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Review article

An extensive review regarding the adipokines in the pathogenesis and progression of osteoarthritis

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ABSTRACT

Osteoarthritis is the most prevalent form of aging-related joint diseases, and its etiology is still not fully understood. Obesity has been recognized as one of the most significant and potentially preventable risk factors for osteoarthritis. Beyond mechanical loading, adipokines, including leptin, visfatin, adiponectin, resistin and others, are demonstrated to have metabolic implications in the pathogenesis and progression in obesity-induced osteoarthritis by modulating the pro/anti-inflammatory and anabolic/catabolic balance, apoptosis, matrix remodeling and subchondral bone ossification. Accordingly, adipokines emerge as potential candidates to link these two entities, and may serve as putative targets for disease-modifying drugs for osteoarthritis, especially for obese patients. Here we summarize studies over the past decades on the pivotal role of adipokine family in osteoarthritis, and aim to shed a light on the causative link between obesity and osteoarthritis. Notably, due to difficulties in separation of the metabolic effect from the mechanical effect of fat excess, researches on osteoarthritis in non-weight-bearing joints may provide a promising direction and more emphasis shall be put on them in future.

1. Introduction

Osteoarthritis (OA) is by far the most common form of arthritis that affects human joints. It is a decades-long process characterized by gradual loss and abrasion of articular cartilage, alterations of extracellular matrix (ECM), subchondral bone ossification and formation of osteophytes [1]. As a leading cause of morbidity and disability, OA carries high socio-economic cost. It is reported that aggregate medical expenditure for the estimated 30.8 million patients with OA and allied disorders in the US averaged $340 billion *per* year from 2008 to 2011 [2].

Intrinsic and extrinsic risk factors are attributable to the

Abbreviations: 15-PGDH, 15-hydroxy-PG dehydrogenase; A/L, adiponectin/leptin; ADAMTS-4/-5, a disintegrin and metalloproteinase with thrombospondin motifs 4 and 5; AdipoR1/2, adiponectin receptor 1/2; AGG, aggrecan; AKt, protein kinase B; AMPK, 5′-AMP-activated protein kinase; AP-1, activator protein-1; AS, atherosclerosis; AT, adipose tissue; bFGF, basic fibroblast growth factor; BMD, bone mineral density; BMI, body mass index; CaMKII, CaM kinase II; CCL2, chemokine (C-C motif) ligand 2; COL II, collagen type II; COMP, cartilage oligomeric matrix protein; COX-2, cyclooxygenase 2; CTX-II, C-terminal crosslinked telopeptide type II collagen; ECM, extracellular matrix; Erk, extracellular signal-regulated kinase; fAd, full-length adiponectin; gAd, globular domain; GEP, granulin-epithelin precursor; GPNMB, glycoprotein (transmebrane) nmb; HDL, high density lipoprotein; HMW, high molecular weight; hsCRP, high-sensitivity C-reaction protein; ICAM-1, intercellular adhesion molecule-1; IFP, infrapatellar fat pad; IGF-1, insulin-like growth factor-1; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1; ITIH5, inter-alpha-trysin inhibitor heavy chain family, member 5; JAK2, janus kinase 2; JNK, jun N-terminal kinase; JSN, joint space narrowing; K&L, Kellgren & Lawrence; Kc, keratinocyte chemoattractant; Knockout, KO; LCN2, lipocalin-2; LDL, low density lipoprotein; LIMK, LIM domain kinase; LKB1, liver kinase B1; LMW, low molecular weight; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMPs, matrix metalloproteinases; MMW, middle molecular weight; mPGES-1, microsomal PGE synthase-1; NAD, nicotinamide adenine dinucleotide; Nampt, nicotinamide phosphoribosyltransferase; NF-kB, nuclear factor Kappa B; NGAL, neutrophil gelatinase-associated lipocalin; NO, Nitric Oxide; NOS2, nitric oxide synthase type II; NUCB2, nucleobind-2; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OASFs, osteoarthritis synovial fibroblasts; OB-Rb, leptin receptors; OBRl, long isoform of leptin receptor; OBRs, short isoform of leptin receptor; PBEF, pre-B-cell colony-enhancing factor; PCDGF, PC-cell derived growth factor; PEPI, proepithelin; PGE2, prostaglandin E2; PGRN, progranulin; PI3K, phosphatidylinositol 3-kinase; PIIANP, N-terminal type IIA procollagen propeptide; PINP, N-terminal type I procollagen propeptide; PKC, protein kinase C; RASF, rheumatoid arthritis synovial fibroblasts; RHoA, ras homolog gene family, member A; ROCK, rho-associated protein kinase; ScAT, subcutaneous adipose tissue; SERPINE2, serpin peptidase inhibitor, clade E member 2; SF, synovial fluid; sGAG, sulfated glycosaminoglycan; SIRT1, sirtuin type 1; SOCS-3, suppressor of cytokine signaling-3; STAT-3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor-beta1; TIMP, tissue inhibitor of metalloproteinase; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TNFR, TNF-receptor; VAS, visual analog scale/score; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; WAT, white adipose tissue; WC, waist circumference; WISP2, Wnt1 inducible signaling pathway protein 2; WOMAC, Western Ontario and McMaster Universities Arthritis Index

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pathogenesis of OA, including congenital defect, aging, gender, trauma, and obesity [3]. These factors impair cartilage homeostasis through dysregulation of intracellular signalings. Obesity has been traditionally thought as one of the most influential but modifiable risk factor of OA. Previously, it is well-recognized that obese individuals are more vulnerable to suffer from OA due to excessive mechanical stress on weight-bearing joints, such as hip and knee joints. However, as our comprehension of OA evolved, we find that, pound for pound, not all the obese individuals are equivalent for the development and progression of OA [4]. Furthermore, high incidence of OA also occurs in non-weight-bearing joints like hands and shoulders [5,6]. Intriguingly, exercise intervention could improve physical functions, instead of deterioration and could reduce pain in OA patients or animal models [7–11]. Taken together, we may propose that increased joint load is inadequate to account for the increased incidence of obesity-induced OA and other factors shall be considered. Recently, obesity has been proved as a low-grade systemic inflammatory disease as well [12], and accumulating evidences have demonstrated a prominent role of metabolic factors, adipokines in particular, in the pathophysiology of OA [13–15].

In addition to energy utilization and storage, adipose tissue (AT) represents a metabolically active organ releasing cytokines collectively named adipokines [16,17]. Adipokines, or adipocytokines, including leptin, visfatin, adiponectin, resistin, omentin-1, chemerin, vaspin and others, are prevailingly or partially produced by by adipocytes from white AT (WAT) or subcutaneous AT (ScAT), and are released into systemic circulation. Previous studies have shown that adipokines could modulate various endocrine axes, regulate energy homeostasis and bone metabolism [18–20]. Meanwhile, adipokines could be partly derived from infrapatellar fat pad (IFP), an intracapsullar and extra-synovial tissue in the knee joint [21]. In addition to AT, other joint tissues including cartilage, synovium, osteophyte, and meniscus, *etc*., especially in OA patients, are also capable of producing certain adipokines [22,23]. Recently, research was expanded to explore the relationship between adipokines and OA as mounting evidences of aberrant expression of adipokines found in OA versus unaffected counterparts [24]. Meanwhile, increasing studies have reported that adipokine may represent as a potential non-radiographic alternative to detect early-stage of OA and to assess disease severity [25,26]. Of note, regulation of adipokines might ameliorate the pernicious effects during OA. To sum up, these findings suggest a critical role of adipokines in OA, and adipokines may serve as surrogate targets for disease-modifying drugs for obese OA individuals. Here we give an extensive review focused on the epidemiology, the possible mechanisms and molecular pathways of adipokines in the onset and progression of OA, and we hope to shed a light on the causative link between obesity and OA.

