Effects of physical activity/exercise on bone metabolism, bone mineral density and fragility fractures

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ABSTRACT

Bone adapts its mass to mechanical stress from muscle contraction and ground reaction forces, with osteocytes playing a central role in transducing mechanical stimuli into biochemical signals that orchestrate bone modeling and remodeling. This suggests that there is a potential benefit to be derived from physical activity (PA)/exercise for preservation of bone mass. This article briefly reviews the existing literature on the effects of PA/exercise on bone metabolism, bone mineral density (BMD), and fragility fractures. Epidemiological studies have demonstrated an inverse relationship between PA level and fracture risk and its determinants, such as low BMD and falls. Conversely, prolonged disuse or unloading are associated with bone loss. Intervention studies have shown that PA/exercise is effective in increasing BMD and reducing fracture risk, with resistance, weight-bearing and high-impact exercise and high-intensity and high-frequency and intermittent training protocols found to provide the most marked effect. These findings support a role for exercise as a non-pharmacological, safe, and low-cost tool against bone loss associated with age and other conditions. However, high-quality studies are needed to establish the optimal exercise prescription. Furthermore, PA/exercise is effective in mitigating weight loss-induced bone loss and has the potential for reducing the increased fracture risk associated with preserved BMD that characterizes individuals with type 2 diabetes.

KEYWORDS

Physical activity/exercise, fracture risk, bone mineral density, body weight loss, obesity, type 2 diabetes.

Introduction

In 1892, Julius Wolff, a German anatomist and orthopedic surgeon, first established the concept of bone adaptation occurring in response to mechanical stress (the so-called Wolff's law) [1]. Beginning in the 1960s, Harold Frost further developed that of a relationship between the shape of a bone and its mechanical function, by describing the "mechanostat", a negative feedback control circuit that regulates bone strength according to the forces applied on it [2]. According to this theory, if the typical local maximum force acting on an area of the bone is reduced, the local deformation (μStrain) will also be reduced, and if it falls below the threshold for bone resorption (i.e., 100-300 μstrain), the local bone geometry will be selectively altered through removal of bone material ("remodeling"). Conversely, if the typical local maximum force acting on an area of the bone is increased, the local deformation (μStrain) will also be increased, and if it rises above the threshold for bone formation (i.e., 1,500-3,000 μstrain), the local bone geometry will be selectively altered through addition of bone material ("modeling"). As a result of these changes, the deformation returns to normal values, thus adapting the local strength in the direction in which the force acts (Fig.1).

Forces acting on bone include muscle contraction, acting via tendon attachment sites, and ground reaction forces (impacts) or gravitational loads, i.e., the forces exerted by the ground on a body in contact with it, which correspond to the individual's body weight during simple standing; in movement, on the other hand, due to acceleration forces, they increase to up to 2-3 times the individual's body weight [3]. The direct and indirect influences of muscle on bone, through contraction and movement-induced increase of ground reaction forces, respectively, point to a central role for the muscle-bone axis in modulating bone (and muscle) mass [4]. However, the coupling between muscle and bone cannot be viewed solely from the perspective of mechanotransduction, as these organs also communicate through myokines and osteokines, respectively, which positively or negatively regulate muscle and bone mass. In addition, a third player, adipose tissue, participates in this biochemical crosstalk through secretion of adipokines, which also impact on muscle and bone formation [5] (Fig. 2).

It is generally agreed that osteocytes act as mechanosensory cells that orchestrate bone modeling and remodeling in re-

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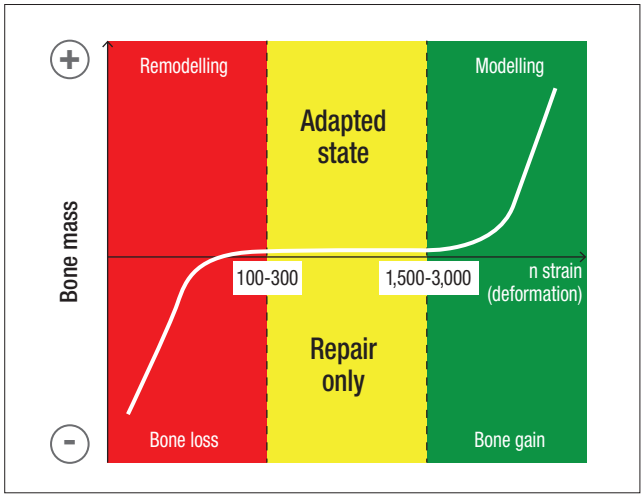
Figure 1 Schematic representation of the "mechanostat" control circuit for bone adaptation to mechanical load.



