

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis**Adipokines: Biomarkers for osteoarthritis?**

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Abstract

Osteoarthritis (OA) is one of the most common degenerative joint diseases in aging population. Obesity is an important risk factor for initiation and progression of OA. It is accepted that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. However, emerging data suggest that additional metabolic factors released mainly by white adipose tissue may also be responsible for the high prevalence of OA among obese people. Adipocyte-derived molecules "adipokines" have prompt much interest in OA pathophysiological research over the past decade since they play an important role in cartilage and bone homeostasis. Therefore, the aim of this review is to summarize the current knowledge on the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for earlier diagnosis, classifying disease severity, monitoring disease progression, and testing pharmacological interventions for OA. In OA patients,

leptin, visfatin and resistin showed increased production whereas adiponectin showed decreased production. Leptin and adiponectin are far more studied than visfatin and resistin. Importantly, altered adipokine levels also contribute to a wide range of diseases. Further experiments are still crucial for understanding the relationship between adipokines and OA.

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Key words: Osteoarthritis; Adipokines; Biomarker; Obesity; Adipose tissue

Core tip: Osteoarthritis (OA) is one of the most common degenerative joint diseases in aging population. Obesity is an important risk factor for initiation and progression of OA. Adipokines have prompt much interest in OA pathophysiological research over the past decade since they play an important role in cartilage and bone homeostasis. Therefore, the aim of this review is to summarize the current knowledge on the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for earlier diagnosis, classifying disease severity, monitoring disease progression, and testing pharmacological interventions for OA.

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INTRODUCTION

The coexistence of obesity and osteoarthritis (OA) has increased remarkably nowadays. OA is the most common degenerative joint disease which affects more than 37% of people whose age are over 60 years^[1]. Due to aging of the population, the prevalence of OA continues to

Table 1 Relationship of adipokines with osteoarthritis

Adipokines	Association with BMI	Plasma levels between genders	Plasma levels between groups	Levels in OA patients
Leptin	positive	women > men	OA > control	SF > plasma
Adiponectin	negative	women > men	control > OA	plasma > SF
Visfatin	positive	unclear	OA > control	SF > plasma
Resistin	unclear	women > men	OA > control	plasma > SF

BMI: Body mass index; OA: Osteoarthritis; SF: Synovial fluid.

increase in the near future^[2]. Osteoarthritis is characterized by articular cartilage degradation, subchondral bone sclerosis, osteophyte formation, and synovial inflammation. The etiology of OA is largely complicated because it includes both genetic and non-genetic factors^[3]. Obesity is considered as a worldwide health problem with low-grade inflammatory status. It has long been recognized as an important risk factor for initiation and progression of OA. Since obesity is a modifiable risk factor, it has received much interest in OA clinical study.

It is primarily accepted that excess body weight may lead to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. However, several studies have revealed the association between obesity and OA in non-weight-bearing joints such as those in fingers and wrists. For example, a study reported a two-fold increase in hand OA risk in obese individuals^[4]. Moreover, emerging data suggest that additional metabolic factors released mainly by white adipose tissue (WAT) may also be responsible for the high prevalence of OA among obese people^[5].

In general, radiography is used to confirm the diagnosis of OA because it can reveal clinical changes at the joint margin, such as the bony outgrowth and joint space narrowing. However, these radiographic evidences are seen only after substantial cartilage loss has already taken place. To avoid severe joint pain or dysfunction, as well as total joint replacement surgery, early detection, especially in the preradiographic stage of the disease are required. Biomarkers offer a potential alternative mean for earlier diagnosis of nonsymptomatic OA. Nowadays, bone and cartilage biomarkers responsible for cartilage degradation are still frequently used in classifying disease severity, monitoring disease progression, and testing pharmacological interventions. Nevertheless, adipocyte-derived molecules "adipokines" have prompted much interest in OA pathophysiological research over the past decade due to the fact that they play an important role in cartilage and bone homeostasis. Moreover, the association of adipokines with obesity, together with its pro- or anti-inflammatory properties suggests that adipokines might be another crucial mediator that links inflammation with obesity and OA. Therefore, the aim of this review is to include the current knowledge of the role of adipokines including leptin, adiponectin, visfatin and resistin in OA and their potential to be used as biomarkers for OA.

