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Review

The Phenotypic Approach to Osteoarthritis: A Look at Metabolic Syndrome-Associated Osteoarthritis

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ABSTRACT

Metabolic syndrome-associated osteoarthritis (Met-OA) is a clinical phenotype defined by the role of obesity and metabolic syndrome as risk factors and by chronic low-grade inflammation. Obesity is an established risk factor for osteoarthritis not only at the knee, but also at the hands. Metabolic syndrome is also a risk factor for osteoarthritis, and a cumulative effect of the various syndrome components combines with an independent effect of each individual component (diabetes, dyslipidemia, and/or hypertension). The higher incidence of osteoarthritis in patients with obesity is related to several factors. One is the larger fat mass, which imposes heavier loads on the joints. Another is endocrine production by the adipose tissue of proinflammatory mediators (cytokines, adipokines, fatty acids, and reactive oxygen species) that adversely affect joint tissues. Obesity-related dysbiosis and sarcopenia were more recently implicated in the association between obesity and osteoarthritis. Finally, patients who have osteoarthritis, with or without metabolic syndrome, are at increased risk for cardiovascular mortality due not only to a sedentary lifestyle, but also to shared risk factors. Among these is the low-grade inflammation seen in patients with metabolic disorders. Thus, primary prevention and appropriate management of obesity and metabolic syndrome may delay the development and slow the progression of osteoarthritis.

1. Introduction

The prevalence of osteoarthritis has doubled since the 1950s, chiefly due to the obesity epidemic and aging of the population. Other factors, however, were recently shown to participate in the rising prevalence of osteoarthritis. A study of human skeletal remains from prehistoric times, the preindustrial era, and the industrial era since 1976 demonstrated a marked increase in knee osteoarthritis since industrialization that was partly independent from age and body mass index (BMI), indicating a role for other factors such as diet, dysbiosis, physical inactivity, and metabolic disorders [1,2].

Cartilage damage, synovial membrane inflammation, and subchondral bone remodeling are hallmark features of osteoarthritis regardless of risk factor patterns in individual patients. Each clinical osteoarthritis phenotype, however, exhibits specific pathophysiological features dependent on the risk factors involved [3]. This review article discusses recent evidence on osteoarthritis associated with metabolic syndrome.

Epidemiological data supporting the concept of osteoarthritis associated with metabolic syndrome

Obesity is a major risk factor for osteoarthritis. Although the association is strongest for the knee, it exists also for the hip and, to a lesser extent, the hands [4,5]. Similarly, the combination of disorders that makes up metabolic syndrome is associated with increased risks of osteoarthritis at the knee, hands, and lumbar spine [6–9]. Nevertheless, several studies suggest an association rather than a causal link, and some of the findings are conflicting, with no association between metabolic syndrome and osteoarthritis in some studies [6,10]. One possible explanation to these discrepancies is that the role for excess body weight in the development of knee osteoarthritis is so considerable as to make the identification of weaker associations with other metabolic factors extremely difficult after adjustment on BMI [6]. One way to circumvent this issue is to study hand osteoarthritis, which is not influenced by mechanical factors related to body weight. Our group has reported a higher incidence and greater severity of radiographic hand osteoarthritis among HIV-positive patients with metabolic

