European Spine Journal (2020) 29:1887–1899
https://doi.org/10.1007/s00586-020-06379-7

ORIGINAL ARTICLE

Exercise for the intervertebral disc: a 6-month randomised controlled trial in chronic low back pain

Patrick J. Owen[1] · Clint T. Miller[2] · Timo Rantalainen[1,3] · Katherine J. Simson[2] · David Connell[4] · Andrew J. Hahne[5] · Guy Trudel[6] · Jon J. Ford[5,7] · Daniel L. Belavy[1]

Received: 15 October 2019 / Revised: 12 February 2020 / Accepted: 14 March 2020 / Published online: 24 March 2020

Abstract

Background context Muscle, bone and tendon respond anabolically to mechanical forces. Whether the intervertebral disc (IVD) can benefit from exercise is unclear.

Purpose To examine whether exercise can beneficially affect IVD characteristics.

Study design/setting This is a single-blinded 6-month randomised controlled trial (ACTRN12615001270505) in an exercise and physiotherapy clinic.

Patient sample Forty patients with chronic non-specific low back pain (NSCLBP) are included in this study.

Outcome measures The primary outcome was lumbar IVD T2 time (MRI). Secondary outcomes included IVD diffusion coefficient and IVD expansion with short-duration lying.

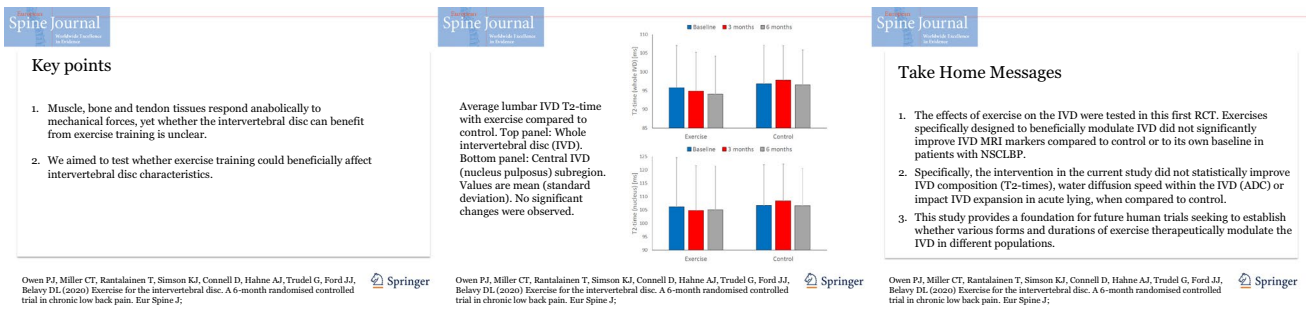
Methods Twenty patients progressively loaded their lumbar IVDs (exercise) via an exercise programme involving progressive upright aerobic and resistance exercises targeting the trunk and major muscle groups and were compared to twenty patients who performed motor control training and manual therapy (control). Testing occurred at baseline, 3 months and 6 months.

Results Seventeen exercise and fifteen control patients completed the interventions. There were no group-by-time differences in T2 time of the entire IVD (exercise 94.1 ± 10.0 ms vs. control 96.5 ± 9.3 ms, $p = 0.549$). Exercise patients had shorter T2 time in the posterior annulus at 6 months (82.7 ± 6.8 ms vs. 85.1 ± 8.0 ms, $p = 0.028$). Exercise patients showed higher L5/S1 apparent diffusion coefficients and decreased IVD height at 3 months (both $p \leq 0.050$). After adjustments for multiple comparisons, differences lost statistical significance. Per-protocol and intent-to-treat analyses yielded similar findings.

Conclusions This trial found that 6 months of exercise did not benefit the IVD of people with NSCLBP. Based on this index study, future studies could investigate the effect of exercise on IVD in different populations, with different types, durations and/or intensities of exercise, and using different IVD markers.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.



Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-020-06379-7) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Keywords Rehabilitation · Physical therapy · Physiotherapy · Spine · Magnetic resonance imaging · Physical activity · Intervertebral disc

Introduction

Most connective tissues are mechanosensitive [1]. Wolff [2] first described a 'law' of bone adaptation to loading in 1892. Since then, successive studies have detailed muscle, bone and tendon responses to exercise. Progressive resistance exercises maximise muscle hypertrophy [3], impact-loading exercises optimise bone mineral density and geometry [4, 5] and burgeoning data favour loading magnitude over type of muscle contraction to increase tendon cross-sectional area [6]. Whether intervertebral discs (IVD) respond to exercise training is less well established [7].

Loading of IVD tissue/cells in vitro resulted in an anabolic response [8, 9]. Cyclical loads of 0.2–0.8 megapascal at 0.1–1.0 Hz for up to eight hours/day lead to an anabolic response [8]. Animal studies reported beneficial modulation of the IVD with exercise; 3 months of exercises in adult dogs improved IVD uptake of glucose, oxygen and glycogen [10]. Eight weeks of treadmill exercise in rats increased IVD matrix production [11] and cell numbers in the IVD stem cell niche and the outer annulus [12]. A different study showed that 11 weeks of treadmill exercises in rats increased IVD glycosaminoglycan concentration [13]. Moreover, treadmill exercises of injured and sham IVDs in rats stimulated cell proliferation in both groups [14]. These animal data support a positive impact of exercise on the IVD of quadrupeds.

Cross-sectional studies have been performed in humans. Highly physically active people had longer lumbar IVD T2 time, on magnetic resonance imaging (MRI), a measure that correlates with glycosaminoglycan and water content [15]. Similarly, long-distance runners and joggers had longer lumbar IVD T2 time compared to sedentary people [16]. Long-distance runners also had greater IVD-to-vertebral body height ratio compared to non-athletic referents, which suggested IVD hypertrophy [16]. Finally, longer lumbar IVD T2 times were associated with loading patterns in the range of fast walking to slow running [16]. Whilst these findings support a beneficial effect of physical activity and exercise on IVD, prospective intervention studies are required to establish causality.

Our aim was to conduct the first-ever randomised controlled trial (RCT) on the effect of exercise training on IVD in humans. We assessed this in people with non-specific chronic low back pain (NSCLBP) as firstly, demonstrating the capacity to improve IVD characteristics in a clinical population group, with pain that may in part stem from IVD degeneration, and would have wider implications, when compared to otherwise healthy population groups, at both the individual (e.g. reduced disability and increased health-related quality of life) and societal levels (e.g. reduced healthcare costs) [17]. Secondly, the exercise training principle of initial values suggests that physiological adaptations are greater in patients with lower baseline values [18], which supports that degenerated IVDs may have greater capacity, if plausible, to improve through appropriately prescribed exercise training. Thirdly, patients with NSCLBP are often sedentary, but have the potential to increase physical activity levels [19]. We included people aged 25–45 years, an age range where IVD adaptations may be more likely than older individuals [2]. Notably, the notion that IVDs can undergo 'regeneration' once established degeneration has occurred remains an ongoing debate within the field [20]. This being the index study, the minimum duration of exercises to obtain measurable effects on IVD in humans is unknown. Tendon adaptations were measured after 3–4 months [21], whilst exercise interventions for bone typically measured changes in bone mineral density after 9–12 months [5]. We set the duration of the exercise intervention at 6 months. We designed an exercise intervention by following the existing recommendations for IVD [7]. This intervention integrated progressive spinal loading and spine-specific physical activity into a general strength and conditioning programme. The control intervention was expected to minimally load the IVD as it involved low-intensity motor control training and manual therapy. Lumbar IVD outcomes included T2 time, apparent diffusion coefficient and rate of IVD expansion in short-duration lying [22]. Our primary hypothesis was that six months of exercise would increase IVD T2 times compared to control intervention in patients with NSCLBP.