sponse to mechanical stimuli [6]. These cells, which derive from osteoblasts, are embedded within bone matrix to form a highly connected network, the lacunae-canaliculi system. By virtue of their connection with bone lining cells, as well as through secreted molecules, osteocytes signal osteoblasts and osteoclasts to produce or break down bone [7]. Mediators of mechanotransduction include the osteoclastogenic receptor activator of NF-ϰB (RANK)-RANK ligand-osteoprotegerin system [8] and the osteoblastogenic Wnt-β-catenin signaling [9].

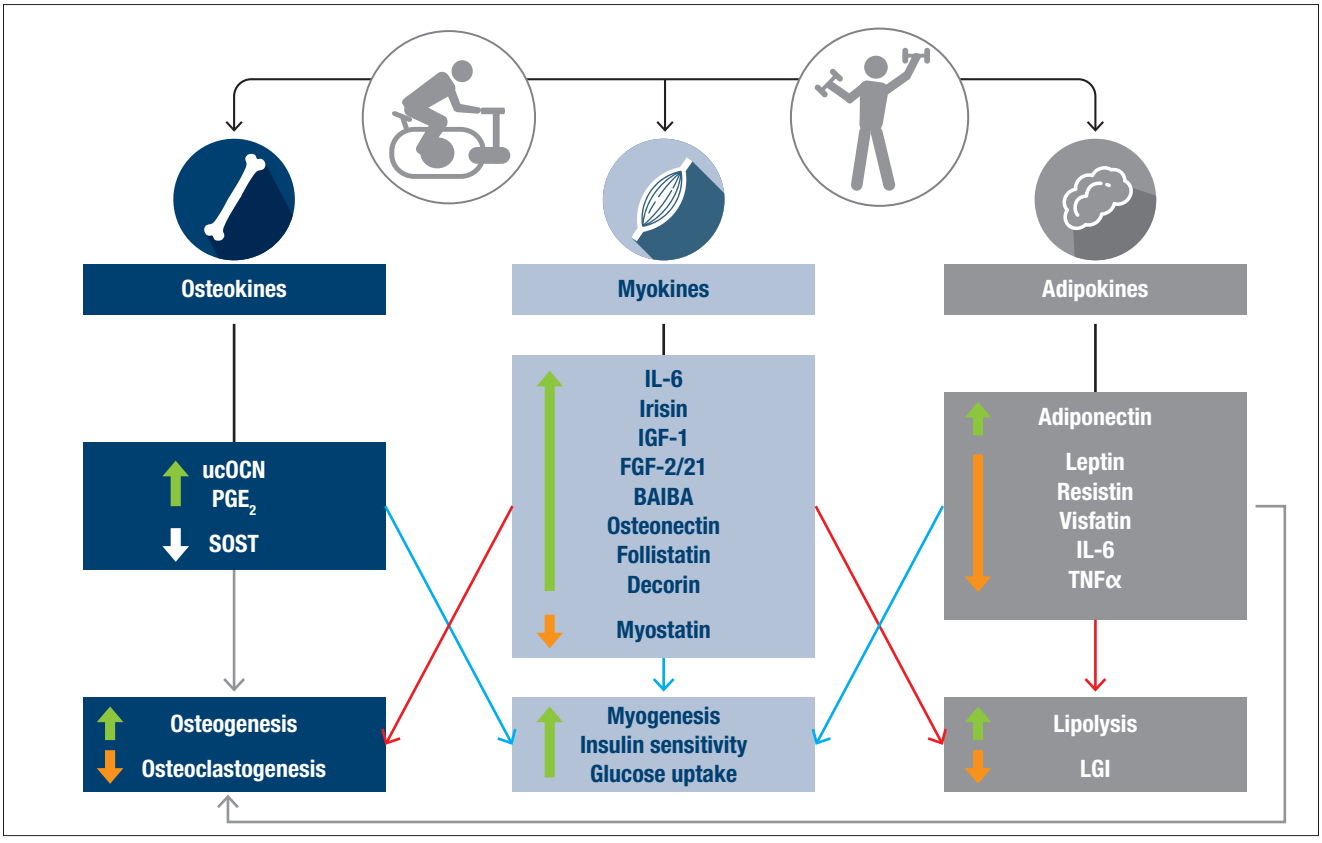
The concept of bone adaptation to mechanical stress and the main role of muscle contraction as a loading stimulus suggest a potential benefit of physical activity (PA)/exercise in preservation of bone mass. This article will briefly review the existing literature on the effects of PA/exercise on bone metabolism, bone mineral density (BMD), and fragility fractures.

