
White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/245752/

Version: Accepted Version

Article:
Boxer, B., Zhang, Z., Folland, J.P. et al. (2026) Acute effect of impact and resistance exercise on Wnt signaling modulators, bone and cartilage metabolism. Journal of Bone and Mineral Research, 41 (3). pp. 282-292. ISSN: 0884-0431

https://doi.org/10.1093/jbmr/zjaf128

© 2025 The Authors. Except as otherwise noted, this author-accepted version of a journal article published in Journal of Bone and Mineral Research is made available via the University of Sheffield Research Publications and Copyright Policy under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/

Reuse
This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: https://creativecommons.org/licenses/

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.


University of Sheffield
UNIVERSITY OF LEEDS
UNIVERSITY of York

Acute effect of impact and resistance exercise on Wnt signalling modulators, bone and cartilage metabolism.

Benjamin Boxer[1,2]: Email: benjamin_boxer@outlook.com

Zhuoyue Zhang[1]: Email: z.zhang4@lboro.ac.uk

Jonathan P Folland[1,2,3]: Email: j.p.folland@lboro.ac.uk

Richard Eastell[4]: Email: r.eastell@sheffield.ac.uk

Fatma Gossiel[4]: Email: f.gossiel@sheffield.ac.uk

Ogulcan Caliskan[1,2,5]: Email: ogulcan.caliskan@afsu.edu.tr

Katherine Brooke-Wavell[1]: Email: k.s.f.brooke-wavell@lboro.ac.uk Phone: +44 (0)1509 222749

Affiliations:
[1] National Centre of Sports and Exercise Medicine, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK.
[2] The Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis, Loughborough University, Loughborough, UK.
[3] National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre, UK.
[4] Mellanby Centre for Musculoskeletal Research, Sheffield University, UK.
[5] Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

Conflicts of interest:

None to declare

Keywords: sclerostin; DKK1; Wnt signalling; bone turnover; cartilage metabolism; men

Abstract

Impact and resistance exercise have potent osteogenic effects and may positively affect cartilage through tissue deformation. These effects may be mediated through inhibitors of Wnt signalling such as sclerostin and Dickkopf WNT signaling pathway inhibitor 1 (DKK1), which may also play a role in cartilage metabolism. This study evaluated the effect of acute bouts of impact and resistance exercise on biomarkers of bone turnover, signalling, and cartilage metabolism.

Healthy young men completed impact or resistance exercise and a control trial in random order. Impact exercise involved 120 maximum-effort multidirectional jumps and hops. Resistance exercise involved 120 high load lower limb lifts. Jumps and lifts were interspersed with 1-3s pauses. In control trial, participants rested in a supine position for same duration as exercise trial. Blood samples were taken pre, immediately and 24h post exercise/rest and analysed for sclerostin, DKK1, C-terminal telopeptide of type I collagen (CTX-I), procollagen I N-terminal propeptide (PINP), procollagen II C-terminal propeptide (PIICP) and cartilage oligomeric matrix protein (COMP). Repeated measures ANOVA compared time points, trials and their interaction.

Participants were 26 men, mean (SD) age 23.4 (2.9) years. Impact exercise increased PINP immediately post exercise (by mean [95%CI] +10.8[4.8,17.2]%, p=0.002) and 24h later (+7.4[0.0,15.3]%, p=0.05) whereas resistance exercise had no effect. A transient increase in sclerostin immediately post exercise occurred in the impact exercise trial only (+36.3[24.6,49.3]%, p<0.001). Both exercise modes transiently increased DKK1 immediately post exercise (impact +32.4[23.1,42.4]%, p<0.001; resistance +30.3[22.8,38.4]%, p<0.001). COMP increased immediately after resistance exercise only (+36.2[16.0,59.8]%, p<0.001). Neither form of exercise affected CTX-I.

Impact and resistance exercise transiently increased Wnt signalling inhibitors. Resistance exercise increased a marker of cartilage turnover but did not affect markers of bone turnover. Impact exercise did not affect cartilage turnover markers.

Increases in bone formation but not resorption markers may reflect positive adaptation to impact loading.

Lay summary

Jumping and resistance training with weights are beneficial to bone strength but less is known of their effects on joint cartilage. In this study, men either jumped 120 times, or did 120 leg resistance exercise and changes were compared to those on a resting day. Blood samples were taken before, immediately after and the day after exercise, to assess changes in biomarkers of bone and joint health.

Both exercises increased levels of molecules that signal between bone cells. Only jumping exercise increased bone formation. Resistance exercise increased cartilage turnover.

Exercise increased signalling between cells and jumping increased bone formation, and cartilage turnover.

Introduction

Osteoarthritis (OA) is a debilitating degenerative joint disease with a multifactorial aetiology that affects articular cartilage, subchondral bone, synovial tissue, and the meniscus[1]. Osteoporosis (OP) is also a systemic disease that affects the skeletal system and is characterised by low bone mass and microarchitectural deterioration, increasing the susceptibility to fractures.[2] The Global Burden of Disease Study (2021) reported OA as the 14th leading global cause of years lived with disability, with an age-standardised rate of 244.5 per 100,000.[3] Likewise, OP has a high incidence, reaching 41.5 million cases globally in 2019, with incidence estimated to reach 263.2 million between 2030-2034, contributing to 128.7 disease-adjusted life years.[4] The developmental years are a key window of opportunity for the prevention of the onset of OA and OP later in life.[5] Therefore, increasing knowledge regarding interventions to improve bone and joint health earlier in life to prevent or delay OA and OP development could reduce suffering and disability globally.[5]

Exercise is a key non-pharmacological intervention that can improve bone and joint health. Loading forces with high strain magnitudes and rates lead to the greatest osteogenic response, with high strain rates increasing fluid flow through the bone.[6] The shear forces generated by the fluid flow may also be detected by osteocytes initiating a cellular response to the applied load.[6] However, the sensitivity of bone to mechanical stimuli declines rapidly after the mechanical stimulus is initiated, with responsiveness reduced within 20-50 load cycles,[7,8] so it is recommended that loading be provided in short bouts separated by recovery intervals.[9]

Like bone, cartilage is dependent on regular mechanical loading[10] and similarly, relatively few (~30) loading cycles are required to maximise stimulation.[11] Ex vivo loading studies show that deformation, and hence stimulation, plateaus after a limited number of cycles.[12] The regulatory effect of tissue deformation on cartilage health is hypothesised to be mediated by chondrocyte stimulation and via facilitating the movement of nutrients and waste products between structures within the joint.[12] Considering cartilage's structural composition and mechanical properties, cartilage interstitial fluid cannot escape from the cartilage instantaneously after the applied

loading.[13] Even though relatively few loading cycles are required to maximise stimulation, sufficient time under tension may be needed for the interstitial fluid to move out of the cartilage, providing the fluid shear stress that stimulates chondrocyte biosynthetic activity.[10] Regarding cartilage health, the optimum dosage and modality of exercise, as well as the underlying mechanism, remains to be elucidated.[14]

High load resistance exercise fulfils several prerequisites for improving bone and cartilage health. Resistance exercises, such as leg presses, involve significant time under tension as the foot remains in contact with the plate throughout the movement, with the load acting through the ankle, knee and hip joints. Resistance exercise causes the muscle-tendon unit to apply force on the bones at the muscle insertion site, causing higher strain magnitude at these sites and providing a stimulatory effect.[15]

High-impact exercise, such as hopping, causes a potent osteogenic response due to the high strain magnitudes and rates generated during the landing phase of the movement and through muscle forces acting on bones during the propulsive phase of movement.[16] However, there is a relatively low time under tension during impact exercise due to the short ground contact time of the foot on the ground, potentially limiting the beneficial effect of this exercise on cartilage.

