Adipokines: Metabolic link between knee osteoarthritis and obesity

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Osteoarthritis (OA) is a heterogeneous and multifactorial process of chronic degenerative joint disorder that involves not only articular cartilage, but also synovium, subchondral bone, and surrounding muscles and ligaments. Obesity is a well known risk factor of the incidence and prevalence of osteoarthritis and is believed to play a deleterious part in knee OA by the increment in mechanical stresses on the joints. The role of obesity in knee OA is much more complicated than previously thought. Adipokines, cytokines mainly produced by adipose tissue, may play a potential role in knee OA. In this review, we summarize the recent advances in adipokine research in knee osteoarthritis, focusing on leptin, adiponectin, visfatin, and resistin, and also the essential role of newly identified adipokines such as chemerin, lipocalin, and omentin.

Keywords: *Adipokines, knee osteoarthritis, obesity*

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Introduction

Osteoarthritis (OA) is a highly prevalent degenerative joint disease estimated to affect more than 37% of people who are over 60 years of age[1]. The disease is characterized by fibrillation of articular cartilage, alterations in subchondral bone, the formation of osteophytes, and low-level synovial inflammation. Its etiology is largely complicated since both genetic factors and non-genetic factors such as age, gender, joint injury and obesity are considered as important risk factors[2]. Knee OA is among the most common burden diseases in developed countries, and its prevalence is set to continue to increase in the near future, likely due to aging of the population[3].

Obesity and osteoarthritis

Obesity has long been considered as an important risk factor for the development and progression of OA. The association between OA and obesity is strongest in the knee; the joint that supports almost the whole weight of our body[4, 5]. A study in the British population revealed that women in the highest body mass index (BMI) tertile had a higher risk of knee OA (6 times) and bilateral knee OA (18 times), compared with women in the lowest BMI tertile[6]. The same trend of results was also obtained from a study in African-American and Caucasian women[7]. In addition, a longitudinal study of both genders indicated a 40% increased risk for developing knee OA[8]. It is generally accepted that obesity may lead to cartilage destruction by increasing the mechanical stress of the joints or alterations of cartilage matrix components. However, quite new advances in the knowledge of white adipose tissue (WAT) suggested that besides from biomechanical effects, metabolic effects are also involved in OA[9]. Moreover, several studies demonstrated that fat excess is also associated with OA in non-weight-bearing joints, such as those of the hand. For example, there was a study which reported a two-fold increase in the risk of hand OA in obese patients[10], suggesting that metabolic factors released mainly by adipose tissue may be responsible for the high prevalence of OA among overweight individuals[11].

Knee osteoarthritis as an inflammatory disease

Although knee OA was described as a 'wear-and-tear' noninflammatory disease, it is now recognized that metabolic and inflammatory environments contribute to the symptoms and progression of knee OA[12, 13]. Findings in the 1990s indicated that cartilage, bone, the synovium and infrapatellar fat pads are sources of inflammatory mediators involved in the pathophysiological changes in OA[14]. Many mediators with inflammatory properties, such as prostaglandins and cytokines can increase matrix metalloproteinases (MMPs) production by chondrocytes and synovial cells, which finally increases cartilage degradation. Therefore, OA has also been mentioned as being part of a metabolic syndrome[15].

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Obesity and adipokines

Obesity is currently classified with a chronic low-grade inflammatory status. The metabolic link between obesity and OA could be the adipocytokines (or adipokines) produced by adipose tissue. White adipose tissue (WAT) is considered mainly to be an energy storage portal. However, it is now recognized as a metabolically active endocrine organ with the capacity to secrete proinflammatory agents including classical cytokines [e.g., interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α)], as well as adipokines, such as leptin, adiponectin, resistin and visfatin[16-18]. Adipokines are hormone and cytokine like substances which play a critical role in several pathways including not only glucose and lipid metabolism but also immune and inflammatory responses[19]. Over the past decade, adipokines have prompted much interest in OA pathophysiological research based on the fact that they play an important role in cartilage and bone homeostasis. The involvement of adipokines in OA can be direct joint degradation or the control of local inflammation. Four main adipokines (leptin, adiponectin, resistin, and visfatin) levels have been locally detected in the synovial fluid of knee OA joints. Adipokines are produced in knee OA joints by chondrocytes, osteoblasts, osteoclasts, as well as infrapatellar fat pads. It was suggested that local (synovial fluid) and systemic (serum) adipokine levels would be associated with cartilage degradation and synovial inflammation[20]. Therefore, the aim of this review is to include the current reports regarding the association between knee osteoarthritis and potential adipokines including leptin, adiponectin, resistin, and visfatin, of which their involvements in osteoarthritis are summarized in Table 1.

