

Osteoarthritis and Cardiovascular Diseases: is Meta-Inflammation the Missing Link?

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further investigation. In any case, if meta-inflammation is truly the pivotal link interconnecting OA, metabolic syndrome, and CVD, managing dyslipidemia, hyperglycemia, hypertension and weight in OA patients may be beneficial not only for cardiovascular reasons but also perhaps to delay OA progression.

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Key words: Osteoarthritis; Cardiovascular diseases; Meta-inflammation; Adipokines; Metabolic syndrome

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ABSTRACT

Osteoarthritis (OA) was found associated with atherosclerosis, metabolic syndrome, more cardiovascular diseases (CVD) and higher cardiovascular morbidity and mortality. However, it remains unclear whether these conditions only coexist in ageing patients presenting shared traditional cardiovascular risk factors, including age, obesity and disability-related sedentary lifestyle, or are further interconnected. Interestingly, the accumulation of metabolic syndrome components was associated with the development and progression of knee OA, supporting the concept of metabolic OA. Recent research suggests key roles of meta-inflammation, and adipokines in the pathogenesis of OA, metabolic syndrome and CVD. While leptin may be one cornerstone mediator linking obesity, metabolic syndrome, OA, and CVD, the exact role of adiponectin remains controversial in both CVD and OA as it may exert both pro-inflammatory and anti-inflammatory properties. However, the relationship between adipokines and OA as well as CVD is being uncovered and require

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting around 6 million individuals in France, mostly elderly with significant comorbidities including cardiovascular diseases (CVD)^[1]. OA of the knee and of the hip is one major cause of pain, disability and functional limitation worldwide, leading to increased morbidity and mortality^[2]. OA is characterized by degradation and loss of articular cartilage, hypertrophic bone changes with osteophyte formation, subchondral bone remodeling and inflammation of the synovial membrane. Muscles and ligaments are also altered during the OA process. Currently, OA is considered as a more complex disease than previously assumed as it involves various joints (hip, knee, hands, spine) and multiple phenotypes within a specific joint, as well as underlying pathophysiological factors including aging, injuries, genetics and obesity, to name a few. Increasing evidence suggests that cardiovascular morbidity and mortality are higher in OA populations, especially in knee and hip OA patients with severe disability^[2-4]. This disease was also found associated with atherosclerosis, metabolic syndrome and more CVD. However, it

remains unclear whether these conditions only coexist in ageing patients presenting shared traditional cardiovascular risk factors, including age, obesity and disability-related sedentary lifestyle, or are further interconnected. Nonetheless, recent research suggests key roles of low-grade systemic inflammation, also termed meta-inflammation, and adipokines in the pathogenesis of OA, metabolic syndrome and CVD.

RELATIONSHIP BETWEEN OSTEOARTHRITIS AND CARDIOVASCULAR DISEASES

Some studies based on large cohorts have shown an independent association between atherosclerosis and knee OA, as well as hand OA^[5], especially distal interphalangeal OA^[6]. In the Reykjavik study^[5], both carotid plaque severity and coronary calcification were associated with hand OA in women and in the Rotterdam study^[7], OA was associated with an increased risk of CVD among both men and women, including an increased risk of angina and heart failure. Conversely, the presence of OA may reduce the potential for rehabilitation after cardiovascular events; for instance, OA-related disability may limit improvement in ambulation level in hemiplegic patients after strokes^[8].

Over the past decades, several explanations have been proposed to understand the increased risk of CVD presented by patients with OA. First, by limiting exercise, OA-related disability is a major cause of sedentary lifestyle, which is a well-known cardiovascular risk factor. This is indeed consistent and logical that higher cardiovascular mortality in OA patients appears to be strongly related to walking disability and reduced physical activity^[2]. Interestingly, patients with moderate-severe knee and hip OA who underwent total joint replacement were recently found less likely than those who did not, to experience serious cardiovascular events^[9]. Second, the symptomatic treatment of OA, which currently consists of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), has several potential cardiovascular side effects. Cardiovascular side effects of NSAIDs (among others including gastro-intestinal and renal side effects) are clearly well established, including myocardial infarction and hypertension^[10], and current OA management guidelines recommend limiting their use to flares. Significant adverse effects of acetaminophen have also been reported including hypertension for doses up to 3 g per day^[11]. Moreover, besides these class-related adverse effects, opioids, by reducing patients' mobility^[12], may also reduce life expectancy by increasing cardiovascular risk; however, this relationship has not been clearly established.

