PREGLEDNI ZNANSTVENI RAD
REVIEWS

Hrvat. Športskomed. Vjesn. 2025; 40:5-20

BONE MARROW FAT AND PHYSICAL ACTIVITY IN HUMANS: A SYSTEMATIC REVIEW

MASNO TKIVO KOŠTANE SRŽI I TJELESNA AKTIVNOST U LJUDI: SUSTAVNI PREGLEDNI RAD

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Cite as: Rakovac M, Lazinica B. Bone marrow fat and physical activity in humans: A systematic review. Croat Sports Med J. 2025; 40(1):5-20.

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DOI: 10.69589/hsv.40.1.1

SAŽETAK

Masno tkivo u koštanoj srži (MTKS) je depo masnog tkiva negativno povezan s mineralnom gustoćom kosti i hematopoezom. Utjecaj tjelesne aktivnosti (TA) na MTKS je još uvijek nedovoljno istražen. Cilj ovoga rada bio je sistematski analizirati objavljene rezultate istraživanja povezanosti TA/tjelovježbe i MTKS-a u ljudi. Pretraživanjem literature (MEDLINE, Scopus, SPORTDiscus, Web of Science) pronađeno je 16 studija (9 presječnih/7 intervencijskih) koje su istraživale: povezanost bavljenja sportom i MTKS-a u sportaša, povezanost TA i MTKS-a u općoj populaciji, utjecaj tjelovježbe tijekom/nastavka kretanja nakon produženog mirovanja na MTKS. Sportaši iz sportova većeg mehaničkog opterećenja imali su nižu razinu MTKS-a od nesportaša u skeletnim regijama koje podnose najveća opterećenja (slabinski kralješci, dijafiza goljenične kosti, vrat bedrene kosti). Aktivni nesportaši imali su niži MTKS od neaktivnih osoba. Visoki volumeni aktivnosti u kojima se podnosi težina tijela bili su povezani sa značajnijom redukcijom MTKS-a. Adipogeni učinak deficijencije estrogena na MTKS uočen je u oligoamenoroičnih sportašica. Dokazi o učinku nastavka kretanja nakon dugotrajnijeg mirovanja su još uvijek nedostatni. Rezultati analiziranih istraživanja ukazuju na to da su aktivnosti većeg mehaničkog opterećenja povezane s nižim MTKS-om u najopterećenijim regijama skeleta. Zasad je nedovoljan broj randomiziranih kontroliranih istraživanja, a izostaje i standardizacija dijagnostike MTKS-a. Buduća bi istraživanja trebala uključiti različite populacije, veće uzorke ispitanika, intervencije duljeg trajanja te analizu različitih skeletnih regija.

Ključne riječi: *dugotrajno mirovanje, masno tkivo u koštanoj srži, sport, tjelovježba, zdravlje kostiju*

ABSTRACT

Bone marrow fat (BMF) is an adipose tissue depot negatively correlated with bone mineral density and hematopoiesis. The influence of physical activity (PA) on BMF is still poorly understood. The aim of this study was to systematically analyze literature investigating the association between PA/exercise and BMF in humans. The literature search (MEDLINE, Scopus, SPORTDiscus, Web of Science) yielded 16 (9 cross-sectional/7 intervention) studies exploring: the relationship between practicing sports and BMF in athletes; PA and BMF in the general population; the effect of exercise during/reambulation after prolonged bed rest on BMF. Athletes practicing high-impact sports had a lower BMF than non-athletes in load-bearing skeletal regions (lumbar vertebra, mid-tibia, femoral neck). Active non-athletes had a lower BMF than inactive persons. High-volume weight-bearing activities were associated with a more significant BMF decrease. The adipogenic effect of estrogen deficiency on BMF was observed in oligo-amenorrheic athletes. The impact of reambulation after prolonged bed rest is still inconclusive. Based on the results of the studies, high-impact PA is associated with lower BMF in load-bearing skeletal regions. There is a lack of randomized controlled trials and a standardized diagnostic methodology. Future studies should include different populations, larger samples, and longer interventions, and analyze different skeletal regions.

Keywords: *bone health, bed rest, exercise, marrow adipose tissue, sport*

INTRODUCTION

Bone marrow fat (BMF) is an adipose tissue depot within bone marrow, interspersed with hematopoietic elements.[26] The bone marrow adipocytes stem from the pool of mesenchymal stem cells (MSC), the origin of different cell types, including osteoblasts, chondrocytes, and myocytes.[26] In fact, the initiation of BMF formation is believed to be the biasing of MSC into the adipocyte instead of osteoblast lineage.[26]

Although BMF accounts for up to 70% of bone marrow volume, and possibly even more than 10% of the overall adipose tissue in adults[26,36], its physiology and function is still insufficiently understood, largely due to its poor anatomical accessibility and related difficulties in methodological assessment.[26,36]

BMF is described as a distinct adipose subtype, with features differing from white and brown adipose tissue, and with distinct metabolic and endocrine functions, e.g., in glucose homeostasis.[36] It increases with age, but also in different health-related states.

The function of BMF is reflected through its quantitative changes in different health disorders. BMF is increased in conditions characterized by low bone density and increased fracture risk, such as osteoporosis and anorexia nervosa, and usage of drugs such as corticosteroids and peroxisome proliferator-activated receptor (PPAR)-γ agonists (e.g., formerly used antidiabetic rosiglitazone), showing inverse relationship with bone mineral density (BMD).[26] On the other hand, BMF increase is also present in high-fed animal models and obese persons, without the increased fracture risk, pointing to its energy depot and endocrine functions.[22,26] BMF is also negatively correlated with hematopoiesis.[42]

Studies in animal models showed that physical activity can reduce BMF, both in high-fed states and despite of use of PPAR-γ agonists, such as the mentioned rosiglitazone, suppressing their negative influence.[26] Physical activity is believed to drive the biasing of osteoblastic lineage.[31]

The importance of physical activity and mechanical loading on BMF and bone is evident in the opposite effect induced by mechanical unloading – in addition to the progressive decrease in BMD, states of prolonged bed rest and immobility are characterized by increased BMF.[39,40]

So far, the studies in humans have investigated the association between practicing different types of sports activities and BMF content[15,43,46], the effect of specific exercise programs on BMF in healthy persons and persons with health disturbances[3,24], and the effectiveness of counteracting bed rest effects with exercise programs or the effect of post-bed rest reambulation[23,39,40]. However, there is no systematic analysis of these studies, and the association between physical activity and BMF is not well known. Therefore, the aim of this review was to systematically analyze the studies that investigated the association and/or effect of physical activity on BMF. The review adds to the increasing body of knowledge on BMF, highlights the directions for future research, and is relevant for the broader research areas studying bone health.

MATERIAL AND METHODS

Search protocol and study selection

This review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in design, analysis, and result reporting.[25] To identify scientific articles that investigated the relationship or influence of physical activity or exercise on BMF, on 2 July 2024 the authors searched four databases: MEDLINE (via PubMed), Scopus, SPORTDiscus, and Web of Science. Search string used to search MEDLINE, Scopus, and SPORTDiscus was: "marrow fat tissue" OR "marrow adipose tissue" OR "bone marrow fat" AND (physical activit* OR exerc* OR training OR "resistance training" OR "endurance training"). Search string to search Web of Science was: ("marrow fat tissue" OR "marrow adipose tissue" OR "bone marrow fat") AND (physical activit* OR exerc* OR training OR "resistance training" OR "endurance training"). The inclusion criteria included the articles: a) published in a peer-reviewed publication, b) published in the English language, c) investigating a relationship or influence of physical activity or exercise on BMF as the outcome measure. No search filters were used in terms of publication date, study design or participant species, age or sex. The authors screened the retrieved articles' titles to exclude duplicate publications and abstracts to exclude records that did not meet the inclusion criteria. The full-texts of the remaining articles were retrieved and a 'snowball' search of the reference lists of the articles included in the final analysis was performed to identify possible additional articles of interest.

Study quality assessment

The quality of the cross-sectional studies was assessed using the Appraisal tool for Cross-Sectional Studies (AXIS).[9] The AXIS tool consists of 20 items assessing the quality of the introduction (item 1), methods (items 2-11), results (items 12-16), discussion (items 17-18), and other aspects (items 19-20) of the cross-sectional studies. The assessed aspects are the study aim, design, sample size and selection, risk factors and outcome variables measurement, data analysis, presentation of results, quality of discussion, and ethical concerns.[9]

The quality of the randomized controlled trials was assessed using The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[13] The tool is used to assess six bias domains: selection bias (randomization and allocation concealment), performance bias (double blinding procedure), detection bias (outcome assessment blinding), attrition bias (assessment of data completeness), reporting bias (whether the outcome report is selective), other sources of bias.[13]

The quality of the non-randomized controlled trials was assessed using the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions.[35] The tool is used to assess three domains of bias: pre-intervention bias (confounding bias and participant selection bias), intervention bias (mis/classification of interventions), and post-intervention bias (due to a deviation from the planned interventions, missing data, bias in outcome measurement or due to selective reporting of the results).[35]

The authors assessed the studies independently. Any disagreements were consensually resolved.

