

DOES OSTEOARTHRITIS FORM PART OF THE METABOLIC SYNDROME?

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ABSTRACT

Osteoarthritis (OA) is among the most frequently encountered sources of complaints in everyday practice. It is generally characterized by a slowly progressive degeneration of articular cartilage, especially in the weight-bearing joints. OA can affect any joint but the most common are hip and knee and the joints of the hand, foot, and spine. Several elements are recognized as predisposing factors for OA. Apart from the classical factors whose involvement in the genesis of this pathology is demonstrated, the metabolic syndrome has recently been the subject of several studies showing its unavoidable involvement in the onset of OA. In this review we will highlight the links between the various elements of the metabolic syndrome and the development of OA, focusing on the cardiovascular risk that these two conditions can bring about.

Keywords: Cardiovascular risk, Metabolic syndrome, Osteoarthritis, ..

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INTRODUCTION

Among the hundreds of rheumatic diseases classified by the Arthritis Foundation, osteoarthritis (OA) is the most common [1]. It accounts for 62% of the visits to physicians with osteoarticular complaints [2]. It is generally characterized by a slowly progressive degeneration of articular cartilage, especially in the weight-bearing joints. It has a high prevalence in women, and its incidence increases with age [3]. In this context, OA symptoms, including joint pain, stiffness, and limitation of movement, tend to be worse with weight bearing and activity and increase with rest [4, 5]. Physical examination often reveals tenderness on palpation, bony exostosis, creak on

movements, and limitation of joint movements [5, 6]. OA can affect any joint but the most common are hip and knee and the joints of the hand, foot, and spine [7]. Several elements are recognized as predisposing factors for OA, such as age, female gender, genetic predisposition, previous trauma, obesity, mechanical factors like malalignment, previous or current occupation, previous inflammatory arthritis, and nutritional factors (low Vitamin C and Vitamin D levels) [8].

Recently, a possible link between OA and metabolic syndrome (MetS) has been established, providing a new approach of both diseases (**Figure 1**) [9].

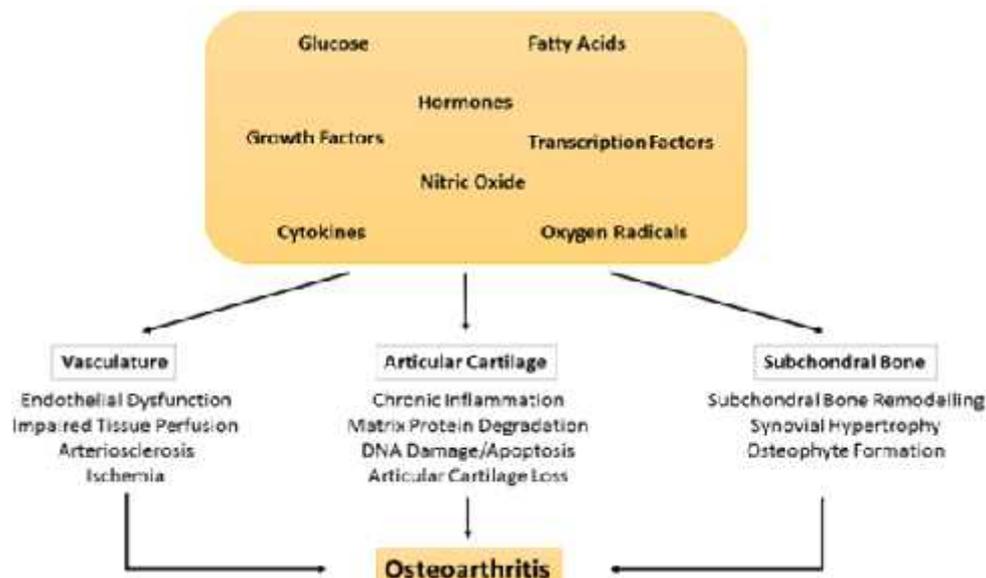


Figure 1: Mediators and pathogenesis of osteoarthritis.

Metabolic OA could now be considered as a subtype of OA, the second most frequent after aging [10]. Indeed, MetS is characterized by a cluster of disorders such as insulin resistance, hypertension, dyslipidemia and visceral obesity, and leads to the development of cardiovascular disease (CVD) and type 2 diabetes mellitus (**Table I**) [11].

