Special Issue Review

BIOMECHANICS, OBESITY, AND OSTEOARTHRITIS. THE ROLE OF ADIPOKINES: WHEN THE LEVEE BREAKS[†]

Running Title: ADIPOKINES IN BIOMECHANICS, OBESITY, AND OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis is a high-incidence painful and debilitating disease characterized by progressive degeneration of articular joints, which indicates a breakdown in joint homeostasis favoring catabolic processes. Biomechanical loading, associated with inflammatory and metabolic imbalances of joint, strongly contributes to the initiation and progression of the disease. Obesity is a primary risk factor for disease onset, and mechanical factors increased the risk for disease progression. Moreover, inflammatory mediators, in particular, adipose tissue-derived cytokines (better known as adipokines) play a critical role linking obesity and osteoarthritis. The present article summarizes the knowledge about the role of adipokines in cartilage and bone function, highlighting their contribution to the imbalance of joint homeostasis and, consequently, pathogenesis of osteoarthritis.

Keywords: Adipokines, biomechanics, inflammation, obesity, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a progressive degenerative disease of entire joint characterized by molecular (abnormal joint tissue metabolism) anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function).[1,2] It is a major cause of pain and disability in the adult population and the most common form of arthritis;[3] however, its etiology is largely unknown. In fact, OA seems to represent a family of pathologic processes that have a common endpoint, but with a multifactorial etiopathogenesis involving genetic, molecular and environmental factors, particularly biomechanical stress.

Under normal physiological conditions, chondrocytes maintain a homeostatic balance between the catabolic and anabolic processes, leading to the slow turnover of the cartilage extracellular matrix (ECM). The progressive degeneration of cartilage indicates an imbalance in the chondrocyte metabolism favoring catabolic processes. Chondrocyte activities are influenced by the action of soluble mediators, such as growth factors and cytokines, local matrix composition, and biophysical factors, including mechanical (sensed by mechanoreceptors) or osmotic stresses.[4] Clinical and animal studies demonstrated that altered joint loading, either single (acute impact event) or repetitive (cumulative contact stress), can lead to alterations in the composition, structure, metabolism and mechanical properties of articular cartilage, subchondral bone, and other joint tissues, and consequently cause OA.[4] Impact loads increase cellular activity and tissue hydration and cause remodeling of subchondral bone and ECM splitting,[5] all characteristics of early stages of OA. Joint instability, induced by meniscectomy[6] or ligand transection,[7] increase hydration, collagen disruption and matrix turnover accompanied by a decrease in the tissue stiffness in tension, compression, and shear.[8–11] Both articular cartilage and synovial fluid (SF) from these OA models show an increase of biomarkers[12] correlated with joint histological damage.[13]

Inflammation also plays an important role in altered loading models of OA. It has been reported that, after traumatic injury, the concentrations of pro-inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)-α were transiently increased in chondrocytes and articular cartilage.[14] Mechanical stress-induced nitric oxide (NO), prostaglandin E2 (PGE_2) and IL-6 production

by chondrocytes,[15,16] while fluid shear stress increased proteoglycan synthesis in isolated chondrocytes.[17,18] Interestingly, chondrocytes embedded in their own ECM show similar increases in pro-inflammatory mediators with stress,[19,20] but not that one's embedded in an agarose matrix,[16] which indicates that native ECM interactions can influence this response. Mechanical stretch also enhances the expression of pro-inflammatory factors in fibroblast-like synoviocytes (namely cyclooxygenase (COX)-2, PGE_2, and IL-1β),[21] and in osteoblasts (in particular, IL-6, COX-2, and IL-8).[22,23] Moreover, inflammatory mediators, such as IL-1β, lL-6, and oncostatin M, affected the osteoblast-chondrocyte crosstalk.[24] Additionally, the administration of nitric oxide synthase inhibitors or IL-1 receptor antagonists decreased OA severity in animal models.[25–27] Altogether, these data evidence that altered biomechanical loading is associated with inflammatory and metabolic imbalances of joint that may eventually lead to OA pathogenesis.[28]