ADIPOKINE LEVELS IN OA

The production of most adipokines is increased with

obesity, except for adiponectin. Adipokine levels are gender dependent, which normally higher in women than in men even after adjusted for body mass index (BMI). This might contribute to higher prevalence of OA in females. Adipokines are produced in knee OA joints by infrapatellar fat pads (IPFPs), synovium, chondrocytes, osteoblasts, as well as osteoclasts^[6,7]. It was suggested that systemic (plasma) and local (synovial fluid) adipokine levels would be related with cartilage degeneration and synovial inflammation^[8]. The information regarding adipokine levels are summarized in Table 1.

Leptin

The leptin concentration in plasma was positively correlated with BMI, in both healthy controls and OA patients. Obese individuals generally display higher levels of circulating leptin than their non-obese counterparts^[9,10]. Premenopausal women show about 3 times higher plasma leptin concentration than men^[11]. It has been reported that higher leptin concentration in plasma was associated with higher odds ratio of having knee OA, after age, ethnicity and BMI adjustments^[12]. Interestingly, synovial leptin levels were 3 to 11 times higher than those in matched plasma sample^[6]. Therefore, local leptin may play more distinct roles in bone metabolism regulation than systemic leptin.

Adiponectin

Adiponectin circulates in high concentrations (0.01% of total plasma protein) in the blood exceeding those in the paired synovial fluid^[7]. Plasma adiponectin levels are negatively correlated with BMI, lower in obese people and increase with weight loss^[13,14]. Women have significantly higher plasma adiponectin levels than men^[15]. Unlike other adipokines, plasma adiponectin levels were reported to be lower in OA patients than in healthy individuals^[16]. In OA patients, adiponectin levels in plasma were almost 100 times higher than in synovial fluid, and these levels showed an inverse correlation^[17]. However, Distel *et al*^[18] have shown the increased adiponectin levels in the IPFPs of knee OA. It has been reported that the amount of HMW relative to total adiponectin in OA synovial fluid was lower than in OA plasma, whereas that of the hexamer was similar and that of the trimer was higher in OA synovial fluid than in OA plasma^[19].

Visfatin

Visfatin levels are increased in obese individuals com-

Table 2 Effects of adipokines on osteoarthritis pathogenesis

Adipokines	Proteases	Cytokines	Inflammation	Cartilage	Bone
Leptin	↑MMP-1	↑IL-1β	↑NOS2	↓Chondrocyte proliferation	↑Osteoblast proliferation
	↑MMP-3	↑IL-6	↑iNOS	↑Proteoglycan synthesis	↑Ossification
	↑MMP-9	↑IL-8	↑PGE2	↑Collagen synthesis	↑ALP
	↑MMP-13	↓FGF	↑COX-2		↑OC
	↑Cysteine proteases	↑TNF-α			
	↑ADAMTS-4	↑IGF-1			
	↑ADAMTS-5	↑TGF-β			
Adiponectin	↑MMP-1	↑IL-6	↑NOS2	↑Chondrocyte proliferation	↑Osteoblast proliferation
	↑MMP-3	↑IL-8	↑PGE2	↑Proteoglycan synthesis	↑Osteoclast differentiation
	↑MMP-9	↑MCP-1	↑VEGF	↑Collagen synthesis	↑RANKL
	↑↓MMP-13	↑VCAM-1		↑Matrix mineralization	↓OPG
	↑TIMP-1				
	↑TIMP-2				
Visfatin	↑MMP-3,	↑IL-1β	↑NO	↓Chondrocyte phenotype	↑Osteoblast proliferation
	↑MMP-13,	↑IL-6	↑PGE2	↓Proteoglycan synthesis	↓Osteoclast differentiation
	↑ADAMTS-4,	↑TNF-α		↓Collagen synthesis	
	↑ADAMTS-5				
Resistin	↑MMP-1	↑IL-6	↑PGE2	↓Proteoglycan synthesis	↑Osteoblast proliferation
	↑MMP-13	↑TNF-α		↓Collagen synthesis	↑Osteoclast differentiation
	↑ADAMTS-4				

