Osteoarthritis and type 2 diabetes mellitus: what are the links?

Alice Courties, Jérémie Sellam

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Alice Courties[a,b], Jérémie Sellam[a,b].

[a]Rheumatology Department, Saint-Antoine Hospital, Assistance Publique–Hôpitaux de Paris

(AP-HP), DHU i2B, Paris, France

[b]Inserm UMR S_938, Sorbonne Universités Univ Paris 06, DHU i2B, Paris, France

Correspondence to :

Prof. Jérémie Sellam
Hôpital Saint-Antoine
Service de Rhumatologie
184 rue du faubourg Saint-Antoine
75012 Paris
Tel: + 33 1 49 28 25 20
Fax: + 33 149 28 25 13
Jeremie.sellam@aphp.fr

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Abstract

Osteoarthritis (OA) is the most frequent joint disorder and one of the leading cause of disability. During a long time, it was considered as the consequence of aging and mechanical stress on cartilage. Recent advances in the knowledge of OA have highlighted that it is a whole joint disease with early modifications of synovium and subchondral bone but also that it is associated with obesity and metabolic syndrome through systemic mechanisms. In the past year, type 2 diabetes has been described in two meta-analyzes as an independent risk factor for OA. *In vivo* models of diabetes corroborated epidemiological studies. Indeed, diabetic rodents display a spontaneous and a more severe experimental OA than their non-diabetic counterparts, which can be partially prevented by diabetes treatment (insulin, pioglitazone). The negative impact of diabetes on joints could be explain by the induction of oxidative stress and pro-inflammatory cytokines but also by advanced age products accumulation in joint tissues exposed to chronic high glucose concentration. Insulin resistance might also impair joint tissue because of a local insulin resistance of diabetic synovial membrane but also by the systemic low grade inflammation state related to obesity and insulin resistant state.

Keywords: osteoarthritis, metabolic syndrome, diabetes mellitus, oxidative stress, glucose

1. Introduction

Osteoarthritis (OA) is the most frequent musculoskeletal disease leading to joint pain, stiffness and disability. Worldwide estimates are that 9.6% of men and 18.0% of women aged ≥60 years have symptomatic OA. It is expected to be the fourth cause of disability by 2020 and so it represents a public health challenge of the future years [1]. OA is a chronic joint disease targeting particularly lumbar spine, knee, hand and hip joints. It is characterized by a loss of cartilage associated with bone hypertrophy and sclerosis and with synovial inflammation. During a long time, ageing and mechanical stress were considered as the single risk factors. However, recent advances in the knowledge of OA has highlighted the involvement of other risk factors such as type 2 diabetes or dyslipidemia, currently included in the so-called metabolic syndrome (MetS), defining thus a new phenotype called metabolic OA, wider than obesity-related OA [2]. For some, obesity and metabolic syndrome increased the risk of knee and hip OA because of the related mechanical impact of overweight on those weight-bearing joints[3–5]. But, surprisingly, obesity or metabolic syndrome also increased the risk of hand OA [6–8] and, occurrence of metabolic disturbances associated with obesity aggravates the association between obesity and OA. Such new data opened to the idea that metabolic diseases could have a systemic influence on joint tissues, similarly to what happens for atherosclerosis. In this context, two recent meta-analyzes reported that type 2 diabetes was an OA risk factor, whatever the localization[9,10]. Moreover, during these last years, several *in vitro* and *in vivo* studies were published to decipher the influence of hyperglycemia and insulin resistance on joint tissues. High glucose exposure displays a local toxicity on joint tissue, increasing locally oxidative stress, cytokines, proteolytic enzymes production and advanced end glycation products (AGE) accumulation[11–13]. Furthermore, human synovial tissues from diabetic patients are insulin resistant and so potentially less responsive to the anti-inflammatory and anti-degradative effect of insulin[14]. Finally, in the field of metabolic

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syndrome, visceral obesity and insulin resistance are associated with a systemic low-grade inflammation state, which may also participate to OA development. In this review, we will develop the available evidence of an association between OA and diabetes, that could thus delineate sub-phenotype within the metabolic OA: the diabetes-induced OA.

