Title:

Exploring thoracic kyphosis and incident fracture from vertebral morphology with high-intensity exercise in middle-aged and older men with osteopenia and osteoporosis: A secondary analysis of the LIFTMOR-M trial

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Abstract

Purpose

The Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men (LIFTMOR-M) trial examined efficacy and safety of an eight-month, supervised, high-intensity progressive resistance and impact training (HiRIT) program compared to machine-based isometric axial compression (IAC) training in middle-aged and older men with low areal bone mineral density (aBMD). The primary purpose of the current work was to explore change in thoracic kyphosis and incident fracture from vertebral morphology following eight-months of HiRIT or IAC training. The secondary purpose was to explore change in clinical kyphosis measures for HiRIT, IAC and a non-randomised, matched control group.

Methods

Men (≥45yrs), with low aBMD were recruited and randomised to HiRIT or IAC, or designated control. Clinical measures of thoracic kyphosis with inclinometry were determined. Cobb angle of kyphosis and vertebral fracture assessment using the Genant semi-quantitative method were determined from lateral thoracolumbar DXA (Medix DR, Medilink, France). Per-protocol (n = 40) and intention-to-treat (n = 93) analyses were conducted.

Results

Forty participants (HiRIT n = 20, IAC n = 20; 66.1±7.8yrs; lumbar spine T-score -0.1±0.8; femoral neck T-score -1.5±0.5) underwent clinical kyphosis measures and thoracolumbar DXA at both time-points. No between-group differences were detected in kyphosis change, however, within-group improvements in neutral (HiRIT -2.3±0.8°; IAC -2.5±0.8°) and 'standing tall' (HiRIT -2.4±0.8°; IAC -2.0±0.8°) postures were observed ($p<0.05$). HiRIT improved Cobb angle (-3.5±1.5°, $p=0.027$) from baseline. Over the eight months, no incident

vertebral fractures nor progression of prevalent vertebral fractures occurred for HiRIT participants. Five incident fractures of thoracic vertebrae occurred for IAC and one wedge fracture progressed. Ninety-three participants underwent clinical kyphosis measures at both time-points (HiRIT n = 34, IAC n = 33, control n = 26). HiRIT exhibited a reduction in 'standing tall' posture compared to control (-2.3±0.6° versus 1.4±0.7°, $p<0.05$), but no other between-group differences were detected.

Conclusions

Although there was no difference in change between intervention groups, thoracic kyphosis appeared to improve in both HiRIT and IAC with exercise exposure. HiRIT improved standing tall posture in comparison to usual activities. HiRIT was not associated with vertebral fracture progression or incident vertebral fracture, and for some IAC participants there was evidence of progression of vertebral fracture severity and incident vertebral fractures, in our small sample. Larger trials are required to confirm the observations of the current work, which was exploratory in nature.

Keywords

Exercise, Kyphosis, Lateral vertebral assessment, Men, Osteoporosis, Vertebral fracture

Mini Abstract

Our aim was to explore change in kyphosis and vertebral fracture incidence following eight months of high-intensity resistance and impact training (HiRIT) or machine-based isometric axial compression (IAC) training in men with osteopenia and osteoporosis. HiRIT and IAC improved posture. HiRIT participants did not experience progression or incident vertebral fracture. IAC participants did experience progression and incident vertebral fracture.

Introduction

Osteoporosis is a progressive systemic skeletal disorder characterised by loss of bone mass and reduced bone strength, that increases the likelihood of fragility fracture [1]. Vertebral fractures are the most common type of osteoporotic fracture, resulting in pain, reduced quality of life, functional decline and mortality [2,3]. Many vertebral fractures occur with minimal or no recognisable trauma, and two-thirds may by asymptomatic thus remaining undetected unless identified during examinations for unrelated health problems [4,5]. Due in part to the asymptomatic nature of vertebral fracture, and a lack of consensus definition of vertebral fracture, the reported prevalence varies from 12-26% in older men [6-9]. The mortality rate after clinical vertebral fracture may be higher for older men than their female counterparts [3,10]. Vertebral fracture in older men may also contribute to excessive thoracic kyphosis (hyperkyphosis) and loss of height [11]. Each incident vertebral fracture may progress kyphotic angle by around 4° [12].

Individuals with osteopenia and osteoporosis are encouraged to engage in physical activity and structured exercise as part of a multifaceted approach to the non-pharmacological management of low bone mass. Previous exercise recommendations have provided guidance on safe and effective exercise regimes for adults with diagnosed low bone mass or osteoporotic vertebral fracture, specifying a combined exercise program of moderate-to high-intensity progressive resistance training, high-challenge balance training and moderate-to high-impact loading exercise (‘Too Fit to Fracture’ consensus [13] and ‘Exercise and Sports Science Australia’ position statement on exercise prescription for the prevention and management of osteoporosis [14]). While intervention studies have been conducted in middle-aged and older men examining the effects of progressive resistance training and weight-bearing impact exercise on regional areal bone mineral density [15-18], none have

reported changes to kyphosis or vertebral morphology as a result of exercise exposure. Thus, the effect of high intensity bone-targeted exercise programs on kyphosis progression and vertebral fracture risk has not been established in men. Moreover, there continues to be uncertainty about the relationship between high-intensity progressive resistance training and high-load impact training with fragility fracture risk. Recently, we reported that high-intensity progressive resistance and impact training (HiRIT) performed twice-weekly for eight months caused no vertebral morphology changes and that thoracic kyphosis improved in postmenopausal women with osteopenia and osteoporosis [19]. Those findings suggest that supervised HiRIT can be a safe form of therapeutic exercise for healthy individuals with low to very low bone mass.

We have previously reported anthropometrics, whole body and regional bone mass and strength, body composition, muscle strength, functional performance, compliance and adverse events of the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men (LIFTMOR-M) trial [20,21]. The primary purpose of this secondary analysis was to explore change in thoracic kyphosis and vertebral fracture from vertebral morphology in participants involved in the exercise arms of the LIFTMOR-M exercise intervention trial who underwent measures at both baseline and eight-month follow up. In particular, we sought to: 1) explore change in inclinometer-determined thoracic kyphosis in standing; 2) explore change in Cobb angle of kyphosis from lateral decubitus thoracolumbar spine Dual-energy X-ray Absorptiometry (DXA) scans; and 3) identify vertebral fractures in the 4^{th} thoracic to 4^{th} lumbar region of the spine using the Genant semi-quantitative method of vertebral morphometry from DXA. Secondly, we sought to explore change in inclinometer-determined clinical thoracic kyphosis in standing for participants in all three

arms of the LIFTMOR-M exercise intervention trial, that is, HiRIT, IAC, and the non-randomised control group who continued with their usual lifestyle activities.

Methods

Ethical approval

The study was approved by the Griffith University Human Research Ethics Committee (AHS/07/14/HREC) and prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR12616000344493). All research activities were conducted in accordance with the *Declaration of Helsinki*. All participants provided written informed consent.

