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Research lectures

Is osteoarthritis a metabolic disease?

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ABSTRACT

Obesity, together with aging and injury, is among the main risk factors for osteoarthritis. Obesity-related osteoarthritis can affect not only the weight-bearing joints, but also the hands, suggesting a role for circulating mediators released by the adipose tissue and known as adipokines. Thus, osteoarthritis may have a systemic metabolic component. Evidence from both epidemiological and biological studies support the concept of metabolic osteoarthritis, defined as a broad clinical phenotype that includes obesity-related osteoarthritis. Thus, osteoarthritis can be related to metabolic syndrome or to an accumulation of metabolic abnormalities. In addition, studies have demonstrated associations linking osteoarthritis to several components of the metabolic syndrome, such as hypertension and type 2 diabetes, independently from obesity or any of the other known risk factors for osteoarthritis. Both in vitro and in vitro findings indicate a deleterious effect of lipid and glucose abnormalities on cartilage homeostasis. Chronic low-grade inflammation is a feature shared by osteoarthritis and metabolic disorders and may contribute to the genesis of both. Thus, osteoarthritis is emerging as a disease that has a variety of phenotypes including a metabolic phenotype, in addition to the age-related and injury-related phenotypes.

1. Introduction

Osteoarthritis is the most common joint disease with nearly 6 millions affected individuals in France. The prevalence of symptomatic knee osteoarthritis has been estimated in France at 4.7% in men and 6.6% in women [1].

Osteoarthritis covers a broad range of presentations in terms of the joints involved (hips, knees, hands. . .), imperfect correlation between the structural damage and the clinical symptoms, considerable interindividual variability in pain severity and functional impairments, and complex pathophysiological mechanisms. The current view is that osteoarthritis is a group of diseases that can be differentiated based on the risk factors involved and the pathophysiological mechanisms underlying the joint damage (aging, obesity, genetic factors, or injury) (Table 1) [2].

Obesity-related osteoarthritis is a readily identifiable phenotype. Converging evidence from numerous studies indicates that obesity-related osteoarthritis is one aspect of a vaster phenotypic group known as metabolic osteoarthritis, which also includes osteoarthritis related to hypertension, type 2 diabetes, and dyslipidemia [2–4] (Fig. 1).

2. Epidemiology of metabolic osteoarthritis

2.1. Osteoarthritis and obesity

Many epidemiological studies have established that lower-limb osteoarthritis is associated with obesity [5–8]. Obese individuals are at increased risk for symptomatic or radiological knee osteoarthritis, particularly with bilateral involvement [5,6]. Obesity is also associated with greater radiological progression of established knee osteoarthritis [6]. A weaker association with hip osteoarthritis has been reported [7,8]. In a recent study, however, obesity was linked to greater osteoarthritis severity not only at the knee, but also at the hip, with earlier and more frequent hip replacement surgery in patients who had high body mass index (BMI) values [9]. Thus, osteoarthritic joints have shorter "lifespans" in obese patients.

One obvious explanation to the link between osteoarthritis of the weight-bearing joints and obesity is increased chronic mechanical stress applied to the joints. In cartilage explant experiments, excessive mechanical stress applied using a dedicated device caused the chondrocytes to release proinflammatory and degradation-promoting mediators responsible for joint inflammation and cartilage matrix breakdown [10–12]. This passage from a physical stimulus (mechanical stress) to a biological effect implies the involvement of mechanoreceptors and a molecular cascade that converts the mechanical signal to a biochemical signal [13]. Similarly, when subjected to compression, subchondral-bone

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Table 1
Suggested classification of osteoarthritis phenotypes.