Obesity, which is associated with a state of low-grade chronic inflammation (a state that is also a distinctive feature of osteoarthritis),[29] is a well-known risk factor for OA incidence, progression, and disability.[30] The effects of obesity on the joint have been initially attributed to mechanical loading and "wear-and-tear" at the surface of cartilage, being bone metabolism also affected;[31,32] however, there is growing evidence of multifactorial, systemic links between obesity and OA.[33] A small reduction of 5Kg in body weight was associated with an over 50% decrease in the risk of OA,[34] and epidemiological data showed that the risk of hand OA, a non-weight bearing joint, is about two-fold in obese people, compared with normal-weight individuals.[35] Additionally, no significant differences were detected comparing the incidence rates of knee OA in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice with controls.[36] These findings indicated that inflammatory mediators, in particular, adipose tissue-derived cytokines (adipokines), play a critical role linking obesity and osteoarthritis. Moreover, it has been reported that adipokines are also produced by joint tissues and infrapatellar fat pad (IPFP) closely associated to the joint.

In the present review, we summarized the effects of adipokines, namely leptin, adiponectin, visfatin, resistin, and other less-studied adipokines

(lipocalin-2, chemerin, and apelin), in cartilage and bone homeostasis and their implication in the pathogenesis of osteoarthritis.

LEPTIN

Leptin, a 16 kDa non-glycosylated protein encoded by the obese (*ob*) gene,[37] is a cytokine-like hormone mainly produced by white adipose tissue (WAT). Its levels are positively correlated with the WAT mass and body mass index (BMI), but its synthesis is also regulated by inflammatory mediators.[38] This hormone regulates body weight homeostasis through its effects on food intake and energy consumption by acting on hypothalamic nuclei, inducing anorexigenic factors and suppressing orexigenic neuropeptides.[39] Furthermore, given the wide pattern of leptin receptor (Ob-R) expression in peripheral tissues, leptin is considered a pleiotropic hormone implicated in the control of several physiological processes, like lipid homeostasis, insulin secretion, reproductive functions, thermogenesis, angiogenesis, or inflammation.[38,40,41]

Obesity is related to an increased risk of OA development and progression, primarily due to excessive joint loading.[42] However, this positive relationship was also verified in non-weigh bearing joints, like hands.[35] Linking obesity and OA, leptin serum levels were directly correlated with the intensity of chronic hand OA pain, but not with hand OA radiographic severity.[35,43,44] But, further studies are needed to clarify the role of this adipokine in hand OA. Leptin levels in SF and its gene expression were significantly correlated with BMI in severe OA patients,[45] and in severely arthritic cartilage,[46] respectively; a gender-dependent correlation was described.[47] Furthermore, extreme obesity is associated with impaired leptin signaling, which induced alterations in the subchondral bone without changing systemic inflammatory cytokine levels or OA incidence.[36,48] Accordingly, leptin-deficient (ob/ob) mice had reduced bone mass as well as altered bone microarchitecture (of note, axial and appendicular bones may be differentially affected) and consequently, modified bone biomechanical properties, with potential effect in bone fracture healing.[49–52] Exogenous leptin administration can act through central nervous system or peripherally, inhibiting[53] or enhancing[54] bone formation, respectively. In humans, high leptin levels observed in obesity were thought to be protective to bone fracture risk, but leptin resistant conditions and overweight lead to poor

bone health outcomes.[55] Exercise prevented bone loss and ameliorated bone biomechanical properties through regulation of leptin levels, suppression of inflammatory factors, and gain of skeletal muscle mass.[56,57]

