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Review

Osteoporosis and osteoarthritis are two sides of the same coin paid for obesity

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ABSTRACT

Obesity is characterized by adipose tissue expansion and chronic low-grade inflammation. Among the inflammatory mediators related to obesity development are the adipokines. These cytokines are released from fatty tissues and act in an autocrine, paracrine, or endocrine manner. Adipocytes influence the comorbidities of obesity such as osteoporosis (OP) and osteoarthritis (OA). It is still controversial as to whether OP is associated with either a low or high body mass index, but it is quite clear that the latter condition increases the risk for OA development. Bone marrow adipocytes (BMAs) have the same precursors of osteoblasts, which are the primary cells involved in bone formation, and the amount of BMAs appears to be inversely related to bone mineral density. Although adipokines released by these adipocytes influence bone loss progress, their exact role remains controversial. Differently, the infrapatellar fat pad (IPFP) is indicated to protect the function of joint regarding OA. However, there is relatively limited information about the secretion of adipokines and other inflammatory mediators by the IPFP. Despite some inconsistencies, nutritional interventions targeting obesity may also benefit patients with OP and OA. The association among obesity, OP, and OA is quite complex, and many factors need to be explored that are mainly related to the role of adipokines derived locally rather than from visceral and subcutaneous adipose tissue. Also, nutritional intervention may affect fatty tissue mass and secretion of inflammatory mediators that may, at least in part, influence other tissues in the organism such as bone and articular cartilage. The aim of this review was to present the latest knowledge about the interrelationship between obesity and OA or OP and to discuss whether a dietary intervention for obesity will hold promise for patients with OA or OP.

Introduction

Obesity, a preventable chronic disease of alarming proportion, has a complex etiology of being a combination of multifactor conditions, of which most are environmental, related to new habits of life as sedentarism and consumption of caloric and processed foods [1]. Because of its systemic effects on the body owing to metabolic and inflammatory alterations, obesity is associated with other chronic diseases, including osteoarthritis (OA) and osteoporosis (OP). Obesity in those older than 65 y of age is a significant health issue, being considered as a possible pain intensifier and complicator in these patients, who also present a risk for fractures [2]. Obesity's interconnection with OA and OP is complex and continues to be an active research area as adipose tissue-derived mediators might be a common denominator.

The main characteristic of obesity is an expansion of adipose tissue associated with chronic low-grade systemic inflammation. The fatty tissue has long been recognized only as an essential energy reservoir, but it is also currently considered a metabolically active endocrine organ, which regulates fat deposits, nutrient homeostasis, and acts on the release of adipokines [3]. These molecules act on the regulation of energy homeostasis, including self-regulation of adipocyte growth and development. In addition to the influence on metabolic functions, adipokines are described as a common link between obesity and the development of musculoskeletal diseases [4,5]. Obesity also induces ectopic adipocyte accumulation in bone marrow cavities, and this may impair bone regeneration and lead to OP [6]. In this review, we present the latest knowledge about the interrelationship between obesity and OA or OP and discuss whether a dietary intervention for obesity will hold promise for patients with OA or OP.

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The epidemiologic relationship of obesity and OP or OA

Bone loss, such as in OP, represents a critical condition mainly because of the risk for fractures related to older adults. The prevalence of OP is estimated to be >200 million people worldwide, and ~30% of all postmenopausal women in the United States and Europe are affected by this disease [7]. Although OP occurs in both sexes, it is a prevalent disease in women and generally occurs in the postmenopausal period [8]. Differently, OA is one of the most common chronic health conditions and the most prevalent form of arthritis [9]. OA affects ~240 million people globally and, >60 y of age, 18% of women and 10% of men have symptomatic OA [9,10]. In 2016, the Osteoarthritis Research Society International (OARSI) published a white paper labeling OA as a severe disease (a life-threatening condition with an unmet medical need) by the FDA to accelerate drug testing [11].

For many years it was widely believed that OA and OP were inversely related, but recent epidemiologic studies showed that both diseases could occur in the same patient. The prospective study on 3000 postmenopausal women (>45 y of age) showed a clear relationship between the scores of the osteoporotic femoral neck and lumbar spine with the severity of OA pain and function disability [12]. This association confirmed a previous study [13], investigating 2942 men and women (>65 y of age) from different European countries. It was shown that OA patients with a worse physical score by either the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire [14] or walking test times also showed a significantly increased incidence of OP and the increased prevalence of obesity. These data indicate that OA and OP are not inversely related and their etiology may have a common denominator.