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; ALP: Alkaline phosphatase; COX-2: Cyclooxygenase-2; FGF: Fibroblast growth factor; GRO: Growth-related oncogene; IGF-1: Insulin-like growth factor-1; IL: Interleukin; iNOS: Inducible nitric oxide synthase; MCP-1: Monocyte chemo-attractant protein-1; MMP: Metalloproteinases; NO: Nitric oxide; NOS2: Type 2 nitric oxide synthase; OC: Osteocalcin; OPG: Osteoprotegerin; PGE2: Prostaglandin E2; RANKL: Receptor activator of nuclear factor kappa-B ligand; TGF-β: Transforming growth factor-beta; TIMP: Tissue inhibitor of metalloproteinases; TNF-α: Tumor necrosis factor-alpha; VCAM-1: Vascular cell adhesion molecule-1; VEGF: Vascular endothelial growth factor.

pared with lean people^[20], which can be reduced by weight loss^[21]. Although very recent study reported no significant differences in plasma visfatin levels between genders, it seems to be higher in female than in male^[22]. OA patients have higher circulating and local visfatin concentrations compared with controls, with levels in OA synovial fluid are greater than paired OA plasma^[23]. It has been shown that OA cartilage and synovium release higher amounts of visfatin than control samples^[24]. Moreover, the visfatin expression in OA IPFPs is also higher than in the matched subcutaneous adipose tissue^[25].

Resistin

Plasma resistin levels were significantly higher than matched synovial levels and increased in obese individuals without direct association with BMI^[26]. Resistin levels in females showed significantly higher than in males. It can be detected in inflamed synovium joints, such as rheumatoid arthritis (RA) and OA^[6,27]. It was demonstrated that resistin levels in both plasma and synovial fluid were elevated after traumatic joint injuries^[28]. In radiographic hand OA patients, plasma resistin levels were higher than in non-radiographic hand OA and controls^[29]. Interestingly, leptin deficient (ob/ob and db/db) mouse models showed elevated levels of circulating resistin, suggesting that resistin levels are slightly dependent upon leptin levels^[30].

tilage, chondrocytes, osteoblasts and osteoclasts as summarized in Table 2.

Leptin

In vivo injection of leptin into the rat knee joints shows catabolic effects in OA cartilage by increasing the production of metalloproteinases (MMPs) enzymes such as MMP-1, -3, -9 and -13, as well as cysteine proteases at both gene and protein levels^[31,32]. In parallel, human OA cartilage treated with small interfering RNA (siRNA) targeted for leptin showed decreased MMP-13 expression^[33]. Moreover, Bao *et al*^[34] have demonstrated that the gene expression of two important aggrecanases, a disintegrin and metalloproteinase with thrombospondin motifs (*ADAMTS*)-4 and -5, were considerably increased after treatment with leptin, whereas it decreases the anabolic factors such as basic fibroblast growth factors (FGF) production in mouse articular cartilage. These evidences suggest a prominent catabolic effect of leptin on cartilage metabolism in OA joints.

In cultured chondrocytes, OA chondrocytes produce higher leptin concentrations than normal chondrocytes. Leptin can stimulate chondrocytes to secrete higher levels of key mediators in cartilage degradation such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, growth-related oncogene (GRO) and monocyte chemo-attractant protein-1 (MCP-1)^[32,35-37]. It has been shown that leptin had proinflammatory and catabolic effects on chondrocyte proliferation. Leptin reduced proliferation of OA chondrocytes after the 48-hour treatment

ROLES OF ADIPOKINES IN OA

Adipokines exert both catabolic and anabolic roles in car-

and reduced chondrocyte proliferation in both control and OA after the 7-day treatment^[38].

