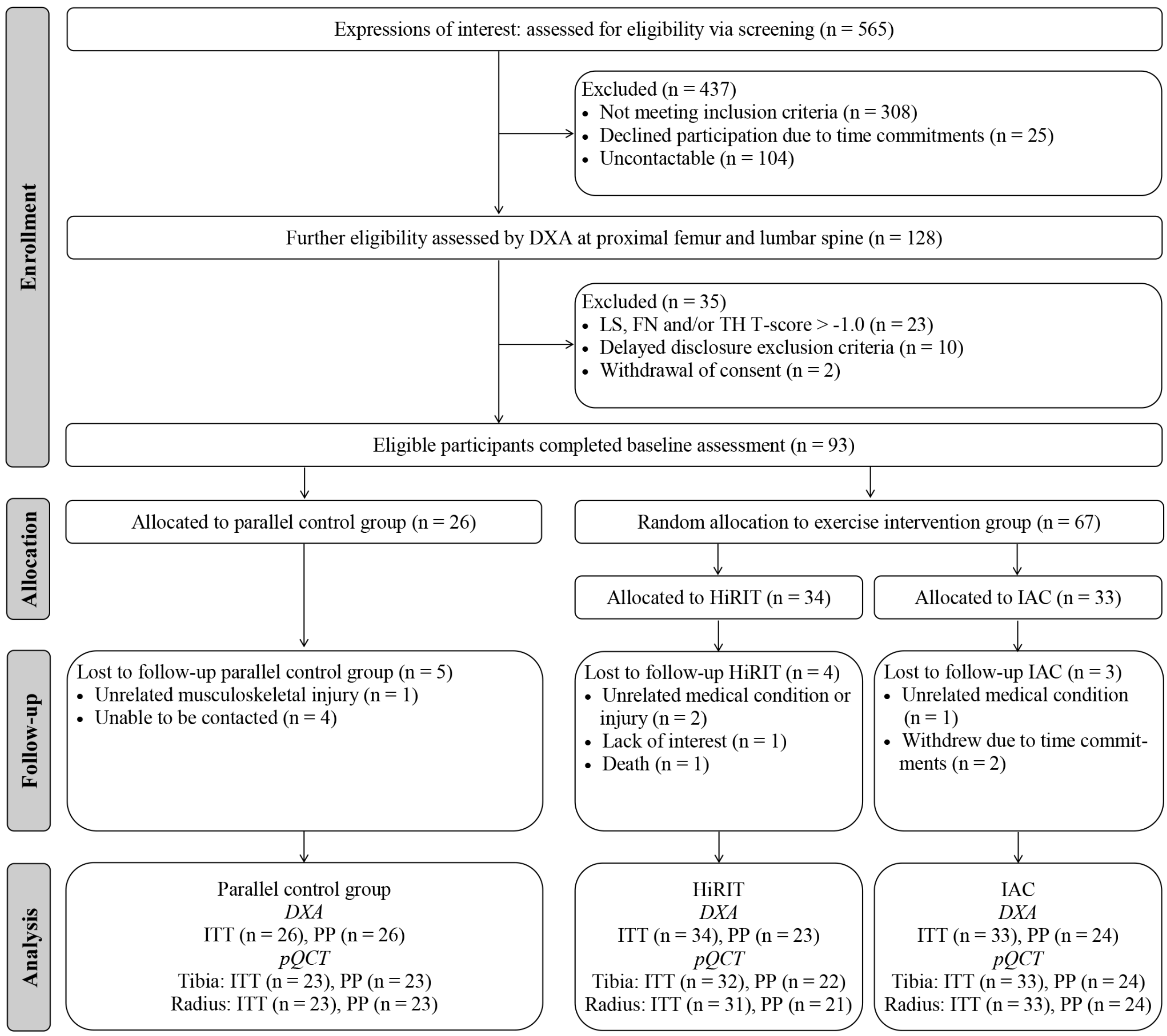

Figure 1. CONSORT diagram of participant flow through the LIFTMOR-M study. Abbreviations: DXA, Dual-energy X-ray Absorptiometry; FN, femoral neck; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; LS, lumbar spine; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography; TH, total hip.

Participant characteristics at baseline are presented in Table 1. At baseline, CON exhibited higher FN aBMD, T-score, trabecular vBMD and total vBMD, and TH trabecular vBMD and total vBMD than HiRIT and IAC. Distal tibia (4% site) total BMC, total vBMD and total BSI, distal radius (4% site) total BMC, and proximal radius (66% site) cortical BMC, area and thickness were also higher for CON than HiRIT and IAC. Distal radius trabecular BSI was higher for CON than IAC. Proximal radius SSIp was higher for CON than HiRIT. Any potential influence of those differences was managed by controlling for initial values in relevant analyses of treatment effects.

Compliance to the training programs did not differ between groups (HiRIT 77.8 ± 16.6% versus IAC 78.5 ± 14.8%, $p = 0.872$). When only those who achieved ≥ 70 % training compliance were included in the comparison, the lack of difference in compliance remained between HiRIT (85.9 ± 6.2%, n = 23) and IAC (84.5± 7.4%, n = 24) ($p = 0.466$).

Table 1. Participant characteristics at baseline, mean ± SD (n = 93)

Characteristic	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%)	0.444 [a]
Alendronate	0 (0.0%)	1 (2.9%)	1 (3.0%)	
Denosumab	0 (0.0%)	1 (2.9%)	1 (3.0%)	
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%)	
aBMD, 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
T-score, SD				
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	-1.78 ± 0.54	0.004 *
Total hip	-0.80 ± 0.58	-1.08 ± 0.62	-1.07 ± 0.51	0.125
Total BPAQ, unitless	39.9 ± 21.4	27.2 ± 20.1	34.3 ± 21.9	0.073
Calcium intake, mg/day	743 ± 426	897 ± 412	1019 ± 603	0.108
Supplementation, n (%)	4 (15.4%)	4 (11.8%)	5 (15.2%)	0.896 [a]

Abbreviations: aBMD, areal bone mineral density; BMI, body mass index; BPAQ, Bone-specific Physical Activity Questionnaire; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression.

[a] X^2 test. [b] Calcium and/or vitamin D supplementation. * Between-group difference ($p \leq 0.05$).

3.2 Eight-month change in DXA-derived 3D hip analysis outcomes at the proximal femur

Eight-month change in 3D hip analysis outcomes are presented in Table 2 (FN), Table 3 (TH), and Table 4 (FN cortical thickness) from ITT analyses. There were no between-group differences in FN or TH BMC, volume and vBMD percent change detected from univariate ANCOVA or absolute change from RMANCOVA. Univariate ANCOVA revealed HiRIT improved percent change in FN medial cortical thickness more than CON (5.6 ± 1.7% versus -0.1 ± 1.9%, $p = 0.028$) and IAC (5.6 ± 1.7% versus 0.7 ± 1.7%, $p = 0.044$) (Figure 2). Within-group analyses indicated that CON improved FN trabecular (0.70 ± 0.31 cm^3, $p = 0.027$) and total volume (0.75 ± 0.32 cm^3, $p = 0.024$), and TH trabecular (2.63 ± 0.92 cm^3, $p = 0.005$) and total volume (2.39 ± 1.00 cm^3, $p = 0.019$). HiRIT improved FN cortical volume (0.09 ± 0.05 cm^3, $p = 0.041$). There were no within-group effects in 3D hip analysis outcomes following IAC. Within-group analyses revealed HiRIT improved total cortical thickness (0.04 ± 0.02 mm, $p = 0.049$) as well as FN medial cortical thickness (0.10 ± 0.03 mm, $p = 0.002$).

Results of the PP analyses of 3D hip outcomes (including participants with ≥ 70 % compliance, n = 73) are presented for the FN in Supplemental Table 1, and the TH in Supplemental Table 2. No between-group differences were detected at the FN or TH, and the within-group change in FN cortical volume was no longer significant for HiRIT. PP analyses of FN cortical thickness (including participants with ≥ 70% compliance, n = 73) revealed no significant between- or within-group differences (Supplemental Table 3).

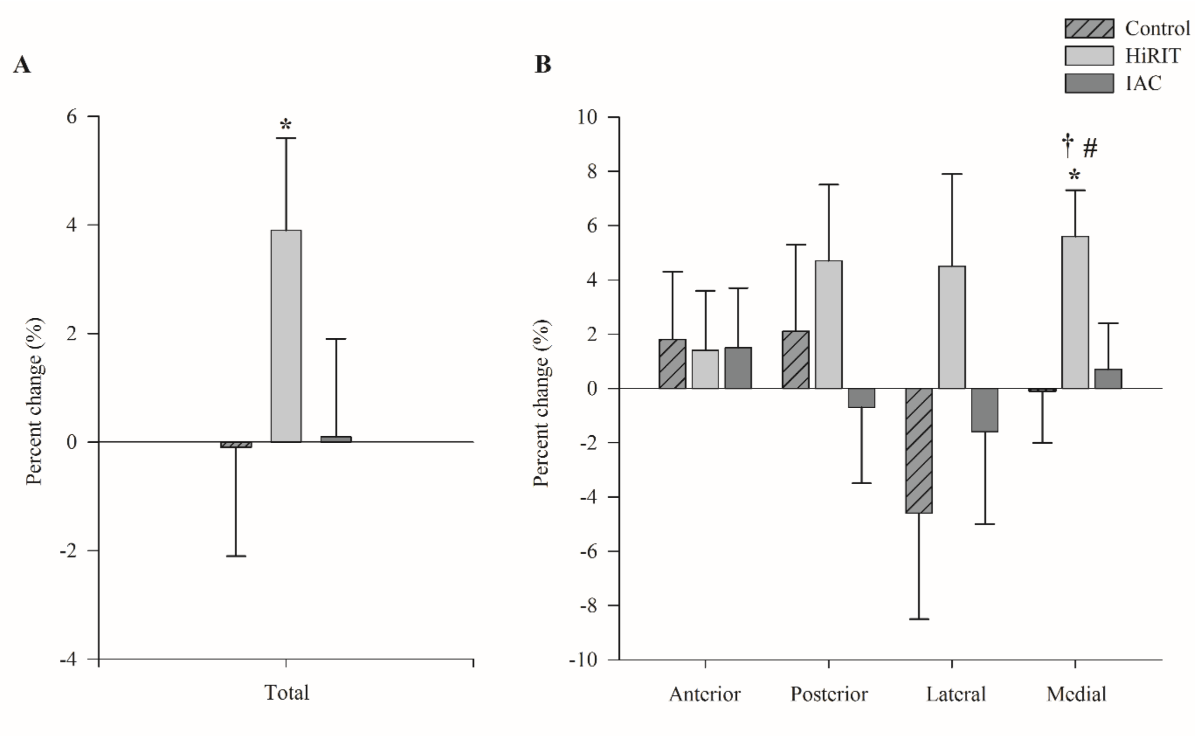

Figure 2. Eight-month percent change (mean ± SE) in cortical thickness for the (A) total femoral neck, and (B) femoral neck subregions of the skeletally non-dominant proximal femur. ITT data n = 93; Control n = 26, HiRIT n = 34, IAC n = 33. * Indicates within-group change from baseline ($p \leq 0.05$); Indicates between-group difference in percent change ($p \leq 0.05$): † HiRIT versus Control, # HiRIT versus IAC. Abbreviations: DXA, Dual-energy X-ray Absorptiometry; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat.