As both bone and cartilage contain high proportions of collagen, (type I and II respectively) markers of collagen formation (e.g. N-propeptide of type I procollagen (PINP) and C-propeptide of type II collagen (PIICP)) and resorption (e.g. carboxyterminal cross-linked telopeptide of type I collagen (CTX-I) and cartilage oligomeric matrix protein (COMP)) can be used to examine responses to an intervention.[17,18] PINP is enzymatically detached leaving insoluble collagen molecules when type I procollagen is secreted into the extracellular space. PIICP has the same origins but relates to type II collagen secretion. CTX-I is released during collagen degradation in bone resorption. COMP is an extracellular matrix protein present in cartilage that binds with collagen and has a prominent role in stabilising the matrix.

Loading induced changes in bone formation may be mediated by Wnt signalling, which plays a prominent role in regulating the differentiation and function of osteoblasts. Wnt signalling pathway inhibitors such as sclerostin and Dickkopf Wnt signalling pathway inhibitor 1 (DKK1) may mediate or modulate subsequent changes in bone formation[19,20] The Wnt signalling pathway also plays a role in chondrocytic cartilage destruction[21] with increased inhibition of Wnt signalling via sclerostin reducing chondrocyte hypertrophy and cartilage degradation; whereas increased inhibition via DKK1 is associated with greater cartilage degradation.[22] Previous research on the effect of impact and resistance exercise has examined such markers of bone formation and resorption, with mixed findings.[23–26] A recent review of bone biomarker response to acute exercise found small and highly variable responses of CTX-I and PINP to an acute bout of exercise, with no response to resistance or impact exercise.[27]

There has been limited research examining the response of sclerostin to impact[25,28] or resistance[29] exercise in young men, with inconsistent findings with an increase[28] or no change[25] seen after impact exercise, and no change in response to resistance exercise.[29] Furthermore, there is a need for research with simultaneous measurements of bone and cartilage turnover, both of which are impacted by Wnt signalling. There has been minimal research on circulating DKK1 concentration. Impact exercise had no significant effect in two studies[25,30] but decreased DKK1 24 h after exercise in another.[31] The effects of resistance training on DKK1 have not been examined. Whilst previous research has thus provided evidence that acute exercise may affect bone turnover and possibly cartilage turnover, findings have been inconsistent with a lack of standardisation for diurnal variation and dietary intakes, which greatly influence bone markers.[32] In addition, many studies have lacked a non-exercise control group.[27]

The aim of this study was thus to assess the acute effect of single bouts of high-impact exercise and resistance exercise, relative to rest, on Wnt signalling mediators and markers of bone and cartilage turnover in healthy young men. We hypothesised

that sclerostin and bone turnover markers would be elevated after both impact and resistance exercise relative to control.

Methods

Experimental overview

This study employed a two-armed, randomised control study design in which young men completed lower body resistance or impact exercise and a supine rest trial in a random counter-balanced order with at least one week between trials (Figure 1). Randomisation was performed using a block randomisation generator (www.randomization.com). This study received ethical approval from the Ethics Approval (Human Participants) Sub-Committee of Loughborough University, Loughborough, United Kingdom (reference: R19P140). Written informed consent was obtained before participation in the study.

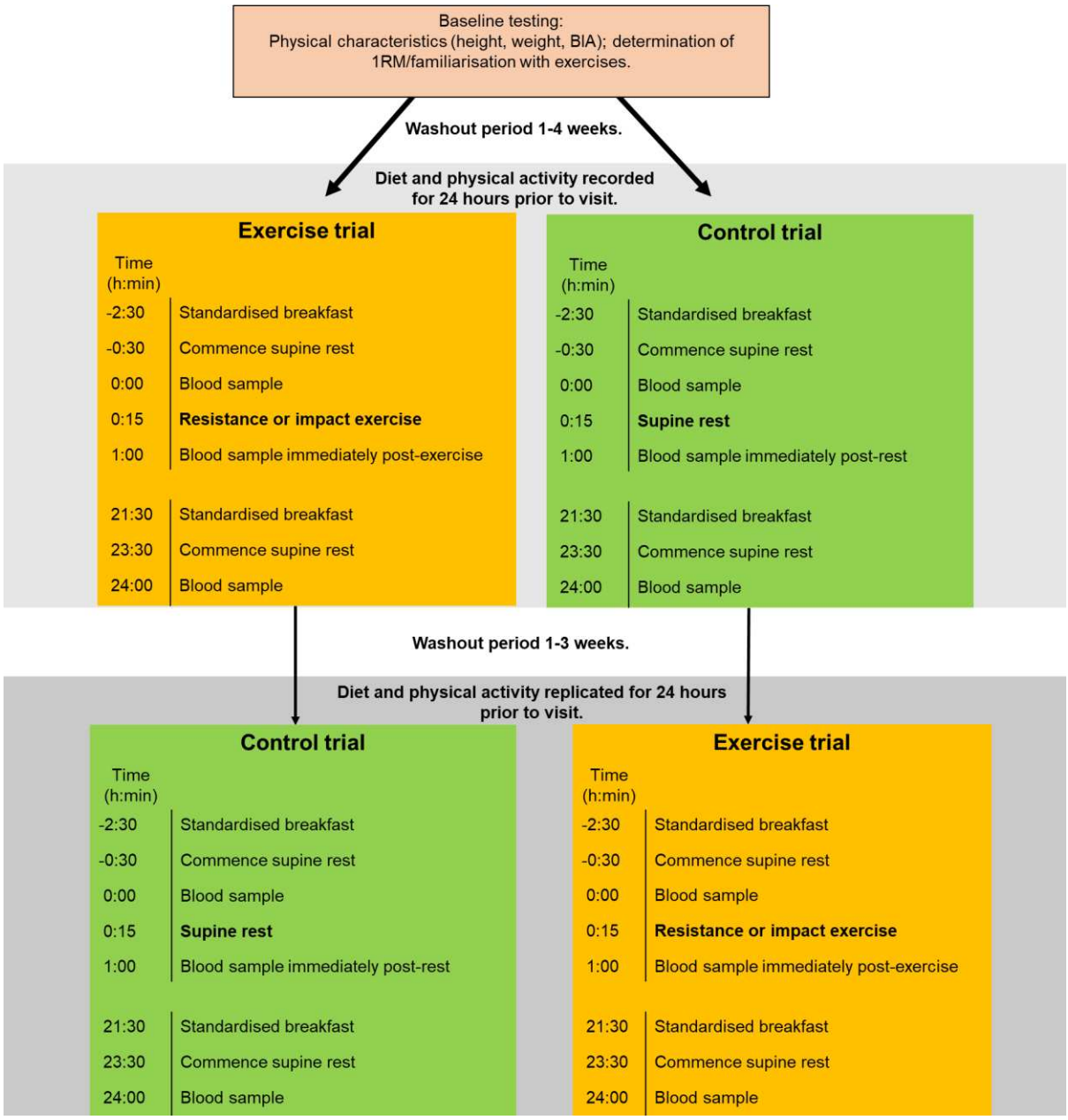


Figure 1. schematic of study design.

Inclusion and exclusion criteria

Inclusion criteria were being recreationally active and able to perform lower body resistance/impact exercise.

Exclusion criteria were assessed by a health screening questionnaire and during familiarisation testing. They were smoking (or vaping); a lower limb bone fracture or traumatic knee injury currently or within the last year; any disease, medication or

restrictive diet that could affect the ability to perform exercise or bone or cartilage metabolism; involvement in any structured resistance or impact exercise training and body mass index (BMI) <18.5 or >25.0 kg/m^2.

Procedures

Baseline familiarisation trial

Body mass was measured on digital scales wearing minimal clothing and standing height was measured using a stadiometer (285 EMR-validated measuring station for height and weight, Seca, Hamburg, Germany). Body fat percentage was measured using bioelectrical impedance analysis (BIA) (MC-780U Multi Frequency Segmental Body Composition Analyzer, Tanita, Tokyo, Japan).