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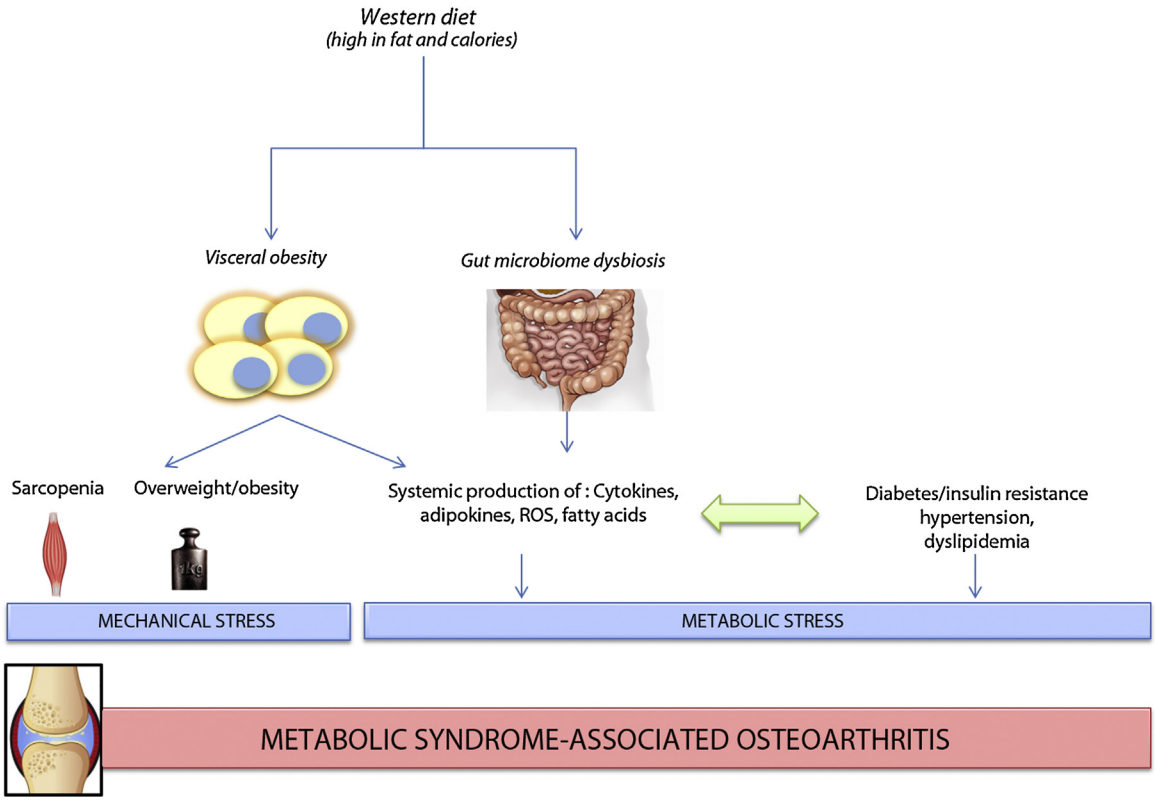

Fig. 1. Mechanisms involved in metabolic syndrome-associated osteoarthritis ROS, reactive oxygen species; HT, hypertension.

syndrome compared to both their counterparts without metabolic syndrome and to the general population [9].

The main effects of metabolic syndrome may be to increase the severity of osteoarthritis, notably regarding the clinical manifestations, and to worsen the prognosis by promoting structural disease progression via a cumulative influence of the metabolic disorders [11,12]. In addition to this cumulative effect, each of the metabolic components of the syndrome may be independently associated with the risk of osteoarthritis. The most robust investigation of this hypothesis was a prospective study in a cohort of nearly 1000 patients [13]. After adjustment on confounders, type 2 diabetes was associated with a 2-fold increase in the risk of undergoing knee arthroplasty. Subsequent studies supported this finding. Thus, two recent metaanalyses demonstrated that the risk of osteoarthritis at any site was higher in individuals with diabetes [14,15]. Regarding type 1 diabetes, the paucity of available data does not allow definitive conclusions.

Dyslipidemia has also been found to be associated with osteoarthritis. Our group recently reported a meta-analysis of 48 publications on links between dyslipidemia and osteoarthritis [16]. Dyslipidemia was far more prevalent in individuals with versus without osteoarthritis (30% versus 8%) and the risk of dyslipidemia was significantly higher in individuals with osteoarthritis at any site and, more notably, at the knees and hands. However, these studies of associations cannot provide proof of a causal link between the two diseases.