Relationship between PA and bone health

The Dubbo Osteoporosis Epidemiology Study found level of PA to be an independent predictor of age-related bone loss in elderly women, together with baseline BMD and weight, and weight change; it also showed that the combination of age, baseline BMD and weight, weight change, and PA accounted for 13% of total variance in the rate of BMD decline [10].

The relationship between PA and bone health is further supported by two lines of evidence. On the one hand, prolonged disuse (e.g., bedridden patients) [11] or unloading (e.g., microgravity) [12] have been shown to be associated with bone loss. On the other hand, epidemiological studies have clearly demonstrated a link between PA level and fracture risk. Among 3,262 men aged ≥44 years followed for up to 21 years, there was an inverse association between baseline self-reported PA and hip fracture risk [13]. Likewise, among 77,206 postmenopausal women enrolled in the Women's Health Initiative prospective cohort study and followed up for an average of 14 years, higher

Figure 2 Bone-muscle-adipose tissue biochemical cross-talk for regulating tissue mass in response to exercise (**ucOCN** = undercarboxylated osteocalcin; **PGE2** = prostaglandin E2; **SOST** = sclerostin; **IL-6** = interleukin 6; **IGF-1** = insulin-like growth factor I; **FGF-2/21** = fibroblast growth factor 2/21; **BAIBA** = β-aminoisobutyric acid; **TNF-α** = tumor necrosis factor α; **LGI** = low-grade inflammation).



total PA was associated with lower total and hip fracture risk; moreover, higher PA mitigated increased total fracture risk associated with sedentary behavior [14]. Among 1,477 elderly participants in the population-based Longitudinal Aging Study Amsterdam, fracture rates over a 3-year follow-up were higher in individuals with low PA, functional limitations, low performance, and poor handgrip strength [15]. Among 4,984,144 middle-aged and older individuals identified through the Korean National Health Insurance Service, fracture risk was found to be progressively lower in those decreasing their PA, increasing their PA, and remaining continuously active compared with individuals who were continuously inactive [16].

As regards determinants of fracture risk, among 7,624 older people from the Activity and Function in the Elderly (ActiFE) in Ulm study, those who were classed as low active showed more falls per hours walked; the highest incidence rates were recorded in low-active persons with slow walking speed or a history of falls [17]. Furthermore, in a study of 65 young male athletes, those who remained active throughout the study showed increased BMD at all sites when compared with 27 male coeval controls; at the final follow up, those who had ended their active careers (former athletes) still recorded higher BMD at the femoral neck, total hip and humerus compared with the controls [18].

Effect of exercise training on fracture risk and its determinants

Intervention studies and meta-analyses have shown that PA/exercise interventions are effective in reducing fracture risk by favorably affecting its determinants, such as BMD and falls. However, the level of evidence is quite low, likely due to the high risk of bias of many of the existing studies and their heterogeneity in terms of participant characteristics and exercise/training protocols. The effects on bone health may in fact vary according to the type, intensity, duration and frequency of exercise. In particular, types of exercise include not only aerobic and resistance, but also low- and high-impact as well as weight-bearing and non-weight-bearing, which are critical for the extent of mechanical loading; moreover, balance and functional training is also important for reducing the risk of falls.

