Epidemiological studies on adipokines and osteoarthritis

Obesity is an important risk factor for not only knee, but also hand, osteoarthritis. Since hand joints do not experience mechanical force like weight-bearing joints such as the knee, other explanations on how obesity leads to osteoarthritis are needed. One of the possible explanations is adipokines, metabolic factors secreted by fat tissue. This paper reviews epidemiological studies on the role of three adipokines (leptin, adiponectin and resistin) in osteoarthritis, and briefly discusses the evidence from experimental research and future agenda on this topic.

KEYWORDS: adipokine ■ adiponectin ■ leptin ■ osteoarthritis ■ resistin

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Osteoarthritis (OA) is a highly prevalent disease; it is estimated that more than 20% of people older than 60 years have OA [1,2]. Once considered a simple degenerative disease, OA is now viewed as a disease of the whole joint with the involvement of cartilage, subchondral bone and synovium [3].

One of the most important risk factors for the development and progression of knee OA is being overweight [4]. It was thought that excess body fat exerts its effect only mechanically; more bodyweight leads to greater mechanical force on the joint, which consequently leads to damage. However, this explanation may be more relevant for weight-bearing than nonweight-bearing joints. In a systematic review published in 2011, it was concluded that obesity is also associated with hand OA [5]. Since humans do not walk on their hands, a sole mechanical explanation is insufficient to explain how obesity can lead to osteoarthritis, and other explanations are needed. One of the proposed mechanisms is the systemic effect of fat. Fat tissue is known to be able to produce factors that can influence distant structures (systemic effects) such as leptin, adiponectin, resisitin and many other products [6,7]. These factors are known under the umbrella name adipokines. Many experimental and epidemiological studies have investigated the role of adipokines in OA. Several reviews have discussed the possible role of adipokines in OA pathophysiology in basic research [8–10]. This article is a narrative review with an emphasis on epidemiological studies on the role of adipokines (leptin, adiponectin and resistin) in OA. This article also discuss the evidence from basic science and the future research agenda in the field of adipokines and OA.

Studies of adipokines in OA

Epidemiological studies can provide circumstantial evidence. It is rational to assume that epidemiological studies generate hypotheses that can be tested further in experimental studies. However, in studies on adipokines in OA, the basic research was initiated earlier than epidemiological research where the effect of adipokines *in vivo* and *in vitro* was mainly tested on cartilage, the central feature of OA [11,12]. Since OA also involves structures other than cartilage, it is warranted to elucidate the role of adipokines in joint structures other than cartilage, for example, in the bone. Bony outgrowth (osteophytes) is also considered to be an hallmark of OA [13], which may be a reflection of excessive bone production. The role of adipokines in bone metabolism can also be derived from studies in the field of bone mineral density. In addition to cartilage loss and bone involvement, OA is also characterized by inflammation processes. Adipokines and inflammation are also easily linked, since many adipokines are presumed to have a role in inflammation [14]. A review of epidemiological studies also suggested the role of synovitis in pain of knee OA patients (Figure 1) [15].

In epidemiological studies, the role of adipokines in OA can be investigated in a cohort study, where the outcome can be the incidence (i.e., newly diagnosed) or progression (i.e., worsening) of OA. There are several ways of measuring progression; by imaging or biomarkers. The most commonly used imaging is radiographs (Figure 2). Progression on radiograph is mainly