RESULTS

The literature search yielded a total of 282 records (88 records in MEDLINE, 49 records in Scopus, 27 records in SPORTDiscus, and 118 records in Web of Science). A total of 110 duplicates were excluded (64 in MEDLINE, 34 in Scopus, 11 in SPORTDiscus, and 1 in Web of Science). The authors examined the titles and abstracts of the remaining 172 records, out of which 125 were excluded from further analysis on account of not meeting the inclusion criteria (74 in Web of Science, 22 in Pubmed, 14 in Scopus, and 15 in SPORTDiscus). The full texts of 47 articles were retrieved and analyzed (44 from Web of Science, two from MEDLINE, and one from SPORTDiscus). Sixteen studies were on animal models, 6 articles were reviews[10,22,26,27,31,42], two studies were summer school reports presenting only abstracts[1,28], and 12 studies were irrelevant to the review topic. Six additional articles were found by searching the reference lists, one of which was excluded as it was an untraceable reference of a poster presentation and another one because it was irrelevant to the topic.[33] An additional article was traced on 18 August 2024.[20] Sixteen studies have met the inclusion criteria and have been included in the final analysis (Table 1). The literature search protocol is presented in the flow diagram in Figure 1.

The characteristics of the studies—aim and design, characteristics of the participants, exercise training, investigated skeletal regions, and the diagnostic methods used to quantify BMF and the results of the 16 selected studies are presented in Table 1.

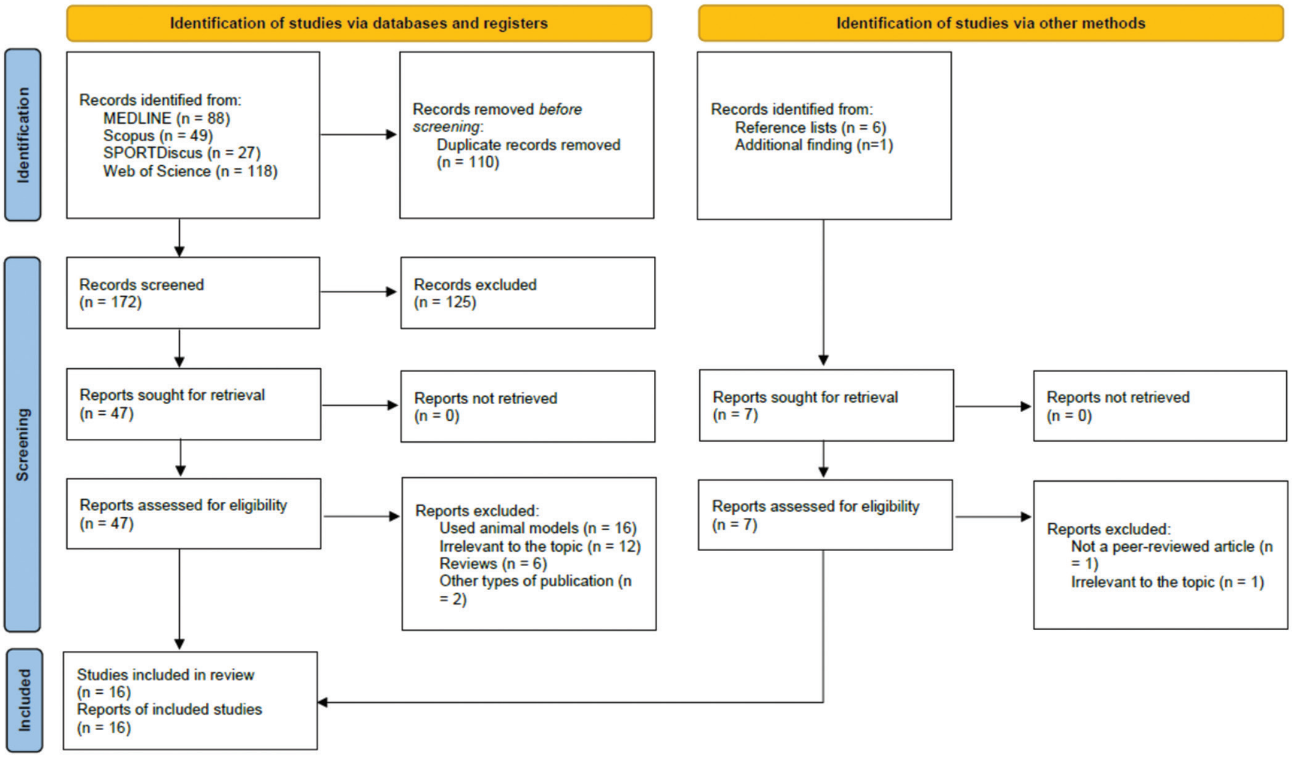

Figure 1. The flow diagram of the literature search protocol[25]
Slika 1. Dijagram protokola pretraživanja literature[25]

Table 1. The characteristics of the studies investigating the relationship between physical activity or exercise and bone marrow fat in humans

Tablica 1. Karakteristike studija koje su istraživale povezanost tjelesne aktivnosti ili tjelovježbe i masnog tkiva u koštanoj srži u ljudi

Author, year, country	**Study aim**	**Study design**	**Participants Total number (N), Groups, F/M, Age (years)**	**Exercise training**	**Skeletal regions**	**Diagnostic method**	**Results**
Labayen et al., 2024, Spain[20]	To explore the effect of exercise on lumbar spine BMF with the mediating role of liver fat.	Nonrando-mized controlled trial.	Overweight/obese children (N=116, 53.4 % F, age 10.5±1.1 years; BMI 25.4±3.2 kg/m^2) **IG** (N=59): family-based lifestyle and psychological well-being program + exercise program **CG** (N=57): family-based lifestyle and psychological well-being program (22 weeks)	22 weeks: • 90-min sessions 3 times per week • high-intensity, aerobic exercise (>76% HR$_{peak}$) + muscle strengthening + stretching	Lumbar spine (L1-L4)	• Testing at baseline and after 22 weeks • MR for lumbar VFF, % liver fat, visceral fat • DXA for total body fat and lean mass	Lumbar VFF: **IG**: • decrease at 22 weeks (effect size [Cohen *d*] −0.42, CI −0.86 to −0.01) • 40.9% of the decrease mediated by decrease in % liver fat, independent of body mass loss **CG**: no change
Ofir et al., 2023, Israel[24]	To explore the effect of weight-loss dietary intervention with and without physical activity on BMF.	Random-ized controlled trial.	Overweight/obese adults with increased metabolic risk, 11.6 % with type 2 diabetes (N=138, 10.1 % F, age 47.8±9.1 years; BMI 31.0±4.0 kg/m^2) – 4 dietary intervention groups with or without PA: • **LF+PA** (N=39) • **LF-no PA** (N=31) • **MED/LC+PA** (N=39) • **MED/LC-no PA** (N=29)	A free yearly gym membership + monthly 60-min workshops. Exercise program (3 sessions per week) with gradual progression: aerobic training from 20 min at 65% HR$_{max}$ to 45 min at 80% HR$_{max}$; resistance training from 10 min to 15 min, one set at 60% to two sets at 80% maximum weight	• Lumbar spine (L3) • Proximal and mid-femur	• Testing at baseline, after six months of dietary intervention, and at 18 months (after 12 months of dietary +/- PA intervention) • MR: % BMF determined by the region of interest (ROI) technique (tissue densities (Fat/ Fat+Water))	• No significant changes in BMF between the four groups • At 6 months of dietary intervention: decrease in L3 BMF (-3.1±5.8 %, P<0.001), no changes in femoral BMF • At 18 months no difference in L3 BMF *vs* baseline, regain (P=0.19) – no effect of PA
Zhang et al., 2023, China[46]	To explore the relation between Chinese martial arts practice and the skeletal and muscular characteristics of the lumbar spine and paraspinal muscles.	Cross-sectional study.	Adults aged 18-25 years (N=45), 3 groups based on sports backgrounds: • **Elite martial arts athletes** (N=9, 5F, age 20.1±1.1 years; BMI 21.7±1.1 kg/m^2; ≥5 trainings per week, over a 10-year experience) • **Amateur martial arts practitioners** (N=18, 10F, age, 21.1±2.0 years, BMI 20.6±1.7 kg/m^2; <3 trainings per week, >1-year experience) • **Sedentary controls** (N=18, 10F, age 21.4±1.5 years, BMI 21.3±2.1 kg/m^2)	• **Elite martial arts athletes** (≥5 trainings per week, over a 10-year experience) • **Amateur martial arts practitioners** (<3 trainings per week, >1-year experience) • **Sedentary controls**	Lumbar spine (L1-L5)	• quantitative MR (T2 mapping and q-Dixon) • FF calculated from the SI of the fat and water as $SI_{fat}/(SI_{fat} + SI_{water}) \times 100\%$, for each vertebral body	Vertebral body FF: • **Elite martial arts athletes:** 30.0%±8.4% • **Amateur martial arts practitioners:** 30.0%±11.2% • **Sedentary controls:** 34.7%± 9.6% (significantly higher than in other two groups (P<0.005)) Weak correlation between the number of years of martial arts training and vertebral body FF (ρ=-0.257, P<0.001).

