

Review Article

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Obesity & osteoarthritis

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The most significant impact of obesity on the musculoskeletal system is associated with osteoarthritis (OA), a disabling degenerative joint disorder characterized by pain, decreased mobility and negative impact on quality of life. OA pathogenesis relates to both excessive joint loading and altered biomechanical patterns together with hormonal and cytokine dysregulation. Obesity is associated with the incidence and progression of OA of both weight-bearing and non weight-bearing joints, to rate of joint replacements as well as operative complications. Weight loss in OA can impart clinically significant improvements in pain and delay progression of joint structural damage. Further work is required to determine the relative contributions of mechanical and metabolic factors in the pathogenesis of OA.

Key words Adipokine - body mass index - cartilage - obesity - osteoarthritis - weight loss

Introduction

Obesity is a well-recognized global epidemic. The WHO estimates from 2008 indicate that more than 1.4 billion adults are overweight and, of these, more than 200 million men and 300 million women are obese¹. The trend is worrying: over the past 30 years, worldwide obesity has more than doubled¹. Obesity is associated with an elevated risk of an array of chronic diseases. The implications for the musculoskeletal system include both degenerative and inflammatory conditions², with the greatest burden resulting from osteoarthritis (OA)². OA is a clinical syndrome of joint pain and dysfunction caused by joint degeneration, and affects more people than any other joint disease³. Currently, nearly 10 per

cent of the population is affected and the prevalence increases with age.

Obesity is the greatest modifiable risk factor for OA⁴⁻⁶. Coggon *et al*⁷ reported that subjects with a BMI > 30 kg/m² were 6.8 times more likely to develop knee OA than normal-weight controls. A recent meta-analysis reported that the pooled odds ratio for developing OA was 2.63 (2.28, 3.05) for obese subjects compared to normal-weight controls⁸. OA affects all aspects of life through pain and limitation of mobility. In direct cost analysis of obesity, it was estimated that the economic burden of OA in the USA was second only to diabetes in obesity-associated conditions⁹. Similar negative economic impact has been published

from UK analyses⁹. The burden of this disease is expected to increase, due to the prevalence of obesity and increased longevity.

The aim of this review is to provide an overview of the impact of obesity on OA in terms of clinical and imaging aspects, pathogenesis and joint replacement outcomes.

Clinical and imaging aspects

The association between obesity and OA is well described². The association with knee OA has been consistently demonstrated but has been less robust for the hip, which maybe the result of different impacts of obesity at these joints or due to differences in the studies that have assessed these. The impact of body mass index (BMI) on incidence of both knee and hip OA were assessed in two recent meta-analyses (including both cohort and case-control studies) by Jiang *et al*^{10,11}. They reported a dose-dependent relationship between BMI and risk of OA at both the knee and the hip (both clinical and radiological). In their analyses, a 5-unit increase in body mass index was associated with a 35 per cent increased risk of knee OA (RR: 1.35; 95% CI: 1.21-1.51) and an 11 per cent increased risk of hip OA (RR: 1.11; 95% CI: 1.07-1.16). Interestingly, they found the relationship for BMI and knee OA to be significantly stronger in women than men (men, RR: 1.22; 95% CI: 1.19-1.25; women, RR: 1.38; 95% CI: 1.23-1.54; $P=0.04$), while for hip OA there was no significant difference in the magnitude of the association for sex.

Early life obesity may be particularly hazardous. Holliday *et al*¹² found that those who became overweight earlier in adulthood showed higher risks of lower limb OA ($P<0.001$ for both knee OA and hip OA). A single large population-based cohort study by Reijman *et al*¹³ investigated the relationship between BMI and both incidence and progression of both radiological knee and hip OA with a mean follow up time of 6.6 years. In their study, being overweight (BMI >25 kg/m²) was associated with incident knee OA (OR 3.3; 95% CI: 2.1-5.3) but not hip OA (OR: 1.0; 95% CI: 0.7-1.5). A high BMI (>27.5 kg/m²) was also associated with progression of knee OA (OR 3.2; 95% CI: 1.1-9.7), assessed by decreased joint-space width on radiograph, but was not significant for hip OA (OR: 1.5; 95% CI: 0.6-3.7). Analysis was adjusted for age, sex, and follow up time. However, the proportion of obese individuals in this cohort was low, limiting the ability to detect increased incidence and progression attributable to this factor for both knee and hip OA. Correlation

with clinical data is also important, given the known discordance between the severity of structural damage and the severity of symptoms¹⁴. Finally, as the authors allude to, existing definitions of OA will probably be revised as MRI becomes more widely accepted in OA research. What is currently identified as early radiological change may in fact represent a later stage of the disease spectrum.