A familiarisation session was completed one to four weeks before the first experimental trial. In the resistance exercise familiarisation session, participants were shown the lifting technique, practiced the technique and then had one repetition maximum (1RM) determined. To determine 1RM, an initial lift was performed at ~80% of the estimated 1RM which was based on the participant's previous experience with resistance exercise (or if they had none, their body weight). The load was then increased in increments until the participant could not lift the weight through the full range of movement (concentric failure), with three min recoveries between attempts. The target was to achieve 1RM load within 3-5 load increments.[33] In the impact exercise familiarisation session, participants were shown jumping techniques and practiced each jump to become familiar with the technique.

At baseline, participants completed a health screening questionnaire to assess their suitability for the study and the International Physical Activity Questionnaire (IPAQ), reporting their physical activity and sedentary time during the last seven days.[34] Total IPAQ score was summed from the duration (minutes) and the frequency (days) for all types of activities in all domains.

Exercise/control trials

Participants were requested to abstain from alcohol and vigorous or high impact exercise in the 24 h prior to and following each main trial. They recorded any

physical activity and dietary intake from 24 h before the first trial until the 24 h post exercise/rest blood sample then replicated this prior to subsequent trials.

Trials were performed in random order starting between 06.30-11.00. Both trials for each participant started at the same time (±15 min). Participants fasted from 22:00 until consuming a standardised breakfast two h before the trial. These consisted of 500 ml of water and three cereal bars (Kelloggs, Salford, UK) providing 390 kcal energy, 9.3 g of fat, 75 g of carbohydrate, 4.8 g of protein, and 600 mg of calcium. A one to three week washout period was allowed between trials.

In the exercise trials, participants rested supine for 30 min prior to the first blood sample, and then warmed up on a cycle ergometer (Monark, Vansbro, Sweden) for five min. The resistance exercise or impact exercise protocol lasted approximately 45 min including recoveries.

The resistance exercise protocol was designed to load the same muscle groups as in the impact exercise trial. The resistance exercise protocol consisted of single and double leg exercises (Table 1) performed on fixed weight machines (Technogym, Cesena, Italy). All exercises were performed at 75% of the participants' pre-determined 1RM. If a participant was unable to perform all repetitions of a set at the pre-determined load, the weight was reduced by one load increment (about five kg depending on the exercise performed) and the participant was instructed to complete any remaining repetitions at this new weight. In total, 120 reps were performed with one min between sets and two min between exercises. Participants performed each exercise with 2-3 s eccentric (lowering) and concentric (raising) phases.

Table 1 Summary of resistance exercises including number of sets and repetitions

Exercise	Leg(s)	Sets	Repetitions
Leg press	Right	3	4
Leg press	Left	3	4
Leg press	Both	3	8
Knee flexion	Both	3	8
Knee extension	Both	3	8

Leg press	Both	3	8

The impact exercise protocol included 120 hops and jumps (Figure 2) with 1 min recovery between sets and two min between exercises. Exercises were performed in three sets of eight repetitions for each of the jumps and three sets of four repetitions per leg for hops. Multidirectional movements were used to provide variety of skeletal loading. Participants were instructed to give maximum effort on each jump. Jumps were performed on a force plate (Kistler Instruments Ltd, Hook, UK) at a sampling rate of 500 Hz. Peak vertical ground reaction force on landing (vGRF) and at take-off (tGRF) were calculated for each jump and expressed as a multiple of body weight (xBW).



Figure 2. Jumps performed in the impact exercise trial. From left to right: single leg hop on right and left leg, countermovement jump, lateral jump over a 30 cm foam hurdle, 180° rotational jump and drop jump.

In the control trial, participants remained in a supine position throughout the trial with a 45 min rest period in place of the 45 min exercise. Blood samples were taken at the same time intervals as during the exercise trials.

Biochemical markers

Venous blood samples were collected after an initial 30 min of rest (pre exercise/rest sample) immediately after exercise/rest and 24 h after the pre exercise/rest sample.

Samples were collected into a nine ml S-Monovette serum tube (Sarstedt, Numbrecht, Germany). Each sample was stored at room temperature for 30 min to allow clotting before being centrifuged at 2000 x gravity for 20 min at 4°C. Serum was pipetted off into four aliquots and immediately frozen at -80°C for subsequent analysis.

Solid phase sandwich enzyme-linked immunosorbent assays (ELISA) with duplicate samples were performed for sclerostin (Sclerostin Quantikine ELISA Kit, R&D Systems, Abingdon, UK), DKK1 (DKK1 Quantikine ELISA Kit, R&D Systems, Abingdon, UK), COMP (COMP Quantikine ELISA Kit, R&D Systems, Abingdon, UK), and PIICP (PIICP ELISA Kit, Elabscience, Houston, Texas, USA). Assays were sensitive to detect sclerostin within the range of 0.370-3.800 pg/mL, minimum detectable dose 1.740 pg/mL; DKK1 assay range of 0.217-0.948 pg/mL, minimum detectable dose 0.419 pg/mL; COMP assay range of 0.005-0.036 ng/ml, mean minimum detectable dose of 0.01 ng/ml; PIICP range 31.25 – 2000 pg/mL, sensitivity of 18.75 pg/m. Duplicates with a coefficient of variance (CV) of >30% were discarded and the data point was treated as missing data. The intra-assay CVs were: sclerostin 3.4%, DKK1 4.5%, COMP 4.4% and PIICP 7.0%.

CTX-I and PINP (total) were analysed using automated electrochemiluminescence immunoassay (ECLIA) analysers (Cobas E411, Roche Diagnostics) with intra-assay CVs of 5.1% and 3.3% respectively.

Statistical analysis

All statistical analysis was performed using IBM Statistical Package for Social Sciences Version 28 (SPSS Inc, Chicago, IL). The statistical level for all tests was set as an α value of 0.05. An a priori power calculation was performed from previous research using a similar protocol and population.[28] This estimated that to detect a change in sclerostin concentration of the magnitude reported previously[28] with 80% power required a minimum of nine participants. To allow for potential dropouts or missing data, our target sample size was 13 participants in each arm.

Data are presented in figures as mean [95%CI] change from pre exercise/rest. Pre exercise/rest data are presented as mean (SD). A Shapiro-Wilk test was used to

assess the parametric assumption of normality of distribution. Group differences in age and BMI were assessed using independent t-tests. Repeated measures analysis of variance (ANOVA) was used to assess whether there was a within subject effect of trial, time or trial*time interaction for each biomarker and exercise type. If a significant trial*time interaction was found, post hoc pairwise comparison was used to determine which means differed.

Where necessary, data were transformed using a natural logarithm of the biomarker values to adjust for a positive skew detected during normality testing. For clarity of reporting, the change in transformed values was then calculated and statistics performed on transformed changes. Back transformed means and 95% confidence intervals are presented.

Results

Participant characteristics

Twenty-six participants completed the study whose characteristics are reported in Table 2. There were no significant differences in participants' body weights, age or BMI between participants who completed the impact exercise or resistance exercise trial ($p > 0.05$).

Table 2. Participant characteristics at pre-exercise/rest

	Impact exercise	Resistance exercise
N	13	13
Height (cm)	176.5 (10.5)	176.8 (5.6)
Weight (kg)	72.2 (8.0)	72.0 (8.8)
Body fat (%)	15.2 (3.1)	15.8 (5.7)
BMI (kg/m^2)	23.1 (1.3)	23.0 (2.1)
Age (years)	23.7 (2.5)	23.2 (3.4)
Total IPAQ score	2896 (1780)	3215 (1545)

Results are presented as mean (SD).