2. Correlation between adipokines and OA

2.1. Leptin

Leptin is a 16 kDa hormone encoded by obese gene and predominantly produced in WAT. It consists of a conserved non-glycosylated polypeptide of 146 amino acids [27]. Leptin is initially described as a satiety factor with neuroendocrine properties, exerting actions in energy homeostasis regulation by inhibiting food intake and promoting energy consumption [28–30]. The biological activity of leptin is mediated by leptin receptors (OB-Rb), which are found in many tissues with several alternatively spliced forms, including two major isoforms in human: a long form (OBRl) and a short form (OBRs) [31,32]. Compared with non-obese counterparts, obese individuals have higher prevalence of OA and enhanced level of leptin, which draws forth the hypothesis that leptin could possibly be the link to obesity-induced OA [33].

In addition to WAT, synovium and IFP are major resident sources of leptin. SF leptin concentration is equivalent or even higher than serum one [22]. Besides, dedifferentiated osteoblast and chondrocyte are also capable of leptin synthesis and secretion, as abundant expression of leptin is observed in OA cartilage and osteophytes while trace amount of leptin is produced in normal cartilage [22,34,35], suggesting a local production of leptin during OA [36,37].

Leptin concentrations in serum [38,39], and SF [40] are distinctly higher in OA patients compared with controls. Moreover, a recent study reported that SF leptin level was specifically elevated in female, but not male OA patients in comparison to healthy individuals, implying a gender-specific distribution of leptin [41]. The expression of negative regulators of leptin-suppressor of cytokine signaling-3 (SOCS-3), is dramatically decreased in cartilage from obese OA patients [42]. Both expression of leptin and OB-Rb are significantly higher in advanced defective area than those in the adjacent intact regions of OA cartilage [43]. It is supposed that extremely high leptin levels in circulation may be indicative of leptin resistance, a state in which the body is hyporesponsive to leptin signaling. Thereby, metabolic disorders developed and diseases including cardiovascular disease and OA possibly progressed [44].

Serum leptin is strongly associated with prevalent and incident radiographic OA according to a survey lasting over a decade [45]. Moreover, serum leptin concentration shows significant correlation with weight, body mass index (BMI), waist circumference (WC), total fat mass, female gender, and bone mineral density (BMD), but slight or no correlations with age, visual analogue scale (VAS), lequesne index, or bone turnover markers of OA [38,42,46–50]. Fowler-Brown et al. further proved that approximately half of the total effect of elevated BMI on knee OA may be mediated by serum leptin [51]. The results regarding the relationship between leptin and radiographic severity of OA are conflicting. Some researchers have reported that both leptin levels in SF [40] and in serum/plasma [52,53], were positively related to OA radiographic severity defined by Kellgren & Lawrence (K&L) or Ahlback's criteria. Whereas others failed to show any association between these two entities [46,48,54]. Recently, a newly published meta-analysis incorporating 11 selected studies supported that increased leptin concentration was strongly associated with disease severity in OA patients, especially among females [39]. Furthermore, a longitudinal survey with 511 participants enrolled reported that premenopausal women with higher baseline serum leptin concentration were predicted poorer mobility-based functioning, including longer stair climb, sit-to-rise, two-pound lift times and shorter forward reach distance after adjustment for confounding factors [44]. Moreover, leptin is positively associated with femoral cartilage volume as well as painful joint burden with OA, particularly among females [55–57]. Nevertheless, Staikos C and colleagues reported that the ratio of SF to plasma leptin might be a more suitable biomarker in evaluation of knee OA severity than plasma leptin alone [53]. As for hip OA, only the joint space narrowing (JSN), but not the presence or severity of osteophytes, was found tightly associated with serum leptin levels [58].

Inflammation is a complex mechanism of cell responses to acute or chronic injuries that highly correlated with OA [59]. Most of the previous studies have indicated that leptin may exert as a pro-inflammatory and catabolic factor in cartilage metabolism by acting alone or synergistically with other pro-inflammatory stimuli, therefore contributing to an increased risk for OA [43,60–62]. Interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) are central inflammatory cytokines that are well-documented for active involvement in the pathophysiology of OA, and both their expressions are elevated after stimulation of leptin [43,63,64]. Leptin could cause concentration- and time-dependent increase in IL-8 production in OA synovial fibroblasts (OASFs) via the OBRl/janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) pathway, as well as the activation of insulin receptor substrate-1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKt)/nuclear factor kappa B (NF-κB) pathway and the subsequent recruitment of p300 [31]. Besides, leptin also increases expression of IL-6 by activation of OBRl/IRS-1/PI3K/Akt and activator protein-1 (AP-1) pathway [32]. The effect of leptin on IL-6, IL-

8 production is abolished by a selective inducible nitric oxide synthase (iNOS) inhibitor, indicating that leptin upregulates pro-inflammation in a nitric oxide (NO)-dependent way [65,66]. Moreover, leptin can also promote inflammation in OA joints either by inducing Th1 phenotype development from stimulated lymphocytes [16,67], or enhancing infiltration of leukocyte and monocyte by upregulating expression of vascular cell adhesion molecule-1 (VCAM-1) [68].

Matrix metalloproteinases (MMPs) could degrade numerous substrates, such as proteoglycans and collagen in articular cartilage, and therefore act as major mediators of cartilage degeneration in OA [69,70]. Prostaglandin E2 (PGE2) is another catabolic factors involved in OA, which could increase MMPs production and may be implicated in joint pain [71]. SF leptin in OA patients positively correlates with MMP-1/-3 [72]. In human cartilage, leptin alone or in combination with IL-1 (or IL-1β) can enhance the expression of iNOS and Cyclooxygenase 2 (COX-2), and production of NO, PGE(2), MMP-1/-3/-9/-13 and tissue inhibitor of metalloproteinase-2 (TIMP-2) possibly through activation of NF-κB, protein kinase C (PKC), and c-jun N-terminal kinase (JNK) pathway [43,65,72,73]. While in bovine cartilage, leptin alone or in synergy with IL-1 also strikingly induces cartilage collagen release and MMP-1/-13 expression by upregulating collagenolytic and gelatinolytic activity, with a concomitant activation of STAT1, STAT3, STAT5, mitogen-activated protein kinase (MAPK), Akt and NF-κB pathway. A disintegrin and metalloproteinase with thrombospondin motifs 4 and 5 (ADAMTS-4/-5) are considered as the most efficient aggrecanases and the best candidates in OA progression. Cathepsin D is attributable to the proteolytic processing of the core protein of aggrecan (AGG) in the initial phase of OA [74,75]. *In vivo* experiment has showed that expression of ADAMTS-4/-5, MMP-2/-9, cathepsin D and collagen II (COL II) are markedly increased, while basic fibroblast growth factor (bFGF) decreased in cartilage after injection of recombinant murine leptin into knee joints of rats. In addition, proteoglycan is also histologically depleted in articular cartilage after treatment with leptin [33]. Another study by Yaykasli et al. also confirmed a role of leptin in upregulating ADAMTS-4/-5/-9 gene expression via MAPK and NF-κB signaling pathway [76]. Of note, there are few studies claimed that physiological dose of leptin has no effect on breakdown of explanted cartilage or meniscus neither in the presence or absence of IL-1α and fatty acids, implying that leptin may mediate OA pathogenesis through an indirect effect [77,78].

