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Exercise may impact on lumbar vertebrae marrow adipose tissue: Randomised controlled trial.

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Code availability: 3D plotting code is available from the authors on request.

ABSTRACT

Background: Animal and human cross-sectional data suggest that bone marrow adipose tissue (MAT) may respond to mechanical loads and exercise. We conducted the first randomised controlled trial of exercise on MAT modulations in humans.

Methods: Forty patients with chronic non-specific low back pain (NSCLBP) were enrolled in a six-month single-blinded randomised controlled trial (ACTRN12615001270505). Twenty patients loaded their spines via progressive upright aerobic and resistance exercises targeting major muscle groups (Exercise). Twenty patients performed non-weightbearing motor control training and manual therapy (Control). Testing occurred at baseline, 3-months (3mo) and 6-months (6mo). Lumbar vertebral fat fraction (VFF) was measured using magnetic resonance imaging axial mDixon sequences.

Results: When compared to baseline (percent change), lumbar vertebral fat fraction (VFF; measured using magnetic resonance imaging axial mDixon sequences) was lower in Exercise at 3mo at L2 (-3.7[6.8]%, $p = 0.033$) and L4 (-2.6[4.1]%, $p = 0.015$), but not in Control. There were no between-group effects. The effects of Exercise on VFF were sex-specific, with VFF lower in men at L2, L3, L4 at 3mo and at L1, L2, L3 and L4 at 6mo (p all$\leq$0.05), but not in women. Leg and trunk lean mass were increased at 3mo in Exercise. Changes in VFF correlated significantly with changes in total fat ($\rho = 0.40$) and lean ($\rho = -0.41$) masses, but not with lumbar BMD ($\rho = -0.10$) or visceral adipose tissue volume ($\rho = 0.23$).

Conclusions: This trial provided first prospective evidence in humans that a moderate exercise intervention may modulate lumbar VFF as a surrogate measure of MAT at 3mo, yet not 6mo. The effect of exercise on MAT may be more prominent in males than females.

Keywords: Exercise; Rehabilitation; Back pain; Spine; Magnetic resonance imaging; Marrow adipose tissue

1. INTRODUCTION

Most musculoskeletal tissues are mechanosensitive [1], as initially postulated by Wolff [2] for bone tissue in 1892 as the 'law' of loading-based bone adaptation. Similar regulation was shown for muscle, bone and tendon when loaded by exercise-based stimuli. For example, progressive resistance training results in muscle hypertrophy [3] and bone density and geometric features are optimised by impact-loading exercises [4,5]. Furthermore, the magnitude of loading most notably increases tendon cross-sectional area [6]. Despite myriad studies examining these tissues, is it unclear whether exercise-based loading adaptation of bone marrow adipose tissue (MAT) occurs [7].

Consisting primarily of hemopoietic progenitor cells and adipocytes, bone marrow is confined within cortical and trabecular bone [8]. At birth, humans mainly display red hemopoietic bone marrow, yet ageing results in conversion to yellow MAT at approximately 7% per decade [9–11] in a centripetal fashion in appendicular bones [12] and from caudal to cephalad in axial bones [13]. Mechanistically, hormonal and nutritional factors have been shown to accelerate this conversion, such as ovariectomy, glucocorticoid administration, anorexia nervosa, caloric restriction during growth, high fat diet and high alcohol intake [14].

MAT modulation is clinically relevant since it has been associated with metabolic processes locally in the bone as well as systemically. MAT is an important modulator of bone homeostasis and hemopoiesis [15] and may negatively impact these processes (e.g., altering osteoblast function); possibly explaining the association between MAT and osteoporosis [16]. As an endocrine organ, MAT increases serum adipokines [17], which subsequently increases cardiometabolic risk [18]. Mechanistically, Rosen and co-workers [15,16] have suggested that

MAT modulation arose from differentiation of marrow progenitor cells to adipose or to bone tissue according to the mechanical loading. Decreased mechanical stress has been reported to increase differentiation to adipocytes in cell cultures consisting of marrow progenitor cells [19]. As we reviewed in prior work [7], studies in rats and mice have shown that exercise results in a reduction or suppression of femoral and proximal tibia MAT accumulation in normal animals and in models of high-fat diet, diet-induced obesity, diabetes, caloric restriction.

In humans, cross-sectional studies have investigated the effect of exercise on MAT. In one study, wrestlers had lower vertebral MAT than untrained men, as measured via magnetic resonance imaging (MRI) [20]. In another study, female athletes with normal menstrual cycles had lower lumbar vertebral MAT than referents, but the difference did not reach statistical significance [21]. Athletes engaging in impact activities had lower tibial diaphyseal adiposity compared with those engaging in non-impact sports and referents, as measured with peripheral quantitative computed tomography [22]. Still in athletes, runners but not cyclists had lower vertebral MAT, assessed via MRI, and showed a dose-response per kilometre run [7]. Finally, people who reported exercising two hours or more per week had three to five percentage points lower lumbar MAT than referents [23]. One longitudinal paediatric study in children aged three to six years old showed that a 10-week exercise intervention decreased femoral MAT [24].

In contrast, physical inactivity, has been documented to increase MAT. Minaire and colleagues [25] measured increased MAT volume on iliac bone biopsies after 12 weeks of paraplegia. Strict bed rest for sixty days increased MAT by 2.4 percentage points in women [26] and 3.6 percentage points in men [27], with this latter study also providing evidence that exercise blunted the MAT increase associated with strict bed rest [28].

Overall, the current literature indicates that exercise in humans may be associated with lower MAT and that some types of exercise have a preferential effect on vertebral MAT. However, evidence in support of causal relationships is lacking due to primarily observational studies to date. To our knowledge, no randomised controlled trial (RCT) has ever evaluated the causal link between exercise and MAT. Our primary aim was to examine whether an exercise program designed for spinal loading [29,30] can reduce vertebral MAT compared to a non-weightbearing control. This aim was a pre-planned secondary end-points analysis of a wider investigation [29,30] examining the effect of exercise on the spine in people with non-specific chronic low back pain (NSCLBP ACTRN12615001270505).

2. MATERIAL AND METHODS

This study was a pre-planned sub-study conducted as part of a prospectively registered single-blinded six-month RCT (Australian New Zealand Clinical Trials Registry ACTRN12615001270505, date registered: 20/11/2015; CONSORT flow chart in Supplemental Figure 1) that examined the efficacy of exercise in people with NSCLBP compared to control in adults with NSCLBP (n = 40 in total, 1:1 allocation ratio). The project protocol and results on the primary end-point were recently published [29,30]. The original sample size calculation was based on primary outcome intervertebral disc outcomes [30]. The project was approved by the institutional ethics review board and ran from December 2015 to December 2016 in Melbourne, Australia with the final follow-completed in May 2017. All patients provided informed written consent prior to participation. There were no changes to the study methods (such as eligibility criteria) after trial commencement.

2.1. Patients

Forty men and women aged 25–45 years with NSCLBP (i.e., greater than three months with no definitive underlying pathology) were included. Exclusion criteria included: 1) history of spinal surgery, 2) history of traumatic injury to spine (e.g., fracture and car accident), 3) scoliosis previously requiring medical consultation, 4) symptoms of nerve root compression, 5) current treatment for NSCLBP, 6) engaging in more than 150 minutes per week of moderate-vigorous exercise training, 7) participation in formal organised sport, 8) participation in gym-based exercise training more than once per week, 9) current smoking, and 10) possession of implants unsuitable for MRI. Pain intensity of the low back was measured with a 100-point visual analogue scale. The modified Oswestry disability index was used to measure patient

disability due to NSCLBP. All patients underwent offsite randomisation procedures by a researcher (AH) who had no contact with volunteers or involvement in data collection/analysis. A randomisation schedule (using block randomisation with random block lengths and stratification for sex obtained from www.random.org) was implemented.

2.2. Exercise: General strength and conditioning

The exercise intervention consisted of up to fifty two one-hour one-on-one gym-based sessions with an exercise physiologist (i.e., tertiary trained clinical exercise allied health professionals [30]). The complete exercise training protocol was published in the protocol paper [29]. In brief: during the first three months, patients attended two sessions per week. During the second three-month period, participants could self-select to attend either one or two sessions per week. Sessions included aerobic and resistance exercises, which were progressed in a time-contingent manner. During the first six weeks, patients were required to complete 5–10 minutes of mental rehearsal of movements they nominated as being fear-inducing for them given this is an established strategy [31] for overcoming fear avoidance behaviours common in those with CLBP [32]. Exercises were designed to result in mechanical dynamic axial loading of the spine [30]. In each session, participants performed 20 minutes of treadmill aerobic exercise, beginning at an intensity of 65–70% of maximal heart rate in the first two weeks and increasing to 65–85% of maximal heart rate. The resistance training program consisted of five, four to six-week mesocycles (familiarisation, muscle strength, single week de-load, local muscle endurance, muscle strength, local muscle endurance). Repetition maximum was determined at the first consultation for each mesocycle, and training intensity remained at two repetitions below volitional fatigue. Resistance exercise was progressed via repetitions, sets, load, or exercise type according to the mesocycle. Resistance exercises were structured throughout the

week to challenge lifting (e.g., squat, deadlift), pushing (e.g., standing cable chest press, dumbbell chest press), pulling (e.g., split stance cable row, single leg opposite arm cable row), trunk flexion (e.g., partial curl ups, Bosu-ball crunches) and trunk extension (e.g., supine bridge, supine swiss-ball bridge). Exercise technique and body posture were monitored by the exercise physiologist and feedback provided where needed. Moreover, patients allocated to exercise were required to complete 20–40 minutes of home-based aerobic training in the form of walking or jogging three times per week throughout the study. Given the nature of the intervention, neither the patients nor the clinicians were able to be blinded.