Finally, another component of metabolic syndrome that is associated with osteoarthritis is hypertension. Patients with hypertension had 2-fold and 1.5-fold increases in the risks of radiographic and symptomatic knee osteoarthritis, respectively, compared to controls in a recent meta-analysis [17]. Hypertension is also associated with greater severity of osteoarthritis responsible, in particular, for worse functional impairments. In the other direction, the risk of hypertension is higher in patients with osteoarthritis. Thus, in a longitudinal study, the risk of developing hypertension was 13% higher in patients with versus without knee osteoarthritis after adjustment on BMI and use of nonsteroidal anti-inflammatory drugs (NSAIDs) [18].

Finally, hyperuricemia was rarely considered in studies of associations linking osteoarthritis and metabolic syndrome yet may act as a confounder, as it is associated with both diseases. In addition, studies suggest that asymptomatic hyperuricemia may be a risk factor for greater severity of osteoarthritis. However, in many epidemiological studies patients with other joint diseases such as those related to crystal deposition were excluded.

2. Pathophysiological data relevant to metabolic syndrome-associated osteoarthritis

2.1. Systemic effects of adipose tissue

That excessive mechanical loading is involved in the association linking obesity to osteoarthritis makes intuitive sense and explains the increased risks of hip and knee osteoarthritis in patients with obesity.(Fig. 1) The link between hand osteoarthritis and obesity, in contrast, must be due to systemic factors. Adipose tissue is an endocrine organ that produces a host of proinflammatory mediators then releases them into the bloodstream. These mediators then exert deleterious effects on many tissues, inducing the metabolic and vascular complications of obesity, and also contribute to cause low-grade joint inflammation. Adipokines and cytokines are the main mediators involved, although reactive oxygen species (ROS), fatty acids, and oxidized low-density lipoproteins (oxLDL) also play a role.

2.1.1. Adipokines

Among the adipokines, leptin and visfatin (also known as nicotinamide phosphoribosyltransferase [NAMPT]) have been the most

Table 1
Examples of saturated and unsaturated fatty acids.

Saturated fatty acids	Unsaturated fatty acids	
	Monounsaturated	Polyunsaturated
Palmitic acid Stearic acid Butyric acid	Palmitoleic acid Oleic acid	Linoleic acid α Linoleic acid Arachidonic acid Eicosapentaenoic acid Docosahexaenoic acid

extensively studied. Although these compounds originate chiefly in adipose tissue, they are also produced by joint tissues. Leptin and visfatin levels in serum and/or joint fluid were higher in patients with osteoarthritis than in controls, and leptin expression by joint chondrocytes correlated closely with osteoarthritis severity [19]. Both leptin and visfatin have demonstrated proinflammatory and prodegradative effects on cartilage and synovial membrane cells in vitro [20]. Mice with leptin deficiency due to a homozygous mutation in the *ob* gene develop major obesity yet are protected against the occurrence of osteoarthritis [21]. Therefore, leptin plays a key role in the development of obesity-associated osteoarthritis. Similarly, intraarticular injection of a visfatin inhibitor limited the development of knee osteoarthritis induced by destabilization of the medial meniscus (DMM) [22].

Other adipokines such as adiponectin and resistin may be involved in adipose tissue-related inflammation and may exert deleterious effects on joints [20,23]. The evidence available to date, however, does not support the concept that adipokines might constitute a direct therapeutic target in osteoarthritis.

2.1.2. Free fatty acids and lipid mediators

Free fatty acids released by triglyceride hydrolysis are a major source of energy between meals. When produced in excessive amounts, however, as occurs during obesity, some free fatty acids promote insulin resistance. Saturated fatty acids have only single bonds, whereas unsaturated fatty acids have one (monounsaturated) or more than one (polyunsaturated) double bonds (Table 1). Some unsaturated fatty acids cannot be produced in sufficient amounts by the body and must therefore be provided by the diet. Examples include the polyunsaturated omega-3 and omega-6 fatty acids. Over time, the omega-6/omega-3 ratio in the diet has increased markedly, from 1:1 to about 10–20:1 in industrialized countries.