Table 1 Involvements of four main adipokines in osteoarthritis

Important issues	Leptin	Adiponectin	Visfatin	Resistin
Association with BMI	positive	negative	positive	not clear
Plasma levels between genders	women > men	women > men	women > men	women > men
Plasma levels between groups	OA > control	control > OA	OA > control	OA > control
Levels in OA patients	SF > plasma	plasma > SF	SF > plasma	plasma > SF
Roles in cartilage homeostasis	- ↑ proteases - ↑ inflammatory cytokines - ↓ growth factor - ↓chondrocytes proliferation	- ↑ proteases - ↑ inflammatory cytokines - ↓ MMP-13 - ↑ TIMP-2	- ↑ proteases - ↑ inflammatory cytokines - ↑ proteoglycan degradation - ↓ proteoglycan production	- ↑ proteoglycan degradation - ↓ proteoglycan production
Roles in bone formation	- expressed in osteoblasts and osteophyte - increase bone growth	- expressed in osteoblasts and osteophyte	- expressed in osteoblasts, osteoclasts and osteophyte	- expressed in osteoblasts, osteoclasts and osteophyte
Associated biomarkers	- bone formation - joint metabolism	- cartilage degradation - collagen degradation	- inflammation - collagen degradation - aggrecan degradation	- joint metabolism
Associated clinical data	- prevalence - progression - grade of cartilage degeneration	- Ahlback score -Lequesne Index - severity (negatively)	KL-score	prevalence

BMI, Body mass index, *KL*, Kellgren-Lawrence, *OA*, Osteoarthritis, *SF*, Synovial fluid

Leptin

Leptin is a 16 kDa nonglcosylated adipokine encoded by the *ob* (obese) gene[21]. The best known effects of leptin are its involvement in body weight homeostasis, since it decreases food intake but increases energy expenditure at the hypothalamic level[22]. It is synthesized exclusively by adipocytes, and its circulating levels are correlated with the amount of body fat[23]. Obese individuals generally produce higher amounts of leptin. This adipokine exerts its biological activities through the activation of its specific receptors (Ob-

R) which belong to the class I cytokine receptor superfamily. In humans, at least five isoforms of leptin receptor, resulting from alternative splicing of the *db* (diabetes) gene exist[24]. However, only the long isoform (Ob-Rb) seems to be functional. The Ob-Rb contains the intracytoplasmic motifs required for the activation of the JAK-STAT system[25]. Mutations in either the *ob* gene or *db* gene results in an obese phenotype in mice[26]. Currently, it is increasingly evident that leptin plays a significant role in the OA pathophysiology by modulating the bone and cartilage metabolism. Moreover, ob/ob leptin-deficient mice develop resistance to antigen-induced arthritis[27].

Leptin and its receptor can be secreted by chondrocytes, osteophytes[28] and the synovium, as well as infrapatellar fat pads[29]. Plasma leptin concentration was significantly correlated with BMI, in both OA patients and normal controls[30], suggesting its role as a metabolic link between OA and obesity. It has been reported that a 1 ng/ml higher plasma leptin concentration was associated with 7% higher odds ratio of having knee OA, after adjustments for age, ethnicity and BMI[31]. Nevertheless, leptin levels in synovial fluid were 3 to 11 times higher than those in paired plasma samples[29]. This difference was more obvious in women than in men. Therefore, locally produced leptin may play more significant roles in bone metabolism regulation than circulating leptin.