In addition to these hypotheses, given that obesity is a well-recognized risk factor for knee OA incidence, the relationship between metabolic syndrome and OA has been largely investigated, leading to focus on the concept of metabolic OA and its potential relationship with CVD^[13].

FROM AN ASSOCIATION BETWEEN OSTEOARTHRITIS AND METABOLIC SYNDROME TO THE CONCEPT OF METABOLIC OSTEOARTHRITIS: THE ROLE OF META-INFLAMMATION

Metabolic syndrome is associated with an increased risk of CVD and its prevalence is increased in OA subjects^[14]. In the USA, it affects about 60% of OA populations compared to 23% in non-OA populations^[14,15]. However, metabolic syndrome lacks a single

definition as several definitions have been proposed^[16-19]. Insulin resistance appears to be a major criteria in all definitions, associated with others including obesity (increased waist circumference), dyslipidemia (based on elevated triglyceride levels and/or decreased HDL-cholesterol levels), and hypertension^[15]. Notably, the prevalence of metabolic syndrome is increased in OA subjects^[14]. Moreover, OA has been associated with several components of metabolic syndrome such as obesity^[20], hypertension^[21], dyslipidemia^[22,23] and type 2 diabetes^[24], alone or in combination: for example, diabetes, hypertension and obesity may be synergistic on the risk of hand OA in middle-aged individuals^[25]. Moreover, an increased risk of hand OA was also found in overweight individuals. These data have led to the current concept of a "metabolic OA" because of shared underlying pathways^[15]. However, although most of the data currently report an impact of metabolic syndrome and its components on OA pathogenesis, one should also consider how OA could in turn influence metabolic syndrome components and contribute to a vicious circle elevating the global cardiovascular risk of OA patients. In this line of thought, low-grade systemic inflammation or meta-inflammation may be the common cornerstone of OA, metabolic syndrome and atherosclerosis. The association between inflammation and cardiovascular risk is well-known and appeared as clinically consistent since the JUPITER trial^[26] in which the absolute risk of first major adverse cardiac events was greater with increasing high-sensitivity C-reactive protein (CRP) levels, a measure of systemic inflammation. Although to a lesser extent, low-grade systemic inflammation was demonstrated to play key roles in metabolic syndrome^[27] and OA^[28]. Dysregulation in pro-inflammatory cytokines and adipokines released by the adipose tissue may contribute to a certain level of systemic inflammation which may initiate and/or perpetuate the OA process, but also promote insulin resistance and other components of metabolic syndrome. Once activated, OA joint cells might in turn release inflammatory factors into the joint and the bloodstream, increasing the low-grade inflammation^[28], which can in turn induce endothelial dysfunction and CVD and reversely promote metabolic syndrome, creating a vicious circle. This concept has to be validated with *in vivo* models but this holistic vision is appealing.

Among the metabolic syndrome components, obesity is a major risk factor for knee OA incidence. While joint overload has long been considered to account for this relationship, increasing evidence suggests the critical role of metabolic factors. Obesity has been associated with a two-fold increased risk of hand OA^[29] yet, obviously, excessive mechanical stress cannot fully explain the link between obesity and OA of non-weight-bearing joints. Hence, showing an increased risk of hand OA in obese patients opened the door to a role of inflammatory mediators such as adipokines. Adipose tissue is now considered an endocrine organ that releases pro-inflammatory cytokines such as TNF-alpha, IL-1 and adipokines. Adipokines (including leptin, adiponectin, visfatin, resistin among others) are cytokines produced by adipose tissue that exert inflammatory and metabolic properties leading to chronic low-grade systemic inflammation - or meta-inflammation - in obese individuals. Adipokines are involved in glucose and lipid metabolism, haemostasis, insulin sensitivity and blood pressure regulation. Individuals with metabolic syndrome have higher levels of leptin, which are related to insulin resistance^[30] and can be decreased by weight loss. On the other hand, subjects with metabolic syndrome have also lower levels of adiponectin, which are inversely proportional to insulin resistance and can be increased with weight loss^[31]. Adiponectin may be thus considered as a protective adipokine on the cardiovascular system.