Study design

The LIFTMOR-M exercise intervention trial was a single-centre, three-arm, semi-randomised controlled exercise intervention trial. The study design and details of eligibility criteria have been previously described [20,22].

Recruitment for the LIFTMOR-M trial commenced in May 2016. The trial protocol manuscript [22] was submitted when participants were still being recruited for, and enrolled in, the trial. The first intake of participants, which primarily included the non-randomised control group, were enrolled before November 2016, which was prior to availability of the DXA software that enabled lateral thoracolumbar scanning and examination of Cobb angle of thoracic kyphosis and vertebral morphology for vertebral fracture assessment (VFA). Therefore, our ability to perform lateral thoracolumbar spine scans occurred after trial registration, but before the protocol paper was published. Here we report the thoracic kyphosis (both clinical and densitometric measures) and VFA findings for participants who completed the HiRIT and IAC exercise interventions and underwent measures at both baseline and follow up, using a per-protocol approach. The purpose of this exploratory work was a preliminary examination of change in thoracic kyphosis and vertebral morphology

following high intensity, bone-targeted exercise in middle-aged and older men with low aBMD. Secondly, we explored change in clinical measures of inclinometer-determined thoracic kyphosis in standing following eight months of HiRIT, IAC and usual activities (non-randomised control group) using an intention-to-treat approach, as inclinometer-based thoracic kyphosis data was available at both time-points for all trial participants.

Participants

Apparently healthy men over 45 years of age with osteopenia (T-score -1.0 to -2.5) or osteoporosis (T-score < -2.5) at the lumbar spine (LS), total hip (TH) and/or femoral neck (FN), screened for medications and medical conditions known to influence bone metabolism, were recruited.

Randomisation

Allocation of eligible participants to the exercise arms of the trial (HiRIT and IAC training groups) was achieved via block randomisation, stratified by the presence (≥ 12 months exposure) or absence of (lack of exposure to) osteoporosis medications. The current report includes thoracic kyphosis and VFA observations for 40 (HiRIT n = 20, IAC n = 20) of the original 93 eligible participants of the LIFTMOR-M trial (i.e. 43% of the entire sample, and 60% of the participants randomised to the exercise arms). The primary reason for missing densitometric thoracic kyphosis and VFA data of controls and 40% of exercise group participants was software unavailability for lateral thoracolumbar scanning. Inclinometer-based thoracic kyphosis observations for all 93 eligible participants of the LIFTMOR-M trial were available.

Exercise interventions

An eight-month, twice-weekly, fully supervised exercise program was conducted for both intervention groups. The HiRIT and IAC training programs have been described in detail elsewhere [22]. Briefly, HiRIT performed five sets of five repetitions (≥ 80-85% one repetition maximum) of the deadlift, squat and overhead press, and five sets of five repetitions of jumping chin-ups with a firm, flat-footed landing. IAC performed one self-initiated near-maximal five-second isometric contraction for each of the four exercises (chest press, leg press, core pull, and vertical lift) using the bioDensity™ machine (Performance Health Systems, Chicago, USA). Exercise intensity corresponded to ≥ 80-85% of one repetition maximum, translating to an RPE of ≥ 16 on the 6-20 point Borg scale [23]. All training sessions were supervised by a qualified Exercise Scientist. Exercise compliance was recorded in training diaries, with 100% compliance defined as completion of 70 sessions over the eight-month trial period.

Control group activities

A parallel control group comprised a sample of middle-aged and older men, 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 self-allocated to 'no intervention'. The control group participants were instructed to maintain their customary physical activity and dietary patterns, and refrain from taking up either of the exercise modalities of the intervention groups, over the eight-month duration of the trial. Physical activity participation was motioned across the trial period (using purpose-designed lifestyle diary entries and Bone-specific Physical Activity Questionnaire scores) and there was no change in the amount of activity observed from baseline [20].

Anthropometrics and lifestyle characteristics

Height was assessed using a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight was measured using a mechanical beam scale (Model 700; Seca, Hamburg, Germany). Body mass index (BMI) was determined per the accepted method (BMI = weight/height^2; kg/m^2). The Bone-specific Physical Activity Questionnaire (BPAQ) [24] was used to quantify lifetime physical activity of relevance to bone. Daily calcium intake was assessed using the AusCal calcium-focused food frequency questionnaire [25], and responses were analysed using Australian-specific dietary analysis software (FoodWorks, Xyris Software, Brisbane, Australia).

Inclinometer-determined thoracic kyphosis

Thoracic kyphosis was assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia) following a procedure similar to MacIntyre and colleagues for determining thoracic spine curvature using a digital inclinometer in older adults with diagnosed osteopenia and osteoporosis [26]. First, participants were asked to remove shoes and clothing covering their back to ensure accurate palpation of bony landmarks. The following landmarks were palpated and marked with the participant in a relaxed standing posture: 1) the uppermost margin of each iliac crest, 2) the 4th lumbar vertebra at the intercristal line (medial to the superior border of the iliac crest), 3) the 12th thoracic to 1st lumbar intervertebral space, and 4) the 7th cervical to 1st thoracic intervertebral space. The 1st thoracic vertebra was located by identifying the most prominent spinous process corresponding to the 7th cervical vertebra, and then palpating inferiorly. To increase repeatability of marker placement, the distance from the intercristal line to the 12th thoracic to 1st lumbar vertebrae interspace, and the distance to the 7th cervical to 1st thoracic interspace

were recorded. The relaxed standing posture involved the participant standing with their feet shoulder width apart while adopting a neutral posture, with their weight equally distributed on both feet, and arms hanging relaxed by their sides. They were instructed to "stand in your normal, relaxed posture keeping your head still". For the standing 'at attention' posture the participant was instructed to stand erect with their feet together, arms relaxed by their sides and to "stand as tall as possible". To determine the angle of thoracic kyphosis, the gravity referenced inclinometer was zeroed at the 12^{th} thoracic to 1^{st} lumbar intervertebral space, and the angle at the 7^{th} cervical to 1^{st} thoracic intervertebral space was recorded. Triplicate measures of each posture were performed, and the average was used for analysis. MacIntyre and colleagues reported the intrarater test-retest reliability of thoracic kyphosis measured using a digital inclinometer for older adults (n = 36, 86% women; 69 ± 8.1 years) at risk for osteoporotic fracture (89% osteoporotic, 11 % osteopenic) to be excellent (ICC = 0.91) [26]. For the purpose of the current study, an inclinometer-determined thoracic kyphosis at baseline ≥ 50° in relaxed standing was defined as 'hyperkyphosis' [27].

Lateral thoracolumbar spine DXA

Lateral thoracolumbar spine DXA scans (Medix DR, Medilink, Mauguio, France) were performed in the left lateral decubitus position with standardised positioning reproduced at both time-points. The lateral thoracolumbar spine scan was acquired in precision mode, with a pixel size of 0.5 mm. Host software (DMS Imaging, Version 4.2.9.0, Mauguio, France) enabled adjustment of magnification, contrast and brightness of the spine image using software imaging filter tools to enhance visualisation of the vertebrae. Daily calibration of a phantom standard was performed throughout the study.