Leptin shows catabolic effects in OA cartilage by increasing metalloproteinases (MMPs) enzymes such as MMP-1, MMP-3, MMP-9 and MMP-13, as well as cysteine proteases production at both the gene and protein levels[32, 33]. In addition, the gene expression of *ADAMTS-4* and -5, which are responsible for the degradation of aggrecan, were considerably increased after treatment with leptin. Moreover, Bao et al. have demonstrated that leptin downregulated the anabolic factors such as basic fibroblast growth factors (bFGF) in mouse articular cartilage. These results suggest a prominent catabolic effect of leptin as a proinflammatory factor on cartilage metabolism in knee OA[34].

Nitric oxide (NO) is a well-known proinflammatory mediator which promotes chondrocyte phenotype loss, apoptosis, as well as MMPs activation. The production of type 2 nitric oxide synthase (NOS2) in cultured human and murine chondrocytes is activated by the combination of leptin and interferon-γ[35]. Recently, leptin has also been reported to enhance cyclooxygenase-2, prostaglandin E2, IL-6, and IL-8 production in human chondrocytes[36]. Interestingly, leptin also had a negative effect on chondrocyte proliferation since it reduced OA chondrocytes proliferation for the short term-treatment (48 hours) and reduced both normal and OA chondrocytes proliferation for the long-term treatment (7 days)[37].

Leptin is also involved in osteoblast dysfunction in OA. It has recently been found that leptin acts as a bone growth regulator by inducing collagen synthesis, osteoblast proliferation, bone mineralization, and also endochondral ossification[38-40]. The increased production of leptin in OA subchondral osteoblasts is associated with the increased levels of alkaline phosphatase, osteocalcin, collagen type I, and TGF-β1 (transforming growth factor-β1)[41]. Moreover, the findings of immunohistochemical studies showed high leptin expression in osteophytes[11]. Berry et al.[42] have revealed that the level of serum leptin was significantly associated with the level of bone formation markers, such as osteocalcin and procollagen type I N-terminal propeptide (PINP). In addition, leptin was positively associated with the cartilage biomarkers such as urine C-terminal telopeptide of type II collagen (uCTX-II), serum cartilage oligomeric matrix protein (sCOMP), and serum procollagen type IIA N-terminal propeptide (sPIIANP), serum hyaluronic acid (sHA) and serum N-terminal propeptide of type III procollagen (sPIIINP) after adjustment for gender and age. In contrast, baseline expression levels of soluble leptin receptors OB-Rb were negatively associated with 2-year changes of the cartilage formation biomarkers PIIANP and osteocalcin levels, but positively associated with cartilage defects scores and cartilage volume loss, independent of age, gender, and BMI[42].

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 baseline. However, the association disappeared after adjustment for BMI[42]. Leptin expression has been reported to be associated with the grade of cartilage degeneration. In advanced grade OA cartilage, leptin and its receptor (Ob-Rb) levels were significantly increased compared to healthy or adjacent mildly affected cartilage[37]. On the contrary, Berry et al. did not find any association between plasma leptin levels and knee OA with grade 4 Kellgren-Lawrence (KL)-score and found no association between baseline plasma leptin levels, 2-year alterations of cartilage volume, and defects in knee OA patients[42].

Adiponectin

Adiponectin is a 244-residue protein that is synthesized mainly by WAT. Its main metabolic properties are that it increases insulin sensitivity, improves glucose metabolism, increases fatty acid oxidation, and antiatherogenesis[22, 43, 44]. In plasma, it is present in three molecular forms: trimers (low

molecular weight complexes), hexamers (mid-molecular weight complexes), and 12- to 18-hexamers (high molecular weight, HMW, complexes)[45]. Adiponectin acts via two receptors, AdipoR1 and AdipoR2. AdipoR1 is found in skeletal muscle, cartilage, bone and the synovium, whereas AdipoR2 is found predominantly in the liver[46, 47]. The adiponectin knockout mice develop severe insulin resistance and exhibit lipid accumulation in muscles when placed on a high fat/sucrose diet[48].

