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Review

Complex interplay among adiposity, insulin resistance and bone health

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Summary

Obesity and osteoporosis are common public health problems. Paradoxically, while obesity is associated with higher bone density, type 2 diabetic obese individuals have an increased fracture risk. Although obesity and insulin resistance co-exist, some obese individuals remain insulin-sensitive. We suggest that the apparent paradox relating obesity, bone density and fracture risk in type 2 diabetes may be at least partly influenced by differences in bone strength and quality between insulin-resistant and insulin-sensitive obese individuals. In this review, we focus on the complex interplay between, adiposity, insulin resistance and osteoporotic fracture risk and suggest that this is an important area of study that has implications for individually tailored and targeted treatment to prevent osteoporotic fracture in obese type 2 diabetic individuals.

Keywords: Adiposity, insulin resistance, osteoporotic fracture.

Introduction

Obesity is a major public health problem around the world. In Australia, approximately 25% of adults are obese (body mass index [BMI] ≥ 30 kg m^{-2}) (1). Obesity is associated with an increased risk of many metabolic diseases, including type 2 diabetes, hypertension, dyslipidemia and cardiovascular disease, as well as cancer (2, 3). Obesity also poses a financial burden because of its chronic nature (1).

Osteoporosis is another common health problem that imposes a significant economic burden. It has been estimated that the residual lifetime risk of fracture is 44% for women and 25% for men >60 years (4).

Obesity and type 2 diabetes are associated with relatively normal or even high bone density (5, 6). Paradoxically, obese individuals, especially those with type 2 diabetes, have an increased fracture risk, greater than that predicted from their bone density (7). In addition, obesity extends length of hospital stay, reduces functional recovery and impairs quality of life after fracture (8).

A growing amount of evidence suggests that bone is an insulin-target tissue and a possible determinant of glucose and energy homeostasis (9). Obesity, particularly central obesity, is closely linked with insulin resistance (10). Although insulin resistance and obesity co-exist, some obese individuals remain insulin-sensitive with low abdominal visceral fat (11–13). In recent years, several studies have suggested that obesity, particularly visceral adiposity, is associated with increased fracture risk, particularly in women (14–16). This relationship appears to be independent of total adiposity, as has been illustrated in a recent study that reported that increased fat mass and percent body fat were positively associated with bone mineral density (BMD), whereas increased central fat had an inverse

association with BMD in females with obesity (17). The apparent paradox among obesity, visceral adiposity, bone density and fracture risk may be related to differences in bone strength and quality between insulin-resistant and insulin-sensitive individuals. In this review, we discuss the complex interplay among adiposity, insulin resistance and osteoporosis.

Methods

We conducted a literature search in PubMed using the keywords 'adiposity', 'insulin resistance' and 'osteoporotic fracture'.

Insulin-resistant and insulin-sensitive obesity

Obesity is closely linked with insulin resistance, a state of decreased responsiveness to the effects of insulin. A compensatory consequence of insulin resistance is hyperinsulinemia, due to both an increase in insulin secretion and a decrease in insulin clearance rate (18). Metabolic abnormalities and cardio-metabolic risk vary among obese individuals, with a proportion of individuals with obesity considered to be 'metabolically healthy'. We have previously argued that this apparently protective phenotype should be defined by the presence of insulin sensitivity in the face of excess adipose tissue ('insulin-sensitive obesity'), rather than by the more commonly used definition based on the absence of features of the metabolic syndrome ('metabolically healthy obesity') (13). Compared to insulin-resistant individuals, insulin-sensitive obese individuals have favourable metabolic features, including lower inflammatory state (measured by circulating C-reactive protein and adiponectin), lower liver and visceral fat, and preserved adipose tissue insulin sensitivity (12, 19, 20). Obese insulin-resistant individuals have a distinct adipose tissue profile, i.e., metabolically dysfunctional. For example, adipose tissue genes regulating inflammation, hypoxia and extracellular matrix formation were up-regulated in obese insulin-resistant individuals compared with obese insulin-sensitive individuals (21). Furthermore, insulin resistance *per se* correlated with circulating pro-inflammatory adipokines (monocyte chemoattractant protein-1 [MCP-1], interleukin-6 [IL-6] and resistin), more so than obesity (22). Dysfunctional adipose tissue may be detrimental to bone health.

Obesity, fat distribution and bone health

Although obesity may be considered beneficial to bone health, with higher BMD being associated with higher weight (23–26), the relationship between excess body fat and osteoporotic fractures is more complex. Several recent studies have challenged the widespread assertion that obesity is protective against osteoporosis, suggesting that obesity is instead a risk factor for certain fractures (27–29).

