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Linking the brain and bone through fat

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ABSTRACT

Over the past years, bone and adipose tissue have gained interest from researchers in the light of their secretory profiles, being able to produce active molecules, with the final effect of regulating energy homeostasis. Both adipocytes and osteoblasts originate in the pluripotent mesenchymal stem cell and this common origin has been proposed as the core of the fat-bone relationship. The central nervous system might be the third player in this association, capable of integrating signals. Numerous adipose tissue secreted factors that influence energy homeostasis and bone have been described: leptin, adiponectin, lipocalin 2, and inflammatory cytokines (e.g. IL-1, IL-6 and TNF-α). Similarly, osteocalcin, the most abundant bone protein, has been shown to elicit numerous central and peripheral endocrine functions. In this paper, we provide a review of the current literature regarding the bone-adipose tissue-central nervous system axis and a brief description of the several underlying molecular mechanisms.

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Introduction

For many years, both bone and adipose tissue have been only considered as storage and support sites. However, in the more recent past, their secretory profiles have gained increasing attention, as it has been shown that both tissues produce molecules with autocrine, paracrine, and endocrine effects, with the final result of regulating energy homeostasis [1, 2]. The interaction between the skeleton and the adipose tissue had initially been studied with focus on mechanical loading and strain, but, as research has gained more insight into the physiology and pathology of both systems, molecular interconnections have started to become apparent.

Both adipocytes and osteoblasts originate from the same precursor – the pluripotent mesenchymal stem cell (MSC) – and this common origin has been proposed as being at the core of the fat-bone relationship [3]. The central nervous system might be a third player in this relationship, capable of integrating signals. MSCs are regulated by endocrine, paracrine, and autocrine signals, and their preferential differentiation towards either adipocytes or osteoblasts might lead to imbalances and contribute to bone loss. However, the interactions are far from being straightforward. Many of the studied molecules have been found to have dual, opposing effects and/or effects that differ in vivo vs. in vitro.

The adipose tissue secretes more than 50 hormones and signaling molecules, called adipokines, which are known to influence the physiological processes involved in glucose metabolism, immunity, and energy [4]. Adipokines have the ability to respond to signals from the central nervous system (CNS) and enable cross-communication between various organs [5], allowing fat tissue to be involved in the complex control of bone biology.

Similarly, in recent years, bone has emerged as an endocrine organ that secretes hormones and regulates energy metabolism, with osteocalcin (the most abundant bone protein) being shown to exert numerous endocrine functions, both centrally and peripherally [6]. Studies have revealed an association between bone metabolism, adipokines, inflammatory cytokines and brain, but these interactions are not fully explained.

In this paper, we aim to provide a review of the current literature regarding the bone-adipose tissue-central

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nervous system axis and a brief description of some underlying molecular mechanisms.

Our review is based on a comprehensive search of the current literature in order to identify the relevant articles published until August 2020 in the PubMed database. The following terms were used in different combinations to generate the search: “adipose tissue”, “bone”, “brain”, “leptin”, “adiponectin”, “lipocalin 2”, “osteocalcin”, “fibroblast growth factor 23”, “inflammatory cytokines”. All identified articles were English language, full-text papers. We selected recent original articles, but some relevant reviews and older articles were also included.

