

# Relationship between body fat mass and bone metabolism

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## KEY WORDS

adipose tissue, bone tissue, obesity

## ABSTRACT

The protective effect of obesity on bone tissue has not been unequivocally demonstrated. On one hand, it is known that obese people have a lower risk of osteoporotic fractures compared with normal-weight individuals. On the other hand, obese patients are characterized by disorders of calcium-phosphate homeostasis and bone metabolism. Moreover, it is not known whether it is fat or lean body mass that determines the development of bone mass. It can be assumed that adipose tissue exerts independent effects on bone remodeling by releasing a number of biologically active substances. Moreover, it seems that the main mechanism of action of these substances is closely related to the type and location of adipose tissue in the body. The present article describes the relationship between fat and bones, including the effect of body weight on bone tissue, the local mechanisms of osteoblast and adipocyte differentiation, and the hormonal activity of adipose tissue.

**Introduction** Osteologists, endocrinologists, and physicians dealing with metabolic disorders have been interested in the relationship between adipose tissue and bone tissue for a long time. It is a complex issue, and this complexity is reflected in divergent results concerning the effect of obesity on bone tissue. It is well known that obese perimenopausal women have higher bone mineral density (BMD) compared with normal-weight women. Evaluation of bone turnover markers suggests a slower rate of bone metabolism in this patient group, and adipose tissue additionally protects against fractures of the proximal femur by cushioning the fall.<sup>1</sup> However, other authors did not confirm the protective effect of obesity on the development of osteoporosis. They observed an increased risk of fractures in children with higher fat content.<sup>2,3</sup> Other investigators indicated that menopause involved both an increased rate of bone loss and increased body fat mass.<sup>4</sup> Most of the available data confirm that adipose tissue exerts an independent effect on bone remodeling and contributes to an increase in bone mass. Mechanisms accounting for this relationship include mechanical load that stimulates bone formation,<sup>5</sup> intensive conversion of androgens into estrogens in the adipose tissue,<sup>6</sup>

lower serum levels of sex hormone-binding globulin (SHBG) (and thus higher levels of free hormones),<sup>7</sup> increased serum leptin levels,<sup>8</sup> increased insulin growth factor production, and hyperinsulinemia.<sup>9</sup> Despite the essential differences between bones and fat, there are also several similarities. Aging affects bone metabolism, causing bone deterioration, and increases the prevalence of obesity. Disorders of both tissues are caused by genetic and environmental factors. Adipose tissue and bone remodeling are regulated through the central and peripheral nervous system. Finally, both adipocytes and osteoblasts derive from the common progenitor/mesenchymal stem cells.<sup>4,10</sup> All changes occurring in these tissues result from complex regulatory mechanisms associated with genetic factors and the activity of the nervous and endocrine systems. Furthermore, given the fact that adipose tissue secretes a number of biologically active substances with hormonal activity (adipokines), one can suspect their modifying effects on bone cells. The aim of this review is to discuss the effect of fat on bone tissue.

**The effect of body weight on bone tissue** Weight gain is associated both with increased bone mass

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and slower bone mass loss due to aging. This relationship has been observed both in adults and children.<sup>11-13</sup> Postmenopausal women with simple obesity without comorbidities are less frequently diagnosed with osteoporosis. However, decreased bone mass is observed in obese women suffering from conditions that increase bone turnover (rheumatoid arthritis, chronic kidney disease).<sup>14,15</sup> It is still unknown whether it is fat or lean body mass that determines the development of bone mass. The results of studies concerning this issue are inconsistent. Reid et al.<sup>16</sup> and Douchi et al.<sup>17</sup> demonstrated that adipose tissue had a protective effect on bone tissue by reducing the risk of osteoporosis. Lau et al.<sup>18</sup> observed that men with vertebral deformities had lower fat content and lower BMD than controls. Finally, Riis et al.<sup>19</sup> showed that patients with rapid bone loss had significantly lower fat mass than those with the normal rate of bone loss. On the other hand, Janicka et al.<sup>20</sup> observed no protective effect of fat on bone loss in young adults, and Hsu et al.<sup>21</sup> found even a higher risk of osteopenia, osteoporosis, and nonvertebral fractures in patients with higher fat mass, regardless of body weight.

