OBESITY AND OSTEOARTHRITIS: MORE THAN JUST MECHANICS

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis worldwide. It results in chronic pain, functional limitations, and significant social and economic burdens. Obesity rates in the developed world are rapidly increasing, leading to warnings of an obesity epidemic. Obesity is associated with increased rates of OA. Traditionally, this increased prevalence was attributed to biomechanical factors including increased joint loading and altered joint dynamics due to the physical burden of obesity. However, a number of factors, including the increased prevalence of OA in non-weight-bearing joints in obese individuals and the increasing awareness of adipose tissue as a functional endocrine organ rather than an inert storage substance, have led to a reappraisal of this viewpoint. Adipose tissue secretes a number of adipokines and cytokines with both local and systemic effects. In addition, adipose tissue has the potential to stimulate a systemic inflammatory state. Differential expression of microRNAs in obese and non-obese osteoarthritic patients has been demonstrated. The potential impact of adipokines on the adipose inflammatory pathway in obese individuals is being actively explored. The traditional view of OA as a mechanical wear-and-tear disease is being revolutionised by the discovery of the key roles of inflammation and cytokines in this most common of joint diseases.

Keywords: Obesity, osteoarthritis, adipokines, inflammation, cytokines, microRNA.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis worldwide.1 There is a significant discrepancy between radiographic changes and patient-reported symptoms in OA. Many patients report no symptoms but have significant radiographic changes of OA.2 Symptomatic OA presents with predominant symptoms of pain and stiffness. This can lead to significant disability and difficulty performing activities of daily living.1,3,4 Severely symptomatic OA frequently necessitates joint replacement surgery, with high attendant costs involved.5

The global prevalences of symptomatic and radiographic OA at the knee and hip are 3.8% and 0.85%, respectively.1 Radiographic hand OA is present in 67% of women and 55% of men aged 55 years and over, with one-fifth of these experiencing symptoms.2,6 In addition, OA at other sites contributes significantly to the high prevalence of many other musculoskeletal complaints such as low back pain, which is the leading cause of ‘years lived with disability’ worldwide.4 OA is strongly associated with ageing and therefore we can expect to see a further increase in prevalence due to the ongoing demographic changes in our population.7 The traditional view of OA maintained that it was a ‘wear-and-tear’ form of arthritis caused by repetitive activity over many years and was an inevitable consequence of ageing.8 Factors resulting in increased joint loading, such as excessive physical activity or body weight, were accepted as risk factors.9 A deeper understanding of the pathogenesis of OA has led to the recognition of genetic factors, biomechanical factors, and inflammatory processes as important elements in the development of OA.10-12
Obesity is rapidly becoming one of the world’s most significant health issues, with 2.1 billion people either overweight or obese in 2013. Obesity has long been recognised as a risk factor for OA. This was initially attributed to increased force through weight-bearing joints. However, this was challenged by the association of obesity with OA of non-weight-bearing joints, such as the hands. Body composition in terms of both reduced skeletal muscle mass and increased fat mass may be more predictive of OA and cartilage loss than body mass index (BMI). Adiposity measures are strongly associated with the need for joint replacement surgery. Adipose tissue was previously regarded as an inert storage vessel but new insights have revealed that it is in fact an endocrine organ actively secreting a variety of adipokines and cytokines with a multitude of local and systemic effects. The purpose of this review is to explore the role of obesity in the development of OA from a metabolic viewpoint (Figure 1).

**ADIPOKINES**

Adipokines are proteins secreted by adipocytes. There are over 100 adipokines identified to date, the most studied of which include leptin, adiponectin, resistin, visfatin, chemerin, and lipocalin 2. In addition to these adipokines, adipose tissue also contains a population of resident macrophages that secrete a variety of cytokines, including tumour necrosis factor alpha (TNFα) and interleukin (IL)-6.

**Leptin**

Leptin is a 16-kDa protein encoded by the *OB* gene, and which circulates in human plasma. Since its discovery 20 years ago it has been considered as the prototype for other adipokines. The key physiological roles of leptins are in satiety and appetite. Leptin levels are associated with fat mass, BMI, and circulating levels of inflammatory markers. Serum leptin levels correlate with the severity of radiographic knee OA.