2.3. Control: Motor control training and manual therapy

The control intervention consisted of twelve 30-minute one-on-one physiotherapy-led sessions in a physiotherapy private practice (Advance Healthcare, Boronia, Melbourne, Australia) [29]. Ten sessions (1–2 per week) were delivered during the first three months and two sessions were provided in the second three months. Manual therapy was provided at the discretion of the clinician and included posterior-anterior and transverse mobilisations using rotation, as well as soft tissue manipulation within the lumbar and pelvic regions. The aim of manual therapy was to reduce segmental hypomobility and facilitate pain modulation of symptomatic spinal levels. Motor control training [33] targeted transversus abdominis, multifidus and pelvic floor musculature in non-weight bearing activities. Progression was on a pain-contingent basis. Including transversus abdominis and multifidus contraction in specific functional activities was only included in treatment if these specific functional activities were part of the patient's goals. There was no prescription of physical activity. Similar to the exercise intervention, blinding was not feasible for the patient, nor clinician.

2.4. Magnetic resonance imaging and blinded analysis

Scanning was performed at baseline, three months (3mo) and six months (6mo). A 3.0T Phillips Ingenia scanner (Amsterdam, Netherlands; software release 4.1.3.4) was used with a spinal coil. The scanner operator was blinded to group allocation. Participants were asked to lay supine with a cushion wedged between both knees and hands placed above their head. 65 true-axial slices with an mDixon sequence (slice thickness: 3.5mm, inter-slice distance: 0mm, repetition time: 3.6ms, echo times: 1.21/2.3ms, field-of-view: 250APx300RLmm interpolated to 432x432pixels, bandwidth: 1526.3Hz) to encompass the spine from the sacrum up to and including T12 were collected. The assessor was blinded to group allocation and study time-point by assigning each data set a random number prior to image analysis (obtained from www.random.org). ImageJ 1.50i (https://imagej.nih.gov/ij/) was used to trace around the vertebra. The spine was segmented to minimise opportunities for operator error in choosing the vertebral levels. After tracing the region of interest, a custom written ImageJ plugin (ROI Analyzer; https://github.com/tjrantal/RoiAnalyzer; https://sites.google.com/site/daniellbelavy/home/roianalyser) output signal intensity for fat and water mDixon images. The percentage of fat for each anatomical slice was then calculated by the formula: fat fraction = 100%*signal intensity fat/(signal intensity fat + signal intensity water; Figure 1). Vertebral fat fraction (VFF) is a surrogate for the vertebral MAT [7,13]. We have implemented this method previously to monitor longitudinal changes [34] and the coefficient of variation for water-fat imaging to quantify marrow adipose tissue in the lumbar spine, pelvis and proximal femurs ranges from 0.69% to 1.70% [35].

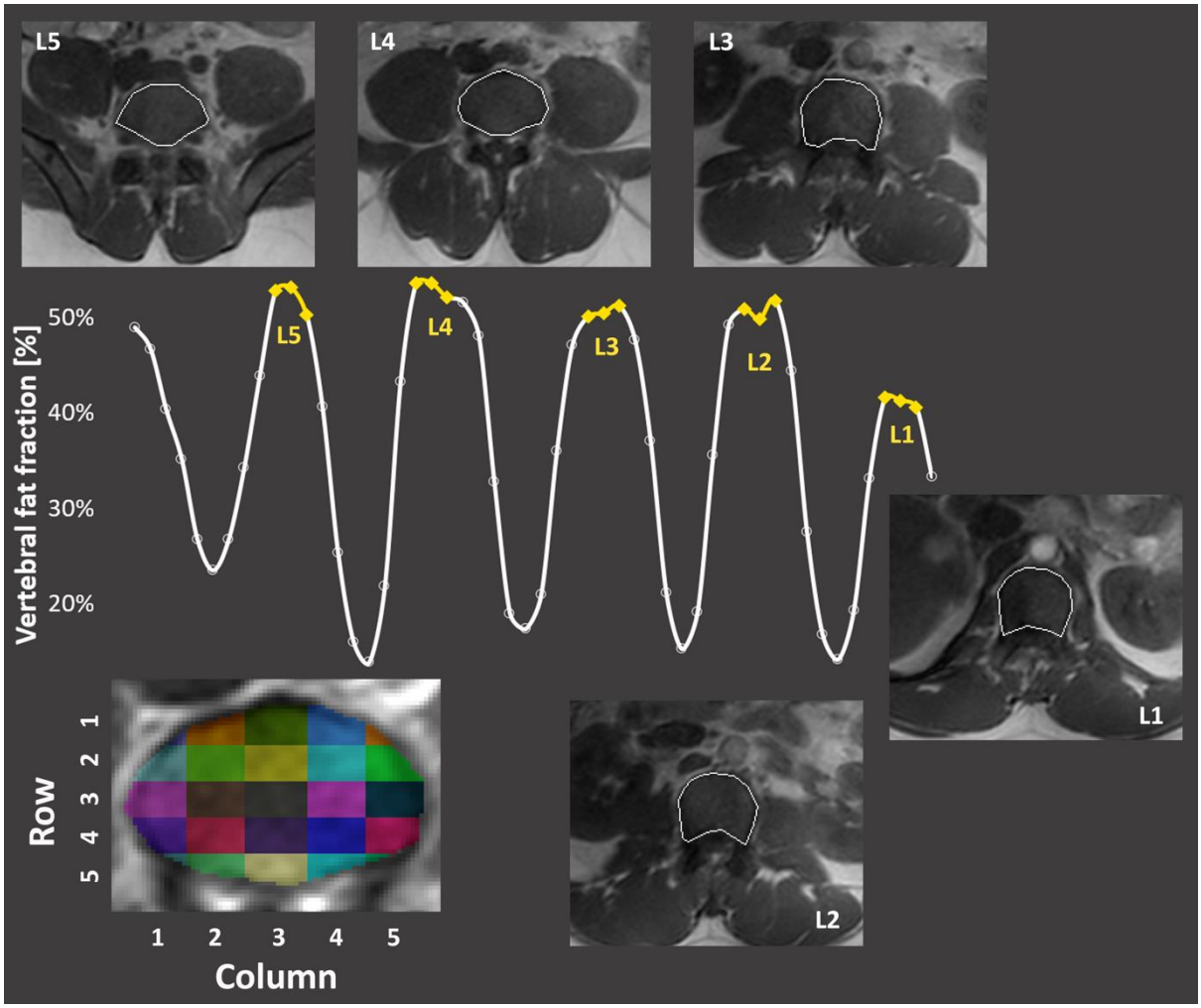


Figure 1. Quantification of vertebral fat fraction.

Example data from one participant are shown. An axial mDixon sequence was used. To minimise operator error, all images from sacrum to immediately cephalad of the first lumbar (L1) vertebra were measured. The operator traced around the vertebra or intervertebral disc. Then, signal intensity in water and fat images were calculated and subsequently the fat fraction calculated. At each vertebral level, VFF of the three contiguous slices of highest average fat fraction were averaged to calculate the vertebral fat fraction (see *Material and Methods* for more detail). The inset at bottom left shows the division of the vertebra into 25 sub-regions for generated three-dimensional plots (Figure 3).

Subsequently, custom written code (in the R statistical environment, version 3.4.2, www.r-project.org) automatically selected, at each vertebral level, the three contiguous slices of highest VFF. The VFF from these three slices was averaged at each lumbar level and used for data analyses. Average data from all lumbar levels was also calculated. Finally, we generated three-dimensional plots of fat distribution by subdividing each vertebra into five equidistant columna and five equidistant rows, creating 25 subregions. For each subregion, the same processes were implemented.