Belavy et al., 2022, Australia[3]	To examine the effect of a spinal-loading exercise program on vertebral BMF compared to a control, non-weightbearing program.	Random-ized controlled trial.	Persons with chronic non-specific low back pain (N=40, 25–45 years). • **IG** (N=20, 10F/10M**):** age 35±5 years; BMI: 27.1±5.4 kg/m^2 • **CG** (N=20, 9F/11M**):** age 35±4 years; BMI: 25.4±3.8 kg/m^2	A six-month protocol: **IG:** the first 3 months 2 trainings per week; months 4-6 either 1 or 2 trainings per week, combination of aerobic (20-min treadmill) and resistance exercises (five, four to six-week mesocycles; lifting, pushing, pulling, trunk flexion and extension) + 20-40 min home-based aerobic training 3 times per week. **CG**: twelve 30-min one-on-one physiotherapy sessions (motor control training (non-weight bearing) and manual therapy)	Lumbar spine.	• Testing at baseline, 3-months and 6-months. • VFF measured by MR axial mDixon sequences, calculated as: $100\%*SIfat/(SI_{fat} + SI_{water})$ • DXA for lean and fat mass (kg and %), and areal BMD	• % change in VFF from baseline to 3 months **in IG lower** at L2 (-3.7[6.8]%, p=0.033) and L4 (-2.6[4.1]%, p=0.015), no effect in **CG**; no between-group differences for VFF • VFF **lower in men** at L2-L4 at 3 months and at L1-L4 at 6 months (p all≤0.05), no effect in **F** • changes in VFF correlated with changes in total fat (ρ=0.40) and lean mass (ρ=-0.41), no correlation with lumbar BMD (ρ=-0.10) or visceral adipose tissue (ρ=0.23).
Liu et al., 2021, France[23]	To investigate the effect of reambulation (up to 2 years) after a 60-day bed rest on the composition of lumbar bone marrow.	Prospect-ive random-ized controlled trial.	Healthy men (N=20, age 34.2±7.8 years, 23.9±1.8 kg/m^2) Nutrition (randomly): **IG** (N=10)**:** supplement (polyphenols, omega-3, vitamin E, selenium) **CG** (N=10): normal diet	**Immobility protocol:** 60 days of -6° head-down tilt bed rest **Reambulation** in the period of 2 years	Lumbar spine (L2-L5)	Serial 3-T MR at baseline, after 57 days of bed rest, at 30, 360, and 720 days of reambulation: • Proton density with and without fat saturation (L2-L5), 2-point Dixon (L2-L5), and single-voxel MR spectroscopy (L4-L5)	**At 57 days of bed rest:** • VFF unchanged *vs* baseline (P>0.05, all 3 MR techniques) **At 30 days of reambulation:** • decrease in mean lumbar VFF (−9.2±1.6 % points (proton density), −8.0±1.3 % points (Dixon), and −12.7±1.2 % points (MR spectroscopy) *vs* baseline (all P<0.05) • decreased fat saturation index (−5.3±1.1 % points, P<0.05) **At 1 year of reambulation:** • VFF lower than baseline (P<0.05; all 3 techniques) • fat saturation index lower than baseline (−3.3±1.2; P<0.05) **At 2 years of reambulation:** • lumbar VFF and fat saturation index returned to baseline values No effect of dietary intervention on VFF at none of the time points.
Wang, et al., 2021, China[43]	To evaluate and compare BMF in different skeletal regions in male soccer players and age-matched controls.	Cross-sectional, case-control, preliminary study.	• **Professional soccer players**, training ≥8 years (N=20; age 20.7±0.9 years; BMI 21.7±1.2 kg/m^2), dominant right leg • • **Age-matched healthy controls** (N=20, age 21.2±0.8 years; BMI 19.9±1.7 kg/m^2)	Regular soccer training: 20 min warm-up; 40–50 min technical exercises, running, plyometrics, isometric exercises; 30–50 min match practice, 10 min cool-down stretching	• 3rd lumbar vertebrae (L3) • bilateral femoral neck • distal tibias	Proton MR spectroscopy (^{1}H-MRS)	Soccer players *vs* controls: • lower FC in L3 and bilateral femoral necks (P<0.05) • higher UI in the left femoral neck (P<0.05) • no difference between the groups in FC and UI of the distal tibias (P>0.05) • in soccer players significant side-to-side difference in the femoral neck

Bertheau et al., 2020, Germany[5]	To investigate the relationship of different types and levels of physical activity on BMF at different body regions in healthy non-athletic adults using whole-body MR.	Cross-sectional study.	Adults, population-based cohort (N=385, 163F/222M, age 56.2±9.1 years, BMI 28.1±4.9 kg/m^2)	Physical activity levels (groups according to % of participants): • 29% >2 h/week • 31% ~1 h/week (regularly) • 15% ~ 1 h/week (not regularly) • 26% inactive	• FF at L1 and L2 vertebrae • FF at femoral head/neck (hip)	• 2-point T1-weighted VIBE Dixon sequence • FF calculated as: mean intensity$_{\text{fat image}}$/(mean intensity$_{\text{fat image}}$ + mean intensity$_{\text{water image}}$)	• mean FF ranged 52.6 to 90%, depending on the region and sex, higher in the hip than spine • lumbar FF inversely correlated to exercise >2 h/week ($P \leq 0.02$), regardless of age, gender, waist circumference, and glucose tolerance • 3.94% lower FF in L1 and 3.51% lower FF in L2 in active vs inactive people • no correlation for hip FF ($P \geq 0.35$) • no correlation between FF and physical activity in groups that were less active • no relation between non-exercise physical activity (e.g., work, transport) and FF
Quittner et al., 2018, Australia/Canada[29]	To investigate the association between the hydration of lumbar intervertebral discs (IVDs) and lumbar VFF, as well as its association with muscle cross-sectional area and function, and physical activity.	Cross-sectional study.	Healthy adults (N=79, 44F/35M, 25–35 years old), age 29.9±3.6 years, BMI 22.9±3.5 kg/m^2	Total weekly physical activity was calculated based on the International Physical Activity Questionnaire (IPAQ; short form)	Lumbar spine (L1/2 to L5/S1)	MR: • Lumbar IVDs T2-relaxation time • Lumbar VFF	Lower VFF correlated with: • greater trunk extensor muscle endurance ($r=-0.26$, $P<0.05$) • habitual physical activity level (MET-mins per week) ($r=-0.24$, $P<0.05$).
Belavy et al., 2018, Australia/Canada[4]	To investigate: 1) the differences in vertebral BMF among runners, cyclists and controls 2) the correlation between objectively measured physical activity and vertebral BMF.	Cross-sectional study.	• **Joggers** (N=30, 17F; age 30.2±3.2 years) • **Long-distance runners** (N=25, 14F; age 30.1±3.9 years) • **High-volume road cyclists** (N=22, 10F; age 30.3±3.5 years) • **Sedentary controls** (N=24, 13F; age 29.3±3.7 years)	• Joggers, 20-40 km/week, ≥5 years • Long-distance runners, ≥50 km/week + resistance training, ≥5 years • High-volume road cyclists, ≥150 km/week, ≥5 years • Sedentary controls	• vertebral bodies T10-L5	• 3T MR • VFF calculated from the SI of the fat and water: $100\%*SI_{fat}/(SI_{fat+}SI_{water})$ • weekly physical activity: 3D accelerometry	**Long-distance runners:** • lower mean VFF than controls at all levels (T10-L5) • lower mean VFF than joggers at all lumbar levels ($P<0.049$) • significant correlation between weekly running volume and mean lumbar VFF ($p=0.0020$); decrease of 0.7% points for every 9.4-km run per week **Joggers:** • lower VFF than controls only at T10-T12 levels ($p \leq 0.023$) **Cyclists:** • mean VFF comparable to controls Women: mean lumbar VFF 5.4 % points lower than men; exercise and VFF association comparable between sexes