Table I: Metabolic conditions or diseases associated with osteoarthritis

Obesity
Diabetes mellitus
Dyslipidemia
Hypertension
Acromegaly
Aging
Diffuse idiopathic skeletal hyperostosis (DISH)
Calcium pyrophosphate dihydrate deposition disease
Hemochromatosis
Basic calcium phosphate crystal disease (apatite-associated arthropathy)

Now, identifying metabolic factors involved in OA development and progression, independently from obesity and increased mechanical loading on the joint, is really challenging for physicians and is critical to develop effective treatments for metabolic OA [12].

The articles reviewed here were limited to papers published in English in PubMed and Researchgate and were selected according to their relevance to the topic and after critical discussion.

EPIDEMIOLOGY OF METS-ASSOCIATED OA

Files from the Third National Health and Nutrition Examination Survey (NHANES III) have shown that the prevalence of OA among U.S. adults aged >35 years is approximately 21% [13].

A more recent analysis of NHANES III data comprising a representative sample of 7,714 subjects (of whom 975 subjects had OA and 6,739 had no OA) showed that metabolic syndrome had a prevalence of 59% in the OA population, but only 23% in the population without OA [14]. In addition, each of the five cardiovascular risk factors that comprise metabolic syndrome was more prevalent in the OA population versus the population without OA: Hypertension (75% vs. 38%), abdominal obesity (63% vs. 38%), elevated triglycerides (47% vs. 32%), low high-density lipoprotein cholesterol (44% vs. 38%), and hyperglycemia (30% vs. 13%). [15]

Depending on its definition [16], patients with MetS have been demonstrated to have an increased incidence of the knee but not hip OA, in models adjusted for age, sex and social factors [17]. This is consistent with large epidemiological studies describing the positive association between MetS and knee OA, but only in models unadjusted for BMI [18, 19]. However, a recent study by Elbaz *et al.*[20] reported a positive relationship with severe knee OA requiring total joint replacement and MetS even in the model adjusted for relative weight. This is in line with the observation by Gowda S *et al.*, [21] who reported higher intensity of knee pain in individuals with an accumulation of MetS components.

COMMON FACTORS OF METABOLIC SYNDROME, CARDIOVASCULAR RISK, AND OSTEOARTHRITIS

The fundamental mechanisms behind the observed link between OA and cardiovascular risk remain uncertain [22], but a number of factors may account for this relationship. Primary, the two diseases have some common risk factors. Epidemiological studies have provided the endorsement for an association between OA and most of the classical cardiovascular risk factors, including hypertension [23], hypercholesterolemia [24], obesity [25], and diabetes [26]. Secondary, OA patients are less physically active because of intense pain in the joints compared with the general population, principally those with knee or hip OA. Physical inactivity is among the leading risk factors for cardiovascular diseases [27].

1. Hypertension

Hypertension is considerably increased in patients with MetS and this may be mediated inevitably by the renin-angiotensin aldosterone system, which acts on endothelial dysfunction and the pathogenesis of hypertension [28]. Hypertensive patients, without MetS at first, are at higher risk of MetS as compared with the general population without hypertension [29]. However, among 38,924 participants from the Melbourne Collaborative Cohort Study, 21% increased incidence of total hip arthroplasty for OA (HR 1.21, 95% CI 1.10-1.33) independently of age, and hypertension, [30]. In the same way, almost 1400 patients with essential arterial hypertension, 50% had decreased glucose metabolism and associated MetS, and risk for CVD in these patients was significantly increased with worse glucose tolerance [31]. OA is related to hypertension (**Figure 2**); among 1000 patients with hip OA, 55% had hypertension or CVD [32]. These results were retained in 2012 in a relevant study showing that among 352 OA patients, after adjustments for age and BMI, 60% presented hypertension [32]