Discussions

Mesenchymal stem cell – the same origin for adipocytes and osteoblasts

Mesenchymal stem cells (MSCs), known as marrow stromal cells, are multipotent stem cells which can be found in most organs and tissues, such as fatty tissue, bone marrow, liver, kidney, lung, muscle, umbilical cord, and placenta [7]. Friedenstein et al. discovered mesenchymal stem cells in 1970 and described them as a non-hematopoietic stem cell population in the bone marrow, spindle-shaped and “adherent” [8]; in the following years, the same research team described that non-hematopoietic stem cells had stem-like characteristics and maintained the potential to differentiate between bone, cartilage, and fibrous tissue in vivo [9, 10]. Caplan was the first to use the term “MSC” in 1991 to describe those cells that were able to differentiate between osteoblasts, chondroblasts, adipocytes, and myoblasts [11]. According to the International Society for Cellular Therapy, one of the most important criteria for a cell to be classified as mesenchymal stem cell (MSC) is the ability to differentiate between an osteoblast, chondroblast, or adipocyte in vitro [12]. Given the fact that adipocytes and osteoblasts share the same origin, the hypothesis that MSCs might play a role in the fat-bone relationship became apparent [13]. An alteration in MSC differentiation where adipocyte lineage formation is favored over the osteoblast lineage might lead to an imbalance in bone turnover and could contribute to bone loss. In vitro experiments have demonstrated that when adipogenesis is stimulated, osteoblast formation is inhibited, and reversely, adipogenesis is inhibited when the factors that favor osteoblastogenesis are dominant [14].

The brain’s effects on the bone

The CNS, especially the hypothalamus, has a major role in the control of energy homeostasis. The arcuate nucleus (ARC), the most important site in the hypothalamus, is involved in a number of neuroendocrine and physiological functions. ARC integrates the actions of metabolic mediators such as leptin, insulin, and ghrelin. Localized in the ARC, agouti-related protein (AgRP) neurons co-expressing neuropeptide Y (NPY) with a role in promoting food consumption and suppressing energy expenditure, also play a role in bone metabolism [15,16]. The anorexigenic neurons that co-express cocaine and amphetamine related transcript (CART) and proopiomelanocortin (POMC) are also involved in energy homeostasis. Cytokines and hormones are responsible for the central control of bone mass. One of them, leptin, is a modulator of NPY, can activate POMC neurons, and could affect bone resorption via central effects on CART [17–19].

Adipose tissue as an endocrine organ

The endocrine function of adipose tissue plays an important role in the crosstalk between organs and tissues. Adipokines present both pro-inflammatory and anti-inflammatory properties. Signals from adipocytes that influence brain control of the bone mass have been identified, revealing the complex relationship between energy metabolism, its regulation, and bone homeostasis. Estrogens and vitamin D have both been studied extensively in the context of fat-bone crosstalk. Higher estrogen levels in obese individuals, owing to adipose aromatase expression, provide one simple molecular explanation for the positive relationship between excessive fat and bone metabolism; on the other hand, decreased vitamin D bioavailability (and secondary hyperparathyroidism), common in obese individuals, are consistent with the negative side of the relationship [20–22].

We now further discuss a number of factors secreted by adipocytes known to affect bone remodeling such as: leptin, adiponectin, pro-inflammatory cytokines (interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor-alpha (TNF-α)).

a. Leptin

Leptin, derived from the Greek word “leptos” (meaning thin) and the product of the ob gene, is a small polypeptide hormone produced predominantly by the adipocyte (white adipose tissue [WAT]), which regulates weight, body metabolism, appetite, and reproductive function via the LEP receptor [23]. The mutation of the ob gene can cause obesity in mice; leptin deficiency in ob/ob mouse mutants leads to morbid obesity, hypothermia, hyperphagia and neuroendocrine abnormalities [24]. In addition, leptin receptor mutations causing leptin insensitivity lead to hyperphagia, morbid obesity, hypercorticism and other neuroendocrine abnormalities in mice (db/db mice) [25]. Leptin’s main site of action is the brain (at the hypothalamic level); intravenous leptin injections activate neurons in the arcuate (ARC), ventromedial, and dorsomedial hypothalamic nuclei [26]. The ARC is located in the third ventricle ventrally and contains neurons that produce cocaine and amphetamine modulates

transcript (CART), POMC, AgRP, neuropeptide Y (NPY), and gamma-aminobutyric acid (GABA), all of which are involved in energy balance regulation. POMC/CART-secreting neurons are involved in catabolic pathways, while NPY/AgRP/GABA producing neurons have anabolic effects [27].

Leptin inhibits the action of NPY and AgRP in the arcuate nucleus of hypothalamus, and increases the action of POMC and CART in order to decrease food intake [28,29].