A meta-analysis of 43 randomized controlled trials (RCTs) involving 4,320 participants found a relatively small effect of exercise. Combination exercise was associated with a lower fracture risk than in control groups and was the most effective for spine BMD, whereas non-weight-bearing high-force exercise was the most effective for femoral neck BMD [19]. Two more recent meta-analyses confirmed the beneficial effect of exercise on fracture risk and BMD. The first included 20 RCTs involving 7,704 older adults and showed a reduced fall-related fracture risk; the significant effect of intervention was detected for studies with longer follow-up and of higher quality [20]. The second included 75 studies for a total of 5,300 post-menopausal women and showed a significant impact of exercise on BMD at all sites [21]. Another meta-analysis including 108 RCTs for a total of 23,407 community-living participants reported that exercise reduced falls by 23%, with programs involving balance and functional training found to be the most effective [22].

Regarding type of exercise, several meta-analyses demonstrated the superiority of resistance, weight-bearing and high-impact exercise in improving BMD [23-25]. Moreover, the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) semi-randomized controlled trial focused on the effect of high-intensity resistance and impact training on bone health. In postmenopausal women with osteopenia/osteoporosis, this training protocol was superior to control in improving BMD, quantitative ultrasound parameters and physical performance [26]. Likewise, in men aged ≥45 years with low bone mass, it was superior to isometric axial compression on bone geometry of the femoral neck and non-dominant distal tibia and radius [27], BMD, quantitative ultrasound parameters, physical function [28], and thoracic kyphosis and incident fracture from vertebral morphology [29]. In the Osteo-cise: Strong Bones for Life trial, a multimodal exercise program incorporating high-speed progressive resistance training, combined with an education and behavioral change program, was effective in improving femoral neck and lumbar spine BMD, together with body composition, muscle strength and physical function in older adults [30].

As regards exercise intensity and frequency, two meta-analyses, conducted in post-menopausal women and in older adults respectively, showed that the higher the exercise intensity and frequency were, the higher the improvements in lumbar spine, but not femoral neck, BMD [31,32]; these results highlighted the importance of progressively increasing the intensity of training and of doing at least 3 exercise sessions/week.

As for exercise duration, animal studies have shown that bone tissue desensitizes to mechanical loading after relatively few exercise repetitions and that recovery periods of variable duration are required to allow the tissue to re-sensitize, thereby indicating the importance of "novelty of strain" and the need for intermittent training protocols in order to maximize the effectiveness of mechanical loading on osteogenesis [33].

Effect of exercise on bone loss associated with body weight loss

Overweight and obesity have consistently been associated with reduced fracture risk [34], which appears to be mediated by the preserved or even augmented BMD, due to increased mechanical loading [35]. Conversely, body weight loss is commonly associated with BMD loss, which is partly attenuated by weight regain only at the hip level [36], thus predisposing to fragility fractures, especially in older individuals [37].

Several studies have suggested a potential role for PA/exercise in mitigating bone loss associated with body weight loss in obese individuals. In a 1-year RCT, physical function increased more, whereas lean body mass and BMD at the hip decreased less in the diet-exercise than in the diet-only group [38]. In the subsequent Lifestyle Intervention Trial in Obese Elderly (LITOE), the combination of aerobic and resistance exercise was the most effective in improving functional status and attenuating BMD loss at the hip [39]; the preserving effect on BMD was also seen at the femoral neck, trochanter and intertrochanter,