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**Figure 1: Proposed pathways linking obesity and osteoarthritis.**

miR: microRNA; TNFα: tumour necrosis factor alpha; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; FFA: free fatty acids; ox-LDL: oxidised low-density lipoprotein; HDL: high-density lipoprotein.
Levels of leptin in synovial fluid also correlate with BMI and severity of OA, and increased expression of the protein has been demonstrated in osteoarthritic cartilage when compared with normal cartilage.\textsuperscript{24,25} Leptin appears to have a biphasic effect on cartilage, with low levels being physiologically important for normal cartilage synthesis and high levels contributing to cartilage degradation.\textsuperscript{26} Serum leptin levels have been shown to correlate with both knee cartilage volume and thickness as assessed by magnetic resonance imaging (MRI) in cross-sectional studies.\textsuperscript{27,28} In addition, a longitudinal study has demonstrated that both baseline serum leptin levels and changes in leptin levels are associated with changes in knee cartilage thickness.\textsuperscript{27}

A further study demonstrated a relationship between higher serum leptin levels and increased development of cartilage defects, bone marrow lesions, synovitis, and effusions as assessed by MRI 10 years later.\textsuperscript{29} The relationships between BMI, adiposity measurements, OA, and cartilage thickness appear to be mediated, at least in part, by leptin.\textsuperscript{27,30} Leptin has also been shown to stimulate the secretion of inflammatory cytokines, including IL-6, from synovial fibroblasts, suggesting that it may play a role in synovial inflammation.\textsuperscript{31} Subchondral osteoblasts overexpress leptin in OA patients and the associated abnormal osteoblast phenotype can be normalised by neutralisation of leptin.\textsuperscript{32} Animal studies have shown that feeding mice a high-fat diet induces OA with corresponding increases in leptin, and that leptin levels correlate with severity of knee OA.\textsuperscript{33,34} In contrast to these positive findings, a number of other studies have not reported an association between leptin and OA, particularly of the hand. A cross-sectional analysis of the NHANES III dataset revealed no association between serum leptin levels and hand OA.\textsuperscript{35} This is supported by other studies in hand OA, which similarly report no association with serum leptin levels.\textsuperscript{36,37}

A number of hypotheses have been proposed to explain these conflicting findings. The regulation of human energy stores, a system in which leptin is integral, is complex, with multiple interactions and feedback mechanisms. As with many homeostatic processes, a view that proposes a direct correlation between leptin and outcomes may be too simplistic. Leptin levels are pulsatile both throughout the day and with a relative nocturnal increase; measurements at a single timepoint may not provide an accurate reflection of functional leptin levels.\textsuperscript{20,21} Leptin is interlinked with the hypothalamic—pituitary axis in the control of body energy stores and factors such as central leptin resistance and leptin tolerance appear to be important in the longer-term effects of this adipokine.\textsuperscript{20} Most but not all human obesity appears to be associated with an insensitivity to leptin; 5-10% of obese humans have relatively low levels of leptin.\textsuperscript{21} Again, this indicates a need for the development of a broader view of leptin functionality analogous to advances in the understanding of type 2 diabetes mellitus (T2DM). A further complication in the interpretation of leptin levels came with the realisation that not only did leptin not correlate directly with adipose tissue volume at an individual level, but there was also production of leptin in other body tissues such as skeletal muscle.\textsuperscript{21} The inference from these findings is not that leptin is not important but rather that our understanding of the complex mechanisms governing its function is incomplete.