In general, adiponectin is detectable in both plasma and synovial fluid but shows different patterns of distribution[29]. In the blood, it circulates in high concentrations (0.01% of total serum protein) exceeding those in the matched synovial fluid[28]. Serum adiponectin levels are inversely correlated with BMI, lower in obese individuals and elevate with weight loss[48,49]. Women have remarked higher plasma adiponectin levels than men[50], whereas the effect of age on circulating adiponectin levels are inconsistent. In OA patients, serum adiponectin levels were reported to be lower than in healthy controls[51]. In addition, the levels of adiponectin in OA plasma were almost 100-fold higher than in OA synovial fluid, and these plasma and synovial fluid levels showed an inverse correlation[47]. Recently, Distel et al. have shown increased adiponectin levels in the infrapatellar fat pads in knee OA[52].

Adiponectin seems to have both catabolic and anabolic effects on pathological changes of several tissues/cells involved in the initiation and progression of OA. For its pro-inflammatory effect, adiponectin plus IL-1β treated chondrocytes and synovial fibroblasts lead to the induction of NO by inducing the expression of NOS2. Similarly, this adipokine also increases the production of key mediators in cartilage degeneration such as IL-6, IL-8, TNF-α, MMP-3, MMP-9, MCP-1 (monocyte chemo-attractant protein-1) and GRO (growth-related oncogene) in chondrocytes[53-55]

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[56].

Plasma adiponectin levels showed positive associations with markers of cartilage degradation such as IL-1 β, uCTX-II and sCOMP, but showed negative associations with high sensitivity C-reactive protein (hsCRP) levels in serum. These associations turned stronger after adjustments for BMI. On the other hand, other studies have suggested positive associations between hsCRP and synovial fluid adiponectin in end-stage knee OA patients[20]. In addition, Kang et al. reported increased levels of collagen type II degradation products in supernatants of OA cartilage explants incubated with adiponectin[57].

Compared to less severely affected subjects, Koskinen et al. found increased plasma adiponectin levels in patients with grade 4-5 radiographic Ahlbäck scores[58]. In addition, a significant association between plasma adiponectin levels and the Lequesne index was found[59]. Filkova et al. also found that serum adiponectin levels were higher in erosive OA patients than in nonerosive OA patients[50]. However, Berry et al. did not find any association between baseline plasma adiponectin levels, cartilage volume changes and defects in knee OA subjects in a 2-year study[42].

Interestingly, several studies have shown a protective effect of adiponectin in knee OA. Chen et al. demonstrated down-regulated IL-1β induced MMP-13 production and up-regulated its associated inhibitor, TIMP-2 (tissue inhibitor of metalloproteinase-2), production in primary chondrocytes at both mRNA and protein levels, suggesting the protective role against cartilage damage[47]. Some clinical data also support that adiponectin could play a protective role against 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-score) knee OA patients compared with controls, but decreased levels in grade 4 (KL-score) knee OA patients[60].

Visfatin

Visfatin, also called pre-B-cell colony-enhancing factor (PBEF) and nicotinamide phosphoribosyl transferase (NAMPT), is a highly conserved 52-kDa protein of 471 amino acids[61]. The major visfatin producing cells are granulocytes, monocytes and macrophages[62, 63]. It was originally discovered in human bone marrow, liver and muscle[61]. Additionally, adipocytes have also been considered as another source for visfatin production[64]. The best characteristic of visfatin is NAD biosynthetic enzyme[65]. It can bind to the insulin receptor *in vivo* and *in vitro*, but its insulin-mimetic effects are under investigation[66]. The elevated plasma visfatin levels have been found in type 2 and type 1 diabetes mellitus patients[67, 68]. It has recently been demonstrated that pharmacological inhibition of visfatin with APO866 (FK866), a NAD biosynthesis inhibitor , decreased collagen-induced arthritis (CIA) severity and pro-inflammatory cytokine production in affected joints[69].