Ground reaction force for different jumps and loads lifted

All participants (n = 13) completed all 120 jumps per protocol. The highest vertical ground reaction force (vGRF) during take-off was observed for the lateral jump with the lowest for the right leg hop (Table 3). The highest vGRF during landing was observed when landing from the jump up phase of the drop jump and the lowest for hopping on the left leg (Table 3).

Table 3. Peak vertical ground reaction forces during impact exercises.

	Force during take off		**Force during landing**	
Exercise (n = 13)	**N**	**xBW**	**N**	**xBW**
Hop right leg	805 (287)	1.2 (0.2)	2578 (909)	3.7 (0.9)
Hop left leg	823 (172)	1.2 (0.2)	2424 (803)	3.4 (0.8)
Countermovement jump	1119 (322)	1.6 (0.3)	4258 (1676)	6.2 (2.1)
Lateral jump	1480 (384)	2.1 (0.3)	3613 (1178)	5.1 (1.4)
180° rotational jump	1218 (324)	1.7 (0.4)	3893 (1404)	5.5 (1.6)
Drop jump (drop phase)*	-	-	3342 (911)	4.9 (1.2)

Drop jump (rebound)*	-	-	4577 (1357)	6.5 (1.3)

Data are presented as mean (SD). Vertical ground reaction force measured in newtons (N) or as a multiple of body weight (xBW). *Drop jumps were performed form a block onto the force plate so takeoff forces were not recorded.

The median weight lifted was 1.2-1.4 times body weight for single leg lifts and 3.2 for lifts involving both legs (Supplementary Table 1)

Changes in biomarkers

There were no significant differences in pre biomarker concentrations between the exercise and control trials ($p > 0.05$, Supplementary Table 2).

Bone turnover markers

PINP

In the impact exercise trial, there were significant effects for trial, and trial*time interaction (F trial = 10.360, p = 0.012; F trial*time = 7.066, p = 0.006) but no independent effect of time (F time = 3.289, p = 0.064) (Figure 3a). Follow-up t-tests showed that there was a significant increase from pre to immediately post exercise (t = -4.168, p = 0.002). Mean change (95% CI) was +10.8 (4.8,17.2) %. Values remained elevated 24 hours post exercise (t = -2.305, p = 0.05 vs pre) mean change +7.4% (0.0,15.3). In the resistance exercise trial, there was no significant effect for trial, time or trial*time interaction (F trial = 0.004, p = 0.950, F time = 0.733, p = 0.493, F trial*time = 0.035, p = 0.966) (Figure 3b).

CTX-I

In the impact exercise trial, there was a significant effect of time (F time = 7.151, p = 0.006) but no significant effect of trial (F trial = 0.117, p = 0.741) or trial*time interaction (F trial*time = 0.204, p = 0.817) (Figure3c).

In the resistance exercise trial, there was a significant effect of time (F time = 18.618, p < 0.001) but no significant effect of trial (F trial = 0.237, p = 0.635) or trial*time interaction (F trial*time = 0.426, p = 0.658) (Figure 3d).

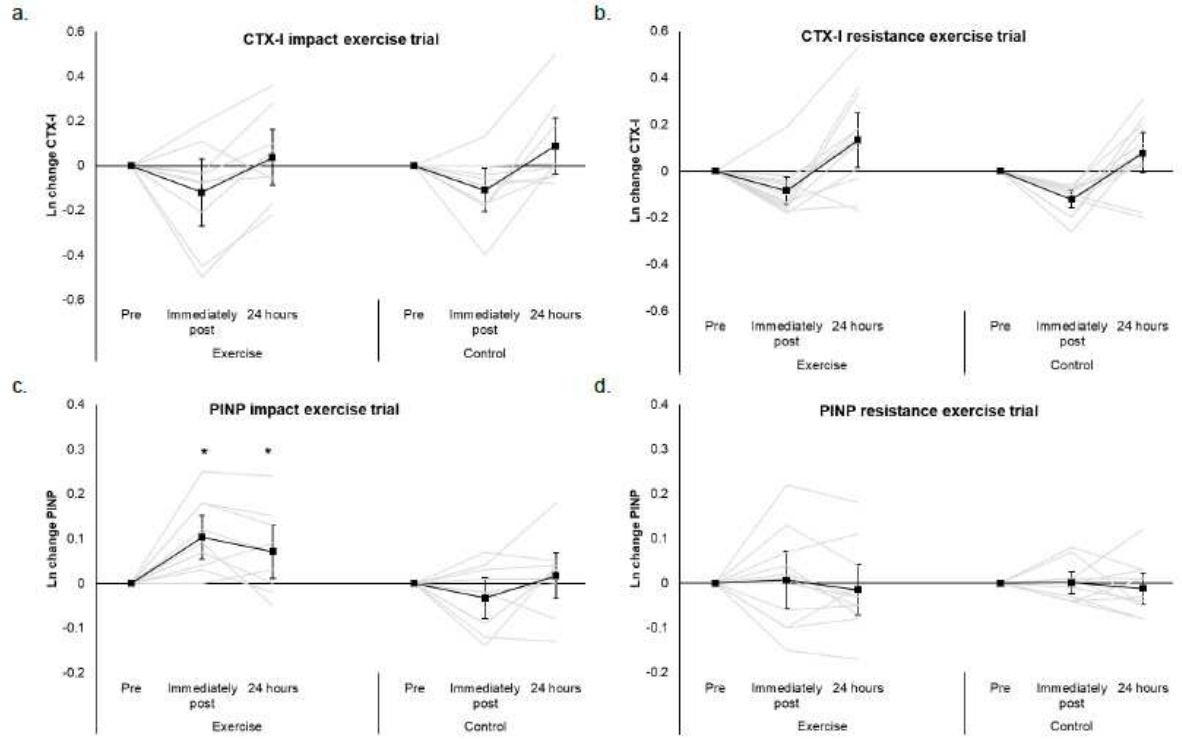


Figure 3. Ln change in CTX-I (panel a and b) and PINP (panel c and d) concentration from pre to immediately and 24 h post exercise/rest. Values are presented as mean and 95% CI in black with the individual data points shown in light grey. * significantly different from pre exercise/rest $p < 0.05$.

Bone signalling markers

Sclerostin

In the impact exercise trial, there was a significant effect for trial, time, and trial*time interaction (F trial = 15.47, p = 0.003; F time = 4.38, p = 0.026; F trial*time = 16.46, p < 0.001). There was a significant increase pre to immediately post exercise (Figure 4a) (t = -7.548, p < 0.001) of +36.3 (24.6,49.3) %, with no significant difference from pre exercise after 24 hours (t = 0.182, p = 0.859).

In the resistance exercise trial, there was a significant effect of time (F time = 4.31 p = 0.025) but not trial (F trial = 0.225, p = 0.644) or trial*time interaction (F trial*time = 0.942, p = 0.404) (Figure 4b).

DKK1

In the impact exercise trial, there was a significant effect for trial, time and trial*time interaction (F trial = 29.38, $p < 0.001$; F time = 24.84, $p < 0.001$; F trial*time = 29.31, $P < 0.001$). There was a significant ($t = -8.41$, $p < 0.001$) increase in the exercise trial between pre and immediately post exercise (Figure 4c) of 32.4 (23.1,42.4) %, with no significant difference between pre and 24 hours post exercise ($t = 1.050$, $p = 0.316$).

In the resistance exercise trial, there were also significant effects for trial, time and trial*time interaction (F trial = 5.67, $p = 0.035$; F time = 84.21, $p < 0.001$; F trial*time = 32.75, $p < 0.001$). In the exercise trial there was a significant increase from pre to immediately post exercise (Figure 4d) ($t = -9.62$, $p < 0.001$) of 30.3 (22.8,38.4) % with no significant difference at 24 hours post exercise ($t = 2.07$, $p = 0.06$).