Table 2. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis outcomes at the femoral neck (ITT analysis, n = 93)

	Control (n = 26)			HiRIT (n = 34)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Trabecular										
BMC, g	2.70 ± 0.53	2.81 ± 0.47	6.4 ± 6.7 (-7.0, 19.8)	2.51 ± 0.49	2.57 ± 0.57	3.5 ± 5.9 (-8.2, 15.2)	2.59 ± 0.70	2.77 ± 0.88	11.4 ± 6.0 (-0.5, 23.3)	0.639
Volume, cm^3	15.50 ± 2.91	16.20 ± 2.83*	5.4 ± 2.2 (1.0, 9.8)	15.93 ± 2.56	16.20 ± 2.67	1.9 ± 2.0 (-2.0, 5.7)	16.78 ± 2.61	17.08 ± 2.57	2.5 ± 2.0 (-1.4, 6.5)	0.468
vBMD, g/cm^3	0.176 ± 0.032^	0.177 ± 0.034	3.0 ± 3.9 (-4.7, 10.6)[a]	0.159 ± 0.025^	0.161 ± 0.035	1.3 ± 3.3 (-5.2, 7.8)[a]	0.154 ± 0.032^	0.161 ± 0.039	4.7 ± 3.4 (-2.0, 11.4)[a]	0.768
Cortical										
BMC, g	1.56 ± 0.38	1.61 ± 0.37	4.6 ± 2.6 (-0.7, 9.8)	1.49 ± 0.31	1.54 ± 0.31	4.4 ± 2.3 (-0.2, 9.0)	1.52 ± 0.28	1.57 ± 0.27	4.2 ± 2.4 (-0.5, 8.9)	0.995
Volume, cm^3	2.64 ± 0.63	2.69 ± 0.58	3.1 ± 2.0 (-0.9, 7.0)	2.57 ± 0.49	2.66 ± 0.48*	4.2 ± 1.7 (0.8, 7.7)	2.66 ± 0.50	2.66 ± 0.40	1.2 ± 1.8 (-2.3, 4.7)	0.462
vBMD, g/cm^3	0.592 ± 0.042	0.601 ± 0.043	1.6 ± 2.5 (-3.3, 6.6)	0.578 ± 0.046	0.578 ± 0.035	0.2 ± 2.2 (-4.1, 4.5)	0.575 ± 0.047	0.594 ± 0.110	3.6 ± 2.2 (-0.7, 8.0)	0.542
Total										
BMC, g	4.26 ± 0.82	4.42 ± 0.73	5.2 ± 4.5 (-3.8, 14.2)	4.00 ± 0.71	4.11 ± 0.74	3.5 ± 4.0 (-4.3, 11.4)	4.12 ± 0.87	4.33 ± 1.06	7.9 ± 4.0 (0.0, 15.9)	0.734
Volume, cm^3	18.14 ± 3.43	18.88 ± 3.32*	4.9 ± 2.0 (1.0, 8.8)	18.50 ± 2.92	18.86 ± 3.04	2.1 ± 1.7 (-1.3, 5.5)	19.44 ± 3.04	19.74 ± 2.81	2.2 ± 1.7 (-1.2, 5.7)	0.497
vBMD, g/cm^3	0.236 ± 0.032^	0.237 ± 0.033	2.0 ± 2.6 (-3.2, 7.2)[a]	0.217 ± 0.027^	0.220 ± 0.034	1.3 ± 2.2 (-3.1, 5.7)[a]	0.212 ± 0.029^	0.219 ± 0.039	3.1 ± 2.3 (-1.4, 7.6)[a]	0.844

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p \leq 0.05$. * Within-group change from baseline $p \leq 0.05$.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Table 3. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis outcomes at the total hip (ITT analysis, n = 93)

	Control (n = 26)			HiRIT (n = 34)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Trabecular										
BMC, g	15.06 ± 2.44	15.19 ± 2.45	1.2 ± 3.8 (-6.4, 8.8)	14.21 ± 2.59	14.30 ± 2.81	1.8 ± 3.3 (-4.9, 8.4)	14.29 ± 3.52	14.85 ± 3.46	6.3 ± 3.4 (-0.4, 13.1)	0.522
Volume, cm^3	91.62 ± 14.26	94.25 ± 13.24*	3.3 ± 1.1 (1.2, 5.4)	93.04 ± 14.86	94.21 ± 15.35	1.4 ± 0.9 (-0.5, 3.2)	97.45 ± 13.32	98.69 ± 12.47	1.5 ± 0.9 (-0.3, 3.4)	0.338
vBMD, g/cm^3	0.167 ± 0.027^	0.163 ± 0.026	-0.2 ± 3.1 (-6.5, 6.0)[a]	0.154 ± 0.021^	0.154 ± 0.030	0.4 ± 2.7 (-4.9, 5.7)[a]	0.146 ± 0.027^	0.151 ± 0.030	3.0 ± 2.8 (-2.5, 8.5)[a]	0.707
Cortical										
BMC, g	10.76 ± 1.89	10.73 ± 1.98	-0.2 ± 2.7 (-5.6, 5.3)	9.97 ± 1.87	10.12 ± 1.55	3.0 ± 2.4 (-1.7, 7.8)	10.49 ± 1.54	10.87 ± 1.74	4.6 ± 2.4 (-0.2, 9.4)	0.425
Volume, cm^3	16.76 ± 2.99	16.54 ± 2.92	-1.0 ± 1.7 (-4.3, 2.3)	15.89 ± 2.64	16.31 ± 2.27	3.5 ± 1.4 (0.6, 6.3)	16.83 ± 2.51	16.93 ± 2.38	0.9 ± 1.5 (-2.0, 3.9)	0.125
vBMD, g/cm^3	0.645 ± 0.059	0.651 ± 0.053	1.1 ± 2.5 (-3.9, 6.2)	0.627 ± 0.062	0.620 ± 0.039	-0.6 ± 2.2 (-5.0, 3.7)	0.625 ± 0.057	0.648 ± 0.113	4.1 ± 2.2 (-0.4, 8.6)	0.320
Total										
BMC, g	25.82 ± 3.87	25.91 ± 3.85	0.5 ± 3.1 (-5.7, 6.6)	24.18 ± 4.14	24.41 ± 4.07	2.1 ± 2.7 (-3.2, 7.5)	24.77 ± 4.71	25.71 ± 4.79	5.3 ± 2.7 (-0.1, 10.8)	0.483
Volume, cm^3	108.38 ± 16.78	110.77 ± 15.89*	2.5 ± 1.0 (0.6, 4.4)	108.93 ± 17.13	110.52 ± 17.25	1.6 ± 0.8 (-0.1, 3.3)	114.28 ± 15.48	115.61 ± 14.33	1.4 ± 0.9 (-0.3, 3.1)	0.658
vBMD, g/cm^3	0.240 ± 0.031^	0.235 ± 0.026	0.2 ± 2.5 (-4.8, 5.2)[a]	0.223 ± 0.026^	0.223 ± 0.034	0.1 ± 2.1 (-4.1, 4.4)[a]	0.217 ± 0.028^	0.223 ± 0.036	2.3 ± 2.2 (-2.0, 6.7)[a]	0.735

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p \leq 0.05$. * Within-group change from baseline $p \leq 0.05$.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Table 4. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis of femoral neck cortical thickness (ITT analysis, n = 93)

	Control (n = 26)			HiRIT (n = 34)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Total, mm	1.20 ± 0.18	1.19 ± 0.16	-0.1 ± 2.0 (-4.0, 3.9)	1.15 ± 0.15	1.19 ± 0.14*	3.9 ± 1.7 (0.5, 7.4)	1.15 ± 0.13	1.15 ± 0.14	0.1 ± 1.8 (-3.4, 3.6)	0.203
Subregion										
Anterior, mm	0.98 ± 0.17	0.99 ± 0.18	1.8 ± 2.5 (-3.2, 6.7)	0.97 ± 0.15	0.98 ± 0.15	1.4 ± 2.2 (-2.9, 5.7)	0.94 ± 0.12	0.94 ± 0.15	1.5 ± 2.2 (-2.9, 5.9)	0.993
Posterior, mm	0.98 ± 0.17	0.99 ± 0.17	2.1 ± 3.2 (-4.3, 8.4)	0.97 ± 0.17	1.00 ± 0.16	4.7 ± 2.8 (-0.9, 10.2)	0.93 ± 0.13	0.91 ± 0.18	-0.7 ± 2.8 (-6.3, 4.9)	0.398
Lateral, mm	0.65 ± 0.16	0.61 ± 0.15	-4.6 ± 3.9 (-12.3, 3.1)	0.58 ± 0.11	0.59 ± 0.11	4.5 ± 3.4 (-2.2, 11.2)	0.61 ± 0.11	0.60 ± 0.14	-1.6 ± 3.4 (-8.5, 5.2)	0.190
Medial, mm	2.09 ± 0.31	2.08 ± 0.27	-0.1 ± 1.9 (-3.9, 3.7)	2.01 ± 0.26	2.11 ± 0.26*	5.6 ± 1.7 (2.3, 8.9)†#	2.04 ± 0.23	2.04 ± 0.22	0.7 ± 1.7 (-2.6, 4.1)	**0.048**

Abbreviations: CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat.
* Within-group change from baseline p ≤ 0.05.
Between-group difference in % change p ≤ 0.05: † HiRIT vs Control, # HiRIT vs IAC. p-values represent between-group comparison of % change.

