Editorial

Osteoarthritis in obese populations: where are we now?

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Introduction

The recent article by Gersing *et al.* (1) reports that weight loss (WL) improves severity of knee symptoms and slowed the rate of cartilage degeneration in obese and overweight patients. This editorial reviews their findings and the current literature assessing the association between obesity and osteoarthritis.

Epidemiology

Osteoarthritis, particularly of the knee, has become a global pathology of huge concern, particularly due to its rapidly progressing incidence and prevalence. Osteoarthritis is estimated to affect more than 37% of adults over the age of 60 (2), and is the leading cause of pain and disability in this age group. Osteoarthritis and the associated consequences accounted for 10.5 billion US dollars in hospital charges in 2006 alone, as shown by the Healthcare Cost and Utilisation project (3). This makes osteoarthritis a more expensive condition than pneumonia, stroke, or diabetes (3). The most likely two important factors that are responsible for the increasing burden of this osteoarthritis are obesity and an ageing population.

Obesity is a now an established epidemic, levels of obesity are estimated to be in the region of 1 billion people by 2030, with up to a quarter of the population in developed countries already classed as obese (4). The United States is one of these developed countries particularly well known to be suffering the consequences of this, where a 10% increase in the rate of obesity has been observed the last two decades, and where over a third of adults are now classed as obese (5).

Obesity and osteoarthritis

A significant body of research is now established which illustrates a strong link between obesity and the development of osteoarthritis, particularly that affecting the knee (6-8). Hart *et al.* (9) demonstrated a clear link, in a British population, that women in the highest tertile of BMI had a 6-fold increased odds of knee osteoarthritis, and almost an 18 times higher odds of developing bilateral knee osteoarthritis compared with their counterparts in the lowest tertile. This has been reiterated by a similar study in the United States of a population of African-American and Caucasian women (10). Coggon *et al.* (8) reported that subjects with a BMI >30 kg/m^2 were 6.8 times more likely to develop knee osteoarthritis compared to healthy weight controls. A recent meta-analysis by Blagojevic *et al.* (11) showed that the pooled odds ratio for developing osteoarthritis was 2.63 (95% confidence intervals, 2.28 to 3.05) for obese subjects compared to healthy-weight controls (11).

Pathology

Until recently, it was thought that predominantly biomechanical factors were thought to be the mechanism linking obesity to knee osteoarthritis. It is well known that osteoarthritis is characterized by an imbalance between the anabolic and catabolic activities of the chondrocytes making up cartilage, and chondrocytes are significantly influenced by mechanical signals in their local microenvironment, which enable them to alter structure and composition of

cartilage (12). Both clinical and animal studies have shown that repetitive abnormal loads imparted on normal joints lead to change in the structure and composition of articular cartilage. Recent *in vivo* studies have illustrated that the mechanical strain environment of the joint is an important factor influencing the activity of chondrocytes (13). Abnormal loads have been implicated in atypical cartilage and chondrocyte function has been attributed to obesity, instability and trauma.

It is important to note that muscle and muscle forces have an important influence on joint loading by nature of controlling how load is distributed with in a joint, and also the stability of a joint. Decreasing muscle forces acting about a joint or misaligned joints, such as weakness of the quadriceps, can lead to inadequate absorption of forces about the knee and can cause greater dynamic loads to be placed on the articular cartilage as a result, resulting in progressive degeneration. Thus, muscle weakness, particularly quadriceps, has been found to be an important risk factor in some studies (14). The role of body composition, and the intimate relationship between muscle loss and fat gain, has been proposed to be an important mechanism of osteoarthritis development, most notably by Roubenoff *et al.* (15).

Recently, there has been a paradigm shift in the overall view of osteoarthritis, shifting from a "wear-and-tear" pathology of biomechanical loading to one with a significant, if not predominant, inflammatory component. This appears to be particularly evident when considering the role of obesity in influencing the development of osteoarthritis. Adipose tissue is now recognized as a highly metabolic endocrine organ, secreting adipocytokines, in particular leptin and adiponectin. A significant body of research has been established in recent years with respect to adipose and its influence on osteoarthritis (16-19). Leptin, adiponectin and resistin have been shown to be actively present in synovial fluid, and are now thought to influence joint degradation directly or through indirect control of inflammatory processes involving cartilage degradation.

Leptin expression has been of particular interest to research into metabolic factors involved in development of osteoarthritis. Higher BMI and body weight have been shown to be associated with increased leptin levels and leptin expression, which has been directly associated with greater cartilage degeneration (20). Furthermore, Leptin has been shown to be metabolically active in synovium, chondrocytes, osteophytes and infrapatellar fat pad, may have a direct catabolic and pro-inflammatory role in cartilage metabolism, leading to cartilage degeneration (18).

Reversible cartilage changes

Cartilage degeneration is associated with altered content of proteoglycans and water and degradation of the fibrillar collagen network (21) in early stages, whereby these early elements of degradation can be reversible before permanent irreversible hyaline cartilage damage occurs. These early reversible changes have been shown to be identifiable through imaging biomarkers, specifically MRI-based T2 relaxation time, and the structural changes of cartilage changes have been shown to be reliably predictable on T2 measurements. Prior studies have shown improvements in cartilage morphology and biomarkers imaged using this technique, with progressive amounts of WL. Thus, using these techniques as surrogate markers of osteoarthritis and cartilage degeneration, it has been indicated that WL may well be effective in slowing and potentially reversing early changes indicative of osteoarthritis. Current research indicates that T2 relaxation times progress less in subjects with >10% of WL compared to their baseline, thus indicating decreased rate of degenerative change compared with their control counterparts (22).

