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BONE AND DIABETES (A SCHWARTZ AND P VESTERGAARD, SECTION EDITORS)

The Impact of Exercise on Bone Health in Type 2 Diabetes Mellitus—a Systematic Review

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Abstract

Purpose of Review Type 2 diabetes mellitus (T2DM) is associated with an increased fracture risk. Weight loss in T2DM management may result in lowering of bone mass. In this systematic literature review, we aimed to investigate how exercise affects bone health in people with T2DM. Furthermore, we examined the types of exercise with the potential to prevent and treat bone fragility in people with T2DM.

Recent Findings Exercise differs in type, mechanical load, and intensity, as does the osteogenic response to exercise. Aerobic exercise improves metabolic health in people with T2DM. However, the weight-bearing component of exercise is essential to bone health. Weight loss interventions in T2DM induce a loss of bone mass that may be attenuated if accompanied by resistance or weight-bearing exercise.

Summary Combination of weight-bearing aerobic and resistance exercise seems to be preventive against excessive bone loss in people with T2DM. However, evidence is sparse and clinical trials investigating the effects of exercise on bone health in people with T2DM are warranted.

Keywords Bone · Bone turnover · Type 2 diabetes mellitus · Insulin resistance · Exercise · Physical activity

Introduction

Type 2 diabetes mellitus (T2DM) and osteoporosis are major public health concerns associated with increased morbidity and mortality globally [1, 2]. T2DM is related to chronic metabolic derangements that may affect multiple organs and lead to serious complications [3]. The International Diabetes Federation (IDF) estimated in 2017 that 425 million (8.8%) adults had diabetes mellitus (DM), 90% of which had T2DM [1]. Osteoporosis is characterized as a state of low bone mineral density (BMD) as well as weakened bone microstructure resulting in reduced bone strength and elevated fracture risk [4]. Osteoporosis is estimated to affect over 200 million people worldwide [2].

In patients with T2DM, the risk of fractures is increased and not sufficiently predicted by BMD estimated by dual-energy X-ray absorptiometry (DXA) scans [5–7]. The fracture risk may be triggered by a deficit in bone quality, though the bone abnormalities in diabetes are not fully clarified [8].

Exercise is recommended as prevention and treatment in both osteoporosis and T2DM and accounts for a great number of health benefits, e.g., preventing cardiovascular events and muscle and bone loss. Exercise is most often referred to as

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"aerobic" and addressed by cardiorespiratory fitness (maximal oxygen consumption, VO_{2max}) [2, 9–11]. Aerobic exercise includes weight-bearing, e.g., jogging, brisk walking, tennis, and soccer, and non-weight-bearing, e.g., swimming and cycling [11]. Resistance exercise refers to strengthening of muscle groups by the use of resistance machines, free weights, or bands, and flexibility exercise refers to stretching or yoga [11]. Weight-bearing and resistance exercises provide a fundamental and beneficial mechanical load to the skeleton [12].

The terms "physical activity" and "exercise" differ slightly in meaning. "Physical activity" refers to any movement of the body resulting in an increase in energy expenditure, whereas "exercise" is planned or structured physical activity [13, 14]. Strong evidence supports that exercise can prevent and treat T2DM [9, 15–17]. IDF states that "physical activity is most effective when it includes a combination of both aerobic exercise and resistance training, as well reduction of sedentary time" [1]. Conversely, bone tissue responds differentially to varying types of exercise. Thus, knowledge about tissue-specific metabolic alterations elicited by exercise in patients with T2DM is essential.

A combination of resistance and weight-bearing aerobic exercise is shown to increase BMD of the femoral neck and lumbar spine in postmenopausal women [18]. Strain exercise of high amplitude and low frequency, e.g., locomotion, running, and jumping [19], or of low amplitude and high frequency, e.g., vibration [20], has been shown to stimulate BMD in bone segments exposed to the strain.

This review aims to analyze and critically evaluate the literature regarding optimal exercise strategies for promoting bone health as well as preventing bone fragility and fractures in people suffering from T2DM. Firstly, the regulatory aspects of bone metabolism in normal conditions and in patients with T2DM will be examined. Secondly, we will evaluate current knowledge on bone adaptation to different types of exercise. Lastly, the content of the systematic literature search regarding the effects of exercise on bone health in patients with T2DM will be discussed.

Methodology

The PRISMA guidelines were followed [21]. A systematic literature search was performed in the database Medline via PubMed using the terms "diabetes mellitus," "insulin resistance," "exercise," "physical activity," "bones," "osteoporosis," and "fractures" (full search string schematization in Supplementary Table 1). Additional relevant articles referenced in the included records were also reviewed for eligibility. The inclusion criteria were studies examining correlations and associations between exercise and bone health in people with T2DM or prediabetes/insulin resistance. Only human studies were eligible. Studies in which the presence of T2DM or exercise was merely adjusted for statistically were not included. Osteoarthritis and joint pain were not considered relevant bone-related outcomes. Records on children (age < 18 years) were excluded. All records were included regardless of the language of the record. The search was limited to records from 2004 or later. Case reports and series, posters, commentaries, and conference abstracts were excluded. The final literature search was performed on February 25, 2020.

In total, 389 records were identified, and 24 articles (Table 1) were included based on the inclusion criteria (see Supplementary Fig. 1 for detailed exclusion process).

Bone Metabolism and Regulation

The relationship between body weight and bone size was acknowledged in the seventeenth century by Galileo [45]. The ability of bone mass to adjust metabolic need and physical strain is pivotal in order to prevent bone fragility and fractures. The following section describes the regulation of bone metabolism and outlines the changes in people with T2DM.