Singhal et al., 2015, USA[34]	To evaluate visceral, subcutaneous adipose tissue and lumbar and femoral BMF fat in young oligo-amenorrheic and eumenorrheic athletes and female non-athletes and to explore associations of these fat depots with BMD.	Cross-sectional study.	Young women (N=41, 18-25 years): • **OA** (oligo-amenorrheic athletes, N=20)): age 21.2±2.2 years, BMI 21.2±2.1 kg/m^2 • **EA** (eumenorrheic athletes, N=10): age 21.1±2.3 years, BMI 22.8±2.3 kg/m^2 • **C** (non-athletes, N=11): age 21.7±1.9 years, BMI 22.5±2.4 kg/m^2	Athlete groups: weight-bearing sports (e.g., track, soccer or field hockey ≥4 hours/week) or running (≥20 miles/week).	• Lumbar spine (L4) • Proximal femoral metaphysis and mid-diaphysis	• single voxel proton MR spectroscopy (1H-MRS) at the L4 vertebral body, proximal femoral metaphysis and mid-femoral diaphysis • HRpQCT for volumetric BMD • DXA for BMD • MR for visceral and subcutaneous adipose tissue	• L4 BMF higher in OA than EA (P=0.03); no difference for femoral BMF • Inverse association of L4 BMF with spine (r=-0.44, P=0.01) and hip (r=-0.36, P=0.02) BMD • Both femoral BMFs with the radius (r≤-0.42, P≤0.01) and tibia (r≤-0.34, P≤ 0.04) volumetric BMD • L4 BMF - independent inverse predictor of the spine and hip BMD and the distal tibia and radius volumetric BMD in all participants • Diaphyseal BMF – independent predictor of the distal tibia and radius volumetric BMD
Huovinen et al, 2015, Finland[16]	To investigate the relationship between BMF UI and exercise history, glycemic state, and other clinical parameters.	Cross-sectional pilot study.	Young adults (N=35, 15–27 years): **Normal-weight (NW**, N=18, 16F/2M): age 20.6±2.9 years, BMI 21.1±2.4 kg/m^2 **Overweight (OW**, N=17, 8F/9M): age 20.3±2.8 years, BMI 34.9±8.7 kg/m^2 • The participants were also divided into early-onset obesity (history of obesity at age <7 years) and control group	• Pedometer and self-reported physical activity level	Proximal tibia.	MR proton spectroscopy (^{1}H-MRS) • UI was calculated as % of the olefinic to total fat • resonance intensity (100 × $I_{olefinic}/(I_{olefinic} + I_{methylene} + I_{methyl})$	• Increase in BMF UI with age in both groups (r=0.408, P=0.015) • no difference in BMF UI between NW (9.8±1.5%) and OW (9.4±1.3%) groups (P=0.43) • No association between BMF UI and sex, physical activity or body fat • no difference in BMF UI between early-onset obesity (9.6±1.6%) and control (9.5±1.3%) groups (P=0.85)
Hu et al., 2014, China[15]	To investigate the relation between lumbar spine BMF and BMD in male wrestlers and inactive men.	Cross-sectional study.	Young men (N=25, 19-28 years): • **wrestlers** (N=14), age 22.9±3.4 years, BMI 23.2±1.5 kg/m^2 • **inactive controls** (N=11), age 24.4±1.6 years, BMI 21.1±2.3 kg/m^2	• **wrestlers** (national level) – history of ≥5 years of training, 6 times per week, 25 h per week • **controls** - <2 h activities weekly	Lumbar spine (L2-L4)	• DXA for body composition and BMD • MR for BMF (sagittal T1-weighted (T1-w) spin-echo (SE) sequence) - averaged bone marrow signal intensity (**SI**) of L2-L4	• Mean SI (L2-L4 BMF) in wrestlers lower than controls (P=0.001) • L2-L4 BMD in wrestlers higher than controls (P<0.001) • Whole sample L2-L4 BMD negatively correlated with mean SI (r=-0.62, P=0.001), independent of body weight • Whole-body and trunk fat % positively correlated with mean SI (r=0.72, P<0.001, both)
Rantalai-nen et al., 2013, Finland[30]	To investigate whether BMF 1) differs between young female athletes from loading-wise different sports and with different bone strengths and 2) is a predictor of tibial bone strength.	Cross-sectional study.	Young adult women (N=220, 17-40 years), three groups: • **Impact**-sport group (N=122), age 23.1±4.8 years, BMI 21.5±2.4 kg/m^2 • **Nonimpact**-sport group (N=57), age 22.2±5.1, BMI 22.7±3.3 kg/m^2 • **CG** (physically active women) (N=41), age 24.1±3.6 years, 22.1±2.4 kg/m^2	History of sport-training, according to impact: **Impact group:** • high-impact (jumpers, hurdlers) • odd-impact (soccer, squash) • low-impact (endurance runners) **Nonimpact group:** • high-magnitude (power lifters) • nonimpact (swimmers).	Mid-tibial bone marrow density	Quantitative computed tomography • bone marrow density calculated as: 1.018+(0.893 · H/1000) mg/cm^3, where H= Hounsfield unit	• **Impact group** had significantly higher (0.5%) marrow fat density (0.964±0.015 mg/cm^3) than **nonimpact** (0.959±0.014 mg/cm^3) and **control group** (0.959±0.013 mg/cm^3) (P<0.05) • midtibial marrow density was an independent predictor of strength strain index, mid-tibial cortical area, endocortical volumetric BMD, and pericortical volumetric BMD (P<0.05) in all women

Casazza et al., 2012, USA[7]	To determine the effect of a short-term physical activity intervention in pre-school children on bone properties.	Inter-vention pilot study.	Children - **IG** (N=10, 44%F)**:** age 4.8±0.2 years, body fat 26.8±1.4% - **CG** (N=10, 53%F)**:** age 5.1±0.1 years, body fat 29.6±2.1%	10-week school-based protocol: **IG:** 30-min moderate intensity physical activity (jumping, hopping, running) and stretching, 3 days per week **CG:** usual activities	- Femoral BMF - Body composition	At baseline and after 10 weeks: - MR for BMF - DXA for body composition	- No between-group differences after the intervention - Significant decrease in BMF in the IG (48.7±6.8 vs 47.4±5.1 cm^3, P=0.04)
Trudel et al., 2012, Germany[39]	To investigate the impact of resistance training with or without whole-body vibration on the VFF in men subjected to bed rest.	Random-ized controlled trial.	Healthy men (N=24, 20-45 years) – three groups: - **RTV** (resistance training with whole-body vibration, N=7): age 34±4 years, BMI 24.9±0.5 kg/m^2 - **RT** (resistance training without whole-body vibration, N=8): age 31±2 years, BMI 23.4±0.8 kg/m^2 - **CG** (control group, no exercise, N=9): age 33±3 years, BMI 24.6±0.7 kg/m^2	**Immobility protocol:** 60 days of -6° head-down tilt bed rest **Exercise intervention:** **RT** – high-load hypertrophy-oriented (leg-press, heel-raises, back- and forefoot raises), single-set, 3 days per week **RTV** – the same as RT + different frequency whole-body vibration (amplitude of 3.5–4.0 mm, frequency of 26 Hz for lower Limbs, 16 Hz for back raise	Lumbar spine (L3, L4, and/or L5)	MR (at baseline, mid-term, at the end of bed rest period): - **fat saturation** (VFF (mean value of L3-L5) calculated as 100 × (Proton density – Proton density with fat saturation/ Proton density) - **proton spectroscopy** (L5 VFF calculated as fat fraction = fat integral/(water integral + fat integral) × 100) - **in- and out-of-phase** (mean L3-L5 VFF calculated as (In phase – Out phase) / (2 × In phase) × 100)	- **CG:** mean absolute VFF increased at mid-term (+3.9±1.3%) and at the end (+3.6±1.2%) (both P<0.05) - **RT:** smaller VFF change vs CG at mid-term (−0.9±1.2% vs+3.9±1.3%, P<0.05) - **RTV:** smaller VFF change vs CG at the end (−2.6±1.9% vs +3.5±1.2%, P<0.05) - no significant between-group interactions between RT and RTV
Trudel et al., 2009, France[40]	To measure lumbar BMF and hematological variables after 60 days of bed rest (with or without exercise or nutrition intervention) and after a year of resuming regular activities in healthy women.	Random-ized controlled trial.	Healthy premenopausal women (N=24, 25–40 years, mean age 32.1 years, mean BMI: 21.4 kg/m^2) – three groups: - **Bed rest + exercise** (N=8) - **Bed rest + nutrition** (N=8) - **CG (bed rest only)** (N=8)	**Immobility protocol:** 60 days of -6° head-down tilt bed rest **Exercise intervention:** 1) resistance training - 19 sessions (10 min supine cycling, submaximal thigh and calf ergometer presses; 4 sets of 7 max concentric and eccentric leg presses; 4 sets of 14 max concentric and eccentric calf presses) 2) aerobic training – 40-min vertical treadmill running on a vertical treadmill (lower body negative pressure -48 to -55 mmHg. **Nutrition intervention:** protein supplementation of 0.6 g·kg body wt^{-1} $\cdot day^{-1}$	Lumbar VFF (L3-L4)	MR: - VFF calculated from the SI of the fat and water: $100\%{*}SI_{fat}/(SI_{fat+}SI_{water})$	In comparison to baseline values, VFF for all participants: - increased after 60 days of bed rest ((mean±SE) +2.5±1.1%, P<0.05) - was still increased 1 yr after (despite resuming regular activities) (+2.3±0.8%, P<0.05) - no among-group differences at any time point

BMD = bone mineral density; BMF = bone marrow fat; CG = control group; DXA = dual X-ray absorptiometry F = females; FC = fat content; FF = fat fraction; HRmax = maximum heart rate; HRpeak = peak heart rate; IG = intervention group; LF = low-fat diet; M = males; MED/LC = Mediterranean/low carbohydrate diet; MR = magnetic resonance; PA = physical activity; SI = signal intensity; UI = unsaturated fatty index; VFF = vertebral marrow fat fraction

The investigations were performed in research centers in Australia[3,4,29], China[15,43,46], Finland[16,30], France[23,40], Germany[5,39], Israel[24], Spain[20], and the USA[7,34].