3.3 Eight-month change in pQCT-derived outcomes at the tibia 4% and 38% sites

Eight-month change in pQCT-derived outcomes at the distal tibia (4% site) are presented in Table 5 and Figure 3 (ITT). HiRIT effects were superior to CON for distal tibia total BMC (0.1 ± 0.3% versus -3.0 ± 0.4%, $p < 0.001$), total vBMD (0.0 ± 0.3% versus -0.8 ± 0.3%, $p = 0.050$), total area (0.0 ± 0.4% versus -2.1 ± 0.5%, $p = 0.001$), total BSI (0.1 ± 0.4% versus -3.9 ± 0.5%, $p < 0.001$), trabecular BMC (0.4 ± 0.4% versus -1.8 ± 0.5%, $p = 0.001$), trabecular area (0.2 ± 0.5% versus -1.6 ± 0.5%, $p = 0.013$), and trabecular BSI (0.7 ± 0.5% versus -1.9 ± 0.6%, $p = 0.001$). IAC maintained or lost less than CON in distal tibia total BMC (-0.4 ± 0.3% versus -3.0 ± 0.4%, $p < 0.001$), total vBMD (0.3 ± 0.2% versus -0.8 ± 0.3%, $p = 0.006$), total area (-0.7 ± 0.4% versus -2.1 ± 0.5%, $p = 0.027$), total BSI (0.0 ± 0.4% versus -3.9 ± 0.5%, $p < 0.001$), trabecular BMC (-0.4 ± 0.4% versus -1.8 ± 0.5%, $p = 0.038$) and trabecular BSI (-0.1 ± 0.5% versus -1.9 ± 0.6%, $p = 0.013$). Within-group analyses indicated CON lost distal tibia total BMC (-11.80 ± 1.44 mg, $p < 0.001$), total vBMD (-2.49 ± 0.88 mg/cm^3, $p = 0.006$), total area (-25.47 ± 5.95 mm^2, $p < 0.001$), total BSI (-0.05 ± 0.01 g^2/cm^4, $p < 0.001$), trabecular BMC (-4.90 ± 1.27 mg, $p < 0.001$), trabecular area (-15.80 ± 5.37 mm^2, $p = 0.004$) and trabecular BSI (-0.02 ± 0.00 g^2/cm^4, $p < 0.001$). No within-group changes were observed for HiRIT or IAC in ITT analysis of distal tibia outcomes. Results of the PP analyses (participants with ≥ 70% compliance) for distal tibia 4% site outcomes are presented in Supplemental Table 4, and largely reflect findings from the ITT analyses.

The results of the ITT analysis of intervention effects on pQCT-derived outcomes at the diaphyseal tibia (38% site) are presented in Table 6 and results of PP analyses are presented in Supplemental Table 5; no between- or within-group differences were detected in either case.

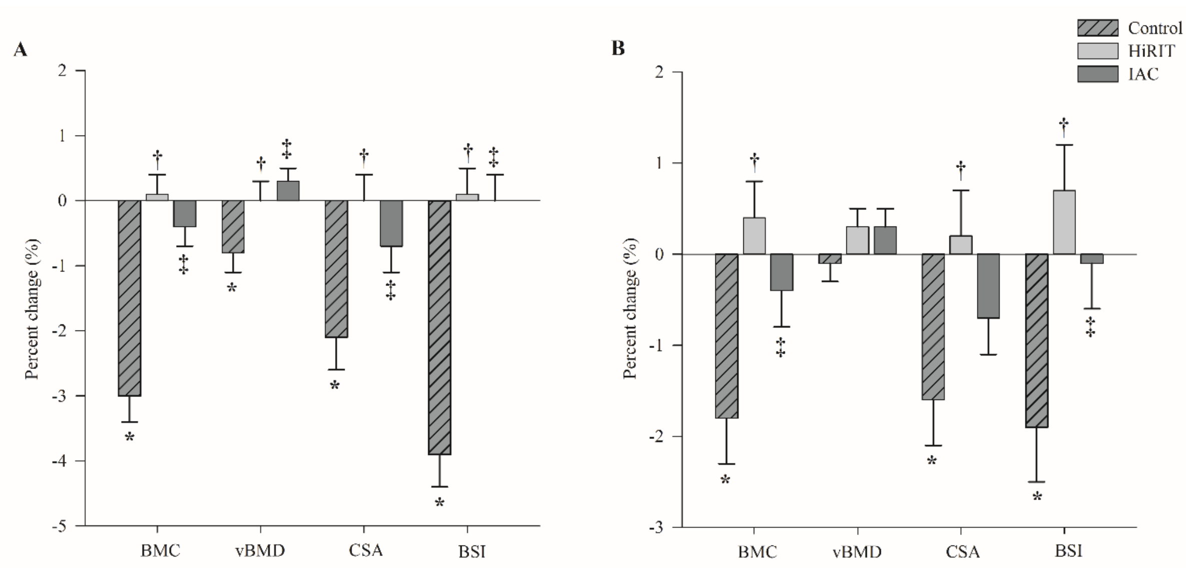

Figure 3. Eight-month percent change (mean ± SE) in pQCT-derived (A) total, and (B) trabecular bone outcomes at the skeletally non-dominant distal tibia (4% site). ITT analyses, n = 88 (n = 93 – 5 participants who did not undergo pQCT tibia scans at baseline); Control n = 23, HiRIT n = 32, IAC n = 33. * Indicates within-group change from baseline ($p \leq 0.05$); Indicates between-group difference in % change ($p \leq 0.05$): † HiRIT versus Control, ‡ IAC vs Control. Abbreviations: BMC, bone mineral content; BSI, bone strength index; CSA, cross-sectional area; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density.

Table 5. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the distal tibia 4% site (ITT analysis, n = 88)

	Control (n = 23)			HiRIT (n = 32)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Tibia 4% site										
Total BMC, mg	404.86 ± 46.17^	393.21 ± 45.27*	-3.0 ± 0.4 (-3.8, -2.2)[a]	363.10 ± 48.60^	362.96 ± 47.99	0.1 ± 0.3 (-0.6, 0.7)[a]†	377.46 ± 51.28^	376.42 ± 54.18	-0.4 ± 0.3 (-1.0, 0.3)[a]‡	**< 0.001**
Total vBMD, mg/cm^3	327.35 ± 35.02^	324.90 ± 36.28*	-0.8 ± 0.3 (-1.4, -0.2)[a]	302.22 ± 35.43^	302.16 ± 35.14	0.0 ± 0.3 (-0.5, 0.5)[a]†	300.45 ± 41.88^	301.43 ± 42.06	0.3 ± 0.2 (-0.2, 0.8)[a]‡	**0.022**
Total area, mm^2	1245.84 ± 157.49	1220.37 ± 159.99*	-2.1 ± 0.5 (-3.1, -1.1)	1209.94 ± 163.91	1209.06 ± 158.84	0.0 ± 0.4 (-0.8, 0.8)†	1266.63 ± 158.58	1257.76 ± 157.96	-0.7 ± 0.4 (-1.5, 0.1)‡	**0.005**
Total BSI, g^2/cm^4	1.33 ± 0.23^	1.28 ± 0.23*	-3.9 ± 0.5 (-4.8, -2.9)[a]	1.11 ± 0.24^	1.10 ± 0.24	0.1 ± 0.4 (-0.7, 0.9)[a]†	1.15 ± 0.28^	1.15 ± 0.29	0.0 ± 0.4 (-0.8, 0.8)[a]‡	**< 0.001**
Trabecular BMC, mg	275.24 ± 39.57	270.34 ± 39.17*	-1.8 ± 0.5 (-2.8, -0.8)	254.07 ± 41.74	254.88 ± 40.34	0.4 ± 0.4 (-0.4, 1.3)†	260.57 ± 39.14	259.64 ± 40.18	-0.4 ± 0.4 (-1.2, 0.4)‡	**0.005**
Trabecular vBMD, mg/cm^3	275.16 ± 28.80	274.81 ± 29.39	-0.1 ± 0.2 (-0.6, 0.3)	258.59 ± 31.97	259.30 ± 31.80	0.3 ± 0.2 (-0.1, 0.7)	254.49 ± 36.02	255.29 ± 35.97	0.3 ± 0.2 (0.0, 0.7)	0.209
Trabecular area, mm^2	1005.92 ± 142.43	990.13 ± 144.37*	-1.6 ± 0.5 (-2.7, -0.6)	987.31 ± 145.28	987.70 ± 140.03	0.2 ± 0.5 (-0.7, 1.1)†	1031.99 ± 143.04	1024.19 ± 141.45	-0.7 ± 0.4 (-1.6, 0.2)	**0.043**
Trabecular BSI, g^2/cm^4	0.76 ± 0.16	0.75 ± 0.15*	-1.9 ± 0.6 (-3.0, -0.8)	0.66 ± 0.17	0.67 ± 0.17	0.7 ± 0.5 (-0.2, 1.7)†	0.67 ± 0.17	0.67 ± 0.17	-0.1 ± 0.5 (-1.0, 0.9)‡	**0.002**

Abbreviations: BMC, bone mineral content; BSI, bone strength index; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography

^ Between-group difference at baseline $p \leq 0.05$. * Within-group change from baseline $p \leq 0.05$.

Between-group difference in % change $p \leq 0.05$: † HiRIT vs Control, ‡ IAC vs Control. [a] Adjusted for initial values. p-values represent between-group comparison of % change.

Note: 5 participants (Control n = 3, HiRIT n = 2) did not undergo pQCT tibia scans at baseline.