However, anabolic activities of leptin in cartilage metabolism have also been reported, suggesting that catabolic effects of leptin may trigger compensatory anabolic responses. Dumond *et al*^[9] have showed that the production of insulin-like growth factor-1 (IGF-1) and transforming growth factor- β (TGF- β) can be induced by intra-articular injection of leptin. In addition, Figenschau *et al*^[39] demonstrated increased chondrocyte proliferation and enhanced proteoglycans and collagen synthesis after leptin incubation. Recent studies revealed that leptin can also promote proliferation, differentiation, type X collagen production and cytoskeletal remodeling in chondrocytes^[40-42]. The ob/ob mice showed reduced type X collagen synthesis in growth plates^[43].

Leptin increases the proliferation and differentiation of osteoblasts by inhibiting adipogenic differentiation of bone marrow cells. It has been found that leptin acts as a regulator for bone growth by inducing collagen synthesis, osteoblast proliferation and differentiation, bone mineralization, as well as endochondral ossification^[44-46]. The increased synthesis of leptin in OA subchondral osteoblasts is associated with the osteoblast dysfunction by increasing levels of alkaline phosphatase (ALP), osteocalcin (OC), collagen type I, and TGF- β ^[47]. The results of immunohistological studies showed that osteophytes expressed high levels of leptin^[5].

Nitric oxide (NO) is a proinflammatory mediator which promotes apoptosis, chondrocyte phenotype loss, as well as MMPs activation. The combination of leptin and interferon- γ can activate the production of type 2 nitric oxide synthase (NOS2) in cultured chondrocytes^[48]. Leptin, alone or in synergy with IL-1 β , has also been reported to enhance the production of inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2) and cyclooxygenase (COX)-2 in human OA cartilage and chondrocytes^[49,50]. Surprisingly, the incidence of knee OA between leptin deficient (ob/ob) obese mice and leptin receptor deficient (db/db) obese mice was not different when compared with wild-type mice^[51], suggesting that obesity alone was unable to induce knee OA and therefore leptin has a significant role in OA pathophysiology.

Adiponectin

Adiponectin seems to have both catabolic and anabolic effects on pathological changes of several tissues/cells involved in the initiation and progression of OA. Adiponectin and adiponectin receptors have been identified in human chondrocytes^[6]. Adiponectin exert a proinflammatory function by stimulating NOS2, MCP-1, MMP-1, -3, -9 and -13, IL-6, IL-8, PGE2, and vascular endothelial growth factor (VEGF) production from chondrocytes and cartilage^[36,52,53]. Adiponectin can induce vascular cell adhesion molecule 1 (VCAM-1) expression in murine and human chondrocytes, suggesting its role to perpetuate cartilage degradation by modulating molecules responsible for leukocyte infiltration at inflamed joints^[54]. In

addition, adiponectin levels in OA synovial fluid was correlated with aggrecan degradation^[55].

Adiponectin enhances proliferation and mineralization of human osteoblasts^[56]. The stimulation of osteoblasts with adiponectin increased the production of the inflammatory mediators IL-6, IL-8, and MCP-1. In grade 1 (non-ossified) osteophytes, adiponectin were detectable in connective tissue fibroblasts. In grade 2-5 (ossified osteophytes) a lower extent of adiponectin was expressed by osteoblasts, suggesting its involvement in early osteophyte formation^[57]. By contrast, adiponectin stimulates receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits the production of osteoprotegerin (OPG) in osteoblasts, which in turn indirectly activates osteoclasts^[58].

Interestingly, several studies have shown a protective effect of adiponectin in knee OA. Chen *et al*^[17] demonstrated down-regulated IL-1 β induced MMP-13 production and up-regulated tissue inhibitor of metalloproteinases (TIMP)-1 and -2 production in primary chondrocytes at both mRNA and protein levels. Moreover, adiponectin can stimulate release of antiinflammatory molecules such as IL-10 and IL-1 receptor antagonist^[59,60], suggesting the protective role against cartilage damage^[17]. In addition, adiponectin has been shown to increase murine chondrocyte proliferation, aggrecan synthesis, matrix mineralization, and upregulated type II and type X collagen expression^[61].