2. OA phenotypes classification

Main OA risk factors are age, joint traumatism/injury, family history of OA corresponding to the genetic component, obesity and metabolic syndrome. They subsequently defined different phenotypes which are: OA related to ageing, post-traumatic OA, genetic OA and metabolic OA (**Table 1**) [2]. This classification is based on the fact that OA affects different population depending on the risk factors involved which, intuitively, may imply also different pathogenic pathways and, in the future, specific therapeutic management.

3. Pathophysiology of OA: not only a cartilage disease but a "whole-joint" disease

OA is a complex joint disease, affecting all joint tissues that are articular cartilage, subchondral bone and synovium. During a long time, it was considered as a "degenerative" and mechanical disease but OA is associated with a local and systemic low-grade inflammation state. The different risk factors are responsible for biological and/or mechanical aggressions, which influence the homeostasis of all tissues and cells.

Articular cartilage is composed of and extracellular matrix that contains a single type of cell: the chondrocyte - which is responsible for the synthesis of this extracellular matrix (anabolism). This matrix is mainly composed of water, proteoglycans and type 2 collagen. There is a low-grade turnover of components of this matrix due to catabolic activity of chondrocytes. One of the roles of cartilage is to absorb the mechanical stresses between 2 mobile bone surfaces. In OA, a biological or mechanical stress is followed by an increase of pro-inflammatory mediators production by chondrocytes (*i.e.*, chondrocyte activation) but

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also by synoviocytes and osteoblasts, in each respective tissue. Among those pro-inflammatory mediators, cytokines (interleukin-1 β (IL-1β), IL-6, Il-17, Tumor necrosis factor-α (TNF- α)), radical oxygen species (ROS), advanced glycation end products (AGE) and bio-active lipids (prostaglandine E_2 (PGE_2)) are the most represented. This local inflammation induces an increase production of the proteolytic enzymes (metalloproteinase (MMP) and aggrecanases) by all 3 cells (i.e., chondrocytes, synoviocytes and osteoblasts) that will digest the cartilage matrix. In addition, chondrocytes dedifferentiate and die by apoptosis, leading to a synthesis of an altered matrix (type 10 instead of type 2 collagen) and to a loss of matrix synthesis respectively. While physiologically cartilage is non-vascularized, neo-angiogenesis is promoted in the deep layer of cartilage facilitating the passage of soluble mediators between subchondral bone and cartilage by specific pro-angiogenic mediators and leads to the development of vascular channel. In addition to cartilage disruption, subchondral bone undergoes remodeling with condensation and overgrowth (osteophytes) under the influence of growth factors such as insulin-growth factor and transforming growth factor. Finally, synovium inflammation occurs in adjacent area of cartilage degradation due to cartilage debris. Infiltration of inflammatory cells such as lymphocytes and macrophages are responsible for overproduction of cytokines, oxidative stress and proteolytic enzymes which in turn aggravate cartilage degradation creating a vicious circle [15].

4. Type 2 diabetes and OA: epidemiological association

Association between diabetes mellitus and OA was first described in 1961[16]. Since then, considering all the published literature, the independent association between OA and type 2 diabetes is quite convincing. The 1st large study with an accurate method exploring this association was from Schett *et al.* in 2007[17]. They demonstrated in a large population based-study that patients with type 2 diabetes had 2 times higher rates of knee or hip arthroplasty for OA- as a maker of OA severity- than non-diabetics. Beyond the number of

subjects included (942 subjects) and the longitudinal follow-up of 20 years, the strength of this study was the numbers of confounders included such as age, low-grade inflammation (us-CRP), body mass index (BMI) and other metabolic diseases, physical activity score or prior joint replacement. They also found that the risk of arthroplasty was correlated with type 2 disease duration and that type 2 diabetic patients had more inflammation of synovium (*i.e.*, synovitis) and more pain. *Eymard et al.* found concordant results since they reported that type 2 diabetes patients had a higher rate of knee OA progression than non-diabetics on a 3 years follow up[18]. The association between OA and type 2 diabetes is also true for hand, especially for young patients. Indeed, 55-62 years old patients with type 2 diabetes had a 2 times higher rate of hand OA than non-diabetics and it seems to be associated with pain in erosive hand OA (i.e., a very destructive hand OA subtype) [6,19].