Other authors assessed the association between fat and bone mass in relation to environmental factors and diet. Reid et al.<sup>22</sup> found an inverse relationship between bone mass and body fat content in subjects with high physical activity. In patients with increased milk intake, increased bone mass during puberty, inhibited bone loss, and reduced incidence of osteoporotic fractures in older age were observed.<sup>23</sup> In addition, the consumption of milk (a rich source of calcium) is considered to reduce the risk of obesity. It has been proved that increased calcium intake promotes reduction of body fat content and prevents weight gain.<sup>24,25</sup>

Studies concerning the association between obesity and the risk of fractures in relation to age showed that obesity was associated with a higher risk of forearm fractures in children, but protected against hip and wrist fractures in the elderly.<sup>26</sup> The relationship between obesity and the risk of fractures seems to depend on ethnicity. It was found that obesity was associated with higher BMD in a population of white women but lower in that of African-American women.<sup>27</sup> However, Afghani et al.<sup>28</sup> demonstrated an inverse correlation between subcutaneous fat and bone mineral content (BMC) in white women, but not in the African-American ones. The authors also described an inverse correlation between visceral adipose tissue and BMC in African-American women, but not in white women.

Because adipose tissue represents only less than 40% of total body weight on average, the mechanical load related to increased fat mass may be insufficient to explain the effect of fat mass on bone tissue.<sup>4</sup> Also, the fact that obesity coexists with osteoporosis in certain clinical conditions, such as the Cushing's syndrome and

type 2 diabetes, only further complicates the issue. Moreover, there are environmental factors that cannot be ignored, such as physical activity, which increases bone mass and reduces fat mass at the same time. The analysis of peri- and postmenopausal periods revealed a natural decrease in BMD and an increase in adiposity.

The above proves that the effect of fat on bone tissue is still ambiguous – it depends on the method of measurement, part of the skeleton examined, patient's age and ethnicity, environmental and genetic factors, hormonal status, and comorbidities.

#### **Local mechanisms affecting the differentiation of osteoblasts and adipocytes in the bone marrow**

As mentioned above, adipocytes and osteoblasts derive from the common progenitor/mesenchymal stem cells. The differentiation is regulated by the Wnt/ $\beta$ -catenin signaling pathways and the activity of peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), which act on stem cells in an opposite manner.<sup>28-30</sup> PPAR- $\gamma$  enhances mesenchymal cell differentiation to adipocytes (at the same time inhibiting differentiation of osteoblasts), while the Wnt signaling pathway favors osteoblastogenesis and inhibits adipocytogenesis. It should be stressed that these processes are limited to the bone marrow microenvironment.

In animal studies, Kirkland et al.<sup>31</sup> found that the activity of PPAR- $\gamma$ , irrespective of the effect on the synthesis of fat cells, was associated with redistribution of body fat and an age-dependent decrease in bone mass. The authors showed a lower expression of PPAR- $\gamma$  in subcutaneous adipose tissue in older individuals and impaired maturation of adipocytes and osteoblasts in the bone marrow caused by PPAR- $\gamma$  gene mutations. Moerman et al.<sup>32</sup> suggested that PPAR- $\gamma$  might be responsible for age-dependent fat accumulation in the bone marrow and suppressed production of osteoblasts. Takada et al.<sup>33</sup> proposed the use of PPAR- $\gamma$  antagonists as potential factors limiting the age-dependent bone loss and adipogenesis in the bone marrow. In an in vitro setting, the authors observed that the combined treatment of PPAR- $\gamma$  and interleukin 1 (which suppresses its function) inhibited adipogenesis and induced osteoblastogenesis of bone marrow-derived mesenchymal stem cells.

The Wnt signaling pathway enhances mesenchymal cell differentiation to osteoblasts and plays an important role in inhibiting adipogenesis.<sup>30</sup> The inhibitory effect is mediated by  $\beta$ -catenin that suppresses the PPAR- $\gamma$  target genes. Additionally, low-density lipoprotein receptor-related protein 5 (LRP5) acts as Wnt coreceptors and its mutations are associated with changes in BMD. Therefore, in humans, in the case of a point mutation in the LRP5 gene, higher bone mass is observed.<sup>34</sup>

