Metabolic stress-induced joint inflammation and osteoarthritis

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Abstract

Osteoarthritis (OA) is a heterogeneous disorder with several risk factors. Among them, obesity has a major impact on both loading and non-loading joints. Mechanical overload and activity of systemic inflammatory mediators derived from adipose tissue (adipokines, free fatty acids, reactive oxygen species) provide clues to the increased incidence and prevalence of OA in obesity. Recently, research found greater OA prevalence and incidence in obese patients with cardiometabolic disturbances than "healthy" obese patients, which led to the description of a new OA phenotype - metabolic syndrome (MetS)-associated OA. Indeed, individual metabolic factors (diabetes, dyslipidemia, and hypertension) may increase the risk of obesity-induced OA. This review discusses hypotheses based on pathways specific to a metabolic factor in MetS-associated OA, such as the role of advanced glycation end products and glucose toxicity. A better understanding of these phenotypes based on risk factors will be critical for designing trials of this specific subset of OA.

Key words: Osteoarthritis, inflammation, metabolic syndrome, obesity, adipokines, oxidative stress.

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Osteoarthritis (OA) is a heterogeneous disorder with several risk factors. Among them, obesity has a major impact on both loading and non-loading joints. Mechanical overload and activity of systemic inflammatory mediators derived from adipose tissue (adipokines, free fatty acids, reactive oxygen species) provide clues to the increased incidence and prevalence of OA in obesity. Recently, research found greater OA prevalence and incidence in obese patients with cardiometabolic disturbances than "healthy" obese patients, which led to the description of a new OA phenotype - metabolic syndrome (MetS)-associated OA. Indeed, individual metabolic factors (diabetes, dyslipidemia, and hypertension) may increase the risk of obesity-induced OA. This review discusses hypotheses based on pathways specific to a metabolic factor in MetS-associated OA, such as the role of advanced glycation end products and glucose toxicity. A better understanding of these phenotypes based on risk factors will be critical for designing trials of this specific subset of OA.

Key words: Osteoarthritis, inflammation, metabolic syndrome, obesity, adipokines, oxidative stress.

Introduction

Osteoarthritis (OA) is a chronic joint disease leading to cartilage degradation that involves synovial inflammation, subchondral bone remodelling and the formation of osteophytes [1,2]. Cartilage degradation results from ruptured joint homeostasis that favors catabolic processes activated by pro-inflammatory mediators such as cytokines, lipid mediators and reactive oxygen species (ROS), which are produced as well by chondrocytes, synoviocytes and osteoblasts[3,4]. These products are responsible for altering anabolism and release of proteolytic enzymes degrading extracellular matrix.

We can differentiate OA phenotypes according to risk factors such as aging, genetics, trauma, obesity and metabolic disorders[4]. Despite eventual joint failure, the pathogenic pathways leading to this end may differ among phenotypes. This review gives epidemiological and mechanistic insights into metabolic syndrome (MetS)-associated OA, in which metabolic disorders and low-grade inflammation have a central role[5]. We discuss especially the relevant mechanisms involved in inflammation related to excess fat mass and metabolic disturbances and their implication in OA and in pain-related OA. The references for this review were limited to papers published in English in PubMed and were selected according to their relevance to the topic and after critical discussion.

Epidemiology of MetS-associated OA

As endemic diseases of the 21st century, obesity and overweight are among the most important risk factors of OA[6,7]. Such an association cannot be solely explained by excessive mechanical stress because the rate of hand OA (HOA) is two-fold higher in obese patients than lean subjects[8]. Thus, excess fat mass has a systemic harmful role in joints.

From an epidemiological perspective, assessing obesity in studies remains a crucial issue [9]. The most accurate anthropometric marker of fat mass distribution is the waist/hip ratio (WHR) [10]. Besides weight, android (or visceral) obesity is highly linked to metabolic comorbidities and cardiovascular (CV) events as compared with gynoid obesity[11, 12,13, 14]. As well, the association of fat mass distribution (i.e., WHR or impedance analysis) and OA has been studied. Hand, knee and hip OA incidence and severity are associated with fat mass distribution and especially visceral and central adiposity[15,16]. However, such associations are fewer than those with body mass index (BMI) for weight-bearing joints (i.e., knee and hip OA) [7].