A further putative role for leptin in OA is as a pain modulator. Both serum and synovial fluid leptin levels have been shown to correlate with pain intensity in chronic OA.\textsuperscript{37,39} In animal studies, the intra-articular administration of leptin has been associated with mixed findings. Bao et al.\textsuperscript{40} found a predominantly catabolic effect with increased levels of matrix metalloproteinase (MMP)-2, MMP-9, cathepsin D, and collagen II with decreased basic fibroblast growth factor and depletion of proteoglycan in articular cartilage. In contrast, an earlier study by Dumond et al.\textsuperscript{24} reported anabolic effects following intra-articular injection of leptin, with increased synthesis of insulin-like growth factor 1 and transforming growth factor beta 1 (TGF-β1). Our evolving understanding of the precise meanings behind changes in cytokine levels may explain some of these apparent discrepancies; for example, TGF-β has also been associated with the induction of OA-like changes.\textsuperscript{41} Taken together, these data suggest that excess leptin has a negative effect on cartilage in the large joints of the lower limbs but not in the small, non-weight bearing joints of the hand. Some of the contribution to OA symptoms may be mediated through nociceceptor effects. This makes leptin antagonists potentially interesting agents for therapeutic investigation in OA. Recombinant leptin and leptin analogues are now available for the treatment of congenital leptin deficiency and lipodystrophy.\textsuperscript{20} However, no clinical studies of leptin antagonists in OA have been conducted.
to date. The prohibitive cost of these agents is a significant hurdle to be overcome before their use in such a common disorder can be considered; currently available leptin analogues cost in excess of €500,000 per patient per year.

**Adiponectin**

Adiponectin is an intriguing 30-kDa adipokine because serum levels inversely correlate with BMI. Its physiological role demonstrates insulin-sensitising, anti-inflammatory, and anti-atherogenic properties. Adiponectin levels are increased in OA but negatively correlate with pain and OA severity. This suggests that adiponectin may play a protective role in OA. Worryingly, an association between increased adiponectin levels and both all-cause and cardiovascular (CV) mortality has been demonstrated. This is despite the negative association of adiponectin and T2DM, and the association of the latter with CV and all-cause mortality. The reasons behind, and the implications of, this apparently conflicting prognostic role for adiponectin are yet to be fully elucidated. Chondrocyte studies have shown that adiponectin increases tissue inhibitor of MMP-2 and decreases IL-1β-induced MMP-13. In contrast, other studies have shown that adiponectin can increase nitric oxide synthase 2, MMP-3, MMP-9, and IL-6. Synovial fibroblast studies have shown increased IL-6 production when stimulated with adiponectin. These apparent discrepancies in the laboratory data mirror the clinical confusion over the role of adiponectin in health and disease, and suggest that we do not yet fully understand this unusual adipokine. Adiponectin agonists are in development, with a goal of treating obesity-related diseases such as T2D. These include an oral small-molecule agonist that has been shown to prolong lifespan and ameliorate diabetes in a mouse model. No such agents have yet been assessed in OA models.

**Other Adipokines**

Resistin, visfatin, and chemerin are the most studied of the plethora of other known adipokines. Resistin is a 12.5-kDa adipokine that is also expressed by macrophages. Resistin levels are elevated in the synovial tissue of OA patients and intra-articular injection of resistin can induce arthritis in a mouse model. Resistin upregulates gene expression and stimulates the synthesis of a large number of pro-inflammatory cytokines. Visfatin has been shown to play an important catabolic role in human OA chondrocytes and in a mouse model of OA. Chemerin levels in synovial fluid correlate with the severity of knee OA. Chemerin expression in synovium and the infrapatellar fat pad is higher in OA patients than in normal individuals.

**CYTOKINES**

In addition to adipokines, a number of other cytokines are released from adipose tissue. The major sources of these are the resident tissue macrophages and other immune cells. Three key cytokines that potentially play a role in OA and have been demonstrated to have increased expression or serum levels in obesity are TNFα, IL-6, and vascular endothelial growth factor (VEGF).

**Tumour Necrosis Factor Alpha**

TNFα is a key cytokine in the inflammatory pathogenesis of rheumatoid arthritis (RA), and anti-TNFα agents are a key part of the rheumatologist’s armamentarium in treating this disease. Expression of TNFα is elevated in obesity and decreases with weight loss. While TNFα levels are elevated in OA, agents targeting this pathway have been disappointing in clinical studies to date. Serum levels of TNFα are associated with knee cartilage loss. Given the emerging understanding of the importance of synovial inflammation in the development of OA, a potential benefit from TNFα blockade is conceivable. It is possible that personalised treatment of OA based on clinical criteria and biomarkers, as has been proposed for RA, would improve outcomes. Further evaluation of patients with higher serum or synovial fluid TNFα levels, greater radiographic or arthroscopic demonstration of synovitis, or indeed obese patients in whom inflammatory change may play a greater role would all be of interest.