Visfatin

Visfatin affects the expression of chondrocyte-specific genes involved in extracellular matrix (ECM) formation. For example, it was observed that visfatin plus IGF-1 reduces the production of proteoglycans and collagen type II^[62]. Similarly, visfatin-treated mouse articular chondrocytes showed increased MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 expression^[24], suggesting a deleterious role of visfatin in articular cartilage. A recent study had shown that visfatin counteracted anabolic IGF-1 signaling and therefore reduced IGF-1-mediated proteoglycan synthesis in human chondrocytes^[62].

Moreover, elevated level of visfatin can reduce the expression of factors essential for the maintenance of the chondrocyte phenotype such as sex determining region Y-box 9 (SOX-9) and type II collagen^[63]. On the other hand, visfatin has also showed some anabolic properties. It was demonstrated that the inhibition of visfatin by pharmacological or siRNA techniques decreased the production of human chondrocyte specific matrix genes such as *collagen type2 alpha1 (COL2A1)* and *aggrecan (ACAN)*^[64]. Moreover, visfatin has been shown to induce the production of IL-1 β , TNF- α , and IL-6 in lymphocytes^[65].

It has been shown that visfatin is related to inflammation at the cartilage level by increasing MMP activity and NO production, as well as proteoglycan release in OA cartilage matrix^[66]. To note, visfatin plus IL-1 β stimulation is able to induce the synthesis of PGE2, a relevant

catabolic factor, in murine and human OA chondrocytes. The knockdown of visfatin expression by using a siRNA confirms this effect^[24].

Visfatin could influence differentiation of mesenchymal stem cells to adipocytes or osteoblasts *in vitro*^[67]. Visfatin is expressed in osteoblasts and osteoclasts in ossified osteophytes^[57]. Apart from the effect of visfatin on osteoblast proliferation and collagen type I synthesis^[68], it has been mentioned that visfatin also participates in osteoclast formation by inhibiting osteoclastogenesis^[65], suggesting its role in osteophyte formation.

Resistin

Although the study regarding the role of resistin in OA is sparse, some studies showed its direct effect on cartilage matrix and cytokine production. In the weeks immediately after joint injury, both plasma and synovial fluid levels of resistin were elevated. Resistin increased expression of MMP-1, -13, and ADAMTS-4 in human articular chondrocytes. In addition, resistin can stimulate inflammatory cytokines, such as IL-6 and TNF- α , as well as PGE₂ synthesis. Furthermore, resistin stimulates proteoglycan degradation, as well as inhibited the production of proteoglycan and type II collagen in mouse and human cartilage explants^[69]. It is produced in osteoblasts and osteoclasts in ossified osteophytes. Recombinant mouse resistin stimulates osteoblast proliferation and osteoclast differentiation, indicating a role in osteophyte formation^[70].

ASSOCIATIONS BETWEEN ADIPOKINES AND OA CLINICAL DATA

Leptin

In a 5-year cohort study, plasma leptin levels seemed to be positively associated with the occurrence of radiographic knee OA. Moreover, it showed a positive association with knee OA progression in subjects who have radiographic knee OA at baseline. However, the association disappeared after adjustment for BMI^[71]. In addition, leptin expression has been reported to be associated with the radiographic severity of OA, suggesting a potential role of leptin as a possible biomarker for quantitative detection of OA^[72]. In advanced grade OA cartilage, leptin and its long isoform receptor (Ob-Rb) levels in synovial fluid were significantly increased compared to healthy or adjacent mildly affected cartilage^[38]. In addition, elevated plasma leptin levels have been detected in the end-stage knee OA patients compared with controls, independent of BMI, age and gender. On the contrary, no association was found between plasma leptin levels and cartilage damage or synovial inflammation parameters in OA patients^[8]. In addition, Iwamoto's group did not find any association between plasma leptin levels and knee OA with grade 4 Kellgren-Lawrence (KL) scores, and Berry *et al*^[71] found no association between baseline plasma leptin levels and 2-year alterations of cartilage volume and defects in knee OA patients.