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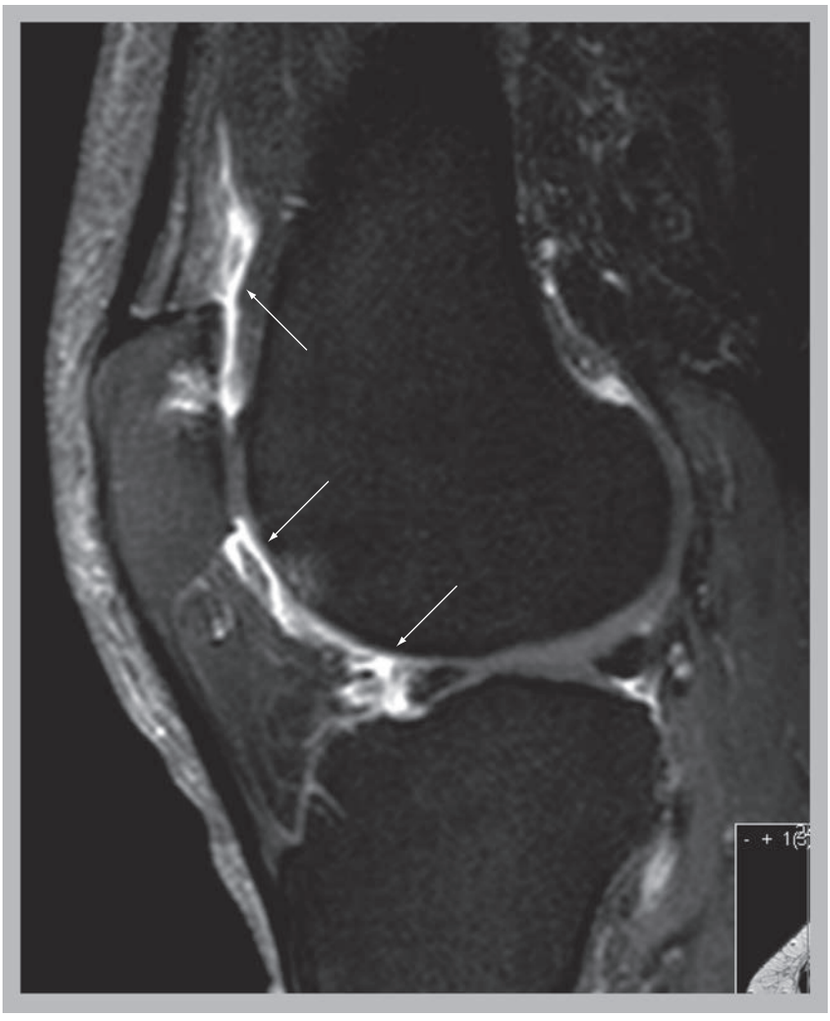

Figure 1. Saggital section of a knee joint on MRI showing inflammation of the synovium (hyperintense signal [arrows]).

assessed by measuring change in joint space narrowing, which is a proxy of cartilage loss [16]. However, radiographs can only indirectly asses cartilage [16]. A modern imaging technique that is able to asses other joint structures (e.g., synovium and bone marrow lesion) that are involved in OA is MRI (Figure 1) [15]. A drawback of using imaging to asses progression is that it can only capture damage done to a joint structure, instead of an actual pathological process. Objective indicators measured in the body fluid, which represent structural damage of the joints (biomarkers), are believed to be more sensitive to change [17]. Since OA is a disease of the whole joint, biomarkers used should be specific in reflecting involved joint structures. Some of the most commonly used biomarkers in OA research are biomarkers for cartilage (e.g., COMP and PIIANP), bone (e.g., osteocalcin and CTX-I) or inflammation (e.g., hsCRP and PIIINP) [18,19]. Last but not least, pain, the main feature of OA, could be also be investigated as a possible outcome of study on adipokines in OA. There are several possibilities in measuring pain as an outcome: increasing pain severity in time, increasing frequency of pain in time and cross-sectional pain severity. It should be kept in mind, however, that pain is a subjective measure that may not relate to the actual state of the disease.

Another type of epidemiological study that is used in investigating the role of adipokines in OA is cross-sectional study. It can efficiently detect associations between adipokines and OA. In pure cross-sectional studies, a study population is defined (e.g., a group of patients awaiting total joint prosthesis) and in this population, OA characteristics and the difference in the adipokines level across radiographic OA severity can be measured. The same holds for case–control studies, where patients with OA are selected as cases and a control group is defined. In published studies, mostly healthy volunteers without OA are selected as controls. The drawback of cross-sectional studies, including case–control studies, is inherent with the study design – that is, that no causality can be determined; higher or lower adipokines can be the cause or the result of OA.

In investigating the role of adipokines in OA, it is rational to assume that nonweight-bearing joints (e.g., shoulder or hand) are more suitable than weight-bearing joints (e.g., hip or knee), since the metabolic effects of adipokines do not need to be separated from mechanical effects. However, the authors observed that knee and hip joints are investigated more often than hand joints, probably since they are larger and, therefore, easier to asses using imaging. It should be recognized that using hand OA as a phenotype has a drawback; a large number of joints need to be scored on radiograph.

