

Adipokines and Osteoarthritis

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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

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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

Table 1 *In vitro* studies examining the link between adipokines and osteoarthritis

Authors	Adipokine Studied	Methods	Results	Conclusion
Francin <i>et al</i> ^[21]	Adiponectin	The expression of adiponectin was assessed in cartilage from healthy persons, and from persons with osteoarthritis. The association between adiponectin and grade of cartilage destruction was assessed	Adiponectin was not evident in the healthy cartilage. It was up regulated in the osteoarthritic cartilage, but was not related to the extent of destruction. There were differences in results different forms of adiponectin and the stimulated of catabolic cartilage enzymes	It was concluded that adiponectin is increased in osteoarthritic cartilage and its production by chondrocytes may influence cartilage modeling, but only the full length isoform was likely to be the active form
Terlain <i>et al</i> ^[33]	Leptin	Rats subjected to injections of leptin were examined	Leptin was strongly expressed in bone and osteoarthritic cartilage in a dose dependent manner, and was related to growth factors	Leptin may link osteoarthritis and obesity and contribute to osteoarthritis pathology
Gosset <i>et al</i> ^[38]	Visfatin	Human chondrocyte visfatin production with and without IL-1beta and the role of visfatin in prostaglandin synthesis were examined. Effects of visfatin on inflammatory mediators was assessed in mouse cartilage chondrocytes	Human osteoarthritic chondrocytes produced visfatin, which was increased by IL-1B. Visfatin increased prostaglandin synthesis Mouse chondrocyte released visfatin had proinflammatory effects	Visfatin has a catabolic function in cartilage and may play a role in osteoarthritis pathology
Comde <i>et al</i> ^[45]	Adiponectin, Leptin	Signal transduction pathways were explored in adipokine stimulated human and murine chondrocyte cell lines	Leptin and adiponectin increased VCAM-1 expression, and had an additive effect on IL-1B. Leptin increased metalloproteinase, cathepsin D, and collagen II, but decreased growth factors in the cartilage. Gene expression of ADAMTS-4 and -5 was increased, and depletion of proteoglycans was observed following leptin treatment	Leptin and adiponectin could perpetuate cartilage-degradative processes Leptin may have catabolic potential in the cycle of osteoarthritis pathology
Bao <i>et al</i> ^[51]	Leptin	Recombinant rat leptin was injected into rat knee joints, 48 h later, messenger RNA expression, growth factors, matrix enzymes and content were analyzed.	Leptin enhanced collagen release, as well as enzymes involved in cartilage breakdown	Leptin has proinflammatory attributes that can act in a catabolic manner to cause cartilage destruction Since IL-Kc was responsive to mechanical, as well as inflammatory, and metabolic stimuli, including visfatin-a relationship between these factors was cited as having a possible deleterious role in OA
Hui <i>et al</i> ^[53]	Leptin	Collagen release was assessed in explant cultures of bovine cartilage by bio assay along with leptin levels in cultures osteoarthritic infrapatellar fat pad tissues	Visfatin induced a 56 fold increase in the chemokine IL-Kc	
Chauffer <i>et al</i> ^[61]	Visfatin	Mouse cartilage explants were subjected to intermittent compression for 4, 6 and 24 hours and a visfatin dosage of 5ug/ml.		

to whether osteoarthritis is a metabolic disease, rather than solely a disease related to age or mechanical factors or genetic factors^[11]. This is because among the various osteoarthritis subgroups that have been established based on their underlying determinants, there appear to be those that represent a cluster associated with hypertension, type 2 diabetes, obesity, and dyslipidemia^[11].

Yet, even though a considerable volume of literature attributes the relationship between osteoarthritis and obesity to the impact of an associated excess loading effect on joints that produces a cascade of biochemical substances that hasten the destruction of joint tissues, this theory does not seem to fully explain why people who are obese may also acquire osteoarthritis of the hand, a non weightbearing joint site. Since it is now known that white adipose tissue acts as a repository of endocrine substances, and is a metabolically active organ that releases toxic substances such as inflammatory cytokines, including interleukin 1 and tumour necrosis factor alpha, plus adipokines into the bloodstream, it is argued that one or more of these biochemical mediators may be responsible for the processes of joint destruction observed in those osteoarthritis cases who are obese, especially those that appear to have accelerated joint pathology and/or hand osteoarthritis^[11].