Methods

This was a single-blinded 6-month RCT that examined the efficacy of exercise compared to control in 40 adults with NSCLBP. The study was conducted from December 2015 to December 2016 in Melbourne, Australia. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615001270505, date registered 20/11/2015) and approved by the institutional ethics review board. All patients provided informed written consent prior to participation. The full study protocol was published [23] and is presented in brief below.

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 min 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 smoker and (10) implants unsuitable for MRI. Pain intensity of the low back was measured with a 100-point visual analogue scale [24]. The modified Oswestry disability index was used to measure patient disability due to NSCLBP [25]. All patients underwent offsite randomisation procedures by a researcher who had no contact with volunteers. A randomisation schedule (using block randomisation with random block lengths and stratification for sex obtained from www.random.org) was implemented.

Exercise: general strength and conditioning

The exercise intervention consisted of fifty-two 1-h one-on-one gym-based sessions with an exercise physiologist (i.e. tertiary trained clinical exercise allied health professionals) [26]. During the first three months, patients attended two sessions per week. During the second 3-month period, participant could self-select to attend either 1–2 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 min of mental rehearsal of movements they nominated as being fearful for them. Prescribed exercises closely followed prior recommendations [7] for the beneficial modulation of IVD: (a) loading was dynamic, rather than static, which aimed to facilitate the transfer of nutrients between vertebral bodies and IVDs [8], (b) axial loading was emphasised, with extreme ranges of motion, torsional activities and flexion with compression avoided [8], (c) the speed at which the concentric and eccentric isotonic exercises were completed remained between 6 and 60 cycles per minute [8] and (d) exercises were chosen [27] that loaded the IVD in the range of 0.2–0.8 megapascal, corresponding to intradiscal pressure of 0.3–1.2 megapascal [8]. In each session, participants performed 20 min of treadmill aerobic exercise, beginning at an intensity of 65–70% maximal heart rate in the first two weeks and increasing to 65–85% of maximal heart rate. Resistance exercise 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 min 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 clinicians, were able to be randomised.

Control: motor control training and manual therapy

The control intervention consisted of twelve 30-min one-on-one physiotherapy-led sessions [23]. 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 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, or clinician.

Magnetic resonance imaging and blinded analysis

A 3 T Phillips Ingenia scanner (Amsterdam, Netherlands; software release 4.1.3.4) was used with a spinal coil for all scans. The following sequences were performed at baseline, three months and six months:

- To measure the rate of IVD expansion with lying a first T2-weighted sagittal scan was used (15 slices, thickness 3 mm, interslice distance 1.5 mm, repetition time 2600 ms, echo time 70 ms) encompassing the entire lumbar spine.
- For quantifying IVD T2 time, a spin-echo multi-echo sequence was used with eight echo times (15.75, 36.75, 57.75, 78.75, 99.75, 120.75, 141.75 and 162.75 ms) from

12 sagittal anatomical slices each (thickness 3 mm, interslice distance 1.5 mm, repetition time 2000 ms, field of view 281 × 281 mm, image resolution 0.366 mm per pixel) encompassing the entire lower spine from left to right.

- For quantifying the apparent diffusion coefficient (ADC), a single-shot echo-planar diffusion-weighted imaging sequence was used (15 slices, thickness 3 mm, interslice distance 1.5 mm, B factors 0 and 400, repetition time 9000 ms, echo time 76 ms, number of excitations/averages 8). The scanner software then calculated the ADC map from these diffusion-weighted images.
- To complete the measure of the rate of IVD expansion with lying a second T2-weighted sagittal scan was performed with the same settings [22]. This scan co-localised with the diffusion-weighted imaging scan. The time between the first and second T2-weighted scans was constant across the study (baseline 29 min, 3 months: 28 min, 6 months: 28 min).

MRI file allocation and study time point were blinded to the assessor using a random number prior to image analysis (obtained from www.random.org). The order of the two T2-weighted scans was also blinded applying an additional random number to each of these scans. Pfirrmann grade was assessed on the baseline T2-weighted images by a radiologist.

ImageJ 1.38x (https://rsb.info.nih.gov/ij/) was used to perform all quantitative MR measures. In the sagittal spin-echo multi-echo images, every IVD from T11/T12 to L5/S1 was measured. After segmenting the IVD, an ImageJ plug-in ('ROI Analyzer'; https://github.com/tjrantal/RoiAnalyzer and https://sites.google.com/site/daniellbelavy/home/roianalyser) was used to rotate the IVDs to horizontal and to measure their area and height. The IVD volume was calculated by linear interpolation of the area data from all slices. The slice number with the spinous process of each vertebrae was noted. Lordosis angle was calculated as the difference between the angle to the horizontal of the region of interest traced around the L5/S1 IVD and that of a region of interest traced around the L1/2 IVD. With the exception of IVD volume, the morphometric data from three central images at the spinous process for each lumbar IVD were averaged. Signal intensity was obtained of the entire IVD as well as five equidistant subregions of the IVD from anterior to posterior (Fig. 1). T2 time was calculated via a linear fit to the natural logarithm of the image intensity in each of the eight MR echo times.

IVD height on T2-weighted images was assessed in a similar fashion: a region of interest was traced manually around each IVD, and the same custom-written ImageJ plug-in was used to calculate average IVD height on the central three slices. The coordinates of the regions of interest were saved for each measurement. The change in IVD height between the first and second T2-weighted scans was calculated as in prior work [22].

To automate the analysis of ADC maps, the coordinates regions of interest saved from the co-localised T2-weighted images were used. Custom-written software in 'R' (version 3.4.2, www.r-project.org) was used to rescale the coordinates of the regions of interest to the pixel resolution and position on the ADC maps. Then a custom-written ImageJ macro was used to load each rescaled region of interest coordinates and corresponding ADC map image. The image intensity, and hence ADC, was calculated for each region of interest (whole IVD). ADC values were averaged from the three slices positioned around the spinous process for each IVD.