Considering the harmful systemic impact of excess fat mass, the role of systemic metabolic disorders in OA has become of interest. MetS is an accumulation of metabolic disorders leading to an increased risk of stroke, type 2 diabetes mellitus and CV diseases[17,18]. Despite several definitions, all disorders include abdominal obesity, increased blood pressure, impaired glucose tolerance and lipid abnormalities such as high triglycerides level and low high-density lipoprotein cholesterol level [19,20,21]. MetS and OA share a strong association with obesity and age, and adjustment for these parameters is crucial to correctly analyze the associations between them. The risk of onset, pain and progression of knee OA as well as rate of knee and hip arthroplasty increase with the accumulation of MetS components [22,23,24]. The cumulative impact of metabolic disturbances in obese patients is also observed in HOA [25]. Whereas an association between MetS and hand OA is quite well demonstrated in the literature, this is not the case for knee OA [26]. As illustrated by Visser *et al.*, this discrepancy could be due to a critical role of overload on weight-bearing joints which could mask any underlying roles of metabolic disorders [27]. Eventually, being obese with other components of MetS confers an increased risk of OA as compared with being only obese. On the other side, OA is associated with increased prevalence of MetS, especially in the youngest population,

and some authors have suggested that a diagnosis of OA before 65 years should lead to a systematic screening for MetS [28].

Beyond the association of OA with MetS, OA could be also linked to each metabolic disorder separately. The most relevant evidence is probably for type 2 diabetes or hyperglycemia [22,29,30]. Type 2 diabetic patients have a two-fold higher need for hip and knee arthroplasty (i.e., suggesting a more severe form of OA) after adjustment for confounding factors and display more frequently knee synovitis on ultrasonography than non-diabetic OA patients [30]. Furthermore, in the Rotterdam study, for patients 55 to 62 years old, type 2 diabetes increased the risk of HOA [25] . In addition, diabetes mellitus is associated with increased pain in erosive HOA [31]. These data on knee and HOA were confirmed in other studies and in a meta-analysis that reported an overall 43% increased risk of OA in type 2 diabetic patients[32,33].

All studies of OA reported high hypertension prevalence, but the independent association remains rare after adjustment for confounding factors such as age or BMI [23,26]. However, 2 recent studies demonstrated an independent but weak association regardless of BMI[22,24]. To date, hypertension should be considered an aggravating factor for OA in subjects with obesity or other metabolic disturbances [25].

Finally, an association between dyslipidemia and OA has been reported. Hypercholesterolemia has been associated with HOA and generalized OA regardless of age, gender and BMI[34,35].

OA, cardiovascular risk and related mortality

The main concern about MetS-associated OA is its potential association with atherosclerosis and death due to CV events. Radiographic OA was found independently associated with atherosclerosis of carotid, femoral and coronary vessels [36,37,38,39]. Furthermore, atherosclerosis

122 severity increases when HOA is associated with knee or hip OA [40]. As well, OA has been
123 associated with higher age- and sex-standardized CV mortality incidence ratio than expected
124 in the general population [41]. However, data remains controversial, and no increase of
125 mortality in the OA population was also reported [42]. Some authors have suggested that OA-
126 related disability could explain the higher CV mortality raising the question of reciprocity
127 between OA and cardiometabolic diseases. Thus, OA induced disability which in turn
128 promotes obesity and its cardiometabolic comorbidities [43]. However, beyond this induced
129 disability, OA may be responsible for a low-grade inflammation state *via* a joint release of
130 inflammatory mediators into the blood stream that could in turn aggravate cardiometabolic
131 diseases such as atherosclerosis[44]. Interestingly, an independent association has recently been
132 shown between increased popliteal artery wall thickness and subsequent knee cartilage
133 degradation seen on MRI in asymptomatic and non-disabled subjects[45].
134