This novel editorial provides a snapshot of the potent chemicals housed in adipose tissue that can possibly mediate or heighten joint destructive processes at one or more joint sites either through the heightened production of systemic inflammatory processes, or local processes at the affected joint site or both. To this end, literature housed in the Academic Search Complete data bases, PubMed, and Web of Science was searched using the terms osteoarthritis and adipokines. All relevant papers published in the English language were retrieved and the most salient are incorporated here with the goal of drawing attention to this topic as this impacts possible novel unexplored opportunities to prevent and ameliorate the severity or onset of osteoarthritis. Excluded however, were related papers dealing with erosive arthritis. In this sense, the present work is generally unique because it focuses solely on the possible distinction of joints as they occur in osteoarthritis, a non-erosive form of this disease, and the most prevalent, but poorly understood form with no known cure. It also focused on the application of this knowledge to hand osteoarthritis, not previously addressed in this context in a comprehensive manner.

RESULTS

Adipokines and osteoarthritis

According to recent research, adipokines, a collective term used to describe adipose-derived peptides^[12], are known to have a diverse range of hormonal functions that involve protein signalling and other functions^[12]. These adipokines or adipose related peptides are also synthesized in tissues other than adipose tissue^[13] including joint tissues^[12]. Often associated with energy metabolism and homeostasis, these peptides can be dysregulated quite significantly and may produce systemic and local effects that may impact the physiology of selected joints^[14]. when abnormal levels of abdominal fat prevail^[15] and the key adipokines likely to impact the onset or development of osteoarthritis in obese adults are adiponectin, leptin, resistin, and visfatin, and novel adipokines yet to be discovered^[16]. That is, these substances which play a key role in the immune system, and inflammatory responses, as well as glucose and adipocyte metabolism^[11] and are found in the serum of people with osteoarthritis appear to predict its radiographic disease progression.

The different categories of adipokines and their role in osteoarthritis as examined in *in vitro* and human studies are discussed below and summarised in tables 1 and 2.

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

Authors	Adipokine Studied	Methods	Results	Conclusion
Honsawek and Chayanupatkul [17]	Adiponectin	76 cases with osteoarthritis and 24 healthy controls were studied.	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 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	Adiponectin may play a protective role in osteoarthritis
Yusuf <i>et al</i> [64]	Leptin, adiponectin, resistin	The association between 3 adipokines and the progression of hand osteoarthritis was assessed	Serum levels of leptin were negatively associated with cartilage thickness, as was body mass index	Adiponectin may be involved in the pathophysiology of hand osteoarthritis
Stannus <i>et al</i> [27]	Leptin	163 subjects were studied with regard to knee cartilage thickness	Leptin levels increased over time, and were higher in this with more definitive disease status Plasma leptin correlated positively with the severity of the osteoarthritis	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 It was concluded that the management of cardiometabolic function such as elevated serum leptin levels may allay the progression of the disease The ratio of synovial fluid to plasma leptin might be a marker of knee osteoarthritic severity
Karnoven-Gutierrez <i>et al</i> [26]	Leptin	Serum leptin levels were correlated with radiographs of women with knee osteoarthritis	No evidence of an association between serum leptin and hand osteoarthritis status was observed Chemirin levels were higher with regard to paired synovial fluid data. These levels were related to the severity of the disease using accepted radiological criteria	The evidence suggested that serum leptin concentrations are not related to hand osteoarthritis status
Staikos <i>et al</i> [60]	Adipokines in plasma and synovial fluid	96 patients with knee osteoarthritis had their plasma and serum adipokine levels assessed The relationship between hand osteoarthritis and serum leptin levels among a national sample of 1,056 persons was assessed.	Compared to controls, patients had higher synovial fluid visfatin concentrations, and these were elevated more profoundly in those with higher degradative scores IL-6 levels were correlated with adiponectin and resistin levels, adiponectin was correlated with TGF-B levels in women.	Chemirin may be involved in both the development and progression of osteoarthritis
Massengale <i>et al</i> [32]	Leptin	The association between chemerin serum levels and synovial fluid levels was assessed in patients with knee osteoarthritis.	Significant levels of resistin that correlated with IL-6 levels were observed, they were also correlated with metalloproteinases, but not with body mass index	Synovial fluid visfatin may be implicated in the cartilage degradation process in osteoarthritis
Huang <i>et al</i> [27]	Chemirin	The synovial fluid of 35 patients with osteoarthritis was examined	Adjusting for age, body mass index, and disease differences, higher leptin and adiponectin and lower adipsin levels were associated with greater burden of painful joint counts among women. Among men, higher resistin levels were associated with lower joint counts	Adiponectin may contribute to metabolic changes in osteoarthritis
Duan <i>et al</i> [69]	Visfatin	Visfatin levels in the synovial fluid and plasma of patients with knee osteoarthritis and cartilage degradation markers were assessed	Nesfatatin-1 gene was expressed in affected osteoarthritic cartilage, and osteoarthritic serum contained higher levels of nesfatatin-1, compared to serum from healthy controls Significant correlations were found between serum nesfatatin-1 and hsCRP levels patients and synovial nesfatatin-1 and IL-18 levels were correlated ($p = 0.0017$)	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 osteoarthritic disease process adversely
Gross <i>et al</i> [66]	Leptin, resistin, adiponectin	The synovial fluid of 35 patients with osteoarthritis was examined	Mean synovial fluid leptin levels were significantly associated with increased pain levels	Joint pain is associated with leptin concentrations, especially among obese women
Koskinen <i>et al</i> [27]	Resistin	Synovial fluid from 88 knee osteoarthritis surgical patients was examines		
Perriccio <i>et al</i> [48]	Leptin, adiponectin, adipsin, resistin	Investigated the association between plasma adipokine levels and the burden of painful hip and knee osteoarthritis		
Jiang <i>et al</i> [69]	Nesfatatin	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.		
Lubekke <i>et al</i> [50]	Leptin	Leptin concentrations and pain were assessed among 219 hip and knee osteoarthritis cases undergoing surgery		