Some other studies have focused on the glycaemia value and OA. During the 90's, Cimmino *et al.* found that the crude fasting plasma glucose level was higher in OA patients compared to non OA patients[20] and such a high level could be predictive of OA knee features using magnetic resonance imagery 10 years later[21]. However, a recent cross-sectional study failed to find an association between Homeostasis Model Assessment of insulin resistance (HOMA-IR), HbA1c or insulin levels and OA in patients without glucose-lowering drugs [22].

All these studies were recently included in two independent meta-analyzes. The first from our group found a greater risk of OA in type 2 diabetic with an odds ratio (OR) = 1.46 (95% confidence interval (CI) :1.08 to 1.96) and a higher risk of diabetes in OA population with OR=1.41 (%95CI: 1.21 to 1.65)[9]. However, studies included did not all adjusted for the weight, which may be a confounding factor. In the 12 studies adjusting for weight, 7 were positive meaning that weight could not explain exclusively its association. As well, Williams

et al., found that the risk of OA in diabetic patients was higher compared to non-diabetic with an OR: 1.25 (95% CI: 1.05 to 1.46) including only studies controlling for weight or BMI [10].

Those 2 meta-analyzes has been yet counterbalanced by two recent negative study. The first study from Nielen *et al*., explored the risk of total joint replacement (TJR) in a case-control studies (type 1 and type 2 diabetes *versus* non diabetic subjects) and found no association between diabetes and TJR. This may be biased to the fact that practitioners preferred the conservative treatment in diabetic patients because of their frailty which was illustrated by the fact that the risk of TJR decreased with increasing HbA1c levels [23]. The 2nd study from Frey *et al.,* did not find any association between type 2 diabetes, its duration or severity and incident hand OA[24]. However, it was based on a UK database with uncertainty of diagnoses and may have underestimated the number of OA and/or diabetic patients.

Surprisingly, the only data available on the specific association between type 1 diabetes and OA comes from an unpublished data of the 2016 *Osteoarthritis research Society International Congress*. This study reported no difference of radiographic hand OA prevalence between type 1 diabetes and age and sex-matched controls. However, patient with less controlled type 1 diabetes displayed higher hand pain[25]. The study of the specific association between type 1 diabetes and OA is of interest because it could evaluate the influence of diabetes in a population with hyperglycemia but without insulin resistance. Such a result needs to be further confirmed in other studies.

5. Type 2 diabetes and OA: pathological association

Type 2 diabetes has pathogenic effect through 2 major pathways. First, as for other organs, chronic hyperglycemia induces oxidative stress, overproduction of pro-inflammatory cytokines and AGEs in joint tissues but it also reduced the stem cells potential of

differentiation. Second, the insulin resistance could play a role locally but also through the systemic low-grade inflammation state. We will discuss the effect of diabetes and glucose on the joint tissues and cells.

5.1 Diabetes and cartilage :

The major advances in the knowledge of the role of high glucose concentration on joint tissues involve mainly chondrocytes and cartilage. Cartilage is a non-vascularized and non-innervated tissue and receives nutrients from its connection with subchondral bone and synovial fluid through joint cavity. However, chondrocytes are glycolytic cells and express glucose transporters (GLUT), especially GLUT-1, GLUT-3 and GLUT-9[26] and are able to sense the glucose concentration in the media and to adapt the GLUT expression and membrane incorporation. Under glucose deprivation, normal chondrocytes increased GLUT-1 expression and membrane incorporation whereas they decreased under high glucose condition. This capacity of normal chondrocytes to adapt themselves to the local glucose level is lost during OA: this is responsible for a high glucose uptake and potential glucose toxicity [27]. Furthermore, GLUT expression is under the control of a number factors. Their expressions raised under pro-inflammatory stimuli as TNF-alpha and IL-1β through phosphokinase C, but also under metabolic and hypoxic factors [28] which are involved and increased during OA.

The 1st negative impact of local high glucose concentration is the reduction of the chondrogenic differentiation of mesenchymal [29] , muscle [30] and adipose-derived stem [31] cells which may further decrease the potential of regeneration of cartilage that is already decreased in OA. As well, adipose derived stem cells from diabetic patient had a spontaneous less chondrogenic differentiation potential than non-diabetic adipose stem cells.