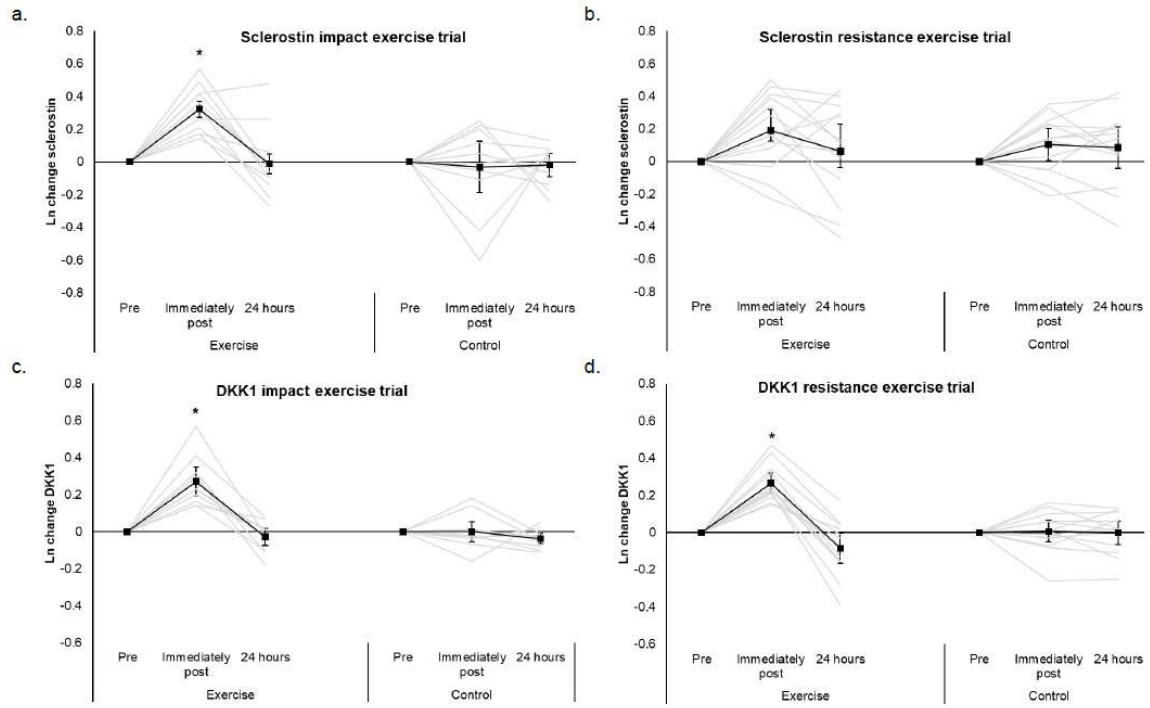


Figure 4. Ln change in Sclerostin (panel a and b) and DKK1 (panel c and d) concentration from pre to immediately and 24 h post exercise/rest. Values are presented as mean and 95% CI in black with the individual data points shown in light grey. * significantly different from pre exercise/rest $p < 0.05$.

Cartilage metabolism markers

COMP

In the impact exercise trial, there was a significant trial*time interaction (F trial*time = 3.67, p = 0.049) but no effect of trial (F = 0.605, p = 0.459) or time (F = 0.924, p = 0.417) (Figure 5a). Values immediately post (t = -1.71, p = 0.115) and 24 post exercise (t = -0.052, p = 0960) were not significantly different from pre exercise.

In the resistance exercise trial, there was a significant trial*time interaction (F trial*time = 19.74, p < 0.001) with no significant effects for trial (F trial = 4.14, p = 0.067) or time (F time = 1.95, p = 0.166) (Figure 5b). In the exercise trial there was a significant increase from pre to immediately post exercise 36.2 (16.0,59.8) % with no significant difference from pre exercise at 24 hours (t = 0.68, p = 0.508). Conversely, in the control trial there was a significant decrease immediately post rest (t = 3.96, p

= 0.002) of -12.9 (-19.3, -5.9) %, with no significant difference from pre rest by 24 hours post rest.

PIICP

In the impact exercise trial, there was a significant trial*time interaction (F trial*time = 4.47, p = 0.023) but no independent effects for trial (F trial = 1.52, p = 0.243) or time (F time = 0.007, p = 0.993) (Figure 5c), Follow up t-tests showed immediately post and 24 post exercise values were not significantly different from pre exercise. In the resistance exercise trial, there were no significant effects for trial, time or trial*time interaction (F trial = 0.92, p = 0.782, F time = 0.120, p = 0.889, F trial*time = 0.081, p = 0.923) (Figure 5d).

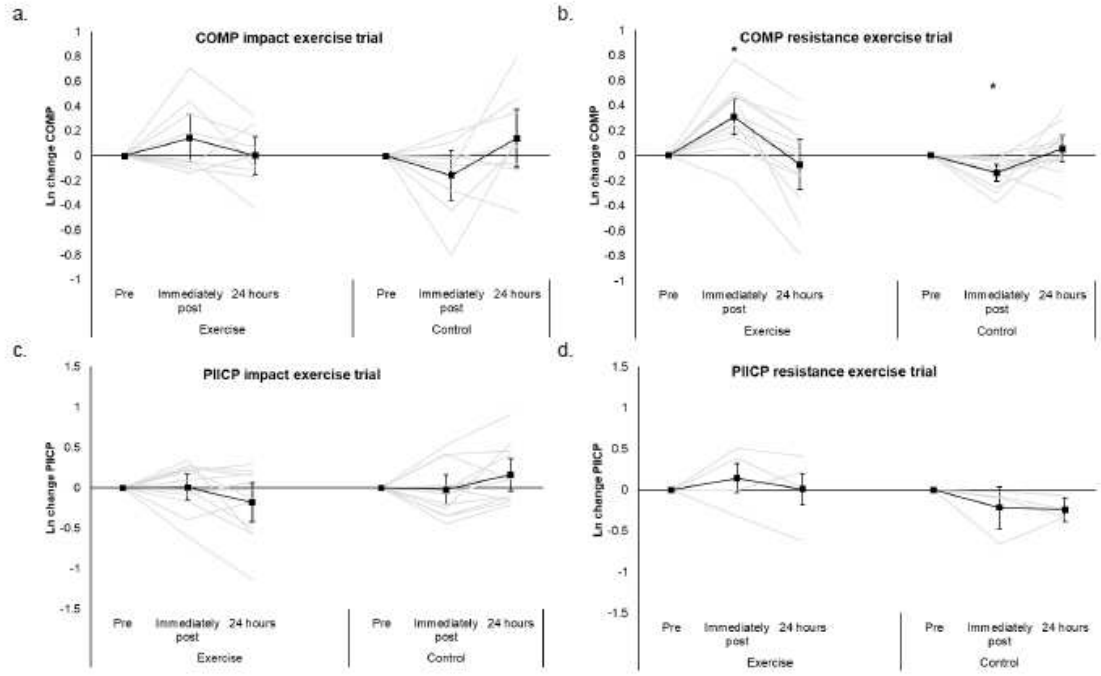


Figure 5. Ln change in COMP (panel a and b) and PIICP (panel c and d) concentration from pre to immediately and 24 h post exercise/rest. Values are presented as mean and 95% CI in black with the individual data points shown in light grey. * significantly different from pre exercise/rest p < 0.05.

Discussion

This study was the first to examine the effect of distinct bouts of impact and resistance exercise on Wnt signalling mediators and markers of bone and cartilage turnover in a group of healthy young men. Time of day was matched between trials with participants requested to match prior exercise and dietary intakes, attempting to control for diet and exercise. Impact exercise significantly increased bone formation marker PINP and Wnt signalling inhibitors sclerostin and DKK1 whilst resistance exercise only increased DKK1. Neither exercise modality affected bone resorption marker CTX-I and only resistance exercise affected cartilage turnover marker COMP. Only the increases in PINP persisted after 24 hours.