Clinical phenotype of osteoarthritis	Post-traumatic	Metabolic	Aging	Genetic	Pain
Age	Young (< 45 years)	Middle-aged (45–65 years)	> 65 years	Variable	Variable
Main causative factor	Mechanical stress	Mechanical stress, adipokines, hyperglycemia/AGEs, estrogen/progesterone imbalance	AGE, chondrocyte senescence	Mutations or genetic polymorphisms	Inflammation, aberrant pain threshold
Main sites	Knee, thumb, ankle, shoulder	Knee, hand, generalized	Hip, knee, hand	Hand, hip, spine	Knee, hip, hand
Treatment options	Joint protection, joint stabilization, fall prevention, surgery	Weight loss, glycemia control, lipid control, hormone replacement therapy, AGE blockade	No specific intervention, AGE blockade	No specific intervention, gene therapy	Analgesics, anti-inflammatory drugs

Adapted from [2].
AGEs: advanced glycation endproducts.

osteoblasts may release soluble mediators that exert deleterious effects on both the bone itself and the overlying cartilage [14].

However, excessive mechanical stress cannot fully account for the association between obesity and osteoarthritis. Obesity and overweight are independently linked to hand osteoarthritis, with a 2-fold risk increase according to a metaanalysis [15]. This fact suggests a role for systemic mechanisms in addition to the mechanical factors known to contribute to hand osteoarthritis.

Thus, the adipose tissue is now viewed not only as an energy storage site, but also as an endocrine tissue that releases soluble mediators into the systemic circulation. Among soluble mediators produced chiefly by the adipose tissue, adipokines such as adiponectin, leptin, and visfatin may act on both weight-bearing and non-weight-bearing joints. These adipokines are involved in regulating glucose and adipocyte metabolism, as well as immune and inflammatory responses [16,17]. They can also be released by other cell types including chondrocytes and synoviocytes. Leptin and visfatin have been identified within osteoarthritic joints [18–20]. In vitro experiments have shown that these adipokines produce similar chondrocyte activation to that seen with mechanical stress and proinflammatory cytokines [16,21]. Serum adiponectin levels may predict radiographic progression of hand osteoarthritis [22]. At the knee, adiponectin released by the infrapatellar fat pad may diffuse into the knee joint [23].

2.2. Osteoarthritis and metabolic syndrome

The association between obesity and hand osteoarthritis suggests a systemic link between the two conditions, mediated by the adipokines. However, obesity also promotes a number of co-morbidities, which, in turn, may increase the risk of osteoarthritis. Metabolic syndrome is a combination of disorders that increase the cardiovascular risk, including dyslipidemia, hypertension, diabetes or insulin resistance, and obesity [24]. The definition of metabolic syndrome is somewhat uncertain, as several criteria have been developed [4]. Osteoarthritis may be associated with either metabolic syndrome or each of its components (Fig. 1).

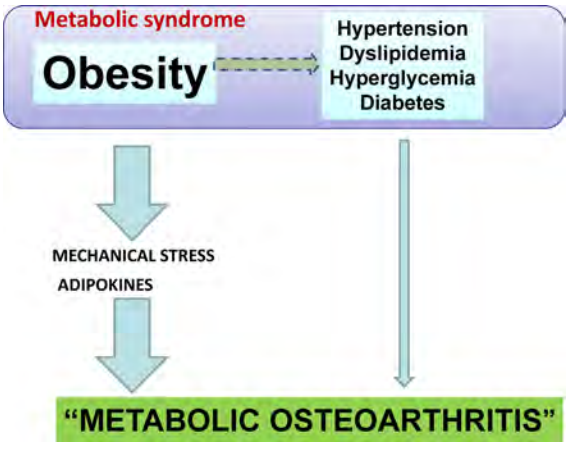

Fig. 1. The metabolic osteoarthritis concept: a broad phenotype that includes obesity-related osteoarthritis.

In a study of the vast NHANES III cohort representing the general population of the US, the prevalence of metabolic syndrome was increased in patients with osteoarthritis even after adjustment for age and BMI [25]. Interestingly, the accumulation of metabolic-syndrome components was associated with a gradual increase in the risk of knee osteoarthritis development and progression in the Japanese Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study [26]. In women, the presence of obesity and at least two other metabolic-syndrome components (cardiometabolic clustering) was associated with a higher risk of knee osteoarthritis compared to obesity alone [27]. A similar additive effect of hypertension and diabetes to that of overweight has been also reported for hand osteoarthritis [28].