Nine studies were cross-sectional studies [4,5,15,16,29,30,34,43,46]. Seven studies were intervention studies, five of which were randomized controlled trials[3,23,24,39,40], one non-randomized controlled trial[20], and one non-randomized pilot study[7].

Five cross-sectional studies investigated the relationship between practicing sports and BMF (e.g., Chinese martial arts[46], soccer[43]), wrestling[15], sports of different skeletal impact characteristics[30], and the relationship between menstrual dys/function and BMF in female athletes[34].

Four cross-sectional studies examined the correlation between the BMF and different levels or different types of exercise in the non-athletic population.[4,5,16,29]

All five randomized-controlled trials investigated the influence of physical activity on lumbar spine BMF.[3,23,24,39,40] One study investigated the impact of aerobic and resistance, spinal-loading exercise programs on vertebral BMF.[3] The other three studies investigated the impact of 60-day bed rest and activity in the following conditions: a) at the end of a 60-day bed rest (with or without a combined training program[40], and with resistance training with or without whole-body vibration[39]); and b) after resuming activities (up to two years of post-bed rest reambulation[23], and after a year of reambulation following the bed rest with or without a combined training[40]). In addition to the effect on the lumbar spine, the study by Ofir et al. [24] investigated the effect of two dietary interventions, with and without a combined aerobic and resistance exercise program on proximal and mid-femoral BMF.

The two non-randomized controlled studies were the only ones that included children, pre-school[7] and school-aged[20]. The pilot study on preschool children investigated the impact of a 10-week physical activity program on femoral BMF[7], while the study on school-aged children explored the impact of a 22-week exercise program on lumbar spine BMF[20]. All the other studies included adult participants, mostly young up to middle-aged, and one study included middle-aged and older adults.[5]

More than half of the studies included participants of both biological sexes.[3-5,7,16,20,24,29,46] Four studies included only male participants[15,23,39,43], and three studies included only women[30,34,40].

Six studies compared athletes and non-athletes[15,30,34,43,46] or active and inactive people[4]. Five studies included healthy adults[23,29,39,40] and children[7]. Four studies included overweight and obese children[20] or adults[5,16,24] and one study included persons with chronic low back pain, who were also overweight[3].

The lumbar spine was the most studied skeletal region, investigated in 13 studies.[3-5,15,20,23,24,29,34,39,40,43,46] In addition to the lumbar spine, Belavy et al.[4] measured also the twelfth thoracic vertebra, three studies investigated the femoral BMF[5,24,34] and one investigated the BMF of the femoral neck and distal tibia[43]. One study measured only femoral BMF[7] and two studies measured only tibial BMF—proximal[16] and mid-tibial[30].

Only one study used quantitative computed tomography to calculate bone marrow density.[30] All the other studies used MR technology to compute marrow fat fraction[3-5,7,15,20,23,24,29,39,40,46], or performed proton spectroscopy[16,34,39,43].

The five cross-sectional studies that explored the relationship between practicing sports and BMF found a more favorable bone marrow composition in athletes *vs* non-athletes and in people practicing high-impact *vs* low-impact activities. Namely, sedentary controls had a higher vertebral body fat fraction (FF) than both elite and amateur Chinese martial arts practitioners ($P < 0.005$).[46] Professional soccer players had lower lumbar and femoral neck fat content and a higher unsaturated fatty index in the femoral neck than untrained controls ($P < 0.05$ for both).[43] Lumbar BMF was lower in wrestlers than controls ($P = 0.001$).[15] Sports activities with higher skeletal impact were associated with a significantly higher mid-tibial marrow fat density than non-impact activities ($P < 0.05$)[30], while in soccer players there was a significant side-to-side difference in the BMF of the femoral neck, possibly indicating a different side-to-side loading.[43] Lumbar BMF was higher in oligo-amenorrheic than eumenorrheic athletes ($P = 0.03$) with no such difference in the femoral BMF but with a significant negative correlation with the spine and hip bone mineral density.[34]

As for the correlation between the BMF and different levels/types of exercise in the general population, Bertheau et al.[5] found a negative correlation between lumbar FF and practicing exercise more than two hours per week ($P \leq 0.02$), a relationship stable regardless of different demographic and metabolic confounders, with a lower lumbar FF in active *vs* inactive participants. Such a correlation was not confirmed for other domains of physical activity (work or transport).[5] Quittner et al.[29] also found a negative correlation between habitual physical activity level and the lumbar VFF, while in the study by Huovinen et al.[16] there was no association between tibial BMF and physical activity in normal-weight and overweight young adults, and no difference in BMF between the two groups. In a comparison of running, cycling and sedentary lifestyle, high-volume distance running was associated with a significantly lower spinal FF than jogging or sedentary lifestyle, jogging was associated with a significantly lower FF than being sedentary, and the lack of impact forces in cycling was reflected by the spinal FF comparable with the one in sedentary controls.[4]

The randomized-controlled trial that investigated a six-month protocol of combined aerobic and resistance, spinal-loading training, found a significant 4.1-6.8 % decrease in lumbar FF ($P = 0.015$, negatively correlated with lean mass) in the intervention group after 3 months of training, no change in the control group, however no between-group differences in FF.[3] The study that investigated the effect of 12-month dietary interventions with and without a combined exercise program on lumbar (L3) and femoral BMF, introduced following solely dietary interventions of a six-month duration which induced a significant 3.1 % decrease in L3 BMF, found no influence of physical activity, and a regain of lumbar BMF matching the baseline values.[24] In the study by Liu et al.[23], at the end of a 60-day bed rest lumbar FF was unchanged with respect to baseline, and returned to such values after two years of reambulation. However, its significant decrease was detected after 30 days and at one year of reambulation.[23] However, in the study by Trudel et al.[40], lumbar VFF increased after 60 days of bed rest, regardless of whether the participants performed a combined training intervention or not, and remained increased in both groups even after a year of reambulation (more than 2 %, $P < 0.05$ for both time points). In the study exploring the impact of resistance training with or without whole-body vibration on lumbar VFF during a 60-day bed rest, there were no significant differences between the impact of the two protocols, however, resistance training induced a VFF decrease *vs* the control group (-0.9 % *vs* +3.9 %) at mid-term, and the addition of the whole-body vibration induced a VFF decrease *vs* the control group (-2.6 *vs* +3.5 %) at the end of the rest period.[39]

The intervention study in preschool children found that a 10-week program of jumping, hopping, and running activities, 30 minutes three days a week decreased the femoral BMF in the intervention group (~2 %), however without between-group differences after the intervention.[7] A longer duration (22 weeks) exercise program in school-aged children resulted in a significant decrease in lumbar VFF with an identified mediating effect of a concomitant decrease in liver fat content.[20]

As for the differences between women and men, Bertheau et al.[5] found a significantly higher femoral neck FF in men than in women (right hip: 89.6 (± 3.3) *vs* 86.1 (± 6.7) %; left hip: 90.0 (± 3.5) *vs* 85.6 (± 6.4) %; $P > 0.001$ for both). Quittner et al.[29] found a higher lumbar VFF in men than women (36.0 ± 6.2 *vs* 31.0 ± 5.8 %, $P < 0.001$). In the study by Belavy et al.[4], women had a 5.4 percentage points lower lumbar VFF than men, but associations of exercise and VFF were comparable between sexes. In the study on normal- and overweight persons, no association between tibial BMF and sex was detected.[16] The intervention study on school-aged children reported no effect of sex on exercise-induced changes in lumbar VFF.[20] The only study that found a sex-specific impact of exercise on BMF was the study by Belavy et al.[3], who found a lower lumbar VFF in men after 3 months (at L2-L4) and after 6 months (at L1-L4) of a spinal-loading exercise program (P all ≤ 0.05), with no detected effect in women. The other studies did not report sex differences regarding BMF.[7,24,46]

In terms of study quality, most studies had some risk of bias. In cross-sectional studies, the main shortcomings included the lack of justification of the sample size, the lack of description of the sample frame, and the lack of data on response rate and/or non-responders (Table 2). The sources of bias in the randomized controlled trials were related to participant selection (randomization and allocation concealment) and the lack of information on blinding of outcome assessment (Table 3). The bias risk in one non-randomized controlled trial includes mainly confounding and no information on missing data (Table 4).