Furthermore, chronic high glucose environment has a noxious effect on chondrocytes metabolism. Human diabetic cartilages produce more IL-6 and PGE_2 under IL1-beta stimulation than non-diabetic cartilage and displayed reduce autophagy and heme oxygenase expression, 2 anti-oxidant pathways[11,32,33]. As well, high glucose concentration sensitizes murine chondrocytes to IL-1 beta inducing a higher production of IL-6 and PGE_2 through oxidative stress compare to IL-1 beta in a normal glucose concentration. Aldose reductase and the polyol pathway seem also involved in this higher responsiveness. High glucose exposure also increases MMP production especially in human OA chondrocytes and decreases the production of collagen II. The pro-inflammatory and pro-degradative effect of high glucose on chondrocyte is partially inhibited by PPAR (peroxisome proliferator-activated receptors) gamma agonists[13,34] (**Figure 2**).

Advanced end glycation products (AGEs) may also participate to diabetes-induced OA. They are known to accumulate in cells and tissues under high glucose concentration. *In vitro*, AGEs induced a pro-inflammatory and pro-catabolic phenotype of chondrocytes via RAGE (receptor of AGE) and toll-like receptor. The activation of these receptors in chondrocytes induced a decrease of PPAR-gamma and an activation of Nf-kappa B and MAP kinase pathways [35–38]. AGEs accumulate with age in OA cartilage modifying its mechanical properties. However, only one *in vivo* studies showed that AGE accumulate in cartilage of diabetic streptozotocin (STZ) rats compared to non-diabetic rats [34] and further studies are needed to demonstrate the implication of AGE in diabetes-induced OA(**Figure 2**).

Several *in vivo* models have explored the role of diabetes on OA using type 1 (STZ models) or type 2 (high fat diet) diabetes models. In type 1 diabetic rats induced by STZ injection, *Atayde et al.* reported first that diabetes induces a spontaneous loss of proteoglycan in OA cartilage compare to non-diabetic rats despite a lower weight in diabetic group[39]. This was confirmed and reinforced by *El Karib et al.* study in which 8 weeks after STZ-diabetes

induction, not only a loss of proteoglycan but a significant and spontaneous cartilage damage appeared compared to non-diabetic rat. This diabetes-induced OA could be prevented by insulin or by a mimicking agent called vanadium in type 1 diabetic rats [40]. As well, PPAR-gamma agonist (pioglitazone) has been shown to reduce the diabetes-induced OA in STZ diabetic mice leading also to a decrease of systemic inflammation (IL-6 and AGE)[34].

Using type 2 diabetic rat model, Onur *et al.* found that diabetic rats spontaneously developed OA[41]. However, in this model, type 2 diabetic rats had significant higher weight than non-diabetic, which is a bias. These results should be interpreted with caution even if *Mooney et al.* previously showed that, whatever the weight gain was, type 2 diabetes and obese mice had the same OA scores, probably because of the systemic metabolic disturbances and low-grade inflammation associated[42]. Finally, in an experimental and mechanical model of OA due to destabilization of medial meniscus in type 2 diabetic mice, rapamycin, a pharmacological activator of autophagy, prevented the diabetes-accelerated OA[43].

5.2 Diabetes and synovium

Less is known about hyperglycemia and synovium. High glucose concentration increases pro-angiogenic factors such as vascular endothelial growth factor (VEGF) expression in human synovial fibroblasts *via* oxidative stress, PI3K, Akt, c-Jun and AP-1 signaling pathways [44]. Synovial angiogenesis is known to induce pro-inflammatory cells locally. Some *in vivo* diabetic models discussed below have shown that diabetes induce more synovial inflammation especially in type 2 models than non-diabetic [43]. This is in the line with the clinical observation of more synovitis in knee OA in diabetic than in non-diabetic patients using ultrasound examination[17]. Such data have been recently corroborated by *Hamada et al.* who reported that the spontaneous OA of type 2 diabetes obese mice under high-fat diet was in part mediated by synovial overproduction of TNF-α in obese diabetic

mice. Furthermore, they showed that human OA fibroblast like-synoviocytes (FLS) expressed insulin receptor and were responsive to insulin which was able to partially counteract the pro-inflammatory and pro-degradative effect of TNFα. As insulin response was blunted in FLS from diabetic patients and TNF expression increased compared to non-diabetics, it could be possible that, because of their insulin resistant state, the FLS of diabetic patients are more sensitive to overproduce local TNF α a[14].

