How obesity links with osteoarthritis: mechanic or metabolic?

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Abstract

Introduction

Osteoarthritis (OA) is a highly prevalent joint disease. Obesity is one of the most important risk factors of new-onset OA and deterioration of OA. Obesity was once considered to cause OA simply by added mechanical force. Yet, more recent studies have shown that metabolic factors produced by fat tissue can also initiate inflammatory cascade that consequently can lead to OA. This is a narrative review of recent literature about how obesity leads to OA. Mechanical loading, metabolic factors and other related issues are discussed. Knowledge on how obesity links with OA will help to identify targets for modifying the metabolic effect for treatment of OA.

Conclusion

Excess of fat plays a role in OA by adding mechanical and metabolic loads. The factor that is more predominant depends on the joint.

Introduction

Osteoarthritis (OA) is the most common joint disease and one of the leading causes of disability. It was once considered as a simple degenerative disease, but now is viewed as a disease of the whole joint with the involvement of cartilage, subchondral bone and synovium.

Being overweight is an important risk factor of OA. Research on OA and obesity is of interest because obesity is a factor that can be modified. Having more knowledge on how obesity is involved in pathophysiology of OA will consequently lead to better measures to prevent the occurrence and the progression of OA. Nowadays, it is assumed that obesity plays a role in OA through two possible mechanisms. First, due to extra mechanical forces in weight-bearing joints (i.e. knees and hips) and second due to excess of metabolic factor (i.e. adipokines) secreted by fat tissues. The purpose of this article was to perform a narrative review of the literature on how obesity links with OA.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Mechanical force

Knee and hip joints endure mechanical force during activities such as walking and jogging. Several studies have investigated the measurement of the force that knee joints endure during several activities as summarized by d’Lima and co-workers. A force of three and four times that of the body weight is transmitted across the knee joint during walking and jogging, respectively. When a subject has an excess of body weight, larger forces are exerted on the weight-bearing joints, which can lead to higher risk of having the deterioration of cartilage in OA. Interestingly, while obesity is consistently shown to be associated with new-onset OA, its association with the worsening of OA is inconsistent. The inconsistency can be explained by the difference of study population used in the studies and due to limitation in epidemiology studies. When a large majority of study population has obesity, for example, it will limit the contrast between patient’s obesity and patients with normal weight. One of the most significant limitations of a prospective cohort study is a patient’s loss to follow-up. Arguably, patients that are overweight are prone to loss of follow-up due to other health problems related to obesity, and precisely in these subjects the effect of obesity on OA is expected. Another possible limitation of prospective studies is the possible bias that can be introduced by how the progression is measured. Progression of OA is often measured using a scoring system with a maximal score. In the scoring system with maximal score, a progression cannot be scored higher than the maximum. However, progression can be mild and it does not reach maximal score. When patients with maximal and mild progression are lumped together in the statistical analysis, it can lead to the dilution of the effect.

Another mechanical effects in the OA pathophysiology that can be taken into account are malalignment and muscle strength. When overweight and malalignment present together, it will give an additional effect. Yusuf and co-workers showed an 18% added effect when overweight and malalignment were...
present together\textsuperscript{8}. Overweight can also influence the strength of lower limb muscles. When muscle strength becomes less, it can reduce the shock-absorbing potential of the knee joint and lead to cartilage fibrillation\textsuperscript{11}. It is also shown that weight loss in combination with exercise is beneficial for muscle strength in patients with knee OA\textsuperscript{12}.

**Metabolic factors**

Mechanical factors cannot fully explain why OA is also associated with the non-weight-bearing joints (e.g., hand joints) as shown by several studies such as studies by Carman et.al\textsuperscript{13} and Oliveria et.al\textsuperscript{14}. The observation that obese subjects has a higher risk in having hand OA has led to a hypothesis that the metabolic effect produced by fat tissue, the so-called adiponectin, can also lead to OA. Among the adipokines, leptin, adiponectin and resistin are subjects of intensive research in OA.

Leptin is a 16-kDa non-glycosylated peptide encoded by ob gene, and it plays a role in the control of body weight\textsuperscript{15}. During starvation, leptin levels decrease and activate the response to cope with limitation of food. Plasma leptin increases with weight gain. This increase activates the processes to reach the state of negative energy balance. The evidence from epidemiological studies point out in the direction of negative effect of leptin on knee OA. For example, Karvonen-Gutierrez and co-workers showed that 5 ng/ml increase in serum leptin gives 1.3 times higher risk of having a new case of knee OA as seen on a radiograph\textsuperscript{16}. Leptin concentrations are also found to be higher in synovial fluid originating from OA patients (median of 4.4 ng/ml, range 0.5–15.8) compared with controls (median 2.1 ng/ml, range 1.0–4.6) in the study by Ku and co-workers\textsuperscript{17}. While increasing number of studies are published showing ‘negative’ effect of leptin on OA, there is no study yet that shows the deteriorating effect of leptin on hand OA.