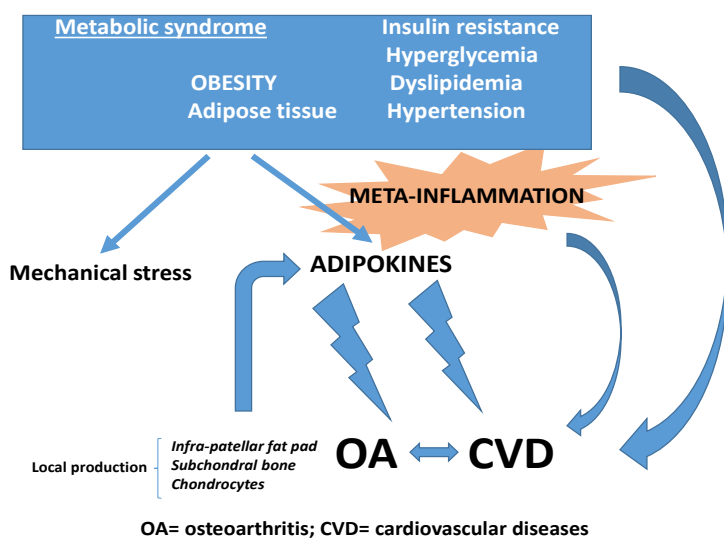
Infrapatellar fat pad (in the knee) and synovial membrane are potential sources of adipokines which could contribute to OA pathophysiology via local production of these adipokines^[32]. Moreover, as subchondral bone osteoblasts have been reported to produce leptin^[33], a local production of leptin in subchondral bone tissue may also contribute to the presence of leptin in articular cartilage. Finally, under inflammatory stimulation, adipokines are also produced by the activated chondrocyte itself.

Associations between adipokine concentrations and OA severity^[34], as well as local synovial tissue inflammation, have been described^[35]. Some studies reported a role of adipokines in knee OA structural progression^[36,37]. Leptin, adiponectin, visfatin and resistin are likely involved in OA pathogenesis with mainly pro-inflammatory activities. Adipokines and inflammatory cytokines promote the activation of the chondrocytes, which in turn contribute to the expression of metalloproteinases (MMPs) and proinflammatory cytokines, initiating a vicious circle. Leptin may promote cartilage loss^[38], and serum leptin levels have been reported to correlate with radiographic knee OA severity^[39]. Indeed, leptin has mostly catabolic properties, but a role in osteophytes development has been also suggested^[40]. It is involved in upregulating the expression of MMPs by chondrocytes, thereby contributing to collagen degradation^[41], of insulin-like growth factor 1 (IGF-1), and of transforming growth factor β (TGF- β) by osteoblasts, enhancing osteophyte formation^[42]. Serum adiponectin levels may predict radiographic progression of hand OA^[34] and increased levels of adiponectin have been reported in women suffering from erosive compared with non-erosive OA of the hands^[43]. However, some reports argue for a protective role of adiponectin in OA with an inverse correlation found between adiponectin levels and cartilage damage or OA severity^[34]. One hypothesis is that adiponectin might play a different role in OA according to the stage and severity of the disease, and also according to the affected joint (hand OA vs knee or hip OA), but its exact role remains elusive as there are limited *in vivo* models. Complex equilibrium could also explain at least by part this heterogeneity. Additionally, visfatin has recently been reported to be involved in

inflammatory pathways in OA^[44].

On the other hand, some studies also reported a pathophysiological role of adipokines in CVD. Increased levels of leptin have been associated with myocardial infarction and stroke^[45,46], independent of traditional cardiovascular risk factors. Low levels of adiponectin have been linked to hypertension^[47], and high levels to lower risk of myocardial infarction in men^[48-50], suggesting a protective vascular role of adiponectin in the general population. By contrast, in patients with coronary artery disease (CAD), elevated levels of adiponectin have been associated with higher mortality and major cardiovascular events^[51-53], while inversely associated with an increasing number of traditional cardiovascular risk factors^[52]. In patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, increased levels of adiponectin have been reported to predict all-cause and cardiovascular mortality^[54]. Consistently, total adiponectin was also associated with an increased 10-year risk of ischemic stroke among healthy middle-aged men in the PRIME study^[55] and with stroke-related mortality in acute stroke patients^[56]. As in OA, the exact role of adiponectin in CVD remains unclear; one meta-analysis of 17 prospective studies reported that higher serum adiponectin was related to an increased risk of ischemic stroke, while not related to CAD or CVD^[57].

