ABSTRACT

BACKGROUND: Osteoarthritis is a prevalent disabling disease linked to obesity. The research community has been active in trying to understand why obesity increases the disability associated with hand osteoarthritis. One area of research is that of the adipokines.

QUESTION: Do one or more adipokines, influence the incidence or severity of hand osteoarthritis in obese patients?

METHODS: All relevant publications in the leading electronic databases were searched using the key terms adipokines and osteoarthritis. There were 205 listings, but here only 69 are examined and discussed. The articles had to be linked in some way to the key question driving the research.

RESULTS: The literature is very tentative at present regarding a definitive role of any adipokine in the osteoarthritic disease process as this affects obese patients in general, and hand osteoarthritis in particular. Both anabolic and catabolic effects are shown with all the derivatives studied, with no consensus emerging.

CONCLUSION: While adipokines may aggravate osteoarthritic processes among obese adults with hand osteoarthritis, more research is needed to translate present findings into prevention or treatment measures. This novel review provides a sound basis for examining adipokines in the specific context of non-erosive arthritis, and especially hand osteoarthritis.

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Key words: Adipokines; Hand; Obesity; Non-erosive arthritis; Osteoarthritis; Rehabilitation


BACKGROUND

Osteoarthritis, the most common joint disease, causes high disability rates among adults 55 years and older[1]. Specifically involving the breakdown of the articular cartilage lining of freely moving joints, along with structural and functional changes in the adjacent bony areas, osteoarthritis frequently produces varying degrees of pain, joint stiffness and swelling, multiple functional challenges, joint inflammation, and low life quality[2].

Unfortunately, despite its enormous individual and societal impact, osteoarthritis remains a chronic disease with no identifiable cure. In addition, existing treatments are not always helpful as far as reducing pain and promoting function, and some forms of treatment such as the use of pain relieving medications or surgery may be contra-indicated for some patients[3]. Moreover, research reveals some medications recommended for reducing osteoarthritic pain may foster, rather than retard, articular cartilage disintegration[4], the main problem associated with this condition. Other pharmaceutical remedies may have toxic side effects[5], or increase the risk for premature death as a result of gastrointestinal factors[6]. Since pain is the main problem experienced by people with osteoarthritis, and pharmacologic treatments as well as surgical interventions are limited to varying degrees in their ability to reduce, reverse or attenuate the disease process[2], a careful examination of all factors contributing to the development of and progression of osteoarthritis may assist in ameliorating the magnitude of this disabling disease to a greater extent than current standard approaches.

One problem identified as being strongly associated with osteoarthritis is obesity[7-10]. There is also increasing discussion as
... and the role of adipokines in osteoarthritis...
### Conclusion
Adiponectin may play a protective role in osteoarthritis.

### Results
Plasma levels of adiponectin were higher in the osteoarthritis patients, but were not significant, but synovial fluid levels were higher. Adiponectin levels in plasma and synovial fluid decreased significantly relative to disease severity.