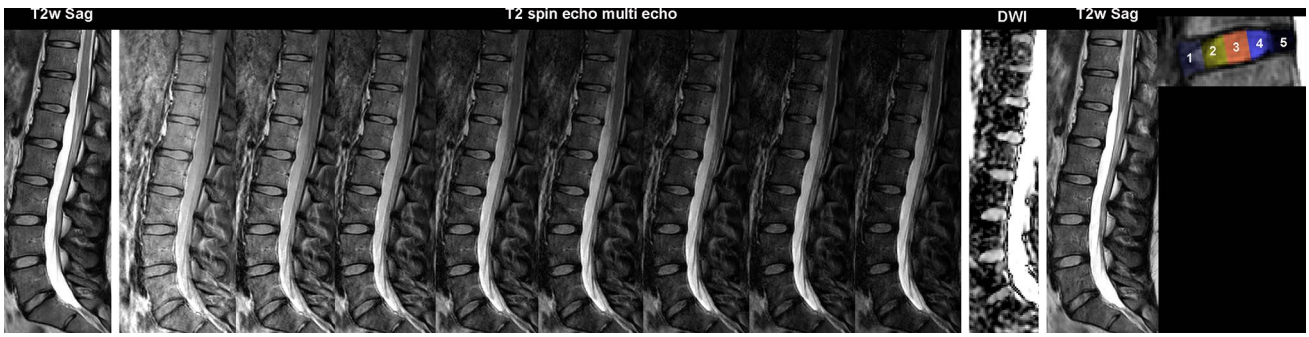


Fig. 1 Magnetic resonance techniques and sequences applied in this study. A T2-weighted sagittal (T2w Sag) scan was performed immediately after pilot scanning. This was followed by a spin-echo multi-echo sequence for the assessment of intervertebral disc T2 relaxation time. (The eight images shown for this sequence show the repeated echoes [at 15.75, 36.75, 57.75, 78.75, 99.75, 120.75, 141.75 and 162.75 ms] at the same anatomical position. Decay of image intensity across echoes is used to calculate T2 time; see "Methods".) A diffusion-weighted imaging (DWI) scan was performed to calculate the apparent diffusion coefficient of the intervertebral disc. Finally, a repeat T2w Sag scan was performed to assess the rate of intervertebral disc expansion in lying. The inset shows the division of the intervertebral disc into five subregions after tracing

Statistical analyses

The 'R' statistical environment (version 3.4.2, www.r-project.org) was used for all statistical analyses. An intent-to-treat analysis approach was first implemented. A linear mixed effects model with allowances for heterogeneity of variance according to study date was used. Then repeated measures analysis of variance examined for differences between groups over time and a priori *T*-tests were performed comparing each follow-up time point to baseline. An alpha level of 0.05 was taken 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 [28]. The primary analysis considered data averaged from all lumbar IVDs. A per-protocol analysis was then completed.

Assuming an alpha of 0.05, power of 0.8 and mean (SD) average lumbar IVD T2 time of 100.6 (12.4) ms and adjusting [29] for a correlation (95% confidence interval) of 0.98(0.95–1.00) (coefficient of variation [95% confidence interval]: 1.8 [1.5–2.1] %; unpublished repeatability data from the senior author's laboratory collected from twelve men across nine repeated time points over the course of one year. This is an appropriate number of measures for this sample size to adequately establish reliability) [30], 18 patients in each group (total $n=36$) were required to detect a 2.2% (effect size 0.17) net difference in average lumbar IVD T2 time between groups at the third time point (i.e. 6 months).

Results

Forty patients (exercise $n=20$, control $n=20$) were randomised. Baseline demographic, pain intensity and disability data are shown in Table 1. Mean attendance was 31/52 sessions (60%) for exercise and 9/12 sessions (77%) for control. Eight patients withdrew from the study between baseline and 6-month follow-up (ex $n=3$; co $n=5$; Fig. 2).

No group-by-time effect was observed for whole lumbar IVD T2 time (Table 2, Fig. 3). A within-group reduction of 2.9% and 3.7% in T2 time of the subregion representing the posterior annulus was observed at 6 months for the exercise and control groups, respectively, albeit only the exercise group reached statistical significance (Table 2). A group-by-time effect was revealed for L2–L3 IVD posterior nucleus T2 time (net mean per cent difference after six months exercise compared to control − 0.7%) and L4–L5 IVD anterior annulus (net mean per cent difference after six months exercise compared to control − 11%) (Supplementary Table 1). T2 time also differed within the group after three months of exercise for L2–L3 IVD posterior nucleus (− 3.9%) and after six months for L1–L2 IVD posterior annulus (− 9.2%) and L4–L5 IVD anterior annulus (− 7.3%; Supplementary Table 1). Within-group differences were similarly observed after three months of control for L2–L3 IVD anterior annulus (− 4.8%; Supplementary Table 1). Importantly, none of these between- or within-group differences in IVD T2 times persisted after controlling for potential false positives.

Table 1 Baseline demographic and intervertebral disc (IVD) morphological data

	Exercise	Control
Age, years	35 (5)	35 (4)
Female, *n* (%)	10 (50)	9 (45)
Height, cm	172.5 (9.1)	169.6 (7.7)
Weight, kg	76.9 (16.8)	77.8 (13.5)
Body mass index, kg/m^2	25.4 (4.2)	27.1 (4.9)
Pain, 0–100 VAS	41 (18)	49 (19)
Disability, % on Oswestry index	24.5 (12.1)	23.4 (8.5)
Average lumbar IVD Pfirrmann grade	2.3 (0.5)	2.3 (0.5)
Lordosis angle, degrees	33.5 (9.0)	32.0 (7.5)

Data are mean (SD) except for number of females. $N=20$ in each group. IVD: intervertebral disc. Pfirrmann grade averaged from all lumbar discs

ADC did not differ between groups over time (Table 3). Although L5–S1 ADC decreased 8.4% in the control group between baseline and 3-month follow-up, this effect was no longer significant after adjusting *p* values for potential false positives (Table 3). No within-group differences were observed for the exercise group (Table 3).

No group-by-time effects were observed for average lumbar IVD volume or height, although average lumbar IVD height increased 1.3% after three months of control (Table 4). L1–L2 IVD volume differed between groups over time (net mean per cent difference after six months exercise compared to control − 7.2%; Supplementary Table 2). L1–L2 IVD volume significantly increased 5.2% within the control group between baseline and 6-month follow-up. L5–S1 IVD height also increased within-group after three months of control (+ 1.6%). Notably, none of these significant effects persisted after adjusting for potential false positives.

Average and individual IVD height expansion after short-duration lying did not differ between groups over time (Table 5). Within the exercise group only, IVD height expansion was 1.1 times less at L3–L4 after six months. At three months, IVD height expansion was also 1.1 and 0.8 times less for the exercise (L4–L5 only) and control (L1–L2 only) groups, respectively. These effects were no longer significant after adjusting for potential false positives.

