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OPINION

Adipokines and bone metabolism: an interplay to untangle

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Recent evidence of increased fracture risk in obese patients has focused the attention on the relationship between adipose and skeletal tissue [1].

Adipocytes secrete a number of bioactive molecules, such as adipokines, which recently have been shown to have a role in bone metabolism. Adipokines are pleiotropic molecules, investigated in many physiological or pathological processes, including inflammation, endothelial damage, atherosclerosis, impaired insulin signaling and hypertension. Adipokine dysregulation has been shown to be a strong determinant of the low-grade inflammatory state of obesity, which promotes a cascade of metabolic alterations leading to cardiovascular complications, insulin resistance or diabetes mellitus [2, 3]. So far, only a few adipokines (adiponectin, leptin, resistin, visfatin and the newly discovered omentin-1) have been studied in the context of bone metabolism.

Leptin was the first adipokine discovered. Circulating levels seem to reflect the amount of energy stored in the adipose tissue; however, a wide variability in leptin levels has been reported in individuals with the same body mass index [4]. A number of factors regulate circulating leptin levels in healthy individuals. In addition, leptin also influences several hypothalamic pituitary peripheral neuroendocrine axes, including the thyroid, gonadal, cortisol and growth hormone axes.

Leptin exerts its effect on bone metabolism by means of both direct and indirect mechanisms. The direct mechanism is probably mediated by the leptin receptor found on osteoblasts and chondrocytes. The indirect effect is mediated by different pathways. Leptin also impacts and regulates osteocalcin, an osteoblast-derived hormone considered a marker of bone formation, which in turn regulates both bone metabolism and insulin sensitivity [4]. Serum leptin levels have been shown to have a strong positive correlation with bone mineral density (BMD) in women, and high levels of leptin were reported to be predictive of low risk of fractures in some but not all studies [4]. Leptin increases osteoprotegerin (OPG), a member of the tumor necrosis factor (TNF) alpha superfamily secreted by osteoblasts which acts as a soluble decoy receptor for the activator of nuclear factor kappa B (RANK), a transmembrane protein expressed by osteoclasts. By preventing the soluble receptor activator of nuclear factor kappa B ligand (RANKL) from binding to RANK, OPG protects bone from excessive resorption.

Adiponectin levels have been shown to be inversely related to visceral fat and body mass index [5]; serum values vary largely depending also on age, sex, menopausal status and comorbidities [6]. Secretion of adiponectin may be inhibited by cytokines, such as TNF alpha, interleukin 6 and hormones (cortisol and testosterone), which are also involved in bone metabolism. Adiponectin receptors have been demonstrated on osteoblasts, but also on muscle and liver, which are organs that interplay with adipose tissue and bone metabolism [7]. Osteoblasts and marrow adipocytes originate from a common mesenchymal progenitor, and adiponectin has been postulated as a potential factor that may induce osteoblast proliferation and differentiation. Interestingly, osteocalcin may upregulate the expression of the adiponectin gene in adipocytes, thus improving insulin sensitivity. Adiponectin has been studied also in different clinical conditions such as non-alcoholic

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steatohepatitis (NASH), which is frequently associated with obesity. Patients with NASH have low circulating levels of adiponectin and often show bone fragility, which may implies that adiponectin could be also involved in the connection between liver and bone metabolism [8]. The link between adiponectin and bone metabolism may be represented by the OPG/RANKL system. Adiponectin activates RANKL and inhibits OPG, resulting in increased osteoclast activity and reduction in BMD. A recent meta-analysis showed a negative association between adiponectin and BMD, whereas high levels of adiponectin may be predictive of high risk of vertebral fractures in men only [9].

Some of the inconsistencies found may be explained by the fact that adiponectin does not circulate as a monomer, but rather, the main circulating forms in human plasma are examer and multimer; it is unclear at present which form of circulating adiponectin may have a role in bone metabolism. Furthermore, it should be considered that some of the experimental conditions obtained "in vitro" are difficult to replicate in "in vivo studies," where counter regulatory mechanisms may obscure the initial effects. This may also be the case for two less studied adipokines, resistin and visfatin. While their role in regulating insulin sensitivity in skeletal muscle and liver has been ascertained [10], a recent meta-analysis did not find convincing data to support an association between these adipokines and BMD [9].

Omentin-1 is secreted by visceral adipose tissue and has a positive association with adiponectin. Interestingly, visceral adipose tissue is associated with lower BMD and altered bone microstructure, in particular greater cortical porosity, lower bone formation rate and lower bone trabecular volume and stiffness. In experimental studies, utilizing co-culture systems of osteoblast and osteoclast precursors, omentin-1 was shown to reduce osteoclast formation via OPG and inhibit RANKL production in osteoblast. Omentin-1 levels appear to be inversely related to BMD and BMI; however, conflicting results have been reported in the literature [11, 12].

The study of Menzel et al. [12] is the first, which simultaneously analyzes two adipokines (adiponectin and omentin-1), which appeared to be both negatively associated with BMD and BMI. They evaluated 637 women from German population-based EPIC-Potsdam cohort considering the calcaneal quantitative ultrasound (QUS), as a surrogate estimation of bone quality, by the measurement of the broadband ultrasound attenuation (BUA). The study has the strength of having investigated both pre- and menopausal status; in fact menopause has been associated with a decrease in body fat-free mass with a simultaneous increase in body fat mass, in particular visceral adipose tissue, which may result in changes of adipokines serum levels. The authors found that premenopausal women had lower mean omentin-1 and adiponectin levels compared to postmenopausal women. The study did not reveal any association between adiponectin and BUA, but a significant negative association was seen between omentin-1 and BUA in postmenopausal women. Even if omentin-1 was positively associated with OPG and negatively with BUA, when the authors performed the statistical analysis including omentin-1 and OPG in the fully adjusted model, OPG became not significantly associated with BUA. Therefore, these findings do not support a mediating effect of OPG in the adipose tissue-bone pathway [12]. However, it should be noted that not absolute values of OPG are important, since the OPG/RANKL ratio is the major determinant of bone metabolism. Moreover, the circulating levels of these cytokines may not reflect their real concentration at skeletal sites. Finally, because adipose tissue secretes other cytokines such as interleukin 6 and TNF alpha, which are thought to have adverse skeletal effects by activating osteoclast resorption, it might be of interest in future studies, to analyze a wider panel of cytokines to better understand the interplay of adipose tissue on bone metabolism.

In conclusion, the possible meaning of adipokines as markers of osteoporosis remains controversial, but they might have a role in cases where osteoporosis is associated with obesity, NASH and metabolic syndromes.

Compliance with ethical standards

Conflict of interest The authors state they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The articles reviewed had compliance with ethical standards, and the Researches involving human participants obtained the informed consent.

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