### Methods
Adiponectin levels in plasma and synovial fluid decreased significantly relative to disease severity.

### Table 2
Sample of human studies examining the link between adipokines and osteoarthritis.

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<tr>
<th>Authors</th>
<th>Adipokine Studied</th>
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<td>Honsawek and Chayanupatkul</td>
<td>Adiponectin</td>
<td>76 cases with osteoarthritis and 24 healthy controls were studied.</td>
<td>Plasma levels of adiponectin were higher in the osteoarthritis patients, but were not significant, but synovial fluid levels were higher. Adiponectin levels in plasma and synovial fluid decreased significantly relative to disease severity.</td>
<td>Adiponectin may play a protective role in osteoarthritis.</td>
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<td>Yunuf et al</td>
<td>Leptin, adiponectin, resistin</td>
<td>The association between adipokines and the progression of hand osteoarthritis was assessed.</td>
<td>Patients in the two highest tertiles of adiponectin had a 70% decreased risk for hand osteoarthritis progression. Leptin and resistin levels were not associated with progression.</td>
<td>Adiponectin may be involved in the pathophysiology of hand osteoarthritis.</td>
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<td>Kostner et al</td>
<td>Leptin</td>
<td>163 subjects were studied with regard to knee cartilage thickness.</td>
<td>Serum levels of leptin were negatively associated with cartilage thickness, as was body mass index.</td>
<td>Serum levels of leptin are related to cartilage thickness measures, and age associations between body mass measures and cartilage thickness were mediated by leptin, suggesting it may be linked to cartilage thinning.</td>
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<td>Kamaven-Gukner et al</td>
<td>Leptin</td>
<td>Serum leptin levels were correlated with radiographs of women with knee osteoarthritis.</td>
<td>Leptin levels increased over time, and were higher in this with more definitive disease status.</td>
<td>It was concluded that the management of cardiometabolic function such as elevated serum leptin levels may allay the progression of the disease.</td>
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<td>Stuikos et al</td>
<td>Adipokines in plasma and synovial fluid</td>
<td>96 patients with knee osteoarthritis had their plasma and serum adipokine levels assessed.</td>
<td>Plasma leptin correlated positively with the severity of the osteoarthritis.</td>
<td>The ratio of synovial fluid to plasma leptin might be a marker of knee osteoarthritis severity.</td>
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<td>Massengale et al</td>
<td>Leptin</td>
<td>The relationship between hand osteoarthritis and serum leptin levels among a national sample of 1,056 persons was assessed.</td>
<td>No evidence of an association between serum leptin and hand osteoarthritis status was observed.</td>
<td>The evidence suggested that serum leptin concentrations are not related to hand osteoarthritis status.</td>
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<td>Huang et al</td>
<td>Chemerin</td>
<td>The association between chemerin serum levels and synovial fluid levels was assessed in patients with knee osteoarthritis.</td>
<td>Chemerin levels were higher with regard to paired synovial fluid data. These levels were related to the severity of the disease using accepted radiological criteria.</td>
<td>Chemerin may be involved in both the development and progression of osteoarthritis.</td>
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<td>Duan et al</td>
<td>Visfatin</td>
<td>Visfatin levels in the synovial fluid and plasma of patients with knee osteoarthritis and cartilage degradation markers were assessed.</td>
<td>Comparably to controls, patients had higher synovial fluid visfatin concentrations, and these were elevated more profoundly in those with higher degenerative scores.</td>
<td>Synovial fluid visfatin may be implicated in the cartilage degradation process in osteoarthritis.</td>
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<td>Gross et al</td>
<td>Leptin, resistin, adiponectin</td>
<td>The synovial fluid of 35 patients with osteoarthritis was examined.</td>
<td>IL-6 levels were correlated with adiponectin and resistin levels, adiponectin was correlated with TGF-B levels in women.</td>
<td>Adiponectin may contribute to metabolic changes in osteoarthritis.</td>
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<td>Koskinen et al</td>
<td>Resistin</td>
<td>Synovial fluid from 88 knee osteoarthritis surgical patients was examined.</td>
<td>Significant levels of resistin that correlated with IL-6 levels were observed, they were also correlated with metalloproteinases, but not with body mass index.</td>
<td>Resistin is present in synovial fluid in osteoarthritis and is released by chondrocytes in cartilage. Resistin is possibly catabolic in nature and associated with inflammatory mediators that influence the osteoarthritis disease process adversely.</td>
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<td>Perricco et al</td>
<td>Leptin, adiponectin, adipin, resistin</td>
<td>Investigated the association between plasma adipokine levels and the burden of painful hip and knee osteoarthritis.</td>
<td>Adjusting for age, body mass index, and disease differences, higher leptin and adiponectin and lower adipin levels were associated with greater burden of painful joint counts among women. Among men, higher resistin levels were associated with lower joint counts.</td>
<td>There is a sex-dependent systemic association between circulating adipokines and pain experienced by hip and knee osteoarthritis cases.</td>
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<td>Jiang et al</td>
<td>Nesfatin</td>
<td>Serum and synovial fluid were collected from cases with knee osteoarthritis and healthy persons, and 5 sets of articular tissues obtained during knee replacement surgery were subjected to immunohistochemistry.</td>
<td>Nesfatin-1 gene was expressed in affected osteoarthritis cartilage, and osteoarthritic serum contained higher levels of nesfatin-1, compared to serum from healthy controls. Significant correlations were found between serum nesfatin-1 and hsCRP levels patients and synovial nesfatin-1 and IL-18 levels were correlated (p = 0.0017).</td>
<td>Nesfatin, present in articular tissues may contribute to the pathology of osteoarthritis.</td>
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<tr>
<td>Lubekke et al</td>
<td>Leptin</td>
<td>Leptin concentrations and pain were assessed among 219 hip and knee osteoarthritis cases undergoing surgery.</td>
<td>Mean synovial fluid leptin levels were significantly associated with increased pain levels.</td>
<td>Joint pain is associated with leptin concentrations, especially among obese women.</td>
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</table>
Adiponectin and osteoarthritis