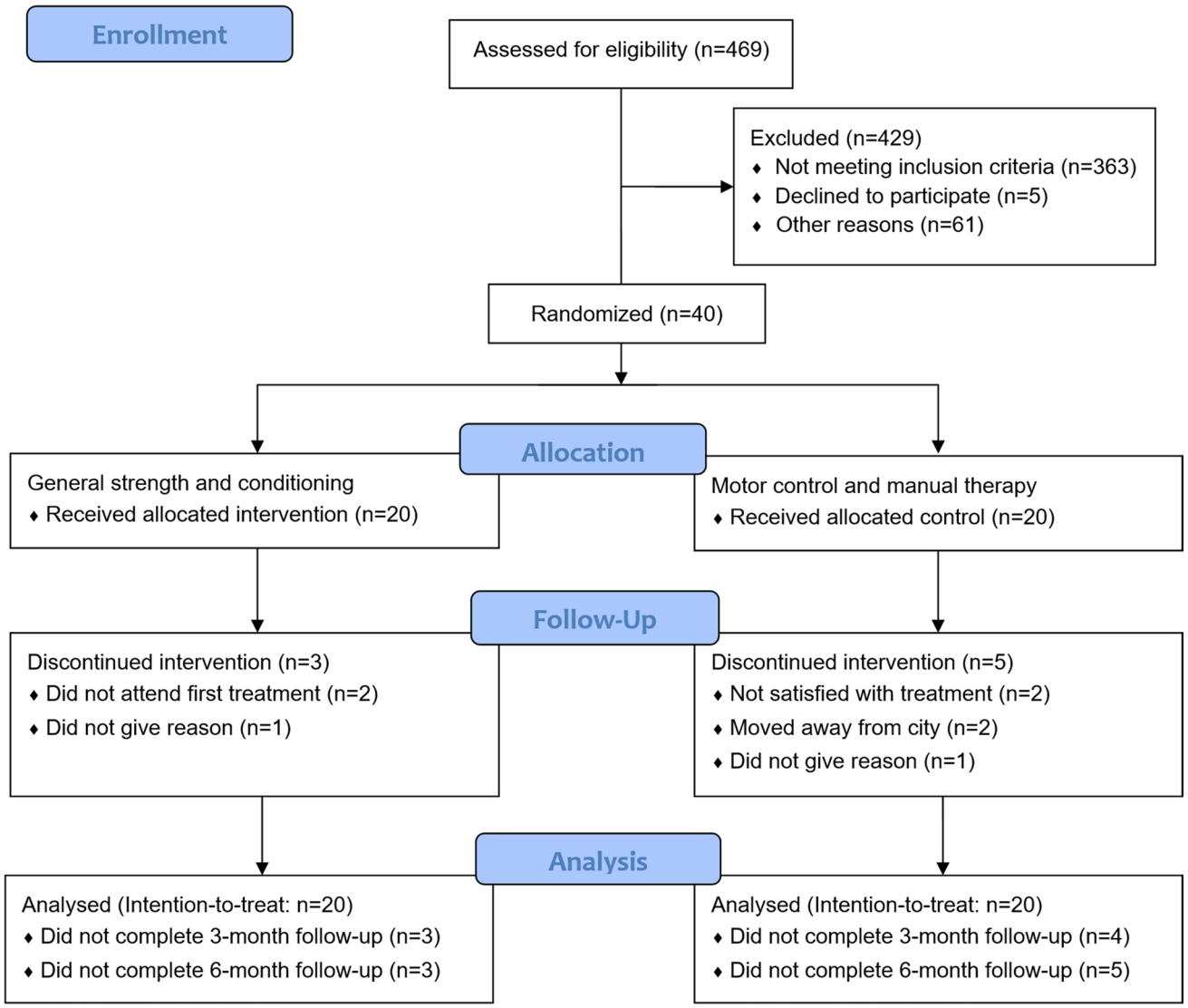


Fig. 2 CONSORT diagram

Discussion

To our knowledge, this was the first RCT to examine the effects of exercise training on the IVD. Prior in vitro, animal and human cross-sectional studies suggested a beneficial effect of exercise on various IVD markers [7]. We recruited sedentary patients with NSCLBP more likely to increase physical activity levels and show IVD changes. Our intervention followed previously recommended exercises for intradiscal pressure and frequency capable of modulating IVD tissues [7]. Despite these careful methodological considerations, we could not measure significant beneficial modulation of IVD with exercise when compared to control. Specifically, the intervention did not increase IVD T2 time, apparent diffusion coefficient or rate of IVD expansion in short-duration lying, which did not confirm our hypothesis.

There were significant changes in the IVD, albeit these effects did not persist after adjustment of p values for potential false positives. For example, we measured shorter IVD T2 times with exercise at 6 months. The prevailing interpretation is for a reduction in IVD water and glycosaminoglycan content [15], a detrimental effect. Other authors have argued that a shorter T2 time might reflect increased binding of water to the collagen matrix [31, 32] which would indicate a beneficial effect. The lower apparent diffusion coefficient in the control group at L5S1 at 3 months may represent reduced IVD free water movement, a detrimental change (ref needed) [33, 34].

The control group had higher average lumbar IVD height at 3 months and larger L1/2 IVD volume at 6 months. We had controlled for time-of-day effects on the spine [35] by performing all scanning after midday. This standardisation