Table 2. Quality assessment of the cross-sectional studies using Appraisal tool for Cross-Sectional Studies (AXIS)[9]
Tablica 2. Procjena kvalitete presječnih studija korištenjem *Appraisal tool for Cross-Sectional Studies (AXIS)*[9]

Question	**Cross-sectional study**								
	Zhang et al., 2023[46]	Wang, et al., 2021[43]	Bertheau et al., 2020[5]	Quittner et al., 2018[29]	Belavy et al., 2018[4]	Singhal et al., 2015[34]	Huovinen et al, 2015[16]	Hu et al., 2014[15]	Rantalainen et al., 2013[30]
Introduction									
1. Were the aims/objectives of the study clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods									
2. Was the study design appropriate for the stated aim(s)?	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the sample size justified?	N	N	Y	Y	Y	N	Y	N	N
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	DK	DK	Y	DK	DK	Y	Y	Y	Y
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	DK	Y	Y	Y	Y	Y	Y	Y	DK
7. Were measures undertaken to address and categorize non-responders?	DK	DK	Y	DK	DK	DK	DK	DK	DK
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., p-values, confidence intervals)	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Results									
12. Were the basic data adequately described?	N	Y	Y	N	Y	Y	Y	Y	Y
13. Does the response rate raise concerns about non-response bias?	DK/ NA	DK	N	NA	N	DK	Y	DK	DK
14. If appropriate, was information about non-responders described?	N/NA	N/NA	Y	NA	Y	N/NA	N	N/NA	N/NA
15. Were the results internally consistent?	Y	Y	Y	Y	Y	Y	Y	Y	Y
16. Were the results presented for all the analyses described in the methods?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion									
17. Were the authors' discussions and conclusions justified by the results?	Y	Y	Y	Y	Y	Y	Y	Y	Y
18. Were the limitations of the study discussed?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other									
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	N	N	N	N	N	N	N	N	N
20. Was ethical approval or consent of participants attained?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y = yes, N = no, DK = don't know, NA = not applicable

Table 3. Quality assessment of the randomized controlled trials using The Cochrane Collaboration's tool for assessing risk of bias in randomized trials[13]

Tablica 3. Procjena kvalitete randomiziranih kontroliranih istraživanja korištenjem *The Cochrane Collaboration's tool for assessing risk of bias in randomized trials*[13]

Bias domains and sources of bias	**Randomized controlled study**				
	Ofir et al., 2023[24]	Belavy et al., 2022[3]	Liu et al., 2021[23]	Trudel et al., 2012[39]	Trudel et al., 2009[40]
Selection bias					
Random sequence generation	?	✓	?	?	?
Allocation concealment	?	✓	?	?	?
Performance bias					
Blinding of participants and personnel	✓	✓	?	✓	✓
Detection bias					
Blinding of outcome assessment	?	✓	?	?	?
Attrition bias					
Incomplete outcome data	✓	✓	✓	✓	✓
Reporting bias					
Selective outcome reporting	✓	✓	✓	✓	✓
Other biases	✓	✓	✓	✓	✓

✓ Low risk of bias, ! High risk of bias, ? Unclear risk of bias

Table 4. Quality assessment of the non-randomized controlled trials using the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions[35]

Tablica 4. Procjena kvalitete nerandomiziranih kontroliranih istraživanja korištenjem ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions[35]

Bias domains	**Non-randomized controlled study**	
	Labayen et al., 2024[20]	Casazza et al., 2012[7]
Pre-intervention		
Bias due to confounding	Low	Moderate
Bias in selection of participants into the study	Low	No information
At intervention		
Bias in classification of interventions	Low	Low
Post-intervention		
Bias due to deviations from intended interventions	Low	Low
Bias due to missing data	Low	No information
Bias in measurement of outcomes	Low	Low
Bias in selection of the reported result	Low	Low

DISCUSSION

The aim of this review was to systematically analyze the published results of the studies investigating the relationship between any type of physical activity and BMF in humans, regardless of sex, age or health condition.

Out of the 16 analyzed studies, the five cross-sectional studies that investigated the relationship between sports practice and BMF highlighted the presumed impact of mechanical loading on BMF, with athletes having a lower BMF than non-athletes[15,43,46] and with practicing high-impact sports (as opposed to low-impact sports) being related to lower BMF in load-bearing skeletal regions, mid-tibia and femoral neck[30,43]. Non-active persons had a higher lumbar BMF than elite or amateur Chinese martial arts practitioners (including Tai Chi, Changquan, and Nanquan practitioners)[46] and wrestlers[15]. Previous reviews indicated, although with insufficient certainty due to inconsistency and poor quality of the reviewed studies, a potential positive effect of Tai Chi practice on BMD of the lumbar spine or femoral neck in perimenopausal and postmenopausal women[14,21,37], arguably influenced by longer duration of practice of adequate intensity, and higher compliance of participants[37]. Tai Chi has previously been described as 'light and soft', combining controlled movements and static contractions, predominantly aimed at the core muscles, with a conscious control of respiration.[14] On the other hand, wrestling is a contact sport in which athletes withstand a significantly higher load on spine, especially in the takedown position, in which high-intensity and forceful motion is required to overpower the opponent, and with the athletes' tendency to prolong this position in order to score points.[12] The lower lumbar spine BMF registered by Hu et al.[15] in wrestlers as opposed to non-athletes can thus be interpreted as congruent with the previous findings of a significantly higher BMD in wrestlers compared to both non-athletes and endurance athletes[32]. The relationship of mechanical bone loading on BMF was emphasized in the study by Rantalainen et al.[30], in which high-impact activities were associated with a significantly lower mid-tibial fat fraction (i.e., higher marrow fat density) than non-impact activities, with the authors suggesting that the exercise-related bone strength increase may be induced by BMF reduction with a consequent increase in osteoblastogenesis.[30]

The relationship between bone loading and BMF content was observed in the study by Wang et al.[43], in which a sample of soccer players had a significantly lower BMF content in their right *vs* left femoral neck, with this side-to-side difference possibly being related to a different loading since all the soccer players used their right leg as dominant, kicking leg. Different types of local mechanical loading have been proven a significant modulator of the balance between osteoblastogenesis and adipogenesis in bovine and rodent bone via the effect on two transcription factors - Runx2 and PPARγ.[8] Mechanical loading stimulated Runx2 and decreased the level of the PPARγ protein, thus promoting osteoblastogenesis over adipogenesis, demonstrated both *in vitro* and *in vivo*.[8]

The interplay between the mechanical loading and the influence of female sex hormones on BMF and BMD was explored in the study by Singhal et al.[34] in which the oligo-amenorrheic athletes, although exposed to weight-bearing sports activities or running, had a significantly higher lumbar BMF than the eumenorrheic athletes ($P = 0.03$), and the lumbar BMF was inversely associated with the spinal and hip BMD.[34] There was a positive association between the BMF increase and the duration of amenorrhea in the oligo-amenorrheic athletes.[34] Estrogen deficiency was previously identified as one of the causal factors of the concurrent BMD decrease and BMF increase in states such as postmenopause or anorexia nervosa.[6,38] The adipogenic influence of the estrogen deficiency on the mesenchymal stem cells is also linked with the increased PPARγ and decreased Runx2 levels, presumably via the SIRT1/FOXO3A axis.[41] Singhal et al.[34] propose decreased leptin levels as another possible determinant of the decreased bone density and increased BMF in the oligo-amenorrheic athletes[17,34], as leptin receptor signaling was found to promote adipogenesis/inhibit osteogenesis by the bone marrow stromal cells[45]. Although femoral metaphyseal and diaphyseal BMF was higher in the oligo-amenorrheic *vs* eumenorrheic athletes, the difference was not significant, and there was an inverse association between the femoral BMF and BMD at the weight-bearing tibia and non-weight-bearing radius.[34]

In the cross-sectional studies exploring the relationship between habitual physical activity and BMF in the general population, being regularly active was associated with a significantly lower lumbar BMF[4,5,29], but the same was not confirmed for the tibial BMF in the study by Huovinen et al.[16]. The lack of association between physical activity and the tibial BMF in the study by Huovinen et al.[16] might have been influenced by the methodological limitation of assessing physical activity by a self-reported questionnaire unable to discern between load-specific physical activities. Kindler et al.[18] found that scores on physical activity questionnaires specifically assessing skeletal loading were related to the measures of tibial bone architecture, suggesting future musculoskeletal research should consider such targeted instruments for physical activity assessment. The importance of discerning between the volume and intensity of bone loading induced by different types of activities was shown in the study by Belavy et al.[4], in which the high-volume distance running was superior to jogging in inducing the decrease in the spinal BMF (every 9.4 km of weekly run was related with a 0.7 percentage point decrease in the lumbar VFF), while the effect of cycling did not differ from being sedentary. This is in line with the finding of Bertheau et al.[5], who did not find a correlation between the BMF and work- and transport-related physical activities, arguably of lower bone loading characteristics.