The relationship between obesity and fracture risk may be determined by body fat distribution (28, 29). As mentioned above, visceral fat is closely correlated with insulin resistance. Waist circumference is a surrogate marker of abdominal fat and BMI is a marker of overall adiposity. In one study, although hip fracture risk was inversely associated with BMI it was positively related to waist circumference, suggesting that central fat distribution, rather than adiposity *per se*, is predictive of fracture risk (27). In both the Nurses' Health Study and the Health Professionals Follow-up Study, waist circumference and waist-to-hip ratio were associated with hip fracture risk in women, but not in men (28). In a cohort from Norway, central adiposity correlated with hip fracture risk in both genders, particularly in those with lower total body fat (29). These results suggest that fracture risk may be more closely related to insulin resistance and intra-abdominal adiposity, rather than total fat mass.

Insulin resistance and bone health

The association between obesity and BMD is tempered by insulin resistance, which is associated with lower BMD. Indeed, accumulating clinical and experimental evidence suggests that insulin resistance, mediated by its association with visceral fat, may contribute to the pathophysiology of osteoporosis. In a cross-sectional study from the Korea National Health and Nutrition Examination Survey, femoral neck strength worsened with increasing quartiles of the homeostatic model assessment of insulin resistance (HOMA-IR), a surrogate measure of insulin resistance (30). In a study by Shin *et al.*, individuals in the lowest quartile of HOMA-IR (i.e. the most insulin-sensitive) exhibited a positive association between fasting plasma insulin and BMD, while those in the third and fourth HOMA-IR quartiles (the most insulin-resistant) showed inverse associations with BMD (31).

The trabecular bone score (TBS) is a parameter of bone texture evaluating pixel grey-level variations in dual-energy X-ray absorptiometry images of the lumbar spine. The TBS is an indirect independent measure of bone quality. Low TBS reflects worse bone quality and impaired microarchitecture. In a study by Kim *et al.*, TBS was inversely related with HOMA-IR, albeit in individuals with diabetes, in whom HOMA-IR is a poor surrogate of insulin resistance (32). Similarly, in a study by Iki *et al.*, TBS was negatively associated with hyperglycemia and insulin resistance (33).

Microindentation and high-resolution peripheral quantitative computed tomography (HR-pQCT) are two other methods to evaluate bone quality. Microindentation is an indicator of bone stiffness. Reference point indentation is one measurement method of microindentation. HR-pQCT

at the radius and tibia provides measures of volumetric density, bone structure and microarchitecture. Bone material strength index by reference point indentation was lower in women with type 2 diabetes compared with leaner non-diabetic women (34). In the Framingham HR-pQCT Study, patients with type 2 diabetes had lower cortical volumetric BMD, higher cortical porosity and smaller cross-sectional area at the tibia (35). These structural deficits may contribute to fracture risk in type 2 diabetes. These findings suggest that low levels of insulin seen in insulin-sensitive individuals may be associated with positive bone effects, or that insulin resistance is associated with reduced bone quality, potentially a direct negative effect of insulin (36).

Bone homeostasis is the balance between the bone-forming osteoblasts and the bone-resorbing osteoclasts. Both cells express insulin receptors (9, 37). Insulin is essential for proliferation, survival and differentiation of osteoblasts and osteoclasts by regulating specific genes (37, 38). Mice lacking osteoblast insulin receptor exhibit impaired postnatal bone formation (38). High-fat fed rats exhibit osteoblastic insulin resistance, resulting in shorter osteoblastic survival (39).

Insulin-resistant obese individuals exhibit a more systemic pro-inflammatory phenotype than insulin-sensitive individuals (40). Indeed, pro-inflammatory cytokines, particularly interleukin-1 (IL-1), IL-6 and tumour necrosis factor-α (TNF-α), are proposed to act as bone resorptive factors stimulating osteoclastic maturation and activation. IL-1 promotes osteoclast precursor fusion, enhancing differentiation of osteoclasts. IL-1 enhances survival of mature osteoclasts in animal models (41). Furthermore, In animals, TNF-α causes loss of bone by up-regulating sclerostin (42). Sclerostin is a secreted 213 amino acid glycoprotein with anti-anabolic effects on bone formation (43). Together, the pro-inflammatory cytokines form a bone resorptive milieu, as has been reported in mouse osteoclast-like cells (44). In humans, the risk of hip fracture in women was related to the soluble receptors (SRs) for IL-6 and TNF (TNF SR1 and TNF SR2) (45, 46). In summary, low-grade inflammation, most likely a *consequence* of insulin resistance, may contribute to bone loss in type 2 diabetes.