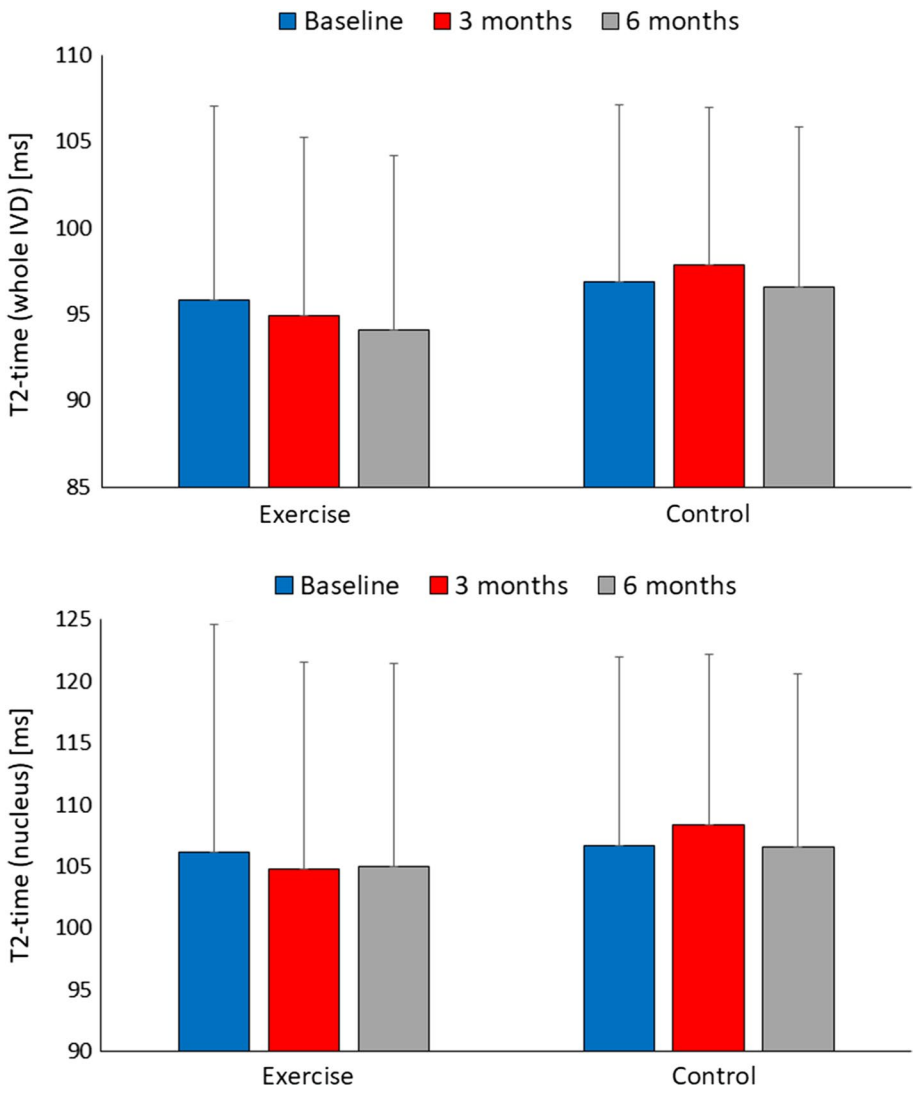


Fig. 3 Average lumbar IVD T2 time with exercise compared to control. Top panel: Whole intervertebral disc (IVD). Bottom panel: Central IVD (nucleus pulposus) subregion. Values are mean (SD). No significant changes were observed

allowed to attribute variation in IVD size to intrinsic IVD changes; but again, the effect did not remain significant after adjusting for potential false positives.

Interestingly, lumbar IVD expansion with short-term lying decreased over the course of the study from 2.2% to −0.1% in the exercise group at L3/4 at 6 months and from 3.1% to 0.5% in the control group at L1/2 at 3 months, despite standardised duration of lying between scans. Healthier lumbar IVDs with lower degeneration grade expand less in acute lying [22]; thus, this may present a beneficial finding. Again, the effect did not remain significant after adjusting for potential false positives.

Whilst we are unaware of previous prospective studies, these findings conflict somewhat with previous cross-sectional studies that showed long-term exposure to running/jogging [16] or vigorous physical activity [36] was associated with better IVD composition markers. Notably, these studies only included people with long-term exposure to physical activity loading the IVD. These cross-sectional studies may therefore suffer survivorship bias (i.e. that people with adverse IVD effects of exercise dropped the activity and were not captured by a cross-sectional design). Alternatively, this may suggest that the six-month intervention in the current study was of insufficient duration to elicit beneficial IVD adaptations. Adaptations of bone density, muscle size and tendon cross-sectional area with exercise take 9–12 months [5], three weeks [37] and 3–4 months [21], respectively, before they are detectable. The time frame after which IVD are expected to respond to exercise is not clear. Sivan and colleagues have been frequently cited as evidence that the IVD is unlikely to ever respond to loading within the human lifespan, given that half-lives for the turnover of collagen (~95 years) [38] and aggrecan (~22 years) [39] are quite long. However, the half-life for the turnover of the adult human femur collagen is approximately 16–22 years (3–4% per year) in women and 22–45 years (1.5–3% per year) in men [40]. Yet, measurable increases in human femur bone mineral

Table 2 T2 relaxation time of the intervertebral disc (IVD) and its subregions

	Baseline and within-group difference						Group × time effect
	Exercise			Control			
	n	Mean (SD)	*p* value	*n*	Mean (SD)	*p* value	*p* value
Total IVD, ms							0.549
Baseline	20	95.8 (11.3)	–	20	96.9 (10.3)	–	
Δ 3 months	17	−0.9 (5.2)	0.480	16	1.0 (4.6)	0.399	
Δ 6 months	17	−1.7 (4.7)	0.150	15	−0.3 (5.4)	0.812	
IVD anterior annulus, ms							0.669
Baseline	20	79.8 (8.3)	–	20	81.0 (7.5)	–	
Δ 3 months	17	0.6 (5.7)	0.665	16	−0.3 (6.0)	0.842	
Δ 6 months	17	−0.9 (8.0)	0.659	15	0.4 (6.4)	0.832	
IVD anterior nucleus, ms							0.349
Baseline	20	93.4 (12.0)	–	20	94.7 (11.6)	–	
Δ 3 months	17	−1.5 (5.4)	0.254	16	1.4 (5.7)	0.351	
Δ 6 months	17	−1.4 (5.2)	0.285	15	0.3 (7.4)	0.863	
IVD centre nucleus, ms							0.375
Baseline	20	106.2 (18.4)	–	20	106.7 (15.3)	–	
Δ 3 months	17	−1.4 (7.8)	0.455	16	1.7 (5.5)	0.220	
Δ 6 months	17	−1.1 (6.8)	0.496	15	−0.1 (6.7)	0.969	
IVD posterior nucleus, ms							0.392
Baseline	20	101.0 (14.9)	–	20	101.5 (14.5)	–	
Δ 3 months	17	−1.3 (7.1)	0.423	16	1.6 (5.6)	0.273	
Δ 6 months	17	−1.4 (6.4)	0.379	15	0.1 (6.1)	0.966	
IVD posterior annulus, ms							0.537
Baseline	20	85.1 (8.0)	–	20	86.6 (9.6)	–	
Δ 3 months	17	0.5 (8.6)	0.818	16	−2.7 (9.9)	0.292	
Δ 6 months	17	−2.4 (4.4)	**0.028**	15	−3.2 (7.5)	0.111	

Data are mean (SD) at baseline and mean (SD) change at 3 and 6 months. Raw (unadjusted) *p* values shown. Bold: $p \leq 0.05$ 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. See Supplemental Table 1 for individual vertebral level data

density were reported after 9 months of exercise [5]. The minimum duration of exercise required to elicit IVD adaptations remains unknown, and our study suggests it may be longer than 6 months.

In future work, it would be appropriate to consider different exercise programmes that may load the IVD in different ways. As highlighted in a prior literature review [7], loading of the IVD needs to be dynamic to elicit an anabolic response. The prior review of the literature suggested that loading should be applied in an axial compressive manner and the magnitude of loading required likely falls within those generated during walking and jogging [7]. The duration of loading required to elicit an anabolic response from the IVD is unclear, with one review suggesting 8 h per day [8]. We are sceptical that this extensive duration of loading is required; however, the minimum required duration is not yet clear. Overall, a potential next attempt for an exercise training protocol to elicit an anabolic response in the IVD could be a progressive walking/running protocol.