135 **Inflammation in MetS and its involvement in OA**

136 During the past decade, obesity and metabolic disorders have been found related to
137 systemic low-grade chronic inflammation characterized by abnormal cytokine production,
138 increased levels of acute-phase reactants and activation of a network of inflammatory
139 signalling pathways [5,46]. Fat mass is the cornerstone of this inflammation, but diabetes,
140 dyslipidemia and hypertension have specific involvement in metabolic inflammation, which
141 could be implicated in OA pathogenesis. Here, we focus on the harmful biological
142 mechanisms of fat mass and metabolic disorders in the joint, with special emphasis on
143 inflammatory factors **(Figure 1)** and possible future developments in this topic.
144

145 **a. The key mechanisms of metabolic stress**

i. Adipokines

Several novel biochemical players were identified in the last 2 decades after the discovery of leptin, in 1994, the forerunner of a large superfamily of proteins collectively called adipokines [47]. Most of these proteins, secreted systematically by white adipose tissue but also by all cells of the joint (including chondrocytes, synovial cells, adipocytes of periarticular fat tissue and bone cells) participate in the degrading process of OA in several ways: supporting chronic inflammation, increasing oxidative stress and participating in other pathologic complications associated with OA (i.e, CV and metabolic diseases) [48, 49]. Likewise, lots of studies have shown adipokines disturbances (i.e., serum level, synovial fluid level or tissular expression) as a common characteristic of chronic inflammation in OA [50]. Although we will not discuss in detail the role of individual adipokines in OA (widely discussed elsewhere [51,52]), we summarize the most salient aspects that link adipokines to OA.

With the exception of adiponectin, circulating levels of adipokines (e.g., leptin, visfatin and resistin) are elevated in patients with OA and are gender-dependent, even after adjustment for BMI, so these molecules might be responsible for the higher prevalence of OA in women than men. Most of the adipokines identified to date have pro-inflammatory activities, by inducing the synthesis of other related pro-inflammatory adipokines and cytokines, increasing the synthesis of aggrecanases and metalloproteases, of ROS levels as well as nitrogen radicals such nitric oxide (NO), and prostaglandin levels.

The most studied adipokine is undoubtedly the leptin. Mainly produced by white adipocytes (but also by joint cells), its serum level correlated to the weight and fat mass. It plays an essential role in homeostasis (thermogenesis, food intake, lipolysis, and gluconeogenesis). Its synovial expression correlates also with BMI [53] and with OA prevalence and severity [54]. In vitro, leptin induces the production of cytokines by synoviocytes (IL-6 and IL-8)[55,56],

chondrocytes (IL-1β, MMP-9 and MMP-13)[54] and cartilage explants (IL-6, IL-8, PGE2)[57]. Leptin levels in chondrocytes could be increased by epigenetic regulations such as DNA methylation of leptin which is decreased in OA chondrocytes. Indeed, DNA methylation of leptin promoter gene leads to an upregulation of leptin expression which in turns increased its catabolic activity through MMP-13 production[58]. However, some anabolic aspects of leptin have been reported. For instance, leptin can induce insulin growth factor 1 (IGF-1) and transforming growth factor-beta in cartilage, perhaps protecting cartilage against osteoarthritic degeneration or participating in osteophyte development [53].

As well, visfatin could increase the rate of IL-6 and MCP-1 by chondrocytes[59] and decrease the pro-anabolic effect of IGF-1 [60]. Also known as nicotinamide phosphoribosyltransferase (NAMPT) , visfatin has been shown to modulate other enzyme expression such as sirtuin 1 (Sirt1), an histone deacetylase, which is an epigenetic regulator[61]. Sitrt1 has been involved in cartilage biology and OA pathogenesis but also in type II diabetes and other aging-related diseases and could be another link between OA and MetS [62,63].

Finally, even adiponectin, in contrast to its protective role in cardiovascular diseases and obesity, shows pro-inflammatory activities like the production of NO synthase 2, IL-6 and MCP-1, triggering matrix degradation by inducing MMP-3 and MMP-9 expression in chondrocytes[64,65].

Eventually, despite the possible protective role of leptin, there is a general consensus that adipokines exert a catabolic and pro-inflammatory effect on cartilage. Only 20 years after the discovery of leptin, the first identified, adipokines are considered to play multiple important biological roles, and the increasing research effort in this area is gradually revealing the intricate adipokine-mediated interplay among white adipose tissue, metabolic disorders and inflammatory degenerative joint disorders such as OA.