However, there are sparse studies available reporting a protective role of leptin in OA by exerting anti-inflammatory and anabolic functions as well. Gross et al. found that the free form of leptin was negatively associated with IL-6, suggesting its free form may down-regulate inflammation [79]. Another study demonstrated that leptin may suppress TNF-α-induced chondrocyte death via JNK pathway in articular chondrocytes [80]. Besides, expression of leptin *in vitro* parallels those of growth factors, such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta1 (TGF-β1), which is consistent with *in vivo* studies, showing that intraarticular leptin injection strongly stimulates chondrocyte anabolism and induces the synthesis of IGF-1 and TGF-β1 at both transcriptional and translational levels [34,35]. Collectively, leptin may have a dual effect on OA in both pro-/anti-inflammatory and catabolic/anabolic ways. Possibly, enhanced catabolic/pro-inflammatory and impaired anabolic/anti-inflammatory roles lead to a detrimental effect overall. Further intensive studies are needed to address this metabolic balance of leptin on OA.

Finally, leptin could participate in subchondral bone formation and cytoskeletal remodeling in chondrocytes. Baseline leptin level is associated with increased levels of bone formation biomarkers, including osteocalcin and N-terminal type I procollagen propeptide (PINP), while soluble OB-Rb is linked with reduced levels of osteocalcin and the cartilage formation biomarker- N-terminal type IIA procollagen propeptide (PIIANP), and increased cartilage volume loss [52,81]. Diminished leptin causes reduction of subchondral bone thickness and elevation of relative trabecular bone volume in the tibial epiphysis [82]. Furthermore, leptin could mediate cytoskeletal remodeling in chondrocytes via the ras homolog gene family, member A (RhoA)/rho-associated protein kinase (ROCK)/LIM domain kinase (LIMK)/cofilin pathway [83] and enhance proliferation of OA osteoblast from subchondral bone mediated by increased phosphorylated extracellular signal-regulated kinase (Erk1/2) and p38 concentrations in a dose-dependent manner [84]. Similarly, leptin administration also stimulates proliferation of nucleus pulposus cells, causing formation of cell cluster and proliferation of fibro-cartilaginous tissue [85]. Since intervertebral disc degeneration resembles OA in involvement of increased cell proliferation, this study might implicate that leptin in local joints could induce proliferation of OASFs and osteoblasts, and subsequently contribute to osteophyte formation.

2.2. Visfatin

Visfatin, initially known as pre-B-cell colony-enhancing factor (PBEF) and later found to be the secretory form of nicotinamide phosphoribosyltransferase (Nampt), is a functionally multi-faceted and ubiquitously protein acting on a variety of diseases including OA [86,87].

Both serum and SF visfatin concentrations are significantly higher in OA patients than those in controls [88,89]. SF visfatin level exceeds those in paired serum [88] and is positively correlated with the K&L grade and degradation biomarker of C-terminal crosslinked telopeptide type II collagen (CTX-II) and AGG [89]. Visfatin is mainly synthesized and released by adipocytes and other inflammatory cells in AT. Additionally, osteophytes, IFP, synovium and OA chondrocytes [8] are also important sources of visfatin. Specifically, visfatin is naturally produced in a dimeric conformation by these OA tissues, which correspond to its enzymatically active form [90]. Visfatin is positively associated with pain hip, but not with knee pain [57,91]. Further study has shown that extracellular visfatin may dose-dependently mediate OA pain via stimulating the expression and release of nerve growth factor by chondrocytes [92].

Visfatin has been generally proved to be involved in the pro-inflammation process in OA. IL-1β or lipopolysaccharide (LPS), the key mediators of cartilage destruction in OA [64], could enhance visfatin expression, showing an association of inflammatory cytokines with visfatin [93]. Visfatin is able to induce secretion of keratinocyte chemoattractant (Kc), a murine equivalent chemokine as IL-8 [94]. Consistently, visfatin has been recently indicated to induce the expression of IL-6, Kc and monocyte chemoattractant protein 1 (MCP-1) greatly in chondrocytes and osteoblasts, thus showing a deleterious impact during OA [90].

Besides, the catabolic function of visfatin has been well recorded in OA. Physiological concentration of visfatin could act synergistically with IL-1/IL-1β to promote degradation of both porcine cartilage and meniscus, as evidenced by increased MMPs activity, NO production and proteoglycan release [77,95]. While in normal human articular chondrocytes, visfatin can dose-dependently inhibit IGF-1-stimulated proteoglycan synthesis by activating the Erk pathway [96]. Moreover, in murine articular chondrocytes, visfatin may promote expression of PGE2, ADAMTS-4/-5 and MMP-3/-13, and reduce synthesis of HMW (high molecular weight) Prostaglandin. Notably, visfatin triggers excessive release of PGE2 due to increased synthesis of microsomal PGE synthase-1 (mPGES-1) and decreased synthesis of nicotinamide adenine dinucleotide (NAD)-dependent 15-hydroxy-PG dehydrogenase (15-PGDH), and this effect could be attenuated in visfatin gene knockout (KO) model [95], or IR expression blockage in chondrocyte. Similarly, another experiment confirmed that inhibition of visfatin activity applying a pharmacologic competitive inhibitor- APO866 also decreased PGE2 release, whereas the addition of exogenous nicotinamide increased it, suggesting the catabolic actions of visfatin involve regulation of IR pathway, and possibly through the control of intracellular Nampt enzymatic activity [87,97].

Intriguingly, visfatin could also possess a unique role in protecting the chondrocytes from differentiation and apoptosis by upregulating sirtuin type 1 (SIRT1), which is an NAD-dependent histone deacetylase regulating gene expression, differentiation, development, and organism life span [98]. Briefly, SIRT1 regulates IL-1β-mediated chondrocyte differentiation dependent on Erk and p38 kinase activities. Subsequently, Erk and p38 activated by SIRT1 induce SIRT1 activation in turn, forming a positive feedback loop to augment downstream signaling of these kinases [93]. In addition, elevation of SIRT1 release or activity in human OA chondrocytes leads to a dramatic increase in cartilage-specific gene expression in a Sox9-dependent fashion [99]. As visfatin is widely known as a primary, rate-limiting enzyme involved in NAD biosynthesis, thus alterations in visfatin could cause changes in NAD + levels, SIRT1 activity, and subsequently the regulation of dedifferentiation as well as cartilage-specific gene expression. Visfatin, therefore, could probably provide a protective role in cartilage by activating SIRT1, and then inducing dedifferentiation of chondrocytes and elevating expression of genes encoding cartilage and ECM [99].

In summary, visfatin shows pleiotropic functions in initiation and progression of OA. From one aspect, it could exert a detrimental effect on chondrocytes via its pro-inflammatory and catabolic function. Nevertheless, from another aspect, it could protect chondrocytes from apoptosis and differentiation with activation of SIRT1. More investigations are required to explore its comprehensive role in the pathogenesis of OA in future.

