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REVIEW ARTICLE

The role of adipocytokines in the pathogenesis of knee joint osteoarthritis

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Abstract Osteoarthritis (OA) is one of the most common causes of musculoskeletal disability in the world. Traditionally, it has been thought that obesity contributes to the development and progression of OA by increased mechanical load of the joint structures. Nevertheless, studies have shown that adipose tissue-derived cytokines (adipocytokines) are a possible link between obesity and OA. Furthermore, according to recent findings, not only articular cartilage may be the main target of these cytokines but also the synovial membrane, subchondral bone and infrapatellar fat pad may be encompassed in the process of degradation. This review presents the most recent reports on the contribution of adipocytokines to the knee joint cartilage degradation, osteophyte formation, infrapatellar fat pad alterations and synovitis.

Keywords Osteoarthritis · Adipocytokines · Obesity · Adipose tissue

Introduction

Osteoarthritis (OA) is a progressive and disabling disease, one of the most common musculoskeletal disorders. OA originates as a result of the action of risk factors such as genetics, old age, female gender, obesity and injury [1, 2]. The disease is characterized by the progressive loss of articular cartilage with concomitant joint space narrowing, osteophyte formation, subchondral sclerosis and synovitis. An important feature of OA is the extension of the spectrum of damage from the articular cartilage to the entire joint structures [3]. The pathological processes taking place in cartilage, bone and synovial membrane result in pain, loss of function and in consequence disability. It has been estimated that in the USA symptomatic knee OA occurs in 10 % of men and 13 % of women aged 60 years or older and it is likely to increase because of the aging of the population and the increasing numbers of obese persons [4].

Although numerous risk factors contribute to the process of joint degradation, over the past ten years the association of obesity and OA has been well documented [5, 6]. One of the most important problems addressed by this intensive research until now is whether the impact of obesity on the development of OA is solely caused by an increased mechanical load in obese individuals, or rather, whether this influence is due to specific biochemical processes activated by, or directly related to the endocrine function of adipose tissue [7, 8]. The white adipose tissue (WAT) has the potential to produce various substances that have some functional similarity to classic endocrine hormones, although they differ from them in many aspects. Those substances were named adipocytokines, and in line with the latter hypothesis, recent investigations reveal a role played by adipocytokines in the degradation of cartilage, synovium and bone [9, 10].

This review summarizes the most recent reports on the role of adipocytokines in the pathogenesis of knee joint OA.

Adipocytokines

Adipocytokines are bioactive proteins secreted mainly by WAT, first identified in the early 1990s. So far, the role of adipocytokines in the metabolism of bone tissue and its contribution to the differentiation of bone marrow cells to

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osteoblasts [11, 12], as well as an important role in the pathogenesis of metabolic syndrome have been demonstrated [13, 14]. Some adipocytokines might also play a direct role in maintaining an inflammatory state in the joints of obese individuals (the so-called *low-grade inflammatory state*) [15]. These proteins have been detected in synovial fluid (SF) and the plasma of patients with OA [16–18]. A putative source of adipocytokine secretion in the region of the knee joint is the infrapatellar fat pad (IPFP) [19, 20]. In addition, recent findings indicate that deteriorated articular cartilage is another source of adipocytokines within the joint [21]. Furthermore, adipocytokines originating from the adipose tissue, which acts as an endocrine organ, can directly initiate the abnormalities in structure and function of articular cartilage in obese individuals [14]. This "external" action is then added to the action of adipocytokines produced inside the joint, which further deteriorates the condition of the joint. Of numerous adipocytokines, the best characterized are leptin, resistin, adiponectin, vaspin, omentin, visfatin and adipsin [22].

Leptin

From all adipocytokines, leptin was discovered first and is best characterized [23]. It is a polypeptide of 146 amino acids, and M_r 16 kDa, encoded by the obese gene (*ob*) localized on chromosome 7q31.3. Leptin is a multi-functional protein. It has s metabolic, neuroendocrine, and immunomodulatory effects. The activity of leptin is mediated by the Ob receptor (ObR) encoded by the diabetes gene (*db*). Leptin is produced mainly in the adipocytes of subcutaneous WAT and in the glandular cells of the stomach, in the liver and in the endothelial cells of the mammary gland [24–26]. The concentration of leptin fluctuates the highest being during the night and the lowest during the day. In healthy individuals, the plasma concentration of leptin ranges from 5 to 15 μg/L [27]. The concentration of leptin is higher in women, which is connected with larger stores of subcutaneous adipose tissue [28]. There are significantly higher ratios of plasma leptin concentrations to fat mass in girls than boys at the late stage of puberty. However, there are no significant differences in leptin concentrations in prepubertal and early pubertal children [29].