Several groups have examined the relationship of BMI and risk of arthroplasty. Data from a prospective cohort study in the UK indicate increasing BMI was associated with an increased relative risk of knee (RR 10.51) or hip (RR 2.47) replacement when comparing the obese group to those with the lowest BMI¹⁵. The authors estimated that 69 per cent of knee replacements and 27 per cent of hip replacements are attributable to overweight and obesity. In another large population-based prospective cohort study, Lohmander *et al*¹⁶ also found that BMI was significantly associated with the incidence of knee (RR 8.1) and hip (RR 2.6) arthroplasty with a continuous dose-response relationship between BMI and arthroplasty risk. The authors adjusted for possible healthy patient selection bias for surgery by excluding patients with other comorbidities from analysis¹⁶. One smaller case-control study¹⁷ found that while there was a positive association between high BMI and total knee replacement in both sexes, there was a weaker association between total hip replacement and BMI, possibly negligible in women. However, weight was estimated by self-report after the surgery, possibly skewing the results. Joint replacement data should be interpreted with care as an outcome measure as uptake of elective joint replacement surgery is highly influenced by patient and doctor preferences, socio-economic factors such as waiting lists and access to private healthcare, and being overweight or obese. In some centres, individuals who are obese are less likely to be offered surgery, and therefore, the above risk estimates may in fact be conservative. What can be concluded thus far is that BMI is associated with incident and progressive knee OA, whereas the evidence remains less clear for hip OA.

MRI has emerged as the most sensitive tool to detect degenerative joint changes and to delineate the early impact of obesity. Laberge *et al*¹⁸ investigated knee MR images at baseline and 36 months from 137 middle-aged individuals with risk factors for knee OA but no radiographic OA from the Osteoarthritis Initiative. They found that obesity was associated with higher prevalence and severity of early degenerative

changes in the knee in middle-aged subjects without radiographic knee OA and with significantly increased cartilage lesion progression. At baseline, the prevalence and severity of knee lesions were positively associated with BMI, with a nearly four-fold increase in meniscal tears and more than two-fold increase in high-grade cartilage defects in obese individuals relative to normal-weight subjects. Over the 36-month follow up period, the number of new or worsening cartilage lesions of any grade was significantly higher in obese subjects ($P=0.039$), while there was no significant difference in meniscal lesion progression. Obesity, however, did not confer an increased risk of meniscal or bone marrow lesion progression over 36 months.

In a cross-sectional analysis of 77 obese subjects (30% of whom had ACR clinical knee OA), BMI was not associated with difference in cartilage quality assessed by delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC), a marker of cartilage glycominoglycan distribution, in the knee joint¹⁹.

A single centre has produced several MRI studies evaluating healthy adults without clinical knee OA²⁰⁻²³. The first study found a beneficial effect of fat-free mass, but a detrimental effect of fat mass, on knee cartilage properties at 10-year follow up²⁰. Increased fat-free mass was associated with higher tibial cartilage volume measured at follow up, whereas increased fat mass was negatively associated with cartilage volume²⁰. Presence of any baseline cartilage defects from these subjects are not known, as MRI assessment was only performed at the 10-year follow up. Also, it is not known how these findings correlated with symptoms at follow up. Three of these MRI studies²¹⁻²³ focused on patella imaging. Their results consistently demonstrated that BMI was inversely associated with patella cartilage volume at baseline, patellar cartilage loss over 10 years and cartilage defects at 10-year follow up. Another research group²⁴ assessing regional changes in knee OA using MRI over two years found that BMI was one of the strongest predictors of cartilage loss from the central area of the medial tibial plateau and medial femoral condyle, the regions with the greatest loss at 24 months.

Pathophysiology

The pathophysiology of obesity-related OA is likely to be multi-factorial. Structural joint damage is thought to result from both mechanical factors, including increased forces about the joint, decreased

muscle strength and altered biomechanics during everyday activities^{25,26}, and metabolic factors,² as being obese also increases the risk of OA in non weight-bearing joints such as the hands²⁷.