2.3. Adiponectin

Adiponectin is encoded by a region on chromosome 3 in humans [100]. Full-length adiponectin (fAd) consists of 247 amino-acids containing an N-terminal signal sequence, a hypervariable domain, a collagen-like domain and a C-terminal globular domain (gAd). gAd is an active peptide generated by proteolytic cleavage [101,102]. Adiponectin is probably the most plentiful circulating adipokine which draws considerable attention in researches. It could modulate energy metabolism and insulin sensitivity, and has shown anti-diabetic and anti-atherogenic properties. A variety of molecular weight forms of adiponectin exists in circulating system, including low (LMW), middle (MMW) and high (HMW) isoform, all of which have different biological properties that mainly mediated through two classical adiponectin receptor subtypes: AdipoR1 and AdipoR2 [103,104].

Plasma/serum adiponectin levels in OA patients are higher than those in healthy individuals [38,105], but there are few studies showing that the difference is not statistically significant after adjustments for age, gender, and BMI [106,107]. Adiponectin level in plasma or released from OA cartilage is positively correlated with high density lipoprotein (HDL) [108], lequesne index [46] and radiological severity of OA [107,109]. Yet no associations between serum level of adiponectin and low density lipoprotein (LDL) [108], cartilage damage [38], or duration of knee OA are seen [46]. However, serum adiponectin concentration is found elevated in female patients with erosive hand OA compared with non-erosive one [110]. Studies regarding the correlation between serum adiponectin and OA pain have aroused controversy. Some researchers claimed a positive association between adiponectin concentration and clinical pain variables, including VAS and Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores [107], while another study argued that plasma adiponectin level was not significantly correlated with VAS score [46]. A recent study revealed that plasma adiponectin level was positively associated with painful joint burden only among female OA patients, implicating this correlation might be gender-specific [56]. SF adiponectin level is remarkably lower with respect to paired serum [106,111–113]. Besides, SF adiponectin level shows significantly positive correlation with degradation markers of AGG, AGG1 and AGG2 [107,113], yet negative correlation with radiographic disease severity, and knee OA pain [57,106]. The percentages of HMW and hexamer form *per* total adiponectin in SF are lower than those in plasma, whereas the trimer form is higher. Further study showed that total adiponectin, rather than HMW form was negatively associated with radiographic progression in patients with hand OA [114], while positively linked with knee OA [115]. Both human and murine chondrocytes express AdipoRs, and the expression of both AdipoR1 and AdipoR2 are significantly higher in lesional than in nonlesional areas of OA cartilage [116]. Alternative study showed that AdipoRs were downregulated in OA chondrocytes compared with normal counterparts, and suggesting that low level of AdipoRs in OA may reduce its tissue sensitivity to adiponectin [117]. A possible explanation for the above discrepancies may be attributable to differences in methodologies, disease progression, populations, and inappropriate controls for normalization [118].

Though extensively studied, the exact effect of adiponectin in OA is still contradictory [119]. On one hand, adiponectin could upregulate TIMP-2 and downregulate IL-1β-induced MMP-13, clearly indicating a chondro-protective role in the progression of OA by exerting anti-inflammatory and anabolic functions [111]. Reversely, emerging studies have established a pro-inflammatory and catabolic role of adiponectin in OA. Adiponectin level in serum or released by OA cartilage is positively correlated with the degradation biomarker, cartilage oligomeric matrix protein (COMP), MMP-3/-13 and mPGES [72,120]. Adiponectin stimulates the expression of IL-6, MMP-1/-3/-13, iNOS production in both chondrocytes and OASFs via the AdipoR1/5′-AMP-activated protein kinase (AMPK), MAPK and NF-κB pathway, leading to inflammation and matrix degradation during OA[72,116,121,122]. Intercellular adhesion molecule-1 (ICAM-1) is a critical adhesion molecule that mediates monocyte adhesion and infiltration during OA. Adiponectin could increase ICAM-1 expression in human OASFs via the liver kinase B1 (LKB1)/CaM kinase II (CaMKII), AMPK, c-Jun and AP-1 signaling pathway, and subsequently promote adhesion of monocytes to OASFs [118]. Besides, adiponectin could increase expression of VCAM-1 in human and murine chondrocytes, and therefore perpetuate cartilage-degrading processes at inflamed OA joints [68]. Furthermore, adiponectin augments the production of PGE2 in OASFs in a concentration-dependent manner [123]. Moreover, adiponectin could increase nitric oxide synthase type II (NOS2), IL-6, MMP-3/-9 and MCP-1 in cultured chondrocytes [124]. The various forms of adiponectin with diverse biological properties in circulating system have been mentioned previously. Recently, fAd, instead of gAd, has been report to increase the production of PGE2 and MMP-13 in human chondrocytes, indicating its single active form [120]. Since the contradictory findings have been observed on the role of total adiponectin in OA, further probe into the relative contribution of each adiponectin isoform to the inflammation response and matrix degradation in OA joint damage is required [125].

2.4. Resistin

Resistin is a prepeptide in circulation as a dimeric protein consisting of two 92-amino acid polypeptides [126]. Since it is firstly found in foci of inflammation as an inflammatory factor [16] and originally described as an adipocyte-specific hormone, resisitin has been suggested to be an important link among inflammation, obesity and OA [127,128].

Serum resistin level is distinctly higher in OA patients compared to controls [38], especially in males or overweight/obese OA patients [36,129,130]. In a cohort study recruiting 1002 subjects with early-stage symptomatic OA, plasma resistin showed positive association with present and incident radiographic knee OA [52]. On the contrary, some studies failed to demonstrate any remarkable association between serum resistin and OA radiographic severity, BMI, BMD, pain or cartilage volume [50,131–133]. In another study performed by De Boer et al., no association between serum resistin level and cartilage damage was found, however weak but positive association of resistin with local synovial tissue inflammation still existed [38], indicating a potential pro-inflammatory role of resistin in OA. Perruccio et al. also showed

that higher plasma resistin level was associated with lower painful joint burden only among men, suggesting the likelihood of a sex-specific role of serum/plasma resistin among OA individuals [56].

Besides, resistin is also abundantly presented in OA joints, and OA cartilage is capable of secreting resistin. SF resistin, but not serum one, is positively associated with articular cartilage damage, symptomatic and radiographic disease severity of OA, as characterized by Noyes scores, WOMAC scores, K&L grades, and physical functions respectively [134]. Other studies have confirmed that SF resistin among OA patients are positively correlated with inflammatory and catabolic factors, including IL-6, MMP-1/-3, and CTX-II [133,134]. Therefore, SF resistin, rather than serum resistin, may serve as a better putative biomarker in disease severity of OA regardless of gender [134].

Evidences from *in vitro* experiments have shown that resistin downregulated COL II and AGG expression and upregulated expression of ADAMTS-4 and MMP-1/-3 in human articular chondrocytes [135]. Besides, recombinant resistin could induce dose-dependent loss of proteoglycan and enhance production of PGE2 in mouse cartilage, and could inhibit synthesis of proteoglycan in human cartilage [136]. Furthermore, a recent study reported that resistin strongly induced substantial sulfated glycosaminoglycan (sGAG) depletion from meniscal tissue explants, indicating a catabolic and pro-inflammatory effect of resistin in OA [137].