Out of the seven intervention studies, five were randomized controlled trials.[3,23,24,39,40] Two of these studies investigated the effect of a combined aerobic and resistance training program lasting either 6 months[3], or 12 months (the latter combined with a dietary intervention)[24], obtaining inconclusive results. The 12-month exercise program consisted of three weekly sessions of a combined aerobic training (progressing from 20 min at 65% HR_{max} to 45 min at 80% HR_{max}) and resistance training (progressing from 10 to 15 min, one set at 60% to two sets at 80% RM) found no influence of the combined exercise on neither lumbar nor femoral BMF in overweight/obese adults with increased metabolic risk.[24] The 6-month program was split into two three-month periods, consisting of two weekly trainings (the first three months) or 1-2 weekly trainings (the final three months) combining a 20-min treadmill aerobic exercise and 4-6-week mesocycles of different spinal-loading resistance exercises and additional home-based aerobic exercises three times per week.[3] The participants were persons with chronic low back pain, the intervention group had lower VFF at L2 and L4 at 3 months (predominantly men), and the result was retained at 6 months for men (significantly lower VFF at L1-L4), but not for women.[3] Also, changes in VFF were not correlated with the lumbar BMD or visceral fat volume, which is an unexpected finding.[3] The control group had no change in VFF, but there was also no difference in VFF between the groups. The prescribed frequency and intensity of exercise might have resulted in mechanical loading insufficient to induce longer-lasting changes in the lumbar VFF, taking into account that the total volume of exercise was decreased after the third month of the program.[3] The sex differences were evident at baseline (VFF was five percentage points higher in men) and in the stable exercise-induced lumbar VFF decrease at three and six months in men, despite their lower program compliance (55% *vs* 68% in women), although without controlling the overall activities the participants were engaging in during the intervention period.[3] A higher baseline value in men was also observed in other studies, for the lumbar VFF[4,29] and the femoral neck FF[5]. In large cohorts, in persons younger than 40 years, the mean lumbar BMF was found to be significantly higher in men than in women (with the largest difference, 12%, in the age group 31-40 years), whereas in persons older than 60 years, the finding was reversed, the BMF was significantly higher (around 10%) in women.[11,19,44] A sharp increase in lumbar BMF was observed in women between the age of 41 and 60 years, whereas in men the life-long age-related increase in BMF was gradual.[44] In both sexes, the increase in BMF coincided with a decrease in the lumbar BMD, showing similar sex-specific dynamics, ascribed in women primarily to the rapid estrogen decrease in the peri- and postmenopausal period.[11,44] A proposed explanation for the BMF difference in younger age groups is the role of BMF in hematopoiesis, i.e., the increased erythropoietic demand in premenopausal women due to menstrual blood loss.[2] A possible sex-related difference in the effect of prolonged inactivity (with or without added exercise intervention/s) and resume of activity was observed in three studies.[23,40] In healthy young men, a 60-day bed rest did not induce lumbar VFF changes in comparison to baseline values[23], whereas in young women the lumbar VFF increased after such an intervention (+2.5 %), regardless of whether they underwent an exercise program during the bed rest period[40]. In another study in men, a protocol of either resistance training or resistance training combined with whole-body vibration performed during the 60-day bed rest managed to counteract the accumulation of lumbar VFF.[39] After a year of reambulation, the lumbar VFF was lower than baseline in men[23], but remained increased in comparison to baseline values in women (+2.3 %)[40].

There were only two intervention studies in children of different age groups, suggesting the importance of a higher exercise volume and longer duration of the intervention on the obtained BMF decrease.[7,20]

There are several limitations of the analyzed studies. Nine studies were cross-sectional, precluding conclusions about the causal effect of physical activity or exercise on the BMF. Most studies had a relatively small sample of participants which could have influenced the interpretation of the statistical tests.[39] Most of the studies included young male participants, or, in some cases, a small number of females[24], so the results are not generalizable to the broader population. Also, the only two intervention studies in children were a pilot study[7] and a non-randomized trial[20]. Most studies investigated BMF in only one skeletal region, so the comparison of the effect of exercise on different regions of the axial and appendicular skeleton is still to be explored.[4,7,40] The randomized controlled trials in which the participants were subjected to a 2-month bed rest still allowed physical activity in the antiorthostatic position, so the effect of complete inactivity and later reambulation on BMF is still not explored.[40] Furthermore, there were limitations of a methodological nature, stemming from a lack of diagnostic standardization, such as using semiquantitative measurement[15], pQCT with lower ability of differentiating yellow and red marrow[30], or a poor resolution MRS[43]. Also, several studies underlined the fact that MRI cannot determine the mechanism of decrease in the BMF, so the microscopic, histological methods should be employed to distinguish between the adipocyte atrophy and apoptosis, i.e., whether the lower BMF is a result of a decrease in the adipocyte number or size.[23,40] A small number of methodologically heterogeneous studies with limited sample sizes precluded statistical pooling of data in this review.

CONCLUSIONS

In conclusion, a literature search of four databases (MEDLINE, Scopus, SPORTDiscus, and Web of Science) yielded a total of 16 studies (nine cross-sectional and seven intervention studies (five randomized controlled trials)) analyzing either the association or the effect of physical activity, sport or exercise on bone marrow fat in humans. Although the number of studies is still limited, a correlation between practicing sport and lower BMF was demonstrated, with the emphasis on the influence of mechanical loading, i.e., high-impact sports being related to lower BMF in load-bearing skeletal regions such as mid-tibia and femoral neck. In the recreationally active general population, a higher volume of load-bearing activities was related to a lower lumbar BMF. No significant sex-mediated differences in the relationship between physical activity or exercise and BMF were observed. However, the adipogenic effect of estrogen deficiency on BMF was observed in oligo-amenorrheic athletes. The effects of reambulation on BMF after a prolonged period of bed rest are inconclusive. Overall, the findings suggest that high-impact and weight-bearing exercises may be useful strategies to reduce BMF. However, future investigations should include larger samples of different populations, and employ interventions of longer duration, with analysis of the effect of exercise on different skeletal regions. There is also a need for a standardized diagnostic methodology.

Funding: This work received no funding.

Disclosure statement: The authors declare no competing interests concerning this manuscript.