Biochemical Regulation of Bone Metabolism

Optimal skeletal structure is dependent on balanced bone remodeling, i.e., strict control of bone resorption and formation [46]. Regulation of bone metabolism includes several metabolically active agents, both endocrine and paracrine, but is highly influenced by exogenous factors as well, such as mechanical load and strain [12].

The number of circulating markers of bone turnover has increased over the last decade and some are used in the clinical setting in addition to BMD, such as C-terminal telopeptide of type 1 collagen (CTX) and N-terminal propeptide of type 1 procollagen (P1NP), which serve to monitor the activity of bone resorption and formation, respectively [47].

Osteocytes are strain-sensitive cells that release controlling factors of bone formation and resorption in response to external mechanical stimuli [12]. Exposure to mechanical forces is crucial in maintaining bone mass equilibrium [48]. The absence of mechanical strain increases osteocyte gene expression of the glycoprotein sclerostin in rodents [49]. Sclerostin reduces bone formation by inhibition of the Wnts; small proteins are secreted from osteocytes to stimulate osteoblast differentiation and promote bone formation [50]. Furthermore, sclerostin signals through increased osteoblastic expression of receptor activator of nuclear factor-kappa beta ligand (RANKL) to stimulate osteoclasts and promote bone resorption [12]. Osteoclasts initialize bone resorption by adhering to the underlying bone and secreting acidic proteases that degrade bone tissue and generate circulating products of resorption, e.g., CTX and Isoform 5b of tartrate resistant acid phosphatase (TRACP5b) [51].

Table 1 Overview of articles included in the systematic literature search—the effects of exercise on bone outcomes in type 2 diabetes. *T2DM*, type 2 diabetes mellitus; *CTX*, C-terminal telopeptide of type 1 collagen; *P1NP*, N-terminal propeptide of type 1 procollagen; *BMD*, bone mineral density; *BMC*, bone mineral content; *Rep.*, repetitions; *BUA*, broadband ultrasound attenuation; *pQCT*, peripheral quantitative computed tomography; *MetS*, metabolic syndrome; *WHO*, World Health Organization; *RCT*, randomized controlled trial; *OR*, odds ratio; *WL*, weight loss; *kcal/d*, kilocalorie/day; *OPG*, osteoprotegerin; *C1CP*, C-terminal propeptide of type I collagen; *OC*, osteocalcin; age in years; level of evidence from "Levels of evidence March 2009" by Oxford Centre for Evidence-Based Medicine

Author	Design and level of evidence	*N*	Population characteristics	Exercise type	Bone outcome and result
Short-term effects of exercise					
Borer et al. [22] America, USA	Acute intervention. Level 3	15	Postmenopausal women, all T2DM. Age: 50–65.	Treadmill exercise: Uphill, 75% of max Downhill 46% of max Time: 40 min ± pre-exercise meal.	CTX: No difference. CICP: Higher after up- and downhill exercise 60 min after meal compared with same exercise before meal.
Levinger et al. [23] Australia	Acute intervention. Level 3	11	Obese non-DM men Age: 58.1 ± 2.2	2 experimental trials (control-rest or exercise), 3 to 5 weeks apart. 1) Rest 2) Acute high-intensity exercise: 4 sets of 4 min. each at 90–95% of max separated by 2 min.	Increase in ucOC after exercise. No change in OC Association between ucOC and insulin sensitivity in obese men after exercise.
Long-term effects of exercise					
Skoradal et al. [24] Faroe Islands	RCT. Level 1b.	55	Men ($n = 28$) and women ($n = 27$) with prediabetes. Age: 55–70.	16 weeks. Exercising group ($n = 27$): Soccer training 30–60 min. 2 times/week. Non-exercising group ($n = 23$).	Increases after 16 weeks (and compared with non-exercise group) in: - BMD (2.5%) at femur. - BMD (3.9%) at lumbar spine. - OC, 23% ± 8%. - P1NP, 52% ± 9%. - CTX, 38% ± 7% - P1NP/CTX-1 ratio.
Beavers et al. [25] America, USA	RCT. Level 1b.	187	Men and women, with metabolic syndrome (MetS). Age: 66.9 ± 4.8	18 months, 3 groups: 1) Weight loss (WL; 7–10% baseline weight). 2) WL + aerobic exercise, walking 4 days/week progressing 45 min/day. 3) WL + resistance exercise, upper and lower body, machines 75% of max 10–12 rep.	2% decrease in hip BMD in all groups with lowest decrease in group 3. BMD lumbar spine increase in group 3 compared with group 2. P1NP: no effect CTX: no effect
Hur et al. [26] South Korea	Case-control. Level 3b.	24	Women. MetS/insulin resistance ($n = 12$). Non-MetS/insulin resistance ($n = 12$). Age: 47.24 ± 2.20	8 weeks supervised resistance exercise, 40 min. 3 times/week, 10 rep., 60–70% of max.	OPG: increased in both groups after moderate resistance exercise but significantly more in the MetS group.
Lipkin et al. [27] and Johnson et al. 2017 [28] (The Look AHEAD Trial) America, USA	RCT. Level 1b.	5145	Men and women with T2DM. 60% women, 63% white. Age: 45–76.	1–4 years. Group 1 (ILI): Intensive lifestyle intervention with reduced calorie intake and increased physical activity to achieve and maintain ≥ 7% weight loss. Group 2 (DSE): Diabetes support and education intervention.	ILI group had higher bone loss (− 1.66%) after 1 year and the loss remained significant after 4 years. ILI group had 39% increased risk of a fragility fracture compared with DSE group (HR 1.39).
Courteix et al. [29] France	RCT. Level 1b.	90 MetS 44 controls	Men and women with MetS. Age: 50–70.	1 year (non-supervised but compliance-monitored) exercise 15–20 h/week + diet restriction. Groups of MetS: 1) High resistance (70%) + moderate endurance (30%) ($n = 34$). 2) Moderate resistance (30%) + high endurance (70%) ($n = 32$).	No difference in BMD or BMC between groups. No difference in BMD or BMC between MetS and control. Compliance analyses: Higher lumbar spine BMC and BMD in more compliant subjects. Higher femoral neck BMD in compliant participants in group 2 than compliant participants in group 1 and controls.