Certain fatty acids such as palmitic acid, linoleic acid, and oleic acid accumulate within joint tissues, notably the chondrocytes and synovial fluid [24,25]. In vitro and in vivo studies have demonstrated proinflammatory and procatabolic effects of palmitic acid and similar fatty acids in osteoarthritis. In mice with obesity induced by a high-fat diet, genetic knockout or pharmacological inhibition of the free fatty acid receptor fatty-acid-binding protein-4 (FABP4) considerably decreased the severity of osteoarthritis [26].

Other fatty acids, in contrast, may protect against osteoarthritis by activating transcription factors such as peroxisome proliferator-activated receptor gamma (PPAR-γ), which is the main transcription factor involved in adipogenesis. The role played by PPAR-γ in insulin sensitivity explains that PPAR-γ agonists such as glitazones have been developed for the treatment of diabetes. PPAR-γ activation within cartilage exhibited anticatabolic and anti-inflammatory effects in vitro and in vivo in mice [27].

A high-fat diet induces osteoarthritis in laboratory animals by causing obesity. However, the severity of the disease varies with the intake of polyunsaturated fatty acids. Thus, as with cardiovascular disease, osteoarthritis was less severe if the omega-6/omega-3 ratio was low or if even small quantities of omega-3 fatty acids were added to the high-fat diet fed to mice [28]. In humans, a few studies have demonstrated associations linking serum levels to the severity of osteoarthritis. Well-designed interventional studies are needed to determine whether increasing the intake of any specific fatty acid translates into clinical benefits in humans.

Among the other lipid mediators that are overproduced in patients with metabolic syndrome, LDL-cholesterol may play a role in osteoarthritis. More specifically, in osteoarthritis, the levels or expression of oxLDL were higher in serum, synovial fluid, and cartilage and were associated with greater disease severity and worse pain in humans [29]. Furthermore, knockout mice for the lectin-like oxLDL receptor-1 did not develop osteoarthritis during aging or after DMM [30].

These abnormalities act in combination to produce associations linking dyslipidemia, obesity, insulin-resistance, and osteoarthritis.

2.1.3. Oxidative stress

Obesity, metabolic syndrome, and osteoarthritis are all related to an increase in oxidative stress. Oxidative stress occurs when the antioxidant capacity is insufficient to handle the amount of ROS produced. ROS and/or nitric oxide (NO) play a central role in the inflammatory processes involved in osteoarthritis. All the joint cells involved with osteoarthritis including chondrocytes, synovial fibroblasts, and adipocytes can produce large amounts of ROS and NO in response to biomechanical or biochemical stimuli. In the presence of IL-1β or of high glucose or fatty acid levels, chondrocytes, osteoblasts, and synovial cells overproduce ROS [31,32], which, in turn, oxidize numerous proteins, lipids, and nucleic acids, thereby altering their structure and function.

2.2. Hyperglycemia and insulin-resistance

Studies in several animal models of diabetes have established that type 2 diabetes is associated with osteoarthritis. Thus, osteoarthritis was more severe in animals with than without diabetes [33]. In humans, epidemiological data also indicate an association between diabetes and osteoarthritis. Several mechanisms have been implicated in the pathophysiology of osteoarthritis induced by diabetes. First, chronic hyperglycemia results in the accumulation of advanced glycation end-products (AGEs), which are proteins irreversibly altered by the post-translational addition of sugar molecules Among patients with osteoarthritis, those with diabetes have larger amounts of AGEs, notably within subchondral bone, compared to those without diabetes [34]. The presence of AGEs adversely affects tissue resistance and activates inflammatory and oxidative pathways within the joint tissues.

Furthermore, hyperglycemia can directly increase oxidative stress and exerts synergistic effects with IL-1β. Thus, hyperglycemia may increase the responsiveness to local low-grade inflammation [35]. This effect of hyperglycemia may be ascribable to increased oxidative stress with NO and ROS overproduction associated with impairments in antioxidant mechanisms [36].