Obesity is characterized by a low grade inflammatory state, leading to its effects on many organ systems²⁸. The precise metabolic pathways through which obesity contributes to joint structural damage are currently not known, although thought to involve aberrant adipokine expression with direct and downstream effects leading to the destruction and remodelling of joint tissue^{29,30}. Adipokines exert effects on the joint tissue, including cartilage, synovium and bone. Leptin and adiponectin are the most abundantly produced adipokines³¹ and their receptors are expressed on the surface of chondrocytes, synoviocytes and subchondral osteoblasts³²⁻³⁴. Leptin has been found to increase levels of degradative enzymes, such as matrix metalloproteinases (MMPs) and nitric oxide, and production of pro-inflammatory cytokines^{32,35-37}. Levels of adipokines in people with obesity may be particularly important, as obesity may produce a biochemical environment in which chondrocytes cannot respond to such challenges. For example, chondrocytes from obese OA patients have been shown to exhibit a response pattern to leptin different from normal or overweight patients³⁸. Less is known about the role of adiponectin in joint disease, with both pro-inflammatory and anti-inflammatory properties being reported²⁹, compared to its systemic anti-inflammatory effects³¹. Levels of leptin and adiponectin are significantly elevated in people with OA compared to controls³⁹. A recent study of significant weight loss in obese subjects with knee OA demonstrated decreased circulating levels of leptin and increased circulating levels of adiponectin⁴⁰.

Some authors have suggested that OA is not simply a disease of ageing or metabolic stress of joints but rather a metabolic disorder in which various interrelated lipid, metabolic, and humoral mediators contribute to initiation and progression of the disease process⁴¹. In a large Japanese cohort study, accumulation of metabolic syndrome components was related to the incidence and progression of knee OA components⁴². The Chingford study⁴³ identified an association between metabolic factors (hypertension, hypercholesterolaemia, and blood glucose) and knee OA in women that was independent of obesity, which further supports the notion that OA has an important systemic and metabolic components in its aetiology. A recent mouse study demonstrated a possible role of high density lipoprotein

(HDL) metabolism in pathobiology of OA⁴⁴; changes in HDL metabolic pathway, together with high-fat diet, were found to predispose to knee OA. Data from the National Health and Nutrition Examination Survey III demonstrated cardiometabolic risk factors and knee OA that were unique for each gender and obesity status⁴⁵. In non-obese men, BMI and insulin resistance were the risk factors most strongly related to knee OA. In obese men, BMI was not related to knee OA, but insulin resistance was again the strongest risk factor. For both non-obese and obese women, BMI continued to be a strong predictor of knee OA, but in contrast to other strata, insulin resistance was inversely related to knee OA in obese women.

In a study of an adult population without clinical knee OA, fat mass was associated with increased cartilage defects and bone marrow lesions (BMLs), which are features of early knee OA. In contrast, skeletal muscle mass was positively associated with cartilage volume, which the authors hypothesize may be due to coinheritance, a commonality of environmental factors associated with cartilage accrual or a protective effect of increased muscle⁴⁶.

Obesity leads to increased loading of the weight-bearing joint, which may be the most important mechanical contribution. Knee adduction moment may be an important mechanical variable associated with the development of knee OA^{47,48}. People with obesity have greater absolute knee adduction moments due to increased body mass, and engage in compensatory gait patterns such as slower walking velocity and increased toe-out angle^{49,50}. There is evidence that in obese people, articular cartilage may not be able to respond to the higher level of absolute knee adduction moment during gait compared to normal weight individuals⁴⁸. Increased joint loading by normal weight individuals has not consistently been shown to be associated with OA: for instance, a longitudinal study of elderly (>60 yr) runners and non-runners showed that the presence of radiographic hip OA and the progression of radiographic knee OA were similar in both groups⁵¹.

Currently the relative contribution of mechanical and metabolic components to joint structural changes, and the importance of metabolic versus mechanical 'initiating' factors are not known. The pathogenesis of primary OA in obese people may begin with expansion of adipose tissue. This may lead to increased synthesis of endocrine factors such as leptin that act on other tissues, and the growth and changes in these tissues will give rise to the alterations seen in OA. Additionally, the

systemic inflammatory effect of the excessive adipose tissue in obese people may play a role in alteration of cartilage characteristics. Once this process is initiated, mechanical and possibly other factors will form a positive feedback loop that is difficult to break⁵².