Damaged or degenerated IVD, such as those associated with NSCLBP [41], may not respond to loading patterns as otherwise healthy IVD would. Cells from healthy IVDs upregulated anabolic extracellular matrix genes following two hours of cyclical exposure to hydrostatic pressure of 0.8–1.7 megapascal at 0.5 Hz [20]. This was not the case for cells from degenerated IVDs [20]. In our study, the IVDs of patients with NSCLBP may have require different stimuli to display an anabolic response. Examining the efficacy of exercise on IVD in non-patient populations, including normal participants, is warranted.

Finally, alternate markers of IVD 'health' could be considered in the future research. For example, the T2 time reflects the glycosaminoglycan and water content of the IVD and the interaction of water with collagens [15, 31, 32]. T2 time therefore reflects the end-points of a number of physiological and cellular pathways. Assessing earlier degeneration markers such as IVD nutrition using diffusion of small solutes into the IVD via studies [42] of diffusion rates of

Table 3 Apparent diffusion coefficient in the intervertebral discs

	Baseline and within-group difference						Group × time effect
	Exercise			Control			
	n	Mean (SD)	*p* value	*n*	Mean (SD)	*p* value	*p* value
AvLx, mm^2/s							0.825
Baseline	20	768.2 (83.1)	–	20	765.7 (104.6)	–	
Δ 3 months	17	1.3 (99.7)	0.959	16	− 7.1 (76.9)	0.714	
Δ 6 months	17	− 20.5 (74.3)	0.278	15	− 7.9 (81.1)	0.708	
L1–L2, mm^2/s							0.678
Baseline	20	819.6 (131.3)	–	20	826.9 (160.5)	–	
Δ 3 months	17	− 27.9 (172.5)	0.511	16	7.5 (127.8)	0.816	
Δ 6 months	17	− 8.7 (94.8)	0.716	15	20.4 (126.5)	0.536	
L2–L3, mm^2/s							0.594
Baseline	20	807.3 (102.3)	–	20	802.6 (141.7)	–	
Δ 3 months	17	− 7.2 (119.8)	0.805	16	31.9 (115.2)	0.277	
Δ 6 months	17	− 17.9 (94.8)	0.456	15	9.8 (110.3)	0.734	
L3–L4, mm^2/s							0.853
Baseline	20	839.7 (106.1)	–	20	784.2 (178.1)	–	
Δ 3 months	17	8.5 (132.8)	0.795	16	− 11.8 (112.4)	0.678	
Δ 6 months	17	− 41.8 (102.9)	0.114	15	− 37.1 (117.5)	0.231	
L4–L5, mm^2/s							0.359
Baseline	20	749.8 (171.5)	-	20	726.6 (151)	–	
Δ 3 months	17	50.0 (141.4)	0.155	16	− 2.6 (123.2)	0.932	
Δ 6 months	17	− 6.2 (149.6)	0.869	15	− 1.2 (147.4)	0.976	
L5–S1, mm^2/s							0.664
Baseline	20	624.9 (162.6)	–	20	688.3 (104.8)	–	
Δ 3 months	17	− 11.8 (172.7)	0.781	16	− 57.5 (95.5)	**0.023**	
Δ 6 months	17	− 19.3 (121.2)	0.529	15	− 29.6 (101.8)	0.269	

Data are mean (SD) at baseline and mean (SD) change at 3 and 6 months. AvLx: Average of lumbar levels. Raw (unadjusted) *p* values shown. Bold: $p \leq 0.05$ 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

Table 4 Volume and height of the lumbar intervertebral discs (averaged between levels)

	Baseline and within-group difference						Group × time effect
	Exercise			Control			
	n	Mean (SD)	*p* value	*n*	Mean (SD)	*p* value	*p* value
Intervertebral disc volume, cm^3							0.256
Baseline	20	8.6 (1.9)	–	20	8.7 (2.9)	–	
Δ 3 months	17	− 0.1 (0.6)	0.505	16	0.3 (0.7)	0.138	
Δ 6 months	17	0.0 (0.6)	0.843	15	0.3 (0.6)	0.084	
Intervertebral disc height, mm							0.054
Baseline	20	8.1 (0.8)	–	20	8.0 (0.8)	–	
Δ 3 months	17	− 0.1 (0.3)	0.158	16	0.1 (0.2)	**0.035**	
Δ 6 months	17	0.0 (0.2)	0.934	15	0.1 (0.2)	0.148	

Data are mean (SD) at baseline and mean (SD) change at 3 and 6 months. Raw (unadjusted) *p* values shown. Bold: $p \leq 0.05$ 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. See Supplemental Table 2 for individual vertebral level data

Table 5 Expansion of intervertebral disc height in short-duration lying

	Baseline and within-group difference						Group × time effect
	Exercise			Control			
	n	Mean (SD)	*p* value	*n*	Mean (SD)	*p* value	*p* value
AvLx, %							0.710
Baseline	20	1.7 (2.6)	–	20	2.0 (2.8)	–	
3 months	17	0.5 (2.2)	0.120	16	0.4 (2.9)	0.076	
6 months	17	0.3 (3.5)	0.157	15	1.5 (3.4)	0.564	
L1–L2, %							0.384
Baseline	20	1.0 (4.0)	–	20	3.1 (3.7)	–	
3 months	17	0.7 (2.7)	0.760	16	0.5 (4.2)	**0.045**	
6 months	17	0.0 (3.9)	0.443	15	1.7 (4.6)	0.296	
L2–L3, %							0.728
Baseline	20	1.6 (3.3)	–	20	2.0 (3.6)	–	
3 months	17	0.2 (3.8)	0.242	16	0.4 (2.9)	0.128	
6 months	17	0.8 (3.2)	0.457	15	2.2 (3.5)	0.866	
L3–L4, %							0.925
Baseline	20	2.2 (2.7)	–	20	2.7 (3.7)	–	
3 months	17	1.4 (2.9)	0.392	16	1.8 (4.8)	0.495	
6 months	17	−0.1 (3.3)	**0.020**	15	1.0 (4.5)	0.186	
L4–L5, %							0.429
Baseline	20	2.5 (3.3)	–	20	1.2 (3.8)	–	
3 months	17	−0.2 (2.4)	**0.008**	16	−0.1 (4.2)	0.285	
6 months	17	0.9 (4.8)	0.246	15	1.6 (3.6)	0.676	
L5–S1, %							0.857
Baseline	20	1.6 (5.8)	–	20	2.2 (6.0)	–	
3 months	17	0.4 (5.8)	0.550	16	0.3 (4.2)	0.265	
6 months	17	−0.2 (5.7)	0.349	15	1.1 (5.8)	0.590	

Data are mean (SD) percentage increase in disc height at baseline and, in contrast to other tables, data at 3 and 6 months are also absolute mean (SD). AvLx: Average of lumbar levels. Raw (unadjusted) *p* values shown. Bold: $p \leq 0.05$ 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

low molecular weights contrast agents (e.g. gadodiamide or gadoteridol) into the IVD may be more promising. An additional approach may be to assess other IVD markers, such as T1rho [43], even if the utility of this measure versus existing approaches such as T2 time is not yet clear. Sodium spectroscopy may have utility for quantifying proteoglycan content in the IVD [44] and sequence protocols that can readily be implemented in living patient collectives are still to be developed.