Table 6. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the diaphyseal tibia 38% site (ITT analysis, n = 88)

	Control (n = 23)			HiRIT (n = 32)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Tibia 38% site										
Cortical BMC, mg	405.42 ± 41.38	403.36 ± 40.39	-0.5 ± 0.3 (-1.1, 0.2)	393.68 ± 50.63	393.63 ± 50.80	0.0 ± 0.3 (-0.6, 0.5)	388.76 ± 40.32	389.85 ± 40.15	0.3 ± 0.3 (-0.2, 0.8)	0.203
Cortical vBMD, mg/cm^3	1141.93 ± 26.64	1141.05 ± 25.84	-0.1 ± 0.2 (-0.5, 0.3)	1143.46 ± 27.86	1143.68 ± 29.27	0.0 ± 0.2 (-0.3, 0.4)	1144.32 ± 25.87	1144.68 ± 26.29	0.0 ± 0.2 (-0.3, 0.4)	0.903
Cortical area, mm^2	355.12 ± 36.06	353.61 ± 35.50	-0.4 ± 0.3 (-1.1, 0.3)	344.11 ± 42.41	343.89 ± 41.61	0.0 ± 0.3 (-0.6, 0.5)	340.02 ± 37.25	340.82 ± 36.45	0.3 ± 0.3 (-0.3, 0.8)	0.333
Cortical thickness, mm	6.27 ± 0.60	6.26 ± 0.60	-0.1 ± 0.2 (-0.6, 0.3)	5.92 ± 0.75	5.93 ± 0.75	0.0 ± 0.2 (-0.4, 0.4)	5.92 ± 0.57	5.93 ± 0.55	0.2 ± 0.2 (-0.2, 0.6)	0.561
Periosteal circumference, mm	76.46 ± 4.26	76.28 ± 4.24	-0.2 ± 0.2 (-0.5, 0.1)	76.85 ± 3.71	76.82 ± 3.66	0.0 ± 0.1 (-0.3, 0.2)	76.14 ± 4.33	76.22 ± 4.35	0.1 ± 0.1 (-0.2, 0.4)	0.286
Endocortical circumference, mm	37.03 ± 5.51	36.92 ± 5.53	-0.3 ± 0.2 (-0.8, 0.1)	39.62 ± 5.06	39.59 ± 5.11	-0.1 ± 0.2 (-0.5, 0.3)	38.96 ± 5.10	38.98 ± 5.09	0.1 ± 0.2 (-0.3, 0.5)	0.465
Polar section modulus, mm^2	2167.58 ± 318.23	2153.83 ± 327.75	-0.6 ± 0.6 (-1.9, 0.7)	2181.03 ± 328.20	2193.44 ± 326.24	0.6 ± 0.5 (-0.5, 1.7)	2130.13 ± 350.06	2138.53 ± 353.84	0.4 ± 0.5 (-0.7, 1.5)	0.326
SSIp, mm^3	2068.22 ± 293.97	2045.95 ± 299.67	-1.0 ± 0.6 (-2.2, 0.1)	2083.44 ± 321.89	2081.98 ± 317.50	0.0 ± 0.5 (-1.0, 0.9)	2039.15 ± 315.16	2046.31 ± 317.70	0.4 ± 0.5 (-0.6, 1.3)	0.148

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography; SSIp, polar strength strain index; vBMD, volumetric bone mineral density.

p-values represent between-group comparison of % change.

Note: 5 participants (Control n = 3, HiRIT n = 2) did not undergo pQCT tibia scans at baseline.

3.4 Eight-month change in pQCT-derived outcomes at the radius 4% and 66% sites

Results of the univariate ANCOVA for eight-month percent change in pQCT-derived outcomes at the distal radius (4% site) are presented in Table 7 and Figure 4 (ITT). HiRIT protected the distal radius from the notable loss observed in CON in total BMC (-0.1 ± 0.7% versus -3.7 ± 0.8%, p = 0.001) and total BSI (1.4 ± 1.4% versus -6.0 ± 1.6%, p = 0.001). Similarly, IAC preserved distal radius total BMC (1.3 ± 0.7% versus -3.7 ± 0.8%, p < 0.001) and total BSI (0.2 ± 1.3% versus -6.0 ± 1.6%, p = 0.004) compared to losses in CON. Significant within-group differences from baseline to follow-up clearly demonstrate the loss in distal radius total BMC (-5.34 ± 1.05 mg, p < 0.001) and total BSI (-0.03 ± 0.01 g^2/cm^4, p < 0.001) in CON.

Percent change in pQCT-derived outcomes at the proximal radius (66% site), with between-group differences from univariate ANCOVA, are presented in Table 8 (ITT). HiRIT lost proximal radius cortical area compared with CON (-3.1 ± 1.0% versus 1.1 ± 1.2%, p = 0.012) and IAC (-3.1 ± 1.0% versus -0.2 ± 1.0%, p = 0.042). Significant within-group losses from baseline to follow up were evident in HiRIT in proximal radius cortical BMC (-3.04 ± 1.05 mg, p = 0.005) and cortical area (-3.15 ± 0.96 mm^2, p = 0.002) but no within-group effects were detected for CON or IAC at the proximal radius.

Results of PP analyses of eight-month change in pQCT-derived outcomes at the distal radius (4% site) are presented in Supplemental Table 6 and largely reflect findings of the ITT analyses. HiRIT maintained distal radius total BMC (0.1 ± 0.9% versus -3.6 ± 0.9%, p = 0.003) and total BSI (2.2 ± 1.8 versus -5.1 ± 1.8%, p = 0.006) compared to a loss for CON, while IAC maintained total BMC (0.6 ± 0.8% versus -3.6 ± 0.9%, p = 0.001) compared to a loss for CON. For PP analyses at the proximal radial (66% site) there were no differences between groups in percent change, and the within-group decline in cortical BMC (-2.68 ± 1.30 mg, p = 0.043) and area (-2.82 ± 1.22 mm^2, p = 0.024) remained significant for HiRIT (Supplemental Table 7).

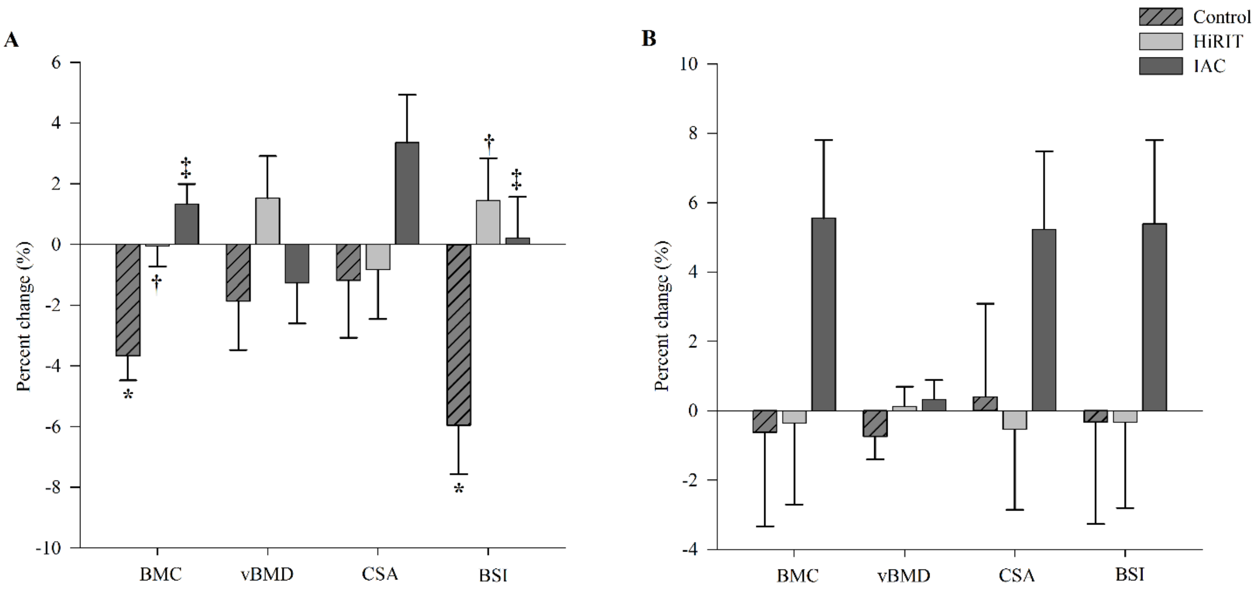

Figure 4. Eight-month percent change (mean ± SE) in pQCT-derived (A) total, and (B) trabecular bone outcomes at the skeletally non-dominant distal radius (4% site). ITT analyses, n = 87 (n = 93 – 5 participants who did not undergo pQCT at baseline and 1 scan excluded due to motion artefact); Control n = 23, HiRIT n = 31, IAC n = 33. * Indicates within-group change from baseline ($p \leq 0.05$); Indicates between-group difference in % change ($p \leq 0.05$): † HiRIT versus Control, ‡ IAC vs Control. Abbreviations: BMC, bone mineral content; BSI, bone strength index; CSA, cross-sectional area; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density.

Table 7. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the distal radius 4% site (ITT analysis, n = 87)

	Control (n = 23)			HiRIT (n = 31)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Radius 4% site										
Total BMC, mg	138.95 ± 20.39^	132.98 ± 17.45*	-3.7 ± 0.8 (-5.3, -2.1)[a]	126.48 ± 18.89^	126.57 ± 19.96	-0.1 ± 0.7 (-1.4, 1.3)[a]†	123.20 ± 19.62^	124.86 ± 19.06	1.3 ± 0.7 (0.0, 2.6)[a]‡	**< 0.001**
Total vBMD, mg/cm^3	348.29 ± 55.36	340.27 ± 53.01	-1.9 ± 1.6 (-5.0, 1.3)	334.62 ± 56.21	338.30 ± 48.49	1.5 ± 1.4 (-1.2, 4.2)	334.88 ± 56.71	328.97 ± 47.80	-1.3 ± 1.3 (-3.9, 1.4)	0.208
Total area, mm^2	407.75 ± 82.09	399.74 ± 74.44	-1.2 ± 1.9 (-4.9, 2.5)	382.65 ± 56.22	378.61 ± 60.93	-0.9 ± 1.6 (-4.1, 2.4)	375.23 ± 74.06	384.15 ± 62.13	3.4 ± 1.6 (0.2, 6.5)	0.098
Total BSI, g^2/cm^4	0.48 ± 0.10	0.45 ± 0.10*	-6.0 ± 1.6 (-9.1, -2.8)	0.43 ± 0.12	0.43 ± 0.11	1.4 ± 1.4 (-1.3, 4.2)†	0.42 ± 0.12	0.42 ± 0.11	0.2 ± 1.3 (-2.5, 2.9)‡	**0.002**
Trabecular BMC, mg	67.48 ± 17.58	66.31 ± 15.73	-0.6 ± 2.7 (-6.0, 4.8)	59.47 ± 13.35	59.03 ± 14.95	-0.4 ± 2.3 (-5.0, 4.3)	57.67 ± 15.73	59.89 ± 13.67	5.5 ± 2.3 (1.0, 10.1)	0.118
Trabecular vBMD, mg/cm^3	231.51 ± 32.07	229.75 ± 32.36	-0.7 ± 0.7 (-2.1, 0.6)	218.77 ± 35.92	218.82 ± 34.94	0.1 ± 0.6 (-1.0, 1.3)	216.83 ± 36.28	217.49 ± 36.66	0.3 ± 0.6 (-0.8, 1.4)	0.447
Trabecular area, mm^2	293.41 ± 71.16	291.00 ± 66.30	0.4 ± 2.7 (-4.9, 5.7)	273.59 ± 51.79	270.10 ± 53.96	-0.5 ± 2.3 (-5.1, 4.1)	268.45 ± 67.37	277.69 ± 56.17	5.2 ± 2.2 (0.8, 9.7)	0.170
Trabecular BSI, g^2/cm^4	0.16 ± 0.05^	0.15 ± 0.05	-0.4 ± 2.9 (-6.2, 5.5)[a]	0.13 ± 0.04^	0.13 ± 0.05	-0.3 ± 2.5 (-5.2, 4.6)[a]	0.13 ± 0.05^	0.13 ± 0.05	5.4 ± 2.4 (0.6, 10.2)[a]	0.183

Abbreviations: BMC, bone mineral content; BSI, bone strength index; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline p ≤ 0.05. * Within-group change from baseline p ≤ 0.05.