Assessment of obesity

While BMI has been a useful tool to assess obesity and has demonstrated dose-dependent relationship with OA risk, there has also been debate as to what measure of obesity best correlates with OA risk. Lohmander *et al*¹⁶ found that BMI had the strongest association with severe OA (which they defined as arthroplasty) compared with other measures of obesity such as waist/hip ratio and body fat percentage (measured by bioelectrical impedance). In contrast, a study conducted by Sowers *et al*⁵³ found that skeletal muscle mass explained more variation in the incidence of radiographic OA than did fat mass. However, another study concluded that 'precise' measures of body composition using lean mass conveyed no advantage over BMI in assessing risk of radiographic knee OA⁵⁴.

A case-control study by Holliday *et al*¹² assessed the risks associated with high BMI and other anthropometric measures of obesity. Authors used a diagram for patients to self-assess body shape. BMI was associated with knee OA (OR: 2.68; 95% CI: 2.33-3.09, $P<0.001$) and hip OA (OR: 1.65; 95% CI: 1.46-1.87, $P<0.001$). Self-reported body shape was also associated with knee OA and hip OA, following a similar pattern to BMI measures. Waist-to-hip ratio (WHR) at baseline did not associate with OA independently of BMI, except in women-only analysis. Waist circumference was associated with lower limb OA risk.

Weight loss in OA

Weight loss has been demonstrated to improve both pain and function in obese subjects with knee OA⁵⁵. Recently Gudbergsen *et al*⁵⁶ demonstrated that weight loss imparts symptomatic relief in obese subjects with knee OA independently of joint damage severity. In their study 175 subjects with BMI >30 kg/m² with clinical knee OA were evaluated by MRI at baseline and 16 wk following a low energy diet. In this study, the majority of patients obtained a significant weight loss (>10%), and 64 per cent of the patients experienced a significant symptomatic improvement defined by the OMERACT-OARSI Responder Criterion. Improvements in pain ($r=-0.05$; $P=0.49$) was associated with change in weight loss per cent but not with structural changes on MRI. Similar results were seen for physical function. This

suggests that severe knee joint degeneration does not preclude clinical improvement with significant weight loss and that obese patients at every stage of OA should be encouraged to lose weight. In another study, Biddal *et al*⁵⁷ randomized obese subjects with radiographic knee OA to low energy diet reinforced with frequent dietician contact versus dietary instruction at baseline only. The mean weight loss at one year follow up was 11 per cent for the intervention group and 4 per cent for the control group, with significantly greater improvement in WOMAC pain in the intervention group. The moderate effect size for the pain reduction in the intervention group surpasses that for simple analgesia⁵⁸.

A recent study by Richette *et al*⁴⁰ found that surgically induced weight loss (mean: 20%) resulted in significant improvement in pain and physical function at six months. Their subjects had a mean BMI of 51 kg/m² at baseline. All WOMAC subscales improved: pain (-50%; $P < 0.001$), stiffness (-47%; $P < 0.001$) and function (-57%; $P < 0.001$). They reported a decrease in serum marker of cartilage degradation (COMP), but did not assess radiographic or MRI outcomes to assess for structural modification. Similarly, Christensen *et al*⁵⁵, in a meta-analysis of four intervention studies involving 454 overweight patients with knee OA, found that weight loss resulted in significant reduction in physical disability.

Weight loss in obese subjects may also provide structure-modifying benefits. It was recently demonstrated that moderate (9%) weight loss in obese subjects with and without knee OA can improve cartilage quality (proteoglycan content estimated using delayed gadolinium-enhanced MRI of cartilage) and quantity (weight loss also led to reduced loss of cartilage thickness)⁹. A study by Hunter *et al*⁵⁹ did not demonstrate an association between weight loss and cartilage changes on MRI, but found an association between weight loss and reduction in bone marrow lesions (BMLs); given the association of BMLs and pain⁶⁰, this may be of particular clinical relevance.