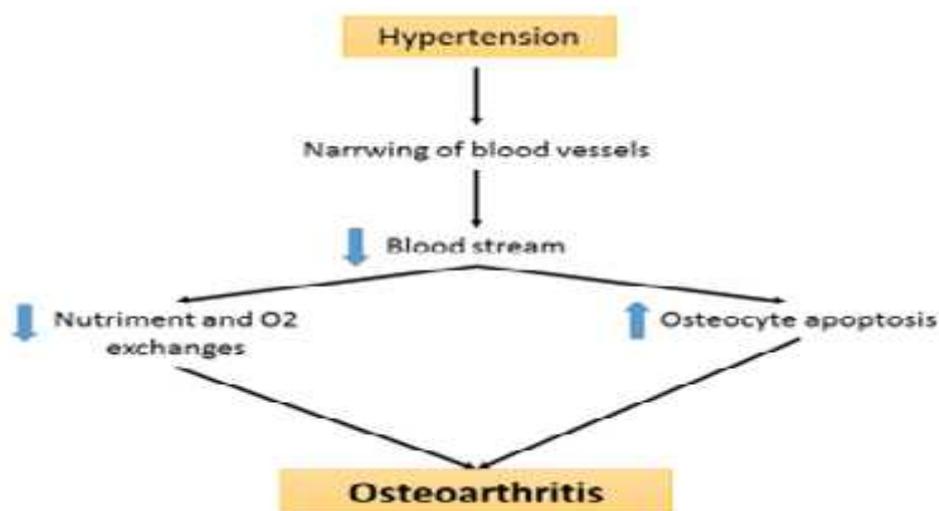


Figure 2: Role of hypertension in osteoarthritis development.

2. Obesity

Evidence is evolving suggesting that obesity plays a primary role in the pathogenesis of OA [33]. The independent effect of dietary fat on cartilage degradation is worth noting with the involvement of several markers.

a- Role of adipokines

Recent studies have shown that overweight and obesity play an important role in the development of osteoarthritis (OA) [34-36]. However, joint overload is not the only risk factor in this disease [37]. Indeed, these patients present a higher risk to develop OA than low-weight patients, even in joints not concerned by the increase in loading, as hands [38]. So, the adipose tissue could play a primary

role in the association of hand OA and obesity, by hormones release, secreting growth factors and adipokines in abnormal concentrations, contributing to cartilage or bone dysfunction [39]. Clinical studies have reported a relationship between

obesity, MetS and OA involving several adipokines, such as leptin, adiponectin, visfatin or resistin (**Figure 3**) [40]

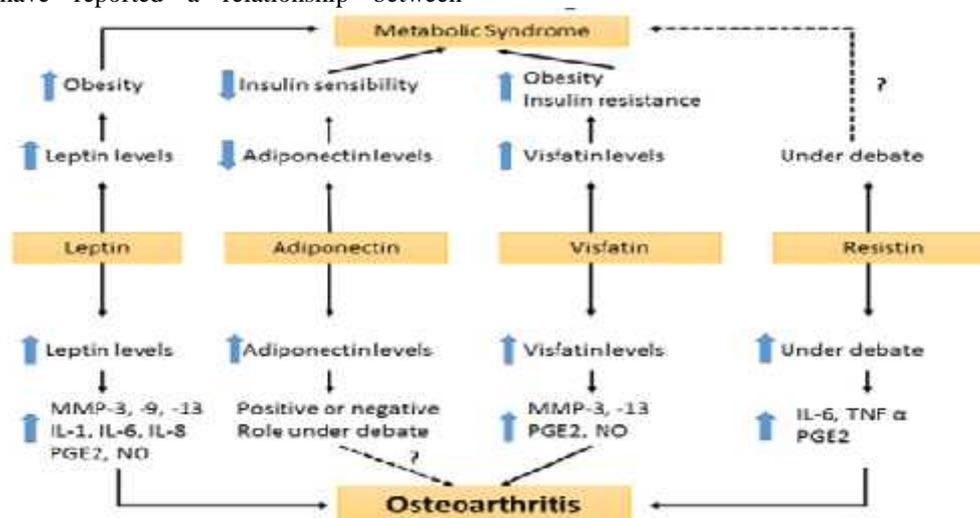


Figure 3: Role of adipokines in metabolic syndrome and osteoarthritis development.

Leptin. : Leptin is an adipokine principally secreted by adipose tissue and is known for satiety control and some anabolic functions (osteoblastic proliferation, induction of collagen synthesis etc.) [41-43]. In the InCHIANTI study [44] including 944 subjects at least 65 years old, collapsed levels of adipocytokines such as adiponectin and leptin were associated with MetS in obese and non-obese patients, regardless of insulin resistance. In addition, adiponectin, leptin, resistin and insulin rates were significantly increased and adiponectin levels significantly decreased in women with MetS [45]. Leptin could also play a significant role in the link between obesity and OA [46]. Indeed, chondrocytes can produce leptin, and leptin receptors are found in articular cartilage [47]. Also, sOb-R is a soluble leptin receptor capable of binding leptin and then inactivating it [48]. In severe OA, levels of leptin and leptin receptors were significantly increased, and in synovial fluid of obese OA patients, leptin levels were increased but sOb-R levels were significantly decreased [49]. In human OA cartilage, leptin is involved in the increase of MMP-3, -9 and -13 production [50], for inducing IL-1b and producing nitric oxide (NO), prostaglandin E2, IL-6 and IL-8 [51].