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

Authors	Adipokine Studied	Methods	Results	Conclusion
Choe <i>et al</i> ^[52]	Resistin, adiponectin	Female subjects with and without radiographic hand osteoarthritis were measured for serum adiponectin and resistin concentrations using an enzyme-linked immunosorbent assay and x-rays.	Resistin was higher in cases with osteoarthritis, and with radiographic features of the disease.	Resistin may play a role in the radiographic presentation of hand osteoarthritis.
Van Spil <i>et al</i> ^[53]	Plasma adipokines, leptin, adiponectin, resistin	Adipokines and their association with radiographic signs of early knee osteoarthritis were assessed among 1002 patients.	Leptin had a positive association with progression of the disease, but not after adjusting for body mass. Resistin correlated with present and incident radiographic knee osteoarthritis that was largely independent of body mass. Adiponectin showed some correlation with certain disease progression features, but not radiographic knee osteoarthritis. All associations were deemed weak.	Adipokines may aggravate the structural effects in early stage knee osteoarthritis, but in a minor way.
Bas <i>et al</i> ^[55]	Leptin, adiponectin, resistin or visfatin levels	Patients with hip and knee OA undergoing total joint arthroplasty were subjected to serum and synovial fluid assays on the day of surgery.	All adipokine levels were significantly higher in the synovial fluid of hip joints compared to knee joints, except for leptin, which tended to be higher in the knee. In both hip and knee patients, serum concentrations of leptin, adiponectin, resistin and visfatin exceeded those in found in the synovial fluid.	Findings support a connection between intra-articular concentrations of several adipokines and osteoarthritis severity. However, the specific adipokines differed by joints: in hip OA, pain was associated with and visfatin and in knee OA with adiponectin; leptin played a role in both hip and knee patients
Pallu <i>et al</i> ^[62]	Leptin	Chondrocytes isolated from OA patients with various body mass index (BMI) were treated with 20, 100 or 500 ng/ml of leptin.	At 20 ng/ml leptin was unable to modulate gene expression in chondrocytes, except for MMP-13 in obese OA patients	Obesity may affect the responsiveness of cultured chondrocytes to leptin. However, gene expression depends not only on the body mass index level, but also on the concentration of leptin.
Chen <i>et al</i> ^[64]	Visfatin	Investigated the distribution of visfatin in paired serum and synovial fluid (SF) samples from patients with osteoarthritis (OA), and in serum from healthy controls.	Serum visfatin concentrations to be higher in patients with OA compared to healthy controls (p<0.05), and SF-visfatin concentrations exceeded those in paired serum (p=0.004). The expression levels of both AdipoR1 and AdipoR2 was markedly higher in lesional than in nonlesional areas of OA cartilage. The increased rate of AdipoR1-positive chondrocytes was twice that of AdipoR2-positive chondrocytes when compared between nonlesional and lesional areas. Adiponectin-stimulated OA chondrocytes showed increased total iNO and MMP-1, -3, and -13 levels compared with non-stimulated cells	Visfatin may be involved in the pathophysiology of OA and may have local effects in the joint during the process of OA.
Kang <i>et al</i> ^[67]	Adiponectin	Cartilage and chondrocytes from the knee joints of primary OA patients were cultured in the presence of adiponectin (0-30 µg/ml). The levels of total nitric oxide (NO), matrix metalloproteinase (MMP)-1, -3, and -13, and tissue inhibitor of metalloproteinase (TIMP)-1 were measured in the conditioned media.	Adiponectin causes matrix degradation in OA cartilage and increases MMPs and iNOS expression	Adiponectin causes matrix degradation in OA cartilage and increases MMPs and iNOS expression