**Interleukin-6**

IL-6 is a pro-inflammatory cytokine for which both serum levels and adipose tissue expression are elevated in obesity. It is proven to be important in the pathogenesis of RA and is targeted in clinical use by the IL-6 blocking agent tocilizumab. Levels are elevated in the serum and synovial fluid in OA, and correlate with knee cartilage loss. IL-6 has been shown to play an essential role in cartilage destruction in an animal model of OA. As yet, no reports on the use of IL-6 blockade in
OA exist. Current evidence suggests that IL-6 might be a therapeutic target in OA, possibly by intra-articular administration.

**Vascular Endothelial Growth Factor**

VEGF is a cytokine and growth factor that is important in angiogenesis. VEGF inhibitors have been developed and are utilised in cancer treatment, as well as other indications. Serum VEGF levels correlate with BMI and are associated with visceral fat accumulation in obese individuals. VEGF levels in serum and synovial fluid are increased in OA patients compared with healthy controls. Synovial fluid VEGF levels correlate with radiographic and functional assessments of knee OA severity. The VEGF-blocking agent bevacizumab has been shown to inhibit the development of post-traumatic OA in an animal model when administered locally or systemically. These data are promising for the potential use of these agents in OA. However, a number of obstacles remain, including the evaluation of potential adverse events in this population and an economic evaluation of the benefit–cost ratio of such a treatment.

**EPIGENETICS**

A number of epigenetic mechanisms may play a role in OA and its links with obesity. The best studied of these are microRNA molecules (miRNAs). Other potentially important mechanisms include DNA methylation and histone acetylation.

**MicroRNA**

Studies of the human genome led to the discovery that only a small minority of the transcribed genome is ultimately translated into protein. The majority remains as noncoding RNA molecules. Initially regarded as ‘junk DNA’, the science of epigenetics has revealed the importance of these molecules in the regulation of gene expression. The miRNAs are a class of short (18-25 nucleotides), highly conserved, noncoding RNA molecules. In terms of gene regulation, miRNAs have been shown to adjust the translational output of coding RNAs both by increasing their degradation and inhibiting RNA translation into protein.

The importance of miRNA in a variety of diseases and pathogenic mechanisms is becoming increasingly evident. It is likely that, as with genetics as a whole, they are important to some degree in almost all disease processes. Iliopoulos et al. evaluated a panel of 365 miRNAs from the cartilage of patients undergoing surgery for OA and compared them with miRNAs from the cartilage of patients with no history of OA undergoing fracture surgery as a control group. They found significant changes in the levels of 16 miRNAs. These included both upregulation (miR-16, miR-22, miR-23b, miR-30b, miR-103, miR-223, miR-377, miR-483, miR-509), denoting a detrimental effect for the implicated miRNAs, and downregulation (miR-25, miR-26a, miR-29a, miR-140, miR-210, miR-337, miR-373), implying a protective effect. They also found that five of these miRNAs were associated with BMI (miR-22 and miR-103 positively, miR-25, miR-29a, and miR-337 negatively), suggesting a role for miRNAs in the link between obesity and OA pathogenesis. Other researchers confirmed the downregulation of miR-140 and reported the negative association of miR-146 and OA grade.

A large number of other miRNAs are potentially of importance in OA pathogenesis, although not necessarily modulated through obesity, and our knowledge in this area is expanding rapidly. Two miRNAs (miR-935 and miR-4772) have been shown to be upregulated in obese individuals who do not respond to a dietary intervention for weight loss. Weight loss following bariatric surgery, but not diet-induced weight loss, has been shown to be associated with both upregulation (miR-221, miR-199a-3p) and downregulation (miR-16-1, miR-122, miR-140-5p, miR-193a-5p) of miRNAs. Targeting miRNA either by using anti-miRNAs or by miRNA mimicry has emerged as a potential therapeutic option in pre-clinical studies. Mimicry of miR-140 using double-stranded miR-140 demonstrated functional effects on OA-related genes, with upregulation of a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTSS) and downregulation of aggrecan. Synthetic miR-146a suppresses extracellular matrix-associated proteins (MMP-13 and ADAMTTS) and IL-1-mediated induction of inflammatory markers (COX2, IL-8).