Leptin

Leptin, a 16-kDa nonglycosylated peptide encoded by *ob* gene, was among the first adipokines discovered [7]. It plays a role in the control of bodyweight. [20]. Dynamic changes in plasma leptin concentration prevents weight change in either direction [20]. Leptin plasma concentrations are sensed by the hypothalamus. When leptin levels decrease during starvation, an adaptive response is activated to cope with the situation. Weight gain increases the plasma leptin concentration, which elicits a response aimed at reaching a state of negative energy balance.

To date, there is no consensus whether leptin is 'good' or 'bad' for cartilage. Several studies pointed out the catabolic role of leptin [21,22].

For example, Bao and coworkers demonstrated that injecting leptin into the knee joints of rats is shown to increase the production of MMP-2 and MMP-9 [21]. On the other hand, Dumond and coworkers showed that intra-articular injection of leptin into the knees of rats stimulated the production of IGF-1 and TGF-β, suggesting an anabolic role of leptin [11].

In animal studies, leptin is shown to increase bone mass by increasing the expression of osteogenic genes [23], increasing osteoblast proliferation, increasing *de novo* collagen synthesis [24,25] and decreasing osteoclastogenesis [26]. Subchondral osteoblasts in OA are shown to exhibit high levels of leptin [27]. Osteophytes are also shown to be able to secrete leptin into synovial fluid [28].

Concerning its role in inflammation, leptin seems to have a bidirectional effect [29]. Inflammatory stimuli increase leptin levels [30,31], and leptin itself is proinflammatory. Leptin and its receptor share structural and functional similarities with the IL-6 family of cytokines [29]. Leptin also amplifies the production of IL-6 and IL-8 in OA cartilage [32]. The bidirectional effect of leptin in inflammation is particularly problematic for cross-sectional studies of adipokines and OA.

To date, the evidence from epidemiological studies shows agreement that leptin is not associated with hand OA. In a cross-sectional study involving 1056 patients, Messengale and coworkers did not find significant differences in the mean serum leptin concentration between males with symptomatic hand OA (7.4 ng/ml) and males without hand OA (8.2 ng/ml) [33]. No difference in mean serum leptin levels was also shown in the female subpopulation (21.6 vs 20.8 ng/ml). These results are in line with results from a study by Yusuf and coworkers that did not find significant differences in the risk of having 6 years of radiographic hand OA progression between patients in the highest tertiles of baseline serum leptin (>8.2 ng/ml) and patients in the lowest tertiles (<4.4 ng/ml), before and after adjusting for BMI [34].

Unlike in hand OA, leptin was associated with knee OA, as shown by several studies. Karvonen-Gutierrez and coworkers measured leptin in a population of 543 women aged between 42 and 52 years old [35]. They showed that baseline serum leptin levels were associated with incident radiographic knee OA: a 5 ng/ml increase in serum leptin was associated with 30% higher odds (odds ratio: 1.3; 95% CI: 1.2–1.4) of having a new diagnosis of knee OA after correcting for BMI [35]. Ku and coworkers compared synovial fluid leptin between 42 OA patients who underwent knee surgery and ten who had no abnormality of articular cartilage during arthroscopic examination [36]. They found that median leptin concentrations in synovial fluid were significantly higher in OA patients (4.4 ng/ml; range: 0.5–15.8) compared with controls (2.1 ng/ml; range: 1.0–4.6; p = 0.006). They also showed that the median synovial fluid leptin level was highest in patients with the worst radiographic score (11.1 ng/ml). Berry and colleagues investigated the association between leptin and biomarkers of cartilage (COMP, PIIANP and C2C) and bone (PINP, osteocalcin, CTX-I and NTX-I) in 117 patients with knee OA [18]. They measured both leptin and biomarkers at baseline and, again, at 2 years of follow-up. They found that baseline leptin was associated with increased biomarkers of bone formation, osteocalcin (β-regression coefficient of 0.9; 95% CI: 0.1–1.6; p = 0.02) and PINP (β-regression coefficient of 1.3; 95% CI: 0.2–2.4; p = 0.02), over 2 years after correction for age, sex and BMI. No significant association between leptin and cartilage biomarkers was seen. Furthermore, in the same study, leptin was not