Adiponectin. : Adiponectin, released by adipocytes in adipose tissue, is known for its anti-inflammatory, anti-diabetic and anti-atherogenic properties [52]. Okamoto et al. [53] have revealed in mice that adiponectin induced an increase in insulin production in β cells, in vitro and in vivo.

Adiponectin serum levels are decreased in obese patients and increased after weight loss [54]. Furthermore, concentrations of adiponectin are inversely correlated with BMI, insulin resistance degree, visceral fat distribution and with type 2 diabetes [55, 56]. Adiponectin is not detected in healthy cartilage, but on the opposing, high levels of adiponectin are found in OA one, where adiponectin contributes to matrix remodeling by increasing PGE2 and MMP-13 production [57]. Limited studies have been conducted on chondrocytes to clarify adiponectin role in OA, and its probable favorable effects are controversial [38, 47].

Visfatin: Visfatin or Nicotinamide phosphoribosyltransferase is secreted by adipose tissue [58]. Its role in MetS is not still elucidated at the present time [59]. It has been reported that visfatin levels were higher in patients with metabolic syndrome [60]. Visfatin is known to have deleterious effects in bone and joint cartilage [61]. Indeed, elevated visfatin levels were associated with inflammation, in relation with increased MMP activity and NO production [62].

Resistin. : In humans, resistin is mainly expressed in macrophages [63]. Its role in MetS is still under debate [64]. Very few studies have been conducted to elucidate the role of resistin in OA [65]. All demonstrated that resistin induced pro-inflammatory cytokine production, as IL-6 and TNF α , and PGE2 synthesis leading to an increase in proteoglycan degradation [66].

b- Role of high fat diet

One of the most important elements of MetS is excessive calorie consumption, which leads to ectopic accumulation of lipids damaging other non-adipose organs [67]. In this sense, such lipid accumulation is detected in heart, and the deposits were larger in subjects with type 2 diabetes or impaired glucose tolerance [68]. A study has demonstrated that in mice, high fat diet induced obesity responsible for knee OA development, and for an increased inflammation which was relative to body fat [69]. However, increased weight on load-bearing joints due to obesity was not sufficient to explain the higher incidence of osteoarthritis of the knee, as regular physical activities had protective effects on the joint [70].

3. insulin resistance & type 2 diabetes

It is well known that chondrocytes custom glucose as a main substrate for energy production, cell homeostasis, and extracellular matrix (ECM) synthesis [71]. Human articular chondrocytes express several isoforms of facilitative glucose transporters—the GLUT/SLC2A transporters—among which glucose transporter-1 (GLUT-1) is mostly relevant as this transporter is regulated by anabolic and catabolic stimuli that affect cartilage synthesis and degradation [72]. Having insulin

resistance and thus type 2 diabetes may increase the risk of having more severe OA and the need for subsequent arthroplasty [73]. In a Scottish population-based cohort study, 927 men and women aged 40 to 80 years were recruited. After approximately 20 years of follow-up (from 1990 to 2010), the rate of knee arthroplasty in patients with type 2 diabetes was more than three times the rate of those without type 2 diabetes (17.7 [95% CI 9.4 to 30.2] and 5.3 [95% CI 4.1 to 6.6] per 1,000 person-years, respectively). After adjusting for age, BMI, and other OA risk factors, having type 2 diabetes was an independent predictor for knee arthroplasty, and the probability increased along with longer diabetes duration [74]. Moreover, skeletal muscle of patients with type 2 diabetes or obese patients, show small mitochondria and decreased insulin sensitivity with Reactive oxygen species (ROS). Increasing anaerobic glycolysis, oxidative phosphorylation and activation of nuclear factor-kappa B (NF-kB) through advanced glycation end-products /Receptor for advanced glycation end-products (AGE/RAGE) axis, will lead to mitochondrial dysfunction, also involved in OA and MetS pathogenesis. (Figure 4) [75]. As well, supplementation with coenzyme Q10, an important composite in the mitochondrial respiratory chain, has had beneficial effects in several components of MetS such as hypertension, diabetes, insulin resistance and obesity [76].