5.3 Diabetes and subchondral bone

Most of the studies on the relationship between bone and diabetes were published in the context of osteoporosis because diabetes is known to decrease bone remodeling. Specific study of subchondral bone and diabetes are rare. Fasting glucose concentration is associated with bone marrow lesions (BML) in knee joint in women using MRI [21]. These BML are known to predict OA structural damages[45]. In diabetic and hypertensive patients with advanced knee OA requiring arthroplasty, the loss of subchondral bone is increased depicted by a lower bone mineral density and a higher porosity, independently of weight[46]. Finally, AGE accumulate in subchondral bone of diabetic patients more than in non-diabetic which may impact the mechanical resistance of subchondral and display pro-inflammatory effects[47].

5.4 Diabetes and joint tissues: systemic impact

Insulin resistance and type 2 diabetes are most of the time the consequences of chronic visceral obesity and meta-inflammation that have been deeply explored [48]. Obesity is not only associated with knee or hip OA but also with hand OA, raising by 2-fold the risk of hand OA[49]. As there is no mechanical link possible, it opens to the idea of a systemic association between obesity and OA. Several mechanisms have been developed in this field. First, visceral fat mass of obese patient is responsible for a higher production of cytokines,

adipokines and acute phase reactant which play a major role in insulin resistance-related[48,50,51]. As well, this chronic low-grade metabolic inflammation (i.e., metainflammation) could be one of the links between insulin resistance and OA. As we discuss below, inflammatory mediators are involved in OA pathophysiology. Griffin *et al.* developed mice models of obesity and insulin resistance using high fat diet and explored their systemic role on OA development. Under high fat diet, mice developed spontaneous OA which is inhibited in leptin deficient mice[52]. This demonstrated that the mechanical impact of weight in obesity-induced OA could not explain all the association. Leptin is one of the major adipokines, secreted mostly by adipose tissue. Its expression in cartilage increased with OA severity and its synovial rate is correlated with BMI [53]. *In vitro*, leptin is able to promote chondrocytes apoptosis but also to increase cytokines (IL-1β and IL-8)[53,54] or metalloproteinase [55] production by chondrocytes[56]. They also reported in an high fat diet model that exercise which do not permit a weight loss -but a decrease in glucose intolerance - reduced OA progression, meaning that the insulin resistance state related to obesity is involved in joint damage[57].

Several adipokines has been also studies in the context of obesity and OA (for complete review see[58]). Indeed, resistin, visfatin (also called nicotinamide phosphoribosyltransferase Nampt) display pro-inflammatory and pro-catabolic effect *in vitro* on chondrocytes[59–63] while the role of adiponectin remains more controversial. *In vivo*, the local knee injection of visfatin inhibitor protected mice from mechanical OA[64]. However, no study has focused on adipokines as a link between OA and diabetes.

Along this line, insulin resistant state and obesity are also associated with elevated free fatty acids (FFA). The dietary content of FFA may modulate OA progression[65]. *In vitro*, palmitate has been shown to display pro-inflammatory effect on chondrocyte through

oxidative stress and pro-apoptotic effect[66,67]. Interestingly, a protective effect of n-3 polyunsaturated acid rich diet and a pro-catabolic effect of n-6 polyunsaturated acid and saturated fatty acid diet was observed in joint mice[68].

Finally, as a new perspective and for now a very hypothetical theory, the role of microbiome in obesity and insulin resistance has emerged as a crucial actor in the pathophysiology of these 2 diseases and may be also involved in the metabolic OA. Indeed, OA patients have higher synovial and serum rate of lipopolysaccaharide (LPS) and LPS-binding protein (LBP) than non-OA patients. In high fat diet mice, modifications of microbiota correlate with OA severity[69,70]. These studies could be the emerging evidence of the involvement of microbiota in metabolic OA.