Leptin impacts bone metabolism through direct and indirect mechanisms, via peripheral and central pathways. In vitro data suggest a direct impact of leptin on bone cells, with a high level of leptin increasing osteoblast differentiation. In their study, Cornish et al. indicate a modest direct effect of leptin on bone cells resulting in a slight reduction of bone fragility. Leptin promotes growth in cultures of osteoblasts and chondrocytes [30]. Steppan et al. show an increase in bone size and bone mass after the in vivo administration of leptin to ob/ob mice [31]. These studies suggest that leptin has direct anabolic effects on osteoblasts. There is also evidence that leptin increases the osteoprotegerin levels and decreases the RANK-ligand levels in human marrow stromal cells; as well, it inhibits osteoclastogenesis in mouse bone marrow cultures [32]. These findings indicate a positive correlation between fat and bone.

Tsuji et al. demonstrated a direct effect of leptin on bone growth through the fibroblast growth factor 23 (FGF-23) [33]. Similar to adipocytes in peripheral body fat, adipocytes in the bone marrow also secrete leptin and these local effects contribute to leptin-bone complexity [34].

Conversely, the intra-cerebroventricular infusion of leptin in ob/ob and wild-type mice reduces bone mass, indicating that, when acting via central mechanisms, leptin decreases bone mass [18]. Leptin's involvement in osteoporosis pathophysiology has been hypothesized, as some authors have found that it correlates positively with bone mineral density (BMD) and bone mineral content (BMC) as indirect clinical indicators of osteoporosis [23,35,36]; however, there have also been studies that found a lack of correlation between leptin, BMD, and bone turnover markers [37,38].

b. Adiponectin

Adiponectin, a protein hormone produced by adipocytes, was first described in 1995 by Scherer and coworkers. It consists of 244 amino acids, with an N-terminal signaling sequence, a hypervariable region, a collagenous domain, and a carboxy-terminal globular domain C1q like [39]. There are two main receptors for adiponectin, AdipoR1 and AdipoR2, which belong to a domain similar to G protein-coupled receptors (GCPR). Another receptor, T-cadherin, binds adiponectin in C2C12 myoblasts and muscle, and it is important for adiponectin-mediated cardioprotection in mice [40,41]. AdipoR1 expression is ubiquitous, but the major expressing tissue is skeletal muscle, while AdipoR2 is predominantly expressed in the liver [42]. These receptors are also expressed in the brain. AdipoR1 and AdipoR2 are involved in glucose and lipid metabolism, mediating increased AMP-activated kinase (AMPK) and PPARs activities [43]. Due to the wide distribution of different receptors in the brain, adiponectin has a variety of central effects, such as thermogenesis regulation, energy expenditure, food intake, locomotor activity, cognition, anxiety, and mood [44]. Also, it is one of the adipokines with anti-inflammatory, antiatherogenic, antidiabetic, and cardioprotective effects [45]. Adiponectin is found in high concentrations in the blood, more specifically within a range of 5-30 ug/mL [46]. The adiponectin level is decreased in obese people compared to lean people [47]. Qi et al. have found that the concentration of adiponectin in the cerebrospinal fluid was 1-4% of that in the serum and demonstrated that the intra-cerebroventricular injection of adiponectin reduced body weight in normal and Lepob/ob mice without affecting food intake [48]. Cisternas et al., using cultured primary rat hippocampal neurons and mouse hippocampus slices, demonstrated a direct role of adiponectin and resistin in glucose metabolism in the hippocampus, through the increase of glucose uptake, ATIP production and glycolysis [49].