This interpretation was further underlined by the therapeutic effect seen with bisphosphonate-based drugs used in OP to slow bone resorption, which also showed beneficial effects on osteoarthritic pain, joint stiffness, and physical function in a meta-analysis including 13 randomized controlled trials [15]. Another meta-analysis of controlled bisphosphonate trials (most on oral risedronate), in patients (N = 2767) with only knee OA showed no significant improvements on pain, function, or radiographic progression. The difference between both studies could be explained by the mechanical overloading owing to body weight as a driving force for knee OA in comparison to either hand, spine, and hip joints [16]. Interestingly, the effect of bisphosphonates may even extend beyond that of inhibiting osteoclast activity as some bisphosphonate drugs might cause apoptosis and necrosis in macrophages as well [17]. To our knowledge, effects of bisphosphonates on obesity or the adipose tissue has not been reported, but these drugs might well modulate the inflammatory response of the adipose tissue next to the beneficial effect on bone in specific subsets of OA patients who display high rates of subchondral bone turnover.

Body mass index in OP and OA

The prevalence of overweight in 2016 was 1.9 billion adults, around 39%, and of these, >650 million were obese, ~13% of the worldwide population [18]. Body mass index (BMI) is a measurement used to classify individuals considering body weight and height. The higher the BMI in infancy, childhood, and adolescence can determine the bone mass in adulthood [19]. However, there is no consensus as to whether OP and fracture risk alter according to body weight. Studies demonstrated that low BMI (<18.5 kg/m^2) in older people is associated with increased risk for fracture and OP [20,21]. Early studies demonstrated that overweight and obese individuals present a modest reduction in the risk for fracture compared with those with normal or low BMI [22,23]. However, recent studies showed that high BMI is associated with increased risk for OP and fractures attributed to adipokine release and metabolic alterations [24,25].

Different from OP, and apart from aging, obesity seems to be a more significant risk factor for the development of OA. Compared with normal weight individuals (BMI 18.5 to <25 kg/m^2), obese individuals (BMI >30 kg/m^2) have 2.5 to 4.5 times increased risk for developing knee OA. Also, overweight individuals are 1.5 to 2.5 times more likely to develop knee OA than normal weight individuals [26,27]. The association between obesity and hip and hand OA is less pronounced. However, several studies indicate an increased risk for the development of hand and hip OA in the obese population [28,29].

Adipose tissue involvement in OP and OA

Obesity and visceral adipose tissue

Adipose tissue is centrally involved in obesity and releases a large number of bioactive mediators, the adipokines, which regulate fat mass and nutrient homeostasis [30]. Changes in the size of adipocytes, as hypertrophy, trigger physical changes in the area surrounding this tissue. Although positive energy balance is one of the contributors to adipocyte hypertrophy and inflammation in obesity, the type of nutrients consumed, such as lipid-rich and high-refined carbohydrate diets, also may specifically interfere with it [31–34]. Abnormal adipokine production and the activation of some proinflammatory signaling pathways in obesity induce various biological markers of inflammation. The adipokines identified until now are highly varied as leptin, adiponectin, visfatin, resistin, and chemerin, and also comprise proteins related to the immune system as the classical cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-6, transforming growth factor (TGF)-β, and chemokine CCL2 [30]. Low-grade inflammation in the adipose tissue of mice and humans is also associated with a progressive infiltration of immune cells into it [35].

Bone remodeling and loss: Osteoporosis

The metabolic functions of bone and its remodeling are fundamental mechanisms to maintain skeletal structural integrity [36]. Alterations of local or systemic factors such as activation of bone remodeling and recruitment of osteoclasts may trigger deleterious changes in bone mass [37]. The osteoprotegerin (OPG)/RANKL/RANK system regulates bone cell function through the control of bone formation and resorption. Cytokines such as TNF and IL-10 modulate this system by directly enhancing RANKL expression [38], whereas IL-6 stimulates bone resorption in osteoclasts [39]. A recent study showed that osteoclasts release extracellular vesicles carrying RANK that promotes bone formation by triggering RANKL reverse signaling [40]. Changes in OPG/RANKL/RANK ratios and cytokine profile may determine either improvement or aggravation of bone diseases and, therefore, is the focus of developing new therapies for OP.