Table 1 (continued)

Author Short-term effects of exercise	Design and level of evidence	*N*	Population characteristics	Exercise type	Bone outcome and result
				3) Moderate-resistance (30%) + moderate endurance (30%) ($n = 34$).	
Al-Shreef et al. [30] Saudi Arabia	RCT. Level 1b.	100	Men. All T2DM. Age: 40–55.	6 months, 3 sessions/week, 40 min: 1) Aerobic exercise, treadmill running 60–80% of max. 2) Resistance exercise, machines, whole body.	Higher Calcium and lower PTH levels after both aerobic and resistance exercise.
Bello et al. 2014 [31] Brazil	RCT. Level 1b.	14	Postmenopausal women Age: 61.3 ± 6.0 Prediabetes and T2DM. 1) Exercise ($n = 7$) 2) Control ($n = 7$)	32 weeks. Community-based exercise program 3 times/week. - 1 aerobic 40 min walking - 1 weight-bearing exercise - 1 aquatic exercise session	No change in BMD at significant sites after exercise 7.8% increase in Ward's triangle BMD after exercise.
Jiang et al. [32] Colombia	RCT. Level 1b.	46	Overweight/obese, men and women ≥ 2 MetS characteristics Age: 26–39	12 weeks. 3 groups: 1) 40 mg simvastatin/day ($n = 9$) 2) Exercise, brisk walking and/or slow jogging, 45 min/day, 5 days/week ($n = 18$). 3) Combination of 1 + 2 ($n = 19$).	No change in OC before to after 12 weeks. CTX higher after 12 weeks of exercise without statins.
Hinton et al. [33] America, USA	RCT. Level 1b.	24	Overweight/obese women with ≥ 2 risk factors of MetS. Age: 19–50	4–6 months aerobic moderate exercise + diet, 10% reduction in body weight. Plus 4–6 months, regain of 50% divided to groups: 1) Continued exercise 2) No exercise	BMD decreased at lumbar spine (− 1.1%) and hip (− 1.6%) after weight loss. No difference after weight-regain intervention with or without exercise. OC increased with weight loss. CTX increased with weight loss.
Kemmler et al. [34] Germany	RCT. Level 1b.	66	Postmenopausal women with MetS. Age: 52.3 ± 2.4	12 months. Group 1) Exercise ($n = 36$): 4–6-week blocks: high-intensity aerobic 75–85% of max for 45 min + resistance exercise 20 min. 10–12 weeks blocks: endurance exercise 65–75% of max for 60 min + resistance 20 min. Group 2) Wellness-control group ($n = 30$), low-intensity.	QCT-BMD at lumbar spine: decreased less after exercise compared with control. DXA-BMD at lumbar spine: increased after exercise. DXA-BMD Hip: No change.
Fernandez-Real et al. [35] Spain	Study 1) Cross-sectional. Level 4. Study 2) Longitudinal. Level 2b.	1) 149 men 2) 26 women 3) 20 men and women	Men and women 1) Overweight men ($n = 149$), age: 50.2 ± 11.7. 2) Sedentary, obese women ($n = 26$), age: 40–60.	16 weeks. Study 2) 3 groups: - Control ($n = 7$) - Diet ($n = 8$) caloric restriction of 500 kcal/d - Diet and resistance training 2 sessions/week ($n = 11$).	1) Positive association between OC and insulin sensitivity, stronger in lean subjects. 2) Similar weight loss. Osteocalcin increased in exercise group.
Daly et al. [36] Australia	RCT. Level 1b.	26	Overweight, sedentary men and women. Age: 60–80. Non-insulin dependent T2DM with HbA1c 7–10%.	12 months. 2 Groups: 1) High-intensity progressive resistance training of 45 min. 75–85% of max, plus moderate weight loss. 2) Control, moderate weight loss plus flexibility (static stretching) training.	No change in total BMD in group 1 after 6 months. Total BMD decreased by 0.9% in group 2 after 6 months. Total body BMD in both groups decreased after 12 months. Lumbar spine and femoral neck BMD decreased in group 2.
Descriptive data					
Huang et al. [37] Taiwan	Retrospective cohort. Level 2b.	22,048	Men and women. T2DM ($n = 3508$)	Descriptive weekly energy expenditure through exercise: < 500 versus > 500 kcal/week.	Higher hip fracture risk in T2DM (HR 1.64) than non-DM. Decreased hip fracture risk in

Table 1 (continued)