The strengths of the current study include its prospective randomised design and the blinded nature of MRI data collection and analyses. Limitations of this study include that we did not have a non-intervention control group without any kind of treatment, and may have increased the likelihood of finding a between-group difference, such as if the intervention reduced the rate of age-related decline rather than necessarily cause improvements versus baseline. This is common of studies of exercise and bone [4, 5]. For ethical reasons, we considered it important to have a control group which received treatment, albeit one designed to not load the IVDs. The sample size, whilst sufficiently powering the trial for the primary repeated measures analysis to detect an ~ 2% difference in IVD T2 time change, will not have been sufficient for smaller effect sizes. It is open whether the effect of the exercise as implemented in the current study on IVD T2 relaxation time is smaller than 2%. Another potential limitation is that despite adopting an intent-to-treat approach for primary analyses to account for dropouts, the study may still have been underpowered. Nonetheless, publishing these results follow strong recommendations by The Lancet and other scientific media outlets [45] to publish studies with negative results permitted that the trial, such as the current study, was preregistered, to combat publication bias and erroneous meta-analyses of the current literature. Whilst we requested that patients completed exercise diaries for their home exercise programme, poor adherence and inconsistent

reporting of this practice limited our capacity to comment on this adherence and consider this as a factor in analyses. The experimental intervention was, superficially, less adhered to than in control (60% versus 77%). We intentionally set a high expectation for a number of treatment sessions for the experimental intervention, communicated this during participant screening and included this in the exclusion criteria, to increase the amount of exercise participants in the intervention group completed. The minimum required number of exercise sessions per week to have an effect on the IVD is, unlike guidelines for exercise for muscle [46] and bone [47], not known. Nonetheless, a per-protocol analysis did not yield different overall findings to the intent-to-treat analysis presented in this paper. Furthermore, the number of comparisons made in the current study should be noted. To account for this, we implemented and presented the outcomes of these analyses with and without adjustment for multiple comparisons.

Conclusion

The effects of exercise on the IVD were tested in this first RCT. Exercises specifically designed to beneficially modulate IVD did not significantly improve IVD MRI markers compared to control or to its own baseline in a small group of patients with NSCLBP. Specifically, the intervention in the current study did not statistically improve IVD composition (T2 times), water diffusion speed within the IVD (ADC) or impact IVD expansion in acute lying, when compared to control. This study provides a foundation for future human trials seeking to establish whether various forms and durations of exercise therapeutically modulate the IVD in different populations.

Acknowledgements The authors thank the participants for taking part in this study and the staff of Imaging@Olympic Park for their support implementing this study. Gerontology Research Center is a joint effort between the University of Jyvaskyla and the University of Tampere.

Funding This study was supported by internal institutional funding (Deakin University School of Exercise and Nutrition Sciences, reference number Belavy 2014–2017).

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts.

References

1. Hawley JA (2008) Specificity of training adaptation: Time for a rethink? J Physiol 586:1–2
2. Wolff J (1892) The law of bone remodeling (Das gesetz der transformation der knochen). Springer, Berlin
3. Schoenfeld BJ, Ogborn D, Krieger JW (2016) Effects of resistance training frequency on measures of muscle hypertrophy: a systematic review and meta-analysis. Sports Med 46:1689–1697
4. Polidoulis I, Beyene J, Cheung A (2012) The effect of exercise on pQCT parameters of bone structure and strength in postmenopausal women—A systematic review and meta-analysis of randomized controlled trials. Osteoporos Int 23:39–51
5. Marques EA, Mota J, Carvalho J (2012) Exercise effects on bone mineral density in older adults: a meta-analysis of randomized controlled trials. Age 34:1493–1515
6. Bohm S, Mersmann F, Arampatzis A (2015) Human tendon adaptation in response to mechanical loading: a systematic review and meta-analysis of exercise intervention studies on healthy adults. Sports Med Open 1:7
7. Belavý DL, Albracht K, Bruggemann G-P, Vergroesen P-PA, van Dieën JH (2016) Can exercise positively influence the intervertebral disc? Sports Med 46:473–485
8. Chan SC, Ferguson SJ, Gantenbein-Ritter B (2011) The effects of dynamic loading on the intervertebral disc. Eur Spine J 20:1796–1812
9. Iatridis JC, MacLean JJ, Roughley PJ, Alini M (2006) Effects of mechanical loading on intervertebral disc metabolism in vivo. J Bone Joint Surg Am 88(Suppl 2):41–46
10. Holm S, Nachemson A (1983) Variations in the nutrition of the canine intervertebral disc induced by motion. Spine 8:866–874
11. Brisby H, Wei AQ, Molloy T, Chung SA, Murrell GA, Diwan AD (2010) The effect of running exercise on intervertebral disc extracellular matrix production in a rat model. Spine 35:1429–1436
12. Sasaki N, Henriksson HB, Runesson E, Larsson K, Sekiguchi M, Kikuchi S, Konno S, Rydevik B, Brisby H (2012) Physical exercise affects cell proliferation in lumbar intervertebral disc regions in rats. Spine 37:1440–1447
13. Ueta RHS, Tarini VAF, Franciozi CES, Tamaoki MJS, Medeiros VP, Nader HB, Faloppa F (2018) Effects of training and overtraining on intervertebral disc proteoglycans. Spine 43:E1–E6
14. Luan S, Wan Q, Luo H, Li X, Ke S, Lin C, Wu Y, Wu S, Ma C (2015) Running exercise alleviates pain and promotes cell proliferation in a rat model of intervertebral disc degeneration. Int J Mol Sci 16:2130–2144
15. Marinelli NL, Haughton VM, Munoz A, Anderson PA (2009) T2 relaxation times of intervertebral disc tissue correlated with water content and proteoglycan content. Spine 34:520–524
16. Belavy DL, Quittner MJ, Ridgers N, Ling Y, Connell D, Rantalainen T (2017) Running exercise strengthens the intervertebral disc. Sci Rep 7:45975
17. Tagliaferri SD, Miller CT, Owen PJ, Mitchell UH, Brisby H, Fitzgibbon B, Masse-Alarie H, Van Oosterwijck J, Belavy DL (2019) Domains of chronic low back pain and assessing treatment effectiveness: A clinical perspective. Pain Pract 20:211–225
18. American College of Sports Medicine (2017) ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins, Philadelphia, USA
19. Owen PJ, Miller CT, Mundell NL, Verswijveren SJ, Tagliaferri SD, Brisby H, Bowe SJ, Belavy DL (2019) Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. Br J Sports Med. https://doi.org/10.1136/bjsports-2019-100886
20. Le Maitre CL, Frain J, Fotheringham AP, Freemont AJ, Hoyland JA (2008) Human cells derived from degenerate intervertebral discs respond differently to those derived from non-degenerate intervertebral discs following application of dynamic hydrostatic pressure. Biorheology 45:563–575
21. Wiesinger HP, Kosters A, Muller E, Seynnes OR (2015) Effects of increased loading on in vivo tendon properties: A systematic review. Med Sci Sports Exerc 47:1885–1895