Over time, bone resorption predominates over the formation that leads to bone loss. This disorder has clinical importance because of the high mortality rate due to the increased risk for frequent fractures in the lumbar and thoracic vertebrae, and especially in the proximal femur [41]. Its prevalence is augmented in women, mainly as a result of estrogen deficiency in the postmenopausal period. Usually, estrogen exerts its function through specific receptors, promoting apoptosis of osteoclasts [42] and improving the differentiation of osteoblasts [43]. Studies in mice have shown that the reduction in the production of sex hormones leads to the alteration in the production of osteoclasts and osteoblasts. These

hormones suppress TNF and IL-6, proinflammatory cytokines that are related to bone resorption [44], and stimulate OPG, which promotes the apoptosis of osteoclasts [45].

Osteoarthritis phenotype

The joint is a structure that connects bones in the body and is responsible for movement and stability. OA is a multifactorial age-related degenerative joint disease affecting the whole joint. It is characterized by progressive joint destruction, including remodeling of subchondral bones and cartilage damage and degradation. The early phase of OA is characterized by enhanced bone resorption [46]; however, later on in the disease, the affected joints show hallmarks of bone regeneration by developing osteophytes and subchondral bone sclerosis. Although the exact pathogenesis of OA remains mostly unknown, many different cells have previously been implicated to be involved in the pathogenesis of OA, including chondrocytes, synoviocytes, and several types of immune cells [47]. Apart from being a significant cause of chronic pain in adults, OA often results in difficulties of mobility and restrictions in executing normal daily activities, which makes it one of the most common reasons of disability in adults worldwide as well [9,48]. Owing to poor understanding of the molecular mechanisms involved in OA, treatment is restricted to symptom management, including pain relief and total joint replacement in the case of severe damage [49].

Role of adipose tissue and bone marrow fat in OP

The relationship and link between OP and obesity is still a matter of debate owing to some inconsistent or contradictory results. Some studies indicate that fat mass may have beneficial effects on bone [50,51]; whereas others suggest that excess fat mass may not protect against OP, and consequently fractures [52,53]. Moreover, obesity is most often related to an increase in visceral fat, but at the same time, an increase in bone marrow fat can occur [6]. Interestingly, osteoblast and adipocytes have the same stem cell precursor, and an increase in adipose cells will be at the expense of osteoblast numbers. Different signaling pathways regulate the formation of osteoblasts. The transcription factor related to Runt (*Runx2*) is considered critical for the differentiation of osteoblasts. Overexpression of *Runx2* inhibits the maturation of osteoblasts, causing osteopenia and multiple fractures [54]. On the other hand, γ-peroxisome proliferator-activating receptor (PPARγ2), an essential factor in adipocyte differentiation, can inhibit osteoblast differentiation via *Runx2* reduction [55].

Bone marrow fat and bone tissue demonstrate a complicated relationship that is not yet fully understood. Studies suggest that these adipocytes might play a role in the pathogenesis of osteoporosis [56,57]. The amount of bone marrow fat is inversely related to bone mineral density (BMD) [58]. More notably, another mechanism that associates obesity and OP is adipokine secretion that interferes with bone development. Among them, adiponectin is described as anti-inflammatory and contributes beneficially to insulin sensitivity in obesity [59]. In several studies, this adipokine is inversely associated with bone density in humans [60,61], although some of them, mainly in animals and in vitro demonstrated activation of osteoblasts and increasing of bone mass [4,62]. It remains controversial specifically for the cases in which osteoporosis is associated with obesity and metabolic syndrome [63]. Differently, osteoblasts produce leptin, which regulates the differentiation and proliferation of themselves [64] and is positively associated with BMD [60]. This adipokine is shown at high levels in obese individuals and animals and is associated with adipose mass and satiety [65]. Possible systemic cross-talk is suggested between bone formation and adipokines, not only derived from bone marrow but also adipocytes elsewhere in the body.

Role of adipose tissue and the infrapatellar fat pad in OA

As discussed, adipose tissue is a rich source of adipokines. Evidence suggests that the adipokine profile present in obese individuals contributes to the pathogenesis of OA. Apart from high circulating levels of leptin in obese individuals, leptin can also be detected in the synovial fluid and cartilage of patients with OA, being higher in these individuals than in healthy controls [66,67]. Furthermore, plasma and synovial fluid levels of leptin positively correlate with BMI, percentage of body fat, pain, disease activity, and cartilage degradation [68–71]. The mechanisms by which increased leptin levels influence OA remains mostly unknown. In vivo injections of leptin in mice [72] and culturing both bovine explants and human OA cartilage with leptin [73] increase the production of metalloproteinases (MMP). Also, culturing primary human chondrocytes with leptin induces expression of both cartilage-degrading enzymes like MMPs and a disintegrin and metalloproteinases with thrombospondin motifs (ADAMTs) and proinflammatory cytokines [74,75], all mediators involved in the pathology of OA and collagen breakdown.