Thus, leptin has been reported as a key player in the pathogenesis of OA. In a study of NEIRID group, it has been shown that expression of leptin was higher in the infrapatellar fat pad (IPFP) and synovial fluid (SF) from OA patients compared to healthy controls.[58] Leptin concentrations in SF exceeded those determined in serum,[59] indicating a local source of leptin in the joint or factors affecting its clearance. In fact, functional Ob-R isoform was detected in human adult articular chondrocytes[60] and leptin levels were higher in human OA chondrocytes than normal chondrocytes.[61] Accordingly, the SF leptin levels were related with the radiographic severity of OA, suggesting leptin as a potential biomarker for quantitative detection of OA.[62,63] Interestingly, leptin-mediated inflammatory processes, thus linking leptin activity with OA pathogenesis. Leptin increased the expression of inducible nitric oxide synthase (NOS2) alone or in combination with IL-1β, via janus kinase 2 (JAK2), phosphoinositide 3-kinase (PI3K) and mitogen-activated kinases (MAP), namely MEK1, extracellular signal-regulated kinases (ERK) 1/2, p38, and c-Jun N-terminal kinases (JNK), in human and murine chondrocytes, as well as in intact cartilage.[64–67] Nitric oxide mediates the action of IL-1 on joint degradation through down-regulation of matrix synthesis and up-regulation of matrix metalloproteinase (MMP) activity.[68] Induction of COX-2 expression and production of PGE_2, IL-6, and IL-8 by leptin alone or in combination with IL-1 was also verified, indicating the role of leptin in enhancing the production of pro-inflammatory mediators in OA cartilage.[64,69] Additionally, leptin can directly induce the expression of MMPs, such as MMP-1, MMP-3, and MMP-13 in human OA cartilage via activation of nuclear factor (NF)-κB, protein kinase PKC and MAP pathways.[70] The cartilage-degrading processes could be perpetuated by leptin by induction of vascular cell adhesion molecule (VCAM)-1 expression, an adhesion molecule responsible for leukocyte and monocyte infiltration at inflamed joints.[71,72] Altogether, these data highlight the pro-inflammatory and catabolic role of leptin on cartilage metabolism. However, leptin also exerts anabolic activities in articular cartilage by stimulating the production of growth factors, in particular transforming growth factor (TGF)-β and insulin-like growth

factor (IGF).[45] Leptin could also contribute to dysregulated osteoblast differentiation and proliferation in OA by modulation of the levels of alkaline phosphatase (ALP), osteocalcin (OC), collagen type I and TGF-β1 (metabolic markers in osteoblasts).[73,74]

Altogether, these data indicated that leptin axis is a critical linker between obesity and OA by regulating both immune and muscle-skeletal systems.[75,76]

ADIPONECTIN

Adiponectin, also called GBP28, apM1, Acrp30, or AdipoQ, is a 244-residue protein with structural homology to collagen type VIII and X, and complement factor C1q. It is prevalently synthesized by adipose tissue and can be found as different molecular forms (trimers, hexamers and also 12-18-monomer forms). Adiponectin acts specifically via two receptors, AdipoR1 predominantly found in skeletal muscle and AdipoR2 mainly present in the liver. The signal transduction of adiponectin by these receptors involves the activation of the AMP-activated kinase (AMPK), peroxisome proliferator-activated receptor (PPAR)-α, and PPAR-γ, among other signaling molecules.[77,78] Circulating levels of adiponectin tend to be low in morbidly obese patients and increase with weight loss and thiazolidinediones treatment (PPAR agonists), which enhances insulin sensitivity.[77,79] It decreases insulin resistance by increasing fatty acid oxidation and glucose uptake in the muscle and reducing glucose synthesis in the liver.[77] Ablation of the adiponectin gene has no dramatic effect in knockout mice in a normal diet, but they develop severe insulin resistance and exhibit lipid accumulation in muscles when placed on a high-fat/sucrose diet.[80]

Adiponectin has been implicated in the development of OA. Serum and plasma levels of adiponectin were significantly increased in OA patients compared to healthy controls,[81] being higher in erosive OA patients compared with non-erosive OA patients,[82] as well as in patients with the radiologically most severe OA disease.[83] No association between adiponectin serum levels and radiographic hand OA severity has been verified.[43] Moreover, an association between adiponectin serum levels, OA biomarkers, and local synovial inflammation was observed.[83,84] Adiponectin has been detected in OA synovial fluids correlating with aggrecan degradation.[85] This adipokine could be