Cobb angle of kyphosis

The Cobb angle of kyphosis was determined via two methods from the lateral thoracolumbar spine images: 1) vertebral body endplate digitisation, and 2) anterior vertebral body margin digitisation, using host image processing software (DMS Imaging, Version 4.2.9.0, Medilink, Mauguio, France). The Cobb angle is considered the current gold standard measure of kyphosis [28], with a larger Cobb angle indicative of greater thoracic kyphosis.

The first approach followed a modified version of that used to measure kyphosis from supine lateral radiographs by Kado and co-workers in older women from the Fracture Intervention Trial [29]. The superior endplate of the 4th thoracic vertebra (T4) and the inferior endplate of the 12th thoracic vertebra (T12) were manually digitised, a perpendicular line from the superior endplate was extended inferiorly and a perpendicular line from the inferior endplate was extended superiorly and the angle at their intersection was measured in degrees. Digitisation of T4 was achieved by placing two markers on the anterior and posterior margins of the superior endplate, and T12 by marking the anterior and posterior margins of the inferior endplate. Obvious osteophytes were excluded.

The second approach took into account endplate angulation and tilt due to vertebral irregularity [30], whereby the anterior vertebral body margins of T4 and T12 were manually digitised, parallel lines from the anterior vertebral body margins were extended until they converged and the angle at their intersection in degrees measured. In three instances, T6 was selected as the superior limit of the curve for Cobb angle estimation as they were the highest readable level on both baseline and follow-up images. T12 was selected as the inferior limit in all cases as it was always readily visible. Cobb angle analyses were conducted by a single technician who was not blind to group allocation (ATH) and verified by an investigator blind

to group allocation for accuracy (BRB). Digitised Cobb angle readings have excellent reliability (intraclass correlation coefficient = 0.984) [29].

Densitometric vertebral fracture assessment (VFA)

The International Society for Clinical Densitometry has adopted VFA as the correct term to denote densitometric spine imaging performed for the purpose of detecting vertebral fractures [31]. We implemented the most widely used paradigms for the identification of vertebral fractures from lateral spine imaging, the semi-quantitative method proposed by Genant and colleagues [32]. This method involves a systematic approach to vertebral fracture diagnosis. VFA of lateral thoracolumbar DXA scans was performed using host software (DMS Imaging, Version 4.2.9.0, Medilink, Mauguio, France). The Medix DR software output provides a classification for deformities by type (wedge, biconcave or crush) and severity/grade (normal/grade 0, mild/grade 1, moderate/grade 2, or severe/grade 3).

At baseline, all vertebrae from T4 to L4 were readable without difficulty on all thoracolumbar DXA images. At follow-up, three participants did not have readable T4 or T5 vertebrae, and one participant did not have morphometry for T4, T5 and T6 due to overlying osseous structures (e.g. aortic calcification) obscuring the uppermost thoracic vertebral features. Thus, morphometry data for 520 readable vertebrae were included at baseline and 511 readable vertebrae were included at follow-up (the number of unreadable vertebrae was 1.7%). Each visualised vertebra from T4 through L4 on the lateral thoracolumbar spine image was labelled. For each vertebra, six morphometry points corresponding to the anterior, middle and posterior vertebral body margins were digitised. The morphometry points were used to assess reductions in anterior, middle and posterior vertebral body heights by determining if one height measure is “reduced” in relation to another height, which is

subsequently used to classify the vertebral fracture type as a wedge, biconcave or crush deformity. The wedge height ratio is calculated by dividing the anterior vertebral body height by the posterior vertebral body height. Biconcavity is calculated by dividing mid-vertebral body height by the posterior height, and the anterior height by the mid-vertebral body height. The calculation of crush fractures makes use of adjacent vertebral body heights. According to the Genant classification scheme for osteoporotic vertebral fractures, vertebral body height loss < 20% is considered normal (grade 0), height loss of 20-25% is considered a mild fracture (grade 1), height loss of 25-40% is considered a moderate fracture (grade 2), and height loss ≥ 40% is considered severe fracture (grade 3) [32].

Prevalent vertebral fractures were defined as those identified at baseline (i.e. semi-quantitative grade ≥1). Incident vertebral fractures were defined as new vertebral fractures detected at follow-up (i.e. from grade 0 at baseline to ≥ grade 1). Worsening vertebral fractures were defined as those that showed reduction in anterior, middle or posterior vertebral height at follow-up at the site of a prevalent fracture (e.g. progressing from grade 1 at baseline to grade 2 at follow-up). Baseline and follow-up lateral thoracolumbar spine images were viewed and analysed sequentially by a single technician who was not blind to group allocation (ATH). Digitised morphometry point placement for each vertebra from T4 to L4 for vertebral fracture identification were systematically crosschecked by two investigators blind to group allocation on separate occasions for accuracy (BRB and BKW).

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 25.0 (SPSS Inc., Chicago, USA). Descriptive statistics were generated for participant characteristics, biometrics and all dependent measures. Between-group comparisons of baseline

characteristics were examined using one-way ANOVA for normally distributed continuous data, and Chi-Square for categorical data. Repeated measures analysis of covariance (RMANCOVA) was performed to examine intervention effects on inclinometer-determined kyphosis angle, Cobb angle of kyphosis, and vertebral body (anterior, middle and posterior) heights from T4 to L4. Both per-protocol (n = 40) and intention-to-treat (n = 93) analyses were performed. We were unable to follow a classical intention-to-treat methodology as a number of participants did not undergo lateral thoracolumbar spine imaging at baseline, thus, a per-protocol approach (including only those who underwent measures at both time-points from the HiRIT and IAC exercise arms of the trial) was undertaken to explore exposure-based efficacy of the exercise interventions. No data were imputed for per-protocol analyses as participants underwent measures at both timepoints. All trial participants were included in the intention-to-treat analyses, with imputation of the mean percentage change value for the relevant group employed in the case of missing follow-up clinical thoracic kyphosis data; this was the case for 12 participants (12.9% of entire sample) lost to follow-up (HiRIT n = 4, IAC n = 3, control n = 5). Potential covariates identified *a priori* were age, initial weight, baseline calcium intake and baseline values. In the event, as only age differed between groups at baseline, it was applied as the lone covariate in the per-protocol analyses (n = 40). As no differences between groups in age, initial weight, baseline calcium intake or baseline values were detected for the intention-to-treat approach (n = 93), we performed unadjusted analyses of clinical thoracic kyphosis measures. To adjust for multiple comparisons, Fisher's least significant difference method was applied. Statistical significance was set at p-value < 0.05.