#### **Endocrine activity of adipose tissue and its effect on bone tissue    Estrogens**    The association between

estrogen deficiency and accelerated bone loss has been well documented.<sup>35</sup> It is known that during perimenopause, gonadal failure leads to a gradual decrease in estrogen levels. In postmenopausal women, serum estrogens (estron) levels are partially maintained due to peripheral aromatization of adrenal androstenedione.<sup>6,36</sup> This process occurs both in the adipose tissue and muscles. As a result of higher adrenal production of androstenedione in obese women, an increased pool of precursors for peripheral conversion is observed.<sup>37</sup> Siiteri<sup>38</sup> showed (in percentage) an increased conversion of androstenedione into estrone in obese women compared with normal-weight women. In addition, adrenal dehydroepiandrosterone is converted to estrone in osteoblasts with the participation of P450 aromatase.<sup>36</sup> Aromatase, which is responsible for the peripheral conversion, is not only produced by gonads, but also by adipocytes. It enhances the transformation of androstenedione and testosterone into estrogen. Cleland et al.<sup>39</sup> showed that the activity of aromatase in fat cells, which increases with age, was associated with the distribution of body fat. Increased activity of this enzyme has been demonstrated in postmenopausal women.<sup>39</sup> Additionally, it has been shown that high estrogen levels in bone marrow mesenchymal cells stimulates bone formation and inhibits the differentiation of mesenchymal cells to adipocytes.<sup>40</sup> Also, the relationship between estrogen levels and the number of fat cells have been described. A reduction in endogenous estrogen levels in postmenopausal women was accompanied by an increase in the number of adipocytes.<sup>41</sup> Probably, this process prevents from a sudden deficiency of endogenous estrogens in postmenopausal women. Gambacciani et al.<sup>42</sup> showed that the use of hormone replacement therapy inhibited the growth of adipose tissue. Obese women are characterized by lower serum levels of SHBG, and thus higher levels of free hormones as compared with normal-weight women.<sup>43,44</sup> Increased production of estrogens in the adipose tissue is one of the potential mechanisms that account for the protective effect of obesity on bone tissue.

**Adiponectin** Compared with normal-weight individuals, obese patients have lower serum levels of adiponectin that increase after weight reduction.<sup>45,46</sup> Numerous studies conducted so far have not clarified the effect of this adipokine on bone metabolism. The experimental studies by Berner et al.<sup>47</sup> and Jürimäe et al.<sup>48</sup> indicated a protective effect of adiponectin on bone tissue. The studied adipokine favored osteoblastogenesis and inhibited osteoclast formation, contributing to an increase in bone mass. On the other hand, Williams et al.<sup>49</sup> demonstrated increased bone density in adiponectin-deficient mice, suggesting an indirect effect of adiponectin on bone tissue, probably through modulation of circulating growth factor activity or insulin sensitivity. They reported that adiponectin decreased circulating

insulin levels, thereby reducing its anabolic effect (e.g., on bone tissue), and that it could modulate the biological activity of several growth factors, which might inhibit bone growth.<sup>50</sup>

The majority of reports have indicated a negative effect of adiponectin on bone tissue. Richards et al.,<sup>51</sup> Jürimäe et al.,<sup>52</sup> and Peng et al.<sup>53</sup> showed an inverse correlation between serum adiponectin and BMD in both women and men. On the other hand, a positive correlation with BMD (evaluated in distal radius) was observed by Tamura et al.<sup>54</sup> only in patients with type 2 diabetes. Lower serum levels of adiponectin in obesity, its inverse correlation with BMD, and its effect on insulin and growth factor levels may partially explain the protective effect of adiponectin on bone tissue.

**Leptin** The effect of leptin on bone metabolism is bidirectional. Both negative and positive correlations between leptin and BMD have been described in humans.<sup>55,56</sup> Leptin is a well-known factor that decreases appetite and increases energy expenditure in malnutrition. Unlike adiponectin, serum leptin levels are increased in obese patients compared with normal-weight individuals. Additionally, leptin is an important regulator of bone remodeling.<sup>57</sup> In vitro studies showed that leptin directly affected human marrow stromal cells by enhancing differentiation to osteoblasts and inhibiting differentiation to adipocytes.<sup>58</sup> It is postulated that the intravenous administration of leptin enhances bone formation<sup>59</sup> and inhibits bone resorption.<sup>60</sup> However, acting through the sympathetic nervous system and cocaine-amphetamine regulated transcript, leptin inhibits bone formation.<sup>61</sup>