Adiponectin might be a mediator of fat-bone relationship. Due to its anti-inflammatory effects, adiponectin suppresses TNF-α-induced nuclear factor kB (NF-kB) activation [50]. Receptors for adiponectin, AdipoR1 and AdipoR2, have been found on both osteoclast and osteoblast; most in vitro research suggests that adiponectin stimulates the proliferation and differentiation of the osteoblast, while inhibiting osteoclastogenesis [51,52]. These effects can be attributed to the involvement of adiponectin in RANK/RANKL/OPG axis. RANKL is a member of the tumor necrosis factor (TNF) family and influences the osteoclast activation responsible for bone resorption by binding to RANK. OPG (osteoprotegerin) secreted by osteoblasts and osteogenic stromal cells acts as a decoy receptor for RANKL and reduces the osteoclast differentiation, thereby inhibiting bone resorption [53]. Shinoda et al. analyzed the adiponectin effects on bone metabolism in adiponectin deficient and overexpressing transgenic mice; their study proposed opposing effects of adiponectin on bone formation, with circulating adiponectin directly inhibiting osteogenesis, but also having positive effects via the enhancement of insulin signaling and with locally produced adiponectin exerting positive effects via autocrine/paracrine pathways [54].

Clinical study results are contradictory when it comes to the association between adiponectin and BMD. Some studies show a negative correlation between adiponectin levels and bone mineral density (BMD) [55–57]. Regarding fractures, Barborur et al. reported that men with a high adiponectin level, had a higher risk of fracture,

independent of age, diabetes, body composition, and hip BMD [58], whereas other studies found no association between the risk of fracture and adiponectin level [59]. Further research is needed for a better understanding of the physiological role of adiponectin in bone biology and central function.

c. Lipocalin 2

Lipocalin-2 (LCN 2), known as neutrophil gelatinase-associated lipocalin (NGAL) or 24p3, is a member of the lipocalin superfamily and is involved in the inflammatory process [60]. LCN2 is expressed especially in WAT [61], but other sources such as the kidney, liver, spleen, immune cells, bone marrow and chondrocytes have been identified. This adipokine is involved in a series of physiological and pathophysiological processes such as metabolic homeostasis, inflammation, the apoptosis of hematopoietic cells, the transportation of fatty acids, and metabolic disorders [62]. Circulating LCL2 concentrations were positively associated with adiposity, hyperglycemia, insulin resistance, and CRP levels [63]. The general view has been that LCN2 levels are mainly associated with excessive adiposity [61], but recent studies have challenged this view, revealing that LCN2 is expressed by osteoblasts at much higher levels (tenfold higher) than in WAT or other organs. Osteoblast-derived LCN2 crosses the blood-brain barrier and suppresses appetite after binding to the MC4R in paraventricular and ventromedial neurons of the hypothalamus with potency-like leptin. This osteoblast-derived ligand for MC4R represents one of the means through which bone coordinates energy balance, via central feedback [64]. The pathways in which LCN2 is involved are, at this moment, not completely understood.

d. Inflammatory Cytokines

Obesity is associated with a higher concentration of pro-inflammatory and anti-inflammatory cytokines, such as: IL-10, IL-6, IL-8, IL-1 receptor antagonist (IL-1Ra) and TNF-α. A various number of cytokines is known to influence bone cell functioning.

Interleukin 1 (IL-1)

Il-1 family has been associated with inflammation more than any other cytokine family. Ten members of the IL-1 family have been identified: IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, IL-36Ra, IL-36α, IL-36β, IL-36γ, IL-37, IL-38 [65]. The peripheral immune system, bone cells, glia, and neural cells in the central nervous system (CNS) are the expression sites of IL-1 [66]. In vitro and in vivo studies showed that IL-1 is a stimulator for bone resorption, with effects on osteoclasts – both direct and indirect, by stimulating RANK production. IL-18 inhibits osteoclastogenesis and it has variable effects on osteoblasts [67–71].

Interleukin 6 (IL-6)

IL-6 is a cytokine that plays different and opposing roles in cells and tissues. A high percentage of circulating IL-6 is derived from adipose tissue, but chondrocytes, osteoblasts, and skeletal and smooth muscle cells also produce it in variable amounts [72,73]. In his study, Wueest demonstrated that IL-6 induces the release of free fatty acid and leptin from adipocytes, therefore affecting glucose metabolism [73]. This interleukin also has a number of effects in the bone, influencing both osteoblast and osteoclast differentiation and activities [74]. IL-6 acts directly on osteoclast progenitors, suppressing their differentiation by inhibiting RANKL signaling pathways, with the final effect of decreasing bone resorption [75]. Yang et al. reported that IL-6 KO mice presented low bone mass and decreased osteoblast number; IL-6 appeared to play a role in the early stages of fracture healing (delayed in IL-6 KO mice) [76]. Because IL-6 acts on both peripheral and central nervous system, the mechanism is still not fully understood.