Bone turnover, insulin kinetics and whole-body glucose homeostasis

Biochemical markers of bone remodelling include the resorption markers C-telopeptide (CTX), N-telopeptide (NTX) and tartrate-resistant acid phosphatase 5b (TRACP 5b); and the formation markers serum bone-specific alkaline phosphatase (BSAP), osteocalcin (OC) and procollagen type 1 N-terminal propeptide (P1NP). In adults, bone turnover occurs through bone remodelling, which involves the coupled activity of osteoblasts and osteoclasts. While high bone turnover is associated with increased bone loss and fractures, renal failure-related adynamic bone disease, a state of low bone turnover, is also associated with increased fracture risk (47). Hence, both high and low bone turnover are associated with deficits in bone microarchitecture and increased stiffness (48). Bone turnover may predict fracture risk independent of BMD, although this requires further study (49).

It is possible that the hyperinsulinemic state that develops in non-diabetic insulin resistance, and insulin therapy in type 2 diabetes, contributes to poor bone quality, and hence, fracture risk, by suppressing bone turnover. In men with type 2 diabetes, increased fracture rate was limited to those treated with insulin (50). In another study, obese hyperinsulinemic volunteers had bone turnover markers that were 17–40% lower than lean gender- and age-matched controls (51). Our group reported that insulin-resistant overweight and obese individuals had lower circulating bone turnover markers than age-matched insulin-sensitive individuals (insulin sensitivity was assessed by both HOMA-IR and hyperinsulinemic–euglycemic clamp) (36). Bone turnover marker levels correlated inversely with fasting insulin levels and visceral adiposity as measured by computed tomography, suggesting that insulin resistance itself may lower bone turnover, possibly via insulin (36).

Some studies have reported an association between serum BSAP levels and glucose metabolism and insulin kinetics (Table 1). BSAP positively correlated with β-cell function, evaluated by the homeostatic model assessment of beta-cell function (HOMA-β) (52). However, there was no significant association between BSAP and fasting plasma glucose or glycated haemoglobin (haemoglobin A1c, HbA1c) in non-diabetic and type 2 diabetic participants (52, 53).

It has been suggested that bone insulin resistance may affect whole-body glucose homeostasis via lower osteocalcin (OC) activity (54). In one study, glycemia was inversely associated with OC (55). In a meta-analysis, OC was associated with HOMA-β and inversely correlated with HbA1c, fasting plasma glucose, HOMA-IR, central obesity and the metabolic syndrome (56–61). Another study reported that higher OC concentration was associated with lower HbA1c in a cohort with type 1 diabetes (62). OC is produced from mature osteoblasts and activated in the low pH of the resorption lacunae. Insulin may regulate OC bioactivity via insulin receptors on osteoblasts (63). Conversely, OC has been reported to influence β-cell proliferation, insulin secretion, insulin sensitivity and adiponectin expression (64), possibly through GPCR6a receptors in β-cells (65).

In another study, P1NP was inversely associated with fasting glucose and HbA1c, and positively associated with HOMA-β, although there was no correlation with HOMA-IR (66). A prospective study failed to demonstrate the predictive power of circulating OC on diabetes development (67).

Table 1 Bone turnover markers, and whole-body glucose homeostasis and insulin sensitivity

Bone turnover marker	Description	Possible effect on whole-body glucose homeostasis
Bone formation		
BSAP	Isoform of ALP on osteoblasts membrane that hydrolyses pyrophosphate and promotes tissue mineralization	1. Positively associated with insulin resistance and β-cell function (52) 2. Negatively associated with insulin sensitivity (52) 3. No significant association among BSAP, and fasting glucose and HbA1c (52, 53)
OC	A non-collagenous protein secreted by osteoblasts that is a constituent of bone extracellular matrix	1. Positive association with HOMA-β (56) 2. Associated with lower HbA1c, fasting plasma glucose levels, HOMA-IR, central obesity and metabolic syndrome (56–61)
P1NP	Extension peptide removed during collagen deposited into matrix	1. Inversely associated with fasting glucose and HbA1c (66) 2. Positively associated with HOMA-β (66) 3. No significant association between P1NP and HOMA-IR (66)
Bone resorption		
CTX	Peptide fragment of collagen released during bone resorption	CTX lower among diabetes patients (68, 69, 71)
NTX	Peptide fragment of collagen released during bone resorption	NTX not lower in type 2 diabetes (71)
TRACP 5b	Osteoclast-specific lytic enzyme	No association between TRACP 5b and HbA1c, fasting plasma glucose and insulin levels (57, 72)

ALP, alkaline phosphatase; BSAP, bone-specific alkaline phosphatase; CTX, C-terminal telopeptide; HbA1c, glycated haemoglobin A1c; HOMA-β, homeostatic model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; NTX, N-terminal telopeptide; OC, osteocalcin; P1NP, procollagen type 1 N-terminal propeptide; TRACP 5b, tartrate-resistant acid phosphatase 5b.