Between-group difference in % change p ≤ 0.05: † HiRIT vs Control, ‡ IAC vs Control.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Note: 5 participants (Control n = 3, HiRIT n = 2) did not undergo pQCT radius scans at baseline, and 1 baseline scan was excluded due to motion artefact (HiRIT, n = 1).

Table 8. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the proximal radius 66% site (ITT analysis, n = 87)

	Control (n = 23)			HiRIT (n = 31)			IAC (n = 33)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Radius 66% site										
Cortical BMC, mg	112.19 ± 19.32^	111.36 ± 17.58	0.6 ± 1.3 (-1.9, 3.2)[a]	97.31 ± 20.98^	94.92. ± 20.87*	-2.9 ± 1.1 (-5.1, -0.7)[a]	100.37 ± 18.18^	100.05 ± 15.02	0.2 ± 1.0 (-1.8, 2.3)[a]	0.057
Cortical vBMD, mg/cm^3	1074.09 ± 42.78	1069.03 ± 42.92	-0.5 ± 0.3 (-1.1, 0.2)	1051.54 ± 44.18	1052.73 ± 47.11	0.1 ± 0.3 (-0.5, 0.7)	1052.21 ± 47.96	1056.55 ± 45.78	0.4 ± 0.3 (-0.1, 1.0)	0.125
Cortical area, mm^2	104.10 ± 15.10^	103.87 ± 13.77	1.1 ± 1.2 (-1.3, 3.6)[a]	92.15 ± 17.98^	89.69 ± 17.33*	-3.1 ± 1.0 (-5.1, -1.0)[a]†#	95.19 ± 15.94^	94.55 ± 12.82	-0.2 ± 1.0 (-2.1, 1.8)[a]	**0.025**
Cortical thickness, mm	2.64 ± 0.50^	2.64 ± 0.47	1.5 ± 1.6 (-1.7, 4.6)[a]	2.29 ± 0.48^	2.26 ± 0.47	-1.6 ± 1.4 (-4.3, 1.1)[a]	2.35 ± 0.47^	2.33 ± 0.45	-0.6 ± 1.3 (-3.2, 2.0)[a]	0.361
Periosteal circumference, mm	48.29 ± 3.47	48.15 ± 3.21	-0.2 ± 0.9 (-2.1, 1.6)	47.77 ± 4.56	47.21 ± 4.80	-1.1 ± 0.8 (-2.7, 0.4)	48.44 ± 4.37	48.60 ± 4.29	0.5 ± 0.8 (-1.1, 2.0)	0.349
Endocortical circumference, mm	31.71 ± 5.61	31.61 ± 5.22	0.0 ± 1.7 (-3.4, 3.4)	33.39 ± 5.50	33.06 ± 5.77	-0.8 ± 1.5 (-3.8, 2.1)	33.66 ± 6.04	33.97 ± 6.34	1.2 ± 1.4 (-1.7, 4.0)	0.619
Polar section modulus, mm^2	494.83 ± 85.13	498.94 ± 74.12	1.3 ± 1.7 (-2.2, 4.7)	440.53 ± 108.13	433.80 ± 96.43	-0.4 ± 1.5 (-3.4, 2.6)	461.36 ± 90.24	450.41 ± 75.59	-1.6 ± 1.5 (-4.5, 1.3)	0.447
SSIp, mm^3	437.78 ± 86.62^	438.55 ± 77.29	2.2 ± 1.6 (-0.9, 5.3)[a]	376.05 ± 98.47^	370.07 ± 92.97	-1.6 ± 1.3 (-4.2, 1.1)[a]	395.36 ± 79.11^	386.48 ± 62.85	-1.5 ± 1.3 (-4.0, 1.1)[a]	0.138

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; ITT, intention-to-treat; pQCT, peripheral Quantitative Computed Tomography; SSIp, polar strength strain index; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline p ≤ 0.05. * Within-group change from baseline p ≤ 0.05.

Between-group difference in % change p ≤ 0.05: † HiRIT vs Control, # HiRIT vs IAC.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Note: 5 participants (Control n = 3, HiRIT n = 2) did not undergo pQCT radius scans at baseline, and 1 baseline scan was excluded due to motion artefact (HiRIT, n = 1).

4 Discussion

The LIFTMOR-M trial was the first study to examine the effects of eight months of supervised high-intensity progressive resistance and impact training (HiRIT) or machine-based isometric axial compression (IAC) exercise on geometric and biomechanical indices of bone strength at the tibia, radius and proximal femur in middle-aged and older men with osteopenia and osteoporosis. The supervised HiRIT program was well-tolerated and associated with only two minor musculoskeletal events, while the IAC program was associated with three minor musculoskeletal events that were slightly more serious than for HiRIT. It is likely the familiarisation period to learn correct technique and full supervision across the trial period accounts for the observed safety of the programs, , however, HiRIT effected the most positive bone strength outcomes. In general, HiRIT improved medial FN cortical thickness more than IAC and CON, and preserved distal tibia and radius indices of bone strength compared to CON, but decreased cortical area at the proximal radial 66% site compared with IAC and CON. IAC reduced loss in some indices of bone strength at the distal tibia and radius compared with CON, but did not notably enhance outcomes at any skeletal site. By contrast, CON lost distal tibia bone strength despite continuing with habitual activity (not including high-intensity resistance training and/or high-impact-type activity) over the eight-month trial period. The superior effect of HiRIT over IAC and CON on aBMD at the LS and proximal femur, body composition, calcaneal bone quality, physical function and muscle strength outcomes have been reported elsewhere [10].

4.1 Proximal femur

HiRIT improved medial FN cortical thickness compared to CON, and IAC. HiRIT also appeared to increase FN cortical volume, and total and medial FN cortical thickness compared to baseline values, but IAC did not improve any proximal femur geometry outcome. Morphological adaptation at the proximal femur following impact training [6], resistance training [9] or combined impact and resistance training [7] has been previously reported in a limited number of exercise intervention trials conducted in men. In the Hip Hop study (within-subject unilateral impact intervention), 12-months of daily hopping increased QCT-derived mid-FN cross-sectional area in the exercise limb by +2.0% in men aged 65 to 80 years [6]. Curiously, mid-FN cross-sectional area also increased by +2.1% in the contralateral 'unloaded' limb, assigned as control, so that no difference between exercise and control limbs was observed. Thus, the 2.7-3 times BW forces detected during landing, corresponding to moderate-intensity impact loading intensity (i.e. 2-4 times BW [12]), appeared to be insufficient to enhance bone geometry to a greater extent than muscle-related loading associated with fixing the 'non-exercise' side in hip flexion during hopping. A short-term male and female exercise trial of barbell-based squats and deadlifts improved FN cortical volume (+1.6%), whereas standing cable-based hip adduction and abduction (cable cuff attached at ankle) improved trochanteric cortical volume (+4.1%), but combined squat, deadlift, hip adduction and abduction training did not result in a significant change in cortical volume at either site [9]. The somewhat non-intuitive reported findings of no effect for combined barbell- and cable-based training may be attributable to the trial period being of an insufficient duration (four months) to detect bone changes despite training frequency (thrice-weekly) and intensity (relatively high) being matched for the three training arms of the study. Furthermore, it is difficult to compare findings with the current study given the sample was younger (22-55 years) and no sex-specific analyses were conducted (≈ 59% of the sample were women). In 50-79 year old men with normal to osteopenic aBMD, 18 months of thrice-weekly weight-bearing impact and progressive resistance training induced a net 1.8% benefit in FN cross-sectional area (from standard two-dimensional DXA scans using Lunar Advanced Hip Analysis software) compared to no exercise, but no effect for any QCT-derived cortical bone structure or strength outcome at the mid-shaft of the femur [7]. It is plausible that the lack of exercise effect at the femoral mid-shaft may have been influenced by moderate exercise program adherence (63%) and the variable impact intensity (1.5-9.7 times BW) and resistance training intensity that varied from moderate to high across the trial period.

Although we observed between- and within-group differences in FN cortical bone volume and thickness in favour of HiRIT, no effects on proximal femur cortical BMC and vBMD, or trabecular bone outcome, were detected at eight months. Our observations may suggest that high-intensity resistance training in combination with high-impact exercise may preferentially affect the cortical bone compartment, potentially via periosteal apposition, reduced endocortical bone loss or both. There is data to suggest that the contribution of trabecular bone to bone strength in the FN is low and cortical bone is the major contributor to bone strength at this site [19], thus the changes observed following HiRIT are highly clinically relevant. Given cortical bone thickness at the proximal femur is positively associated with FN failure loads ($r = 0.34$, $p < 0.05$) [20], our observation of HiRIT-induced improvements in total cortical thickness and FN cortical thickness for the medial subregion is suggestive of fracture prevention benefits. Similarly our observation that HiRIT improved FN cortical volume, in light of previous observations that lower FN cortical volume is associated with greater likelihood of hip fracture in men over the age of 65 years [21], also suggests HiRIT will confer a reduced risk of fracture. Notably, our HiRIT-induced improvements in FN cortical volume and total cortical thickness in middle-aged and older men are comparable with the changes reported for the identical HiRIT program in postmenopausal women [22].

4.2 Tibia

There have been only a limited number of exercise studies of men to report tibial outcomes; two trials involving middle-aged to older men [7, 8], and two examining young adult male military recruits [23, 24]. While the military studies have shown short-duration (≤ 13-weeks) military training enhances the tibia of young adult male recruits, the relevance of such intensive training is questionable for middle-aged and older adults with reduced bone mass at increased risk of fracture. Furthermore, high-volume military training is associated with an elevated risk of bone stress injury, limiting translation to previously sedentary older adult populations. A five-month trial of lower extremity targeted high-intensity resistance and plyometric training was implemented in male sprint athletes aged 40-85 years alongside their usual sprint training, and comparisons were drawn with those continuing with their habitual training schedule [8]. While no change in pQCT-derived distal tibia (5% site) bone outcomes was observed, the intervention group had a net 2% improvement in tibial mid-shaft (50% site) cortical thickness. Again, comparability with the current study is limited given their sample included men with a long-term masters sprint training background (including national and international level competitors) representing a considerably more physically active group than our sample of men aged 45-81 years, and their relatively short trial period.