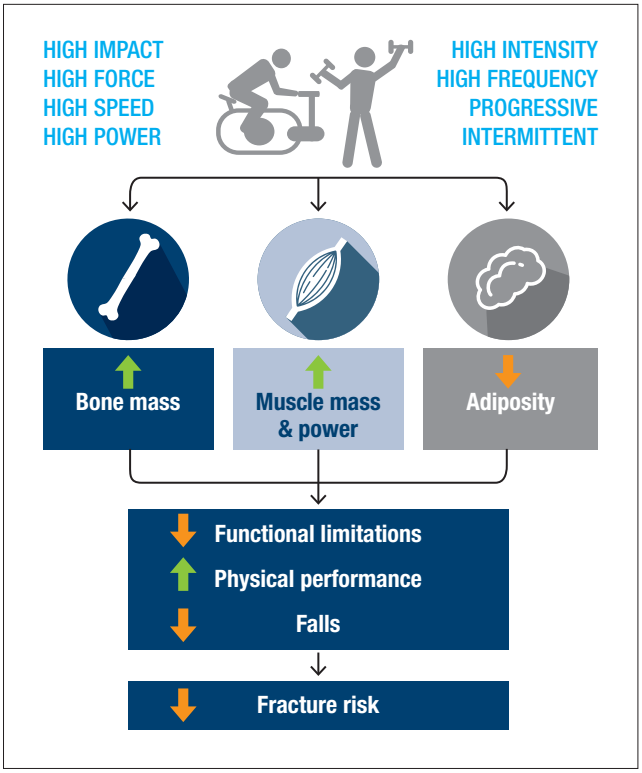
but not at the lumbar spine and one-third radius [40]. Moreover, the Cooperative Lifestyle Intervention Program (CLIP) II showed that adding resistance but not aerobic training to diet minimized long-term hip bone loss [41] and, in the Look AHEAD (Action in Health for Diabetes) trial, the BMD-preserving effect of exercise was observed in men, but not in women [42]. Meta-analyses confirmed the efficacy of exercise training in attenuating BMD loss after body weight loss induced by diet [43] and bariatric surgery [44], and that resistance exercise is the training modality that partially preserves bone mass during calorie-restricted diets [45].

Effect of exercise on bone fragility associated with type 2 diabetes

Despite normal-to-elevated BMD, people with type 2 diabetes have an increased fracture risk, which has been attributed to poor bone quality [46]; it remained after adjustment for BMD and falls [47]. Combination of weight-bearing aerobic and resistance exercise seems to prevent excessive bone loss in these individuals during weight loss [42, 48].

However, it is unclear whether, in individuals with preserved BMD, exercise is effective in increasing bone quality, and whether improved quality results in increased bone strength and reduced fracture risk. An ongoing RCT, the Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes, is assessing the efficacy of a 2-year exercise training program, specifically designed for improving bone quality and strength, compared with standard care [49]. The primary endpoint is baseline to end-of-study change in the trabecular bone score, a parameter of bone quality consistently shown to be reduced in these individuals. Falls and asymptomatic and symptomatic fractures, evaluated over 7 years, including a 5-year post-trial follow up, are secondary endpoints.

Figure 3 Exercise modalities for improving bone, muscle and adipose tissue health and reducing fracture risk and its determinants.



Conclusions

The role of muscle contraction in modulating bone homeostasis suggests that, in terms of preserving bone heath, there is a potential benefit to be derived from PA/exercise.

Current evidence supports a role for PA/exercise as a non-pharmacological, safe, and low-cost tool for preventing and treating bone loss associated with age and various disease conditions, and provides important insights into the exercise modalities that are most suited for improving bone, muscle and adipose tissue health (Fig. 3). A recent systematic review evaluating the quality of osteoporosis guidelines from the perspective of PA-based intervention concluded that moderate- or high-intensity exercise is encouraged by many guidelines, the majority of which are of good quality, although they lack specific indications on exercise protocols [50], indicating the need for further high-quality RCTs to establish the optimal exercise prescription.

Furthermore, PA/exercise may be useful for mitigating BMD loss associated with body weight loss and for reducing fracture risk also in individuals with preserved BMD such as those with type 2 diabetes.