WL saves cartilage and improves symptoms

Gersing *et al.* (1) aimed to combine the various techniques of grey-level co-occurrence matrix (GLCM) texture analysis (specific in detection of compositional and structural changes within the cartilage matrix for osteoarthritis) and change in cartilage T2 relaxation time, to correlate varying degrees of WL with evidence of cartilage degenerative change and additionally with clinical symptoms and signs. The patients were selected from an on-going, longitudinal, prospective multi-centre cohort study (the Osteoarthritis Initiative). Four time points were selected for data collection, in addition to baseline data collection and imaging, at regular intervals at 12, 24, 36 and 48 months, resulting in a 48-month prospectively collected, and retrospectively analysed, comparative study. The primary outcome was assessment of change in cartilage structure resembling degenerative change with variable amounts of WL, using markers of T2 relaxation time and changes in GLCM texture analysis. Secondary outcomes comprised change in clinical knee function and symptoms with WL, and correlation of this to degenerative change visualized by the aforementioned techniques.

Patients were divided into those with "steady" weight and "uneven" weight change. Those deemed to have uneven WL (eight patients), by this method, were excluded in order to select patients with linear and steady WL trajectory thus avoiding bias in results from patients who "cycle" through gain and loss over the 48-month follow-up period, skewing results and introducing inaccuracy in any conclusions drawn regarding the effect of weight on knee cartilage. Additionally, patients who developed co-morbidities of cardiac failure, cancer or any other severe disease over the course of the 48 months were excluded using the Katz comorbidity questionnaire. The remaining 1,981 patients were eligible for inclusion. This cohort was divided into groups based on their WL over a 48-month period, consisting of moderate loss (5–10% BMI decrease), large loss (>10%), and stable weight (BMI change <3%) all at 48 months. Subjects from each of these three groups were selected in a randomized manner and matched for sex, age, baseline BMI, and KL in order to form three matched groups in addition to a stable weight matched group. Thus the impact of age, sex, baseline BMI, KL were all minimized, resulting in a greater reliability of results and thus in any conclusions drawn. A total of 78 patients were included in the >10% WL group and 180 subjects in the 5–10% WL group were included, which allowed for sufficient power (90%).

The principle finding of this study was the significantly smaller T2 in the >10% WL group when compared with the stable weight group (P<0.001), when the medial tibial compartment was considered. This suggested less progression of cartilage degeneration over the 48-month follow-up period when compared with their stable weight group counterpart. Additionally, when more severe grades of osteoarthritis were excluded from analysis there was a significant observable decrease in mean T2 (P=0.002) in all compartments examined, when >10% WL group was compared with the stable weight group. These findings were supported by the secondary outcomes assessed with a significantly lower level of change in GLCM over all compartments (P=0.04) when the >10% WL group was compared with the stable weight group. This suggests a significantly lower rate of cartilage inhomogeneity and increased orderliness in the >10% WL group. However, no significant change in cartilage thickness was observed between stable weight and any of the WL groups.

This is the first study that assessed the correlation between clinical symptoms and function with the effect of WL and imaging evidence of cartilage regeneration. The authors used the widely accepted Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (23). Increase of T2 signal in the medial tibia was significantly associated with increase (worsening) in WOMAC subscales for pain and disability (P=0.02 and P=0.03 respectively). Indeed, over all compartments, increase in T2 was significantly associated with increased WOMAC score for stiffness (P=0.004). Although not significant, WOMAC subscale for disability showed an increasing trend with increased T2, suggesting increased rate of cartilage degeneration is associated with observable clinical worsening.

Limitations

There were limitations associated with this study, most of which have been recognized by the authors. Firstly, the study design was retrospective in nature, which meant certain variables could not be controlled for. The variability in type of activity such as weight/strength training, overall activity levels, and diet could directly influence rate of cartilage degeneration and overall structure, rather than WL independently. Secondly, the >10% WL group is not defined. The actual mean amount of weight lost in this population is not stated, and so we are not informed how significant this WL was. The at risk cohort from which this population was selected is also not defined, i.e., the particular characteristics which make the population at risk of developing osteoarthritis is not specified. Finally as the authors note, their study does not explore the effect of weight gain on cartilage degeneration i.e., is the correlation true when considered in reverse?

Conclusions

The study by Gersing *et al.* (1) provides robust evidence to suggest that there is a strong correlation between progressive WL, and a decreasing rate of degenerative structural change in cartilage. Additionally, these degenerative changes correlate to observable clinical symptoms and signs, with increasing degenerative changes associated with a worsening clinical picture. The strongest association of WL and reduced cartilage degeneration was observed in the medial tibia, which supports prior hypotheses that WL is most protective in the medial weight bearing compartments. Previously, studies have provided evidence of a strong link between obesity and rate of progression of osteoarthritis (22,24) however the literature had not up to this point been

able to provide quantitative links between amount of WL and relative rate of cartilage degeneration.

Future

To further justify a link between obesity and osteoarthritic changes, and to quantify amount of WL and rate of slowing of cartilage degeneration studies should be undertaken with longer follow-up periods. Furthermore, studies should be prospective in design (in order to control for variables not accounted for in this study, such as factors associated with WL such as level of activity, type of activity, and diet, which may influence cartilage quality and thickness). Perhaps future populations could be matched for ethnicity, family history, and for conditions associated with the metabolic syndrome that have been implicated in development of osteoarthritis, such as diabetes. Future studies may benefit from further stratification of the population according to degree of WL, such as 10–20% and 20–30% or greater, in order to be able to further quantify how quantity of WL can influence rate of osteoarthritis progression.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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