Although many issues remain unclear, several possible avenues that these works have opened can be sketched. In particular, from a metabolic point of view, one should remember that the primary causes of obesity-related hyperproduction of detrimental adipokines are generally nutritional and lifestyle factors such as overeating and physical inactivity and that front-line treatment essentially involves the correction of these factors. Knowledge of the actions of the newer adipokines is still too incomplete to generate well-supported therapeutic hypotheses. However, by the rate at which their roles are being clarified, they will soon be central to pharmacotherapeutic approaches to obesity-induced inflammatory diseases. For example, in light of the pro-inflammatory role of visfatin on joint cells, this adipokine has been therapeutically blocked in a murine model of OA with efficacy [59,66].

ii. Oxidative stress

Oxidative stress is a cellular response in which the synthesis of intracellular ROS goes beyond the ability of the cell to neutralize the molecules, thus leading to final cellular damage and in some cases cell death [67]. Oxidative stress has been involved in several pathophysiological conditions including aging, cancer, and CV diseases as well as metabolic diseases and obesity [68,69]. ROS and or nitrogen radicals (nitric oxide [NO]) are important players in the inflammatory process occurring in OA [70,71]. Actually, almost all the OA joint cells, including chondrocytes, synovial fibroblasts and adipocytes, can produce large amounts of ROS and NO in response to biomechanical or biochemical stimuli. In this regard, most of biomechanical-induced ROS are likely produced by mitochondria, and recent evidence suggests that mitochondrial dysfunction may contribute to the development of OA [72]. Indeed, *in vitro* data showed that in certain biomechanical conditions, mitochondria can release large amounts of ROS in cartilage, thus leading to cell death (REF A DEMANDER préciser les certain biomechanical conditions) . ROS are thought to participate in several processes of the inflammatory response in OA in particular by triggering specific intracellular pathways such

those elicited by nuclear factor kappa B (NF-kB), hypoxia-inducible factor 1 alpha (HIF-1α) or activating protein 1 (AP-1) [73]. Although high levels of ROS are clearly detrimental to joint cell populations, some evidence suggests that cellular energy supply in chondrocytes relies on the availability of mitochondrial ROS to produce ATP, which suggests that physiological or sublethal levels of these molecules may have implications in cartilage biology. Indeed, *in vivo* studies suggest that physical exercise (at both extremes: high-intensity or sedentary activity) is related to high levels of ROS and therefore increased risk of cartilage lesions. In contrast, moderate physical exercise, with low ROS levels, may favour healthy cartilage. Thus, a low adequate level of ROS might have a cartilage-protective role by eliciting increased matrix synthesis and/or activating specific protective pathways that finally lead to inflammation suppression or control, with imbalanced ROS synthesis and accumulation leading to degenerative effects [74]. Of note, several adipokines, but also high glucose level, may be considered the link between oxidative stress and the mechanisms of obesity-associated metabolic syndrome[75]. Actually, leptin, adiponectin and lipocalin-2 can induce accumulation of NO and activation of NO synthase type 2 in chondrocytes and other joint cells [76].

iii. Free fatty acids and the high-fat diet

The increased dietary fat content that characterizes the diet of industrialized countries in the last 30 to 40 years clearly contributes to both obesity and the metabolic dysfunction associated with type 2 diabetes. Nutritional aspects, particularly fat intake, are involved in the development of OA-associated obesity. Dietary polyunsaturated fatty acids (PUFAs) of both the n-3 and the n-6 series are essential for human health but may have opposite effects on inflammatory responses: n-6 PUFAs likely give rise to inflammatory eicosanoids, whereas n-3 PUFAs are generally anti-inflammatory. High levels of fatty acids are found in joint tissues in OA and are associated with severe tissular lesions [77]. *In vitro*, palmitate, a saturated free fatty acid (FFA) induced pro-inflammatory cytokines production by chondrocytes and

synoviocytes via the Toll-like Receptor -4 (TLR-4) and has pro-apoptotic effects[78]. In animal models, a high-fat diet accelerated the progression of OA; n-3 PUFAs limited disease severity, thus corroborating their anti-inflammatory and anti-degradative effect on chondrocytes, and n-6 PUFAs had no detrimental effect[79,80,81]. A diet containing significant levels of eicosapentaenoic acids and docosahexaenoic acids may reduce joint stiffness and tenderness in arthritic patients [82,83].