2.5. Chemerin

Chemrin, isolated as the natural ligand of the G protein-coupled receptor ChemR23, is a secreted protein with a complex but well-documented role in immune function [138,139]. Both chemerin and ChemR23 are produced or expressed in human adipocytes, chondrocytes and OASFs [140,141]. SF chemerin level is significant lower with regard to paired serum, and is correlated with disease severity evaluated by K&L grading score [142].

Though studies regarding possible mechanism of chemerin in OA are limited, chemerin is speculated to have an implication in OA initiation and progression via regulating pro-inflammatory functions. As stated above, chemerin could significantly increase toll-like receptor 4 (TLR4) mRNA expression and synthesis of the chemokine (C-C motif) ligand 2 (CCL2) in SF, proposing a role of chemerin in innate immune system-associated inflammation [141]. Besides, chemerin stimulates migration of leukocytes to sites of inflammation and also increases inflammatory signaling in chondrocytes, suggesting its function in local joint inflammation. Therefore, the role of chemerin in metabolism and inflammation in local joint supports the hypothesis of positive relationship between chronic inflammation and obesity-related OA [143,144]. However this idea remains rather tempting, further studies are still required to elucidate the precise role of chemerin in OA.

2.6. Omentin-1

Omentin, also termed as intelectin-1, is a recently identified visceral adipose tissue-derived cytokine that is abundant in plasma [145,146]. It is encoded by omentin-1 and omentin-2 gene, and the former is the major circulating form in human extracellular fluid [147].

Few but consistent studies with respect to the causative link between omentin-1 and OA have been performed. A cross-sectional study has been designed to assess the correlation between omentin-1 and OA radiographic severity. Though they failed to detect any significant differences in serum omentin-1 between knee OA patients and healthy controls or among patients with different radiographic severity, further multinomial logistic regression analysis revealed a negative correlation between SF omentin-1 level and K&L scores in OA patients after adjustment for confounding factors [148]. Another study also demonstrated that omentin-1 in SF, but not in serum, was inversely correlated with self-reported pain, and physical disability in knee OA patients, indicating it might serve as a potential independent predictive biomarker for symptomatic severity of OA [149]. However, these results might be flawed due to several limitations. Firstly, both studies did not collect SF samples from healthy controls for ethical concerns, thus whether there is a difference of SF omentin-1 level in these two groups still remains unknown. Secondly, both studies have been designed as cross-sectional studies with a relatively small sample size, which limited the statistical power for assessment [148,149]. Lastly, subjects recruited in both studies are Chinese, while data in other races are lacking, which may bring in some bias. Therefore, prospective longitudinal studies with a larger population are still needed to confirm these results and may reveal more detailed information on the pathogenic role of omentin-1 in OA.

A recently published study showed that omentin-1 suppressed expression of MMP induced by IL-1β in human chondrocytes. Consistently, omentin-1 could inhibit the degradation of COL II and AGG induced by IL-1β in a dose-dependent manner, therefore indicating a potential chondroprotective capacity of omentin-1 *in vitro* [150].

2.7. Vaspin

Vaspin is a newly identified adipokine majorly derived from visceral AT with insulin-sensitizing effects [151–153]. More abundant vaspin gene expression was detected in visceral AT from obese individuals than the lean peers [154]. Expression of vaspin gene and protein are observed in joint tissues, including cartilage, synovium, meniscus, IFP, and osteophyte, suggesting vaspin may undergo specific metabolic pathways in the joint cavity during OA [155].

Serum vaspin levels exceed those in paired SF in OA paitents, but the difference is not observable. Besides, serum or SF vaspin level is not associated with age, gender or BMI [155]. Recently, vaspin has been suggested to exert as a compensatory mediator for abrogating obesity and its inflammatory complications [156]. Serum vaspin level in OA patients is markedly lower than the healthy controls, showing an inverse tendency compared to other adipokines, which indicates that vaspin may play an opposing role from other adipokines [155]. Treatment of vaspin in chondrocytes shows neither catabolic nor anabolic effects. However, low concentrations of vaspin can dose-dependently suppress the IL-1β-triggered production of MMP-2/-9, ADAMTS-5, cathepsin D, COX-2, PGE2 and iNOS, suggesting an indirect anti-catabolic and anti-inflammatory effect of vaspin in response to IL-1β on chondrocytes. Thus, vaspin may possess an anti-catabolic and anti-inflammatory effect in chondrocytes and possibly be a potential protective adipokine during OA [75].

2.8. Lipocalin-2

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NGAL), 24p3, or p25, is a recently characterized mechanoresponsive adipokine [157,158]. LCN2 is a 25 kDa glycoprotein encoded by the LCN2 gene, and circulates in a covalent complex with MMP-9 [159]. LCN2 promoter region contains the binding sites of key inflammatory transcription factors, including NF-κB, STAT1/3 and C/EBP. Additionally, LCN2 acts as an anti-inflammatory factor in regulating macrophage polarization via NF-κB–STAT3 loop activation [160]. Expression of LCN2 in osteoblasts and chondrocytes is augmented by various inflammatory factors [157,159].

LCN2 levels are upregulated in SF and cartilage in OA patients, which underlies possible mechanisms on cartilage degradation via blockage of MMP-9 auto-degradation and suppression of chondrocyte proliferation [157,161]. Moreover, couples of studies have revealed the role of LCN2 as a sensor of mechanical load, inflammatory status and catabolic stimuli of the joint, suggesting its involvement in OA pathophysiology [162,163]. Nevertheless, a recent study reported that LCN2 is not sufficient to cause OA cartilage destruction, as LCN2-KO mice model was observed with no alteration in cartilage destruction induced

by destabilization of the medial meniscus [164]. Further studies are demanded to reveal the role of LCN2 in human OA development.

2.9. Progranulin

Progranulin (PGRN), also known as granulin-epithelin precursor (GEP), proepithelin (PEPI), acrogranin, or GP88/PC-cell derived growth factor (PCDGF), is a cysteine-rich secretory glycoprotein encoded by the GRN gene. PGRN is abundantly expressed in many cell types, showing complex functionality in multiple processes, including anti-inflammation. PGRN is a key regulator of inflammation, as it directly interacts with TNF receptors and consequently acts as an antagonist of TNF/TNF-receptor (TNFR) signaling. Furthermore, PGRN suppresses production of chemokines and induces Treg population, but counteracts with several proteinases like MMP 9/12/14 and ADAMTS-7 [165,166].

Moreover, PGRN has been implicated in the pathogenesis of OA. Aged PGRN-KO mice may develop OA-like phenotype featured by breakdown of cartilage structure [167]. Whist non-aged PGRN-KO mice showed a severe OA phenotype in surgically-induced OA model [168]. Meanwhile, both recombinant PGRN and PGRN-derived Atsttrin could effectively prevent the onset and progression of OA in these models, as well as other non-surgically induced rat model [167,169–171]. Intra-articular injection of etanercept (sTNFR2, a PGRN blocker), which was known to be effective in treating patients with rheumatoid arthritis, caused more joint destruction in OA model conversely [169,172,173]. This seemingly paradox result may explain the protective role of PGRN in OA pathogenesis. PGRN expression was induced in IFP and synovial tissues of OA patients [174]. Cumulatively, the protective actions of PGRN also come in two pathways: Firstly, PGRN activates ERK2 and trigger anabolic biomarkers through TNFR2 pathway; Secondly, PGRN inhibits TNF-α, IL-1β and LPS mediated inflammation and catabolism [170,171,174]. Therefore, PGRN turns out to be promising target for treatment of OA.