References

1. Wolff J. Das Gesetz der Transformation der Knochen. Berlin, Germany:Verlag von August Hirschwald; 1892.
2. Frost HM. Bone "mass" and the "mechanostat": a proposal. Anat Rec. 1987;219(1):1-9.
3. Laurent MR, Dubois V, Claessens F, et al. Muscle-bone interactions: from experimental models to the clinic? A critical update. Mol Cell Endocrinol. 2016;432:14-36.
4. Herrmann M, Engelke K, Ebert R, et al. Interactions between muscle and bone - Where physics meets biology. Biomolecules. 2020;10(3):432.
5. Kirk B, Feehan J, Lombardi G, Duque G. Muscle, bone, and fat crosstalk: the biological role of myokines, osteokines, and adipokines. Curr Osteoporos Rep. 2020;18(4):388-400.
6. Bonewald LF. The amazing osteocyte. J Bone Miner Res. 2011;26(2):229-38.
7. Bellido T. Osteocyte-driven bone remodeling. Calcif Tissue Int. 2014;94(1):25-34.
8. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008;473(2):139-46.
9. Choi RB, Robling AG. The Wnt pathway: an important control mechanism in bone's response to mechanical loading. Bone. 2021;153:116087.
10. Nguyen TV, Sambrook PN, Eisman JA. Bone loss, physical activity, and weight change in elderly women: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res. 1998;13(9):1458-67.
11. Rolvien T, Amling M. Disuse osteoporosis: clinical and mechanistic insights. Calcif Tissue Int. 2021 Mar 18.
12. Coulombe JC, Senwar B, Ferguson VL. Spaceflight-induced bone tissue changes that affect bone quality and increase fracture risk. Curr Osteoporos Rep. 2020;18(1):1-12.