Each of the components of metabolic syndrome is also associated with osteoarthritis, although published data are somewhat conflicting [4]. The main weakness found in available studies is failure to adjust the data on known risk factors for osteoarthritis such as age and BMI. Some of the discrepancies across studies can be ascribed to differences in the definitions of metabolic abnormalities and/or knee osteoarthritis. For instance, knee osteoarthritis was defined as the presence of osteophytes on non-weight-bearing radiographs in the NHANES III cohort and as a Kellgren-Lawrence stage of 2 or more on weight-bearing radiographs in the ROAD study [26,29].

The first study suggesting a link between type 2 diabetes and osteoarthritis was published in 1961 [30]. Subsequent data from better-designed studies supported this link. Thus, in the NHANES III cohort, a 1-point increase in the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) was associated with an increase in the knee osteoarthritis risk of 18% in non-obese males and 34% in obese males after adjustment on several factors including age [29]. In females, the HOMA-IR did not affect the risk of knee osteoarthritis, which was independently associated with serum leptin elevation. These data suggest that the impact of metabolic disturbances may differ between males and females, perhaps due to differences in hormonal and anatomical factors [31]. In the ROAD study, glucose intolerance was independently associated with the development and progression of radiographic knee osteoarthritis [26,32]. Finally, in a recent study of nearly 1000 patients followed up for 20 years, type 2 diabetes was a risk factor for severe osteoarthritis defined as a need for joint replacement surgery (hazard ratio, 2.1; 95% confidence interval, 1.1-3.8), independently from age and BMI [33]. Although independent associations between

osteoarthritis and type 2 diabetes were also demonstrated in other populations, the existence of negative studies should be borne in mind [34,35].

A few studies support an independent association between hypertension and osteoarthritis [25,36]. As obesity is associated with hypertension, adjustment on BMI is required to obtain robust data. Thus, the interpretation of several studies has been challenged [25,36]. In the Chingford study from the UK, hypertension was associated with bilateral knee osteoarthritis after adjustment on age and BMI [37]. In the more recent ROAD study, both the presence and the progression of knee osteoarthritis were associated with hypertension after adjustment on numerous confounders [26]. Hypertension may add to the effect of overweight on the risk of hand osteoarthritis [28].

Dyslipidemia and cholesterol levels have also been evaluated for effects on the risk of osteoarthritis. In the Chingford study, serum cholesterol elevation was associated with knee and hand osteoarthritis independently from BMI [37], and hypercholesterolemia was associated with osteoarthritis in other studies [38,39]. Interestingly, in women who were symptom-free at baseline, hypercholesterolemia and hypertriglyceridemia were associated with the presence of subchondral bone lesions visible by magnetic resonance imaging 2 years later [40].

The associations linking osteoarthritis to glucose metabolism abnormalities, dyslipidemia, and hypertension indicate a need for evaluating potential associations of osteoarthritis with the clinical complications of metabolic syndrome, namely, atheroma and cardiovascular mortality. One study suggested associations between hand osteoarthritis severity and carotid artery atherosclerosis or coronary artery calcifications [41]. Popliteal artery wall thickness was greater in patients with generalized osteoarthritis than in patients without osteoarthritis [42]. Patients with knee or hip osteoarthritis have excess mortality that is chiefly ascribable to cardiovascular disease and directly related to the degree of functional impairment [43]. However, this type of association does not imply a causal link, although osteoarthritis may lead to physical inactivity, a factor independently associated with cardiovascular disease. The role for chronic low-grade inflammation in both osteoarthritis and cardiovascular disease is discussed below. Another finding supporting a systemic metabolic component to osteoarthritis is an independent association between hand osteoarthritis and cardiovascular mortality in males [44].

3. Pathophysiology of metabolic osteoarthritis

The association between osteoarthritis and metabolic syndrome can be approached from two different angles. If the metabolic disturbances are viewed as risk factors for osteoarthritis, then it makes sense to study the impact of each component of the syndrome (glucose, lipids, hypertension) on joint tissues and cells. The other approach sees chronic low-grade inflammation as the link between the two conditions via the induction of systemic complications including type 2 diabetes, dyslipidemias, hypertension, and osteoarthritis.

3.1. Role for chronic hyperglycemia

Glucose is required for chondrocyte homeostasis. However, excessive amounts of glucose may disrupt chondrocyte homeostasis via multiple direct and indirect mechanisms.