2.5. Dual X-ray absorptiometry

Total and regional lean and fat mass (kg), total body percent lean and fat mass (%), and areal bone mineral density (aBMD) were assessed by DXA using software version 12.30.008 and enCORE CoreScan software version 16 (Lunar iDXA, GE Lunar Corp., Madison WI). Moreover, trabecular bone score (TBS; unitless) was determined using TBS iNsight software version 2.1 (MediMaps, Mérignac, France). Participants were assigned an individual study identifier code which allowed for blinded assessment of all DXA scans. Patient positioning and manual segmentation using custom regions of interest followed previously established protocols [36]. Manual review and adjustments were made by the researcher (PJO), as needed. The appendicular regions were defined as the tissue distal to a line bisecting the shoulder joint for the upper limbs and bisecting the hip joint for the lower limbs. Appendicular lean mass (ALM) was calculated as the aggregate of lean mass in both arms (kg) plus both legs (kg). Visceral adipose tissue was estimated using the CoreScan option of the enCORE software. Regional scans were performed for BMD of the lumbar spine (L1–L4). For DXA-derived outcomes within our laboratory, short-term coefficients of variation were 0.6–1.0% for BMD and 1.0–1.7% for lean mass.

2.6. Statistical analyses

The R statistical environment (version 3.4.2, www.r-project.org) was used for all analyses. An intent-to-treat analysis approach was implemented. A linear-mixed effects model with allowances for heterogeneity of variance according to study date was performed. Next, repeated-measures analysis of variance examined for differences between group over time, and *a priori t*-tests were performed comparing each follow-up time-point to baseline. An alpha-level of 0.05 was chosen for statistical significance. To minimise the risk of type I errors and aid interpretation of the findings, *p*-values were also adjusted by the false discovery rate method [37]. The primary analysis evaluated vertebral fat fraction at each vertebral level given known level-specific differences in lumbar spine tissue [38]. As MAT content is known to be greater in men than women [12], we also explored pre-planned sex-specific differences in the response to the intervention. To give insight into potential relationships between changes in MAT and bone, lean and fat changes in other body regions Spearman's correlation coefficients were calculated between VFF and DXA variables. Spearman's correlation coefficients were also calculated controlling for participant sex. Values presented are mean(SD) unless otherwise stated.

RESULTS

Forty patients were randomised into the exercise or control conditions (20 patients in each group). Supplemental Table 1 presents an overview of baseline characteristics; baseline values for outcome parameters are included in Tables 1–3. Mean attendance was 31/52 sessions (60%; males: 55%, females: 68%) for exercise and 9/12 sessions (77%) for control over six months. Eight patients withdrew from the study between baseline and 6mo follow-up (exercise: n = 3; control: n = 5; Supplemental Figure 1). No adverse events were reported.

3.1. Effects of the exercise intervention on VFF

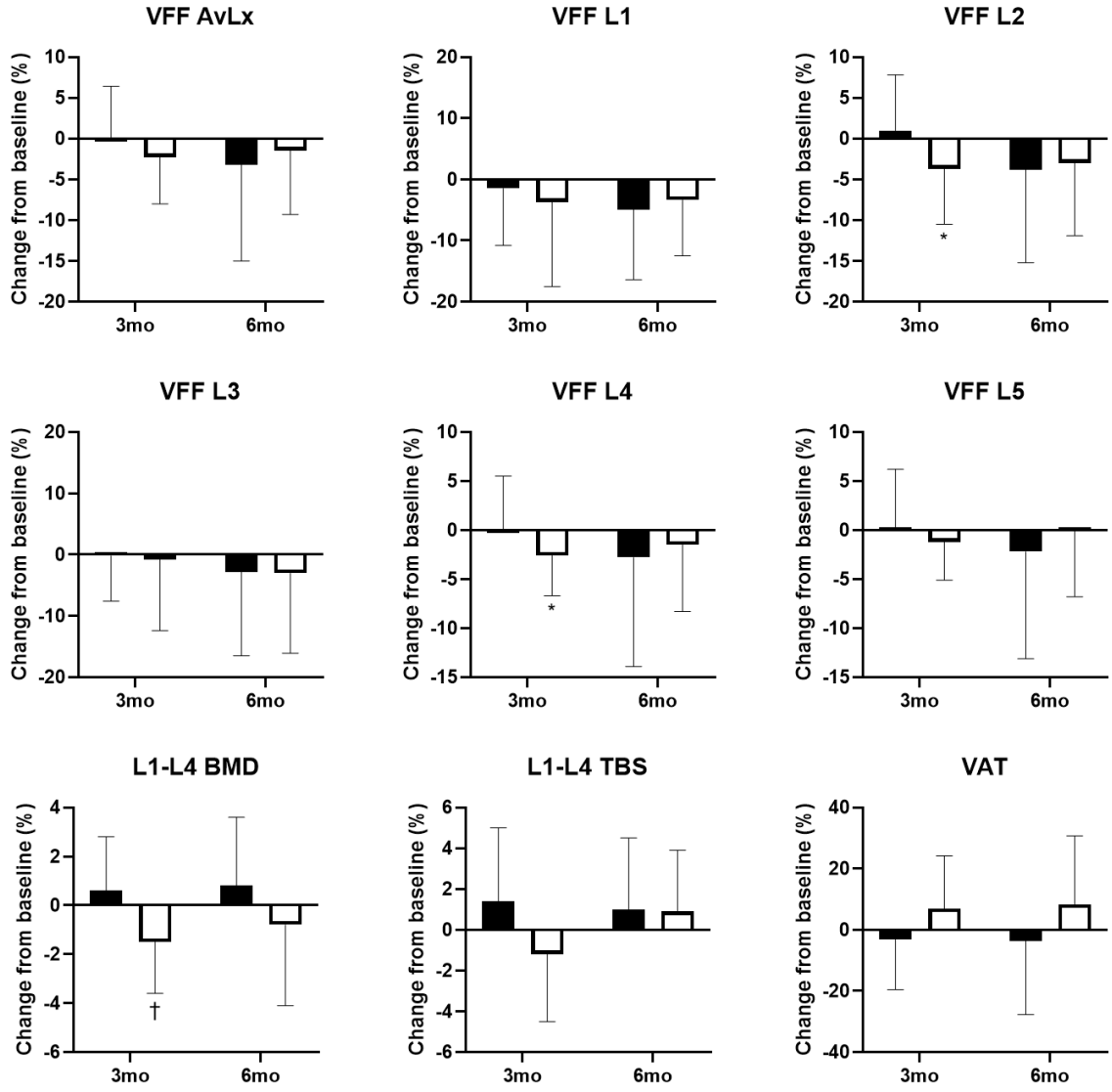
At 3mo, VFF decreased in Exercise at L2 (-3.7[6.8]%, p = 0.033) and L4 (-2.6[4.1]%, p = 0.015), but not in Control (Table 1; Figure 2). This effect was no longer significant at 6mo and the group×time interaction was not significant. These effects did not persist after adjustment of p-values for type I error via the false discovery rate (p = 0.079). At other vertebral levels, the changes in VFF were not statistically significant. Figure 3 presents absolute regional changes in VFF within the vertebral body. Interestingly, there was a distinct sex-specific effect of exercise on VFF. Significant reductions in VFF were measured in male participants at L2, L3, L4 at 3mo and at L1, L2, L3, L4 at 6mo (Table 2). The group×time interaction was significant at L2 and L4 in male participants. After p-value adjustment for the false discovery rate, the reductions in VFF at 6mo in males remained statistically significant at L1, L3 and L4 (p < 0.011). The sex×time interaction was significant at L3 (p = 0.010) and for the average of all lumbar levels (p = 0.044). The sex×group×time interaction was not (p > 0.14).

Table 1. Changes in vertebral fat fraction (VFF), lumbar bone, visceral adipose tissue and body composition over time among the total sample (n=40).