There was an increase in PINP after impact exercise that was sustained 24 h later, but no change following resistance exercise. A systematic review of previous studies[27] reported small increases in PINP within 15 min after some aerobic or low to moderate impact exercise (effect size 0.18) although they concluded that there was no evidence of changes at 24-48 h or after high impact exercise. When examining specific studies, no change in PINP was found after jumping exercise [24,35], and high impact exercise also did not ameliorate the reduced PINP in response to energy deficiency.[36] One explanation for discrepant findings on high impact exercise could be differences in exercise intensity, but Rantalainen et al.[24] and Hutson et al.[36] reported similar ground reaction forces to those seen in the current study (~6xBW), whereas ground reaction forces were not measured by Hilkens et al.[35] However, Hilkens et al.[35] used shorter recovery intervals and Rantalainen et al.[24] used an exhaustive protocol, that may have limited responses. In the Hutson et al.[36] study, effects of energy restriction may have constrained the response to exercise. Another potential explanation for the inconsistency is our use of an assay that detected total PINP whilst intact PINP was assessed in previous studies.[24,35,36] The intact PINP assay measures the larger PINP trimer, whereas the total assay used in the current study also detects both the larger (trimer) and the smaller (monomeric) forms. The trimer is cleared by the liver, and the monomeric form by the kidney, and this may account for differences in responses. However, a previous study utilising the intact

PINP assay did see a small increase post resistance exercise, but this study lacked a non-exercise control so this could reflect diurnal variation.[37] It has also been proposed that longer duration interventions are required to detect changes in osteoblast-mediated bone formation and hence any acute changes may be reflective of other processes occurring.[35]

Carboxyterminal propeptide of type I procollagen (PICP) (the other propeptide of type I collagen, which is produced in equimolar quantity to PINP) has been reported to decrease in the 24h after resistance exercise with a subsequent increase in the days after.[38] However, this later increase may be explained by lack of control for diet and activity at this time: a more carefully standardised trial saw no significant effects,[39] or it could be explained by the temporality of the bone remodelling cycle, with formation being preceded by resorption.

No significant changes in bone resorption marker CTX-I were detected in the 24 h following impact or resistance exercise in this study. In previous resistance exercise trials, CTX-I decreased immediately[40] or did not change.[26] In previous high impact exercise trials, CTX-I decreased at 12 h[24,25] but increased 48 h after exercise.[24,25] However, in the studies that involved more careful control and standardisation of participants' diet with the provision of standardised meals[26] and refraining from other forms of exercise,[35] no effect of resistance[26,35] or impact[35] exercise on CTX-I were observed, either immediately after exercise or 24 h later. In the current study, participants' diet and exercise were replicated between trials which may account for the lack of difference in biomarker levels between trials. The significant changes in CTX-I that have been previously found may be due to methodological differences e.g. more sustained exercise interventions that may increase PTH and/or greater volume of loading cycles that may contribute to microdamage and consequent increased remodelling[27] compared to the lower number of loading cycles participants performed in the current study.

Exercise induced changes in bone formation may be mediated by changes in Wnt signalling.[19,20] This study found an increase in sclerostin following a bout of impact exercise, but not resistance exercise. Most previous research in men[28,41,42] and

women[40,43–45] has found an immediate post exercise elevation in sclerostin, with a return to close to pre exercise levels after 24 h. This contrasts with findings from preclinical models where sclerostin expression decreased after sustained periods of mechanical loading of bone,[21] especially in regions of high strain, and led to increased bone formation at these regions.[20,28,46]

In addition, there was an increase in DKK1 immediately post exercise which, unlike for sclerostin, was statistically significant in the resistance as well as the impact exercise trial. The differences between impact exercise and resistance exercise trials may relate to a greater increase in skeletal fluid flow with impact exercise than resistance exercise, resulting in more pre-existing sclerostin being released following impact exercise. Previous studies reported no change[30] or decreases[31] in DKK1 after high impact exercise in boys and girls and no change in healthy men.[25] Exercise intensities (e.g. ground reaction forces) were not reported in these studies, however, and it is possible that the forces generated were not sufficiently different from habitual loading to stimulate an osteogenic response. In the study by Dekker et al.[31] that reported a decrease in DKK1 at 24 h post exercise there was no control group or control for physical activity or dietary intake which may contribute to the significant decrease. Further well-controlled research is needed to confirm the acute effects of exercise on DKK1.

The concurrent elevation of PINP, a marker of bone formation, and the Wnt inhibitors sclerostin and DKK1 following impact exercise may initially appear paradoxical, given the established inhibitory role of these proteins on Wnt/β-catenin signalling. One plausible explanation, as proposed by Falk et al.[28] is a transient redistribution of sclerostin from the osteocytic lacuno-canalicular network into the systemic circulation. This redistribution may reduce local sclerostin concentrations at the bone surface, thereby diminishing its inhibitory effect on Wnt signalling and permitting a localized pro-osteogenic response, despite elevated systemic levels. This mechanism is supported by the sustained increase in PINP observed at 24 hours post-exercise. Other explanations include changes in renal excretion/uptake.[28,43] Alternatively, it is possible that post-exercise Wnt inhibition is mediated via pathways

independent of sclerostin and DKK1, or that other signalling mechanisms are concurrently activated to promote bone formation. It should also be considered that sclerostin is expressed by other tissues, e.g. by hypertrophic and articular chondrocytes[21,22] with research in mice showing that the Wnt signalling pathway and hence sclerostin is required for chondrocyte proliferation.[47] In addition, sclerostin has extra-skeletal roles.[45] Changes in sclerostin may thus effect expression or metabolism in tissues other than bone. It is important to note that acute increase in sclerostin and DKK1 contrast with chronic decreases reported with regular exercise.

Resistance exercise may affect cartilage metabolism, with an increase in COMP immediately after exercise and a decrease following rest. This may reflect changes in proteolytic matrix degradation[48] and a reduction after rest is consistent with previous findings.[48] Alternatively, the changes in serum COMP may just reflect changes in COMP mobilisation following exercise.[48] Neither resistance nor impact exercise affected PIICP, although assay sensitivity may have limited ability to detect changes in the low levels in healthy young men. Few previous studies have examined effects of exercise on PIICP: running exercise also did not change PIICP[49] although it has a different loading profile. Resistance exercise, but not impact exercise, may affect cartilage degradation.

In relation to cartilage metabolism, mechanical loading in human cartilage explant models induced excessive Wnt signalling activation that reduced chondrocyte mechanoresponsiveness, with a corresponding downregulation of catabolic enzymes such as Matrix Metallopeptidase 1 (MMP1) and Matrix Metallopeptidase 13 (MMP13), ultimately leading to reduced cartilage degradation compared to loading alone.[50] This is consistent with the transient decrease we observed in the resistance exercise trial, but in the impact exercise trial, where an increase in sclerostin was observed, there were no changes in COMP levels. This suggests that elevated Wnt inhibition may have attenuated cartilage catabolic activity. Conversely, neither exercise modality resulted in increased cartilage formation, as indicated by the absence of change in PIICP, potentially reflecting limited effects on cartilage metabolism. It is important to consider that changes in biomarker concentrations may

also reflect a release of pre-existing markers into the systemic circulation or an increased expression from other tissues than bone, and these factors could also contribute to findings.