There is currently one hypothesis that suggests some forms of osteoarthritis may represent a systemic rather than an age associated local disorder, where lipid homeostasis is disordered\(^\text{[16]}\). However, even though adipokines, such as adiponectin have been identified as mediators between metabolic and rheumatic disorders\(^\text{[17]}\), the specific role of adiponectin is not established. This is because some studies show it actually has a protective role as far as mediating osteoarthritis severity\(^\text{[17]}\). Other studies show it has proinflammatory tissue destructive effects, and its presence in the synovial fluid of osteoarthritic joints was found correlated with aggrecan fragments\(^\text{[18]}\). De Boer et al\(^\text{[19]}\) for example, reported serum levels of adiponectin were increased in cases of erosive osteoarthritis as compared to non erosive cases, a finding reported by Fulkova et al\(^\text{[20]}\) for female patients. However, Francin et al\(^\text{[21]}\) found no strong association between the grade of cartilage destruction in people with osteoarthritis. Rather they found a positive correlation between adiponectin and the expression of type 2 collagen, aggrecan and Sox9, suggesting elevated adiponectin levels in osteoarthritic chondrocytes might contribute to osteoartritic remodeling. However, studies that are cross-sectional cannot pinpoint cause, and many related studies suggesting a linkage between cartilage damage and adiponectin conducted on cartilage explants or mice, such as that of Lago et al\(^\text{[22]}\) who found adiponectin increased levels of some degradative enzymes, but not others, may not reproduce the human situation at all effectively. As well, findings from studies involving rheumatoid arthritis patients may not apply to cases with osteoarthritis. Again, Conde et al\(^\text{[23]}\) recount a recent study by Yusef et al\(^\text{[24]}\) where patients with high adiponectin levels had a decreased risk for osteoarthritis progression, even though adipokines reportedly produce inflammatory states that can affect joints and bone\(^\text{[25]}\). As well, Chen et al\(^\text{[26]}\) found adiponectin to be involved in the modulation of cartilage destruction in chondrocytes by up-regulating TIMP-2 and down-regulating IL-1beta-induced MMP-13, findings that clearly indicate adiponectin may act as a protective role in the progression of osteoarthritis.

Leptin and osteoarthritis

The adipokine leptin, produced by adipose tissue cells, with a highly correlated plasma concentration related to obesity levels\(^\text{[27]}\), does appear to be important in explaining obesity\(^\text{[16-24]}\). It also appears to have a proinflammatory role in the process of osteoarthritis, by inducing the production of proinflammatory substances in chondrocytes\(^\text{[29]}\). Sannous et al\(^\text{[27]}\) found serum levels of leptin were related to reductions in cartilage thickness in cases with osteoarthritis. They suggested as well that the observed associations between adiposity levels and cartilage thickness were mediated by leptin. But again, even though de Boer et al\(^\text{[28]}\) found these levels associated with body mass index and being female in cases of severe knee osteoarthritis,
and Vuilteenaho et al[38] found evidence supporting the concept that leptin is a possible factor linking obesity to osteoarthritis, de Boer et al[39] conclude it is unclear as to whether leptin is always destructive as regards articular cartilage tissue or whether there is a possible anabolic function that it can also serve. Conde et al[21] suggested that high levels of circulating leptin in obese individuals may be protective in the context of osteoarthritis cartilage degeneration. Yet, they also pointed out that leptin expression is higher in osteoarthritic cartilage than normal human cartilage as observed by Dumond et al[30], while others found highest levels of leptin in advanced disease stages[36]. Although plasma leptin levels correlated positively with the severity of knee osteoarthritis, the level of obesity in the latter cases were not reported and synovial fluid plasma leptin ratios correlated negatively with different disease stages[30]. Moreover, while leptin levels may be elevated in patients with rheumatoid arthritis[36], knee osteoarthritis[28,31], and in the infrapatellar fat pad and synovial tissues of osteoarthritis cases[31], in the case of hand osteoarthritis Conde et al[21] concluded that there is no association between leptin levels and the progression of hand osteoarthritis, despite its association with hand pain intensity[32]. As well, even in the case of rheumatoid arthritis, it remains unclear as to whether leptin can damage or protect joint structures[19] because it is reported that chondrocytes stimulated with leptin increased the synthesis of cartilage constituents[16,29,31], physiologic concentrations of leptin had no effect on the breakdown of cartilage explants[24], and endogenous leptin might also enhance chondrocyte proliferation[9]. Other data show leptin increases in synovial fluid in advanced osteoarthritis that may act as a catabolic factor in progression of the disease[9], but what causes leptin secretion into either the systemic circulation or synovial fluid is unclear.