Adiponectin

Plasma adiponectin levels were significantly increased in end-stage knee OA patients compared with healthy controls independent of age, gender and BMI^[8]. Compared to less severely affected subjects, Koskinen *et al*^[73] found increased plasma adiponectin levels in patients with the radiologically most severe OA, grade 4-5 Ahlback scores, compared with patients who have less severe disease. Likewise, a significant association between plasma adiponectin levels and the Lequesne index was found^[74]. Filková *et al*^[15] also found that plasma adiponectin levels were higher in erosive OA patients than in nonerosive OA patients. The study of Gandhi *et al*^[75] showed an elevation in the adiponectin expression in IPFP from end-stage knee OA compared with that from early stage OA.

However, some clinical data support the protective roles of adiponectin as a molecule against cartilage damage in OA. Honsawek and Chayanupatkul showed an inverse correlation between plasma adiponectin and radiographic knee OA severity. They found increased adiponectin levels in grade 2 KL-scores knee OA patients compared with controls, but decreased levels in grade 4 KL-scores knee OA patients^[76]. In addition, it has been reported that patients with high adiponectin levels had a decreased risk for hand OA progression^[4]. However, another study showed no association between plasma adiponectin levels and radiographic hand OA severity^[77]. In addition, Berry *et al*^[71] did not find any association between baseline plasma adiponectin levels, cartilage volume changes and defects in knee OA subjects in a 2-year study. Interestingly, leptin/adiponectin ratio in synovial fluid was proposed to be a predictor of pain in knee OA patients. A lower leptin/adiponectin ratio correlated with lower knee OA pain when measured by the McGill Pain Questionnaire-Short Form (MPQ-SF) pain scale^[78].

Visfatin

Levels of visfatin in plasma and synovial fluid appeared to be associated with lipid metabolism, inflammation and clinical disease activity. Plasma visfatin concentrations showed a positive correlation with C-reactive protein (CRP), an inflammatory marker, indicating that it may be related to lipid metabolism and inflammatory processes^[79,80]. Visfatin levels in synovial fluid were increased in OA patients with more radiographic damage compared with patients with less severe disease. Synovial visfatin levels in grade 4 KL-scores were significantly higher than those of grade 3 KL-scores^[81].

Resistin

Gómez *et al*^[49] found no association between baseline plasma resistin levels and cartilage volume loss. Plasma resistin concentrations were positively associated with the prevalence of radiographic knee OA, independently with BMI, but it was not associated with the disease progression. Interestingly, the association between resistin and the presence of radiographic knee OA was more obvious