Visfatin is highly produced in the adipose tissue with increased levels in obese people compared with lean people[64], and its level can be

reduced by regular exercise[68]. In general, visfatin synthesis is regulated by other factors such as glucocorticoids, TNF-α, IL-1β, IL-6, and growth hormone (GH), and its circulating-level positively correlates with IL-6 levels[70,71]. Very recently, Jurdana et al. reported no significant differences in serum visfatin concentrations between genders, however, it seems to be higher in women than in men[72].

OA patients had significantly higher plasma and synovial fluid concentrations of visfatin compared with controls, with levels in synovial fluid higher than paired serum samples[73]. It was showed that OA infrapatellar fat pads release higher amounts of visfatin than the matched subcutaneous adipose tissue[74]. Moreover, the visfatin expression in OA cartilage and the synovium was also higher than in normal samples[75].

The role of visfatin in cartilage is still unclear since it showed association with both catabolic and anabolic processes; however, more evidences point visfatin to be a pro-catabolic inflammatory, rather than anabolic mediator. For example, it has been shown that visfatin increased MMP activity and NO production, as well as proteoglycan release in OA cartilage matrix[76]. A recent study had shown that visfatin counteracted anabolic IGF-1 signaling, and therefore reduced IGF-1-mediated proteoglycan synthesis in human chondrocytes[77]. Moreover, elevated level of visfatin can reduce the expression of factors essential for the maintenance of the chondrocyte phenotype such as Sox-9 and type II collagen[78]. On the other hand, visfatin has also showed some anabolic properties. It was demonstrated that the inhibition of visfatin by small interfering RNA (siRNA) decreased the production of human chondrocyte specific matrix gene such as *collagen2a1* and *aggrecan*[79].

Visfatin is also expressed in osteoblasts, osteoclasts and osteophyte, suggesting its role in early osteophyte formation[56]. Plasma visfatin concentrations showed a positive correlation with CRP, indicating that it may be related to lipid metabolism and inflammatory process[70,80]. Likewise, synovial visfatin concentrations were shown positively correlated with the degradation biomarker of collagen type II, CTX-II, and two degradation biomarkers of aggrecan: AGG1 (G1-1H11), and AGG2 (6D6-G2)[81].

Resistin

Resistin is a macrophage/monocyte-derived adipokine which has an important role in inflammatory processes[82]. This dimeric protein is secreted mainly by adipocytes, but other cell types such as macrophages and neutrophils have been found to produce resistin as well[83]. The association of resistin with obesity, together with its proinflammatory properties suggests that resistin might be a remarkable mediator that links inflammation with OA and obesity.

Resistin levels in serum were significantly higher than the levels in matched synovial fluid specimens and increased in obese individuals[84]. This adipokine showed significantly higher levels in females than in males. Interestingly, serum resistin levels were positively associated with histologically determined grades of synovial inflammation[85]. It can be detected in inflamed synovium joints, in both rheumatoid arthritis (RA) and OA[29, 85]. Serum resistin levels in OA patients were positively associated with age, but not BMI and were significantly higher than in controls[20]. Resistin production can be induced by proinflammatory cytokines such as IL-1, IL-6 and TNF[86].

Resistin can induce inflammatory cytokines and PGE2 synthesis. It is produced by osteoblasts and osteoclasts in ossified osteophytes, indicating a role in osteophyte formation. Moreover, resistin stimulated proteoglycan degradation as well as inhibited proteoglycan production in mouse and human cartilage explants[87]. Plasma resistin concentrations were positively associated with sPIIINP and the prevalence of radiographic knee OA, independently with BMI; however, it was not associated with the disease progression. Interestingly, the association between resistin and the presence of radiographic knee OA was more obvious in OA patients with higher adiponectin levels[59].