Chondrocytes normally adjust their glucose transport capabilities by regulating their expression of the main membrane glucose transporter, GLUT-1, according to the concentration of extracellular glucose [45–47]. Normal chondrocytes exposed to high extracellular glucose concentrations (30 mM) had low GLUT-1 expression and intracellular glucose uptake [46]. In contrast, chondrocytes from osteoarthritic joints exposed in vitro to the same extracellular glucose concentration failed to decrease their expression of GLUT-1 and were unable to adjust their glucose uptake. These chondrocytes accumulated more glucose than did their normal counterparts and, consequently, produced larger amounts of reactive oxygen species (ROSs). ROSs can be generated not only by glucose itself, but also by proinflammatory cytokines, and they can promote cartilage matrix breakdown and cell death [46]. High glucose concentrations also induce initiation of the catalytic program (induction of the metalloproteases MMP-1 and MMP-13) in the osteoarthritic chondrocyte [48]. In vivo data corroborate these findings: insulin-dependent diabetes induced in rats by a streptozotocin injection was associated with major alterations in collagen composition in the cartilage, synovial membrane, and ligaments, with a lower body weight compared to nondiabetic animals and loss of cartilage proteoglycans [49]. Interestingly, STR/Ort mice, which develop osteoarthritis spontaneously, also exhibit several features of metabolic syndrome including hyperglycemia with insulin resistance and hypertriglyceridemia [50].

In addition to the direct effects of glucose on cells, chronic hyperglycemia increases the occurrence of nonenzymatic glycation reactions, which are associated with oxidative stress, as well illustrated in patients with diabetes [51]. This intertwining of glycation and oxidation, known as glycoxidation, manifests as the binding of a simple ose (glucose, fructose, ribose) to amine groups on proteins (arginine, lysine) and as multiple oxidation reactions that ultimately generate advanced glycation endproducts (AGEs) [51,52]. AGEs can accumulate within tissues. The protein alterations related to the addition of oses, together with the generation of ROSs during most glycation reactions, result in effects of AGEs on numerous events (inflammation, tissue remodeling, changes in antigenicity, apoptosis). AGEs are also ligands for various membrane receptors including RAGE (AGE receptor), a 45-kDa glycoprotein expressed at the surface of many cell types [53].

AGEs are generated in increased amounts during aging, and studies of AGEs in osteoarthritis have focused on older individuals [52,54]. Cartilage remodeling is slow and the half-life of cartilage proteins commensurately long. As a result, during aging, proteins such as collagen II, whose half-life exceeds 100 years, are particularly susceptible to glycation [55]. AGEs have been shown to accumulate within the osteoarthritic cartilage in amounts that increase with age and correlate negatively with the amount of matrix produced [56]. AGEs modify the biomechanical properties of the matrix in ways that increase stiffness and therefore render the cartilage more vulnerable to mechanical stress [57]. In vitro, AGEs can induce chondrocyte activation characterized by the production of proinflammatory cytokines, prostaglandin E_2 (PGE_2), and proteases, as well as by a decrease in cartilage anabolic activity via the activation of signaling pathways such as the MAP kinase pathway [58–60].

Thus, AGEs exert well-characterized effects on the cartilage and chondrocyte, and their presence within the osteoarthritic cartilage has been studied in aging individuals. However, very few data on AGE levels in cartilage from patients with diabetes are available. The only published data come from a small pilot study in which the AGE pentosidine was increased in osteoarthritic cartilage from diabetic patients [61].

3.2. Role for lipids

The epidemiological evidence has been corroborated by animal studies. In mice that were genetically modified to induce abnormalities in HDL metabolism and dyslipidemia, knee osteoarthritis developed despite the absence of abnormal weight gain compared to wild-type mice [62]. Early lipid deposition within the

cartilage and, more specifically, in the chondrocytes has been reported [63]. The levels of total fatty acids and arachidonic acid within chondrocytes from osteoarthritic cartilage were found to increase markedly with the severity of the cartilage damage [64]. In addition, the expression of genes regulating cholesterol uptake by chondrocytes was diminished in osteoarthritic cartilage [65]. According to one hypothesis, lipid alterations that affect chondrogenesis, osteogenesis, and adipogenesis may induce abnormalities in mesenchymatous cell differentiation [66].