Author Short-term effects of exercise	Design and level of evidence	*N*	Population characteristics	Exercise type	Bone outcome and result
					T2DM when exercising ≥ 500 kcal/week (HR 0.67).
Raska et al. [38] Czech	Cross-sectional. Level 4.	112 T2DM 171 non-DM	Postmenopausal women with and without T2DM. Age, T2DM: 65.6 ± 9.4 Age, non-DM: 64 ± 9.5	Questionnaire of daily walking activity.	Osteoporosis prevalence in T2DM 25%. Sclerostin higher in those with low daily walking activity < 2 h daily compared with those walking > 2 h daily.
Davies et al. [39] Great Britain	Cross-sectional. Level 4.	186 rugby players 5186 controls	Men. Age: > 50 Self-reported physician-diagnosed morbidity.	Former elite rugby players and controls.	Higher prevalence of osteoporosis but lower prevalence of DM among former rugby players.
Nilsson et al. [40] Sweden	Cross-sectional. Level 4.	99 T2DM 954 non-DM	Women. Age: 75–80	Physical function measurement: - 1 leg standing - Chair-stand test - Timed up and go - Walking speed	Higher total BMD in T2DM. Higher cortical porosity in T2DM. Lower physical performance in T2DM.
Paccou et al. [8] Great Britain	Cross-sectional. Level 4.	29 DM 303 non-DM	Men and women. Age: 72.1–81.4.	Self-reported physical activity by interview.	Higher cortical porosity in T2DM men and tendency in women. Equally self-reported physical activity.
Kamalanathan et al. [41], India	Cross-sectional. Level 4.	194 T2DM 262 non-DM	Men and women with and without T2DM. Age: 30–50	Global physical activity questionnaire by WHO.	BMD lower in T2DM than control at the hip and spine Physical activity did not significantly affect BMD.
Melton et al. [42] America, USA	Retrospective cohort. Level 2b.	1964	Men and women. All T2DM, 51% men. Age: 61.7 ± 14.	Physical activity assessment on 6-point scale.	Lower fracture risk with higher physical activity (HR 0.6).
Korpelainen et al. [43] Finland	Retrospective population-based. Level 2b.	1222	Women. Self-reported medical history (T2DM). Age: 70–73	Paffenbarger Questionnaire for physical activity.	Low lifelong physical activity was associated with low BMD (UL calcaneus), high fracture risk (OR 3.7) and DM (OR 0.2). T2DM was associated with low distal radius BMD.
Luis Román et al. [44] Spain	Cross-sectional. Level 4.	92	Spanish men and women. All T2DM, mean age 63.3 ± 9.1. 56 women, 36 men.	Physical activity questionnaire, retrospective.	Exercise habits among 87.5% of those without osteoporosis and only 25% exercise habit among those with osteoporosis. Osteoporosis prevalence of 0.073% among people with T2DM who exercise.

Osteoblasts are primers of bone formation at the resorption site and perform bone mineralization which releases products of formation, e.g., P1NP [52]. In addition to RANKL and sclerostin as regulators of bone, osteoprotegerin (OPG) is produced by osteoblasts and functions as a decoy receptor for RANKL [46, 53].

Osteocalcin (OC) is another osteoblast-secreted protein. OC undergoes decarboxylation and activation by the acidic environment created by osteoclasts in the extracellular matrix [54]. Undercarboxylated OC (ucOC) has been suggested to perform endocrine functions, e.g., inducing insulin expression [54].

Bone-Specific Alterations in T2DM

Impaired bone quality appears to be multifactorial and affected by several modifiable and non-modifiable factors [55]. Compromised insulin pathways in T2DM are assumed to cause a deficit in bone structure, reduced osteoblast activity, and a lower number of osteoclasts [56]. The increased fracture risk in T2DM predominantly pertains to the hip (relative risks approx. 1.4–2.0) [5, 6, 57], but vertebral and humerus fractures are also increased [5, 6, 58, 59]. A central diagnostic criterion of osteoporosis is based on BMD measurements by DXA scan and is defined as a *T*-score below − 2.5 SD [60]. Despite an increased fracture risk, people with T2DM have 5–10% higher BMD than people without T2DM [5, 61]. Thus, diagnosis of fragile bones in people with T2DM is underestimated by BMD and by FRAX [62], which emphasizes the importance of prevention strategies.

Meta-analyses have shown decreased bone turnover in people with T2DM compared with people without DM [63, 64]. This involves decreased circulating levels of CTX, P1NP, and OC and increased OPG and sclerostin [64]. However, bone-specific alkaline phosphatase (ALP) is reported as normal or increased, suggesting that the bone matrix may become hypermineralized in patients with T2DM [65].

Exercise-Induced Metabolic Responses in Bone Tissue

Bone is a metabolically active tissue similar to muscle and adipose tissue [66] and requires flexibility to promote adaptations during mechanical load and increased energy demand [67]. Chronic and acute changes in whole-body metabolism are reported to affect bone turnover [68]. This indicates that bone tissue provides more than just mechanical strength to the body. However, the exercise-induced metabolic response in bone tissue seems to differ from muscle and adipose tissue, mainly depending on mechanical loading [69]. In the following, we evaluate how bone tissue responds when exposed to different types of exercise.

Exercise-Induced Changes in Bone Turnover

Bone tissue is commonly believed to respond to mechanical load by stimulation of the mechanosensors of the osteocytes. However, short-term studies report bone turnover markers to be affected in response to not only acute weight-bearing [19, 70–72] but also non-weight-bearing [73, 74] and resistance [26•, 75] exercise.

It is generally accepted that sclerostin expression in rodents decreases in response to loading and increases in response to inactivity [49, 76, 77]. One study reports increases in CTX and sclerostin 5 min after both weight-bearing and non-weight-bearing exercise based on intensity-matched interval exercise on either bike or treadmill in healthy young men [78]. The same study also reported a return of both sclerostin and CTX to baseline after 1 and 28 h of rest, respectively. However, the increase in sclerostin observed 5 min after exercise may reflect a release of stored sclerostin rather than increased production (Fig. 1). In humans, the majority of long-term studies report decreasing sclerostin levels in response to exercise, e.g., based on self-reported physical activity (minutes per week), after 2 months of moderate exercise 120 min four times per week [79], after 12 months of resistance or jump exercise three times a week [70], or after 12 weeks of cardio exercise [80]. All of these studies collected blood samples in the fasted state and after a minimum of 12 h following the last exercise session.