Tumor necrosis factor alpha (TNF-α)

TNF-α and TNF-β are two similar peptide members of the TNF superfamily. Adipocytes produce TNF-α, but macrophages in the stromal vascular fraction are the main source. TNF-α is also produced by monocytes, endothelial cells, astrocytes, lymphocytes, neutrophils, and smooth muscle cells. It is a pro-inflammatory cytokine and a potent lipid metabolism and insulin signaling receptor. TNF-α also exerts multiple actions on bone cells, such as inducing bone resorption (both in vitro and in vivo) by stimulating the proliferation and differentiation of osteoclasts precursors or activating mature osteoclasts; a direct inhibitory effect on osteoblasts has also been reported [77,78].

Another interesting manner through which TNF-α and IL-1β impact bone health is through upregulation of osteoblast expression of 11β-HSD1, enhancing the negative effects of cortisol [79].

Other interleukins

The effects of other interleukins have also been described. For example, interleukin 4 inhibits osteoclast and osteoblast activity, interleukin 11 stimulates osteoclastogenesis and osteoblast differentiation, interleukin 8 stimulates bone resorption, interleukin 10 inhibits osteoclastogenesis and osteoblastogenesis, interleukin 12 inhibits osteoclastogenesis, interleukin 13 inhibits osteoclast and osteoblast activity, interleukin 15 stimulates osteoclastogenesis, and interleukin 7, 17 have variable effects [69].

Bone as an endocrine organ

a. Osteocalcin

Osteocalcin (OC), also known as bone γ-carboxy glutamic acid protein, is the most abundant non-collagenenous protein in bone and vitamin K-dependent protein. OC is an endocrine hormone and it regulates multiple organs, such as the brain, the pancreas, and the gonads. A low-level of OC has been reported in the

vascular smooth muscle cell, the brain, the kidney, the intestine, the bone marrow megakaryocytes, and the endothelial progenitor cells [80-82]. OC is produced by osteoblasts and it is a marker of bone formation, mostly involved in the process of mineralization. Its secretion by osteoblasts is controlled by the osteotesticular protein tyrosine phosphatase (OST-PTP) encoded by Esp (embryonic stem cell phosphatase) gene expressed in osteoblasts [81]. OC exists in two forms: undercarboxylated (uOC) and carboxylated (cOC). Esp-deficient mice produce more undercarboxylated osteocalcin resulting in more insulin secretion, better insulin sensitivity, and hypoglycemia, while overexpression of Esp produces the opposite results. In their study, Lee et al. showed that uOC regulates glucose metabolism in mice [82] by increasing the expression of adiponectin by adipocytes. OC also increases B-cell proliferation and insulin production [83]. Ferron et al. (2012) tested the therapeutic potential of the intermittent administration of osteocalcin; daily injections with uOC were found to improve insulin resistance and glucose tolerance in obese mice on a high-fat diet [84]. A relationship between glucose, fat metabolism, and osteocalcin has also been described in humans [85]. Serum osteocalcin has been widely used to evaluate bone metabolism as a bone formation marker, but new evidence suggests that it might also represent an endocrine link between bone and energy metabolism, with central roles. The uncarboxylated form of OC can pass through the blood-brain barrier, accumulate in the brainstem, thalamus, and hypothalamus, and bind to neurons [86]. One study indicated that osteocalcin might function as a neuropeptide in the brain [87], while other studies revealed a central effect of OC through the stimulation of the neurotransmitter production [83]. A new study on mice and humans by Karsenty et al. (2019) has revealed that immediately after the brain recognizes a threatening situation, circulating osteocalcin levels quadruple very quickly (within 2 minutes in mice). In the absence of normal adrenal function, adrenalectomized rodents and adrenal-insufficient patients can develop a normal stress response; these findings showed that circulating levels of osteocalcin are enough to induce the acute stress response [88]. Based on these results, we can classify bone as a stress organ, and osteocalcin as a stress hormone. Further studies are necessary to unravel the link between brain and the glutamatergic neurons in bone and establish other inter-organ relationships.