6. Conclusion and perspectives:

Epidemiological association between OA and type 2 diabetes is robust, beyond their common association with age or obesity. Type 2 diabetes is now considered as an additional risk factor of OA. Several mechanisms coming from *in vivo* and *in vitro* animal studies but also from studies of diabetic patients joint tissues support such an association. Diabetes may act on joint tissues through hyperglycemia and insulin resistance, notably through oxidative stress which is a therapeutic target in OA in general[71,72]. However, we do not know yet whether diabetes control and prevention can modulate OA occurrence and progression in humans. Such an issue needs to be explored for a better personalized care.

Conflicts of interest: A.C : none, J.S : none.

Table 1: OA phenotype classification and characteristics, adapted from Bijlsma *et al*[2].

	Post-traumatic OA	OA -related to ageing	Genetic OA	Metabolic OA
Patient age	Young (<45 years)	Middle-Age (45-65 years)	Variable	Old (> 65 years)
Main causative factor	Acute Mechanical stress	AGE Senescence associated phenotype Oxidative stress Inflammaging	Polymorphism – Gene related factors	Adipokines Chronic mechanical stress Hyperglycemia Insulin resistance FFA and dyslipidemia
Main localization	Knee, Ankle, thumb, Shoulder	Hand, knee, Hip	Hand, Hip, Spine	Generalized, knee, hand, spine

Abbreviations: AGE : Advanced End Glycation products; FFA: free fatty acids; OA : osteoarthritis.

Figure Legends:

Figure 1: Pathological joint features of osteoarthritis. Osteoarthritis is characterized by impairment of all joint tissues with osteophytes and sclerosis of subchondral bone, synovial membrane inflammation and cartilage degradation leading to cartilage debris in the joint cavity.

Figure 2: Diabetes-induced osteoarthritis (OA): involvement of hyperglycemia in local chondrocyte activation.

High-glucose concentration induces advanced glycation end products (AGEs) formation in cartilage. AGEs interact with receptor of AGE (RAGE) and Toll-like receptor 4 to downstream peroxisome proliferator-activated receptor gamma (PPAR-γ), which induces oxidative stress (mitochondrial reactive oxygen species [mROS] and nitric oxide [NO]) and cytokine release by chondrocytes. AGEs also modify cartilage stiffness and resistance. High-glucose rate increases metalloprotease (MMP) expression and oxidative stress in chondrocytes but also synergizes the interleukin 1β (IL-1β) effect on cytokine release.