produced by synovial fibroblasts, IPFP, osteophytes, cartilage and bone tissues within the joint.[59] In OA cartilage and in human primary chondrocytes, adiponectin led to the increased production of NO, IL-6, IL-8, VCAM-1, tissue inhibitor of metalloproteinases (TIMP)-1, MMP-1, -3 and -13.[69,71,72,83,86] However, a protective role for adiponectin in the OA pathogenesis was also been suggested. This adipokine inhibited IL-1β-induced MMP-13 expression and up-regulated TIMP-2 production in human chondrocytes.[87] Furthermore, the serum adiponectin concentration in a spontaneous animal OA model (STR/Otr mice) was lower when compared with control group.[88] But, only a few clinical data support the protective role of adiponectin against OA.[89] These contradictory data can be explained by patient heterogeneity and study protocols, or different adiponectin significance according to the phase and severity of OA. Exercise was associated with increased adiponectin levels compared to high-fat-sedentary and control animals, with potential effect in preventing bone loss.[56] Furthermore, mechanical loading up-regulated adiponectin and its receptors in skeletal muscle.[90] Adiponectin stimulated osteoclast proliferation and mineralization, via p38 MAPK signaling pathway and bone morphogenetic protein (BMP)-2,[91,92] but contradictory results showed inhibition of osteoclast differentiation and promotion of apoptosis.[93] Thus, adiponectin altered bone metabolism and biomechanical properties;[94,95] however, more studies will be necessary to clarify the exact role of adiponectin in the joint cartilage and bone and in the pathogenesis of osteoarthritis.

RESISTIN

Resistin, also known as adipocyte-secreted factor (ADSF) or found in inflammatory zone 3 (FIZZ3), is a cysteine-rich secretory protein that circulates as dimers in human blood.[96] Its receptor has not been identified yet, but toll-like receptor 4 (TLR4) was suggested to mediate resistin-induced pro-inflammatory factors secretion.[97] The main source of resistin in rodents is adipocytes,[98] while in humans is macrophages.[99] Thus, non-adipocyte resident inflammatory cells are the main resistin source in human adipose tissue.[100] In fact, the resistin levels in serum increased with obesity (associated with adipose tissue inflammation).[101] Additionally, resistin was proposed to link obesity and

diabetes.[96] Resistin promoted insulin resistance in animal models[96] via suppressor of cytokine signaling (SOCS)-3,[102] being this effect less clear in humans.[103] Interestingly, resistin downregulates AMPK activation in skeletal muscle, liver and adipose tissue.[104,105] Resistin also plays significant roles in autoimmune diseases, nonalcoholic fatty liver disease, cardiovascular diseases, and bone metabolism.[106,107]

Resistin stimulated osteoblast proliferation and its expression is augmented during osteoclast differentiation, through protein kinase C (PKC) and protein kinase A (PKA) signaling pathways.[108] In chondrocytes, resistin up-regulated several cytokines and chemokines (TNF-α, IL-6, and IL-12), through NF-κB and CCAAT/enhancer-binding protein (C/EBP)β.[109] Moreover, low shear stress modulated resistin-induced COX-2 expression in human OA chondrocytes[110] via NF-κB, cAMP response element binding protein (CREB), AMPK and SIRT1, indicating the interplay between mechanical shear stress and resistin activity.[110] Mechanical stretch also regulated the resistin expression in vascular smooth muscle cells[111] and cardiomyocytes.[112]

Resistin is augmented in serum and SF after traumatic joint injuries,[113] as well as in OA patients versus healthy controls with no signs of radiological OA.[84] But, the association between resistin and cartilage or radiographic damage is not clear. Some studies have shown that this adipokine was not associated with cartilage damage or volume, and hand OA progression,[35,43,84] while another study suggests a positive correlation between resistin and radiographic damage in OA patients.[114] It was also demonstrated that resistin levels were augmented in SF from OA patients, being correlated with resistin released from OA cartilage.[115] Of note, SF resistin positively correlates with IL-6, MMP-1 and MMP-3 levels in SF.[116] Given the pro-inflammatory profile of resistin together with its association with obesity and its effects on bone metabolism and chondrocytes activity, this adipokine might be another potential linker between obesity, inflammation, and OA.[94]

VISFATIN

Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in the biosynthetic pathway of nicotinamide adenine dinucleotide (NAD) by conversion of nicotinamide into nicotinamide mononucleotide. NAMPT is a

52 kDa protein firstly identified as pre-B-cell colony-enhancing factor (PBEF), a cytokine-like protein that induced early B-cell maturation in the presence of IL-17 and stem cell factor[117] and inhibits the apoptosis of neutrophils.[118] NAMPT is a homodimeric protein which functions as both an intracellular form (iNAMPT) and an extracellular form (eNAMPT).