Our CON group (no resistance training or impact-type activity) lost bone and bone strength at the predominantly trabecular distal tibia (4% site), while the HiRIT and IAC groups maintained distal tibia bone and bone strength. However, no within- or between-group differences were observed in the predominantly cortical bone of the tibial diaphysis at the 38% site. The latter observation is consistent with findings of an 18-month trial of combined weight-bearing impact exercise and progressive resistance training in men aged 50-79 years [7], the only intervention study to include tibial outcomes. Despite a ten month longer trial duration than ours, and training frequency being higher (thrice-weekly), no exercise effect was observed in QCT-derived total, cortical and medullary area, or cortical vBMD, at the mid-shaft of the tibia; no predominantly trabecular site was examined. As men with osteoporosis (i.e. FN or total hip T-score ≤ -2.5) were excluded, it is not possible to determine if an exercise effect would have occurred in those with lower initial BMD, given the osteogenic response to exercise is typically greatest in those with the lowest initial values [25]. In fact, it is not clear from either study if the tibial diaphysis is unaffected by even high intensity exercise training, or if QCT (including pQCT) is insufficiently sensitive to detect change.

In light of the fact that BSI (a composite measure of area and density) at the distal tibia predicts 85% of the variance in failure load when loaded in compression [17], maintenance of distal tibia total and trabecular BSI through HiRIT and IAC likely confers resistance to fracture at this site. Indeed, evidence from several population-based studies indicate that lower pQCT-derived indices of bone strength at the distal tibia are associated with a higher low trauma fracture risk in men [5, 26], thus, preservation of bone strength at this site is clinically important.

4.3 Radius

As there have been no other trials of resistance training alone or in combination with impact loading exercise that include upper extremity outcomes in middle-aged and older men, it is not possible to compare our findings with those of others. A six-month, twice-weekly, supervised exercise program designed specifically to load the wrist (incorporating push-ups and isolated wrist flexion) in postmenopausal women aged 52-72 years, did not provide a measurable osteogenic stimulus at the predominantly cortical proximal radius site, but improved distal radius cortical cross-sectional area (2.8%) and BMC (3.2%), however, the reverse effect was seen for trabecular BMC (-3.4%) [27]. It is likely that the loading intensity of the exercises was minimal and not of a progressive nature (repetition number progressed from 10 to 25, but not load which was maintained at 0.5 kg), thereby applying insufficient mechanical stimulus to notably sustain an adaptive bone stimulus at the non-weight bearing upper extremity.

The reductions in distal radius total BMC and BSI observed in the CON group resulted in a between-group effect in favour of HiRIT and IAC which amounted to a preservation of bone, rather than notable gain. Thus, it appears that HiRIT and IAC attenuated loss of bone mass and strength at the distal radius. As BMC at the distal radius is a significant predictor of failure load during a simulated fall on an outstretched hand ($r^2 = 0.79$, $p < 0.001$) [28], simple maintenance of bone at the site would be advantageous in the prevention wrist fracture. In light of other positive bone adaptations following HiRIT, the loss of proximal radius (66% site) cortical BMC and area was non-intuitive and difficult to interpret, but may be a function of insufficient statistical power (i.e. cortical BMC 49.0%; cortical area 68.7%) and a number of outlier values. When outliers were statistically identified and excluded (1.5 x the interquartile range from the quartiles, in line with Tukey's outlier detection method) the between-group differences in cortical area at the proximal radial 66% site were no longer significant. Our observations are otherwise largely consistent with the null findings from a meta-analysis of two studies reporting the effect of site-specific upper body exercise on upper extremity bone structure and strength in postmenopausal women [29].

4.4 Strengths and limitations

There are several strengths to this study including the unique focus on middle-aged and older men with osteopenia and osteoporosis, high participant compliance to training, and the comprehensive assessment of bone morphology and biomechanical strength at appendicular sites. Furthermore, this is the first study in men to document site-specific effects in both the upper and lower extremity on bone geometry and strength from 3D analysis of DXA and pQCT following high-intensity exercise. Given lack of time has been identified as a major barrier to exercise engagement in older adults [30], the time-efficient nature of the exercise intervention (30 minutes, twice-weekly) provides an attractive alternative to more time-consuming programs typically recommended for osteoporosis. However, several limitations of the current study warrant acknowledgement. First, the target sample size was not met despite an extensive recruitment strategy being implemented over a two-year period. A low dropout rate optimised the sample size achieved and where power was low, significant within-group improvements for HiRIT in 3D hip outcomes were greater than the coefficient of variation for the corresponding measure, revealing effects beyond measurement error. Second, the men enrolled in the study were relatively healthy community-dwelling men, limiting findings to a similar demographic. The fact that only a small number of potential participants were excluded due to having 'normal' bone mass (i.e. T-score > -1.0) after undergoing preliminary phone screening likely reflects specifically targeting men with low bone mass during recruitment, and we believe our sample was largely representative of aBMD in the general population. And finally, the study was not a fully randomised controlled trial, as controls were allowed to self-select to their group and continue with their habitual lifestyle patterns. Our decision to engage a parallel control group was guided by our experiences during piloting of the trial, whereby participants randomised to 'sham' home-based low-intensity exercise independently initiated other novel exercise programs (including high-intensity resistance training) external to the study activities. Furthermore, we felt it was unethical to randomise individuals at increased risk of fragility fracture to a no-exercise group, potentially withholding an effective therapy and thereby placing them at increased risk of harm. Therefore, the study design was adopted for pragmatic and ethical reasons.

5 Conclusions

In conclusion, our findings demonstrate that the supervised HiRIT program, incorporating multi-joint, compound movement, high-intensity progressive resistance training and high-impact jumping exercise improved or maintained indices of bone strength at the tibia and proximal femur in middle-aged and older men. Machine-based IAC exercise did not result in any significant improvement in bone strength at any skeletal site examined, but may mitigate age-related loss of indices of bone strength at the distal tibia and radius. Injuries and dropout rates for both exercise interventions were low, and compliance was comparable. Dose response investigations are indicated to determine optimal exercise prescription of HiRIT to enhance bone strength and risk factors for falls and fractures in middle-aged and older men.

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Authors' roles:

Study design – ATH, BKW, SLW, LJW, and BRB. Study conduct - ATH, BKW, SLW, and BRB. Exercise intervention supervision – ATH. Data collection – ATH, and CL. Data analysis - ATH, BKW, CL, SLW, and BRB. Data interpretation - ATH, BKW, CL, SLW, and BRB. All authors revised the manuscript for intellectual content and approved the final version of the manuscript. ATH, BKW, and BRB take responsibility for the integrity of the data analysis.

Declaration of interest:

BRB and LJW are Directors of The Bone Clinic, Brisbane, Queensland, Australia. ATH, BKW, CL, and SLW declare that they have no conflict of interest.

Registration:

Australian New Zealand Clinical Trials Registry (ANZCTR12616000344493).

Protocol:

The full trial protocol has been published – Harding, A. T., Weeks, B. K., Watson, S. L., and Beck, B. R. The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass. BMJ Open (Rehabilitation Medicine), 2017, 7 (e014951); doi: 10.1136/bmjopen-2016-014951

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Supplemental Table 1. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis outcomes at the femoral neck (PP analysis, n = 73)

	Control (n = 26)			HiRIT (n = 23)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Trabecular										
BMC, g	2.70 ± 0.53	2.81 ± 0.47	6.4 ± 7.5 (-8.6, 21.5)	2.47 ± 0.54	2.51 ± 0.63	3.0 ± 8.0 (-12.9, 19.0)	2.58 ± 0.76	2.79 ± 0.95	14.9 ± 7.8 (-0.8, 30.5)	0.556
Volume, cm^3	15.50 ± 2.91	16.20 ± 2.83*	5.4 ± 2.5 (0.4, 10.3)	15.50 ± 2.87	15.79 ± 3.02	2.1 ± 2.6 (-3.2, 7.4)	16.62 ± 2.71	16.98 ± 2.73	3.1 ± 2.6 (-2.0, 8.3)	0.650
vBMD, g/cm^3	0.176 ± 0.032^	0.177 ± 0.034	3.0 ± 4.3 (-5.6, 11.5)[a]	0.161 ± 0.025^	0.162 ± 0.040	0.6 ± 4.4 (-8.3, 9.4)[a]	0.154 ± 0.032^	0.164 ± 0.041	6.3 ± 4.4 (-2.5, 15.1)[a]	0.650
Cortical										
BMC, g	1.56 ± 0.38	1.61 ± 0.37	4.6 ± 2.9 (-1.2, 10.3)	1.45 ± 0.35	1.49 ± 0.33	3.8 ± 3.1 (-2.4, 9.9)	1.50 ± 0.27	1.54 ± 0.29	4.4 ± 3.0 (-1.6, 10.4)	0.980
Volume, cm^3	2.64 ± 0.63	2.69 ± 0.58	3.1 ± 2.1 (-1.2, 7.4)	2.52 ± 0.55	2.59 ± 0.52	3.8 ± 2.3 (-0.7, 8.4)	2.61 ± 0.49	2.60 ± 0.38	0.8 ± 2.2 (-3.6, 5.3)	0.618
vBMD, g/cm^3	0.592 ± 0.042	0.601 ± 0.043	1.6 ± 2.8 (-3.9, 7.2)	0.576 ± 0.048	0.575 ± 0.030	0.0 ± 3.0 (-5.9, 5.9)	0.577 ± 0.052	0.599 ± 0.128	4.3 ± 2.9 (-1.4, 10.1)	0.575
Total										
BMC, g	4.26 ± 0.82	4.42 ± 0.73	5.2 ± 5.1 (-5.0, 15.3)	3.92 ± 0.80	4.00 ± 0.82	3.0 ± 5.4 (-7.7, 13.8)	4.08 ± 0.92	4.34 ± 1.16	10.0 ± 5.3 (-0.6, 20.5)	0.642
Volume, cm^3	18.14 ± 3.43	18.88 ± 3.32*	4.9 ± 2.2 (0.6, 9.3)	18.02 ± 3.29	18.38 ± 3.45	2.3 ± 2.3 (-2.4, 6.9)	19.23 ± 3.12	19.58 ± 2.93	2.7 ± 2.3 (-1.9, 7.2)	0.665
vBMD, g/cm^3	0.236 ± 0.032^	0.237 ± 0.033	2.0 ± 2.9 (-3.8, 7.8)[a]	0.219 ± 0.027^	0.220 ± 0.038	0.5 ± 3.0 (-5.4, 6.5)[a]	0.212 ± 0.029^	0.221 ± 0.042	3.9 ± 3.0 (-2.1, 9.9)[a]	0.726