13. Kujala UM, Kaprio J, Kannus P, Sarna S, Koskenvuo M. Physical activity and osteoporotic hip fracture risk in men. Arch Intern Med. 2000;160(5):705-8.
14. LaMonte MJ, Wactawski-Wende J, Larson JC, et al. Association of physical activity and fracture risk among postmenopausal women. JAMA Netw Open. 2019;2(10):e1914084.
15. Stel VS, Pluijm SM, Deeg DJ, Smit JH, Bouter LM, Lips P. Functional limitations and poor physical performance as independent risk factors for self-reported fractures in older persons. Osteoporos Int. 2004;15(9):742-50.
16. Han S, Jang HD, Choi S, et al. Changes in physical activity and risk of fracture: a Korean nationwide population-based cohort study. Sci Rep. 2020;10(1):16266.
17. Klenk J, Kerse N, Rapp K, et al. Physical activity and different concepts of fall risk estimation in older people--results of the ActiFE-Ulm study. PLoS One. 2015;10(6):e0129098.
18. Nordström A, Olsson T, Nordström P. Sustained benefits from previous physical activity on bone mineral density in males. J Clin Endocrinol Metab. 2006;91(7):2600-4.
19. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011;(7):CD000333.
20. Wang Q, Jiang X, Shen Y, et al. Effectiveness of exercise intervention on fall-related fractures in older adults: a systematic review and meta-analysis of randomized controlled trials. BMC Geriatr. 2020;20(1):322.
21. Shojaa M, Von Stengel S, Schoene D, et al. Effect of exercise training on bone mineral density in post-menopausal women: a systematic review and meta-analysis of intervention studies. Front Physiol. 2020;11:652.
22. Sherrington C, Fairhall NJ, Wallbank GK, et al. Exercise for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2019;1(1):CD012424.
23. Bolam KA, van Uffelen JG, Taaffe DR. The effect of physical exercise on bone density in middle-aged and older men: a systematic review. Osteoporos Int. 2013;24(11):2749-62.
24. Kemmler W, Shojaa M, Kohl M, von Stengel S. Effects of different types of exercise on bone mineral density in postmenopausal women: a systematic review and meta-analysis. Calcif Tissue Int. 2020;107(5):409-39.
25. Ponzano M, Rodrigues IB, Hosseini Z, et al. Progressive resistance training for improving health-related outcomes in people at risk of fracture: a systematic review and meta-analysis of randomized controlled trials. Phys Ther. 2021;101(2):pzaa221.
26. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR. High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. J Bone Miner Res. 2018;33(2):211-20.
27. Harding AT, Weeks BK, Lambert C, Watson SL, Weis LJ, Beck BR. Effects of supervised high-intensity resistance and impact training or machine-based isometric training on regional bone geometry and strength in middle-aged and older men with low bone mass: the LIFTMOR-M semi-randomised controlled trial. Bone. 2020;136:115362.
28. Harding AT, Weeks BK, Lambert C, Watson SL, Weis LJ, Beck BR. A comparison of bone-targeted exercise strategies to reduce fracture risk in middle-aged and older men with osteopenia and osteoporosis: LIFTMOR-M semi-randomized controlled trial. J Bone Miner Res. 2020;35(8):1404-14.
29. Harding AT, Weeks BK, Lambert C, Watson SL, Weis LJ, Beck BR. Exploring thoracic kyphosis and incident fracture from vertebral morphology with high-intensity exercise in middle-aged and older men with osteopenia and osteoporosis: a secondary analysis of the LIFTMOR-M trial. Osteoporos Int. 2021;32(3):451-65.
30. Gianoudis J, Bailey CA, Ebeling PR, et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: a community-based randomized controlled trial. J Bone Miner Res. 2014;29(1):182-91.
31. Kistler-Fischbacher M, Weeks BK, Beck BR. The effect of exercise intensity on bone in postmenopausal women (part 2): a meta-analysis. Bone. 2021;143:115697.
32. Zitzmann AL, Shojaa M, Kast S, et al. The effect of different training frequency on bone mineral density in older adults. A comparative systematic review and meta-analysis. Bone. 2021;154:116230.
33. Turner CH, Robling AG. Mechanisms by which exercise improves bone strength. J Bone Miner Metab. 2005;23 Suppl:16-22.
34. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.
35. Johansson H, Kanis JA, Odén A, et al. A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res. 2014;29(1):223-33.
36. Kammire DE, Walkup MP, Ambrosius WT, et al. Effect of weight change following intentional weight loss on bone health in older adults with obesity. Obesity (Silver Spring). 2019;27(11):1839-45.
37. Ensrud KE, Ewing SK, Stone KL, Cauley JA, Bowman PJ, Cummings SR; Study of Osteoporotic Fractures Research Group. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. J Am Geriatr Soc. 2003;51(12):1740-7.
38. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011;364(13):1218-29.
39. Villareal DT, Aguirre L, Gurney AB, et al. Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med. 2017;376(20):1943-55.
40. Armamento-Villareal R, Aguirre L, Waters DL, Napoli N, Qualls C, Villareal DT. Effect of aerobic or resistance exercise, or both, on bone mineral density and bone metabolism in obese older adults while dieting: a randomized controlled trial. J Bone Miner Res. 2020;35(3):430-9.
41. Beavers KM, Walkup MP, Weaver AA, et al. Effect of exercise modality during weight loss on bone health in older adults with obesity and cardiovascular disease or metabolic syndrome: a randomized controlled trial. J Bone Miner Res. 2018;33(12):2140-9.
42. Lipkin EW, Schwartz AV, Anderson AM, et al; Look AHEAD Research Group. The Look AHEAD Trial: bone loss at 4-year follow-up in type 2 diabetes. Diabetes Care. 2014;37(10):2822-9.
43. Mesinovic J, Jansons P, Zengin A, et al. Exercise attenuates bone mineral density loss during diet-induced weight loss in adults with overweight and obesity: a systematic review and meta-analysis. J Sport Health Sci. 2021;10(5):550-9.
44. Bellicha A, van Baak MA, Battista F, et al. Effect of exercise training before and after bariatric surgery: A systematic review and meta-analysis. Obes Rev. 2021;22 Suppl 4:e13296.
45. Yazdanpanah Z, Beigrezaei S, Mohseni-Takalloo S, et al. Does exercise affect bone mineral density and content when added to a calorie-restricted diet? A systematic review and meta-analysis of controlled clinical trials. Osteoporos Int. 2022;33(2):339-54.
46. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. Osteoporos Int. 2007;18(4):427-44.
47. Schwartz AV, Sellmeyer DE, Ensrud KE, et al; Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab. 2001;86(1):32-8.
48. Viggers R, Al-Mashhadi Z, Fuglsang-Nielsen R, Gregersen S, Starup-Linde J. The impact of exercise on bone health in type 2 diabetes mellitus-a systematic review. Curr Osteoporos Rep. 2020;18(4):357-70.
49. Balducci S, Conti F, Sacchetti M, et al; SWEET BONE Investigators. Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes: study protocol for a randomised clinical trial. BMJ Open. 2019;9(11):e027429.
50. Iolascon G, de Sire A, Curci C, et al. Osteoporosis guidelines from a rehabilitation perspective: systematic analysis and quality appraisal using AGREE II. Eur J Phys Rehabil Med. 2021;57(2):273-9.

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