It has been reported that circulating levels of visfatin were increased in metabolic diseases and in inflammation, although its role is still a matter of intense debate.[119,120] Leukocytes from obese patients, mostly granulocytes, and monocytes, produce higher amounts of visfatin when compared with lean subjects.[121,122] Adipose tissue-derived macrophages have also been described as a source of visfatin production.[123] In models of acute injury and sepsis, the expression of visfatin is up-regulated, being its synthesis controlled by glucocorticoids, TNF-α, IL-6 and growth hormone.[118] Moreover, visfatin has been described to induce the chemotaxis and the production of IL-1β, TNF-α, and IL-6 in lymphocytes.[124] Accordingly, Busso and colleagues reported a functional link between NAD metabolism and inflammation, suggesting the potential contribution of NAD-dependent enzymes in the regulation of pro-inflammatory cytokine production.[125] Besides its involvement in inflammation, visfatin is up-regulated by mechanical stress via reduction of DNA methylation levels and activation of the mechanical stress-inducible region in the visfatin promoter, in pulmonary artery endothelial cells;[126,127] however, at our knowledge, the effect of mechanical loading in visfatin expression at the joint tissues is unknown.

At cartilage level, visfatin increased the production of PGE_2, MMPs, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which suggests a pro-destructive role of this adipokine.[128] In fact, clinical data revealed that serum and SF levels of visfatin were higher in OA patients, which are correlated with degradation of collagen type II (CTX-II) and aggrecans (AGG1 and AGG2).[129,130] NAD levels were associated with the increase of visfatin levels during osteogenic differentiation.[131] Visfatin also stimulated the osteoblasts proliferation,[132] and induced IL-6 and monocyte chemotactic protein 1 (MCP)-1 expression in osteoblasts.[106] Additionally, different joint structures, namely IPFP, synovium, and osteophytes, contributed to the local production of visfatin in OA.[130]

Altogether, these data suggested that visfatin exerts inflammatory and catabolic functions at cartilage level and it can play an important role in OA pathophysiology.

OTHER ADIPOKINES

Lipocalin-2

Lipocalin-2 (LCN2), also named siderocalin, 24p3, uterocalin or neutrophil gelatinase-associated lipocalin (NGAL), is a glycoprotein originally identified in mouse kidney cells and human neutrophil granules,[133,134] although WAT was thought to be the main source.[135] LCN2 circulates as a 25 kDa monomer, a 46 kDa homodimer and in a covalent complex with MMP-9.[136,137] The members of lipocalin family contain a hydrophobic ligand binding pocket, which confers the ability to bind and transport steroids, lipopolysaccharides (LPS), fatty acids, iron, and in the case of NGAL, siderophores.[138,139] Besides its role in transport small lipophilic molecules, LCN2 has been involved in the induction of apoptosis in hematopoietic cells,[140] modulation of inflammation[141] and metabolic homeostasis.[142] LCN2 expression is elevated in obesity, which can be reversed by treatment with thiazolidinediones.[143] Furthermore, LCN2 concentrations in plasma have been associated with several metabolic and inflammatory parameters.[142–145] The pro-inflammatory transcription factor NF-κB has been shown to transactivate LCN2 expression, indicating that this adipokine might be involved in inflammatory responses.[146] However, the detailed role of LCN2 in obesity-associated pathologies has not been fully elucidated so far.

LCN2 is expressed in joint tissues,[147–149] being a mechano-responsive adipokine whose expression is induced by inflammatory mediators. In osteoblasts, the absence of mechanical loading induced LCN2 expression, which seems to contribute to bone metabolism via stimulation of pro-osteoclastogenic factors, receptor activator of nuclear factor kappa-B ligand (RANKL) and IL-6, and inhibition of anti-osteoclastogenic factor osteoprotegerin.[150] Accordingly, LCN2 levels have been correlated with an increased fracture risk in aged individuals[151] and with bone microenvironment.[152] Inflammatory factors TNF-α and IL-17 also increased LCN2 in osteoblasts.[153] Moreover, in chondrocytes, the LCN2 expression is induced by stimulated osteoblast conditioned medium,[74] IL-1β, adipokines