Findings are less consistent for bone resorption markers. Jiajue *et al.* (68) and Yamamoto *et al.* (69) reported that CTX levels were lower in individuals with impaired fasting glucose and type 2 diabetes compared to a normoglycemic group. However, Shu *et al.* found that CTX and NTX were unaffected by type 2 diabetes status (70). A meta-analysis reported that CTX levels were significantly lower in diabetes vs. non-diabetes; however, NTX was not different between the groups (71). No association was found between TRACP 5b and HbA1c, fasting plasma glucose and insulin concentrations (57, 72).

In a prospective study, higher bone remodelling correlated with protection from diabetes (73). Diabetes was associated with suppressed bone turnover, which may explain increased fracture risk, independent of BMD (68).

In summary, studies have demonstrated interrelationships between bone turnover and whole-body glucose homeostasis. Insulin may impact bone metabolism. Bone turnover markers may play a role in influencing whole-body glucose homeostasis, although the direction of association in humans remains unclear. These hormones may be important in linking insulin resistance and diabetes with metabolic bone disease.

Effects of exercise and diabetic therapies on bone health and fractures

As discussed above, previous studies suggest that there is an interplay between insulin resistance, insulin itself, abdominal adiposity and various aspects of bone biology. This has led to studies investigating the effects of diabetes medications that affect insulin resistance and insulinemia, and other factors affecting whole-body insulin resistance and glucose regulation, including exercise, on bone turnover, bone density and fracture risk (Table 2).

Exercise

Weight bearing exercise preserves bone strength (74) while improving insulin sensitivity (75, 76). Exercise improved insulin sensitivity and reduced bone loss in Otsuka Long-Evans Tokushima Fatty Rats (77). Both acute bouts of exercise and long-term training improved insulin sensitivity and increased serum OC in obese men (78, 79). Improved insulin sensitivity with exercise is associated with a change in OC (80). It remains unclear as to whether the exercise-induced effects on insulin sensitivity increase bone formation, or vice versa.

Metformin

Metformin, a biguanide, has been used to treat diabetes mellitus for many decades (81). It is widely employed as the first-line type 2 diabetes medication (82). Its mechanism of action largely remains unknown, but reduction in hepatic glucose output and enhancement of peripheral glucose uptake have been suggested (83) via activation of adenosine monophosphate-activated protein kinase (AMPK) (84). Adipose tissue AMPK activity is lower in insulin-resistant vs. insulin-sensitive obese individuals (85).

Table 2 Effect of exercise and anti-diabetic therapies on bone health and fractures

Anti-diabetic therapy	Associations with bone health and fractures
Exercise	Improves bone health (77–80)
Metformin	Improves bone health and reduces fracture risk (87–90)
Thiazolidinediones	Increase fracture risk (93)
Dipeptidyl peptidase-4 inhibitors	May reduce fracture risk (99)
Sodium glucose co-transporter-2 inhibitors	Canagliflozin, but none of the other SGLT-2 inhibitors, associated with increased fracture risk (103–105)
Glucagon-like peptide-1 receptor agonists	Liraglutide may reduce and exenatide may increase fracture risk (109)
Insulin	Increases fracture risk (111)

SGLT-2, sodium glucose co-transporter-2.

Interestingly, AMPK activation plays a central role in the regulation of bone formation and bone mass. Both cortical and trabecular bone were smaller in the AMPK α-1-deficient mice compared to the wild type mice (84). Metformin is a potent stimulator of AMPK in primary osteoblasts (84). Furthermore, metformin inhibits osteoclast differentiation and activity (86).

Metformin may be protective against osteoporosis. Treatment with metformin for 2 months in rats prevented bone loss induced by ovariectomy (87). In some epidemiological studies, diabetes patients treated with metformin had a lower fracture rate (88–90), although this finding has not been consistent (91).