iv. PPAR gamma and autophagy

Peroxisome proliferator-activated receptors (PPARs) are lipid-activated transcription factor of the nuclear receptor superfamily and play a major role in homeostasis. Among them, PPAR gamma (PPARγ) is the pivotal transcription factor leading to adipogenesis and increasing sensitivity to insulin explaining why PPARγ agonists such as glitazones take place in the therapeutic armentorium against diabetes mellitus[84]. Interestingly, the role of PPARγ has been studied in OA too. Its expression seems to be decreases in the OA joint tissues[85]. *In vitro*, PPARγ agonists are protective by decreasing the production of pro-inflammatory and catabolic mediators by chondrocytes and synoviocytes[86,87,88]. As well, PPARγ inducible-cartilage knockout mice develop accelerated OA with increased cartilage degradation and decreased autophagy responsible for an impairment of cartilage homeostasis[89]. Interestingly, loss of autophagy is also observed in obesity and other metabolic diseases[90]. All these data suggest that PPARγ plays a crucial role in maintaining homeostasis of the joint and could be one of the mechanisms linking OA to obesity and other metabolic comorbidities.

v. Advanced glycation endproducts

Advanced glycation endproducts (AGEs) result from the non-enzymatic and posttranslational addition of reduced sugars on proteins or apolipoproteins. Because of their multiple ways of formation and their different half-lives, they constitute a heterogeneous group of chemical

species. The most famous AGE is glycated hemoglobin A (HbA1c), used in clinical practice to monitor diabetes. Pentosidine and N-epsilon-carboxy methyllysine, because of their antigenic properties, have also been studied[91]. The molecules accumulate in tissues during aging, but their production is also highly related to glycemia [92] . These AGEs are involved in diabetes onset and complications [93]. Some steps of AGE formation depend on PUFA peroxidation and oxidative stress, so they are also associated with obesity [94,95].

First, accumulation of extracellular AGEs exerts a harmful role by modifying the mechanical properties of the tissue. Indeed, their accumulation in the collagen network increases the stiffness and fragility of cartilage and bone[96,97]. AGEs accumulate in retina, kidney, vessels or skin in diabetic patients, but also in diabetic OA joint tissues[98,99 ,100,101]. OA patients show a higher rate of pentosidine in the subchondral bone than do non-diabetic patients[102]. They also act by triggering a receptor-dependent pathway, involving the receptor of AGE (RAGE). *In vitro* studies demonstrate that binding of AGEs on RAGE activates NF-kB and p38 mitogen-activated protein kinase signaling pathways leading to the production of pro-inflammatory cytokines, proteolytic enzymes and ROS in chondrocytes and synoviocytes [103, 104, 105, 106, 107, 108]. AGEs also induce chondrocyte apoptosis[109]. A potential limitation of these receptor-related studies could be the use of a non-specific mixture of AGEs like glycated albumin which may not be relevant to the glycated proteins expected in cartilage such as type II collagen. .

Hyperglycemia and insulin resistance

Diabetes mellitus-related OA belongs to the MetS-associated OA phenotype. Hyperglycemia and insulin resistance may explain the relationship between diabetes and OA. In the streptozotocin-induced diabetic rat model, characterized by a strong hyperglycemia due to chemical destruction of pancreatic β-cells, type 2 collagen and proteoglycan content was

spontaneously decreased in cartilage, which suggests a noxious role of hyperglycemia in cartilage [111]. Glucose incorporation in chondrocytes is mediated by glucose transporters (GLUTs). The main GLUTs expressed by chondrocytes are GLUT-1, -3 and -9 [112]. GLUT-3 expression is constitutive, whereas GLUT-1 and -9 are inducible by cytokines (e.g., interleukin 1β [IL-1β]) and glucose concentration, thereby allowing chondrocytes to adapt glucose incorporation depending on the extracellular concentration[113]. *In vitro*, human OA chondrocytes lose this ability, which leads to increased incorporation in a high-glucose environment[75]. Once integrated in the cell, glucose is metabolized via different pathways such as the glycolysis and polyol pathways but also the protein kinase C and pentose/hexosamine pathways, all known to result in ROS production in other cell types and could explain why high glucose concentration increases ROS formation in chondrocytes[114,115].