(leptin and adiponectin), LPS and dexamethasone.[147,154] Interestingly, NO is able to exert a control on LCN2 expression in chondrocytes, suggesting the existence of a feedback loop regulating its expression.[155] Furthermore, LCN2 levels were increased in OA synovial fluid[148,149,156] and OA cartilage.[156] LCN2 is involved in cartilage degradative processes by blocking MMP-9 auto-degradation[74,148] and by reducing chondrocyte proliferation.[157] Furthermore, it was reported that LCN2 expression is induced by glucocorticoids alone or in combination with IL-1, through corticoids receptors and PI3K, ERK1/2 and JAK2.[158] The transcription factors E74-like factor 3 (ELF3) and NF-κB were reported as modulators of LCN2 expression.[159]

Therefore, LCN2 acts as a sensor of mechanical load and inflammatory status of the joint, leading to alterations in subchondral bone, cartilage and bone-cartilage crosstalk underlined to OA pathophysiology.

Chemerin

Chemerin, also known as tazarotene-induced gene 2 (TIG2) and retinoic acid responder 2 (RARRES2), is a strong chemotactic adipokine that binds to the G protein-coupled receptor chemokine-like receptor 1 (CMKLR1 or ChemR23).[160,161] Two other receptors for this adipokine were described, namely CCRL2 and GPR1,[162] but their functional significance is largely unknown. Chemerin is secreted as an inactive precursor, prochemerin, which is activated by proteolytic C-terminal cleavage by neutrophil-derived proteases (elastase and cathepsin G), mast cell products (tryptase), proteases of the coagulation cascade,[163,164] and certain bacterial proteases[165] at the inflammatory site. Since ChemR23 is expressed primarily by antigen-presenting cells, like dendritic cells (DCs), natural killer cells and macrophages, chemerin/ChemR23 signaling pathway may serve as a bridge between innate and adaptative immunity.[166,167] Chemerin and its receptor are both expressed in adipose tissue.[168] In fact, chemerin expression correlates with BMI in humans and obesity, being up-regulated in adipose tissue of obesity and T2DM sand rats.[168–170] This adipokine also seems to promote adipocyte differentiation.[169] Chemerin is also expressed in preosteoblastic cells, having a possible role in osteoblast differentiation.[171,172]

Apelin

Apelin is an adipose-secreted cytokine, identified as the ligand for the orphan G protein-coupled receptor (GPCR) APJ, also known as the apelin receptor.[173,174] Apelin is secreted as a 77 amino acid prepropeptide, which is then cleaved into various active forms, namely apelin-13, -16, -17, -19 and -36, the shorter forms with more potent functionality. A pyroglutamyl form of apelin-13 also showed a high activity.[173] Several evidence suggest that apelin might act as a proinflammatory adipokine that contributes to vascular wall inflammation.[175] Enteric apelin expression is increased by exposure to LPS, IL-6 or IFN-γ in rodents.[176] Furthermore, TNF-α act as a direct regulator of apelin expression in human and mouse adipocytes, and intraperitoneal (i.p.) injections of TNF-α increased the apelin expression in adipose tissue and enhanced its levels in plasma.[177] Altogether, these data indicate that apelin may have a potential role linking obesity and inflammation.

Apelin levels were higher in SF of OA patients compared with healthy controls, being positively correlated with the severity of the disease.[178] It has been demonstrated that apelin can stimulate the chondrocytes' proliferation and increase the expression of catabolic factors, like MMP-1, -3, -9 and IL-1β *in vitro*. Intra-articular injection of apelin up-regulated the expression of MMP-3, -9, and IL-1β and decreased collagen II level. Furthermore, apelin injection markedly increased ADAMTS-4 and -5 mRNA levels and depleted proteoglycan in articular cartilage.[178]

CONCLUSIONS

There is now strong evidence that local and systemic pro-inflammatory mediators and cytokines are crucial players in the progressive degeneration of joint tissues and development of osteoarthritis. Many studies demonstrated that the mechanical stress of the joint (abnormal, altered or injurious loading) increases the expression of pro-inflammatory factors by joint cells, which may be in part responsible for the catabolic processes that occur in osteoarthritic cartilage. But, the precise relationship between biomechanical factors and inflammation are not fully understood and additional knowledge would be beneficial to understand the onset and progression of osteoarthritis. Obesity, one of the primary risk factors for OA, is associated with a state of low-grade