Results

Participant characteristics at baseline: per-protocol

Participant characteristics at baseline are presented in Table 1. A total of 40 men underwent lateral thoracolumbar spine DXA and VFA following completion of the eight-month exercise intervention (HiRIT n = 20, IAC n = 20) and are included in the current per-protocol analyses. Of the 40 participants, 38 were Caucasian, one was Asian, and one was Eurasian. Applying the World Health Organisation criteria, all participants had low bone mineral density (LS, TH and/or FN T-score ≤ -1.0); 38 had osteopenia (HiRIT n = 20, IAC n = 18), and two had osteoporosis (both IAC) according to the lowest T-score detected at either site. Two participants were taking antiresorptive osteoporosis medications (both in HiRIT group). Using an inclinometer-determined kyphosis in relaxed standing cut-off of ≥ 50°, nine participants (22.5%) were classified as hyperkyphotic; three in HiRIT and six in IAC ($p = 0.256$). Only age differed between groups at baseline, with HiRIT being younger than IAC (61.9 ± 6.7 years versus 70.3 ± 6.7 years, $p < 0.001$), thus analyses were adjusted for age. Exercise program compliance was high and did not differ between groups (HiRIT 78.0 ± 15.7% versus IAC 76.3 ± 14.9%, $p = 0.730$).

Table 1. Participant characteristics at baseline, mean ± SD (per-protocol, n = 40)

Characteristic	HiRIT (n = 20)	IAC (n = 20)	p-value
Age (years)	61.9 ± 6.7	70.3 ± 6.7	**< 0.001***
Weight (kg)	84.2 ± 13.2	82.6 ± 12.4	0.701
Height (cm)	175.4 ± 6.8	174.8 ± 7.2	0.763
BMI (kg/m^2)	27.4 ± 4.0	27.0 ± 3.6	0.787
Osteoporosis medications, n (%)	2 (10.0%)	0 (0.0%)	0.147[a]
Total BPAQ	26.6 ± 21.6	34.1 ± 18.2	0.242
Calcium intake (mg/day)	916.0 ± 404.8	997.3 ± 725.7	0.664
Lumbar spine T-score	-0.09 ± 0.80	-0.04 ± 0.83	0.833
Lumbar spine aBMD (g/cm^2)	1.094 ± 0.134	1.105 ± 0.136	0.800
Femoral neck T-score	-1.38 ± 0.41	-1.65 ± 0.49	0.070
Femoral neck aBMD (g/cm^2)	0.819 ± 0.061	0.777 ± 0.071	0.054
Total hip T-score	-0.88 ± 0.55	-1.00 ± 0.44	0.433
Total hip aBMD (g/cm^2)	0.981 ± 0.094	0.958 ± 0.073	0.395
Thoracic kyphosis			
Inclinometer neutral posture (°)	39.2 ± 9.0	42.4 ± 11.5	0.329
Inclinometer 'standing tall' (°)	31.6 ± 9.3	35.0 ± 11.9	0.320
Cobb angle endplate method (°)	35.9 ± 9.1	37.2 ± 12.6	0.697
Cobb angle anterior body method (°)	36.1 ± 9.6	38.4 ± 12.7	0.520
Thoracic hyperkyphosis ≥ 50°, n (%)	3 (15.0%)	6 (30.3%)	0.256[a]
Prevalent vertebral fractures, n (%) [b]			
None at baseline	16 (80.0%)	14 (70.0%)	0.735[a]
1 fracture at baseline	3 (15.0%)	4 (20.0%)	
2 fractures at baseline	1 (5.0%)	1 (5.0%)	
3 fractures at baseline	0 (0.0%)	1 (5.0%)	

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] Genant semi-quantitative method; * Between-group difference ($p < 0.05$)

Participant characteristics at baseline: intention-to-treat

Participant characteristics at baseline are presented in Table 2. A total of 93 men underwent clinical measures of thoracic kyphosis using an inclinometer (HiRIT n = 34, IAC n = 33, control n = 26) at baseline and eight-month follow up and are included in the intention-to-treat analyses. Four participants were taking antiresorptive osteoporosis medications (HiRIT n = 2, IAC n = 2). Using an inclinometer-determined kyphosis in relaxed standing cut-off of ≥ 50°, 22 participants (23.7%) were classified as hyperkyphotic; four in HiRIT, ten in IAC, and eight in the non-randomised control group (p = 0.123). There were no characteristic differences between groups at baseline excepting FN T-scores and aBMD which were higher for control in comparison to both exercise intervention groups. Exercise program compliance was high and did not differ between groups (HiRIT n = 30: 77.8 ± 16.6% versus IAC n = 30: 78.5 ± 14.8%, p = 0.872).

Table 2. Participant characteristics at baseline, mean ± SD (intention-to-treat, n = 93)

Characteristic	HiRIT (n = 34)	IAC (n = 33)	Control (n = 26)	p-value
Age (years)	64.9 ± 8.6	69.0 ± 6.8	67.4 ± 6.3	0.072
Weight (kg)	83.4 ± 11.7	81.2 ± 12.9	81.6 ± 10.0	0.720
Height (cm)	175.2 ± 7.0	174.6 ± 6.1	176.0 ± 7.3	0.712
BMI (kg/m^2)	27.2 ± 3.5	26.6 ± 4.0	26.3 ± 2.8	0.636
Osteoporosis medications, n (%)	2 (5.9%)	2 (6.1%)	0 (0.0%)	0.444[a]
Total BPAQ	27.2 ± 20.1	34.3 ± 21.9	39.9 ± 21.4	0.073
Calcium intake (mg/day)	897.1 ± 411.5	1018.5 ± 602.7	743.1 ± 426.3	0.108
Lumbar spine T-score	-0.22 ± 0.95	-0.17 ± 1.03	0.27 ± 1.15	0.149
Lumbar spine aBMD (g/cm^2)	1.072 ± 0.154	1.082 ± 0.171	1.153 ± 0.190	0.158
Femoral neck T-score	-1.62 ± 0.56[b]	-1.77 ± 0.54[c]	-1.28 ± 0.57	**0.004**
Femoral neck aBMD (g/cm^2)	0.781 ± 0.083[b]	0.758 ± 0.080[c]	0.832 ± 0.085	**0.004**
Total hip T-score	-1.08 ± 0.62	-1.07 ± 0.51	-0.80 ± 0.58	0.125
Total hip aBMD (g/cm^2)	0.947 ± 0.107	0.948 ± 0.088	0.996 ± 0.100	0.105
Inclinometer-based thoracic kyphosis				
Neutral posture (°)	39.2 ± 8.4	43.0 ± 10.0	43.9 ± 10.0	0.124
'Standing tall' (°)	32.3 ± 8.7	35.8 ± 10.1	37.5 ± 9.1	0.093
Thoracic hyperkyphosis ≥ 50°, n (%)	4 (11.8%)	10 (30.3%)	8 (30.8%)	0.123[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] X2 test; [b] Between-group difference ($p < 0.05$): HiRIT versus control; [c] Between-group difference ($p < 0.05$): IAC versus control.