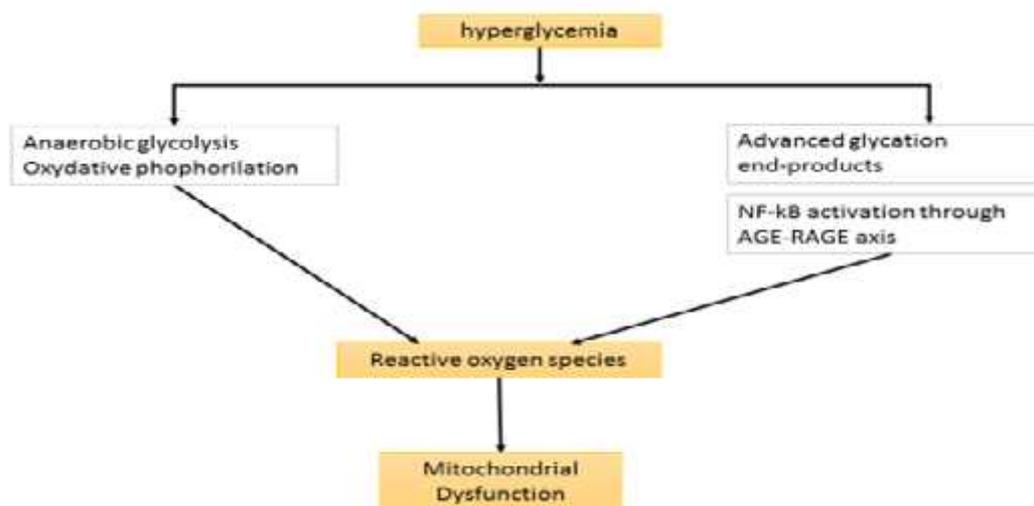


Figure 4: Link between hyperglycemia and mitochondrial dysfunction.

4. Decreased physical activity

Effects of physical activity on OA are related to the intensity and volume of activities and whether a concomitant joint injury has occurred [77]. A number of longitudinal population-based studies

have found no effect of recreational physical activities on the development of radiographic knee OA [78, 79]. Conversely, osteoarthritis can lead to a decrease in physical activity due to the functional repercussions that it can generate [80]. Reduced physical activity is a predictable independent risk

factor for metabolic syndrome and mortality [81]. Indeed, a decrease in lipoprotein lipase has been suggested to underlie the correlation between increased LDL and sedentary behavior [82]. In addition, sedentary time was related to glucose tolerance, triglyceride, and high-density lipoprotein cholesterol levels in adults [83]. The likelihood of having hypertension, diabetes, cardiovascular diseases, cancer, and combined chronic diseases are associated with sitting time, independent of other potentially confounding factors [84]. A relevant study found that sedentary behavior is associated with increased risk for all-cause mortality, which was lower in participants with non-sitting works and high levels of free time activity [85].

THERAPEUTIC IMPLICATIONS

There is little information in the literature about the effects of therapeutic management on metabolic disorders in OA patients with the metabolic syndrome and how such attitudes affect or improve metabolic components. However, it is known that weight reduction in insulin-resistant obese patients increases insulin sensitivity. Also, treatment of obesity with gastric bypass surgery improves the insulin sensitivity in a fast and prolonged time [86]. In the same sense of these results, there are observational studies that demonstrated a relationship between weight loss and improvement in many comorbid problems related to obesity after bariatric surgery [87].

The statins, intended for the treatment of dyslipidemias, are provided with anti-inflammatory effect and their effects on the amelioration of the metabolic syndrome and osteoarthritis symptoms are demonstrated [88]. If walking or running during osteoarthritis can be difficult, muscle strengthening may be more tolerable and can lead to a decrease in insulin resistance and improvement of diabetes and high blood pressure [89]. In several studies, most patients experience improvement or even resolution of diabetes as well as significant improvement of hyperlipidemia, hypertension, and OA [90-92].

CONCLUSION:

A great body of evidence indicates that OA is part of a general metabolic disorder in which various correlated metabolic and hemodynamic factors contribute to the progressive degradation of articular cartilage, which is the pathological highlight of OA. The question that arises is how to effectively and safely treat osteoarthritis with all these comorbidities. Investigation of other therapy ways like anti-adipokines therapies in OA are being developed and the currents are relevant.

AUTHOR'S CONTRIBUTION

All authors discussed the aim and the conception of this review. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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