Group	Vertebral fat fraction				
	Baseline	3mo	6mo	Δ 3mo	Δ 6mo
			VFF AvLx (p = 0.30)		
Control	49.4(6.8)	49.4(6.0)	47.8(7.6)	0.1(6.3)%	-3.2(11.8)%
Exercise	50.7(9.4)	49.6(8.5)	50.0(8.9)	-2.3(5.7)%	-1.5(7.8)%
			VFF L1 (p = 0.78)		
Control	46.6(6.6)	45.9(6.4)	44.3(7.1)	-1.5(9.3)%	-4.9(11.5)%
Exercise	47.9(8.4)	46.1(9.9)	46.2(8.6)	-3.7(13.8)%	-3.4(9.1)%
			VFF L2 (p = 0.10)		
Control	47.8(7.5)	48.3(7.1)	46.0(8.2)	1.0(6.8)%	-3.8(11.4)%
Exercise	49.5(9.5)	**47.6(8.3)***	48.0(8.8)	**-3.7(6.8)%***	-3.0(8.9)%
			VFF L3 (p = 0.72)		
Control	49.5(6.8)	49.5(5.7)	48.2(8.0)	-0.2(7.4)%	-2.8(13.7)%
Exercise	51.2(11.1)	50.8(9.2)	51.0(9.6)	-0.8(11.6)%	-0.3(13.1)%
			VFF L4 (p = 0.13)		
Control	51.4(6.9)	51.5(5.9)	50.0(7.6)	0.1(5.4)%	-2.8(11.1)%
Exercise	52.5(9.2)	**51.1(8.4)***	51.7(8.9)	**-2.6(4.1)%***	-1.5(6.8)%
			VFF L5 (p = 0.38)		
Control	51.5(7.7)	51.6(6.8)	50.3(8.2)	0.3(5.9)%	-2.2(10.9)%
Exercise	52.7(9.9)	52.0(8.9)	52.6(9.4)	-1.2(3.9)%	-0.1(6.7)%
			L1-L4 bone mineral density [g/cm2] (p = 0.02)		
Control	1.20(0.10)	1.21(0.09)	1.21(0.09)	0.6(2.2)%	0.8(2.8)%
Exercise	1.20(0.16)	**1.18(0.14)†**	1.19(0.15)	**-1.5(2.1)%†**	-0.8(3.3)%
			L1-L4 trabecular bone score [no unit] (p = 0.10)		
Control	1.46(0.11)	1.48(0.09)	1.47(0.08)	1.4(3.6)%	1.0(3.5)%
Exercise	1.48(0.09)	1.46(0.08)	1.47(0.08)	-1.2(3.3)%	-0.9(3.0)%
			Visceral adipose tissue volume [l] (p = 0.22)		
Control	0.81(0.74)	0.78(0.65)	0.78(0.64)	-3.2(16.4)%	-3.6(24.1)%
Exercise	0.91(0.62)	0.97(0.56)	0.98(0.58)	7.0(17.2)%	8.3(22.4)%

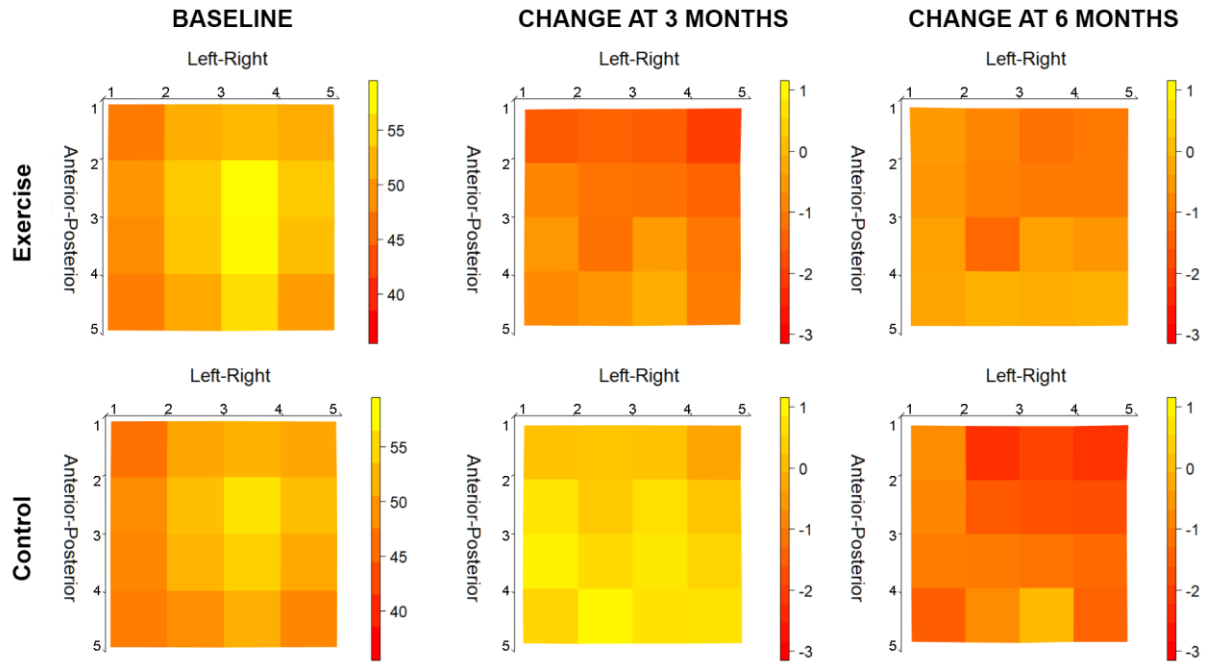
Data are mean(SD) at baseline, 3-months and 6-months in percent as well as mean(SD) percentage change in this value at 3-months (Δ 3mo) and 6-months (Δ 6mo). *: unadjusted P<0.05 and † unadjusted P<0.01 versus baseline before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives. P-values next to the vertebral level indicate significance of the group*time interaction. AvLx: average of all lumbar vertebrae. See Table 3 for data from males and females separately.

Figure 2. Percent change in vertebral fat fraction (VFF), lumbar bone mineral density (BMD), lumbar trabecular bone score (TBS) and visceral adipose tissue (VAT) among the total sample (n=40).



Data are percent change from baseline. *: unadjusted P<0.05 and † unadjusted P<0.01 versus baseline before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives. □ Exercise, ■ Control.

Figure 3. Regional fat fraction change within the lumbar vertebrae among the total sample (n=40).



Values at baseline are absolute vertebral fat fraction (in percentage points), at 3 months and 6 months values are change in vertebral fat fraction (in percentage points). Data are averaged from all lumbar vertebrae. Colour code: from yellow (more adipose tissue) to red (more hemopoietic tissue). See Figure 1 for details of subregion analyses.

Table 2: Changes in vertebral fat fraction (VFF) over time by sex.

Group	Male					Female				
	Baseline	3mo	6mo	Δ 3mo	Δ 6mo	Baseline	3mo	6mo	Δ 3mo	Δ 6mo
			AvLx (p = 0.10)					*AvLx (p = 0.77)*		
Control	50.3(6.3)	50.6(5.1)	46.9(8.8)	0.5(5.7)%	-6.8(15.2)%	48.4(7.4)	48.1(6.9)	48.7(6.0)	-0.7(7.0)%	0.5(4.4)%
Exercise	54.1(7.0)	**51.9(6.7)***	**51.2(6.5)‡**	**-4.0(4.6)%***	**-5.3(3.7)%‡**	46.6(12.0)	46.6(11.0)	48.3(11.3)	0.0(6.6)%	3.5(8.8)%
			L1 (p = 0.86)					*L1 (p = 0.95)*		
Control	47.9(6.7)	46.8(6.6)	44.3(8.7)	-2.3(7.5)%	-7.5(13.2)%	45.3(6.8)	44.9(7.1)	44.8(5.5)	-0.8(10.4)%	-1.2(5.1)%
Exercise	50.0(7.5)	47.1(10.7)	**46.6(6.8)†**	-5.8(17.2)%	**-6.8(4.9)%†**	45.3(12.0)	44.6(11.2)	45.4(11.5)	-1.5(8.9)%	0.2(10.5)%
			L2 (p = 0.029)					*L2 (p = 0.93)*		
Control	49.5(7.4)	50.6(7.0)	45.9(9.2)	2.3(6.0)%	-7.2(13.6)%	46.2(7.4)	46.1(6.9)	46.5(6.0)	-0.1(7.3)%	0.7(4.8)%
Exercise	53.1(5.9)	**50.1(4.7)***	**49.8(5.4)***	**-5.6(5.7)%***	**-6.2(7.6)%***	45.0(11.6)	44.5(10.8)	45.6(11.1)	-1.0(7.3)%	1.4(9.5)%
			L3 (p = 0.16)					*L3 (p = 0.66)*		
Control	50.3(6.4)	50.5(5.1)	46.7(9.2)	0.4(6.4)%	-7.2(16.6)%	48.8(7.5)	48.4(6.8)	49.8(6.1)	-0.8(8.4)%	2.0(6.8)%
Exercise	55.4(7.2)	**53.2(6.5)***	**51.6(6.6)‡**	**-4.0(4.3)%***	**-6.9(5.0)%‡**	45.9(14.0)	47.6(11.9)	50.0(12.0)	3.7(16.7)%	8.8(17.1)%
			L4 (p = 0.048)					*L4 (p = 0.75)*		
Control	52.1(6.6)	52.7(5.5)	49.1(8.4)	1.0(5.2)%	-5.7(13.3)%	50.7(7.8)	50.2(7.0)	51.0(6.5)	-1.1(5.4)%	0.6(4.4)%
Exercise	55.8(7.2)	**53.6(6.9)***	**53.0(6.6)‡**	**-4.0(4.4)%***	**-5.0(2.6)%‡**	48.4(10.7)	48.1(10.1)	49.9(10.6)	-0.7(2.8)%	3.1(7.0)%
			L5 (p = 0.33)					*L5 (p = 0.46)*		
Control	51.8(7.1)	52.5(6.0)	49.6(9.2)	1.2(5.2)%	-4.4(14.5)%	51.1(8.1)	50.7(7.7)	51.1(6.6)	-0.8(7.1)%	0.0(3.8)%
Exercise	56.1(7.6)	55.2(6.8)	54.4(7.0)	-1.6(4.2)%	-3.0(5.3)%	48.5(11.5)	48.2(10.8)	50.4(11.1)	-0.7(3.2)%	3.7(6.4)%