Obese subjects with OA who lose weight may see improvement in their OA symptoms for several reasons. A study by Messier *et al*⁶¹ from the ADAPT cohort showed a 1:4 ratio of loss of body weight to decrease of load on the knee joint, indicating that 1 kg of weight lost will result in a 4 kg reduction in the mechanical load exerted on the knee joint per step during daily activities. Forsythe *et al*⁶², in a meta-analysis of 66 weight-loss interventions, found that weight loss was

associated with decreases in inflammatory makers such as c-reactive protein (CRP), tumour necrosis factor (TNF) and interleukin-6 (IL-6)^{40,63-65}, which have been associated with impaired physical function⁶⁶. Reduced pain and physical disability may increase activity levels and improve physical fitness, which may further enhance physical function, including increased muscular strength in the muscles surrounding the knee joint^{66,67} as well as reduced levels of circulating inflammatory markers.

Weight loss is important for both preventing and managing knee OA. Current recommendations are largely based on expert opinion. Bariatric surgery in obesity is increasingly popular. A recent systematic review⁶⁸ concluded that it may benefit obese patients with hip or knee OA, but currently the role and indications for bariatric surgery remain unclear.

Joint replacement outcomes

The increasing worldwide prevalence of obesity together with an ageing population has led to an escalating need for joint replacement surgery. Obesity is also associated with earlier age at hip and knee arthroplasty. In a study by Changulani *et al*⁶⁹, the mean age of patients with class III obesity (BMI >40 kg/m²) undergoing hip and knee replacement surgery compared with those of normal BMI was 10 and 13 years younger, respectively.

The effect of obesity on joint replacement surgery outcomes has also been studied. In a case-control study⁷⁰ from the UK with an 8-year follow up, overweight was not found to be a predictor of poor outcomes of hip replacement surgery. However, only a small number of participants followed up were obese (n=36) and, therefore, conclusions about the effects of obesity cannot be drawn. In contrast, in a large multicenter cohort study of more than 20,000 primary total hip replacements, high preoperative BMI was associated with decreased mobility over a 15-year follow up period, but there were no differences in pain outcomes⁷¹. In another study⁷² of revision hip arthroplasty, obese patients undergoing surgery had more complications, most evident with BMI more than 35 kg/m². The adjusted hazard ratios for surgical site infections and dislocation were 4.1 and 3.5, respectively, when the obese group was compared with the non-obese group. This is pertinent as severely obese patients are younger at the time of surgery and more likely to require revision surgery. It is also apparent that the problems associated with joint replacement surgery are more

pronounced with high-grade obesity. A recent analysis of prospectively collected data from 653 patients who had undergone a primary total hip replacement⁷³ looked at patients' self-perceived outcomes one year following total hip replacement. The study found the influence of comorbidities and surgical complications on physical function and health-related quality of life to be stronger than the influence of BMI itself after total hip replacement.

Several studies have also evaluated outcomes after knee replacement surgery. One study found that BMI >35 kg/m² was associated with greater self-reported pain following total knee replacement⁷⁴. However, another study⁷⁵ found that BMI was not associated with functional outcomes assessed two years following unicompartmental knee arthroplasty. In the latter study, a moderate positive correlation of BMI with visual analogue scale (VAS) of pain was found, but the study was retrospective and outcome assessment was not blinded⁷⁵. A third study⁷⁶ followed patients two to eight years after total knee arthroplasty. Improvements in SF-36 physical function score were smaller in patients who were obese, however, BMI >30 kg/m² was not a significant predictor of change in physical function from pre-surgery to follow up. A Canadian prospective observational study of 520 primary joint arthroplasties⁷⁷ evaluating the effects of obesity on patterns of recovery from total knee and hip arthroplasty found that severe obesity is an independent risk factor for slow recovery over three years for both total knee and total hip arthroplasty. In this study, baseline pain and functional scores were similar regardless of BMI classification. Severe obesity was a significant risk factor for worse pain and functional recovery at six months but no longer at three years following total hip and knee arthroplasty.

Conclusion

What can be concluded so far is that obesity contributes to incidence and progression of OA, with the strongest relationship being at the knee. Obesity also is a leading driver of arthroplasty demand and imposes increased risk of operative complications. Weight loss improves both symptoms of OA and can slow disease progression. The current evidence points to obesity-related OA as both a problem of excessive joint loading and hormonal and cytokine dysregulation. Determining the metabolic mechanisms of obesity-related joint changes offers another potential approach towards the goal of disease-modifying therapy in OA, through the development of therapeutic strategies to

counteract dysregulation of proinflammatory adipokine production and downstream events. Further work is required to determine the relative contributions of metabolic and mechanical factors in the pathogenesis of knee OA.

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