Although Hu et al[30] reported evidence that leptin was necessary to promote osteoarthritis damage in obese mice, according to Berry et al[39] the relationship between biomarkers of knee osteoarthritis and leptin is independent of body mass, as observed by Karvonen-Guteierrez et al[30], and the effects of obesity-induced osteoarthritis may not be through the direct effect of leptin on cartilage[14]. Although Ku et al[21] suggested leptin levels were related to the severity of knee osteoarthritis, among cases of similar body mass, these levels were reportedly lower than those for the United States general population[26].

Other adipokines and osteoarthritis

Resistin, another adipocyte-secreted factor often present in the synovium of inflamed joints may be implicated in the progression of osteoarthritis, and chronic inflammatory joint diseases[9]. But again more evidence is needed in this regard[19] because even though reported to stimulate cartilage degradation in explants of cartilage[12,35], Berry et al[39] found no correlation between cartilage volume loss and baseline serum resistin levels in their study. Yusuf et al[24] also found resistin levels were not associated with the progression of hand osteoarthritis, even though Ghandi et al[30] reported elevated serum resistin was associated with increased prevalence of hand osteoarthritis.

Another adipokine named chemerin was found by Huang et al[37] to possibly be involved in the pathophysiology of the development and progression of osteoarthritis. After surveying the chemerin levels in the serum and synovial fluid of patients with osteoarthritis, chemerin levels in the synovial fluid were found to be correlated with the degree of disease severity as evaluated radiographically. This may be important as chemerin is reportedly predominantly released by adipocytes and its production and serum levels are increased in obesity[37]. As well, chemerin correlates positively with circulating levels of inflammatory cytokines in obese cases and chemerin levels associated with inflammation in rheumatoid arthritis are also present at comparable levels in the joint fluids of patients with osteoarthritis[37]. However, the authors also mention chemerin may have a protective role under some conditions.

According to Hu et al an additional adipokine named visfatin should be considered an inflammatory mediator in certain circumstances, as well as the pathogenesis of osteoarthritis[37]. This conclusion was based on a study where visfatin synthesis was increased by a pro inflammatory mediator in a culture context, and that it exhibited a catabolic effect as regards cartilage aggrecan production. Gossett et al[30] also concluded visfatin may have an important catabolic role in the osteoarthritic disease process. They based this on examination of human chondrocytes from osteoarthritic patients as well as immature mouse chondrocyces. Duan et al[29] who studied cases with primary knee osteoarthritis found visfatin levels in the synovial fluid were positively correlated with a degradation biomarker of collagen II, as well as aggrecan. These findings suggest that visfatin located in the synovial fluid might involved in cartilage matrix degradation. Other adipokines that may play a role in the arthritic processes associated with osteoarthritis are apelin, vaspin and omentin[36]. Senalet et al[38] for example recently found different levels of vaspin and omentin at the site of local inflammation, but these were decreased as far as levels of vaspin were concerned and increased as far as levels of omentin were concerned in the synovial fluid of patients with osteoarthritis compared with those with rheumatoid arthritis, so their role in the osteoarthritic disease process is not clear.