Several studies have shown that specific fatty acids such as linoleic acid can modulate chondrocyte activation, most notably by decreasing the production of PGE_2 and nitric oxide (NO), thereby inducing protective effects, at least in vitro [67]. Another current hypothesis is that oxidized low-density lipoproteins (oxLDL), in addition to their involvement in atherosclerosis, may promote the inflammatory component of osteoarthritis [68]. A role for oxLDLs may explain the association between atherosclerosis and osteoarthritis. A harmful effect of free fatty acids has been suggested, particularly as these molecules can also contribute to the development of insulin resistance [69].

3.3. Role for hypertension

Few clues are available to explain the association between hypertension and osteoarthritis. One hypothesis involves subchondral bone ischemia due to a blood flow decrease in the subchondral microvessels [70,71]. The resulting decrease in the supply of nutrients and oxygen may impair exchanges between the subchondral bone and the overlying cartilage. Alternatively, the ischemia may result in accelerated apoptosis of the subchondral osteocytes with subsequent abnormalities in subchondral bone remodeling [4,72].

3.4. A shared foundation: chronic low-grade inflammation

At present, a prevailing hypothesis regarding metabolic syndrome is that chronic low-grade inflammation may be responsible, at least in part, for the development of systemic abnormalities such as glucose and lipid dysregulation, hypertension, atheroma, and osteoarthritis [73]. Both osteoarthritis and the components of metabolic syndrome are associated with a number of mediators induced by proinflammatory cytokines, such as oxidative stress agents, oxLDL, adipokines, proinflammatory lipid mediators, and NO. NO contributes to endothelial dysfunction and has documented deleterious effects on chondrocyte activation [74,75]. Chronic low-grade inflammation is associated with accelerated aging and cell senescence, most notably under the influence of ROSs, which are responsible for oxidative stress. The term “inflammaging” was coined recently to designate this combination of aging and inflammation [76]. Inflammaging is the chronic inflammation that occurs during aging and is associated with the development of age-related health conditions such as metabolic and joint disorders. The inflammaging concept may be particularly useful for investigating osteoarthritis, whose development may be related to both inflammation and aging. One finding that illustrates this possibility is that the amount of MMP-3 released by chondrocytes in response to interleukin-1β increases with the age of the cell donors [77].

4. Therapeutic implications

Dietary therapy combined with physical exercise and bariatric surgery are effective treatments not only for obesity, but also for the associated metabolic disturbances and knee osteoarthritis [78,79]. In contrast, there is no proof that interventions designed to control hypertension, diabetes, or dyslipidemia alleviate the symptoms of osteoarthritis. Furthermore, to date, statin therapy has not demonstrated relevant clinical efficacy on knee osteoarthritis [80].

In the current state of our knowledge, the metabolic osteoarthritis concept is most useful when viewed as a target for prevention in patients at cardiovascular risk, particularly when several risk factors co-exist. Puenpatom et al. have suggested that early osteoarthritis strongly suggests a need for routine diagnostic investigations designed to detect the components of metabolic syndrome [25].

5. Conclusion

Obesity-related osteoarthritis can now be viewed as one aspect of the broader metabolic osteoarthritis phenotype. Robust epidemiological studies support a role for metabolic factors in osteoarthritis, and accumulating experimental data suggest that diabetes, dyslipidemia, and hypertension may independently promote joint damage, even in the absence of obesity. Interestingly, many of the same molecules seem involved in the pathophysiology of both osteoarthritis and metabolic disturbances, and the production of these molecules is related to systemic chronic inflammation occurring as a characteristic of cell aging, a process known as inflammaging.

Osteoarthritis has been described as the fifth component of metabolic syndrome [4]. This novel nosological and phenotypic approach to osteoarthritis, together with fresh insights into the associations linking osteoarthritis and metabolic syndrome, will no doubt open up new avenues toward specific treatments for each of the osteoarthritis phenotypes.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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