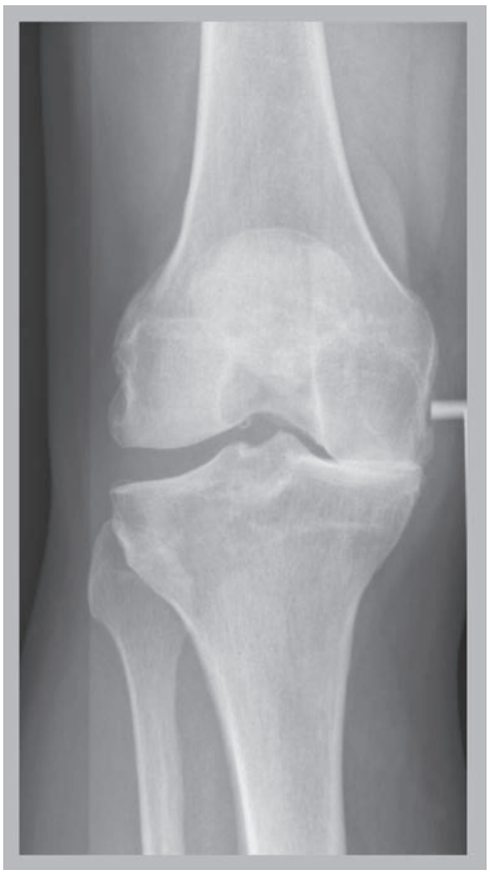

Figure 2. Radiograph of a knee joint showing a severe joint space narrowing, reflecting severe cartilage loss of the medial compartment.

associated with worsening of cartilage loss over 2 years, as measured by MRI. However, positive studies have not only been published regarding leptin and knee OA. A recent study by Van Spil and coworkers in a population with knee pain showed that leptin was not associated with radiographic progression and incidence of knee OA after adjustment for age, sex and BMI. The same study did show a cross-sectional association between leptin and PIIANP and PIIINP after correction for age, sex and BMI [19].

Studies on the effect of leptin and pain are limited. A recent pilot study by Messengale and coworkers involving 44 hand OA patients, showed that leptin was associated with pain severity, as measured using the visual analog scale [37].

There are several possible explanations why leptin was associated with OA of the knee, but not of the hand. First, the difference in mechanical loading. Obesity has been consistently shown as a risk factor for knee OA [4], perhaps mainly owing to mechanical loading. The effect of mechanical loading may be so great that it cannot be removed, even after adjustment for BMI, and every measurement related to obesity will show an association with knee OA. Second, the possibility of residual confounding. There are several variables in knee joints that may influence OA. However, they are not measured (e.g., muscle mass or muscle strength). These variables could give residual confounding. Last, it cannot be excluded that scoring systems for hand OA, which summarize many joints, may dilute the size of the effect.

Putting the evidence concerning leptin altogether, the authors can conclude that experimental research suggests that leptin has a role in OA pathophysiology concerning cartilage, bone and inflammation. However, this evidence is only partly supported by epidemiological studies. A 'positive' association between leptin and knee OA was shown by several studies; however, it remains difficult to differentiate mechanical from systemic effect.

Adiponectin

Adiponectin is a 244 amino acid-long polypeptide coded by the *ADIPOQ* gene that plays a role in glucose homeostasis [38]. Among adipokines, adiponectin is unique; serum adiponectin decreases with increasing obesity. It is still a matter of debate whether adiponectin is pro- or anti-inflammatory [14]. Adiponectin has three forms: a trimer (low molecular weight) form, a hexamer (trimer–dimer) form of medium molecular weight and a larger multimeric high molecular weight form [39]. It is possible to measure these isoforms and it is even advisable to do so, since the different isoforms may have different biological properties [39].

Adiponectin seems to have a protective role in cartilage. It induces the production of a tissue inhibitor of MMP-2, which consequently reduces matrix metalloproteinase-induced cartilage defect [40]. Studies on adiponectin's role in bone metabolism have not reached a consensus; one study showed that adiponetin stimulates osteoblast proliferation [41], but another study showed that adiponetin suppressed osteogenesis [42]. Concerning its role in inflammation, adiponectin seems to have an anti-inflammatory effect by downregulating IL-1β [40].