chronic inflammation (a cardinal trait that is common also to OA). Significant evidence shows that increase of body weight by itself, may not be a risk factor for joint degeneration. However, the dysfunction of the abdominal white adipose mass together with interactions between joint mechanical overloading and local and/or systemic inflammation may prompt the pathogenesis and the development of osteoarthritis (Fig. 1). In this context, adipokines are pleiotropic molecules synthesized and up-regulated by adipocytes as well as by chondrocytes and other cell types from joints (including immune infiltrating cells) that play a lead role in promoting and sustaining both inflammatory processes as well as ECM degradation. The studies described in this review showed that adipokines are crucial factors in the unbalance of joint homeostasis and development of osteoarthritis. However, many of the aspects of the adipokine network, especially the interplay between inflammatory paths and mechanical and metabolic processes in the cartilage and bone disorders remain still unclear. Doubtless, further insights into the intimate mechanisms regulating peripheral and central adipokines activity might be a great advantage for future treatments to osteoarthritis.

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Figure Legend:

Figure 1. Fat mass accumulation and dysregulation promote and sustain inflammation and ECM degradation in muscle-skeletal system

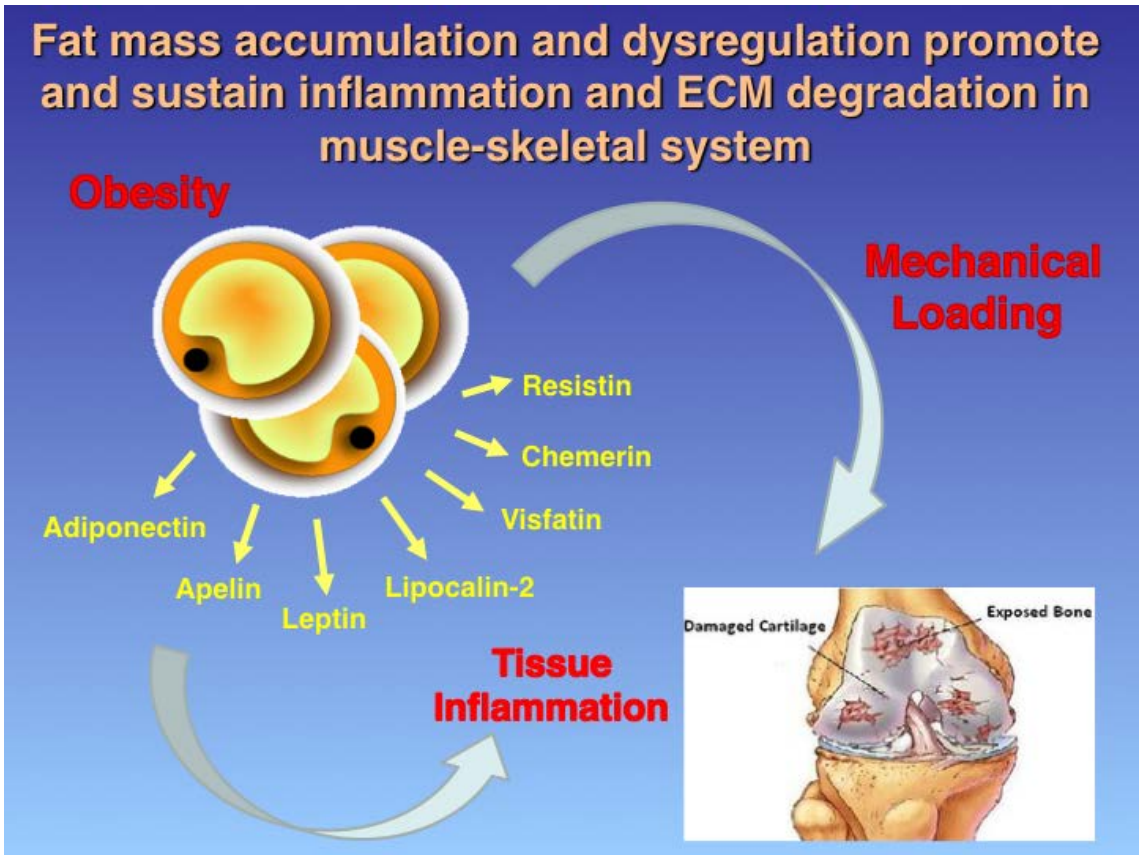

Figure 1