Eight-month change in thoracic kyphosis: per-protocol

Baseline and eight-month thoracic kyphosis outcomes, with unadjusted absolute degree change are presented in Table 3 for the per-protocol analyses (n = 40). Following the eight-month supervised exercise interventions there was no difference in inclinometer-determined thoracic kyphosis angle or Cobb angle of kyphosis between HiRIT and IAC groups. Within-group analyses indicated HiRIT reduced clinical kyphosis in neutral posture (-2.3 ± 0.8°, 95% CI -3.9 to -0.6°, p = 0.009) and 'standing tall' (-2.4 ± 0.8°, 95% CI -4.0 to -0.9°, p = 0.003), and also improved Cobb angle of kyphosis using the anterior vertebral body method (-3.5 ± 1.5°, 95% CI -6.5 to -0.4°, p = 0.027). For IAC, within-group improvements in neutral posture (-2.5 ± 0.8°, 95% CI -4.2 to -0.9°, p = 0.004) and 'standing tall' (-2.0 ± 0.8°, 95% CI -3.5 to -0.4°, p = 0.014) were detected (Figure 1).

[Insert Figure 1]

Adjusting for the difference in baseline age, RMANCOVA analyses produced similar findings to the unadjusted analyses, with no between-group differences in thoracic kyphosis (p = 0.312-0.596). Adjusted within-group analyses indicated HiRIT reduced clinical kyphosis in neutral posture (-1.9 ± 0.9°, 95% CI -3.7 to -0.1°, p = 0.042) and 'standing tall' (-1.9 ± 0.8°, 95% CI -3.5 to -0.2°, p = 0.028). Within-group improvements in neutral posture (-2.9 ± 0.9°, 95% CI -4.7 to -1.1°, p = 0.003) and 'standing tall' (-2.5 ± 0.8°, 95% CI -4.2 to -0.9°, p = 0.004) were also detected for IAC. There were no within-group changes in Cobb angle of kyphosis from thoracolumbar spine DXA using either the vertebral body endplate or anterior vertebral body margin method for either HiRIT or IAC (p > 0.05).

Eight-month change in thoracic kyphosis: intention-to-treat

Baseline and eight-month inclinometer-based thoracic kyphosis outcomes, with unadjusted absolute degree change are presented in Table 4 (n = 93). Following the eight-month supervised exercise interventions there was no difference in inclinometer-determined thoracic kyphosis in neutral posture between HiRIT or IAC in comparison to the non-randomised control group, and no difference between exercise groups. Within-group analyses indicated HiRIT (-2.0 ± 0.6°, 95% -3.2 to -0.8 °, p = 0.001) and IAC (-2.4 ± 0.6°, 95% -3.7 to -1.2 °, p < 0.001) reduced clinical kyphosis in neutral posture, while no change for control was detected (p = 0.572). The HiRIT group exhibited a reduction in 'standing tall' thoracic kyphosis posture measured by inclinometer compared to an increase for control (-2.3 ± 0.6°, 95% CI -3.5 to -1.2° versus 1.4 ± 0.7°, 95% CI 0.0 to 2.7°, p < 0.05). For IAC, a reduction in clinical kyphosis in 'standing tall' was observed in within-group analyses (-1.8 ± 0.6°, 95% -3.0 to -0.6 °, p = 0.004).

Table 3. Raw baseline and eight-month measures of clinical thoracic kyphosis and densitometric Cobb angle of kyphosis, with unadjusted absolute change and 95% confidence intervals in degrees (mean ± SE) (per-protocol, n = 40)

Outcome	HiRIT (n = 20)			IAC (n = 20)			p-value
	Baseline	Follow-up	Degree change (95% CI)	Baseline	Follow-up	Degree change (95% CI)	
Inclinometer neutral posture (°)	39.17 ± 2.02	36.90 ± 2.13	-2.27 ± 0.82 (-3.92, -0.61)*	42.40 ± 2.57	39.90 ± 2.56	-2.50 ± 0.82 (-4.15, -0.85)*	0.841
Inclinometer 'standing tall' (°)	31.63 ± 2.08	29.20 ± 2.08	-2.43 ± 0.76 (-3.97, -0.90)*	35.03 ± 2.66	33.07 ± 2.75	-1.96 ± 0.76 (-3.51, -0.43)*	0.667
Cobb angle of kyphosis endplate method (°)	35.87 ± 2.04	33.61 ± 2.23	-2.27 ± 1.24 (-4.78, 0.25)	37.24 ± 2.82	36.99 ± 2.64	-0.25 ± 1.24 (-2.77, 2.27)	0.259
Cobb angle of kyphosis anterior body method (°)	36.08 ± 2.15	32.61 ± 2.46	-3.48 ± 1.51 (-6.52, -0.43)*	38.39 ± 2.83	38.50 ± 3.20	0.11 ± 1.51 (-2.94, 3.15)	0.101

Abbreviations: CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression

* Within-group change from baseline ($p < 0.05$)

Table 4. Raw baseline and eight-month measures of inclinometer-based clinical thoracic kyphosis measures, with unadjusted absolute change and 95% confidence intervals in degrees (mean ± SE) (intention-to-treat, n = 93)

Outcome	HiRIT (n = 34)			IAC (n = 33)			Control (n = 26)			p-value
	Baseline	Follow-up	Degree change (95% CI)	Baseline	Follow-up	Degree change (95% CI)	Baseline	Follow-up	Degree change (95% CI)	
Neutral posture (°)	39.24 ± 1.45	37.23 ± 1.43	-2.01 ± 0.61 (-3.21, -0.80)*	42.97 ± 1.74	40.53 ± 1.70	-2.44 ± 0.62 (-3.66, -1.22)*	43.88 ± 1.96	43.49 ± 1.75	-0.39 ± 0.69 (-1.77, 0.98)	0.077
'Standing tall' (°)	32.31 ± 1.49	29.99 ± 1.45	-2.33 ± 0.59 (-3.50, -1.16)*[a]	35.85 ± 1.77	34.08 ± 1.84	-1.77 ± 0.60 (-2.96, -0.58)*	37.46 ± 1.78	38.81 ± 1.82	1.36 ± 0.68 (0.02, 2.70)*	< 0.001

Abbreviations: CI, confidence interval; HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression

* Within-group change from baseline ($p < 0.05$); [a] Between-group difference in change ($p < 0.05$): HiRIT versus control.

Eight-month change in site-specific prevalence of vertebral fractures: per-protocol

Figure 2 shows the site-specific prevalence and grading of vertebral fractures at baseline and eight-month follow-up for HiRIT (n = 20) and IAC (n = 20). Ten participants (HiRIT n = 4 [20.0%], IAC n = 6 [30.0%]) exhibited vertebral height loss of ≥ grade 1 at baseline, indicative of prevalent vertebral fracture. At baseline, one HiRIT participant taking osteoporosis medication had prevalent grade 1 wedge fractures at T5 and T6. One HiRIT participant had a grade 1 wedge fracture at T6, another had a grade 1 wedge fracture at T8, and one participant had a grade 2 wedge fracture at T8. For IAC, one participant had three wedge fractures: T7 grade 1, T8 grade 2 and T9 grade 2. One IAC participant had two vertebral wedge fractures: T6 grade 1 and T7 grade 1. Three IAC participants had a single wedge fracture; T6 grade 1, T8 grade 1, and T12 grade 1. One IAC participant had a grade 2 crush fracture of L4. Following HiRIT, there were no incident vertebral fractures and no fractures progressed in severity. Following IAC, one wedge fracture progressed from grade 1 (mild) to grade 2 (moderate) at T8, and there were five incident wedge fractures identified at eight months: T5 grade 1, T6 grade 1, T8 grade 1, and T9 grade 1. Overall, no between-group differences for HiRIT and IAC were observed for change in anterior, middle or posterior vertebral body height.