Finally, joint tissues of patients with type 2 diabetes may exhibit peripheral insulin resistance. Insulin exerts anabolic and anti-inflammatory effects within joints. In vitro, synovial cells from patients with type 2 diabetes exhibited a blunted response to insulin perhaps due in part to more severe synovial inflammation [37].

2.3. Role for atherosclerosis and hypertension

Whether hypertension is associated with osteoarthritis remains unproven. According to the main hypothesis, hypertension-induced atheroma lesions may cause damage to the joint tissues, notably the subchondral bone. When a high-fat diet was given to knockout mice for apolipoprotein E or the LDL receptor, early

diffuse atheroma developed and, compared to wild-type mice, experimental osteoarthritis was more severe, with greater synovial inflammation and more osteophyte formation [38]. A correlation has been reported between atheroma lesion size and osteoarthritis severity in these mouse models [39]. Similarly, hypertensive rats spontaneously developed more severe subchondral bone damage with geodes compared to normotensive rats. These findings establish a role for hypertension that is independent from obesity, an inactive lifestyle, or long-term NSAID exposure [40].

2.4. Gut microbiome

Another hypothesis currently under investigation is that the gut dysbiosis seen in obesity and metabolic syndrome may play a role in osteoarthritis. In an obese rat model, quantitative changes in microbiome components such as *Lactobacillus* spp. and *Methanobrevibacter* spp. predicted the severity of osteoarthritis [41]. Similarly, in the DMM model, osteoarthritis was less severe in germ-free mice than in specific pathogen-free mice, suggesting an influence of the gut microbiome and bacterial environment on osteoarthritis. In mice with obesity induced by a high-fat diet, quantitative and qualitative microbiome alterations with fewer beneficial bacteria and more proinflammatory bacteria have been demonstrated. Oligofructose supplementation lessened these alterations without affecting body weight and, after DMM, decreased the synovial and systemic inflammation, as well as the severity of osteoarthritis [42]. Conceivably, microbiome alterations in patients with obesity may modify endotoxin levels, thereby inducing innate immune responses within the joint tissues. Thus, in patients with knee osteoarthritis, the serum and joint-fluid concentrations of lipopolysaccharide and of its binding protein correlated with synovial-membrane macrophage counts and knee osteoarthritis severity [43].

2.5. Sarcopenia

Sarcopenia is another musculoskeletal complication of obesity. Sarcopenia has major consequences, since muscles are not only the main site of glucose consumption, but also contribute to joint homeostasis. In rats fed a high-fat diet, fat accumulated within muscles, and inflammatory cells including macrophages were recruited to muscles from day 3 onward ([44], review in [45]). Sarcopenia correlated closely with the severity of metabolic syndrome-associated osteoarthritis in rats with obesity induced by a high-fat diet [45]. Among humans with obesity, those who also have sarcopenia have a 3-fold higher risk of knee osteoarthritis compared to those whose muscle mass is normal, resulting in a higher risk than seen with obesity or sarcopenia alone [46]. Thus, the muscle changes seen in patients with obesity may promote the development and/or progression of osteoarthritis. A causal link is difficult to prove, however, since osteoarthritis results in disabilities that in turn lead to physical inactivity and, consequently to sarcopenia.

3. Therapeutic implications

Metabolic syndrome-associated osteoarthritis is probably the phenotype in which preventive and etiological treatments are most likely to be effective in slowing the progression of the joint alterations.

3.1. Weight loss, bariatric surgery

That weight loss achieved by dietary intervention or bariatric surgery has beneficial effects on knee osteoarthritis is now indisputable. Bariatric surgery is a radical treatment that has major consequences. Nevertheless, within 3 months after bariatric surgery, patients with painful knee osteoarthritis experienced significant functional improvements, notably when returning to sporting activities [47]. Interestingly, improvements in pain sensitization were noted not only at the knees, but also at other sites [48].