Abbreviations: BMC, bone mineral content; CI, confidence interval; DXA, Dual-energy X-ray Absorptiometry; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p < 0.05$. * Within-group change from baseline $p < 0.05$.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Supplemental Table 2. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis outcomes at the total hip (PP analysis, n = 73)

	Control (n = 26)			HiRIT (n = 23)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Trabecular										
BMC, g	15.06 ± 2.44	15.19 ± 2.45	1.2 ± 4.3 (-7.4, 9.7)	13.90 ± 2.84	13.87 ± 3.04	1.4 ± 4.5 (-7.7, 10.5)	14.08 ± 3.69	14.70 ± 3.52	7.7 ± 4.5 (-1.2, 16.6)	0.500
Volume, cm^3	91.62 ± 14.26	94.25 ± 13.24*	3.3 ± 1.1 (1.0, 5.5)	90.83 ± 16.63	92.17 ± 17.08	1.6 ± 1.2 (-0.8, 4.0)	97.13 ± 14.23	97.92 ± 13.19	1.1 ± 1.2 (-1.3, 3.4)	0.382
vBMD, g/cm^3	0.167 ± 0.027^	0.163 ± 0.026	-0.1 ± 3.5 (-7.0, 6.9)[a]	0.154 ± 0.022^	0.153 ± 0.035	-0.3 ± 3.6 (-7.4, 6.8)[a]	0.145 ± 0.028^	0.151 ± 0.031	4.0 ± 3.6 (-3.2, 11.1)[a]	0.651
Cortical										
BMC, g	10.76 ± 1.89	10.73 ± 1.98	-0.2 ± 3.0 (-6.1, 5.8)	9.87 ± 2.14	9.83 ± 1.67	1.7 ± 3.2 (-4.6, 8.1)	10.42 ± 1.58	10.76 ± 1.92	4.4 ± 3.1 (-1.8, 10.7)	0.570
Volume, cm^3	16.76 ± 2.99	16.54 ± 2.92	-1.0 ± 1.8 (-4.5, 2.5)	15.75 ± 2.95	15.95 ± 2.39	2.4 ± 1.9 (-1.3, 6.2)	16.65 ± 2.58	16.61 ± 2.46	0.2 ± 1.8 (-3.5, 3.8)	0.404
vBMD, g/cm^3	0.645 ± 0.059	0.651 ± 0.053	1.1 ± 2.8 (-4.5, 6.8)	0.625 ± 0.067	0.615 ± 0.037	-1.0 ± 3.0 (-7.0, 5.1)	0.629 ± 0.064	0.655 ± 0.131	4.8 ± 2.9 (-1.1, 10.7)	0.388
Total										
BMC, g	25.82 ± 3.87	25.91 ± 3.85	0.5 ± 3.5 (-6.4, 7.4)	23.77 ± 4.61	23.70 ± 4.41	1.4 ± 3.7 (-6.0, 8.7)	24.50 ± 4.87	25.47 ± 4.99	5.9 ± 3.6 (-1.2, 13.1)	0.511
Volume, cm^3	108.38 ± 16.78	110.77 ± 15.89*	2.5 ± 1.0 (0.5, 4.6)	106.58 ± 19.28	108.12 ± 19.16	1.7 ± 1.1 (-0.5, 3.9)	113.77 ± 16.40	114.53 ± 15.04	0.9 ± 1.1 (-1.2, 3.1)	0.558
vBMD, g/cm^3	0.240 ± 0.031^	0.235 ± 0.026	0.3 ± 2.8 (-5.3, 5.9)[a]	0.224 ± 0.027^	0.222 ± 0.038	-0.8 ± 2.9 (-6.5, 4.9)[a]	0.215 ± 0.028^	0.223 ± 0.038	2.7 ± 2.9 (-3.0, 8.5)[a]	0.678

Abbreviations: BMC, bone mineral content; CI, confidence interval; DXA, Dual-energy X-ray Absorptiometry; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p < 0.05$. * Within-group change from baseline $p < 0.05$.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Supplemental Table 3. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in 3D hip analysis of femoral neck cortical thickness (PP analysis, n = 73)

	Control (n = 26)			HiRIT (n = 23)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Total, mm	1.20 ± 0.18	1.19 ± 0.16	-0.1 ± 2.1 (-4.3, 4.2)	1.15 ± 0.16	1.18 ± 0.14	3.3 ± 2.3 (-1.2, 7.8)	1.13 ± 0.13	1.12 ± 0.14	-0.2 ± 2.2 (-4.6, 4.2)	0.459
Subregion										
Anterior, mm	0.98 ± 0.17	0.99 ± 0.18	1.8 ± 2.6 (-3.5, 7.1)	0.97 ± 0.17	0.96 ± 0.16	0.2 ± 2.8 (-5.4, 5.8)	0.92 ± 0.11	0.92 ± 0.15	0.5 ± 2.7 (-5.0, 6.0)	0.904
Posterior, mm	0.98 ± 0.17	0.99 ± 0.17	2.1 ± 3.4 (-4.8, 8.9)	0.95 ± 0.19	0.98 ± 0.17	4.3 ± 3.6 (-3.0, 11.5)	0.92 ± 0.13	0.89 ± 0.20	-2.6 ± 3.6 (-9.7, 4.5)	0.391
Lateral, mm	0.65 ± 0.16	0.61 ± 0.15	-4.6 ± 4.2 (-12.9, 3.7)	0.58 ± 0.12	0.60 ± 0.12	6.2 ± 4.4 (-2.6, 15.0)	0.60 ± 0.11	0.59 ± 0.14	-1.7 ± 4.3 (-10.3, 7.0)	0.197
Medial, mm	2.09 ± 0.31	2.08 ± 0.27	-0.1 ± 2.1 (-4.2, 4.0)	2.00 ± 0.28	2.08 ± 0.23	4.7 ± 2.2 (0.3, 9.1)	2.00 ± 0.23	2.01 ± 0.24	1.3 ± 2.2 (-3.0, 5.6)	0.286

Abbreviations: 3D, three-dimensional; CI, confidence interval; DXA, Dual-energy X-ray Absorptiometry; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; 3D, three-dimensional.

p-values represent between-group comparison of % change.

Supplemental Table 4. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the distal tibia 4% site (PP analysis, n = 69)

	Control (n = 23)			HiRIT (n = 22)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Tibia 4% site										
Total BMC, mg	404.86 ± 46.17^	393.21 ± 45.27*	-3.1 ± 0.4 (-3.9, -2.2)[a]	349.74 ± 40.43^	350.40 ± 40.17	0.4 ± 0.4 (-0.4, 1.3)[a]†	378.92 ± 52.05^	377.60 ± 56.29	-0.5 ± 0.4 (-1.3, 0.3)[a]‡	**< 0.001**
Total vBMD, mg/cm^3	327.35 ± 35.02^	324.90 ± 36.28*	-0.8 ± 0.3 (-1.5, -0.2)[a]	297.89 ± 34.26^	297.61 ± 33.93	0.0 ± 0.3 (-0.7, 0.6)[a]	305.05 ± 39.92^	305.86 ± 40.53	0.3 ± 0.3 (-0.4, 0.9)[a]	0.062
Total area, mm^2	1245.84 ± 157.49	1220.37 ± 159.99*	-2.1 ± 0.5 (-3.1, -1.0)	1184.51 ± 163.54	1186.73 ± 156.47	0.3 ± 0.5 (-0.8, 1.4)†	1247.54 ± 134.06	1238.23 ± 133.15	-0.7 ± 0.5 (-1.7, 0.3)	**0.008**
Total BSI, g^2/cm^4	1.33 ± 0.23^	1.28 ± 0.23*	-4.0 ± 0.5 (-5.1, -3.0)[a]	1.05 ± 0.21^	1.05 ± 0.21	0.5 ± 0.5 (-0.5, 1.5)[a]†	1.17 ± 0.29^	1.17 ± 0.30	-0.2 ± 0.5 (-1.1, 0.7)[a]‡	**< 0.001**
Trabecular BMC, mg	275.24 ± 39.57^	270.34 ± 39.17*	-1.7 ± 0.6 (-2.8, -0.6)[a]	245.14 ± 37.41^	246.59 ± 35.33	0.7 ± 0.6 (-0.5, 1.8)[a]†	261.93 ± 35.94^	260.88 ± 37.69	-0.5 ± 0.5 (-1.5, 0.6)[a]	**0.018**
Trabecular vBMD, mg/cm^3	275.16 ± 28.80	274.81 ± 29.39	-0.1 ± 0.2 (-0.6, 0.3)	254.95 ± 31.78	255.77 ± 31.64	0.3 ± 0.2 (-0.2, 0.8)	259.50 ± 33.96	260.27 ± 34.08	0.3 ± 0.2 (-0.2, 0.8)	0.296
Trabecular area, mm^2	1005.92 ± 142.43	990.13 ± 144.37*	-1.6 ± 0.6 (-2.8, -0.5)	968.15 ± 144.54	970.65 ± 137.06	0.4 ± 0.6 (-0.8, 1.6)	1014.41 ± 118.69	1006.12 ± 116.27	-0.8 ± 0.6 (-1.9, 0.4)	0.055
Trabecular BSI, g^2/cm^4	0.76 ± 0.16^	0.75 ± 0.15*	-1.9 ± 0.6 (-3.1, -0.7)[a]	0.63 ± 0.16^	0.64 ± 0.15	1.1 ± 0.6 (-0.2, 2.3)[a]†	0.69 ± 0.16^	0.69 ± 0.16	-0.2 ± 0.6 (-1.3, 1.0)[a]‡	**0.006**

Abbreviations: BMC, bone mineral content; BSI, bone strength index; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography.

^ Between-group difference at baseline $p < 0.05$. * Within-group change from baseline $p < 0.05$.

Between-group difference in % change $p < 0.05$: † HiRIT vs Control, ‡ IAC vs Control. [a] Adjusted for initial values. p-values represent between-group comparison of % change.