Many epidemiological studies did not investigate the isoforms of adipokines separately, but as total adiponectin. Yusuf and colleagues reported that being in the highest tertile of adiponectin (>28.4 µg/ml) was associated with reduced (70%) risk (risk ratio: 0.3; 95% CI: 0.2–0.7) of having radiographic hand OA progression in 6 years after adjustment for age, sex and BMI [34]. Another study on adiponectin and OA was performed by Filkova and colleagues [43]. In a case–control study, they compared the mean serum levels of adiponectin between patients with erosive hand OA (n = 48) with nonerosive hand OA (n = 27) and healthy controls (n = 20). They found that the mean serum adiponectin levels was higher in patients with erosive hand OA (28.7 µg/ml; standard deviation [SD]: 13.1) than nonerosive hand OA (21.3 µg/ml; SD: 11.4) and healthy controls (21.2 µg/ml; SD: 10.9). The differences between these two studies can be explained by the use of two different study types and differences in research question. The study from Filkova and coworkers was cross-sectional in nature and compared patients with a severe phenotype of hand OA with 'usual' hand OA [43], while the study by Yusuf and coworkers was a cohort study and did not specifically look at patients with 'severe' hand OA [34]. Adiponectin may be the 'cause' of joint damage in erosive hand OA, but it may be also the consequence of joint damage. A cross-sectional study cannot infer this causal relation. Another possible explanation is that adiponectin may have an effect on bone, since erosive hand OA is characterized by subchondral bone collapse [44]. Massengale and coworkers did not find an association between adiponectin and radiographic hand OA severity, as measured using the Kallman scoring system in a linear regression analysis [37]. It cannot be excluded that the small study population underlies the 'negative' result.

Honsawek and Chayanupatkul investigated adiponectin in knee OA in a case–control study [45]. They compared 76 patients with radiographic knee OA with 24 healthy controls. They did not find a significant difference ($p = 0.4$) between adiponectin plasma levels in OA cases (2.4 μg/ml) and controls (2.0 μg/ml). However, using another analysis, they showed that plasma adiponectin levels and adiponectin in synovial fluid were inversely correlated with radiographic severity, as measured using the Kellgren and Lawrence radiographic criteria ($r = -0.7$; $p < 0.001$ and $r = -0.5$; $p < 0.01$, respectively). The discrepancy in the results of this study may be caused by the use of difference analysis. Therefore, it may be advisable to report several analyses in epidemiological studies. Berry and coworkers did not find a significant association between adiponectin at baseline with increasing loss of cartilage of knee joints on MRI during 2 years of follow-up [18]. In addition, no association was shown by Van Spil and coworkers [19]. However, Van Spil show that adiponectin was weakly associated with cartilage markers CTX-II in the urine and COMP in the serum of patients with knee pain.

The evidence regarding adiponectin leans toward a protective role of this adipokine in OA. However, the contradictory effect in erosive OA should also be noted. OA is not a static disease, it evolves in time: from early where symptoms are present but no damage can be seen on radiograph to extensive damage where cartilage defect is seen as well as defect of subchondral bone (erosive OA). It is plausible that adiponectin and other adipokines have different roles in different stages of OA. Experimental and epidemiological research should take different stages of OA into account.

Adiponectin:leptin ratio

Metabolic functions of leptin and adiponectin are considered to be complimentary. In fields other than OA, several studies have used the leptin–adiponectin ratio as an index to glucose intolerance [46,47]. This approach can also be used in OA, as has been carried out by several investigators in OA research, such as Gandhi and coworkers [48]. They showed that the adiponectin–leptin ratio was associated with a higher pain level, as measured by short form McGill pain scores, in knee OA patients awaiting knee replacement surgery. This additional analysis (leptin to adiponectin ratio or *vice versa*) in an OA study may not help much in elucidating the role of adipokines in the pathophysiology of OA, but it may help in the studies investigating the possible role of adiponectin as a predictor of OA progression.

Resistin

Resistin is a cysteine-rich protein that is encoded by the *RETN* gene [49]. Its name is derived from its effect; injecting resistin into mice leads to insulin resistance [50]. To the best of our knowledge, no specific basic science study on the effect of resistin on cartilage has been published. Resistin appears to have a role in osteoclastogenesis by increasing differentiated osteoclasts and stimulated NF-κB promoter activity [51]. Resistin stimulates the release of proinflammatory cytokines, such as TNF-α, IL-1β and IL-6 [52].

To date, no studies have shown an association between resistin and hand OA. Yusuf and coworkers did not find any difference in the risk of having 6 years of radiographic hand OA progression between patients in the highest tertiles of baseline serum resistin (>1.4 ng/ml) and patients in the lowest tertiles (<0.8 ng/ml), before and after adjusting for BMI [34]. Filkova and coworkers did not show a significant difference in the mean serum resistin levels in patients with erosive hand OA (4.6 ng/ml; SD: 1.9), nonerosive hand OA (5.4 ng/ml; SD: 2.7) and healthy controls (5.1 ng/ml; SD: 2.5) [43].