In contrast to leptin, adiponectin levels are reduced in obese individuals [76]. Although this adipokine is considered as an anti-inflammatory mediator, in certain autoimmune or inflammatory diseases, it is also known for its proinflammatory effects. Adiponectin is found in the synovial fluid of joints affected by OA and compared with chondrocytes in healthy cartilage, which do not contain adiponectin, chondrocytes in damaged cartilage of OA patients do contain adiponectin [77]. Elevated serum levels of adiponectin are found in patients with the most severe radiographic OA and those with erosive OA of the hand [78,79]. However, other studies report significantly lower adiponectin levels in plasma and synovial fluid of patients with knee OA with higher radiographic severity and a higher level of adiponectin also has been associated with a lower risk for hand OA progression [80,81]. Because of these conflicting findings, the role of adiponectin in OA joints remains uncertain. Studies reporting both destructive and protective effects of adiponectin on cartilage are present. Downregulation of tissue inhibitor of metalloproteinase-2 (TIMP-2) and IL-1 β-induced MMP-13, and upregulation of collagen type II and aggrecan could protect the cartilage [82,83]. On the other hand, the observation that culturing chondrocytes and synovial fibroblast with adiponectin increases the production of proinflammatory cytokines and chemokines, nitric oxide and matrix-degrading enzymes like MMP1, MMP3, and MMP13 indicates a more destructive role for adiponectin [78,84]. More research is needed to elucidate the specific roles of adiponectin and leptin and especially their ratio in OA pathology.

Apart from visceral fat tissue, the infrapatellar fat pad (IPFP), the adipose tissue located in the knee joint, is also involved in OA. The IPFP is considered an active component of the joint that can influence neighboring cells and tissue, including the synovium and articular cartilage. Functions of the IPFP include distribution of synovial fluid and absorbance of biomechanical forces through the knee joint [85,86]. There are indications that the IPFP has a protective function regarding OA, as several studies show that greater IPFP volume is associated with higher knee cartilage volume, fewer structural abnormalities, and reduced knee pain [87,88]. However, there is relatively limited information about the secretion of adipokines and other inflammatory mediators by the IPFP. Some studies show that the IPFP could indeed be a source of cytokines and adipokines found in the knee joint. Compared with subcutaneous adipose tissue, the IPFP secretes higher levels of several inflammatory mediators, including IL-6, IL-6 receptor, adipsin, adiponectin, and

visfatin [86,89]. The vascularization, inflammatory infiltration and mediator production is increased in the IPFP of patients with OA compared with healthy controls [90]. Production of basic fibroblast growth factor (bFGF), vascular endothelin growth factor (VEGF), TNF-α, and IL-6 was detected in the IPFP tissue and synovial fluid of patients with OA, but no real association could be found between these two sites in the same patient [91]. It was indicated that the presence of these cytokines in the IPFP does not mean that they are also released from IPFP and end up in the synovial fluid. Because soluble mediators secreted by the IPFP compromise a mixed pro- and anti-inflammatory phenotype their role in the pathophysiology of OA is challenging to predict.

Effects of diet on bone disorders

Studies have described the effect of nutrients on bone loss. Those conducted in both rodents and humans have demonstrated a relationship between fructose and glucose intake and disruptions in bone mineral homeostasis [92,93]. Cross-sectional studies have shown an increased risk for fractures in teenagers who regularly consume soft drinks [94,95]. Animal studies have shown the harmful effects of sugar consumption on bone morphology and strength [96,97]. Moreover, foods presenting a higher dietary glycemic index and glycemic load are related to an increase in the risk for osteoporotic fracture [98]. Similarly, mice fed a high-fat diet (60% kcal) for 12 wk had lower bone volume than those fed with low-fat diet [99]. Saturated-rich diets adversely affect bone metabolism in mice associated with an impaired antioxidant capacity [100]. Also, an increased intake of polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids was associated with a premenopausal bone loss in women [101]. Although diets rich in carbohydrate or fat appear to increase bone loss, a comparison between both types of diets demonstrated that dietary carbohydrate instead of dietary fat is a more significant nutritional factor to change RANKL level and RANKL/OPG ratio in mice [102]. Controversially, some data indicate a higher bone mass in animals when fed a high-fat diet [103] or a high-refined carbohydrate diet [104]. Therefore, these studies show that nutrition may differently influence bone metabolism.