Most of the improvement in pain seemed to occur within the first year after bariatric surgery, with 77% to 80% of patients having clinically meaningful improvements in knee pain and function scores after 1 year [49]. Factors associated with greater knee pain relief after bariatric surgery were younger age, male sex, higher income, less depression at baseline and decreasing depression during follow-up, worse symptoms before surgery, and greater weight loss [49]. In addition to the clinical improvements, decreased radiographic progression of knee osteoarthritis has been reported after weight loss [50]. Studies of potential changes in hand osteoarthritis indicating a systemic effect of a decrease in fat mass would be of interest, but none is available to date.

3.2. Antidiabetic drugs, statins, and antihypertensive drugs: current knowledge

Whether antidiabetic treatments influence osteoarthritis remains unclear. PPAR-γ has demonstrated anticatabolic effects in rats but, in the only available case-control study in humans, pioglitazone therapy failed to affect the risk of knee or hip arthroplasty [51]. In rats with diabetes, insulin therapy was associated with decreased osteoarthritis severity, and this effect was amplified by simultaneous treatment with vanadium, which has insulin-like effects. Insulin-treated patients with diabetes had less osteophyte production compared to patients with non-insulin-dependent diabetes [52]. Finally, no association between metformin therapy and osteoarthritis was found in a study of a primary-care database from the UK.

Another issue of interest is whether statin therapy influences the risk of osteoarthritis. In a longitudinal study, statin users had more radiographic progression of knee osteoarthritis compared to non-users, despite adjustment on confounders including BMI and metabolic disorders [53]. Similarly, a 7-year study found that statin users had a higher risk of developing spinal degenerative disease compared to non-users [54]. However, within the group of users, a higher statin dosage was associated with a lower risk of spinal degenerative disease. These findings should be viewed with circumspection, as they were obtained by retrospectively assessing a database. Consequently, whether statin therapy is associated with osteoarthritis remains unclear.

Finally, only meager information is available on potential links between antihypertensive drug therapy and osteoarthritis. In an exploratory study including 2938 patients from the Osteoarthritis Initiative cohort, alpha-adrenergic therapy was associated with decreases in both pain and radiographic progression of knee osteoarthritis, whereas beta-adrenergic blockers were associated only with less radiographic progression [55]. In another cohort study, however, beta-adrenergic blocker therapy was associated with both less pain and less opioid consumption in patients with knee and/or hip osteoarthritis [56], indicating a need for further studies. Finally, intraarticular therapy with the calcium channel antagonist verapamil, a Wnt/β-catenin pathway inhibitor, prevented the development of osteoarthritis in rats [57]. No data are available in humans.

3.3. Physical activity

In male mice fed a high-fat diet responsible for obesity, aerobic exercise slowed the progression of knee osteoarthritis and decreased the expression of proinflammatory cytokines, independently from effects on body weight [58]. In patients with obesity,

physical activity responsible for weight loss alleviates the symptoms of knee osteoarthritis. Thus, physical activity not only causes weight loss by increasing energy expenditures, but also exerts systemic antiinflammatory and immunomodulating effects that may alleviate the effects of obesity and metabolic complications on joints [59]. For instance, in elderly women with knee osteoarthritis, moderate exercise increased the plasma concentrations of brain-derived neurotrophic factor, which is involved in pain perception and exerts antiinflammatory effects [60].

4. Conclusion

Important advances have been made in our understanding of the epidemiology and pathophysiology of metabolic syndrome-associated osteoarthritis. Among the risk factors that define this osteoarthritis phenotype, obesity is the most potent, although the concomitant metabolic disorders that exacerbate the effects of obesity also play a role. Type 2 diabetes is the metabolic risk factor for which the epidemiological and basic-science data are the most robust. In contrast, the potential associations linking dyslipidemia and hypertension to osteoarthritis remain controversial. Importantly, a distinctive feature of the metabolic syndrome-associated osteoarthritis phenotype is the involvement of modifiable risk factors. Increased awareness of this phenotype among physicians and other healthcare professionals may allow interventions capable of slowing the osteoarthritis epidemic, including application of the well-known measures used for the primary and secondary prevention of metabolic syndrome and cardiovascular disease.

Disclosure of interest

The authors declare that they have no competing interest.

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