While no association was shown in hand OA, resistin was shown to be associated with an incidence of radiographic knee OA after correction for age, sex and BMI [19]. In the same study, resistin was shown to be weakly associated with the synovium marker PIIINP. Using MRI as the outcome, Berry and coworkers did not find a significant association between resistin at baseline with increasing loss of cartilage and bone biomarkers during 2 years of follow-up [18].

Resistin was not associated with severity of pain in hand OA, as shown in the same pilot study by Massengale and coworkers [37]. Among the adipokines discussed in this review, resistin seems to have the weakest link with OA in epidemiological studies. This is partly caused by limited published data. We cannot exclude the possibility that limited published data is caused by publication bias and that 'negative' results are difficult to get published.

Adipokines & other possible pathophysiology pathways

Obesity is also a strong risk factor for coronary heart disease and the role of adipokines in this field is often investigated [53,54]. It is tempting to link OA and coronary heart disease; adipokines may be the factor that links OA and atherosclerotic vascular disease. It is possible that adipokines play a role in atherosclerosis, not only in large vessels [55–57], but also in small vessels.

Impaired circulation owing to atherosclerosis can initiate bone defects and lead to a cascade that results in cartilage loss and synovitis of the subchondral bone [58]. The adipokines discussed in this review have been shown to be related to atherosclerosis. For example, leptin [57] and resistin [55] have been shown to encourage the formation of atherosclerotic plaques, while adiponectin seems to protect against the formation of these plaques [56].

A comment should also be made on the role of Hoffa's infrapatellar fat pad. This local fat depot, which is unique to the knee joint, has been shown to play a role in inflammation [59,60], and it can be assumed that it also secretes adipokines. Its vicinity to the joint may also be important in the pathophysiology of OA in knee joints. It is possible that in knee joints, but not in other joints, adipokines secreted by Hoffa's fat pad contribute to the concentration of adipokines that are secreted elsewhere and filtered into the joint. This can also explain why the knee joint is the joint in which the role of adipokines is frequently shown in epidemiological studies.

Conclusion & future perspective

Adipokines are a hot topic in OA research. However, additional work is clearly needed in elucidating the role of adipokines in OA. The lack of epidemiological studies on the relation between adipokines and synovitis is surprising, since many adipokines are linked with inflammatory properties in experimental studies. More studies on adipokines and other features of OA, such as bone marrow lesions (as seen on MRI), are also warranted to understand OA as a disease of the whole joint. Using multiple measurements of adipokines in time and relating these measurements with, for example, increasing cartilage loss, will shed more light on the role of adipokines in OA. It is also rewarding to investigate the role of adipokines in pain, the main symptom of OA, in epidemiological studies and in experimental research; we can speculate that adipokines may activate nociceptors in the joint. The challenge remains on how to combine the results of different adipokines. The effect of one adipokine is perhaps interrelated with other adipokines in OA pathophysiology.

At present, published data are not sufficient for any possible application of adipokines in clinical practice. Within 10 years, we may be more conclusive about the contribution of adipokines in OA and perhaps be able to make a next step – that is, conducting clinical trials that modify adipokines to prevent OA progression. In the shorter time frame, we may use adipokines in predicting OA progression.

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Executive summary

Background

- Obesity is not only associated with osteoarthritis (OA) of weight-bearing joints, but also with nonweight-bearing joints, such as hand joints, implying that excess fat plays a role in the pathophysiology of OA through systemic and mechanical effects.
- Adipokines are secreted by fat tissue and have systemic effects.
- Leptin, adiponectin and resistin are among the adipokines that have an effect on cartilage, bone and inflammation.
- Epidemiological studies on the role of adipokines in OA use outcomes such as cartilage defects, as measured using radiograph, defects of joint structures (e.g., bone marrow lesions), as visualized using MRI, and biomarkers specific for the processes involved.

Leptin

- Several epidemiological studies in the knee OA population showed that leptin plays a 'negative' role in OA.

Adiponectin

- There are epidemiological studies showing the protective role of adiponectin in OA.

Resistin

- Resistin does not appear to be associated with OA in the epidemiological studies reviewed in this article.

Future perspective

- Further studies on the role of adipokines in synovitis (a feature of OA) and in pain (a central feature of OA) are needed.
- Further studies on adipokines should take into account the different phases of OA and the possible inter-relationship between adipokines.

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