An acute aerobic exercise session, e.g., 80–90% of maximal capacity, seems to increase the circulating bone resorption marker CTX with no significant response in the formation marker P1NP in healthy participants [71, 73, 81, 82]. However, circulating P1NP is also found to increase in response to exercise [81, 83] (Fig. 1). Alkahtani et al. reported increased levels of P1NP after running at 60% of maximal capacity for 40 min independent of running flat or downhill. P1NP levels returned to baseline after 24 h [83•]. No differences in CTX were observed immediately or 24 h after exercise.

The high-intensity exercise study did not observe any difference in P1NP [78], suggesting that high-intensity exercise favors immediate bone resorption, whereas moderate-intensity exercise favors bone formation (Fig. 1). This is supported by increased resting levels of P1NP 1 month after moderate endurance exercise for 90 min 3–4 times a week compared with before exercise and compared with sedentary controls [84].

A randomized controlled trial (RCT) including healthy men with osteopenia (*T*-score between − 1.0 and − 2.5) estimated bone turnover markers after 6 months of supervised jumping or resistance exercise [19]. The authors reported increased OC after 6 months and a further increase after 12 months in both interventions [19] (Fig. 1). In addition, the study reported a reduction in CTX after 6 months and a return to baseline after 12 months.

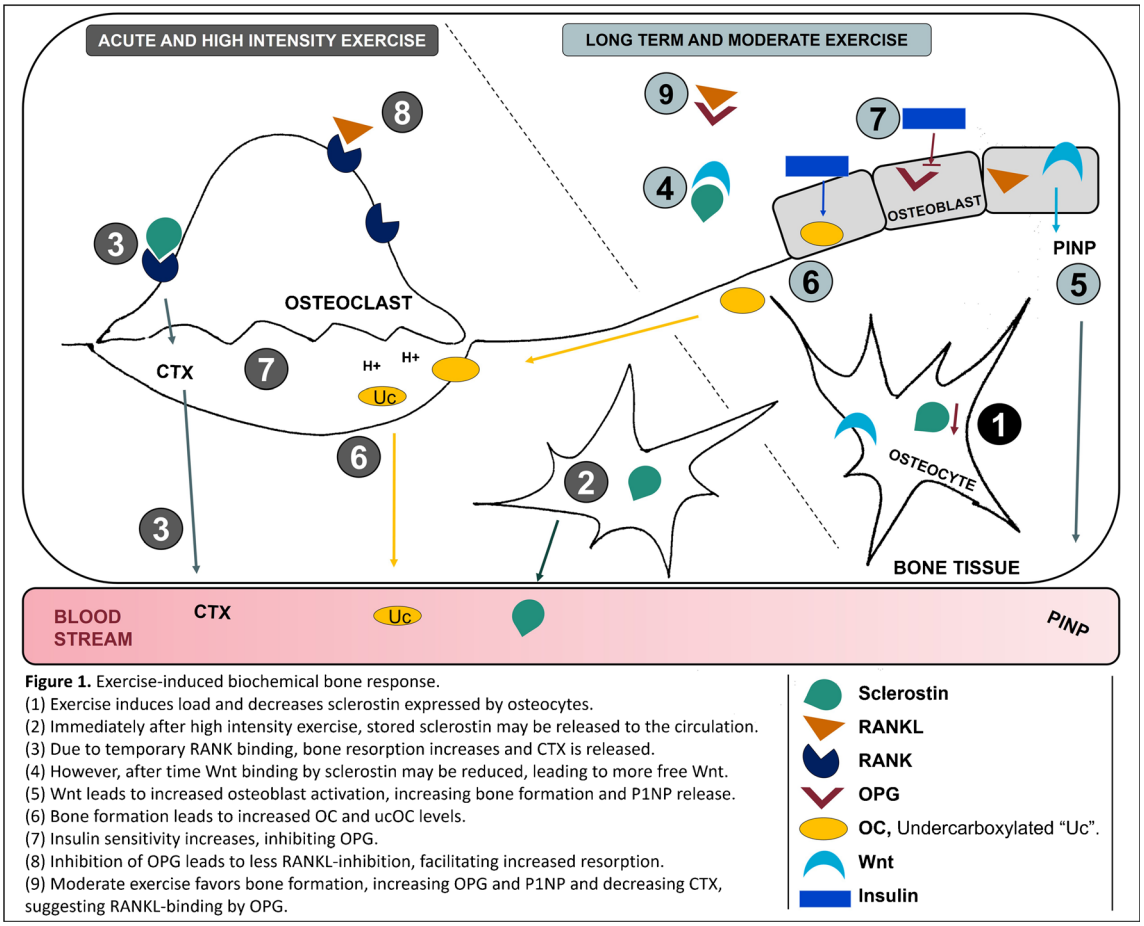

Figure 1. Exercise-induced biochemical bone response.
(1) Exercise induces load and decreases sclerostin expressed by osteocytes.
(2) Immediately after high intensity exercise, stored sclerostin may be released to the circulation.
(3) Due to temporary RANK binding, bone resorption increases and CTX is released.
(4) However, after time Wnt binding by sclerostin may be reduced, leading to more free Wnt.
(5) Wnt leads to increased osteoblast activation, increasing bone formation and P1NP release.
(6) Bone formation leads to increased OC and ucOC levels.
(7) Insulin sensitivity increases, inhibiting OPG.
(8) Inhibition of OPG leads to less RANKL-inhibition, facilitating increased resorption.
(9) Moderate exercise favors bone formation, increasing OPG and P1NP and decreasing CTX, suggesting RANKL-binding by OPG.