In summary, leptin may be one cornerstone mediator linking obesity, metabolic syndrome, OA, and CVD. The exact role of adiponectin remains controversial in both CVD and OA as it may exert both pro-inflammatory and anti-inflammatory properties, probably due differential effects of its different isoforms (low molecular weight, high molecular weight, globular) on 2 different receptors (adipoR1 and adipoR2). Altogether, these data suggest a role of meta-inflammation in both OA and CVD^[28] (Figure 1). However, the relationship between adipokines and OA as well as CVD is being uncovered and require further investigation. Moreover, adipokines are a growing family of white adipose tissue-produced factor and, perhaps in the future, other adipokines will be found to have greater impact on these conditions than those known at present.



Adapted from Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint bone spine : revue du rhumatisme*. 2013;80:568-573; and Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2013;21:16-21

Figure 1 Osteoarthritis was associated with either metabolic syndrome or each of its components, supporting the concept of metabolic osteoarthritis. Meta-inflammation and adipokines may play key roles in both osteoarthritis and cardiovascular diseases.

Interestingly, the accumulation of metabolic syndrome components was associated with the development and progression of knee OA in the Japanese Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study^[58]. Knee OA progression increased with the number of metabolic syndrome components. However, among the metabolic syndrome risk factors, body mass index (BMI) was the only factor that was significantly associated with knee OA occurrence and progression. Although a recent magnetic resonance imaging (MRI) study reported similar data^[59], another showed that the accumulation of metabolic syndrome components was associated with the incidence of total knee replacement, independently of BMI^[21]. In the latter study, central obesity (increased waist circumference) (hazard ratio 1.59, 95% confidence interval 1.25-2.01) and hypertension (1.24, 1.05-1.48) were the two factors which were associated with the incidence of total knee replacement in multivariate analysis, adjusted on BMI among other factors. Altogether, these data suggest the cumulative impact of metabolic syndrome components on the risk of severe knee OA^[60].

Finally, although the link between obesity and OA is well established, the effect of weight loss on OA symptoms and progression remains unclear. Recently, weight loss via bariatric surgery was reported to result in symptomatic improvement in knee OA patients in pain, stiffness, and physical function as assessed by both the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee injury and Osteoarthritis Outcome Score (KOOS) at 12 months after surgery^[61]. Another study using a low-energy diet reported an improvement in WOMAC total score, and pain and physical function subscales. The authors concluded that a weight loss of 10% improved physical function by 28%^[62]. Interestingly, these patients, who had lost weight and whose clinical symptoms improved, also experienced a decrease in low-grade systemic inflammation. However, the impact of such weight loss on OA tissue structural changes remains unknown.

TOWARD A HOLISTIC CARDIOVASCULAR MANAGEMENT OF PATIENTS WITH OSTEOARTHRITIS BASED ON PERSONALIZED MEDICINE

Besides weight loss, it remains unknown whether controlling other metabolic syndrome components such as hypertension, diabetes and dyslipidemia might be beneficial for OA. Statins have anti-inflammatory and immuno-modulatory properties and have been expected to show disease-modifying OA drug (DMOAD) effects^[63]. However, although recently associated with lower prevalence of generalized OA^[64], statin use has so far not been associated with clinical efficacy in OA^[65,66]. Nonetheless, the Rotterdam study^[67] reported that statin use was associated with reduced incidence and progression of knee OA. Going one step further, this leads to the expectation of benefits of OA management in cardiovascular outcomes in these patients. Reduction of fat mass via modification of lifestyle or any therapeutic intervention can be expected to improve both OA progression and cardiovascular survival. A knee OA trial (www.clinicaltrials.gov; NCT01906281), which is currently recruiting, aims at assessing the impact of adipokines levels on both the inflammatory phenotype of the knee and on carotid atheromatous disease and cardiovascular risk factors. Targeting metabolic syndrome via adipokines may be a future research avenue for both OA and cardiovascular related morbi-mortality. It is suggested that inhibition of leptin expression or intra-articular injection of a leptin antagonist

could be a research avenue in DMOAD management, especially in obese patients. However, the pleiotropic function of adipokines could counteract the expected effects.

In any case, the metabolic concept of OA argues for a specific prevention management for CVD and a tight control of cardiovascular risk factors. If meta-inflammation is truly the pivotal link interconnecting OA, metabolic syndrome, and CVD, managing dyslipidemia, hyperglycemia, hypertension and weight in OA patients may be beneficial not only for cardiovascular reasons but also perhaps to delay OA progression.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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