Considering that obesity is a major risk factor for OA, a diet that promotes the development of it—for example, a diet high in total or saturated fat—also indirectly increases the risk for OA. In a large prospective cohort study with patients with OA, high total and saturated fat intake were associated with increased knee joint space width (JSW) loss [105]. In addition, high or elevated serum cholesterol levels are considered a risk factor for OA in women [106]. Mice fed a cholesterol-rich diet showed markedly enhanced ectopic bone formation during collagenase-induced OA [107]. Also, wild-type and apolipoprotein E knockout mice fed a cholesterol-rich diet showed high levels of low-density lipoprotein (LDL) associated with apolipoprotein B accumulation, S100 A8 alarming expression and TGF-β activation, indicating that enhanced synovial activation and oxidized LDL might, in particular, be responsible for the increased ectopic bone formation [108]. Apart from contributing to obesity and impairing bone health, high sugar consumption also appears to be associated with OA. In a prospective cohort study investigating the effects of soft drink intake on radiographic progression of knee OA, high soft drink intake (five or more times a week) in men was associated with a decrease in JSW compared with men with no or low soft drink intake [109].

Diet intervention on bone loss and OA

The first recommended intervention for the treatment of obesity is the modification of the usual diet to reach a balanced diet. A recent meta-analysis evaluated the effect of dietary intervention and exercise on body weight and body composition profile parameters in peri- and postmenopausal women [110]. The analysis observed that dietary intervention improved the parameters evaluated, more than exercise alone, but workout potentiated the effect of the dietary intervention [110]. Lower calorie intake is advised according to the total energy intake recommended for each, but decreasing calorie intake may have limited short-term influence with other strategies being necessary to prevent weight regain [111]. Because the macronutrient composition of meals influences appetite, the control of body weight, and energy compensation, it is important to take into account the proportion and type of these nutrients, mainly carbohydrates and lipids in obesity treatment [111].

Because nutrients also affect bone health, it is important to realize that their participation in improving the nutritional intake may represent an avenue for bone loss prevention. Generally, the improvement of bone loss is associated with calcium and vitamin D availability for bone maintenance [112]. Recently, it was pointed out that calcium intake should be according to the recommendation, and a higher amount can be harmful [113]. Also, vitamin D appears to contribute minimally to the improvement of bone loss [113]. In addition, calcium and vitamin D and other nutrients are also considered essential to complement and support bone homeostasis. It was already suggested that vitamin K plays a crucial role in increment bone health when it is supplemented in association with vitamin D and calcium [114]. However, others have shown no additional benefit of vitamin K for bone health in older adults [115]. The consumption of fruit and vegetables contributes to protection against premenopausal bone loss [101,116]. Controversial data exist about the effect of ω-3 fatty acid supplementation on BMD [117]. However, olive oil, which is rich in monounsaturated fatty acids, improved BMD on an experimental model and patients with OP [118]. Thus, micronutrient maintenance appears to have more influence in the treatment of bone loss than macronutrients, differently from that observed in obesity.

To date, the gold standard for the nonpharmacologic treatment of obese patients with OA is weight loss, most often reached via nutritional interventions in combination with increased exercise [119]. Pain reduction observed after weight loss is usually independent of structural damage, meaning that pain improves regardless of improvement of structural damage [120,121]. Apart from weight loss, dietary interventions targeted at specific macro- or micronutrients and their benefits for patients with OA are also investigated. As high ω-6 PUFA levels are associated with synovial inflammation and accumulation of ω-6 PUFAs is observed in OA joints, the effects of improving the ratio of ω-6 to ω-3 PUFAs on OA progression and symptoms are investigated quite extensively [122,123]. A low dose of fish oil supplementation resulted in significant benefits to Western Ontario and McMaster Universities Osteoarthritis Index pain and function score in patients with knee OA compared with a high, potentially anti-inflammatory dose [124]. Another study concluded that 2-y supplementation of a high dose of ω-3 fish oil did not alter bone loss in patients with knee OA [125]. Dietary interventions targeted at patients with OA also have been focused on reducing serum cholesterol levels, as high serum cholesterol is a risk factor for OA [106]. The increased intake of viscous fibers or plant stanols and sterols could reduce cholesterol levels [126,127].