b. Fibroblast growth factor-23 (FGF23)

FGF23, a member of the FGF family, is a glycoprotein produced predominantly in bone by osteoblasts and osteocytes with low levels in other tissues such as the ventrolateral thalamic nucleus of the brain [89]. FGF23 regulates mineral metabolism by inhibiting urinary phosphate reabsorption and suppression of 1,25(OH)2D3 production in the kidney. Klotho, localized in the proximal and distal tubules in the kidney, testis, sinoatrial node, and possibly bone, is a co-receptor for FGF23 [90–92]. The absence of Klotho or FGF23 leads to increased serum levels of 1,25 (OH)2D3, therefore Klotho-deficient mice and FGF23-deficient mice have been reported with hypercalcemia and hyperphosphatemia [93]. Murali et al. found that FGF23 controls osteopontin secretion indirectly by suppressing alkaline phosphatase transcription and phosphate production in osteoblastic cells in a Klotho-independent manner [92].

High levels of plasma FGF23 have been found in patients with chronic kidney disease, cardiovascular diseases, and inflammatory and metabolic diseases [94]. Inflammation proved to be a significant trigger of FGF23 formation, and inflammatory cytokines are direct regulators of FGF23 in osteoblast; TNF-α plays a predominant role in FGF23 production [95,96]; Glosse et al. demonstrated that a high fat diet stimulates FGF23 production through TNF-α formation in rodents [97]. Leptin administration increases serum FGF23 concentration and decreases serum 1,25(OH)2D3 concentration in leptin-deficient ob/ob mice to values observed in lean control mice [33].

There is no clear evidence that FGF23 is produced by adipose tissue, but adipocytes express other members of the FGF family (FGF19, FGF21) that could be involved in energy regulation [98,99]. A number of clinical studies have described an independent association between higher FGF23 levels and adiposity (expressed through BMI and abdominal adipose tissue) in non-CKD population, suggesting that FGF23-related mechanisms might provide additional explanation for the skeletal changes seen in obesity [100, 101].

Highlights

- ✓ Adipose tissue plays an important role in the crosstalk between organs and tissues.
- ✓ Leptin impacts bone metabolism through direct and indirect mechanisms, via peripheral and central pathways.

Conclusions

Recent discoveries in the fields of molecular biology, enzymology, and physiology confirm the existence of a biocybernetic connection between fat and bone, modulated by the central nervous system. Understanding the interdependence between these systems is crucial in developing new drugs, treatment guidelines, and reducing the prevalence of metabolic and cardiovascular diseases in general.

Following the introduction of the term internal homeostasis by Claude Bernard in the 19th century, it was only a matter of time to subdivide and extrapolate this notion to smaller systems as our understanding of their functions and interactions to each other has increased.

Studies on metabolic homeostasis identified leptin as a central modulator for the neuroendocrine axes and linked its levels to bone turnover. The hormones produced by the adipose tissues can stimulate adipogenesis and limit osteoblastogenesis in vitro, but the intricacy of the mechanisms seems to be insufficiently elucidated since there are uneven results in vivo. In this regard, further clarification of the inter- and intracellular signaling that governs the molecular crosstalk between bone and fat is needed. Furthermore, bone formation, resorption, and utilization of energy substrates are under subcortical control involving the hypothalamus, various cytokines, and multi-synaptic pathways. The complex relationship between these three different systems should be reconsidered using a unitary approach on energy and metabolic homeostasis in order to translate possible therapeutic implications into useful and safe future drugs.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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