References

1. Amorim T, Trivanovic D, Benova A, Li H, Tencerova M, Palmisano B. Young minds, deeper insights: a recap of the BMAS Summer School 2023, ranging from basic research to clinical implications of bone marrow adipose tissue. Biol Open. 2024; 13: bio060263.
2. Beekman KM, Regenboog M, Nederveen AJ, Bravenboer N, den Heijer M, Bisschop PH, et al. Gender- and age-associated differences in bone marrow adipose tissue and bone marrow fat unsaturation throughout the skeleton, quantified using chemical shift encoding-based water-fat MRI. Front Endocrinol. 2022; 13: 815835.
3. Belavy DL, Miller CT, Owen PJ, Rantalainen T, Connell D, Hahne AJ, et al. Exercise may impact on lumbar vertebrae marrow adipose tissue: Randomised controlled trial. Bone. 2022; 157: 116338.
4. Belavy DL, Quittner MJ, Ridgers ND, Shiekh A, Rantalainen T, Trudel G. Specific modulation of vertebral marrow adipose tissue by physical activity. J Bone Miner Res. 2018; 33: 651-57.
5. Bertheau RC, Lorbeer R, Nattenmüller J, Wintermeyer E, Machann J, Linkohr B, et al. Bone marrow fat fraction assessment in regard to physical activity: KORA FF4–3-T MR imaging in a population-based cohort. Eur Radiol. 2020; 30: 3417-28.
6. Bredella MA, Fazeli PK, Miller KK, Misra M, Torriani M, Thomas BJ, et al. Increased bone marrow fat in anorexia nervosa. J Clin Endocrinol Metab. 2009; 94: 2129-36.
7. Casazza K, Hanks LJ, Hidalgo B, Hu HH, Affuso O. Short-term physical activity intervention decreases femoral bone marrow adipose tissue in young children: A pilot study. Bone. 2012; 50: 23-7.
8. David V, Martin A, Lafage-Proust MH, Malaval L, Peyroche S, Jones DB, et al. Mechanical loading down-regulates peroxisome proliferator-activated receptor gamma in bone marrow stromal cells and favors osteoblastogenesis at the expense of adipogenesis. Endocrinology. 2007; 148: 2553-62.
9. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016; 6: e011458.
10. Frechette DM, Krishnamoorthy D, Pamon T, Chan ME, Patel V, Rubin CT. Mechanical signals protect stem cell lineage selection, preserving the bone and muscle phenotypes in obesity. Ann N Y Acad Sci. 2017; 1409: 33-50.
11. Griffith JF, Yeung DKW, Ma HAT, Leung JC, Kwok TC, Leung PC. Bone marrow fat content in the elderly: A reversal of sex difference seen in younger subjects. J Magn Reson Imaging. 2012; 36: 225-30.
12. Hewett TE, Pasque C, Heyl R, Wroble R. Wrestling injuries. Med Sport Sci. 2005; 48: 152-78.
13. Higgins JPT, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928.
14. Hou J, Mao H, Xie P, Cui Y, Rong M. The effect of different traditional Chinese exercises on bone mineral density in menopausal women: a systematic review and network meta-analysis. Front Public Health. 2024; 12: 1430608.
15. Hu M, Sheng J, Kang Z, Zou L, Guo J, Sun P. Magnetic resonance imaging and dual energy X-ray absorptiometry of the lumbar spine in professional wrestlers and untrained men. J Sports Med Phys Fitness. 2014; 54: 505-10.
16. Huovinen V, Viljakainen H, Hakkarainen A, Saukkonen T, Toiviainen-Salo S, Lundbom N, et al. Bone marrow fat unsaturation in young adults is not affected by present or childhood obesity, but increases with age: A pilot study. Metabolism. 2015; 64: 1574-81.
17. Indirli R, Lanzi V, Mantovani G, Arosio M, Ferrante E. Bone health in functional hypothalamic amenorrhea: What the endocrinologist needs to know. Front Endocrinol. 2022; 13: 946695.
18. Kindler JM, Ross HL, Laing EM, Modlesky CM, Pollock NK, Baile CA, et al. Load-specific physical activity scores are related to tibia bone architecture. Int J Sport Nutr Exerc Metab. 2015; 25:136-44.
19. Kugel H, Jung C, Schulte O, Heindel W. Age- and sex-specific differences in the1H-spectrum of vertebral bone marrow. J Magn Reson Imaging. 2001; 13: 263-8.
20. Labayen I, Cadenas-Sánchez C, Idoate F, Gracia-Marco L, Medrano M, Alfaro-Magallanes VM, et al. Effects of exercise on bone marrow adipose tissue in children with overweight/obesity: Role of liver fat. J Clin Endocrinol Metab. 2024; dgae547.
21. Li J, Guo J, Wang X, Zhang X, Zhang Y, Bu M, et al. Efficacy and safety of tai chi exercise on bone health: An umbrella review. Osteoporos Int. 2023; 34: 1853-66.
22. Little-Letsinger SE, Pagnotti GM, McGrath C, Styner M. Exercise and diet: Uncovering prospective mediators of skeletal fragility in bone and marrow adipose tissue. Curr Osteoporos Rep. 2020; 18: 774-89.
23. Liu T, Melkus G, Ramsay T, Sheikh A, Laneuville O, Trudel G. Bone marrow reconversion with reambulation. Invest Radiol. 2021; 56: 215-23.
24. Ofir N, Mizrakli Y, Greenshpan Y, Gepner Y, Sharabi O, Tsaban G, et al. Vertebrae but not femur marrow fat transiently decreases in response to body weight loss in an 18-month randomized control trial. Bone. 2023; 171: 116727.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.

26. Pagnotti GM, Styner M. Exercise regulation of marrow adipose tissue. Front Endocrinol. 2016; 7: 94.
27. Pagnotti GM, Styner M, Uzer G, Patel VS, Wright LE, Ness KK, et al. Combating osteoporosis and obesity with exercise: leveraging cell mechanosensitivity. Nat Rev Endocrinol. 2019; 15: 339-55.
28. Palmisano B, Tencerova M. Abstracts BMAS Summer School 2023—2nd Bone Marrow Adiposity Society Summer School Meeting 2023. J Gerontol A Biol Sci Med Sci. 2024; 79: 1–9.
29. Quittner M, Rantalainen T, Ridgers ND, Trudel G, Sheikh A, Connell D, et al. Intervertebral disc status is associated with vertebral marrow adipose tissue and muscular endurance. Eur Spine J. 2018; 27: 1704-11.
30. Rantalainen T, Nikander R, Heinonen A, Cervinka T, Sievänen H, Daly RM. Differential effects of exercise on tibial shaft marrow density in young female athletes. J Clin Endocrinol Metab. 2013; 98: 2037-44.
31. Rubin J, Styner M, Uzer G. Physical signals may affect mesenchymal stem cell differentiation via epigenetic controls. Exerc Sport Sci Rev. 2018; 46: 42-7.
32. Sagayama H, Kondo E, Tanabe Y, Ohnishi T, Yamada Y, Takahashi H. Bone mineral density in male weight-classified athletes is higher than that in male endurance-athletes and non-athletes. Clin Nutr ESPEN. 2020; 36: 106-10.
33. Shen W, Scherzer R, Gantz M, Chen J, Punyanitya M, Lewis CE, et al. Relationship between MRI-measured bone marrow adipose tissue and hip and spine bone mineral density in african-american and caucasian participants: The CARDIA study. J Clin Endocrinol Metab. 2012; 97: 1337-46.
34. Singhal V, Maffazioli GDN, Cano Sokoloff N, Ackerman KE, Lee H, Gupta N, et al. Regional fat depots and their relationship to bone density and microarchitecture in young oligo-amenorrheic athletes. Bone. 2015; 77: 83-90.
35. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355: i4919.
36. Suchacki KJ, Tavares AAS, Mattiucci D, Scheller EL, Papanastasiou G, Gray C, et al. Bone marrow adipose tissue is a unique adipose subtype with distinct roles in glucose homeostasis. Nat Commun. 2020; 11: 3097.
37. Sun Z, Chen H, Berger MR, Zhang L, Guo H, Huang Y. Effects of tai chi exercise on bone health in perimenopausal and postmenopausal women: a systematic review and meta-analysis. Osteoporos Int. 2016; 27: 2901-11.
38. Syed FA, Oursler MJ, Hefferanm TE, Peterson JM, Riggs BL, Khosla S. Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women. Osteoporos Int. 2008; 19: 1323-30.
39. Trudel G, Coletta E, Cameron I, Belavy DL, Lecompte M, Armbrecht G, et al. Resistive exercises, with or without whole body vibration, prevent vertebral marrow fat accumulation during 60 days of head-down tilt bed rest in men. J Appl Physiol. 2012; 112: 1824-31.
40. Trudel G, Payne M, Mädler B, Ramachandran N, Lecompte M, Wade C, et al. Bone marrow fat accumulation after 60 days of bed rest persisted 1 year after activities were resumed along with hemopoietic stimulation: The women international space simulation for exploration study. J Appl Physiol. 2009; 107: 540-8.
41. Tseng PC, Hou SM, Chen RJ, Peng HW, Hsieh CF, Kuo ML, et al. Resveratrol promotes osteogenesis of human mesenchymal stem cells by upregulating RUNX2 gene expression via the SIRT1/FOXO3A axis. J Bone Miner Res. 2011; 26): 2552-63.
42. Vanhie JJ, De Lisio M. How does lifestyle affect hematopoiesis and the bone marrow microenvironment? Toxicol Pathol. 2022; 50: 858-66.
43. Wang J, Yi P, Huang Y, Yu Q, Mei Y, Chen J, et al. Quantitative evaluation of bone marrow fat content and unsaturated fatty index in young male soccer players using proton magnetic resonance spectroscopy (1H-MRS): A preliminary study. Quant Imaging Med Surg. 2021; 11: 4275-86.
44. Yu A, Huang M, Wang L, Zhang Y, Li K, Lou L, et al. Age and gender differences in vertebral bone marrow adipose tissue and bone mineral density, based on MRI and quantitative CT. Eur J Radiol. 2023; 159: 110669.
45. Yue R, Zhou BO, Shimada IS, Zhao Z, Morrison SJ. Leptin receptor promotes adipogenesis and reduces osteogenesis by regulating mesenchymal stromal cells in adult bone marrow. Cell Stem Cell. 2016; 18: 782-96.
46. Zhang Y, Ran J, Xia W, Liu C, Deng C, Li X. Beneficial effects of Chinese martial arts on the lumbar spine: A case series analysis of intervertebral disc, paraspinal muscles and vertebral body. Heliyon. 2023; 9: e23090.