[Insert Figure 2]

Discussion

The overarching aim of the LIFTMOR-M trial was to examine the efficacy of supervised high-intensity progressive resistance and impact training (HiRIT) or machine-based isometric axial compression (IAC) exercise on determinants of falls and fracture risk in middle-aged and older men with osteopenia and osteoporosis, and compare intervention effects with a non-randomised control group of age-matched men who continued with their usual activities for eight months in parallel. We have previously reported that HiRIT was effective for improving parameters of bone mass and strength, body composition, physical function and strength outcomes compared with control and IAC [20]. The HiRIT and IAC programs were well tolerated and associated with few and minor musculoskeletal adverse events (i.e. musculoskeletal discomfort requiring rest) [20]. The primary purpose of the current secondary analysis was to explore change in thoracic kyphosis and incident fracture from vertebral morphology following eight months of HiRIT or IAC using a per-protocol approach. Secondly, we explored change in inclinometer-determined thoracic kyphosis in standing following eight months of HiRIT, IAC and usual activities (non-randomised control group). Although there was no difference in effect detected between exercise groups observed in either per-protocol or intention-to-treat analyses for any kyphosis outcome, in general, both HiRIT and IAC improved inclinometer-derived measures of thoracic kyphosis. There was no between-group difference in change in inclinometer-determined thoracic kyphosis in neutral posture detected between HiRIT or IAC in comparison to the non-randomised control group, nor was there a difference between exercise groups at eight months. By contrast, the HiRIT group improved thoracic kyphosis in the ‘standing tall’ posture in comparison to the worsening of thoracic kyphosis observed for controls. In per-protocol analyses, HiRIT also improved Cobb angle of kyphosis using the anterior vertebral body method and we observed no incident vertebral fracture deformities or progression of

prevalent vertebral fracture following eight months of supervised training. Following eight months of IAC, one pre-existing wedge fracture progressed from grade 1 (mild) to grade 2 (moderate) and five incident wedge fractures occurred. Taken together, while between-group differences could not be detected due to sample size limitations, our exploratory findings are suggestive that both supervised bone-targeted HiRIT and IAC may improve thoracic kyphosis posture, however, for some IAC participants there was vertebral deformity progression and incident vertebral fracture across the trial period, in this small sample.

Thoracic kyphosis

Following the eight-month supervised exercise interventions there was no detectable difference in effect on inclinometer-determined thoracic kyphosis angle or Cobb angle of kyphosis between exercise groups. In per-protocol analyses, however, HiRIT improved inclinometer-determined thoracic kyphosis via reductions in kyphosis angle in neutral posture (-2.3°) and 'standing tall' (-2.4°), and a similar effect was seen for IAC (-2.5° and -2.0°, respectively). Intention-to-treat analyses showed HiRIT improved 'standing tall' thoracic kyphosis posture measured by inclinometer compared to an increase for control, however, no significant difference in change was detected between IAC and control or HiRIT and IAC for either weight-bearing posture.

A recent systematic review found that exercise programs targeting the back extensor muscles may partially reverse kyphosis, but methods of kyphosis measurement varied across trials and exercise intensities applied were only low-to-moderate [33]. Similar magnitude improvements in kyphosis to those observed in the current study have been reported following supervised strength and posture training [27,34] in the limited number of exercise-based intervention trials aimed at reducing hyperkyphosis in men. The SHEAF trial (Study of

Hyperkyphosis, Exercise, and Function) of older adults (≥ 60 years, 31.4% men in the active intervention group) with hyperkyphosis (≥ 40°) reported a 3.3° reduction in Cobb angle of kyphosis and 3.8° reduction in kyphometer-derived kyphosis following six months of supervised thrice-weekly strength and posture training [27]. Both radiographic (net 3.0° difference, $p < 0.05$) and clinical (net 3.0° difference, $p < 0.05$) measures of kyphosis improved relative to inactive controls who received only monthly health education classes. In order to examine sex-specific intervention effects, the exercise program was replicated (albeit only twice-weekly) for three months, and no differences in Cobb angle change (men -1.4° versus women -1.0°, $p > 0.05$) or kyphometer-derived kyphosis change (men -4.3° versus women -3.1°, $p > 0.05$) were observed between sexes [34]. Unlike the SHEAF trial, wherein sexes were combined, no difference in Cobb angle was detected between the intervention and control groups (net 1.7° difference, $p > 0.05$). It is possible the three-month intervention period was insufficient duration to effect Cobb angle changes.

To date, only one other study [19] has examined changes in kyphosis with the application of a bone-targeted exercise program (i.e. HiRIT). Following eight months of twice-weekly HiRIT in the LIFTMOR trial, postmenopausal women with osteopenia and osteoporosis improved inclinometer-determined thoracic kyphosis by approximately 5° [19]. In sum, previous findings suggest that exercise programs incorporating a targeted back extensor muscle strengthening component may reverse hyperkyphosis or prevent kyphosis progression, with around a 3-4° improvement in thoracic kyphosis in men.

Although improvements in clinical kyphosis outcomes were observed in the current study for both exercise groups, only HiRIT improved densitometry-determined Cobb angle of kyphosis. Although the standing lateral spine radiograph is the acknowledged reference

standard to quantify Cobb angle, for reasons of feasibility, supine lateral spine radiographs have been employed in large scale population-based studies; the Osteoporotic Fractures in Men study ('MrOs') [35] and the Study of Osteoporotic Fractures ('SOF') [36]. Kyphosis measured by Cobb angle from supine lateral thoracic radiographs versus standing Debrunner kyphometer differed by only 4° in older women with low aBMD in the Fracture Intervention Trial (FIT) [29]. We therefore contend it is reasonable to determine Cobb angle of kyphosis from a decubitus lateral thoracolumbar spine DXA scan with image resolution equivalent to a supine lateral thoracic radiograph.

While the cause and progression of kyphosis are multifactorial, back extensor muscle weakness has been identified as a significant contributor to hyperkyphosis [37]. While we observed significant exercise-induced improvements from baseline in kyphosis for neutral posture (HiRIT -2.3°, IAC -2.5°) and 'standing tall' (HiRIT -2.4°, IAC -2.0°), and an average increase for the sub-group included in the current per-protocol exploratory work (n = 40) of 25.0% and 12.8% in back extensor strength in HiRIT and IAC, respectively ($p = 0.263$), curiously change in kyphosis was not significantly associated with change in back extensor strength ($r = 0.156$-0.235, $p > 0.05$). The SHEAF trial also observed beneficial changes in kyphosis in the counter-intuitive absence of significant change in spinal muscle extension torque following postural exercise intervention [27]. While the small sample size may account for our observation, the lack of relationship of thoracic kyphosis improvement to muscle strength may be attributable to other muscle properties such as muscle activation patterns, neuromuscular coordination, or enhanced spinal mobility, which have previously been linked to thoracic kyphosis in older adults [28]. Given kyphosis typically increases by approximately 1% per annum in older men [38] and kyphosis is associated with physical

dysfunction in older men [39,40], our observed ≈ 6% improvement in neutral posture thoracic kyphosis for HiRIT and IAC is clinically important.