Data are mean(SD) at baseline, 3-months and 6-months as well as mean(SD) percentage change in this value at 3-months (Δ 3mo) and 6-months (Δ 6mo). *: unadjusted P<0.05, † unadjusted P<0.01 and ‡ unadjusted P<0.001 versus baseline before adjustment for multiple comparisons using the false discovery rate method. P-values next to parameter names indicate significance of the group*time interaction. After p-value adjustment

for the false discovery rate, the reductions in VFF at 6mo in males remained statistically significant at L1 (p = 0.011), L3 (p = 0.0060) and L4 (p = 0.0004). It is unlikely that exercise compliance explain the sex-differences observed. Compliance in the Exercise group was lower in magnitude in male Exercise participants (mean completion of total number of planned exercise sessions: 55%) than females (mean: 68%)

3.2. Effects of the exercise intervention on other outcome measures

Lumbar (L1-4) bone mineral density was reduced at 3mo in Exercise (-1.5[2.1]%, $p = 0.0054$; Table 1; Figure 2), with no significant change in Control. The group×time interaction was significant ($p = 0.02$). Trabecular bone score and visceral adipose tissue volume did not change significantly (Figure 2). Leg lean mass (3mo: 1.8[3.3]%, $p = 0.026$; 6mo: 2.6[6.1]%, $p = 0.09$) was increased with Exercise at 3mo, but not Control (group×time interaction: $p = 0.15$; Table 3). Trunk lean mass increased (3mo: 3.4[5.8]%, $p = 0.019$; 6mo: 2.2[5.1]%, $p = 0.09$) at 3mo in Exercise but not Control (group×time interaction: $p = 0.03$). There was not a sex-specific effect of exercise on the DXA outcome measures (Supplemental Tables 2 and 3).

Table 3: Changes in body composition over time in the total sample (n=40).

Group	Outcome measures				
	Baseline	3mo	6mo	Δ 3mo	Δ 6mo
		Arm bone mass [kg] (p = 0.81)			
Control	0.38(0.09)	0.38(0.08)	0.38(0.08)	0.4(1.4)%	0.1(1.2)%
Exercise	0.36(0.08)	0.37(0.07)	0.37(0.07)	0.6(2.7)%	0.7(2.9)%
		Leg bone mass [kg] (p = 0.43)			
Control	1.05(0.26)	1.05(0.23)	1.05(0.23)	-0.1(0.8)%	-0.1(0.9)%
Exercise	0.97(0.16)	0.98(0.15)	0.98(0.15)	0.2(1.0)%	0.2(0.7)%
		Trunk bone mass [kg] (p = 0.71)			
Control	0.82(0.15)	0.82(0.14)	0.83(0.13)	0.4(2.5)%	1.0(2.7)%
Exercise	0.80(0.16)	0.79(0.15)	0.80(0.14)	-0.2(3.3)%	0.3(2.4)%
		Total bone mass [kg] (p = 0.86)			
Control	2.82(0.52)	2.83(0.46)	2.83(0.45)	0.1(0.9)%	0.3(0.9)%
Exercise	2.70(0.38)	2.70(0.35)	2.70(0.35)	0.1(1.1)%	0.2(0.7)%
		Arm fat mass [kg] (p = 0.99)			
Control	2.69(1.00)	2.70(0.88)	2.66(0.86)	0.4(8.1)%	-1.1(9.3)%
Exercise	2.79(1.08)	2.82(0.99)	2.78(1.00)	0.8(6.9)%	-0.5(8.9)%
		Leg fat mass [kg] (p = 0.65)			
Control	8.42(2.52)	8.28(2.19)	8.25(2.15)	-1.7(8.1)%	-2.1(8.9)%
Exercise	9.06(4.41)	9.02(4.07)	9.14(4.08)	-0.4(6.7)%	0.8(7.2)%
		Trunk fat mass [kg] (p = 0.53)			

					-
Control	12.66(5.76)	12.59(5.06)	12.65(4.97)	-0.5(9.4)%	0.1(11.1)%
Exercise	14.00(6.86)	14.15(6.28)	14.50(6.34)	1.1(6.2)%	3.6(8.8)%
		Total fat mass [kg] (p = 0.60)			
Control	24.66(8.76)	24.47(7.67)	24.46(7.52)	-0.8(8.3)%	-0.8(9.4)%
Exercise	26.75(12.06)	26.89(11.05)	27.31(11.15)	0.5(5.4)%	2.1(7.7)%
		Arm lean mass [kg] (p = 0.26)			
Control	5.69(2.06)	5.71(1.85)	5.88(1.81)	0.4(5.4)%	3.3(6.4)%
Exercise	5.58(1.47)	5.70(1.35)	5.67(1.35)	2.0(4.4)%	1.6(4.2)%
		Leg lean mass [kg] (p = 0.15)			
Control	17.57(4.64)	17.56(4.17)	17.69(4.10)	0.0(1.9)%	0.7(4.7)%
Exercise	17.23(3.20)	**17.55(2.91)***	17.68(3.04)	**1.8(3.3)%***	2.6(6.1)%
		Trunk lean mass [kg] (p = 0.03)			
Control	22.71(4.94)	22.53(4.38)	22.85(4.34)	-0.8(3.6)%	0.6(5.4)%
Exercise	21.62(3.40)	**22.36(3.18)***	22.09(3.13)	**3.4(5.8)%***	2.2(5.1)%
		Total lean mass [kg] (p = 0.03)			
Control	49.18(11.57)	49.02(10.34)	49.64(10.20)	-0.3(2.4)%	0.9(4.5)%
Exercise	47.67(7.77)	**48.83(7.15)†**	48.66(7.27)	**2.4(3.5)%†**	2.1(4.5)%

Data are mean(SD) at baseline, 3-months and 6-months as well as mean(SD) percentage change in this value at 3-months (Δ 3mo) and 6-months (Δ 6mo). *: unadjusted P<0.05, † unadjusted P<0.01 and ‡ unadjusted P<0.001 versus baseline before adjustment for multiple comparisons using the false discovery rate method. P-values next to parameter names indicate significance of the group*time interaction.

3.3. Correlation analyses

At 3mo, the change in average lumbar VFF (Table 4) correlated positively with changes in total ($\rho = 0.40$), trunk ($\rho = 0.35$) and leg ($\rho = 0.46$) fat mass and correlated negatively with total ($\rho = -0.41$) and arm ($\rho = -0.48$) lean mass. No statistically significant correlations existed with changes in lumbar (L1-L4) bone mineral density ($\rho = -0.10$), trabecular bone score ($\rho = -0.25$) and visceral adipose tissue volume ($\rho = 0.23$). At 6mo, a similar pattern was seen, but with significant correlations persisting with changes in fat mass only. Similar correlations were

found at individual vertebral levels (Table 4). The correlations remained after adjustment for participant sex (Supplemental Table 4).

Table 4: Correlations between changes in vertebral fat fraction (VFF) after 3 months (top panel) and 6 months (bottom panel) in the total sample (n=40)