Leptin is secreted in a free form or is bound to its receptor. The bound form regulates mainly the energy balance. Leptin plays the role of a "guardian" of adipose tissue stores in the body. As a result of direct action on the central nervous system, it restrains hunger evoking the feeling of satiety and regulating thermogenesis as well as increasing energy expenditure [30]. Acting similarly to insulin, leptin lowers blood glucose level [24, 30]. It was also suggested that leptin acts as an acute phase protein having pro-inflammatory action through T-lymphocyte stimulation resulting in the liberation of cytokines such as interleukins (ILs) and tumor necrosis factor-α (TNF-α) and increasing the activation level of NK cells, macrophages and neutrophils [31].

Resistin

Resistin is a polypeptide of 105 amino acids and M_r 12 kDa encoded by the *RSTN* gene localized on chromosome 19p13.3 [32]. It is produced mainly in WAT and also in bone marrow, the spleen, lungs, placentas and the pancreas. Resistin takes part in adipogenesis, insulin resistance and inflammatory processes and exhibits a positive correlation with the occurrence of obesity, insulin resistance, and chronic inflammation [33]. It induces the secretion of pro-inflammatory cytokines such as IL-1, IL-6, IL-12 and TNF-α in a NF-κB-mediated fashion [34, 35]. Resistin elevates the concentrations of TNFα, IL-1β and IL-6 in plasma and increases catabolism and proteoglycan levels after experimental joint injury [36]. It has also been demonstrated that resistin up-regulates the intercellular adhesion molecule-1 (ICAM1), vascular cell-adhesion molecule-1 (VCAM1) and chemokine ligand 2 (CCL2) [37].

Adiponectin

Adiponectin is a polypeptide of 244 amino acids, but it spontaneously polymerizes to form trimers, hexamers and dodecamers. Adiponectin is encoded by the *ADPOQ* gene, which is localized on chromosome 3q27. It is produced by the majority of WAT cells and to a lesser extent by visceral adipose tissue (VAT). It takes part in the metabolism of carbohydrates and lipids, and plays an important role in thermoregulation by combusting ectopic adipose tissue. It also increases the insulin sensitivity of muscle and liver tissues. The plasma concentration of adiponectin reveals sexual dimorphism with females having higher levels than males. It ranges from 500 to 30,000 μg/L [24] and increases in degenerative joint disease and rheumatoid arthritis [15]. Adiponectin binds to a number of G protein-coupled receptors and the expression level of these receptors is elevated in articular cartilage, which is affected by degeneration [38]. The role of adiponectin played in the inflammatory process is not completely elucidated. It was suggested that it affects IL-1β, IL-6, MMP-13 [39], MMP-1, MMP-3, NO [38], and MMP-9 secretion [40].

Visfatin

Visfatin is a protein of M_r 52 kDa, a nicotinamide phosphoribosyltransferase enzyme, which acts as a dimer. Visfatin, first detected in skeletal muscles, liver and bone marrow, is encoded by the *PBEF1* gene [41]. It is secreted by visceral fat tissue [42] and is implicated in a number of

conditions, such as aging, atherosclerosis, pathogenesis of type 2 diabetes and rheumatoid arthritis [43]. Its role in metabolic processes is still controversial, but it has been reported that the properties of visfatin are similar to insulin. It has been suggested that the levels of visfatin are higher in obese [44, 45] and in OA patients [46]. In an experimental study, it has been found that visfatin level could be down-regulated by the overexpression of miR34a, which binds directly to the 3′UTR of visfatin mRNA. In obese mice, adipocytokine level correlated inversely with the elevated levels of miR-34a [47].

Other adipocytokines

Omentin is also known as an intestinal lactoferrin receptor. It is a 313-amino-acid protein encoded by the *ITLN1* gene, which is secreted by the visceral stromal vascular cells of the abdominal adipose tissue (but not by adipocytes), and is also synthesized in small intestine, lungs and heart muscles [48, 49]. Omentin causes vasodilation and attenuates C-reactive protein-induced angiogenesis via the nuclear factor kappa B signaling pathway. Although its function is not completely elucidated, it is known that it potentiates the effect of insulin on glucose metabolism [48] and its gene expression is altered in inflammation and in obese patients [50].