Insulin resistance may also be implicated. Insulin levels are higher in overweight patients with OA than without OA [116]. Chondrocytes and synoviocytes are insulin-sensitive cells because they express the insulin receptor. Recently, synoviocytes in diabetic patients were found to be insulin-resistant [117]. Furthermore, with high glucose concentrations, chondrocytes lose their responsiveness to IGF-1. Insulin is an anabolic hormone inducing matrix component synthesis, so insulin resistance may limit anabolic processes of cartilage[118].

vi. Vascular involvement

Oxygenation and nutrients arrive at avascular cartilage from synovial fluid and subchondral bone. Since OA is associated with hypertension and atherosclerosis, compromised vascularization of the subchondral bone may be responsible for OA exacerbation [119,120]. Two phenomena can induce impaired blood flow: reduced arterial inflow (such as ischemia) and obstruction of venous outflow. Early bone-marrow lesions observed on MRI in OA could correspond to ischemic lesions but, to date, no histological proof is

available. In a female rat model, inducing thrombosis of subchondral bone in a temporo-mandibular joint led to OA, which suggested the role of vascularization in joint homeostasis [121]. Furthermore, angiogenesis, to counteract ischemia, is involved in OA pathogenesis. Indeed, abnormal vascular channels occur in calcified cartilage during OA, which enhances the permeability to inflammatory mediators[122]. However, a specific relation with hypertension or atherosclerosis needs further investigation.

a. Other paths?

i. Gut microbiota

Another systemic connection between MetS, obesity and OA could be gut microbiota [123]. The absorption of endotoxins across the intestinal tract seems highly implicated in systemic low-grade inflammation related to obesity and metabolic disorders[124]. Modification of dietary intake, such as a high-fat diet, affects gut microbiota, thereby increasing the inflammatory state, regardless of weight loss [125]. For example, the relation between a high-fat diet and OA previously described suggests the effect of microbiota on OA; indeed, a high-fat diet markedly affects gut microbiota by modifying the bacterial composition and functional response [126]. Furthermore, bacterial lipopolysaccharide strongly induces pro-inflammatory chondrocytes *via* TLR-4, for a potential mechanism to explain how endotoxinaemia may favor OA[127]. Data are limited in this field, and the role of microbiota in OA onset and inflammation-related OA in the MetS-associated OA phenotype need further investigation.

ii. Genetics

Lifestyle and environment seem key factors in the onset and progression of metabolic diseases, but obesity and type 2 diabetes are also subject to genetic susceptibility, and risk of OA onset in obese subjects could be affected by common genetic factors[128,129]. Since 2007, the single nucleotide polymorphism in the fat mass and obesity-associated (FTO) gene has

been associated with risk of excess fat mass and obesity in several populations, so investigating this gene in OA could be of interest[130]. A genome-wide study demonstrated that knee and hip OA were associated with the FTO polymorphism, but this association was mediated by BMI [131,132]. Interestingly, obesity, metabolic disorders and OA are associated with IL-6 or leptin polymorphisms, which could be involved in MetS-associated OA pathogenesis[133,134,135].

Chronic low-grade inflammation: consequence or cause of pathological aging?

A common hypothesis is that metabolic disturbances precede and induce systemic chronic inflammation, which causes joint deterioration. Another theory has raised the concept of "inflammaging" (for inflammation and aging), with inflammation as the direct consequence of aging. Aging is associated with cellular senescence, immunosenescence, debris accumulation and harmful products such as ROS and also microbiota change (i.e., endotoxin accumulation) leading to exacerbated and sustained pro-inflammatory processes [136]. All these factors are also involved in other age-related diseases (e.g., cancer, atherosclerosis, Alzheimer disease). Thus, inflammaging could be the common biological background of all these age-related diseases. However, the phenomenon is probably more complex because inflammation, whatever its cause, is also responsible for accelerated aging.