VFF at level..	L1-L4 bone mineral density	L1-L4 trabecular bone score	Visceral adipose tissue volume	Arm bone mass	Leg bone mass	Trunk bone mass	Total bone mass	Arm fat mass	Leg fat mass	Trunk fat mass	Total fat mass	Arm lean mass	Leg lean mass	Trunk lean mass	Total lean mass
Spearman's correlation between changes at 3 months vs. baseline															
AvLx	-0.10	-0.25	0.23	0.02	0.20	0.02	-0.01	0.25	**0.46†**	**0.35***	**0.40***	**-0.48†**	-0.32	-0.29	**-0.41***
L1	-0.20	-0.20	0.25	-0.15	0.32	0.07	0.13	0.02	0.32	0.21	0.25	-0.34	-0.30	-0.24	-0.30
L2	-0.14	-0.22	0.09	0.05	0.16	-0.08	-0.06	0.24	0.34	0.26	0.30	**-0.35***	**-0.40***	-0.24	**-0.37***
L3	-0.04	-0.21	0.19	0.15	0.05	-0.02	-0.07	0.31	**0.38***	0.30	0.34	-0.46†	-0.25	-0.24	**-0.37***
L4	-0.07	-0.10	0.15	-0.05	0.18	-0.07	-0.14	0.19	**0.41***	0.26	0.32	**-0.41***	**-0.35***	-0.22	**-0.36***
L5	0.00	-0.20	0.12	0.16	-0.03	0.13	0.00	0.24	**0.38***	0.21	0.29	-0.47†	-0.20	-0.30	**-0.39***
Spearman's correlation between changes at 6 months vs. baseline															
AvLx	-0.22	-0.27	0.24	-0.02	0.11	0.04	0.05	0.18	**0.47†**	**0.42***	**0.40***	-0.21	-0.20	-0.30	-0.28
L1	-0.27	-0.06	-0.05	0.06	-0.05	-0.05	-0.01	-0.02	0.27	0.19	0.18	-0.33	-0.35	**-0.37***	**-0.40***
L2	-0.25	-0.16	0.26	-0.11	0.10	-0.01	0.05	0.13	**0.42***	**0.40***	**0.37***	-0.15	-0.25	**-0.38***	-0.34
L3	-0.21	-0.30	0.25	-0.03	0.07	0.08	0.07	0.16	**0.44***	**0.42***	**0.39***	-0.18	-0.17	-0.21	-0.20
L4	-0.14	-0.12	0.14	0.00	0.16	0.09	0.11	0.14	**0.37***	0.31	0.32	-0.32	-0.31	-0.30	**-0.35***
L5	-0.18	-0.27	0.17	-0.01	0.09	0.12	0.08	0.25	**0.48†**	**0.39***	**0.39***	-0.10	-0.07	-0.21	-0.15

Values are spearman's correlation co-efficient. *: $p < 0.05$, † $p < 0.01$ and ‡ $p < 0.001$. AvLx: average of all lumbar vertebrae.

3. DISCUSSION

A six-month exercise intervention resulted in reductions in VFF at some lumbar vertebral levels in patients with chronic low back pain. This effect was predominantly in male participants. There was no change in VFF in the control group. There were, however, no between-group differences for VFF. Leaner leg, trunk and total mass attested to the effectiveness of the exercise intervention on the musculoskeletal system. Decreases in VFF correlated with changes in peripheral fat mass and negatively with changes in lean mass, but were not significantly correlated with lumbar bone mineral density, trabecular bone score, or visceral adipose tissue volume.

To our knowledge, this was the first prospective RCT to examine the effects of exercise on MAT in adults; as quantified by the surrogate measure VFF. The data demonstrated prospective downregulation of VFF with exercise after three months. These findings add to prior cross-sectional evidence supporting that exercise or regular physical activity is associated with lower MAT (reviewed in [7]). Load-bearing exercise [7] may be required for this effect. One prior prospective study [24] found lower femoral MAT after a ten-week exercise intervention in children aged three to six years. Our findings were also consistent with experiments using resistive exercise [27] in a bed rest model that prevented the MAT accumulation [26,27]. Notably, both Exercise (significant) and Control (not significant) CLBP patients showed lower VFF at three months and six months. Mobilisation of this chronically inactive population could potentially serve to explain the results. In adults, bone marrow adipose conversion is estimated at 7% per decade of life [9–11], or 0.35 percentage points in six months. Based on these normative data, the size effect of the exercise intervention in the current trial at 3mo at L2 (-3.7 percentage points) and L4 (-2.6 percentage points), was equivalent to 5.2 and 3.7 years of

normal aging, respectively. The null hypothesis that exercise has no effect would have translated in 0.35% higher VFF in the participants over 6 months. The absence of a third non-intervention group does not rule out that both groups benefitted from the trial.

The reductions in VFF in the exercise group at three months were no longer significant at six months. This may be attributable to the small sample size, and the mixed-sex sample. An alternative non-competing explanation may be the reduced requirements for exercise training after three months. The protocol included a planned reduction from 2–3 sessions to 1–2 sessions per week in the exercise group and may explain the loss of statistical significance.

Interestingly, our data show evidence of a sex-specific impact of exercise on vertebral MAT. Male participants showed consistent and significant reductions in VFF in the exercise group at most vertebral levels and at both three months and six months. In contrast, there was no effect of the intervention on vertebral MAT for female participants. We accounted for the number of comparisons made in the current study and presented data with and without adjustment for multiple comparisons. Exercise compliance is unlikely to explain the sex differences as male subjects attended, on average, fewer exercise sessions than females. However, we were not able to monitor exercise outside of monitored sessions. The MAT reduction with exercise in male participants persisted after adjustment. Different levels of vertebral marrow fat between sexes have been well established [12,39]. Men have higher VFF than premenopausal women [10,40,41]. This was the case in our trial, the difference being a higher VFF in men of five percentage points at baseline. A hormonal modulation was postulated to explain this difference [42], which disappears when comparing men and post-menopausal women [10,40,41]. However, we were unaware of literature reporting different modulation of VFF between men and women with exercise or with any other intervention. One study [43] reported similar MAT

changes in caloric restricted male and female rodents. Further investigation of sex-specific impacts of interventions on MAT in humans seems warranted. The prominent effect of sex-hormones on MAT, that can be species-specific and bone-specific [43,44], stress the need to design sex-balanced cohorts in the study of MAT modulation.

We correlated changes in VFF with prospective longitudinal changes in trunk and limb BMD, fat and lean masses. Correlations with BMD did not reach statistical significance, but we found positive correlations between changes in VFF and trunk and leg fat mass at 3mo and 6mo respectively. Previous reports in anorexia nervosa showing that reductions in peripheral fat occurred alongside increases in MAT [45] suggested segregated regulation of peripheral and bone marrow adipose tissues. Shen et al. [46–48] reported consistently negative correlations between MAT and BMD, but inconsistent correlations between MAT and subcutaneous, total and visceral adipose tissue in three cross-sectional studies in adults. Interestingly, despite increased trunk fat mass in the exercise group at 6mo and marginally lower VFF, trunk fat mass correlated negatively with VFF. Our data from a randomised control trial support segregated modulation of MAT and peripheral fat with exercise and underscore the need for further work to understand the mechanisms of marrow and peripheral adipose tissue modulation in humans, especially in interventions such as those involving restricted caloric intake and/or exercise.

4.1. Clinical relevance of the findings

This clinical trial was conducted in patients with chronic low back pain, a largely sedentary population whose physical activity level is chronically limited by spinal pain. The limited exercise and control interventions we administered were well tolerated, with a low dropout rate. The interventions were moderate, involved low load, low impact and did not require high levels of balance control. As such, they could be applied to large sections of the general

population, including patients with osteoporosis and the geriatric population. Although a measurable change in lumbar vertebrae BMD may only have become apparent after more than 6 months, the duration of our trial, demonstrating the feasibility of the current protocol to lower VFF constituted a fundamental step towards defining effective interventions on MAT. While a higher VFF has been associated with a number of negative outcomes including osteoporosis, malnutrition, anaemia, and metabolic syndrome through the secretion of adiponectin, the clinical implications of the magnitude of changes in VFF we observed still needs to be determined. The literature provides examples of divergent control of peripheral vs visceral vs marrow adipose tissue. Therefore, the generic effect of exercise on increasing caloric expense does not linearly predict bone marrow adipose tissue content whose regulation appears more complex involving hormonal, diet, age and gender as well as exercise [4,5].

4.2. Strengths and limitations

Strengths of the current study include its prospective randomised controlled design and the blinded nature of MRI data collection and analyses. Limitations include the absence of a third control group without any intervention, which may have increased the likelihood of finding between-group differences [4,5]. We also consider our study to be a pilot RCT, as prior data did not exist for adequate sample size estimation. The sample size in this study was small but sufficient to find statistically and clinically significant changes in key outcome measures. For ethical reasons, we provided the control group with an intervention, albeit one not loading the spine. Similarly, we recruited both men and women, which facilitated the finding of sex-specific differences in the main outcome but decreased the power of sex-specific sub-analyses. Notably, we did not collect data on movement-specific fears and therefore cannot conclude whether fears differed by sex and potentially mediated treatment outcomes.

4. 3. Conclusion

Exercise lowered lumbar marrow adipose tissue in male patients with CLBP in this first interventional RCT. The effect was not significant in females. Given the association between higher MAT and many chronic conditions, this index study supports further examination of whether exercise can modulate MAT in different population groups.