This study has some strengths such as the incorporation of a sedentary control trial, attempted standardisation of diet and exercise and measurement of markers of bone signalling, cartilage metabolism and reference markers for the measurement of bone turnover[17] which were conducted on automated analysers at a highly experienced research centre. However, this study also has several limitations; we acknowledge that serum measurements of locally-acting Wnt pathway modulators sclerostin and DKK1 may not reflect the paracrine action of these molecules in the bone and we did not include other crucial pathways for bone physiology such as the receptor activator of NFkB ligand (RANKL)-osteoprotegerin (OPG) axis. In addition, the study was of a relatively short duration compared to the bone and cartilage physical adaptions in response to exercise and due to this limited duration we did not measure any imaging outcomes of bone or cartilage health such as cartilage properties from MRI or bone mineral density (BMD) from dual energy x-ray absorptiometry. The findings of this study cannot be extrapolated to predict what imaging outcomes might have occurred but can be used to inform longer-term studies including imaging outcomes. However, blood biomarkers offer a means to evaluate the acute changes in bone and cartilage interventions, that may not be detected by imaging outcomes. In addition, ideally the same participants would complete all three arms of the trial (control, resistance exercise and impact exercise) instead of completing just two (either impact exercise and control or resistance exercise and control) so that direct within participant comparisons could be made. However, all participants completed both an exercise and a control trial, and participants in impact exercise and resistance exercise trials had similar characteristics with no difference in age or BMI ($p > 0.05$).

In conclusion, both impact and resistance exercise increased bone signalling molecule DKK1, whereas only impact exercise increased sclerostin and bone formation marker PINP. The increase in bone formation seems in contrast to the

increase in sclerostin; it is uncertain whether the increase in sclerostin relates to an increase in synthesis, an increased distribution of pre-existing sclerostin from bone to systemic circulation (with lowered bone sclerostin potentially contributing to localised increases in bone formation) or another factor relating to its extraskeletal roles. Neither exercise modality affected bone resorption whilst only resistance exercise increased cartilage turnover marker COMP. The previously demonstrated benefits of impact and resistance exercise on bone health may be mediated through increases in bone signalling for both exercise modalities, and formation in the case of impact exercise. The mechanisms of possible effects of resistance exercise on cartilage metabolism need further exploration.

Acknowledgement

We are grateful to Nick Cox, SSEHS, Loughborough University for support in conducting some assays.

Author contribution

Benjamin Boxer: conceptualisation, project administration, formal analysis, visualisation, writing – original draft preparation, writing – reviewing and editing,

Zhuoyue Zhang: formal analysis, writing – original draft preparation, writing – reviewing and editing

Jonathan P Folland: conceptualisation, writing – original draft preparation, writing – reviewing and editing, supervision

Richard Eastell: conceptualisation, writing – reviewing and editing, supervision

Fatma Gossiel: project administration,conceptualisation, writing – reviewing and editing

Ogulcan Caliskan: formal analysis, writing – reviewing and editing

Katherine Brooke-Wavell: conceptualisation, project administration, formal analysis, visualisation, writing – original draft preparation, writing – reviewing and editing, supervision

Data availability

Data is available upon request.

References

1. Chen D, Shen J, Zhao W, et al. Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. *Bone Res*. 2017;5(August 2016). doi:10.1038/boneres.2016.44

2. Compston JE, Mcclung MR, Leslie WD. Seminar Osteoporosis. *The Lancet*. 2019;393:364-376. doi:10.1016/S0140-6736(18)32112-3

3. Ferrari AJ, Santomauro DF, Aali A, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*. 2024;403(10440):2133-2161. doi:10.1016/S0140-6736(24)00757-8

4. Zhu Z, Yu P, Wu Y, et al. Sex Specific Global Burden of Osteoporosis in 204 Countries and Territories, from 1990 to 2030: An Age-Period-Cohort Modeling Study. *J Nutr Health Aging*. 2023;27(9):767-774. doi:10.1007/S12603-023-1971-4

5. Going SB, Farr JN. Exercise and Bone Macro-architecture: Is Childhood a Window of Opportunity for Osteoporosis Prevention? *Int J Body Compos Res*. 2010;8:1. Accessed January 27, 2025. https://pmc.ncbi.nlm.nih.gov/articles/PMC3903297/

6. Turner CH. Three Rules for Bone Adaptation to Mechanical Stimuli. 1998;23(5):399-407.

7. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am*. 1984;66(3):397-402. Accessed May 31, 2019. http://www.ncbi.nlm.nih.gov/pubmed/6699056

8. Umemura Y, Ishiko T, Yamauchi T, Kurono M, Mashiko S. Five jumps per day increase bone mass and breaking force in rats. *Journal of Bone and Mineral Research*. 1997;12(9):1480-1485. doi:10.1359/jbmr.1997.12.9.1480

9. Robling AG, Burr DB, Turner CH. Recovery periods restore mechanosensitivity to dynamically loaded bone Alexander. *J Exp Biol*. 2001;204:3389–3399. Accessed May 31, 2019. http://jeb.biologists.org/content/jexbio/204/19/3389.full.pdf

10. Eckstein F, Hudelmaier M, Putz R. The effects of exercise on human articular cartilage. *J Anat*. 2006;208(4):491-512. doi:10.1111/j.1469-7580.2006.00546.x

11. Eckstein F, Lemberger B, Stammberger T, Englmeier KH, Reiser M. Patellar cartilage deformation in vivo after static versus dynamic loading. *J Biomech*. 2000;33(7):819-825. doi:10.1016/S0021-9290(00)00034-8

12. Wong M, Carter DR. Articular cartilage functional histomorphology and mechanobiology: a research perspective. *Bone*. 2003;33(1):1-13. doi:10.1016/S8756-3282(03)00083-8

13. Ateshian GA. The role of interstitial fluid pressurization in articular cartilage lubrication. *J Biomech*. 2009;42(9):1163-1176. doi:10.1016/j.jbiomech.2009.04.040

14. Collins NJ, Hart HF, Mills KAG. Osteoarthritis year in review 2019: rehabilitation and outcomes. *Osteoarthritis Cartilage*. 2019;27(3):378-391. doi:10.1016/j.joca.2018.11.010

15. Zehnacker CH, Bemis-Dougherty A. Effect of weighted exercises on bone mineral density in post menopausal women. A systematic review. *J Geriatr Phys Ther*. 2007;30(2):79-88. Accessed June 19, 2019. http://www.ncbi.nlm.nih.gov/pubmed/18171491

16. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. Physical Activity and Bone Health. *Med Sci Sports Exerc*. 2004;36(11):1985-1996. doi:10.1249/01.MSS.0000142662.21767.58

17. Vasikaran S, Cooper C, Eastell R, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine Position on bone marker standards in osteoporosis. *Clin Chem Lab Med*. 2011;49(8):1271-1274. doi:10.1515/CCLM.2011.602

18. Roberts HM, Law RJ, Thom JM. The time course and mechanisms of change in biomarkers of joint metabolism in response to acute exercise and chronic training in physiologic and pathological conditions. *Eur J Appl Physiol*. 2019;119(11-12):2401-2420. doi:10.1007/s00421-019-04232-4

19. Choi RB, Robling AG. The Wnt pathway: an important control mechanism in bone's response to mechanical loading. *Bone*. Published online July 5, 2021:116087. Accessed July 5, 2021. https://linkinghub.elsevier.com/retrieve/pii/S8756328221002490

20. Hong AR, Kim SW. Effects of Resistance Exercise on Bone Health. *Endocrinology and Metabolism*. 2018;33(4):435. doi:10.3803/ENM.2018.33.4.435

21. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697-1707. doi:10.1002/art.34453

22. Chan BY, Fuller ES, Russell AK, et al. Increased chondrocyte sclerostin may protect against cartilage degradation in osteoarthritis. *Osteoarthritis Cartilage*. 2011;19(7):874-885. doi:10.1016/j.joca.2011.04.014

23. Sherk VD, Chrisman C, Smith J, et al. Acute Bone Marker Responses to Whole-Body Vibration and Resistance Exercise in Young Women. *Journal of Clinical Densitometry*. 2013;16(1):104-109. doi:10.1016/j.jocd.2012.07.009

24. Rantalainen T, Heinonen A, Linnamo V, Komi P V., Takala TES, Kainulainen H. Short-term bone biochemical response to a single bout of high-impact exercise. *J Sports Sci Med*. 2009;8(4):553-559.