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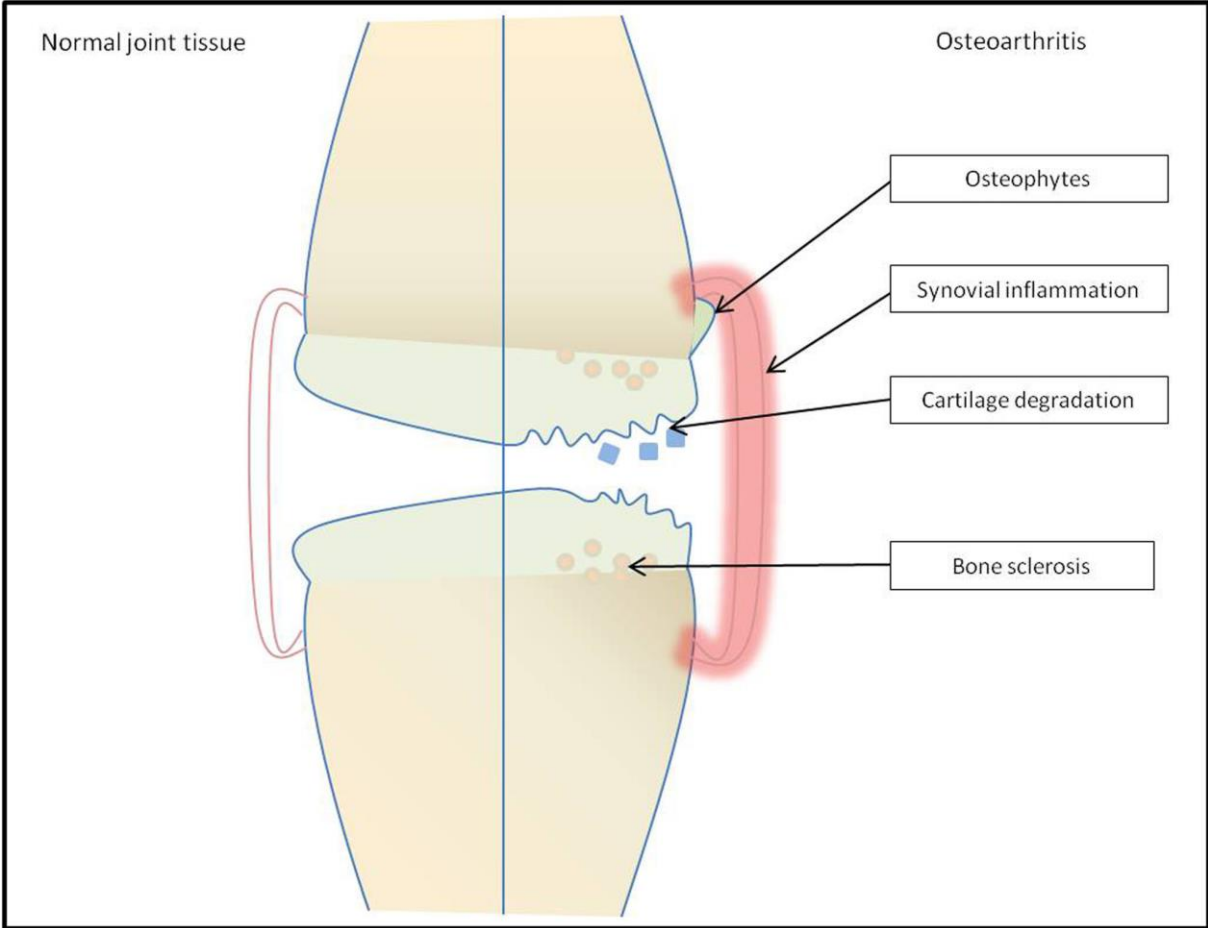
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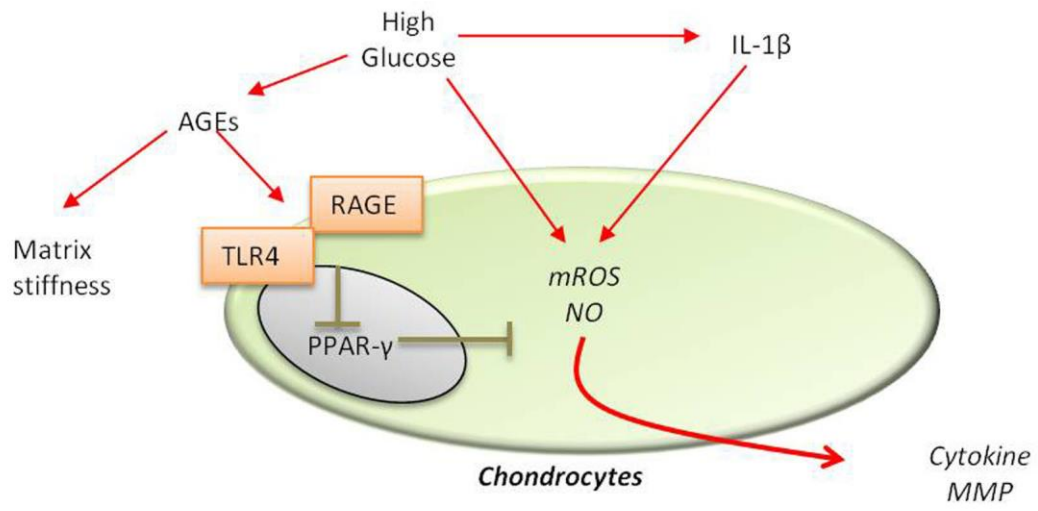
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Normal joint tissue

Osteoarthritis

Osteophytes

Synovial inflammation

Cartilage degradation

Bone sclerosis

Fig. 1

Effect of chronic high glucose exposure on chondrocyte

Fig. 2