Vertebral fracture assessment

Whilst a small number of randomised, controlled trials have been conducted to examine change in vertebral body heights and vertebral morphology with exercise in postmenopausal women [19,41,42], no intervention trials have specifically examined those outcomes in men. Ours is the first study to explore the prevalence and incidence of vertebral fracture from vertebral morphology using lateral thoracolumbar DXA imaging pre- and post- high-intensity exercise in middle-aged and older men with osteopenia and osteoporosis, which enables us to explore preliminary vertebral morphology in a small sample of men. At baseline, four HiRIT participants had five prevalent vertebral fractures and six IAC participants had nine prevalent fractures (i.e. vertebral height loss ≥ grade 1). We note that the prevalence of vertebral fractures at baseline for our sample (50%) is higher than the typical older, community-dwelling male population (ranging from 12-26%) [6-9]. Our higher incidence likely reflects the purposeful recruitment of men at increased risk of fragility fracture, that is men ≥ 45 years of age with low to very low bone mass (T-score -1.0), including men with a history of fragility fracture. A number of factors may have contributed to the greater number of incident vertebral fractures identified at follow-up in the IAC group, including older age and higher baseline prevalence of densitometric-determined vertebral fractures (9 for IAC versus 5 for HiRIT). Both factors are risk factors for future fracture. Indeed, a single vertebral fracture increases the risk of subsequent vertebral fracture two-fold in older men [9]. Furthermore, *in vivo* flexion moments and compression and shear loads in the thoracolumbar spine of individuals with osteoporosis and a history of vertebral fracture are higher than those with osteoporosis and no vertebral fracture [43]. There is evidence to suggest that interventions

that reduce thoracic kyphosis may assist in normalising spine load profiles, even in those with osteoporosis [43], suggesting that back extensor exercise, far from being contraindicated for kyphosis, could be employed to reduce future load-related risk as appeared to be the case for HiRIT. In principle, two of the machine-based IAC isometric manoeuvres (i.e. the core pull and vertical lift exercises) may constitute movement patterns which the recommendations suggest should be avoided in individuals with osteoporosis and vertebral fractures [13,44]. This is particularly relevant if optimal spine alignment (i.e. neutral spine) is not maintained during the exercises. There were no clinical signs or symptoms of vertebral fracture reported by IAC participants during delivery of the supervised exercise intervention or across the trial period, therefore, we are unable to determine when the five incident vertebral fractures and progression of one prevalent vertebral fracture occurred in these individuals. No HiRIT participant reported acute onset severe back pain suggestive of clinical vertebral fracture during the supervised exercise training sessions, nor did they experience any clinical symptoms of incident vertebral fractures throughout the trial period outside of the training sessions. Of note, five of five existing thoracic wedge fractures were unchanged at follow-up after HiRIT and eight of nine deformities did not progress following IAC training.

As there have been no other exercise intervention trials examining vertebral safety using imaging in men it is not possible to compare our findings with others. An updated Cochrane review reported that evidence regarding the effects of exercise for improving outcomes after osteoporotic vertebral fracture, particularly for men, is scarce [45]. Moreover, no exercise intervention trials conducted in men with osteopenia and osteoporosis have objectively measured incident vertebral fracture as an outcome. By contrast, there have been a small number of studies examining change in vertebral body height and/or vertebral morphology pre- and post-intervention in postmenopausal women [19,41,42]. The earliest was a

secondary analysis of change in lateral DXA-derived vertebral body heights in postmenopausal women by Webber and colleagues following six months of home-based exercise which showed exercise was not associated with deleterious changes in vertebral height, however, the authors highlighted that further investigation was required as the analysis included only a sub-group of participants from a larger randomised controlled trial [41]. The multicentre 'Build Better Bones with Exercise' (B3E) pilot randomised controlled trial identified several radiographic-determined vertebral fractures in the intervention group following the 12-month, home-based, multi-modal exercise program, although it was unclear if they were related to delivery of the exercise intervention itself [42]. The sole other supervised exercise intervention trial to monitor vertebral body heights and vertebral morphology with high-intensity exercise exposure was the women's LIFTMOR trial [19]. The identical HiRIT protocol to the LIFTMOR-M trial was implemented in postmenopausal women with osteopenia and osteoporosis, and no incident vertebral fractures or evidence of progression of vertebral deformities were identified using the Genant semi-quantitative method [19]. Our exploratory observation that HiRIT was associated with an absence of incident vertebral fracture or progression of prevalent vertebral fracture demonstrates that supervised bone-targeted, high-intensity resistance and jump training was well tolerated in our small sample of middle-aged and older men with low aBMD. It is important to emphasise that close supervision of high-intensity resistance and impact training for technique and load progression is vital in older adults at risk of fragility fracture. While IAC participants did experience five incident vertebral fractures and progression of one prevalent vertebral fracture at eight months, we are unable to determine exactly when those fractures occurred. As the current study is the first to explore vertebral morphology following supervised machine-based IAC in our small sample, further evidence is required to establish the risk to benefit ratio of this exercise mode.

Strengths and limitations

LIFTMOR-M is the first trial to explore change in thoracic kyphosis and incident fracture following bone-targeted, high-intensity progressive resistance training in middle-aged and older men with osteopenia and osteoporosis, and is therefore highly novel. Both exercise programs were designed according to key loading principles of osteogenesis in animal models, and the principle of progressive overload in resistance training. The intervention period was of adequate length to observe adaptive changes and participants were randomly allocated to groups blinded to the study hypotheses. The inclusion of both clinical and densitometric measures of thoracic kyphosis, with verification of the latter by two investigators blind to group allocation is also a strength.