The role of inflammation in OA pain: is MedS OA the most painful phenotype?

Pain during OA is a complex phenomenon involving subchondral bone, synovium and articular capsule because cartilage is not innervated. Furthermore, pain in the setting of MetS-associated OA is somewhat peculiar: BMI as well as MetS is associated with increased OA pain intensity in all localisations (knee, hip and hand) [26,137]. Moreover, mechanical load and increased IL-1β level as well as adipokine levels increase nerve growth factor released by chondrocytes, an important mediator of pain related to OA[138]. Because

dietary intake could modify the inflammatory state, it may be also implicated in OA-related pain [139]. However, depression, frequent in the obese population, is also associated with increased serum IL-6 and tumor necrosis factor α levels. These pro-inflammatory cytokines may decrease serotonin levels via tryptophan depletion and sustained hypothalamo-pituitary-adrenocortical stimulation, which leads to cortisol resistance in depression pathophysiology [140]. Finally, a complex vicious circle results because pain induces disability, which in turn promotes obesity (**Figure 2**). All these data are therefore to be considered in the development of new therapeutic strategies of MetS-associated OA (**Table 1**).

Conclusions

OA is now classified according to several phenotypes based on risk factors. Here, we describe the relevant mechanisms implicated in one of these phenotypes, MetS-associated OA, with chronic inflammation as the cornerstone. Through multiple pathogenic pathways (i.e., adipokines, AGEs, oxidative stress) related to fat mass and metabolic disturbances, systemic inflammation leads to joint degradation. The concept allows for better understanding how loss of weight or modification of dietary intake may be beneficial for the joint in addition to decreasing mechanical load. Beyond modifying the excess fat mass, better control of each metabolic disturbance should slow the onset and progression of OA and should be considered in the therapeutic objectives of MetS-associated OA. Despite no strong conclusions about statins because of contradictory results, pioneering studies for OA treatment have recently been published [141,142,143]. We can consider new therapeutic strategies targeted to specific mechanisms such as oxidative stress or AGE production[144]. Other OA phenotypes such as post-traumatic and aging OA need investigation, and because OA seems to affect the onset of other chronic diseases, the impact on metabolic disturbances needs to be investigated[145]. The description of this new MetS-associated OA phenotype should lead to designing clinical trials in this specific subset of OA patients.

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All authors made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted

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Research agenda

- Link between hypertension and osteoarthritis
- Effect of antidiabetic drugs in OA
- Effect of antihypertensive drugs in OA
- Investigation of anti-adipokines therapies in OA
- Investigation of PPAR gamma agonists in OA
- Is OA an independent risk factor for metabolic and cardio-vascular diseases?
- AGEs in type 2 diabetes-related OA pathophysiology and "anti-AGE" therapies in OA
- Insulin resistance of joint cells in type 2 diabetes and obesity
- Gut microbiota in OA and especially in obese patients
- Pain mediators and OA in the metabolic OA phenotype

Figure legends:

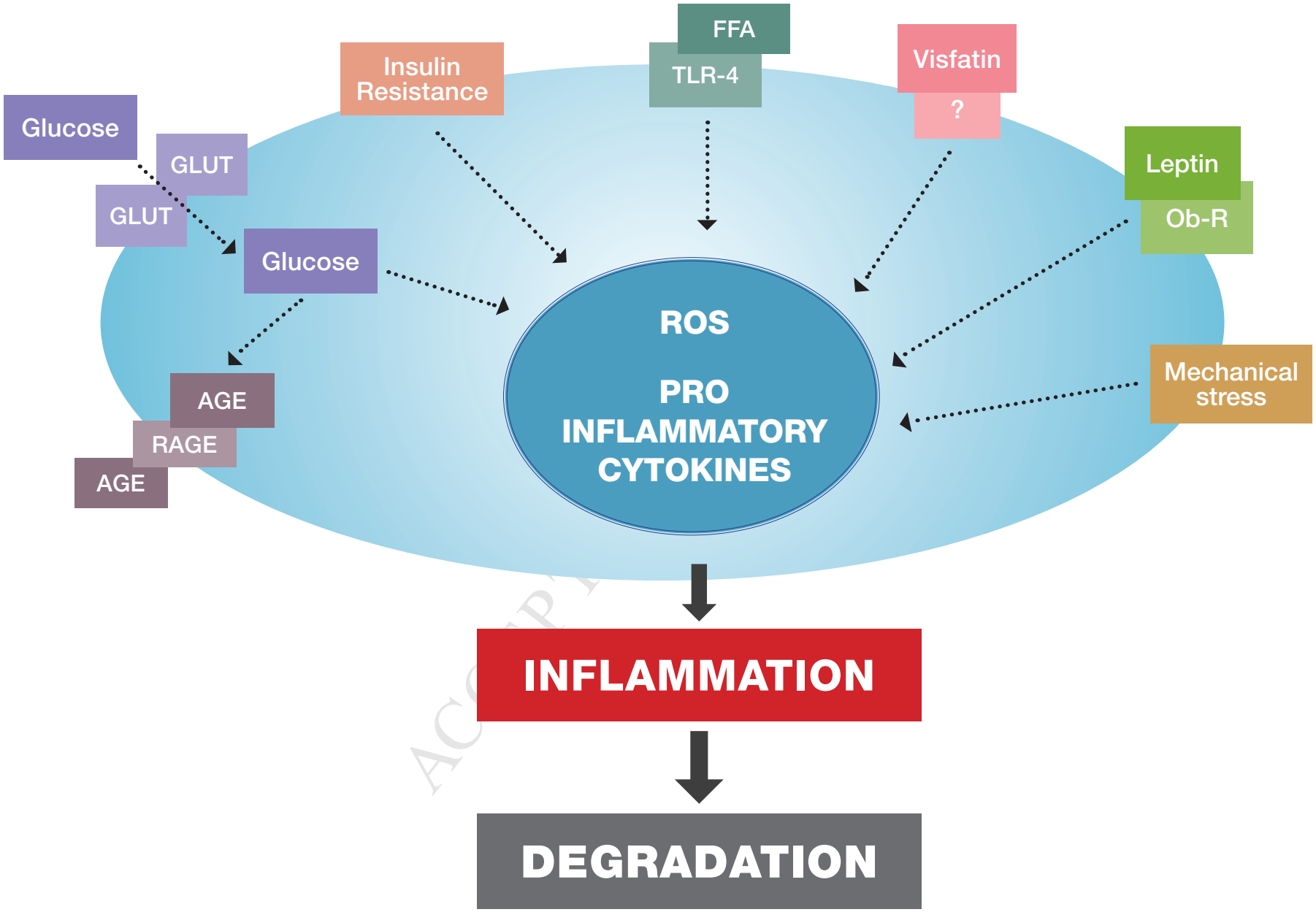
Figure 1: Major metabolic stress inducing inflammation in chondrocytes.

We hypothesize that, in the metabolic OA phenotype, several pathways and metabolic stress factors are involved: i) obesity activates chondrocytes through mechanical signals but also through adipokines (i.e. leptin and visfatin) ii) insulin resistance limits pro-anabolic effects of insulin and enhances free fatty acid (FFA) production which is also responsible for chondrocyte activation via TLR-4 iii) at end-stage, diabetes mellitus induces reactive oxygen species (ROS) and cytokine production triggered by hyperglycemia and advanced glycation end products (AGE). All these stresses induce ROS and pro-inflammatory cytokines which both play a major role in joint inflammation, proteolytic enzymes production and subsequent cartilage degradation.

AGE: advanced glycation end products; RAGE : receptor for AGE; GLUT: glucose transporter; FFA: free fatty acid; Ob-R: receptor for leptin; TLR-4: toll-like receptor-4.

Figure 2: How chronic inflammation related to obesity and metabolic syndrome could lead to osteoarthritis pain; the vicious circle of pain.

Table 1: Research agenda


FFA
TLR-4
Insulin Resistance
Visfatin
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Glucose
GLUT
GLUT
Glucose
Leptin
Ob-R
ROS
PRO INFLAMMATORY CYTOKINES
Mechanical stress
AGE
RAGE
AGE
INFLAMMATION
DEGRADATION