**Other Epigenetic Mechanisms**

While undoubtedly important in OA pathogenesis, other epigenetic mechanisms potentially linking obesity and OA remain to be fully explored. Leptin expression has been shown to correlate with DNA methylation. In addition, Iliopoulos et al. demonstrated the negative association of leptin
methylation in OA chondrocytes, as well as a role for histone acetylation in the leptin promoter.

### MECHANICAL LOADING

Mechanical loading has the potential to alter joint biology in addition to its direct physical effects. Abnormal mechanical loading of resident chondrocytes increases the expression of catabolic factors such as MMPs, and decreases proteoglycan, DNA, and collagen synthesis. In addition, increased loading can alter the chondrocyte inflammatory phenotype, with increased release of IL-1 and TNFα. This combination of effects has the end result of predisposing the articular cartilage to a degradative state.

### LIPID AND GLUCOSE METABOLISM

Abnormalities of lipid metabolism, in particular in relation to fatty acids and cholesterol, have been suggested to play an important role in the pathogenesis of OA. Lipid metabolic dysfunction is a characteristic of obesity, with increases in triglycerides, free fatty acids, and low-density lipoprotein (LDL) cholesterol, accompanied by a decrease in high-density lipoprotein (HDL) cholesterol. Omega-3 polyunsaturated fatty acids (PUFAs) have a potential role in protection from OA through decreased production of inflammatory cytokines, free radicals, and eicosanoids. An animal model of OA has demonstrated a protective effect of omega-3 PUFAs on OA development, which is in contrast to the increased synovitis, osteophytosis, and OA severity observed with increased saturated fatty acid consumption. A clinical study in humans showed an association between a greater proportion of omega-3 PUFAs and protection from cartilage degradation, as well as increasing levels of synovitis with omega-6 PUFAs. A mechanistic link between these fatty acid abnormalities and joint damage is suggested by the ability of free fatty acids to activate macrophages.

Abnormalities in both HDL and oxidised (ox)-LDL have been linked to OA development. Reduced or dysfunctional HDL may contribute to OA. Serum HDL levels are reduced in patients with OA and increased HDL protects from the development of subchondral bone marrow lesions. Animal studies with functional HDL-knockout mice fed a high-fat diet have shown increased rates of cartilage degradation and catabolic mediators. Ox-LDL correlates with BMI and is found in OA synovial fluid. Ox-LDL stimulates MMP release and decreases chondrocyte proteoglycan synthesis. A murine model has demonstrated the ability of ox-LDL to increase synovitis, inflammatory mediators, and clinical arthritis, as well as a therapeutic potential for receptor blockade. Sustained hyperglycaemia results in a low-grade systemic inflammatory state and has direct deleterious effects on cartilage by inducing chondrocyte dysfunction and subchondral bone destruction.

### CONCLUSION

Both obesity and OA are increasing health problems in our society. While the major contributor to the increase in OA is related to an ageing population, obesity is mainly determined by diet and lifestyle. Both conditions share an important genetic component to their pathogenesis. Increasing evidence points towards a significant contribution of obesity to OA. This raises concerns of a ‘knock-on’ effect of the current obesity epidemic on future OA rates. Aside from biomechanics, the effects of obesity on OA are also likely to be mediated by a number of other factors including adipokines, cytokines, and miRNAs. Among adipokines, leptin and adiponectin are the most studied. Leptin appears to have a negative effect on OA, with increased levels being associated with more severe disease in most studies. Adiponectin’s role appears more complicated, with increased levels found in OA patients but conflicting laboratory data on the functional effects of this adipokine. As in RA, cytokines appear to play a role in OA, at least in some patients, with the greatest evidence for TNFα, IL-6, and VEGF, all of which are overexpressed in individuals with obesity. Epigenetics, and miRNAs in particular, are an expanding science likely to be of relevance in OA pathogenesis. A number of different miRNAs appear to be either protective or harmful in OA. Our knowledge of these aspects of OA remains in its infancy, with no agents yet in clinical trials. Further exploration has the potential to open new frontiers in the management of this debilitating condition, which currently has no effective disease-modifying therapy.
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