Fig. 1 Exercise-induced biochemical bone response. (1) Exercise induces load and decreases sclerostin expressed by osteocytes. (2) Immediately after high-intensity exercise, stored sclerostin may be released to the circulation. (3) Due to temporary RANK binding, bone resorption increases and CTX is released. (4) However, after time Wnt binding by sclerostin may be reduced, leading to more free Wnt. (5) Wnt leads to increased osteoblast activation, increasing bone formation and P1NP release. (6) Bone formation leads to increased OC and ucOC levels. (7) Insulin sensitivity increases, inhibiting OPG. (8) Inhibition of OPG leads to less RANKL inhibition, facilitating increased resorption. (9) Moderate exercise favors bone formation, increasing OPG and P1NP and decreasing CTX, suggesting RANKL binding by OPG

Findings concerning the impact of exercise on bone turnover markers are conflicting and depending on exercise type and duration of exercise intervention as well as timing of the sample collection. However, the majority or studies suggest that bone resorption markers respond to acute and high-intensity exercise and swiftly return to baseline. In contrast, the long-term effects of exercise reported are in favor of bone formation possibly by decreased sclerostin levels (Fig. 1).

Exercise-Induced Effects on Bone Structure

The International Osteoporosis Foundation states that a 10% loss of spine BMD doubles the risk of vertebral fractures and a 10% loss of hip BMD increases fracture risk in the hip by a factor of 2.5 [2]. Walking is shown to prevent age-related reduction in hip BMD, although it does not affect spine BMD [85, 86]. The previously cited RCT by Hinton et al. found a 0.6% increase in whole-body BMD and a 1.3% increase in spine BMD after 6 months, which was maintained after 12 months in both exercise groups (jumping or resistance) [19]. Total hip BMD was only increased (0.8%) in the resistance exercise group after 6 months with no further improvement after 12 months [19].

It is estimated that a combination of aerobic and resistance exercise reduces BMD loss in both spine and hip by 3.2% and 1.0%, respectively [11]. Approximately 60% of the variation in bone strength can be attributed to variation in BMD, measured by DXA [87]. More recent measuring methods have reported the natural age-related bone loss to be located in cortical bone rather than trabecular bone: a distinction which cannot be made by DXA [88, 89]. Resistance exercise is reported to increase cortical bone density measured by peripheral quantitative computed tomography (pQCT) [90, 91]. The high-resolution pQCT (HRpQCT) enables more accurate estimation of trabecular and cortical bone structure. However, the use of HRpQCT in exercise intervention studies is sparse. Thus, RCTs estimating changes in bone microstructure in response to exercise are warranted.

Exercise-Induced Effects on Bone Compartments

Haddock et al. investigated the metabolic and hemodynamic responses to exercise in healthy volunteers using whole-body positron emission tomography (PET) and magnetic resonance imaging (MRI) [92•]. They measured bone [^{18}F]NaF-uptake and fitted time-activity curves to a three-compartment (one of which represents fluoride binding into the bone matrix) tracer kinetic model, whereby they could estimate bone mineralization using non-linear regression. They reported a higher resting mineralization in trabecular than in cortical bone. However, after a stepping exercise producing a higher strain on the left than on the right leg, bone mineralization increased in cortical bone and decreased in trabecular bone with no difference between left and right leg.

Bone marrow is another important facilitator of bone remodeling. Heinonen et al. found increased bone marrow glucose uptake during exercise using PET and tracer technique [93•]. Additionally, they found increasing glucose uptake in bone marrow with increasing exercise intensity but with no significant difference between moderate and high intensity. Furthermore, the ratio between glucose uptake in bone marrow and muscle tissue decreased significantly with higher exercise intensity from less than a half to less than one-third, indicating glucose uptake in favor of muscles rather than bone during higher-intensity exercise.

The ability of tracer techniques to reveal direct bone metabolism in response to exercise may enable further knowledge of the bone-specific metabolic differences or inconsistent response between trabecular and cortical components. These changes may identify regional differences or improper responses to external stimuli inside bone that may not be detectable by neither circulating markers nor structural imaging.

The Potential of Bone-Induced Effects on Glucose Metabolism

OC and ucOC are found to increase in men in response to acute high-intensity exercise [23] as well as after long-term exercise [33, 94] (Fig. 1). Some studies report that ucOC, but not total OC, increases acutely after exercise and correlates positively with insulin sensitivity [23, 35], although another study found no change in OC after 12 weeks of exercise [32]. Insulin may also inhibit expression of OPG in osteoblasts and thereby stimulate bone resorption resulting in lower pH at the resorption sites [12] (Fig. 1). Low pH allows decarboxylation and activation of OC (Fig. 1). Still, the evidence for an effect of ucOC on glucose metabolism in humans is very limited and the hypothesis is based on an animal model [95] which is not sufficiently supported by human trials.

The Effect of Exercise on T2DM and Bones

Low cardiorespiratory fitness is an independent predictor of mortality in people with T2DM [15, 96]. Today, weight loss achieved through diet and exercise is a standard recommendation when encountering a newly diagnosed T2DM patient [97]. A common goal is 150 min of exercise per week [98]. However, exercise per se is not necessarily beneficial for all metabolic compartments, e.g., muscle, adipose, and bone tissue. Contrarily, patients with osteoporosis are recommended to ensure adequate nutrient intake and specifically weight-bearing exercise, as the osteoporosis phenotype is often quite different from the patient with T2DM. The effect of exercise on bone health is not only determined by the mechanical load and type of exercise but also by substrate metabolism, insulin sensitivity, and glucose disposal. In the following, effects of exercise on bone health in patients with T2DM will be discussed.