CONCLUSION

Osteoarthritis, a debilitating degenerative joint disease is often cited as being influenced adversely by the presence of excess body weight[10]. In particular, the linkage between excess hand osteoarthritis disability and obesity, where direct joint loading effects are not obvious, has recently been attributed to the adverse influence of members of the adipokine family of peptides, produced by fat cells or adipocytes. Although potentially useful in helping to understand this well documented clinical observation, the present review suggests that the evidence for adipokine related disability in obese hand osteoarthritis patients is not equivocal (Table 1 and 2). In this regard, it is the author’s view that without strong supportive evidence demonstrating adipokines as consistently and significantly influential in mediating the onset and progression of hand osteoarthritis outcomes among overweight patients, other competing hypothesis for why obesity is a risk factor for hand osteoarthritis must be considered. For example, other biomechanical evidence suggests that as fat mass encroaches on muscle, it may render the muscle less able to protect joint in a timely way. Moreover, non-weight bearing joints may still be subject to joint forces of excess magnitude during daily activities, especially those that are repetitive such as screwing, hammering, twisting, and other occupational movements and that produce fatigue. As with those of normal weight, the presence of inflammation and swelling consequent to this series of events might explain the heightened destruction of hand joints in those cases considered to be obese. Alternately, the joint cartilage itself may be less well lubricated in people with painful hand osteoarthritis who are obese because they use their joints less and fluid flow through the joint itself is diminished. In negative studies, misclassification of osteoarthritis and being underpowered have been evoked as additional explanations for the lack of proof.
that adipokines are mediators of hand osteoarthritic damage in obese adults\(^{[39]}\).

To resolve the conundrum as to why hand osteoarthritis is apparently worse in obese cases than non-obese cases, it is the author’s view that these and other hypotheses should be examined in parallel to establish the best explanation for this finding. It is possible too, those with severe hand osteoarthritis, are unable to pursue even the most minimal form of activity, and become obese as a result of eating precooked meals, sedentary lifestyle modifications in response to pain, and reduced calorie usage due to splintering of hands, or adoption of a passive lifestyle, and these responses to the problem alone or in combination, produce obesity as a secondary problem-along with an increased susceptibility to inflammation\(^{[40]}\), that varies depending on extent of physical activity, and obesity level, so the associations detected are secondary not causative.

In the interim, the present key topic of investigation in this realm focuses on adipokines, hormones released by the hypothalamus with multiple functions but also by adipocytes, rather than biomechanical explanations. However, as discussed, these data have not produced any unequivocal conclusions, as far as osteoarthritic pathology is concerned, regardless of which adipokine is studied because all adipokines show both anabolic and catabolic mechanisms of action in this regard, and although they may all be involved in inflammation, this can occur with opposite effects. For example, Gross et al\(^{[36]}\) found both resistin and adiponectin to exhibit pro-inflammatory activity, while the free form of leptin appeared to down-regulate inflammation. Moreover, adipokines secreted by excess central fat or infrapatellar fat in the case of the knee joint\(^{[15]}\) cannot explain why many cases of osteoarthritis who are obese experience unilateral rather than bilateral joint problems or problems in one finger and not the other if the fat mass is equally distributed. Extreme obesity due to impaired leptin signaling was also found to induce alterations in subchondral bone morphology without increasing the incidence of knee OA\(^{[36]}\), and the correlations between the individual adipokines and the pain scales were low to moderate and consistently less than that for the corresponding adiponectin/leptin (A/L) ratio\(^{[65]}\). Thus, in addition to improving the quality and design of related studies, including more specific studies on cases with hand osteoarthritis, in particular, such studies should be designed to control more effectively for mechanical loading impacts and vascular comorbidities. As well, factors other than excess pro inflammatory adipokines need to be explored as explanatory mechanisms for excess joint destruction reported in obese hand osteoarthritic cases. In the meantime, given that adipokines may have an aggravating structural effect in early-stage knee osteoarthritis\(^{[36,37]}\), and cause similar effects to those observed for inflammatory arthritis\(^{[36]}\), and may be useful for monitoring disease progression\(^{[36]}\), we concur with Garner et al\(^{[34]}\) and Massengale et al\(^{[35]}\) that more research is desirable. These researchers also indicated that a focus on obesity prevention or reduction is crucial in efforts to minimize disability accompanying both hand osteoarthritis and other forms of painful osteoarthritis, even if calorie restriction in mice, had no impact on the incidence of later osteoarthritic lesions\(^{[39]}\), especially if leptin is a probable contributing metabolic risk factor for osteoarthritis\(^{[29,42]}\), along with adipocytokines, in general\(^{[64,45]}\).

This novel review could be used a starting point for further differentiating the role of adipokines in the etiology of osteoarthritis, as distinct from erosive arthritis. It could also be used as a springboard to explore why hand osteoarthritis is more painful in obese cases of the disease when compared to non-obese cases.

**CONFLICT OF INTERESTS**

The authors declare that they have no conflict of interests and received no financial support.

**REFERENCES**


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