2.10. Nesfatin-1

Nesfatin-1, an 82-amino-acid peptide, is firstly identified as an anorexigenic factor derived from nucleobind-2 (NUCB2) [175], and then characterized as an adipokine particularly secreted from ScAT to induce proinflammatory cytokines and lipid accumulation [176,177]. Limited but explicit findings were concluded as for the role of nesfatin-1 in OA. Apart from AT, nesfatin-1 is also expressed in osteophytes, synovium, cartilage and IFP [178,179]. Level of nesfatin-1 is significantly higher in OA serum, in comparison to SF samples and serum from healthy controls [178]. Of note, serum nesfatin-1 levels were positively correlated with high-sensitivity C-reaction protein (hsCRP) and IL-18, suggesting the role in OA pathology via inflammation[180]. Moreover, serum and SF nesfatin-1 concentrations were tightly associated with OA severity, which demonstrates the potential to determine OA progression [181].

2.11. Other novel adipokines

A couple of very recently characterized adipokines, including serpin peptidase inhibitor, clade E member 2 (SERPINE2), Wnt1 inducible signaling pathway protein 2 (WISP2), glycoprotein (transmebrane) nmb (GPNMB) and inter-alpha-trysin inhibitor heavy chain family, member 5 (ITIH5), have been demonstrated to be produced in chondrocytes, synovial tissues and IPF of OA patients [182–186]. Further analyses showed that enhanced expression of SERPINE2 but suppressed expression of ITIH5 in OA synovial tissues in comparison to healthy controls [186]. Increase expression of WISP2 was observed in IPF of OA patients as compared to healthy controls, suggesting its involvement in the fibrosis of IFP [186]. As SERPINE2 and ITIH5 family are known to be involved in regulation of metalloproteinases or extracellular matrix stabilization in other cell types [187,188], mechanisms on their similar or more pleiotropic involvement in the pathophysiology of the synovial tissues during OA require further elucidation.

3. Adipokines and inflammation in IFP

Situated within the knee capsule and located closely to the synovial layers and cartilage surfaces, IFP is composed of adipocytes, immune cells (primarily macrophages and lymphocytes), fibroblasts, blood vessels and collagen matrix. Thus IPF serves both as a local source of adipokine and a local modulator of inflammatory responses contributing to the initiation and progression of knee OA [189]. IPF-derived adipokines exhibit unique patterns of secretion and distribution, imparting direct impact on articular cartilage degeneration [190]. For instance, with the exception of leptin and resistin, the other adipokines are more actively secreted by IFP than by ScAT in the same OA individual [21]. Notably, leptin secretion is reduced approximately 40%, while secretion of adiponectin is elevated nearly 70% in IFP compared with paired ScAT samples [191,192]. Also, certain MMPs expressions were induced by the culture media from OA patients' IPF adipocytes [61]. Moreover, while the circulating adipokines profile could play an endocrine effect in vascular system, the adipokines profile in joints might affect through local paracrine inflammation [191,193]. The OA patients' fat pad cells showed a certain inflammatory phenotype, including increased levels of proinflammatory cytokines (such as TNF-α, IL-6, MCP-1 and VEGF) and down-regulation of anabolic peptide (such as CD44).[60,192,194]. Culture medium from IPF obtained from end-stage OA patients contained a higher number of M2 macrophages than subcutaneous fat [195]. Further histopathological studies confirmed crown-like structures of macropahges infiltration adjacent to adipocytes in IFP, whose grades of infiltration were positively related to levels of MCP-1 and IL-6 [194,196]. Both M1 and M2 macrophages were reported in the infiltrated IPF yet, implying the local inflammatory niche must be heterogeneous [192]. Hence, classical polarization notion could be oversimplified in OA pathophysiology. Further studies on the regional diversity of macrophage phenotype and function are needed.

4. Adipokines and its specific role in OA among non-weight-bearing joints

Admittedly, the metabolic effect of adipokines in obesity-induced OA has been documented over the decades. However, since it is pretty difficult to separate the metabolic effect from the mechanical effect of fat excess, most studies concerning the relationship between adipokines and obesity-induced OA within weight-bearing joints could be biased. Hence, the non-weight-bearing joints, such as hands and shoulders, are rendered as much more ideal targets to investigate the metabolic role of adopokines in OA.

At present, available data on OA within non-weight-bearing joints are sparse. The available literature, however, is presented, in order to encourage further intensive researches in this field.

A prospective cohort study involving more than 1000 patients demonstrated that obesity is significantly linked with the development of clinical and radiological hand OA [197]. Serum leptin, together with BMI and coronary artery disease are associated with the intensity of chronic hand OA pain [54]. Serum adiponectin, instead of leptin and resistin, can reduce the risk of hand OA progression defined as a change in the sum of JSN score using Osteoarthritis Research Society International (OARSI) atlas after adjustment for age, sex and BMI [198]. While another study showed serum adiponectin was positively associated with hand OA severity [110]. Furthermore, serum resistin level in radiographic hand OA patients was also higher than those in controls, and the elevated resistin was associated with an increased risk of subchondral erosion [199,200]. Moreover, a recent study revealed that visfatin was significantly higher in erosive HOA patients in comparison to non-erosive hand OA and normal control group [200].

Table 1
Recently published articles in regard to the relationship between adipokines and OA.