Supplemental Table 5. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the diaphyseal tibia 38% site (PP analysis, n = 69)

	Control (n = 23)			HiRIT (n = 22)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Tibia 38% site										
Cortical BMC, mg	405.42 ± 41.38	403.36 ± 40.39	-0.5 ± 0.4 (-1.2, 0.2)	385.37 ± 51.87	384.81 ± 52.21	-0.2 ± 0.4 (-0.9, 0.6)	382.95 ± 35.93	383.78 ± 35.17	0.2 ± 0.3 (-0.5, 0.9)	0.366
Cortical vBMD, mg/cm^3	1141.93 ± 26.64	1141.05 ± 25.84	-0.1 ± 0.2 (-0.5, 0.4)	1149.03 ± 29.97	1147.83 ± 32.89	-0.1 ± 0.2 (-0.5, 0.3)	1145.80 ± 25.76	1145.82 ± 27.02	0.0 ± 0.2 (-0.4, 0.4)	0.935
Cortical area, mm^2	355.12 ± 36.06	353.61 ± 35.50	-0.4 ± 0.4 (-1.1, 0.4)	334.80 ± 39.61	334.58 ± 39.25	-0.1 ± 0.4 (-0.8, 0.7)	334.56 ± 33.94	335.27 ± 33.03	0.3 ± 0.4 (-0.5, 1.0)	0.478
Cortical thickness, mm	6.27 ± 0.60^	6.26 ± 0.60	-0.1 ± 0.3 (-0.6, 0.4)[a]	5.77 ± 0.76^	5.77 ± 0.77	0.1 ± 0.3 (-0.5, 0.6)[a]	5.83 ± 0.53^	5.84 ± 0.51	0.2 ± 0.3 (-0.3, 0.7)[a]	0.699
Periosteal circumference, mm	76.46 ± 4.26	76.28 ± 4.24	-0.2 ± 0.2 (-0.6, 0.1)	76.35 ± 2.99	76.30 ± 2.92	-0.1 ± 0.2 (-0.4, 0.3)	75.81 ± 4.22	75.85 ± 4.23	0.0 ± 0.2 (-0.3, 0.4)	0.529
Endocortical circumference, mm	37.03 ± 5.51	36.92 ± 5.53	-0.3 ± 0.2 (-0.8, 0.2)	40.12 ± 4.76	40.02 ± 4.91	-0.3 ± 0.2 (-0.8, 0.2)	39.19 ± 5.07	39.15 ± 5.05	-0.1 ± 0.2 (-0.6, 0.4)	0.774
Polar section modulus, mm^2	2167.58 ± 318.23	2153.83 ± 327.75	-0.6 ± 0.7 (-2.0, 0.8)	2129.91 ± 273.52	2138.41 ± 271.36	0.4 ± 0.7 (-1.0, 1.8)	2099.66 ± 326.31	2102.38 ± 323.46	0.2 ± 0.7 (-1.1, 1.5)	0.546
SSIp, mm^3	2068.22 ± 293.97	2045.95 ± 299.67	-1.0 ± 0.6 (-2.2, 0.1)	2045.10 ± 288.59	2041.58 ± 285.51	-0.2 ± 0.6 (-1.4, 1.1)	2008.04 ± 286.87	2014.01 ± 286.75	0.3 ± 0.6 (-0.8, 1.5)	0.253

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography; SSIp, polar strength strain index; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p < 0.05$.

[a] Adjusted for initial values. p-values represent between-group comparison of % change.

Supplemental Table 6. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the distal radius 4% site (PP analysis, n = 68)

	Control (n = 23)			HiRIT (n = 21)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Radius 4% site										
Total BMC, mg	138.95 ± 20.39^	132.98 ± 17.45*	-3.6 ± 0.9 (-5.3, -1.9)[a]	123.24 ± 19.31^	123.88 ± 21.63	0.1 ± 0.9 (-1.6, 1.8)[a]†	121.32 ± 18.06^	122.0 ± 16.49	0.6 ± 0.8 (-1.0, 2.2)[a]‡	**0.002**
Total vBMD, mg/cm^3	348.29 ± 55.36	340.27 ± 53.01	-1.9 ± 1.7 (-5.4, 1.6)	336.63 ± 59.57	342.29 ± 48.98	2.2 ± 1.8 (-1.5, 5.9)	331.87 ± 53.28	326.15 ± 40.37	-1.1 ± 1.7 (-4.5, 2.4)	0.246
Total area, mm^2	407.75 ± 82.09	399.74 ± 74.44	-1.2 ± 2.0 (-5.3, 2.9)	369.88 ± 49.01	364.62 ± 54.50	-1.2 ± 2.1 (-5.5, 3.1)	373.25 ± 76.15	377.67 ± 56.80	2.5 ± 2.0 (-1.4, 6.5)	0.329
Total BSI, g^2/cm^4	0.48 ± 0.10^	0.45 ± 0.10*	-5.1 ± 1.8 (-8.6, -1.5)[a]	0.42 ± 0.13^	0.43 ± 0.12	2.1 ± 1.8 (-1.4, 5.8)[a]†	0.40 ± 0.09^	0.40 ± 0.08	-0.9 ± 1.7 (-4.3, 2.5)[a]	**0.022**
Trabecular BMC, mg	67.48 ± 17.58^	66.31 ± 15.73	1.8 ± 2.8 (-3.9, 7.5)[a]	56.07 ± 11.86^	55.70 ± 14.02	-2.0 ± 2.9 (-7.8, 3.80)[a]	58.00 ± 15.40^	59.19 ± 11.49	3.5 ± 2.7 (-1.9, 8.9)[a]	0.381
Trabecular vBMD, mg/cm^3	231.51 ± 32.07	229.75 ± 32.36	-0.7 ± 0.7 (-2.1, 0.6)	215.80 ± 38.18	216.58 ± 37.59	0.5 ± 0.7 (-1.0, 1.9)	218.56 ± 34.51	218.46 ± 35.01	0.0 ± 0.7 (-1.4, 1.3)	0.489
Trabecular area, mm^2	293.41 ± 71.16	291.00 ± 66.30	0.4 ± 2.9 (-5.4, 6.2)	262.04 ± 43.99	257.19 ± 44.84	-0.9 ± 3.1 (-7.0, 5.2)	268.05 ± 67.62	273.43 ± 48.51	4.5 ± 2.9 (-1.3, 10.2)	0.405
Trabecular BSI, g^2/cm^4	0.16 ± 0.05^	0.15 ± 0.05	-0.2 ± 3.2 (-6.5, 6.2)[a]	0.12 ± 0.04^	0.12 ± 0.05	-0.6 ± 3.3 (-7.1, 5.9)[a]	0.13 ± 0.04^	0.13 ± 0.04	3.8 ± 3.0 (-2.2, 9.9)[a]	0.538

Abbreviations: BMC, bone mineral content; BSI, bone strength index; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density.

^ Between-group difference at baseline $p < 0.05$. * Within-group change from baseline $p < 0.05$.

Between-group difference in % change $p < 0.05$: † HiRIT vs Control, ‡ IAC vs Control. [a]Adjusted for initial values. p-values represent between-group comparison of % change.

Note: 1 baseline radius scan excluded due to motion artefact (HiRIT, n = 1).

Supplemental Table 7. Baseline and eight-month measures (mean ± SD) with percent change (mean ± SE) in pQCT-derived outcomes at the proximal radius 66% site (PP analysis, n = 68)

	Control (n = 23)			HiRIT (n = 21)			IAC (n = 24)			p-value
	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	Baseline	Follow-up	% change (95% CI)	
Radius 66% site										
Cortical BMC, mg	112.19 ± 19.32	111.36 ± 17.58	-0.5 ± 1.3 (-3.0, 2.1)	98.22 ± 23.35	95.54 ± 23.23*	-2.6 ± 1.3 (-5.3, 0.1)	102.23 ± 17.50	101.87 ± 14.50	0.4 ± 1.3 (-2.1, 2.9)	0.257
Cortical vBMD, mg/cm^3	1074.09 ± 42.78	1069.03 ± 42.92	-0.5 ± 0.3 (-1.2, 0.2)	1055.77 ± 49.00	1057.58 ± 49.12	0.2 ± 0.4 (-0.5, 0.9)	1062.45 ± 47.60	1069.24 ± 42.51	0.7 ± 0.3 (0.0, 1.3)	0.066
Cortical area, mm^2	104.10 ± 15.10	103.87 ± 13.77	0.0 ± 1.2 (-2.5, 2.5)	92.57 ± 20.09	89.75 ± 19.37*	-2.8 ± 1.3 (-5.4, -0.2)	96.09 ± 15.45	95.20 ± 12.60	-0.3 ± 1.2 (-2.7, 2.1)	0.237
Cortical thickness, mm	2.64 ± 0.50	2.64 ± 0.47	0.3 ± 1.6 (-2.8, 3.5)	2.31 ± 0.54	2.27 ± 0.52	-1.0 ± 1.6 (-4.3, 2.2)	2.46 ± 0.46	2.43 ± 0.45	-0.6 ± 1.5 (-3.6, 2.5)	0.824
Periosteal circumference, mm	48.29 ± 3.47	48.15 ± 3.21	-0.2 ± 1.0 (-2.3, 1.8)	47.66 ± 4.97	46.96 ± 5.24	-1.4 ± 1.1 (-3.5, 0.7)	47.31 ± 4.27	47.34 ± 3.85	0.3 ± 1.0 (-1.7, 2.3)	0.502
Endocortical circumference, mm	31.71 ± 5.61	31.61 ± 5.22	0.0 ± 1.9 (-3.8, 3.7)	33.15 ± 5.87	32.69 ± 6.07	-1.1 ± 2.0 (-5.0, 2.8)	31.87 ± 5.82	32.04 ± 5.80	1.0 ± 1.8 (-2.7, 4.7)	0.740
Polar section modulus, mm^3	494.83 ± 85.13	498.94 ± 74.12	1.3 ± 1.6 (-1.9, 4.5)	438.05 ± 124.71	432.28 ± 111.24	0.0 ± 1.7 (-3.4, 3.3)	454.91 ± 84.02	443.35 ± 77.95	-2.1 ± 1.6 (-5.3, 1.0)	0.318
SSIp, mm^3	437.78 ± 86.62	438.55 ± 77.29	0.6 ± 1.5 (-2.4, 3.6)	378.23 ± 112.26	372.17 ± 105.74	-0.5 ± 1.6 (-3.6, 2.7)	394.53 ± 70.67	385.62 ± 62.81	-1.8 ± 1.5 (-4.7, 1.2)	0.547

Abbreviations: BMC, bone mineral content; CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression; PP, per-protocol; pQCT, peripheral Quantitative Computed Tomography; SSIp, polar strength strain index; vBMD, volumetric bone mineral density.

* Within-group change from baseline $p < 0.05$. p-values represent between-group comparison of % change.

Note: 1 baseline radius scan excluded due to motion artefact (HiRIT, n = 1).