Obesity and osteoarthritis

Obesity and osteoarthritis: more complex than predicted!

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Dysregulation of lipid homeostasis is one of the mechanisms leading to osteoarthritis

Osteoarthritis is usually considered to be a joint disorder the central pathological feature of which is cartilage destruction. However, this concept has evolved, and today osteoarthritis is generally regarded as a disease that may affect the whole joint (bone, muscles, ligaments and synovium). Although the aetiology of osteoarthritis is not established, the main risk factors are well known and commonly include mechanical, biochemical and genetic factors. Of these risk factors, obesity is beyond doubt considered a prominent one.

MECHANOBIOLOGY IN OBESITY-INDUCED OSTEOARTHRITIS

The overload effect on joint cartilage may explain part of the increased risk of osteoarthritis, at least for osteoarthritis of the knee, in overweight people. A recent discovery in the discipline of cartilage biology is the presence of mechanoreceptors at the surface of chondrocytes, which are sensitive to pressure and link extracellular environment to intracellular signalling cascades. Three types of mechanoreceptors have been described on chondrocytes: the stretch-activated channels, the α-5β1 integrin and CD44. Compression and stretch stimulate integrins and stretch-activated channels leading to the activation of signalling pathways (mitogen-activated protein kinase, NF-κB), as well as the release of second messengers (calcium, Inositol triphosphate and Adenosine monophosphate cyclic). [1] After mechanoreceptor activation, cytokines, growth factors and metalloproteinases may be expressed, and mediators such as prostaglandins or nitric oxide may be produced.[2] As experimental studies have shown that under specific conditions overload may trigger both inhibition of matrix synthesis and cartilage degradation, we can speculate that obesity may induce cartilage damage through activation of these mechanoreceptors. In the same manner, the mechanoreceptors expressed on osteoblasts[3 4] may also be involved in the impaired response of chondrocytes to the obesity-induced overload.

ADIPOKINES: THE METABOLIC LINK BETWEEN OBESITY AND OSTEOARTHRITIS?

Even if it is usually accepted that mechanical loading contributes to joint cartilage destruction in overweight patients, recent advances in the physiology of adipose tissue add further insights in understanding the relationship between obesity and osteoarthritis. Indeed, the positive association between overweight or obesity and osteoarthritis is observed not only for knee joints but also for non-weight bearing joints, such as hands.[5] Furthermore, if weight loss may prevent the onset of osteoarthritis, the loss of body fat is more closely related to symptomatic benefit than is the loss of body weight.[6] These patterns of joint involvement suggest that joint damage may be caused by systemic factors such as adipose factors, so called adipokines, which may provide a metabolic link between obesity and osteoarthritis. Today, adipose tissue, traditionally viewed as a passive store of energy, is considered to be a real endocrine organ that releases a large number of factors, including cytokines, such as interleukin 1 and tumour necrosis factor α, as well as adipokines, such as leptin, adiponectin, resistin, visfatin, and so on, and new ones that are yet to be discovered. These adipokines exhibit pleiotropic functions mediated through both central and peripheral systems, including haemostasis, lipid and glucose metabolism, reproductive functions, blood pressure regulation, insulin sensitivity, bone formation and angiogenesis.[7] So, recent data strengthen the hypothesis that osteoarthritis is a systemic disorder in which dysregulation of lipid homeostasis can be one of the pathophysiological mechanisms leading to osteoarthritis.[8]

Recent studies provide evidence for a key role of leptin in cartilage homoeostasis. Leptin and its functional receptor have been identified in human chondrocytes and trigger intracellular signal transduction through the activation of STATs 1 and 5, but not STAT 3.[9] Leptin may have important biological effects in chondrocytes, on both growth factor synthesis and anabolism, and also on catabolism. Leptin expression is strongly upregulated in various articular tissues that undergo strong structural and biochemical changes during osteoarthritis—for example, cartilage, osteophytes and subchondral bone—when compared with normal tissues.[10 11] Interestingly, the pattern and level of leptin expression are related to the grade of cartilage destruction, and parallel those of growth factors (insulin-like growth factor I and transforming growth factor β-1). The intra-articular injection of leptin into the rat knee joint has a stimulatory effect on proteoglycan synthesis and is associated with increased expression of insulin-like growth factor I and TGFβ-1. In addition to mature cartilage, leptin is also produced in resting and prehypertrophic chondrocytes in the growth plate of mice.[12] In cultured human chondrocytes, leptin increases both the proliferation and the extracellular matrix synthesis, but in a biphasic manner, with a reduced stimulating effect at the highest concentrations. Leptin may thus have a beneficial effect on cartilage synthesis either directly or through the upregulation of growth factors. However, an excess of leptin may account for decreased extracellular matrix synthesis and may lead to lesions similar to those found in osteoarthritis with a high intra-articular level of growth factors.[13] The increased expression of leptin in markedly damaged cartilage suggests that leptin may trigger cartilage destruction, especially when associated with some local factors. The adipokine synergises with proinflammatory cytokines, such as interleukin 1, to increase nitric oxide production, which is known to interfere with chondrocytes function resulting, in the loss of cartilage matrix through induction of apoptosis, activation of metalloproteinases, and inhibition of proteoglycan and type II collagen synthesis.[14]