In peri- and postmenopausal women, a positive correlation between leptin and BMD and a negative with selected markers of bone turnover have been observed (dependent on body mass index [BMI] and fat content).<sup>15,62,63</sup> In postmenopausal women with osteoporosis, the above correlations are weaker in comparison with healthy women in the same age group.<sup>64</sup> However, in obese postmenopausal women, the correlations between leptin and BMD and bone turnover markers are stronger (particularly for bone resorption markers) than in lean women in the same age group. This association is explained by resistance to leptin in the central nervous system and disproportion between leptin levels in serum and cerebrospinal fluid in obese patient (in normal-weight individuals, the cerebrospinal-fluid/serum leptin ratio is normal; in obesity, serum leptin levels are much higher than in the cerebrospinal fluid).<sup>64-66</sup> Polish authors suggested a protective effect of high leptin levels on bone tissue due to the interaction between leptin and the RANKL/RANK/OPG system.<sup>63,67</sup> It was suggested that the beneficial effect of leptin on bone tissue was a consequence of the inhibited expression of receptor activator of nuclear factor- $\kappa$ B ligand and increased expression of osteoprotegerin.<sup>68</sup>

**Interleukin 6** Adipose tissue is responsible for the production of  $\frac{1}{3}$  the amount of interleukin 6 (IL-6) in patients without active inflammation. In obese individuals, higher IL-6 levels are observed compared with normal-weight subjects.<sup>69</sup> Although IL-6 is widely recognized as bone resorption factor, it has also been reported that IL-6 stimulates both proliferation and differentiation of osteoblasts.<sup>70,71</sup> The biological effects of IL-6 strictly depend on the site of action. Central administration has been observed to be associated with increased energy expenditure and decreased body fat in animal model, while peripheral administration induced hyperlipidemia, hyperglycemia, and insulin resistance.<sup>72</sup> In addition, Franchimont et al.<sup>73</sup> demonstrated that IL-6 was an important factor that enhanced bone formation in the case of increased bone turnover. On the other hand, the authors suggested that because the IL-6-deficient mice remained healthy and showed no changes in bone tissue, IL-6 might not be crucial for bone homeostasis.

**Visfatin** Visfatin, also known as pre-B-cell colony-enhancing factor, is a newly described adipocytokine. Higher visfatin levels are observed in obese patients and patients with type 2 diabetes.<sup>74</sup> It was demonstrated that visfatin, due to affinity to insulin receptor (IR), activates the insulin signaling pathways (IR, IR substrate [IRS]-1, and IRS-2 phosphorylation; pi3-K binding to IRS-1 and IRS-2; Akt and MAPK phosphorylation) and thus mimics the action of insulin. Visfatin may decrease glucose levels with no significant effect on insulin concentration.<sup>75</sup>

Because IR is found in osteoblasts, the anabolic effect of visfatin on bone tissue seemed possible. In 2007, Xie et al.<sup>76</sup> demonstrated that regulation of glucose uptake, proliferation, and type I collagen production by visfatin in human osteoblasts involved IR phosphorylation. Visfatin enhanced bone matrix mineralization, had no effect on osteoblast alkaline phosphatase activity, and, surprisingly, downregulated osteocalcin secretion.

However, Zhang et al.<sup>77</sup> showed no relationship between visfatin and the serum levels of N-terminal telopeptides of type I collagen and bone alkaline phosphatase. Considering the positive correlation between fat mass and BMD, it seems that visfatin may be just one of many factors influencing bone turnover, especially that recent studies in postmenopausal women have found no association between BMD (measured in the femoral neck, lumbar spine, and forearm) and serum visfatin levels.<sup>77</sup> Of note, bone marrow cells can differentiate both into osteoblasts and adipocytes. Therefore, the paracrine effect of visfatin on osteoblastic cells cannot be excluded.