Thiazolidinediones (glitazones)

In contrast to metformin, thiazolidinediones lead to bone loss and increased fracture risk. Thiazolidinediones are agonists of peroxisome proliferator-activated receptor γ (PPARγ). They have been employed as insulin sensitizers for the treatment of type 2 diabetes. However, they also have direct deleterious effects on bone, as PPARγ is expressed in stromal cells of the bone marrow, osteoblasts and osteoclasts. Thiazolidinediones impair the differentiation of osteoblasts and increase adipogenesis in bone marrow (92). In a recent meta-analysis, thiazolidinediones were associated with an increased fracture risk in women (93), but not in men (94), and in non-diabetic individuals with insulin resistance (95). Interestingly, a novel thiazolidinedione analogue (MSDC-0602) may have neutral skeletal effects while maintaining the insulin-sensitizing properties (96).

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) is an adipokine that impairs insulin sensitivity in an autocrine and paracrine fashion (97). A recent study has suggested that low DPP-4 activity may have a protective role on bone metabolism. Postmenopausal women in the highest quartile of DPP-4 activity had higher HOMA-IR and lower BMD compared with participants in the lowest quartile. The authors suggest that higher DPP-4 activity may be a risk factor of osteoporosis (98). This is supported by a meta-analysis of randomized clinical trials that suggested that DPP-4 inhibitors may protect against bone fractures (99). However, two recently published studies did not support this notion (100, 101).

Sodium glucose co-transporter-2 inhibitors

Sodium glucose co-transporter-2 (SGLT-2) inhibitors improve glycemic control by inhibiting glucose reuptake by SGLT-2 in the proximal tubule of the kidney. SGLT-2 inhibitors may affect calcium and phosphate homeostasis, bone mass and fracture risk (102). Canagliflozin increased bone turnover markers and decreased BMD at the total hip, but not at other sites, in proportion to weight loss (103) and increased fracture risk (104). However, a recent meta-analysis did not support these findings (105).

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists have also been shown to influence bone metabolism. GLP-1 receptor agonists may uncouple osteoclast and osteoblast activity, leading to greater bone formation and reduced bone resorption (106). In the Liraglutide versus glimepiride monotherapy for type 2 diabetes LEAD-3 study, liraglutide had no effect on total BMD over 2 years (107). In another study, liraglutide increased bone formation and prevented bone loss following weight loss (108). A meta-analysis showed different effects with different GLP-1 receptor agonists, suggesting that liraglutide may reduce the risk of bone fractures, whereas exenatide may increase fracture risk (109).

Insulin

Studies investigating the effect of insulin treatment on fracture risk are inconsistent. In rats, insulin treatment reversed the negative effects of type 2 diabetes on bone defect regeneration by enhancing osteoblast function and bone formation (110). In men with type 2 diabetes however, increased fracture rate was limited to those treated with insulin (50). In the study of osteoporotic fractures, foot fractures, but not other fractures, were increased in insulin-treated female

diabetic patients (111). In contrast, in a Danish case–control study, there was a non-significant trend towards lower risk of any fracture with insulin (89).

Effects of anti-osteoporotic therapies on insulin resistance

Bisphosphonates

Bisphosphonates are commonly used medications for the treatment of osteoporosis. They bind at the bone mineral surface to inhibit osteoclast-mediated bone resorption. In postmenopausal women, zoledronic acid induced insulin resistance acutely (112). However, in a longer term study, zoledronic acid had a neutral effect on fasting glucose, weight and diabetes risk (113).

Denosumab

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks binding to RANK, inhibiting the development and activity of osteoclasts, reducing bone resorption. The RANKL/RANK/OPG signalling pathway may affect glucose metabolism. However, findings are conflicting. Denosumab was not associated with induction of insulin resistance in postmenopausal women (114). In a study by Passeri *et al*., a single dose of denosumab improved hepatic insulin sensitivity in postmenopausal women (115). However, these studies were based on small cohorts.

Summary

In summary, the majority of epidemiological and experimental studies have highlighted the interaction between insulin resistance and bone health which may be mediated by visceral adiposity and circulating insulin levels. However, long-term prospective studies are required to more extensively elucidate the association of insulin resistance and bone health and fracture risk. Importantly, the effect of therapeutic interventions aimed at improving insulin resistance should be further investigated and considered when treating individuals presenting with simultaneous insulin resistance and osteoporosis.

Conflict of Interest Statement

No conflict of interest was declared.

Author contributions

JRG conceptualized and designed the review. CM drafted initial manuscript. All authors critically revised it for its intellectual content.

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