Different from the macromolecules, nutrition may also contain extracellular vesicles (EVs), which are lipid bilayer nanoparticles derived from cells containing proteins, mRNA, and microRNA [128]. The intake of EVs from commercial bovine milk improves cartilage depletion and inflammatory response in models of arthritis [129]. Moreover, it was also demonstrated that milk EVs increase osteoblast differentiation [130] and even rise osteoclast

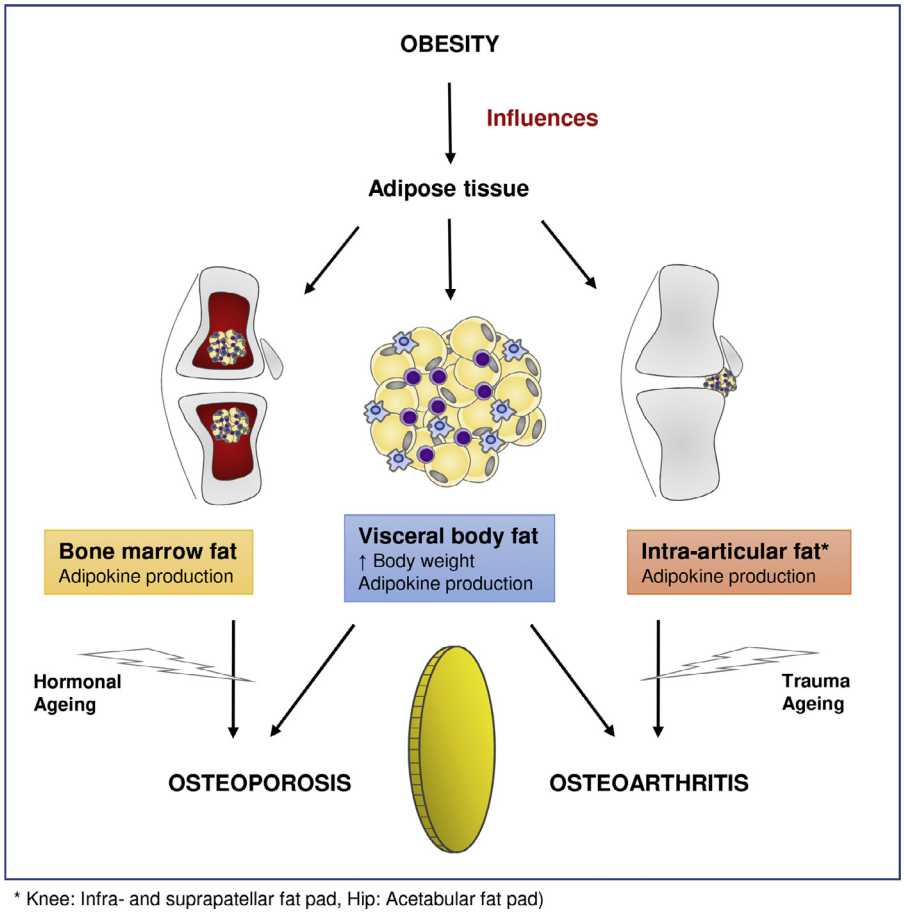

Fig. 1. Obesity is a major influence on adipose tissue because adipocyte hypertrophy, mainly on visceral adipose tissue, may contribute to inflammatory and metabolic alterations, disrupting adipokine release. Although visceral adipose tissue appears to contribute to the development of osteoporosis and osteoarthritis, local fat pads, such as from bone marrow and infrapatellar, also interfere via adipokine production. Hormonal factors and aging are commonly associated with osteoporosis evolution, differently from osteoarthritis in that it is related to trauma in the joint as well as aging. However, obesity is a common denominator, which whether present, affects these disorders. *Knee: infra and suprapatellar fat pad; hip: acetabular fat pad.

differentiation, but the latter with a reduction in their activity in vitro [131]. These data suggest the potential of milk EVs to contribute to the treatment of patients with OP and OA.

Conclusions

OP and OA are associated with obesity, and although the visceral adipose tissue might contribute to the adipokine-related effects on bone remodeling and the osteoarthritic process, the relative contribution of bone marrow and articular fat on both disorders is unknown as is the effect of the nutritional intervention on these extra-visceral fat stores. We might conclude that obesity is not the cause of both diseases, and additional triggers, such as hormonal changes in OP and joint trauma in OA, are needed but adipokines definitely contribute to the pathologic processes (Fig. 1). Therefore, a common denominator, namely obesity, may interfere in the progression and treatment of OP and OA, even in different contexts. However, studies are still necessary to establish which type of influence some mediators, such as adipokines, could have on it.

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