Little is known about the contribution of adiponectin and resistin in osteoarthritis-affected joints. Available data related to the potential effects of these adipokines in joint disorders indicated that they may have an active role in the pathogenesis of chronic inflammatory joint diseases such as rheumatoid arthritis.[15 16] The inducing effect of adiponectin on metalloproteinase 1 expression in synovial fibroblasts from patients with osteoarthritis suggests that this adipokine may also be associated with key pathways of cartilage matrix degradation.[15]

In patients with osteoarthritis, leptin, adiponectin and resistin are detected in both the synovial fluid and in the plasma.[17 18] The adipokines exhibit different patterns of distribution between the joint and the circulating compartment: plasma levels of resistin and adiponectin exceed those in the paired synovial fluid, whereas leptin concentrations in synovial fluid are higher than their plasma counterparts.[18] As was found in plasma from obese people when compared with normal subjects, the leptin to adiponectin ratio was shown to be higher in the synovial fluid of patients with osteoarthritis than in plasma. The resulting imbalance between two adipokines known to have opposite biological effects in various diseases such as diabetes or inflammation may contribute to the initiation and/or progression of osteoarthritis. Interestingly, this high level of leptin is associated with a decline in the soluble leptin receptor level, leading to a large rise in free leptin in synovial fluid, the presumed biologically active form of this adipokine. Moreover, a larger amount of free leptin is found in the synovial fluid from female patients with osteoarthritis than in that from male patients, and may explain why obesity and female sex are both risk factors for the development of osteoarthritis.

To date, no clear mechanism could explain the changes in the adipokine levels in the synovial fluid compared with plasma. Various tissues obtained from human osteoarthritis-affected joints release leptin and adiponectin. Among these tissues, the synovium and infrapatellar fat pad produce the highest amounts of adipokines.[18] Until recently, the fat pad, which is an extrasynovial but an intra-articular tissue, had been neglected. However, this adipose tissue is able to release growth factors, cytokines and adipokines.[19] Cross talk between the adipocytes and other cells located in the fat pad (macrophages), or in its vicinity (synoviocytes), may also regulate the production of various factors in the joint. Interestingly, osteophytes, which are osteocartilaginous metaplastic tissues, represent the major source of leptin but not of adiponectin. Altogether, these findings indicate that further investigations on the effect of the infrapatellar fat pad and its derived adipokines on chondrocyte metabolism would be helpful to better understand the pathogenesis of (knee) osteoarthritis.

IS THERE A ROLE FOR OBESITY-INDUCED ATHEROSCLEROSIS?

In addition to osteoarthritis, obesity is commonly associated with vascular disease. An interesting hypothesis about the role of atherosclerosis in the progression of osteoarthritis has recently been proposed.[20] Microvascular changes predominantly affecting the venous circulation are early events occurring in subchondral bone during osteoarthritis. This vascular disease in subchondral bone may accelerate the osteoarthritis process either by altering cartilage nutrition or through direct ischaemic effects on bone. The vascular obstruction and the resulting intraosseous hypertension may also alter the mechanical properties of the bone, which exhibits thereafter a reduced ability to absorb shocks, leading to increased susceptibility of the cartilage to breakdown. Whether the use of statins as a specific treatment for the atheromatous vascular disease would be beneficial for osteoarthritis remains to be established.

IS THERE ANY ROLE FOR OBESITY-INDUCED DIABETES MELLITUS?

Obesity-associated diabetes mellitus may represent an additional factor in the pathophysiology of osteoarthritis through the formation of advanced glycation end products (AGEs). The accumulation of AGEs found in articular cartilage during osteoarthritis progression leads to increased stiffness of collagen due to AGE cross-linking.[21] This damage to the collagen network may alter the mechanical properties of the extracellular matrix, and may lead to cartilage changes associated with osteoarthritis. In addition, articular chondrocytes express the functional receptor for AGEs, which induces mitogen-activated protein kinase, NF-κB activity and metalloproteinase 13 production when stimulated with ligands.[22] Modifications of normal cartilage by AGEs also increase matrix degradation and decrease proteoglycan synthesis by chondrocytes.[23] Further studies are required to determine whether diabetes-induced accumulation of AGEs occurs in cartilage from obese patients, providing thereby a molecular mechanism by which obesity is a risk factor for the development of osteoarthritis.

In conclusion, many recent studies allow us to better understand the relationships between osteoarthritis and obesity. Although it is evident that mechanical components contribute to joint destruction in overweight people, osteoarthritis is considered not only a disease of articular cartilage but also a systemic disorder in which circulating factors linked to altered lipid and glucose metabolism may explain the diversity of pathophysiological changes found in generalised osteoarthritis. However, the potential contribution of adipose-derived cytokines in osteoarthritis would not preclude the involvement of other mechanisms, including activation of mechanoreceptors, vascular dysfunction in subchondral bone and accumulation of AGEs in cartilage. Further investigations are thus needed to find new pharmacological tools and new orientations in the treatment and prevention of this joint disease.

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