Vaspin (visceral adipose tissue-derived serine protease inhibitor) is a protein of 395 amino acids, with a M_r of 45.2 kDa, encoded by the *Serpina12* gene. Its expression in adipose tissue is regulated in a fat depot-specific manner and is associated with obesity, insulin resistance, and abnormal glucose metabolism. It is produced by visceral tissue adipocytes, shares about 40 % sequence homology with α_1-antitrypsin, and its secretion alters glucose tolerance and insulin sensitivity [51]. These findings indicate that vaspin exerts an insulin-sensitizing effect targeted toward WAT in states of obesity. Vaspin structure is similar to adiponectin and it acts as an anti-inflammatory agent, suppressing TNFα, leptin and resistin secretion [52, 53].

Adipsin (complement factor D) is a protein encoded by the *CFD* gene. It affects both the lipid and glucose metabolism. It is a serine protease that stimulates glucose transport for triglyceride accumulation in fats cells and inhibits lipolysis. It has been initially indicated that adipsin level correlates with obesity, dyslipidemia, insulin resistance and cardiovascular diseases [54].

Adipocytokines in cartilage degradation

A crucial feature of OA is the progressive loss of articular cartilage. Cartilage degradation is a result of the increased expression of genes encoding proteolytic enzymes such as metalloproteinases (MMPs) and aggrecanases (AGGs), as well as inflammatory cytokines, nitric oxide (NO) and prostaglandins (PGEs). The secretion of enzymes involved in the degradation of cartilage accompanied by insufficient cartilage repair result in the breakdown of homeostasis and a shift toward catabolic processes. Adipocytokines acting in an autocrine or paracrine manner stimulate chondrocytes in a dual way. One of the first studies on the impact of leptin on cartilage cells revealed that this peptide increases the anabolic activity of chondrocytes by inducing IGF-1 and TGF-β expression at both mRNA and protein levels [55]. However, further studies have shown contradictory results. Leptin was reported to increase MMP-2, MMP-9, cathepsin D and type II collagen expression in vivo, at both mRNA and protein levels. This peptide also up-regulated ADAMTS-4 and ADAMTS-5 expression, causing proteoglycan depletion from the articular cartilage of rats [46]. The latest data suggest that leptin induces ADAMTS-4, ADAMTS-5, and ADAMTS-9 gene expression by mitogen-activated protein kinases and NF-κB signaling pathways in human chondrocytes, which results in the subsequent increase of inflammatory processes [56]. Vuolteenaho et al. [57] showed that leptin enhanced NO synthesis and PGE2, IL-6 and IL-8 secretion in OA cartilage. Berry et al. [58] found that the presence of the soluble leptin receptor (sOB-Rb) is associated with reduced cartilage synthesis and increased levels of the tissue degradation marker (N-terminal type IIA procollagen propeptide, PIIANP).

Similarly, adiponectin has both a pro- and anti-inflammatory effect on tissues. Acting in vitro, this peptide induced iNOS activity and IL-6, MMP-3, MMP-9 and MCP-1 (monocyte chemattractant protein-1) expression [40]. In the study of Francin et al. [59] the adiponectin transcript level was significantly correlated with those encoding prostaglandin E2 and MMP-13. By contrast, Chen et al. [60] showed the protective effect of adiponectin on articular cartilage by up-regulating the tissue metallo-proteinase inhibitor (TIMP-2) and decreasing IL-1β-mediated MMP-13 expression. In patients with severe OA, higher plasma adiponectin levels were found and their chondrocytes expressed both adiponectin receptors (AdipoR1 and AdipoR2) and AdipoR1 was mainly expressed in the superficial layers of OA cartilage [40]. Visfatin had a catabolic effect on articular cartilage. Produced by OA chondrocytes it increased MMP-3, MMP-13 as well as ADAMTS-4 and ADAMTS-5 activity in a mouse model [61]. Yammani and Loeser [62] demonstrated that, in human cartilage, visfatin inhibited IGF-1 and led to IGF-1-mediated proteoglycan synthesis. Moreover, Hong et al. [63] suggested that visfatin could alter the expression, of chondrogenic factors such as the sex-determining region Y-box 9 (SOX-9) and type II collagen. In OA patients visfatin SF level positively correlated with the degradation markers of collagen, (CTX-II) and aggrecans (AGG1, AGG2) [64]. Recent studies show that most articular visfatin derives from synovium, and the activity of visfatin is involved in

chondrocyte and osteoblast activation, so targeting this enzymatic activity to disrupt joint tissue interactions may be novel in OA therapy [65].