Other Adipokines

Chemerin

Chemerin, a recently described chemo-attractant adipokine, is an18 kDa protein which is also known as tazarotene-induced gene 2 or retinoic acid receptor responder 2[88]. Its functions involved in adipocyte development and metabolic function, as well as glucose metabolism via the G coupled receptor chemokine-like receptor 1[89]. Chemerin and its receptor are mainly expressed in adipose tissue but can also be produced by dendritic cells, macrophages, fibroblast-like synoviocytes, and chondrocytes[90]. Molecules which drive inflammatory processes such as IL-1β, along with leptin and glucocorticoids, are able to modulate the expression of this adipokine[18]. Chemerin significantly increases the synthesis of Toll-like receptor 4 and CCL2 in OA fibroblast-like synoviocytes[91]. In addition, it stimulates the production of proinflammatory cytokines and matrix metalloproteinase in chondrocytes[92]. Moreover, chemerin levels in OA synovial fluid were associated with disease severity[93], demonstrating an important role of chemerin in OA pathophysiology.

Lipocalin

Lipocalin 2 (LCN2), a 25 kDa glycoprotein, is also named 24p3, uterocalin, siderocalin, and neutrophil gelatinase-associated lipocalin. It is a monomer adipokine produced mainly from adipose tissue and neutrophils but has recently been identified in chondrocytes[94]. It can exist as a 46 kDa homodimer and its cellular receptor named megalin (GP330)[95]. Its expression can be regulated by leptin, adiponectin, IL-1β, LPS, and dexamethasone[18]. This adipokine is likely to be involved in matrix degradation.

Omentin

Omentin is a 40 kDa protein which has previously been recognized as intelectin (a new form of Ca^{2+}-dependent lectin). It is secreted predominantly by omental adipose tissue and its plasma concentration is high. Several studies have shown the involvement of this adipokine in OA pathogenesis. For example, inflammatory states and obesity have been shown to alter omentin gene expression[96]. Recently, Senolt et al. found a difference in levels of omentin in the synovial fluid between RA and OA patients[97].