25. Guerriere KI, Hughes JM, Gaffney-Stomberg E, Staab JS, Matheny RW. Circulating sclerostin is not suppressed following a single bout of exercise in young men. *Physiol Rep*. 2018;6(10):1-9. doi:10.14814/phy2.13695

26. Rogers RS, Dawson AW, Wang Z, Thyfault JP, Hinton PS. Acute response of plasma markers of bone turnover to a single bout of resistance training or plyometrics. *J Appl Physiol*. 2011;111(5):1353-1360. doi:10.1152/japplphysiol.00333.2011

27. Dolan E, Dumas A, Keane KM, et al. The Bone Biomarker Response to an Acute Bout of Exercise: A Systematic Review with Meta-Analysis. *Sports Medicine*. 2022;52(12):2889-2908. doi:10.1007/S40279-022-01718-8/FIGURES/3

28. Falk B, Haddad F, Klentrou P, et al. Differential sclerostin and parathyroid hormone response to exercise in boys and men. *Osteoporosis International*. 2016;27(3):1245-1249. doi:10.1007/s00198-015-3310-z

29. Philippou A, Maridaki M, Kollias L, Papadopetraki A, Pennas I, Koutsilieris M. Hormonal Responses After Eccentric Exercise In Humans. *Med Sci Sports Exerc*. 2017;49(January):613. doi:10.1249/01.mss.0000518607.01362.40

30. Klentrou P, Angrish K, Awadia N, Kurgan N, Kouvelioti R, Falk B. Wnt Signaling–Related Osteokines at Rest and Following Plyometric Exercise in Prepubertal and Early Pubertal Boys and Girls. *Pediatr Exerc Sci*. 2018;(8):1-9. doi:10.1123/pes.2017-0259

31. Dekker J, Nelson K, Kurgan N, Falk B, Josse A, Klentrou P. Wnt Signaling-related Osteokines and Transforming Growth Factors Before and After a Single Bout of Plyometric Exercise in Child and Adolescent Females. *Pediatr Exerc Sci*. Published online 2017:1-29. doi:10.1123/pes.2017-0042

32. Redmond J, Fulford AJ, Jarjou L, Zhou B, Prentice A, Schoenmakers I. Diurnal rhythms of bone turnover markers in three ethnic groups. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(8):3222-3230. doi:10.1210/JC.2016-1183/SUPPL_FILE/JC-16-1183.PDF

33. Niewiadomski W, Gąsiorowska A, Cybulski G, Laskowska D, Langfort J. Determination and Prediction of One Repetition Maximum (1RM): Safety

Considerations. *J Hum Kinet*. 2008;19:109-120. doi:10.2478/v10078-008-0008-8

34. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-Country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB

35. Hilkens L, Bons J, Nyakayiru J, van Loon LJC, van Dijk JW. A single bout of jumping exercise does not modulate serum markers of bone formation or bone resorption throughout a 24 h period. *Bone*. 2024;188:117216. doi:10.1016/J.BONE.2024.117216

36. Hutson MJ, O'Donnell E, Brooke-Wavell K, et al. High-impact jumping mitigates the short-term effects of low energy availability on bone resorption but not formation in regularly menstruating females: A randomized control trial. *Scand J Med Sci Sports*. 2023;33(9):1690-1702. doi:10.1111/sms.14437

37. Aussieker T, Hilkens L, Holwerda AM, et al. Collagen Protein Ingestion during Recovery from Exercise Does Not Increase Muscle Connective Protein Synthesis Rates. *Med Sci Sports Exerc*. 2023;55(10):1792-1802. doi:10.1249/MSS.0000000000003214

38. Virtanen P, Viitasalo JT, Vuori J, Väänänen K, Takala TE. Effect of concentric exercise on serum muscle and collagen markers. *J Appl Physiol (1985)*. 1993;75(3):1272-1277. doi:10.1152/jappl.1993.75.3.1272

39. Whipple TJ, Le BH, Demers LM, et al. Acute effects of moderate intensity resistance exercise on bone cell activity. *Int J Sports Med*. 2004;25(7):496-501. doi:10.1055/s-2004-820942

40. Gombos GC, Bajsz V, Pék E, et al. Direct effects of physical training on markers of bone metabolism and serum sclerostin concentrations in older adults with low bone mass. *BMC Musculoskelet Disord*. 2016;17(1):1-8. doi:10.1186/s12891-016-1109-5

41. Kouvelioti R, Kurgan N, Falk B, Ward WE, Josse AR, Klentrou P. Cytokine and Sclerostin Response to High-Intensity Interval Running versus Cycling. *Med Sci Sports Exerc*. Published online 2019:1. doi:10.1249/mss.0000000000002076

42. Kouvelioti R, LeBlanc P, Falk B, Ward WE, Josse AR, Klentrou P. Effects of High-Intensity Interval Running Versus Cycling on Sclerostin, and Markers of Bone Turnover and Oxidative Stress in Young Men. *Calcif Tissue Int*. 2019;104(6):582-590. doi:10.1007/s00223-019-00524-1

43. Pickering ME, Simon M, Sornay-Rendu E, et al. Serum Sclerostin Increases After Acute Physical Activity. *Calcif Tissue Int*. 2017;101(2):170-173. doi:10.1007/s00223-017-0272-5

44. Sharma-Ghimire P, Chen Z, Sherk V, Bemben M, Bemben D. Sclerostin and parathyroid hormone responses to acute whole-body vibration and resistance exercise in young women. *J Bone Miner Metab*. 2018;37(3):358-367. doi:10.1007/s00774-018-0933-0

45. Kouvelioti R, Kurgan N, Falk B, Ward WE, Josse AR, Klentrou P. Response of Sclerostin and Bone Turnover Markers to High Intensity Interval Exercise in Young Women: Does Impact Matter? *Biomed Res Int*. 2018;2018:1-8. doi:10.1155/2018/4864952

46. Galea GL, Lanyon LE, Price JS. Sclerostin's role in bone's adaptive response to mechanical loading. *Bone*. 2017;96:38-44. doi:10.1016/j.bone.2016.10.008

47. Wang M, Shen J, Jin H, Im HJ, Sandy J, Chen D. Recent progress in understanding molecular mechanisms of cartilage degeneration during osteoarthritis. *Ann N Y Acad Sci*. 2011;1240:61-69. doi:10.1111/j.1749-6632.2011.06258.x

48. Niehoff A, Müller M, Brüggemann L, et al. Deformational behaviour of knee cartilage and changes in serum cartilage oligomeric matrix protein (COMP) after running and drop landing. *Osteoarthritis Cartilage*. 2011;19(8):1003-1010. doi:10.1016/j.joca.2011.04.012

49. Cattano NM, Driban JB, Cameron KL, Sitler MR. Impact of physical activity and mechanical loading on biomarkers typically used in osteoarthritis assessment: current concepts and knowledge gaps. *Ther Adv Musculoskelet Dis*. 2017;9(1):11-21. doi:10.1177/1759720X16670613

50. Castro-Viñuelas R, Viudes-Sarrión N, Rojo-García A V., Monteagudo S, Lories RJ, Jonkers I. Mechanical loading rescues mechanoresponsiveness in a human osteoarthritis explant model despite Wnt activation. *Osteoarthritis Cartilage*. 2025;(33):692-702. doi:10.1016/j.joca.2024.02.945