22. Belavy DL, Quittner M, Ling Y, Connell D, Rantalainen T (2018) Cervical and thoracic intervertebral disc hydration increases with recumbency: A study in 101 healthy volunteers. Spine J 18:314–320
23. Simson KJ, Miller CT, Ford J, Hahne A, Main L, Rantalainen T, Teo WP, Teychenne M, Connell D, Trudel G, Zheng G, Thickbroom G, Belavy DL (2017) Optimising conservative management of chronic low back pain: Study protocol for a randomised controlled trial. Trials 18:184
24. Ohnhaus EE, Adler R (1975) Methodological problems in the measurement of pain: A comparison between the verbal rating scale and the visual analogue scale. Pain 1:379–384
25. Fritz JM, Irrgang JJ (2001) A comparison of a modified oswestry low back pain disability questionnaire and the Quebec back pain disability scale. Phys Ther 81:776–788
26. Exercise & Sports Science Australia (2019) What is an accredited exercise physiology? https://www.essa.org.au/Public/Consumer_Information/What_is_an_Accredited_Exercise_Physiologist_.aspx. Accessed 18/03/2019
27. Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE (1999) New in vivo measurements of pressures in the intervertebral disc in daily life. Spine 24:755–762
28. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate - A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300
29. Borm GF, Fransen J, Lemmens WA (2007) A simple sample size formula for analysis of covariance in randomized clinical trials. J Clin Epidemiol 60:1234–1238
30. Glüer C-C, Blake G, Lu Y, Blunt B, Jergas M, Genant H (1995) Accurate assessment of precision errors: How to measure the reproducibility of bone densitometry techniques. Osteoporos Int 5:262–270
31. Antoniou J, Pike GB, Steffen T, Baramki H, Poole AR, Aebi M, Alini M (1998) Quantitative magnetic resonance imaging in the assessment of degenerative disc disease. Magn Reson Med 40:900–907
32. Mwale F, Iatridis JC, Antoniou J (2008) Quantitative MRI as a diagnostic tool of intervertebral disc matrix composition and integrity. Eur Spine J 17:S432–S440
33. Antoniou J, Demers CN, Beaudoin G, Goswami T, Mwale F, Aebi M, Alini M (2004) Apparent diffusion coefficient of intervertebral discs related to matrix composition and integrity. Magn Reson Imaging 22:963–972
34. Beattie PF, Morgan PS, Peters D (2008) Diffusion-weighted magnetic resonance imaging of normal and degenerative lumbar intervertebral discs: A new method to potentially quantify the physiologic effect of physical therapy intervention. J Orthop Sports Phys Ther 38:42–49
35. Tyrrell AR, Reilly T, Troup JD (1985) Circadian variation in stature and the effects of spinal loading. Spine 10:161–164
36. Bowden JA, Bowden AE, Wang HN, Hager RL, LeCheminant JD, Mitchell UH (2018) In vivo correlates between daily physical activity and intervertebral disc health. J Orthop Res 36:1313–1323
37. Seynnes OR, de Boer M, Narici MV (2007) Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. J Appl Physiol 102:368–373
38. Sivan SS, Wachtel E, Tsitron E, Sakkee N, van der Ham F, DeGroot J, Roberts S, Maroudas A (2008) Collagen turnover in normal and degenerate human intervertebral discs as determined by the racemization of aspartic acid. J Biol Chem 283:8796–8801
39. Sivan SS, Tsitron E, Wachtel E, Roughley PJ, Sakkee N, van der Ham F, DeGroot J, Roberts S, Maroudas A (2006) Aggrecan turnover in human intervertebral disc as determined by the racemization of aspartic acid. J Biol Chem 281:13009–13014
40. Hedges RE, Clement JG, Thomas CD, O'Connell TC (2007) Collagen turnover in the adult femoral mid-shaft: Modeled from anthropogenic radiocarbon tracer measurements. Am J Phys Anthropol 133:808–816
41. de Schepper EI, Damen J, van Meurs JB, Ginai AZ, Popham M, Hofman A, Koes BW, Bierma-Zeinstra SM (2010) The association between lumbar disc degeneration and low back pain: The influence of age, gender, and individual radiographic features. Spine 35:531–536
42. Arun R, Freeman BJ, Scammell BE, McNally DS, Cox E, Gowland P (2009) 2009 ISSLS prize winner: What influence does sustained mechanical load have on diffusion in the human intervertebral disc? An in vivo study using serial postcontrast magnetic resonance imaging. Spine 34:2324–2337
43. Yoon MA, Hong S-J, Kang CH, Ahn K-S, Kim BH (2016) T1rho and t2 mapping of lumbar intervertebral disc: Correlation with degeneration and morphologic changes in different disc regions. Magn Reson Imaging 34:932–939
44. Wang C, McArdle E, Fenty M, Witschey W, Elliott M, Sochor M, Reddy R, Borthakur A (2010) Validation of sodium MRI of intervertebral disc. Spine 35:505
45. Horton R (2019) Offline: The gravy train of systematic reviews. The Lancet 394:1790
46. American College of Sports Medicine (2009) American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc 41:687.
47. Beck BR, Daly RM, Singh MA, Taaffe DR (2017) Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. J Sci Med Sport 20:438–445

Affiliations

Patrick J. Owen[1] · Clint T. Miller[2] · Timo Rantalainen[1,3] · Katherine J. Simson[2] · David Connell[4] · Andrew J. Hahne[5] · Guy Trudel[6] · Jon J. Ford[5,7] · Daniel L. Belavy[1]

✉ Patrick J. Owen
p.owen@deakin.edu.au

✉ Daniel L. Belavy
d.belavy@deakin.edu.au; belavy@gmail.com

Clint T. Miller
c.miller@deakin.edu.au

Timo Rantalainen
timo.rantalainen@jyu.fi

Katherine J. Simson
katie_simson@hotmail.com

David Connell
d.connell@iop.net.au

Andrew J. Hahne
a.hahne@latrobe.edu.au

Guy Trudel
gtrudel@toh.ca

Jon J. Ford
jford@advancehealthcare.com.au

[1] Deakin University, Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Geelong, Australia

[2] Deakin University, School of Exercise and Nutrition Sciences, Geelong, Australia

[3] Gerontology Research Center and Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[4] Imaging@Olympic Park, Melbourne, Australia

[5] Low Back Research Team, College of Science, Health & Engineering, La Trobe University, Bundoora, Australia

[6] Bone and Joint Research Laboratory, Division of Physical Medicine and Rehabilitation, The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada

[7] Advance HealthCare, Boronia, Australia