Exercise as a Hindrance to or Facilitator of Bone Loss in T2DM

Low lifelong physical activity appears to be associated with lower BMD, higher fracture risk, and T2DM in one study [43], but another study reports no effect of physical activity on BMD in T2DM based on WHO questionnaires [41]. Large cohort studies not only confirmed the increased fracture risk among men and women with T2DM but also reported that those with higher physical activity had lower fracture risk [37, 42]. A cross-sectional study on former rugby players found lower prevalence of T2DM but higher prevalence of osteoporosis [39]. A small RCT ($n = 14$) did not find any difference in BMD after 32 weeks of aerobic or resistance exercise in postmenopausal women with prediabetes [31]. Another study reported that healthy exercise habits were associated with higher BMD in patients with T2DM [44]. However, Nilsson et al. confirmed higher BMD (DXA-scan) and cortical porosity (HRpQCT) among elderly women with T2DM but interestingly found reduced physical performance, i.e., walking speed and one-leg standing, compared with people without T2DM [40]. In addition, Nilsson et al. only included elderly women aged over 75 years and found a significantly higher BMI among participants with T2DM. Paccou et al. estimated volumetric BMD (vBMD) by HRpQCT in people with and without T2DM with equal self-reported physical activity [8]. They reported higher cortical bone density, pore volume, and porosity in participants with T2DM compared with those without T2DM [8].

Skoradal et al. performed a mixed-gender RCT investigating the effect of soccer on bone health in elderly people with prediabetes [24••]. Femoral (neck, trochanter, and shaft) and lumbar spine BMD increased by 2.5–3.9% after soccer training 30–60 min twice a week for 16 weeks. As a combination

of aerobic exercise and mechanical load, soccer may be an easily accessible exercise type to improve bone health in weight-bearing sites, i.e., spine and hip. However, it is possible that the majority of patients with diagnosed T2DM have physical limitations. Thus, soccer may be related to greater risk of falling and injuries, overturning the beneficial effects on bone structure.

Vibration may be an effective exercise form in T2DM patients with physical limitations. It is found to effectively improve lumbar spine and femoral neck BMD in people without DM [20]. In patients with T2DM, vibration exercise has been suggested to enhance glycemic control and decrease HbA1c [99]. However, studies on humans are sparse and the evidence is mostly based on animal trials [100].

These conflicting results may be caused by different methods of assessment of physical performance in (e.g., questionnaires [44] versus tests [40]). Even though BMD loss can be reduced in elderly, it is possible that physical activity during adolescence is an important factor to prevent BMD loss during adulthood.

Prevention of Bone Loss During Weight Loss

In 2005, Daly et al. reported that progressive resistance training in patients with T2DM should be combined with dietary modification in order to prevent a decrease in BMD [36].

An RCT by Courteix et al. reported beneficial and protective effects of exercise in participants with metabolic syndrome (MetS) who were compliant to the exercise program [29]. This was quantified by a reduction of bone loss during weight loss in participants compliant with the exercise intervention compared with those who were non-compliant [29]. An RCT by Beavers et al. investigated structural and biochemical bone alterations in people with MetS exposed to weight loss alone or in combination with either aerobic or resistance exercise [25••]. The planned weight loss was 0.3 kg/week with a total of 7–10% body weight loss over 18 months. The exercise sessions were either aerobic by walking or resistance exercise for 45 min four times a week. They observed a greater weight loss when dietary intervention was combined with exercise. Furthermore, they reported a significant reduction in total hip BMD by 2% in all groups after 18 months of intervention. However, after 30 months, they observed an increased lumbar spine BMD and attenuated BMD loss in the hip in the resistance exercise group but not in the aerobic exercise group. Estimation of vBMD by computed tomography (CT) scan suggested a beneficial effect in the resistance exercise group by a smaller reduction in vBMD [25••] which was supported by another RCT [34]. They did not observe any differences in bone turnover markers [25•]. Thus, resistance exercise enabled bone tissue to adapt to whole-body requirements and maintain bone mass despite whole-body weight loss. However, it seems that a significant loss of BMD persists in the first year following a weight loss intervention in obese adult [101]. It is possible that bone loss in obese people after diet-induced weight loss can be prevented by GLP-1 receptor agonists, a commonly used drug in the treatment of T2DM [102].

The Look AHEAD trial has previously confirmed a significant bone loss at the hip and spine in both men and women with T2DM after 1 year of intensive lifestyle intervention including weight loss and physical activity [27••]. After 3 years of weight maintenance, the bone loss proceeded in the hip in men but not in women [27••]. Further analyses revealed a 39% increased risk of frailty fracture but no difference in incident fracture risk [28]. This observed increase in risk of frailty fractures was mainly driven by pelvic and hip fractures and may be due to falls related to the physical activity. However, the absolute number of frailty fractures was relatively low [28].

Obesity is a major burden in T2DM, but it seems that intensive weight loss induces bone loss years after the intervention and may even increase the risk of fragility fractures. However, the addition of weight-bearing exercise may induce an osteogenic response, adaptation, and the ability to maintain bone mass and prevent fractures despite whole-body weight loss.

Exercise-Induced Biochemical Bone Responses in T2DM

Human studies on the acute effect of exercise on bone turnover markers in subjects with T2DM are sparse [22, 38]. Borer et al. designed a study on postmenopausal women with T2DM to reveal the effects of meals on the osteogenic response before and after up- and downhill treadmill exercise [22••]. They did not find any differences in CTX. However, they found higher circulating levels of C-terminal propeptide of type I collagen (C1CP), a marker of bone formation, after up- or downhill exercise 60 min after a standardized meal compared with the same exercise in the fasting state: with the highest levels measured after the uphill exercise. Rŏska et al. reported that women with T2DM and daily walking activity less than 2 h had higher sclerostin levels compared with those walking more than 2 h daily [38].