Adipokine	Anatomic joints	Source	Correlation with other biomarkers	Authors	Year	References
Leptin	Knee	SF	Correlated with BMI	Dumond et al.	2003	[35]
	Knee	SF↑	Correlated with radiographic severity of OA	Ku et al.	2009	[40]
	Knee	SF↑	Correlated with BMI, female gender and WC	Gandhi et al.	2010	[49]
	Knee	Plasma	Correlated with BMI, gender. Not correlated with age, duration of disease, radiographic severity, VAS score and lequesne index	Fioravanti et al.	2011	[46]
	Knee	Serum	Positively correlated with body weight, total fat mass	Iwamoto et al.	2011	[47]
	Knee	Serum↑	Associated with female gender and BMI, and not associated with cartilage damage	de Boer et al.	2012	[38]
	Knee	Plasma	Correlated with BMI, duration of disease, not correlated with age, pain, disability, muscle strength, functional performance, and radiographic severity	Durmus et al.	2012	[48]
	Hand	Serum	Associated with the intensity of chronic pain. Not associated with radiographic severity.	Massengale et al.	2012	[54]
	Hip	Serum	Correlated with hip JSN. Not correlated with presence or severity of osteophytes	Stannus et al.	2012	[58]
	Knee	Plasma	Positive associated with presence and progression of radiographic OA.	Van Spil et al.	2012	[52]
	Knee	Serum	Associated with prevalent and incident of OA	Karvonen-Gutierrez et al.	2013	[45]
	Knee	SF/plasma ratio	SF/plasma ratio negatively correlated with OA stage	Staikos et al.	2013	[53]
	Hip/knee	SF	Positively associated with OA pain	Bas et al.	2014	[57]
	Hip/knee	Plasma	Positively associated with painful joint burden among women	Perruccio et al.	2014	[56]
	Knee	Serum	Mediates almost half of the total effect of BMI on OA	Fowler-Brown et al.	2015	[51]
	Knee	SF↑	None	Hooshmand et al.	2015	[41]
	Knee	Serum	Positively correlated with clinical features, including stair climb, sit-to-rise, 2-pound lift times and forward reach distance	Karvonen-Gutierrez et al.	2015	[44]
	Knee	Plasma	Negatively associated with femoral cartilage volume	King et al.	2015	[55]
	Knee	SF	Associated with pain and function	Calvet et al.	2017	[91]
	Knee	Serum	Negatively associated with BMD at total body, hip, total femur, femoral neck and femoral shaft	Wu et al.	2018	[50]
Visfatin	Knee	Serum↑/SF↑	None	Chen et al.	2010	[88]
	Knee	SF↑	Positively correlated with K&L grading scores, CTX-II, and AGG	Duan et al.	2012	[89]
	Hip	SF	Positively associated with OA pain	Bas et al.	2014	[57]
	Knee	SF	Associated with function	Calvet et al.	2017	[91]
	Hand	Serum↑	Positively associated with erosion of hand joints	Fioravanti et al.	2017	[200]
Adiponectin	Knee	Plasma↑/SF	Both plasma and SF adiponectin are negatively correlated with OA radiographic severity	Honsawek et al.	2010	[106]
	Knee	Plasma	Correlated with lequesne index. Not correlated with BMI, gender, age, duration of disease, radiographic severity and VAS score	Fioravanti et al.	2011	[46]
	Knee	SF	Correlated with AGG1 and AGG2. Not correlated with CTX-II	Hao et al.	2011	[113]
	Knee	Plasma	Positively correlated with radiographic severity of OA	Koskinen et al.	2011	[109]
	Hand	Serum	Not associated with the presence of OA radiographic changes	Choe et al.	2012	[199]
	Knee	Serum↑	Associated with female gender, BMI and IL-1β. Not associated with cartilage damage	de Boer et al.	2012	[38]
	Hand	Serum	Not associated with OA radiographic severity	Massengale et al.	2012	[54]
	Knee	SF	Negatively associated with OA pain	Bas et al.	2014	[57]
	Hand	Serum	Total adiponectin, but not HMW adiponectin, negatively associated with radiographic progression	Klein-Wieringa et al.	2014	[114]
	Hip/knee	Plasma	Positively associated with painful joint burden among women	Perruccio et al.	2014	[56]
	Knee	Serum↑	Positively correlated with K&L scores, VAS and WOMAC total scores	Cuzdan Coskun et al.	2015	[107]
	Knee	Serum↑	Total adiponectin, rather than HMW adiponectin was positively associated with severity of OA	Toussirot et al.	2017	[115]
	Knee	SF	Associated with pain	Calvet et al.	2017	[91]
	Knee	Serum	Negatively associated with BMD at total femur and femoral shaft	Wu et al.	2018	[50]
Resistin	Hand	Serum↑	Correlated with the presence of radiographic changes and subchondral erosion	Choe et al.	2012	[199]
	Knee	Serum↑	Not associated with cartilage damage. Positively associated with synovial inflammation.	de Boer et al.	2012	[38]
	Hand	Serum	Not associated with OA radiographic severity.	Massengale et al.	2012	[54]
	Knee	Plasma	Positively associated present and incident radiographic OA.	Van Spil et al.	2012	[52]
	Knee	Serum/SF	Not correlated with gender, and BMI	Koskinen et al.	2014	[133]
	Hip/knee	Plasma	Negatively associated with painful joint burden among men	Perruccio et al.	2014	[56]
	Knee	Serum/SF	SF resistin, but not serum resistin, are positively associated with Noyes scores, K&L and WOMAC scores, physical functional scores, and CTX-II.	Song et al.	2015	[134]
	Knee	Serum	Not associated with radiographic severity and cartilage volume	Zheng et al.	2015	[131]
	Knee	SF	Associated with function	Calvet et al.	2017	[91]
	Hand	Serum↑	None	Fioravanti et al.	2017	[200]
	Hip	Serum↑	Increase COL I α1/α2 ratio, Wnt signaling activation, osteoblast metabolic activity, and bone nodule formation	Philp et al.	2017	[130]
	Knee	Serum	Not associated with BMD	Wu et al.	2018	[50]

(*continued on next page*)

Table 1 (*continued*)

Adipokine	Anatomic joints	Source	Correlation with other biomarkers	Authors	Year	References
Chemerin	Undefined	SF	Promote expression of TLR4 mRNA and synthesis of CCL2	Eisinger et al.	2012	[141]
	Knee	Serum/SF	SF chemerin correlated with radiographic severity of OA	Huang et al.	2012	[142]
Ometin-1	Knee	Serum/SF	SF omentin-1 negatively correlated with pain	Li et al.	2012	[149]
	Knee	Serum/SF	SF omentin-1 negatively correlated with K&L grades	Xu et al.	2012	[148]
Vaspin	Knee	Serum↓/SF	Both serum and SF vaspin are not related to age, gender, or BMI	Bao et al.	2014	[155]
Lipocalin-2 (LCN2)	Knee	SF↑	MMP-9/LCN2 complex is enriched in SF	Gupta et al.	2007	[161]
Progranulin	–	Cartilage↑	Significantly elevated in patients with OA	Abella et al.	2016	[174]
Nesfatin-1	–	Plasma	Negatively correlated with BMI, percentage body fat, body fat weight, and blood glucose	Tsuchiya et al.	2010	[176]
	Knee	Serum↑/SF	Nesfatin-1 in OA serum exceeded those in paired SF. Correlated with expression of hsCRP and IL-18	Jiang et al.	2013	[178]
	Knee	Serum↑/SF	Markedly associated with increased K&L grades.	Zhang et al.	2015	[181]
SERPINE2	Knee	Synovium↑	None	Conde et al.	2015	[186]
WISP2	Knee	IFP↑	None	Conde et al.	2015	[186]
ITIH5	Knee	Synovium↓	None	Conde et al.	2015	[186]

Notes: ↑ increased level in OA patients compared with healthy controls; ↓ decreased level in OA patients in comparison to healthy controls.
Abbreviations: AGG, aggrecan; BMI, body mass index; CCL2, Chemokine (C-C motif) ligand 2; COL I, Type I collagen; CTX-II, C-terminal crosslinked telopeptide type II collagen; HMW, high molecular weight; hsCRP, high-sensitivity C-reaction protein; IL-18, interleukin-18; IL-1β, interleukin-1beta; ITIH5, inter-alpha-trysin inhibitor heavy chain family, member 5; JSN, joint space narrowing; K&L, Kellgren & Lawrence; LCN2, Lipocalin-2; MMP, Matrix metalloproteinases; SERPINE2, serpin peptidase inhibitor, clade E member 2; SF, synovial fluid; TLR4, toll-like receptor 4; VAS, visual analog scale/score; WC, waist circumference; WISP2, Wnt1 inducible signaling pathway protein 2; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

As to shoulder joint, Gandhi et al. showed that OA shoulders contained adipokines at levels correlated with BMI. Furthermore, both OB-Rb and AdipoRs are expressed on the surface of chondrocytes of late-stage OA shoulders [200,201]. Nevertheless, there are also a few studies demonstrating that no significant association between serum levels of leptin [202], adiponectin [54,199], or resistin [54] and hand OA status were found. Though contradicting results remained, we may still assume a possible role of adipokines in OA within non-weight-bearing joints. The failed reproduction of some results may be probably owing to the classification criteria for OA or the insufficient sample size. More large follow-up studies with a consensus on the diagnosis and classification of OA are warranted to gain insight into the potential utility of adipokines as biochemical determinants of OA process.