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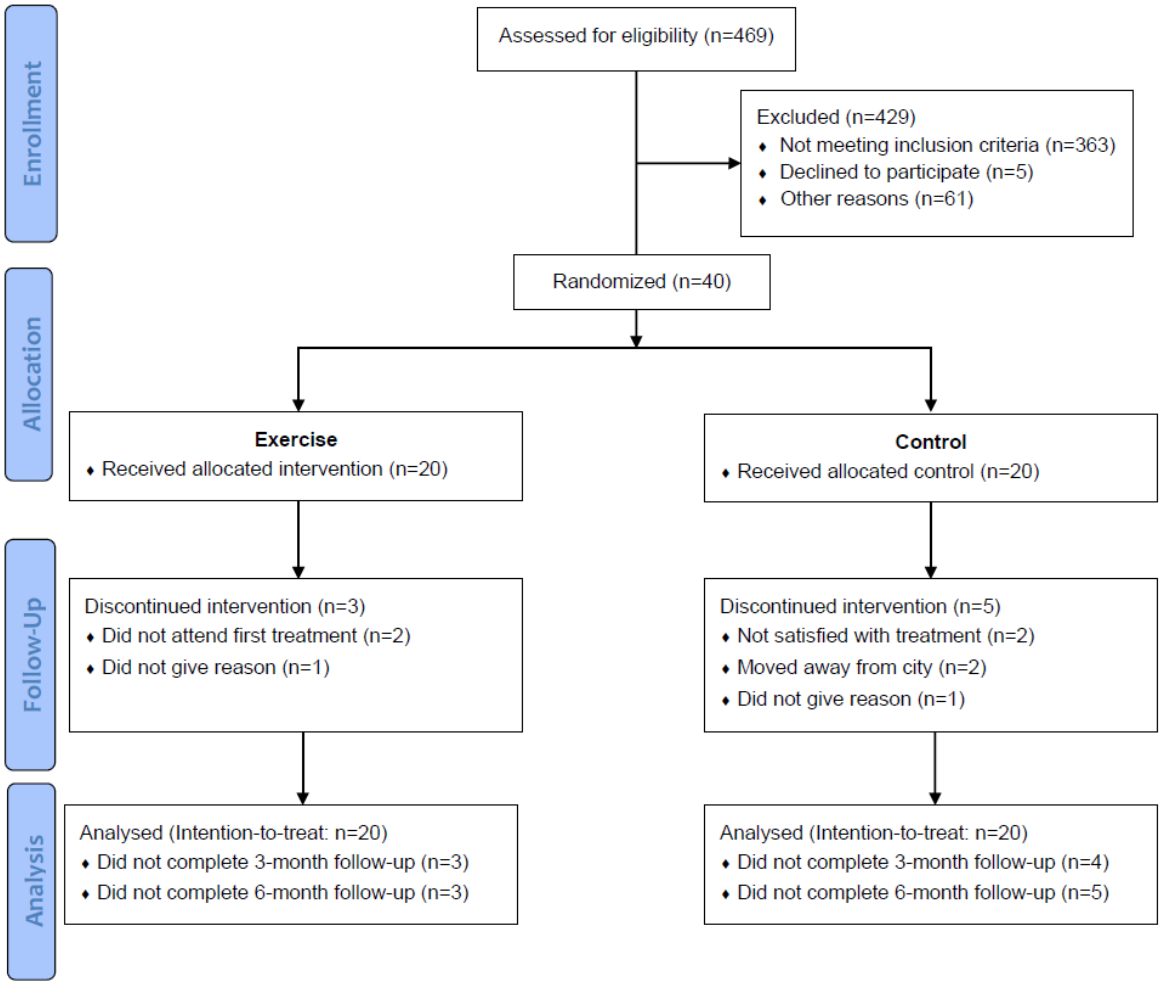
Supplemental Figure 1. CONSORT diagram.



Supplemental Table 1: Overview of baseline characteristics among the total sample (n=40).

	Exercise group	**Control group**
N (male, female)	10 male, 10 female	11 male, 9 female
Age (yrs)	35(5)	35(4)
Weight (kg)	77(17)	78(14)
Height (cm)	173(9)	170(8)
Body mass index (kg/m²)	27.1(5.4)	25.4(3.8)
Visual Analogue Scale low back pain (mm)	41(18)	49(19)
Oswestry disability index	25(12)	23(9)
Lumbar BMD (g/cm2)	1.20(0.16)	1.20(0.10)
Total body fat mass (kg)	26.75(12.06)	24.66(8.76)

None of the participants reported having diabetes. One participant (female, Exercise group) reported a co-morbidity of endometriosis, and another (female, Exercise group) reported rheumatoid arthritis. All female participants were premenopausal. One female participant (Exercise group) reported using a contraceptive pill and another (Control group) reported using an intra-uterine device containing levonorgestrel.

Supplementary Table 2: DXA areal lumbar spine bone measures in males and females

Group	Males (N=21)					Females (N=19)				
	Baseline	3mo	6mo	Δ 3mo	Δ 6mo	Baseline	3mo	6mo	Δ 3mo	Δ 6mo
	L1-L4 bone mineral density [g/cm2] (P=0.35)					*L1-L4 bone mineral density [g/cm2] (P=0.02)*				
Control	1.20(0.10)	1.21(0.09)	1.22(0.09)	0.7(2.6)%	1.9(3.2)%	1.21(0.10)	1.22(0.09)	1.20(0.09)	0.6(1.8)%	-0.5(1.9)%
Exercise	1.14(0.15)	1.13(0.14)	1.15(0.14)	-1.1(2.6)%	0.6(3.3)%	1.27(0.14)	1.25(0.13)†	1.24(0.14)	-1.9(1.5)%†	-2.1(3.0)%
	L1-L4 trabecular bone score [no unit] (P=0.51)					*L1-L4 trabecular bone score [no unit] (P=0.13)*				
Control	1.45(0.14)	1.48(0.12)	1.47(0.11)	1.8(3.8)%	0.9(4.1)%	1.46(0.08)	1.48(0.05)	1.48(0.04)	1.3(4.3)%	1.4(3.5)%
Exercise	1.43(0.07)	1.43(0.07)	1.43(0.06)	-0.1(3.0)%	-0.1(1.4)%	1.54(0.10)	1.50(0.08)*	1.51(0.08)	-2.6(3.3)%*	-2.0(3.5)%
	Visceral adipose tissue volume [l] (P=0.93)					*Visceral adipose tissue volume [l] (P=0.02)*				
Control	1.14(0.83)	1.11(0.73)	1.10(0.75)	-2.6(15.8)%	-4.2(23.1)%	0.44(0.41)	0.42(0.36)	0.43(0.34)	-5.5(13.3)%	-1.7(18.8)%
Exercise	0.86(0.67)	0.86(0.60)	0.86(0.61)	0.0(16.6)%	-0.6(18.5)%	0.97(0.53)	1.12(0.49)*	1.15(0.52)*	15.3(14.8)%*	18.8(21.7)%*

Data are mean(SD) at baseline, 3-months and 6-months as well as mean(SD) percentage change in this value at 3-months (Δ 3mo) and 6-months (Δ 6mo). *: unadjusted P<0.05, † unadjusted P<0.01 and ‡ unadjusted P<0.001 versus baseline before adjustment for multiple comparisons using the false discovery rate method. P-values next to parameter names indicate significance of the group*time interaction.