**Resistin** Resistin was described for the first time by Steppan et al.<sup>78</sup> in 2001 as an adipocyte-secreted factor. Its plasma levels increase proportionally to the degree of obesity. Resistin has been

observed to increase insulin resistance and inhibit adipocyte differentiation in animals.<sup>79</sup> In humans, the role of resistin is not entirely clear. Its concentration correlates positively with the content of subcutaneous and visceral adipose tissue as well as fat deposits in the pericardium and aorta.<sup>80</sup> In most studies, no significant correlation between serum resistin and insulin resistance has been observed.<sup>81</sup> The effect of resistin on bone tissue has been assessed only in a few studies, and the results are inconclusive. Thommesen et al.<sup>82</sup> showed that resistin activated both proliferation and differentiation of osteoblasts and osteoclasts, thus influencing bone remodeling. In contrast, Oh et al.<sup>83</sup> revealed an inverse correlation between serum resistin and BMD in the lumbar spine. In recent studies conducted in men<sup>84</sup> and postmenopausal women,<sup>77</sup> no significant correlation between serum resistin and the markers of bone turnover and BMD measured in several parts of the skeleton has been observed. It seems that the main mechanism of action of cytokines secreted by the adipose tissue is closely related to the site of this tissue. According to Wajchenberg et al.,<sup>85</sup> adipokines released from visceral adipose tissue play an important role in the pathogenesis of cardiovascular diseases and have a greater impact on hepatic metabolism of carbohydrates, lipids, and hepatic secretion of acute phase proteins, regardless of their auto- or paracrine actions on the adipose tissue. Subcutaneous adipose tissue releases primarily adipokines that have a protective effect, such as leptin and adiponectin. Additionally, subcutaneous fat is less sensitive to glucocorticoids. In 2004, Klein et al.<sup>86</sup> assessed the effect of liposuction on metabolic risk factors for coronary heart disease in obese women. Reduction of subcutaneous fat did not alter insulin sensitivity, serum concentration of adipokines, or cardiovascular risk. However, in later years, a protective effect of subcutaneous fat on the development of metabolic risk factors for coronary heart disease was suggested again. Porter et al.<sup>87</sup> analyzing the population of the Framingham study, found that subcutaneous fat was not associated with a linear increase in the prevalence of all risk factors among obese patients. As for the bone tissue, it seems that mechanical load is a more important determinant of bone mass than the adipose tissue, irrespective of its location in the body.<sup>88</sup> An increase in body weight in obese subjects is mainly, but not exclusively, a consequence of increased body fat.

**Conclusions** The risk of osteoporotic fractures increases in proportion to a decrease in BMI. For this reason, obesity is considered as a factor protecting against osteoporosis. Obese patients have a lower risk of osteoporotic fractures compared with normal-weight individuals. On the other hand, they suffer from disorders of calcium-phosphate homeostasis and bone metabolism, caused by low physical activity, unbalanced diet, and low exposure to ultraviolet



light. The results of the available studies remain inconclusive – some suggest that obesity protects bone tissue, others report contradictory findings. Thus, the protective effect of obesity on bone tissue has not been definitely established. Perhaps, a long-term follow-up of bone metabolism in obese people will reveal whether, and to what extent, the rate of bone turnover in this patient group differs from that observed in normal-weight individuals.

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# Związek między masą tkanki tłuszczowej a metabolizmem kości

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## SŁOWA KLUCZOWE

otyłość, tkanka  
kostna, tkanka  
tłuszczowa

## STRESZCZENIE

Ochronny wpływ otyłości na układ kostny nie został dotąd jednoznacznie potwierdzony. O stopniu złożoności problemu świadczą pośrednio rozbieżne wyniki badań dotyczące wpływu otyłości na tkankę kostną. Z jednej strony wiadomo, że ryzyko złamań osteoporotycznych u osób otyłych jest mniejsze niż u osób o prawidłowej masie ciała. Z drugiej strony, osoby otyłe charakteryzują się zaburzeniami gospodarki wapniowo-fosforanowej i przemiany kostnej. Nie wiadomo również, czy to tłuszczowa, czy beztłuszczowa masa ciała determinuje kształtowanie się masy kostnej. Można założyć, że tkanka tłuszczowa wywiera niezależny wpływ na procesy przebudowy kości, wydzielając liczne substancje biologicznie aktywne. Wydaje się również, że pierwotny mechanizm działania tych substancji wiąże się ściśle z anatomiczną lokalizacją depozytów tkanki tłuszczowej. W poniższym artykule przedstawiono powiązania między tkanką tłuszczową i kostną z uwzględnieniem wpływu masy ciała na tkankę kostną, miejscowych mechanizmów wpływających na różnicowanie się osteoblastów i adipocytów oraz aktywności hormonalnej tkanki tłuszczowej.

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