Adiponectin and osteoarthritis

There is currently one hypothesis that suggests some forms of osteoarthritis may represent a systematic rather than an age associated local disorder, where lipid homeostasis is disordered^[16]. However, even though adipokines, such as adiponectin have been identified as mediators between metabolic and rheumatic disorders^[15], 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^[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^[18]. De Boer *et al*^[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*^[20] for female patients. However, Francin *et al*^[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 osteoarthritic 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*^[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*^[23] recount a recent study by Yusef *et al*^[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^[15]. As well, Chen *et al*^[25] 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^[12], does appear to be important in explaining obesity^[10,26]. It also appears to have a proinflammatory role in the process of osteoarthritis, by inducing the production of proinflammatory substances in chondrocytes^[10]. Stannus *et al*^[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*^[19] found these levels associated with body mass index and being female in cases of severe knee osteoarthritis,

and Vuilteenaho *et al*^[26] found evidence supporting the concept that leptin is a possible factor linking obesity to osteoarthritis, de Boer *et al*^[19] 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*^[23] 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*^[29], while others found highest levels of leptin in advanced disease stages^[15]. 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^[15], knee osteoarthritis^[28,31], and in the infrapatellar fat pad and synovial tissues of osteoarthritis cases^[15], in the case of hand osteoarthritis Conde *et al*^[23] 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^[15] because it is reported that chondrocytes stimulated with leptin increased the synthesis of cartilage constituents^[16,29,33], physiologic concentrations of leptin had no effect on the breakdown of cartilage explants^[34], 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*^[9] reported evidence that leptin was necessary to promote osteoarthritis damage in obese mice, according to Berry *et al*^[35] the relationship between biomarkers of knee osteoarthritis and leptin is independent of body mass, as observed by Karvonen-Guteirrez *et al*^[28], and the effects of obesity-induced osteoarthritis may not be through the direct effect of leptin on cartilage^[34]. Although Ku *et al*^[31] 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^[28].

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*^[35] 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*^[36] 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^[57]. 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^[57]. 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^[9]. 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*^[38] 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 chondrocytes. Duan *et al*^[39] 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 be involved in cartilage matrix degradation. Other adipokines that may play a role in the arthritic processes associated with osteoarthritis are apelin, vaspin and omentin^[9]. Senalt *et al*^[58] 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^[60]. 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 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 osteoarthritis damage in obese adults^[28].

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 splinting 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 osteoarthritis 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*^[56] 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^[65], 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^[66]. 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 osteoarthritis cases. In the meantime, given that adipokines may have an aggravating structural effect in early-stage knee osteoarthritis^[63,67], and cause similar effects to those observed for inflammatory arthritis^[68], and may be useful for monitoring disease progression^[69], we concur with Garner *et al*^[41] and Massengale *et al*^[42] 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^[59], especially if leptin is a probable contributing metabolic risk factor for osteoarthritis^[29,43], along with adipocytokines, in general^[44,45].

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.

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