5. Prospect of further research

The prevalence of obesity among adults and children is increasing worldwide, so as the increased incidence of obesity-induced OA [203,204], then accordingly causing substantial health risks and financial costs [205]. An intense research focused on members of the adipokine family has taken place over the past years. Accumulating studies *in vivo, in vitro and ex vivo* have been performed to investigate the metabolic link between adipokines and OA, and the recently published data are shown in this review (chronologically listed in Table 1). Hopefully, it would provide new leads in prevention of obesity-induced OA and exploration of new drug targets [206]. However, the role of adipokines in OA could be more complex than we have expected [207]. Although plenty of evidences have supported their relationship, direct mechanisms of adipokines in OA still remain extensively unknown. Moreover, controversial results of some clinical trials and original experiments cause failed reproduction of studies (a brief summary of potential involved mechanisms is illustrated in Fig. 1). For further thorough elucidation of the mechanisms, the following suggestions could be considered.

Above all, pertinent consensus on the diagnosis and classification of OA should be achieved and applied in research. Currently, the diagnosis and severity of OA are mostly delineated and classified by clinical symptoms and X-ray radiography, whereas the gradual process of OA progression is now claimed to be divided into five sections as pre-OA initiation, silent molecular, pre-radiological, radiographic, and joint replacement phase successively [208], in which pain is usually vague and changes are rarely seen on X-ray in early-stage. Thus, OA subjects enrolled in previous studies are usually in their end-stages. The aforementioned evidences suggest that adipokines might be ideal surrogate biomarkers to quantitatively detect early-stage OA, monitor OA progression, and assess the effectiveness of new therapies in clinical trials, while actually studies on early-stage OA are barely seen [52]. Moreover, different criteria for OA classification may be applied in different studies, and the discrepancies in baseline demographics could lead to some bias and subsequently cause failed duplication of results. Nowadays, it has been well-established that MRI enables us better understand the trajectory of radiographic history of OA from the earliest phases [209]. Therefore, further direct confirmations of the role of adipokines in early-stage OA are demanded with the utility of a more precise OA definition and classification by using MRI or other advanced tools in clinical trials [210].

Secondly, studies on adipokines in OA within non-weight-bearing joints are essential. Patients and their counterparts recruited in majority of the studies are limited to the knee or hip OA, while few are on hand or shoulder OA. In order to elucidate the role of obesity-induced OA without bias of mechanical effects, well-designed prospective large follow-up clinical studies with interest in OA within non-weight-bearing joints are required. They would probably provide more information on the critical metabolic effect of adipokine in OA.

Thirdly, given the fact that correlations between the individual adipokine and clinical variables of OA are low to moderate, more importance should be attached to the integration of different adipokines in clinical trials. For instance, it has already been proved that a greater SF adiponectin/leptin (A/L) ratio is significantly associated with less pain measured by the short-form McGill pain questionnaire, while the correlation between pain scale and each adipokine alone was less remarkable, indicating the A/L ratio may present a better biomarker of pain for knee OA [211]. However, our knowledge regarding the integration of each adipokine is poor, further studies are needed to testify that whether the combination of these adipokines could serve as a superior predictor for OA.

Finally, it is promising to explore the link between OA and other most extensively studied chronic inflammation disorders as well, such

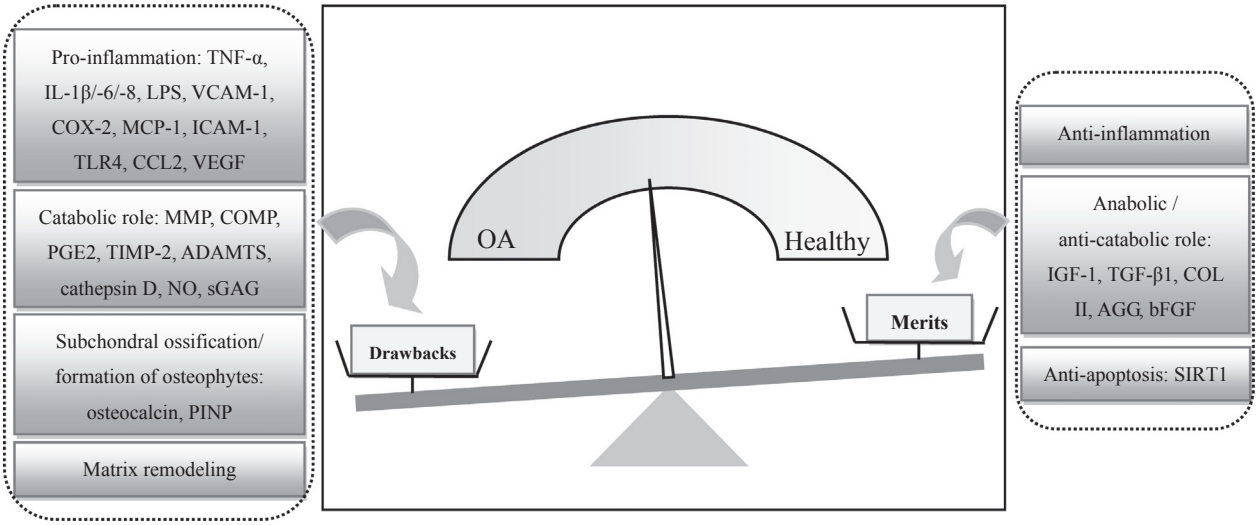

Fig. 1. Schematic diagram showing the mechanisms involved in the process of OA. Adipokines may have a dual role during OA. On one hand, they could provide some beneficial effect through their role in anti-inflammation, anti-apoptosis, and anabolism or anti-catabolism. While on the other hand, they may aggravate the OA process by displaying a cluster of "drawbacks", including pro-inflammation, catabolism, subchondral ossification, formation of osteophytes, and matrix remodelin. Probably, the drawbacks outweigh the merits, and thus the equilibrium between physiologic synthesis and degradation of articular cartilage and ECM induced by various adipokines is disrupted. Therefore, the unbalanced production of mediators determines aberrant alterations in cartilage as well as other tissues in joints, and subsequently leads to the pathological features of OA in overall.

as atherosclerosis (AS). As OA shares much in common with AS, another age-, obesity- and chronic inflammation- related degenerative disease, it is tempting to speculate that adipokines might stimulate the formation of atherosclerotic plaques that subsequently limit the blood flow to the joint [13], or OA chondrocytes could even transform into foam cells as well. If proven true, this intriguing theory linking AS and OA may open avenues to novel therapeutic interventions for OA since we may take advantage of previous knowledge from adipokine in AS [212].

So far, there are still many unrevealed questions about the role of adipokines in obesity-induced OA. Looking ahead, we envision extended advances will be applied in adipokines to clarify the comprehensive metabolic network of obesity in the pathophysiology of OA. A better understanding of adipokines in OA may lead to the identification of potential targets for therapeutic intervention.

Conflict of interest

The authors declare that there are no conflicts of interest that would influence the work.

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