Adiponectin is 244-amino acid long polypeptide coded by ADIPOQ gene, and it plays a role in glucose homeostasis\textsuperscript{18}. It has three forms: trimer (low molecular weight), a hexamer (trimer–dimer) of medium molecular weight and a larger multimeric high-molecular-weight form\textsuperscript{18}. Yet, many studies up to date do not perform separate analysis of the different forms. Interestingly, in contrast to other adipokines where its levels increase with increasing excess of fat, serum adiponectin decreases with increasing obesity. This is perhaps caused by the negative feedback to reach homeostasis\textsuperscript{18}. Adiponectin seems to have a protective role on OA; it induces the production of tissue inhibitor of MMP-2, which consequently reduced matrix MMP-induced cartilage defect\textsuperscript{19}. A prospective study by Yusuf and co-workers also point out in this direction: being in the highest tertile of adiponectin (>28.4 μg/ml) was associated with 70% less risk of having worsening hand OA as seen on a radiograph during 6 years follow-up\textsuperscript{20}.

Resistin is a cysteine-rich protein that is encoded by the RETN gene\textsuperscript{21}. The name implies its effect: injecting resistin into mice leads to insulin resistance. The role of resistin in OA is inconclusive. Resistin is shown to be associated with incidence of radiographic knee OA\textsuperscript{22} in one study, while in another study no effect in knee OA was shown\textsuperscript{23}.

**How do mechanical and metabolic forces lead to OA?**

As reviewed above, mechanical and metabolic forces can lead to OA. Yet, how do they do this? Perhaps, the answer is by inflammation. The role of inflammation in OA is increasingly recognized. Synovitis has been shown to be one of the structural changes that is involved in OA\textsuperscript{24}. Another structural change, the so-called bone marrow lesion, might also result from inflammatory processes\textsuperscript{25}.

Increased weight can lead to the activation of the mechanoreceptors within the cartilage (such as stretch-activated channels and CD44), which consequently leads to the expression and production of cytokines, metalloproteinases and mediators such as prostaglandins and nitric oxide\textsuperscript{26}. The presence of these products can lead to cartilage damage.

Leptin, adiponectin and resistin are also shown to be able to induce inflammatory response. Leptin, for example, can amplify the production of interleukins (IL)-6 and IL-8 in OA cartilage\textsuperscript{27} and resistin stimulates the release of proinflammatory cytokines such as TNF-alfa, IL-1beta and IL-6\textsuperscript{28}. Again, these proinflammatory cytokines can lead to the deterioration of cartilage and damage of other structures involved in OA.

Formation of atherosclerotic plaques in small vessels might be another explanation for how metabolic factors can lead to cartilage damage in OA. Obesity is also a strong risk factor of having coronary heart disease\textsuperscript{29} due to the formation of atherosclerotic plaques\textsuperscript{30}. It can be speculated that this plaque formation might be not only in large vessels but also in small vessels. Impaired circulation due to atherosclerosis can initiate bone defect and lead to a cascade that leads to cartilage loss and synovitis of subchondral bone. Leptin\textsuperscript{31} and resistin\textsuperscript{32} play a role in the formation of atherosclerotic plaques.

**Hoffa’s fat pad and knee joint**

Excess of body fat exerts its effect by added mechanical force on weight-bearing joints and by the production of metabolic factors (adipokines). The effect that is more predominant will depend on the joint under research because different joints have different biomechanics, and the role of obesity will not be uniform across the joints.

Knee joints endure dual forces: mechanical and metabolic. As...
shown above, knee joints endure added mechanical force when someone is walking, jumping or jogging. Interestingly, in the approximation of knee joint, a collection of fat tissue is present—the so-called Hoffa’s fat pad. This fat pad has been shown to have inflammatory characteristics. Knee joint is a bit more complicated when it is used to investigate the effect of metabolic effect. Next to the presence of Hoffa’s fat pad, it is also difficult to differentiate the metabolic from mechanical effect in epidemiological studies. One solution is by correcting the effect of overweight with body mass index (BMI). However, the mechanical effect might be so large that the mechanical effect, measured by BMI, cannot be totally removed. This might explain why studies show association between adipokines and knee OA but not with hand OA. Another solution is by using hand OA as phenotype. Arguably, hand joints do not endure large mechanical force since we do not walk on our hands. The drawback in using hand OA is the workload of scoring the damage on hand joints.

Measurement of excess of fat
Obesity is considered as excess of fat. Traditionally, like in all studies mentioned above, BMI is used in epidemiological studies on OA. However, BMI is actually just only a proxy of human body fat, which is based on weight and height. It should be considered to use other measurements of excess of fat when the effect of overweight in OA is investigated.

Therefore, the product of fat itself should be used in future epidemiological studies. Using the products of fat tissue as the measurements of excess of fat will bring us to the closer end of the causal path on the association between obesity and OA. Apart from adipokines, other measurement of fat products such as cholesterol and triglycerides should be pursued in the studies on OA.

Conclusion
Excess of fat plays a role in OA by adding mechanical and metabolic loads. The factor that is more predominant depends on the joint. Understanding the metabolic effect of fat in OA is rewarding because we can identify and target what might be able to be modified in order to treat OA. At present, opinions are still divided on whether leptin, adiponectin and resistin are ‘good’; ‘bad’ or do not play a role in OA. Knee and hip joints are easy to investigate because they are large. However, it will be difficult to differentiate the metabolic from mechanical effect in these joints. Joints of the hand are arguably more suitable when the purpose of the study is investigating the metabolic effect, but this is at the cost of large amount of joints that need to be assessed.

References
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