Supplementary Table 3: DXA body composition measures in males and females

Group	Males (N=21)					Females (N=19)				
	Baseline	3mo	6mo	Δ 3mo	Δ 6mo	Baseline	3mo	6mo	Δ 3mo	Δ 6mo
	Arm bone mass [kg] (P=0.63)					*Arm bone mass [kg] (P=0.87)*				
Control	0.46(0.06)	0.46(0.06)*	0.46(0.06)	0.9(1.1)%*	0.1(1.2)%	0.31(0.04)	0.31(0.04)	0.31(0.04)	-0.4(1.4)%	0.2(1.0)%
Exercise	0.42(0.04)	0.42(0.04)	0.42(0.04)	1.0(2.8)%	1.0(3.0)%	0.30(0.04)	0.30(0.04)	0.30(0.04)	0.1(2.3)%	0.2(2.8)%
	Leg bone mass [kg] (P=0.52)					*Leg bone mass [kg] (P=0.01)*				
Control	1.26(0.17)	1.26(0.15)	1.26(0.15)	0.1(0.7)%	0.3(0.7)%	0.83(0.11)	0.83(0.10)	0.83(0.09)†	-0.4(0.8)%	-0.8(0.7)%†
Exercise	1.09(0.10)	1.09(0.09)	1.09(0.09)	0.2(1.1)%	0.0(0.6)%	0.84(0.11)	0.84(0.10)	0.84(0.10)	0.3(0.6)%	0.5(0.8)%
	Trunk bone mass [kg] (P=0.81)					*Trunk bone mass [kg] (P=0.87)*				
Control	0.92(0.12)	0.93(0.10)	0.94(0.11)	0.7(2.2)%	1.2(3.2)%	0.71(0.10)	0.71(0.09)	0.72(0.09)	0.0(2.4)%	0.7(1.5)%
Exercise	0.82(0.14)	0.82(0.13)	0.83(0.13)	-0.1(3.1)%	0.5(2.1)%	0.76(0.17)	0.76(0.16)	0.76(0.16)	-0.4(3.5)%	0.0(2.9)%
	Total bone mass [kg] (P=0.65)					*Total bone mass [kg] (P=0.86)*				
Control	3.22(0.39)	3.23(0.35)	3.24(0.35)	0.3(0.6)%	0.5(0.8)%	2.42(0.24)	2.42(0.21)	2.42(0.20)	-0.1(1.0)%	0.0(0.8)%
Exercise	2.87(0.32)	2.88(0.29)	2.88(0.29)	0.3(1.0)%	0.3(0.6)%	2.48(0.34)	2.47(0.32)	2.48(0.32)	-0.2(1.2)%	0.1(0.9)%
	Arm fat mass [kg] (P=0.60)					*Arm fat mass [kg] (P=0.43)*				
Control	2.60(1.02)	2.64(0.88)	2.56(0.90)	1.5(10.2)%	-1.7(11.9)%	2.78(1.03)	2.76(0.92)	2.77(0.86)	-0.6(6.0)%	-0.3(6.1)%
Exercise	2.23(0.74)	2.24(0.67)	2.24(0.68)	0.1(8.2)%	0.3(9.6)%	3.48(1.07)	3.52(0.99)	3.44(1.00)	1.2(6.1)%	-1.1(7.8)%
	Leg fat mass [kg] (P=0.43)					*Leg fat mass [kg] (P=0.31)*				
Control	7.81(2.77)	7.71(2.39)	7.60(2.43)	-1.2(10.4)%	-2.6(11.8)%	9.04(2.24)	8.86(1.96)	8.91(1.84)	-2.0(6.4)%	-1.5(6.3)%
Exercise	6.79(2.53)	6.49(2.33)	6.74(2.34)	-4.5(7.8)%	-0.7(8.8)%	11.83(4.64)	12.09(4.35)	12.05(4.36)	2.2(4.9)%	1.8(5.7)%
	Trunk fat mass [kg] (P=0.80)					*Trunk fat mass [kg] (P=0.41)*				
Control	13.74(6.29)	13.62(5.51)	13.56(5.61)	-0.9(10.5)%	-1.3(12.9)%	11.57(5.28)	11.57(4.66)	11.75(4.39)	-0.1(8.3)%	1.5(8.8)%
Exercise	11.40(5.39)	11.22(4.89)	11.48(4.93)	-1.7(5.7)%	0.6(8.2)%	17.16(7.00)	17.71(6.54)	18.16(6.59)*	3.2(5.7)%	5.8(7.4)%*
	Total fat mass [kg] (P=0.63)					*Total fat mass [kg] (P=0.47)*				
Control	25.10(9.77)	24.91(8.51)	24.68(8.65)	-0.8(10.0)%	-1.7(11.7)%	24.22(8.12)	24.02(7.14)	24.27(6.71)	-0.8(6.9)%	0.2(7.0)%

Exercise	21.35(8.40)	20.87(7.62)	21.37(7.74)	-2.2(4.9)%	0.1(7.9)%	33.35(12.27)	34.18(11.48)	34.51(11.54)	2.5(4.8)%	3.5(6.0)%
		Arm lean mass [kg] (P=0.35)					*Arm lean mass [kg] (P=0.88)*			
Control	7.48(1.02)	7.51(1.02)	7.74(1.04)	0.5(5.9)%	3.4(6.6)%	3.90(0.69)	3.91(0.62)	3.99(0.58)	0.3(3.3)%	2.3(3.7)%
Exercise	6.69(0.66)	6.85(0.59)	6.75(0.59)	2.4(3.5)%	0.9(3.5)%	4.23(0.92)	4.30(0.85)	4.36(0.85)	1.5(5.9)%	3.0(6.0)%
		Leg lean mass [kg] (P=0.32)					*Leg lean mass [kg] (P=0.13)*			
Control	21.28(3.23)	21.31(2.91)	21.58(3.08)	0.1(1.5)%	1.4(5.0)%	13.86(2.13)	13.82(1.88)	13.73(1.77)	-0.3(2.8)%	-0.9(2.8)%
Exercise	18.83(1.96)	19.16(1.73)	19.20(2.07)	1.8(2.6)%	2.0(6.5)%	15.27(3.36)	15.58(3.13)	15.82(3.16)	2.0(4.3)%	3.6(5.3)%
		Trunk lean mass [kg] (P=0.05)					*Trunk lean mass [kg] (P=0.39)*			
Control	26.40(3.94)	26.22(3.44)	26.72(3.62)	-0.7(3.6)%	1.2(5.7)%	19.02(2.40)	18.87(2.07)	18.98(2.05)	-0.8(3.7)%	-0.2(4.9)%
Exercise	23.63(2.41)	24.48(2.34)†	23.80(2.27)	3.6(3.6)%†	0.7(2.6)%	19.17(3.25)	19.83(2.83)	20.03(2.77)	3.4(8.3)%	4.5(7.7)%
		Total lean mass [kg] (P=0.05)					*Total lean mass [kg] (P=0.28)*			
Control	58.59(7.69)	58.46(6.89)	59.49(7.34)	-0.2(2.6)%	1.6(5.1)%	39.78(4.85)	39.58(4.30)	39.69(4.09)	-0.5(1.9)%	-0.2(2.5)%
Exercise	52.50(4.28)	53.85(3.96)‡	53.07(4.31)	2.6(1.7)%‡	1.1(3.6)%	41.78(7.67)	42.77(6.95)	43.28(7.02)	2.4(5.4)%	3.6(5.9)%

Data are mean(SD) at baseline, 3-months and 6-months as well as mean(SD) percentage change in this value at 3-months (Δ 3mo) and 6-months (Δ 6mo). *: unadjusted P<0.05, † unadjusted P<0.01 and ‡ unadjusted P<0.001 versus baseline before adjustment for multiple comparisons using the false discovery rate method. P-values next to parameter names indicate significance of the group*time interaction.

Supplemental Table 4: Partial correlations whilst controlling for participant sex between changes in vertebral fat fraction (VFF) after 3 months (top panel) and 6 months (bottom panel) among the total sample (n=40).

VFF at level..	L1-L4 bone mineral density	L1-L4 trabecular bone score	Visceral adipose tissue volume	Arm bone mass	Leg bone mass	Trunk bone mass	Total bone mass	Arm fat mass	Leg fat mass	Trunk fat mass	Total fat mass	Arm lean mass	Leg lean mass	Trunk lean mass	Total lean mass
Spearman's partial correlation between changes at 3 months vs. baseline															
AvLx	-0.10	-0.29	0.28	0.05	0.23	0.00	0.02	0.24	**0.44***	0.33	**0.38***	**-0.46†**	-0.32	-0.27	**-0.41***
L1	-0.15	-0.20	0.31	-0.08	**0.36***	0.05	0.18	0.02	0.31	0.20	0.22	-0.34	-0.29	-0.20	-0.28
L2	-0.09	-0.22	0.16	0.10	0.18	-0.02	0.00	0.27	0.32	0.29	0.31	**-0.37***	**-0.39***	-0.25	**-0.40***
L3	-0.02	-0.25	0.22	0.19	0.11	-0.05	-0.02	0.32	0.31	0.29	0.30	**-0.38***	-0.25	-0.20	-0.34
L4	-0.06	-0.17	0.20	-0.02	0.24	-0.05	-0.11	0.22	**0.42***	0.26	0.34	**-0.44***	**-0.36***	-0.24	**-0.39***
L5	-0.01	-0.26	0.18	0.07	-0.07	0.13	0.01	0.21	**0.41***	0.20	0.31	**-0.53†**	-0.23	-0.34	**-0.44***
Spearman's partial correlation between changes at 6 months vs. baseline															
AvLx	-0.10	-0.26	0.34	0.06	0.24	0.01	0.03	0.24	**0.53†**	**0.40***	**0.45***	-0.28	-0.09	-0.30	-0.25
L1	-0.18	-0.02	0.04	0.03	0.09	-0.08	-0.04	-0.02	0.27	0.13	0.18	**-0.41***	-0.33	**-0.38***	**-0.39***
L2	-0.13	-0.11	0.25	-0.07	0.19	-0.01	0.06	0.10	**0.38***	0.28	0.30	-0.27	-0.19	**-0.43***	-0.34
L3	-0.01	-0.27	0.32	0.04	0.22	0.01	0.00	0.23	**0.49†**	**0.40***	**0.43***	-0.20	-0.02	-0.17	-0.11
L4	-0.01	-0.06	0.22	0.02	0.29	0.15	0.15	0.26	**0.45†**	**0.35***	**0.39***	-0.34	-0.14	-0.32	-0.31
L5	-0.03	-0.22	0.23	0.04	0.13	0.14	0.07	0.27	**0.50†**	**0.38***	**0.43***	-0.15	-0.01	-0.23	-0.16

Values are Spearman's partial correlation coefficient. *: $p < 0.05$, † $p < 0.01$ and ‡ $p < 0.001$. AvLx: average of all lumbar vertebrae.