Adipocytokines in osteophyte formation

Osteophyte formation is one of the hallmarks of OA. It has been suggested that osteophytes result from the abnormal healing response of subchondral trabeculae, or from the blood vessels penetration into the degrading cartilage [66]. It has been also shown that in OA the patient's osteophytes express TGF-β, which induces osteophyte formation in an experimental model [67, 68]. Thomas et al. [11] suggested that the action of leptin on bone tissue may be a result of bone marrow stromal cell stimulation and enhanced cell differentiation into osteoblasts with limited differentiation into adipocytes. In the study of Berry et al. [58], high leptin levels were associated with increased bone formation markers, such as osteocalcin and PINP (N-terminal type I procollagen propeptide). However, no associations were found between adipocytokine level and bone resorption markers (CTX-I, NTX-I and ICTP). Another study revealed that in subchondral bone osteoblasts of OA patients leptin expression levels were about fivefold than in normal osteoblasts and protein level was approximately twofold in OA cells compared to normal [69]. In the magnetic resonance imaging (MRI)-assessed knee joints, leptin levels were also strongly associated with osteophyte formation. Higher adipocytokine levels were found among women with larger osteophytes (>10 mm) than in those with no or smaller osteophytes (<10 mm) [70]. Visfatin has been also found to influence osteoblasts proliferation and type II collagen production [71].

Adipocytokines secretion by infrapatellar fat pad

The infrapatellar fat pad (IPFP), situated within the knee joint capsule, contains in addition to adipocytes, macrophages, lymphocytes and granulocytes, and may serve as a local source of adipose tissue-derived cytokines [72]. Several studies demonstrated that IPFP-derived adipocytokines could have a direct impact on articular cartilage. When the subcutaneous fat tissue (SCFT) and fat pad tissue (FPT)-derived cells were compared, IPFP adipocytes showed a twofold increase in IL-6 gene expression and in IL-6 release. Interestingly, leptin secretion was 40 % lower and adiponectin was increased by 70 % in IPFP cells compared with the subcutaneous adipose tissue [73]. Moreover, it was demonstrated that the culture media from OA patients' IPFP adipocytes induced *MMP13* and *MMP1* expression in articular chondrocytes and that the leptin level positively correlated with the expression of both MMPs and cartilage collagen destruction [20]. The end-stage OA patients' fat pad cells also showed an increased expression of inflammatory cytokines and down-regulation of anabolic peptides, such as VCAM1 (vascular cell adhesion molecule-1), CTGF (connective tissue growth factor) and CD44 (cluster of differentiation) [74].

Adipocytokines and synovitis

Changes of the synovial membrane in the course of OA include synovial hyperthrophy and hyperplasia, sometimes accompanied by tissue thickening. It is believed that a low-grade inflammatory state induced by synovial membrane may enhance IL-1β and TNF-α expression, which contributes to cartilage degradation [75]. Adipocytokines can be detected locally both in the synovium and synovial fluid (SF) of OA individuals. Nevertheless, the exact role of these peptides in inducing synovitis is unknown. Several studies provide information regarding this issue. De Boer et al. [9] have found that serum leptin, resistin and adiponectin levels were significantly correlated with the inflammation of local synovial tissue, but no association was found between adipocytokine level and cartilage damage markers as well as GAGs content. However, Hao et al. [76] demonstrated that the SF adiponectin level correlated with aggrecan depletion markers (AGG1 and AGG2), but not with the type II collagen degradation marker (CTX-II). By contrast, Honsawek et al. [77] found that SF adiponectin level was lower in severe OA and negatively correlated with OA grade and BMI. Correspondingly, the SF/plasma leptin ratio has been found to be significantly lower in the end-stage OA compared to early stages of the disease [78]. More recently, a study by Bas et al. [79] revealed that low SF adiponectin level and high SF leptin level were associated with worse pre-operative pain scores in the knees of OA patients.

Conclusions

Adipocytokines participate in numerous metabolic and inflammatory processes in the body. The currently published data suggest their pivotal role in the course of OA. It has been shown that in the knee joint the source of cytokines is not only systemic but also local, since cartilage, synovium or infrapatellar fat could be the source itself. Therefore, the role of obesity as a risk factor and cause of OA may not be limited to biomechanical loading, but also associated with adipose tissue secretory activity. Given the epidemic of obesity and OA, it is clear that these two conditions cannot be ignored and a modifiable risk factor, such as being overweight, should be targeted in order to reduce knee OA incidence.

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Conflict of interest The authors declare that they have no conflict of interest.

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