Exercise enhances insulin sensitivity and improves glycemic control in patients with T2DM [103–105], both after aerobic [106] and resistance exercise [107]. However, the effect is most pronounced when a combination is used, suggesting a synergistic effect between aerobic and resistance exercise when treating people with T2DM [105, 108]. Hur et al. reported increased circulating levels of OPG in women with MetS after moderate resistance exercise 3 days a week for 5 weeks with an additional decrease in HOMA-IR [26•] (Fig. 1). Borer et al. reported a lower HOMA-IR after uphill exercise following a meal compared with an equivalent downhill exercise

[22••]. Furthermore, they discovered a delayed rise in the ratio of C1CP/CTX when exercising uphill compared with downhill. This finding may be an expression of increased muscle energy expenditure in the beginning of uphill exercise, compared with the lower cardio-respiratory intensity and higher mechanical load on the skeleton during downhill exercise. The rise in cardio-respiratory requirement may favor muscle energy supply compared with bone [93•]. However, a T2DM rat model suggests that non-weight-bearing exercise, e.g., swimming, may mitigate suppressed bone turnover based on higher RANKL/OPG levels [109] (Fig. 1).

In addition to higher BMD after 16 weeks of soccer training in participants with prediabetes, Skoradal et al. found 23–52% increased bone turnover markers, i.e., osteocalcin, CTX, and P1NP, after the intervention period [24••]. The ratio between P1NP and CTX also increased with no changes observed in the control group. This indicates a stimulated bone formation relative to bone resorption and an anabolic response to the combined weight-bearing and aerobic exercise intervention.

In summary, the biochemical bone response to exercise is poorly investigated in T2DM. However, it seems that sclerostin decreases after exercise along with increasing formation markers. In addition, aerobic exercise with high cardio-respiratory requirement may benefit muscle tissue in favor of bone remodeling compared with a bone-protective effect after low-intensity or combined aerobic and resistance exercise.

Discussion

Exercise has proven pivotal in the prevention and treatment of both T2DM and osteoporosis. A study including 450 participants with T2DM identified that over 70% had knowledge about the effect of exercise in prevention of osteoporosis [110]. However, only half of the population identified weight-bearing exercise as important [110]. Based on the current evidence, the optimal osteogenic stimulus in people without T2DM seems to be obtainable with a combination of both resistance and aerobic exercise. This is similar to the effect on glycemic control, suggesting a synergistic effect [105, 108]. However, clinical trials investigating effects of exercise on bone-specific outcomes in people with T2DM are sparse. Thus, this review is limited by the number of published studies.

Bone resorption appears to be stimulated shortly after exercise by increased levels of sclerostin and CTX (both aerobic and weight-bearing) in healthy adults. Knowledge about the short-term effects of exercise in T2DM is sparse. However, two studies [22, 23] report increased bone formation compared with resorption. The overall long-term effects of exercise in people with T2DM seem to be driven by an increase in bone turnover in favor of formation, e.g., decreased sclerostin, increased P1NP/CTX-ratio, and increased BMD.

The combination of increased hip fracture risk and weight loss–associated BMD loss at the hip is troublesome in patients with T2DM. Hip BMD benefits from resistance exercise and walking more than spine BMD does. This may explain why physical activity (and not exercise per se), e.g., walking, has been shown to reduce hip fractures in both men and women [2]. Intensive weight loss in patients with T2DM may benefit from accompanying resistance exercise to reduce bone loss.

The presented studies include data on both men and women and on both structural and biochemical bone outcomes. Most of the current knowledge on bone health is based on BMD measurements by DXA scans. Only one of the presented intervention studies measured bone microstructure [34], and only one study reported data on biochemical bone measurements in participants diagnosed with T2DM after an exercise intervention [22••]. However, increased cortical porosity may be an important estimate when appraising bone health in patients with T2DM [8]. Thus, studies investigating the long-term effects of exercise on bone microstructure, e.g., by HRpQCT, are warranted. Currently, results from an RCT comparing standard T2DM care with a supervised exercise program for 2 years regarding bone-related outcomes are awaited [111].

The exercise protocols differ greatly among the included studies, e.g., exercise intensity, duration, and mechanical load, making it difficult to compare study results. Meta-analyses of graded exercise intensities in T2DM patients found that both aerobic and resistance exercise with higher intensity resulted in greater reduction in HbA1c compared with lower intensity exercise studies [17, 112, 113]. However, the presented results mainly include participants with prediabetes or MetS and cannot conclude if current weight loss recommendations and exercise strategies are sufficient in order to prevent bone loss in T2DM. Future studies investigating the effect of exercise on bone health in T2DM could simplify the exercise modality by focusing on the known beneficial effects on glycemic control and test if this applies to bone outcomes. Hence, exercise intervention RCTs on T2DM patients including measurements of bone markers, e.g., CTX, P1NP, and sclerostin, and bone microstructure are of great interest. The measurements of bone markers should be performed in a standardized steady state along with microstructural measurements before and after a minimum of 3-month intervention period. Lastly, it would be interesting to test if anti-diabetic drugs, e.g., GLP-1 receptor agonists and metformin, impact the potential exercise-induced protective effects on bones in T2DM.

In conclusion, the evidence behind the beneficial effects of aerobic exercise and weight loss on physical health and glycemic control in people with T2DM is persuasive. Weight-bearing exercise during weight loss is paramount in the prevention of bone fragility and fractures. Thus, when guiding

patients with T2DM, it may be favorable to encourage a combination of weight-bearing aerobic and resistance exercise, e.g., downhill running, jumping, or alternating mechanical loading sessions, as well as ensuring adequate nutrition supply prior to the exercise session. Personalized diet and exercise strategies that favor both metabolic and bone health are advisable in order to reduce bone loss and fracture risk in people with T2DM.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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