Nevertheless, there were several limitations. First, for technical reasons related to device availability, only a sub-group of the LIFTMOR-M participants underwent thoracolumbar spine DXA imaging at both time-points to examine Cobb angle of kyphosis and vertebral morphology (n = 40). Using a sub-group of participants in the per-protocol analysis of vertebral body height and thoracic kyphosis outcomes may increase the chance of a type-1 error. Vertebral fracture incidence and change in thoracic kyphosis were not primary outcome measures of the LIFTMOR-M trial, and the trial was not powered for those outcomes. Considerably larger trials are required to confirm the observations of the current work, which was exploratory in nature. Second, the sample included apparently-healthy, ambulatory, community-dwelling men which may have implications for the generalisability of our results to a frailer population. Recruitment was based on the presence of osteopenia and osteoporosis at the lumbar spine, total hip and/or femoral neck (i.e. T-score $\leq$ -1.0) rather than degree of kyphosis, thus, only 9 of the 40 participants included in the current comparative efficacy

analysis were hyperkyphotic at baseline (inclinometer-determined thoracic kyphosis ≥ 50° in relaxed standing). Given the number of individuals with hyperkyphosis was low this may have influenced our ability to see change in kyphosis. It was our intention to collect a representative sample of middle-aged and older men with low bone mass from the community, and for this reason we did not screen out men on osteoporosis medications. The small numbers of men taking osteoporosis medications resulted in strata with low numbers in this exploratory analysis, and this was not included as a covariate in line with our *a priori* statistical analysis plan. Third, although conventional standing lateral spine radiographs are considered the gold standard to quantify thoracic kyphosis and vertebral morphometry, we used DXA-derived lateral thoracolumbar spine scans in the decubitus position. Despite not being fully validated against the 'gold standard' standing lateral spine radiograph, DXA-derived Cobb angle of kyphosis assessment and VFA is increasingly used for a number of reasons. Advantages of DXA-derived lateral thoracolumbar scans over conventional radiography include a high quality image with low radiation dose as well as convenience and low cost as imaging can be conducted at the same time as bone densitometry to provide diagnostic and therapeutic information [46]. In fact, the assessment of vertebral morphology using DXA has been shown to detect vertebral fracture with acceptable precision in comparison to conventional radiographic imaging in older men [47], although detection of grade 1 fractures requires caution [48]. In the current study, 98.3% of vertebrae could be assessed for VFA, which is considerably higher than that reported from an examination of DXA-derived vertebral fracture morphometry in community-dwelling older adults ≥ 65 years (94.4% readable from T4 to L4) [49]. As most fractures were located in the mid-lower thoracic region, we do not believe this affected our observations.

Conclusion

Notwithstanding within-group effects, no between-group difference in kyphosis change was detected for HiRIT and IAC. HiRIT did, however, improve clinical kyphosis in 'standing tall' posture in comparison to continued worsening of the degree of thoracic kyphosis for the control group who continued with their usual lifestyle, suggesting HiRIT may be an effective countermeasure to age-related deterioration in posture. Our exploratory findings are suggestive that eight months of supervised twice-weekly HiRIT improved clinical measures of thoracic kyphosis and did not cause incident vertebral fractures or progression of prevalent fractures in our small sample of middle-aged and older men with osteopenia and osteoporosis. Machine-based IAC training also improved clinical measures of thoracic kyphosis, however, IAC participants experienced five incident vertebral fractures and progression of one wedge fracture from mild to moderate over the intervention period. Taken together, our exploratory observations are suggestive that HiRIT enhances posture and did not cause incident vertebral fracture, while IAC also enhances posture but participants in this group did experience progression in severity of prevalent vertebral fractures and there was evidence of incident vertebral fractures across the trial period. Our early observations suggest that supervised HiRIT represents an effective exercise intervention for middle-aged and older men with low to very low bone mass and was not associated with vertebral fracture progression or incident vertebral fracture after a total of 1747 training sessions in our small sample; the exercise intervention did not, in any way, alter vertebral morphology from baseline indicating eight months of HiRIT did not induce crush or wedge fractures. We concede that vertebral fracture was not a primary outcome measure of the LIFTMOR-M trial, and the trial was not powered to examine it. Despite our promising preliminary observations, a larger trial is required to definitively examine the question of fracture risk during HiRIT and IAC training. We recommend larger scale trials designed with vertebral morphology as a

primary outcome measure be conducted to examine the issue with sufficient statistical power to examine between group differences.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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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.

Conflict of Interest:

Belinda R. Beck and Lisa J. Weis are Directors of The Bone Clinic, Brisbane, QLD, Australia. Amy T. Harding, Conor Lambert, Steven L. Watson and Benjamin K. Weeks declare that they have no conflicts of interest.

Registration:

Australian New Zealand Clinical Trials Registry (#12616000344493).

Protocol:

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 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).

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Figures

Fig. 1 Unadjusted eight-month percent improvement (mean ± SE) in inclinometer-determined thoracic kyphosis outcomes (per-protocol, n = 40)

HiRIT n = 20, IAC n = 20; * Indicates within-group change from baseline ($p < 0.05$)

Abbreviations: HiRIT, high-intensity progressive resistance and impact training; IAC, isometric axial compression

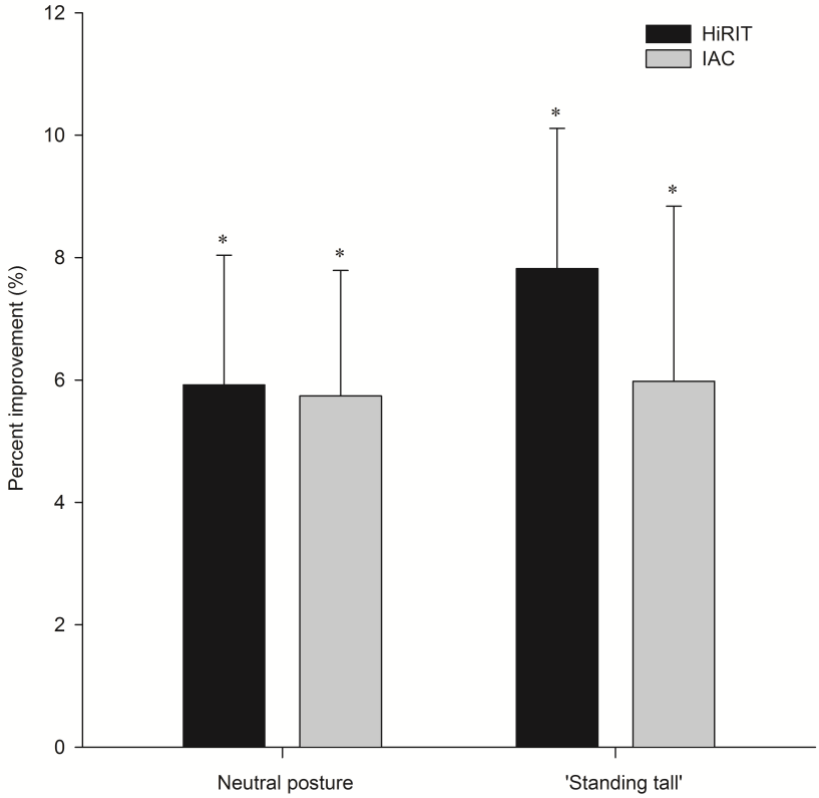

Fig. 2 Site-specific location and grading of vertebral fractures using the Genant semi-quantitative method for the HiRIT group at (a) baseline and (b) eight months, and for the IAC group at (c) baseline and (d) eight months (per-protocol, n = 40)

HiRIT n = 20, IAC n = 20; Abbreviations: IAC, isometric axial compression; HiRIT, high-intensity progressive resistance and impact training; L, lumbar; T, thoracic