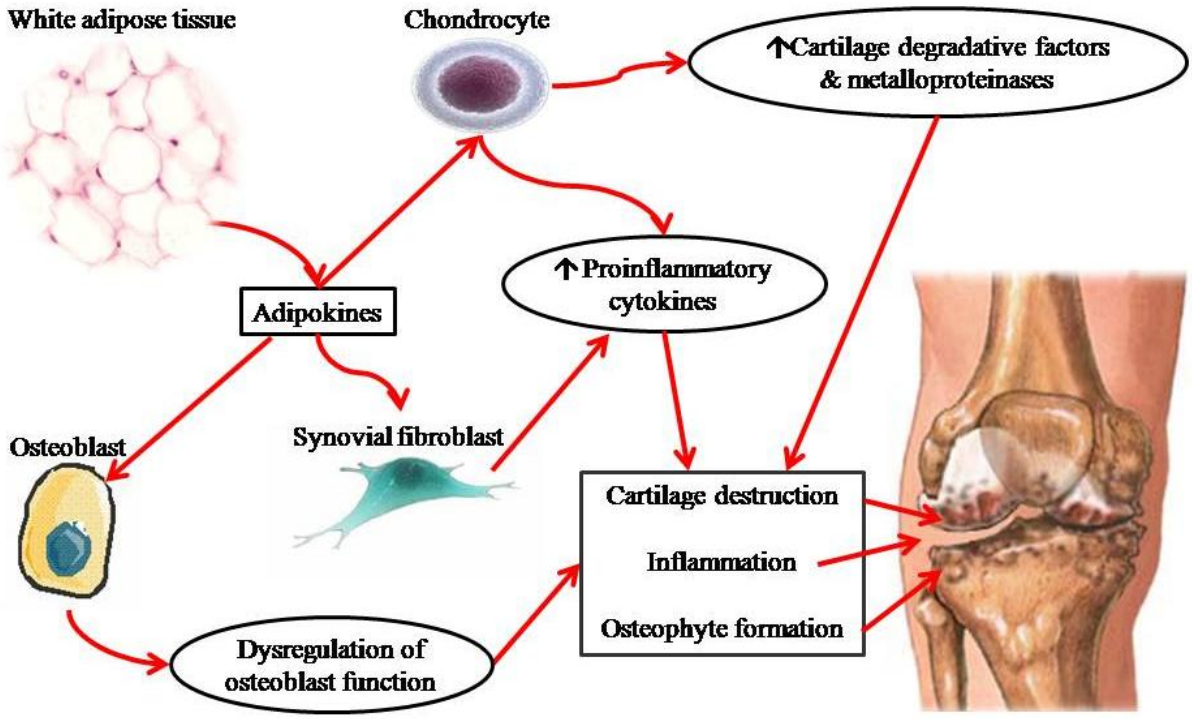

Fig. 1 Complex network links excess white adipose tissue, bone, and articular cartilage in knee osteoarthritis.

Conclusion

Taken together, this review sheds light on a potential role of adipokines in OA development as shown in Fig. 1. Leptin and visfatin seem to be more interesting as the targets of both prevention and treatment for knee osteoarthritis since they obviously showed catabolic effects on articular cartilage, whereas the effects of adiponectin and resistin are heterogenous. However, these two adipokines also play a crucial role in many other physiological processes, thus more clinical studies together with more research on the other adipokines are warranted. It is noteworthy that women have higher adipokines levels than men, which may be the reason for a higher prevalence of OA in women.

Obesity is undoubtedly associated with increased risk of knee OA. However, the use of BMI alone for measurement of excess body weight seems inadequate to reveal the physiological changes that link obesity to OA because it reflects both fat and skeletal muscle mass. The main source of adipokine production is adipose tissues, thus the other explicit measurements of body fat such as waist-hip circumference or Dual-energy X-ray absorptiometry-assessed total fat mass will be useful techniques to investigate the relationship between obesity, adipokine production and OA. Moreover, the study of interactions between metabolic factors and the other OA risk factors such as mechanical stress and genetic alteration, resulting from obesity may improve the understanding on the pathogenesis of OA.

Lastly, although the knowledge gained from present literatures is still incomplete for knee OA prevention and therapeutic intervention by pharmacological strategies, it is possible to state that an available preventive strategy is to stay in shape.

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Conflict of interest

None

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ความสำคัญของอดิโพไคน์กับความเชื่อมโยงระหว่างโรคข้อเข่าเสื่อมและโรคอ้วน

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โรคข้อเสื่อมเป็นโรคข้อที่เกิดจากการเสื่อมสภาพอย่างเรื้อรังของกระดูกอ่อนผิวข้อ กระดูกใต้ชั้นกระดูกอ่อน เยื่อหุ้มข้อ ตลอดจนกล้ามเนื้อและเส้นเอ็น เนื่องมาจากสาเหตุหลายประการ โรคอ้วนเป็นหนึ่งในปัจจัยเสี่ยงที่สำคัญและมีส่วนเกี่ยวข้องกับอุบัติการณ์และความชุกของโรคข้อเสื่อม และเชื่อว่ามีบทบาทอย่างมากต่อกระบวนการเกิดโรคข้อเข่าเสื่อม โดยมีผลไปเพิ่มความเค้นเชิงกลต่อข้อ บทบาทของโรคอ้วนในโรคข้อเข่าเสื่อมมีความซับซ้อนมากและเกี่ยวข้องกับไซโตไคน์อดิโพไคน์ (adipokines) จัดเป็นไซโตไคน์ชนิดหนึ่งซึ่งถูกสร้างขึ้นมาจากเนื้อเยื่อไขมันเป็นหลัก และมีบทบาทสำคัญมากต่อโรคข้อเข่าเสื่อม บทความปริทรรศน์นี้ได้รวบรวมความรู้ความก้าวหน้าอันทันสมัยจากการศึกษาวิจัยอดิโพไคน์ในโรคข้อเข่าเสื่อม โดยมุ่งเน้นถึงเลปติน (leptin) อดิโพเนคติน (adiponectin) วิสฟาติน (visfatin) และรีซิสติน (resistin) รวมถึงเคเมริน (chemerin) ไลโพคาลิน (lipocalin) และโอเมนติน (omentin)