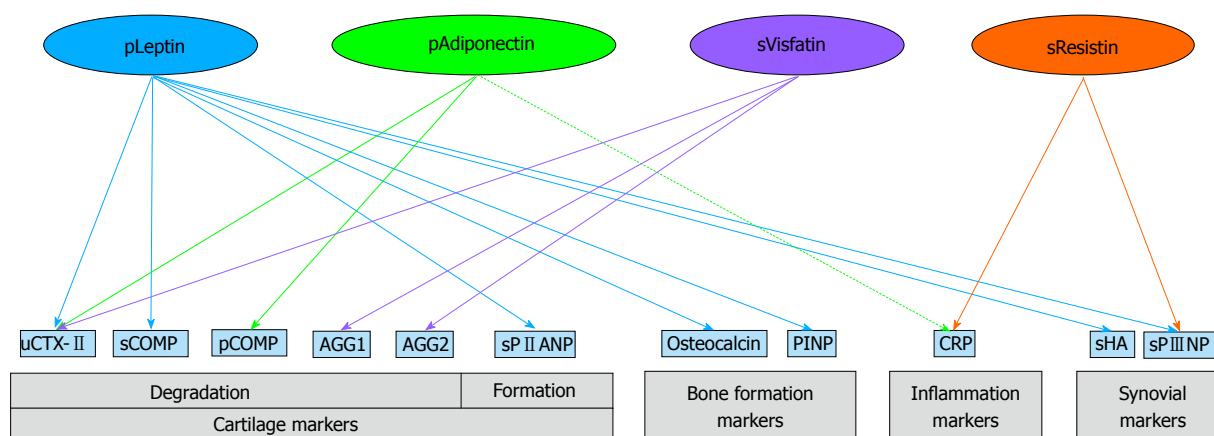


Figure 1 Association between adipokines and other osteoarthritis biomarkers. Solid lines represent positive association; dashed lines represent negative association. AGG: Aggrecan; PINP: N-terminal type I procollagen propeptide; COMP: Cartilage oligomeric matrix protein; CRP: C-reactive protein; CTX- II : C-terminal telopeptide of type II collagen; HA: Hyaluronic acid; P II AN: N-terminal propeptide of type II A procollagen; P III NP: N-terminal propeptide of type III procollagen; p: Plasma; s: Synovial fluid; u: Urine.

in OA patients with higher adiponectin levels^[74]. Moreover, plasma resistin levels were positively associated with histologically determined grades of synovial inflammation^[27]. The presence of radiographic changes such as subchondral erosion in hand OA was shown to be related with plasma resistin levels^[29].

ASSOCIATIONS BETWEEN ADIPOKINES AND OTHER OA BIOMARKERS

Leptin

Berry *et al*^[71] have revealed that plasma leptin was significantly associated with the level of bone formation markers, such as osteocalcin and N-terminal type I procollagen propeptide (PINP). In addition, leptin was positively associated with the cartilage biomarkers such as urine C-terminal telopeptide of type II collagen (uCTX- II), synovial cartilage oligomeric matrix protein (sCOMP), and synovial N-terminal propeptide of type II A procollagen (SP II ANP), as well as synovial markers such as synovial hyaluronic acid (sHA) and synovial N-terminal propeptide of type III procollagen (SP III NP) after adjustment for gender and age. However, after additional adjustment for BMI, these associations disappeared except for sPIIANP and sP III NP. In contrast, baseline expression levels of soluble leptin receptors OB-Rb were negatively associated with 2-year changes of the cartilage formation biomarkers P II ANP and bone formation markers, osteocalcin levels.

Adiponectin

Plasma adiponectin levels showed positive associations with markers of cartilage degradation such as uCTX- II and plasma COMP (pCOMP), but showed negative associations with plasma high sensitivity C-reactive protein (hsCRP) levels. These associations turned stronger after adjustments for BMI. In addition, Kang *et al*^[53] reported increased levels of collagenase-cleaved type II collagen

neopeptide in supernatants of OA cartilage explants incubated with adiponectin.

Visfatin

Synovial visfatin concentrations also showed positive correlation with uCTX- II, and two aggrecan degradation biomarkers: aggrecan (AGG) 1 and AGG 2^[81]. In addition, visfatin increases the release of a marker of cartilage breakdown sulfated glycosaminoglycans (s-GAG), suggesting its involvement in cartilage matrix degradation^[66].

Resistin

Plasma resistin concentrations were positively associated with sP III NP and hsCRP levels^[74]. In addition, A positive correlation has been found between synovial resistin levels and systemic markers of inflammation^[82]. Association between adipokines and other OA biomarkers are illustrated in Figure 1.

CONCLUSION

Prevention and early diagnosis are undoubtedly important for OA management. This review demonstrates that the levels of leptin, visfatin and resistin are elevated in OA patients, suggesting the catabolic role of these adipokines. In contrast, adiponectin is upregulated in OA patients and seems to play protective roles against OA. Adipokines might be also produced in other tissues and altered adipokine levels are also contributes to a wide range of obesity-related health problems such as autoimmune diseases, cardiovascular diseases and metabolic disorders. Therefore, the use of adipokines alone may not be enough for the prediction of OA risk. Nevertheless, adipokines exhibit prominent role in OA pathophysiology and show associations with OA progression. Thus it may become possible to use adipokines as biomarkers for monitoring disease progression and following the efficiency of therapeutic interventions. In addition, the ratio

of different adipokines levels or the ratio of adipokines and other biomarker levels might be used to better reflect the net effect of these molecules. Importantly, further experiments are needed to understand paradoxical relationship between adipokines and OA in both genders. However, uncertainty still remains whether adipokines could be utilized as biomarkers in clinical practice for OA.

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