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Metabolic osteoarthritis and its different aspects- An article review

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Introduction

Osteoarthritis (OA) of the knee is a widely prevalent disease characterized by pain and limitations in daily activities caused by gradual deterioration and inflammation of the articular cartilages [1] The worldwide health and economic burden of knee OA will increase in the future; as longer life expectancy will lead to a growing elderly population. The pathophysiologic mechanisms of OA are under debate, but there is general agreement that biomechanics and increased dynamic loading of the joint are involved. [3]

Still, it is suggested that other factors such as genetic and metabolic factors may also contribute to increased incidences of knee OA. Metabolic syndrome (MetS) includes a number of conditions, including obesity, atherogenic dyslipidemia, impaired fasting glucose and hypertension (HTN). Nonetheless, a significantly increased risk of cardiovascular disease6 and mortality are reported among patients with metabolic syndrome. MetS has shown greater attention due to an association with knee OA and an increased risk of deep venous thrombosis after procedures related to knee OA, such as total knee arthroplasty (TKA) in musculoskeletal fields.[4] Obesity, plays a major role in MetS. It is well known to be associated with knee OA with respect to mechanical load and it is also linked with excessive proinflammatory cytokine production which could play an important pathophysiologic role in OA. Moreover, it has also been also reported that atherogenic effects related to HTN could change the microvasculature of subchondral bone and could have an effect on the development of knee OA. In a published analysis of NHANES III data, authors have discussed that about 59% of population was suffering from metabolic syndrome along with OA. Hypertension (75%), abdominal obesity (63%), hyperglycemia (30%), elevated triglyceride (47%) and low HDL (44%) were the major metabolic syndromes associated with it [5]. The authors understanding the increasing prevalence of this metabolic factors in pathogenesis of OA, have stated term ‘‘metabolic osteoarthritis’’ and considered as a subtype of OA. Classification – phenotypes of OA Pelletier et al., presented a summary about the major phenotypes of OA. Post-traumatic OA Age-related OA Metabolic syndrome associated with OA (MetOA)

Post-traumatic OA

A patient with a post-traumatic OA of may be of age < 45 years with OA in the knee, hip, ankle, or shoulder caused by repetitive mechanical stresses or by a unique acute joint trauma (joint fracture, meniscectomy, etc.)

Age-related OA Patients >65 years are affected with age-related OA in the hip, knee, or hand without any history of trauma or MetS.

Metabolic syndrome associated with OA (MetOA) MetOA affects the patients of age between 45 and 65 years with generalized OA, overweight or obese, with at least one of the component of the MetS (diabetes mellitus, hypertension, dyslipidemia). Adipokines, insulin resistance, systemic low-grade inflammation, and lipid toxicity are some of the triggers for initiation of the OA process. In a study report by Issa et al., authors have explained pathobiology of metabolic syndrome and OA. The authors have explained in detail the role of biochemical mediators in relation to the metabolic syndrome plays important role as it in the pathogenesis of OA [6]. Authors give explanation on the of study results where cardiometabolic diseases are clustered with increased risk of OA even when patients are controlling BMI. In this respect it is suggested that there are common metabolic factors which are associated with cardiovascular and OA disease conditions. Both the disease conditions are correlated with common mechanism of disease which involves altered lipid metabolism coupled with increased systemic and cellular expression of proinflammatory mediators. In support to the above statement authors have taken results of study where it is found that obesity also increased the risk of developing OA in non-weight bearing joints, such as, hand where systemic inflammatory mediators plays major role. Adipose tissue especially from abdomen is a rich source of producing pro-inflammatory cytokines which are often referred as adipokines and play a role in metabolic syndrome. This adipokines is increased in metabolic syndrome and mediate synovial tissue inflammation and upregulated cartilage degradation. [7] The concept of metabolic osteoarthritis has been supported by various studies that show that there is increased incidence of OA in patients suffering from metabolic syndrome. Metabolic syndrome is defined as any or many conditions, such as, insulin resistance (identified by type 2 diabetes, impaired fasting glucose or impaired glucose tolerance), hypertension, elevated plasma triglycerides, decreased high-density lipoprotein cholesterol, obesity and proteinuria. OA is part of a generalized metabolic disorder in which various interrelated metabolic factors contribute to the OA process. A recent logistic regression analysis which assessed the association between MetS and population-weighted variables in a representative sample showed appealing results. Interestingly, MetS was prevalent in 59% of the OA population and in 23% of the population without OA. Each of the five CV risk factors that comprise MetS was more prevalent in the OA population.[8] Hence, the above interpretation indicates that there is independent role of metabolic factors which are associated with increased risk of OA. This concept in recent scenario classified as a separate phenotype of OA, termed as metabolic osteoarthritis.

Role of subchondral bone – as a cartilage supporter

Knee OA is a problem of articular cartilage as well as the whole joint disease, involving the other joint tissues, such as subchondral bone. For example, the role of subchondral bone is to provide mechanical support and nutrition supply to overlying articular cartilage as well as subchondral bone and articular cartilage act as a unit to maintain the structural and functional integrity of joint. In addition, there are various evidences showing that subchondral osteoblasts in OA alter the cellular behavior of articular chondrocytes. Hence, such studies indicate that interaction with subchondral bone disturbance plays an important role in pathomechanism of OA and contributes to the progression of disease. In same study, authors have established the interrelation between subchondral bone loss and metabolic syndrome. Authors have observed that there is significant bone loss at subchondral plate at medial tibial plateau and these results in reduced BMD

and porosity in patients suffering from Type 2 diabetes mellitus and hypertension when compared with subjects without any comorbidities.

Vascular abnormality and MetOA-detrimental effects on subchondral bone

The emerging view of joint pain and disorder in OA related to abnormality of vascular supply due to metabolic syndrome, such as, hypertension has been explained by Wen et al. Proposed below the mechanism for the deteriorations of overlying articular cartilage by various authors. Metabolic OA and vascular pathology are intimately linked. [9] Using hypertension model various facts have been known with evidences that may suggest the final common pathway for cellular or chondrocyte changes observed in OA. In this regard Findlay has provided an important evidence. There is an important evidence of vascular pathology role in the initiation and/or progression of the major disease of joints: osteoarthritis (OA). Potential mechanisms include: episodically reduced blood flow through the small vessels in the subchondral bone at the ends of long bones, and reduced interstitial fluid flow in subchondral bone. Reduction of blood flow may be venous occlusion and stasis or by the development of microemboli in the subchondral vessels. There are many effects of subchondral ischemia: the first of these is compromised nutrient and gas exchange into the articular cartilage, a potential initiator of degradative changes in the cartilage. The second is apoptosis of osteocytes in regions of the subchondral bone, which would initiate osteoclastic resorption of that bone and at least temporarily reduce the bony support for the overlying cartilage. It may be important to recognize these potential etiological factors in order to develop more effective treatments to inhibit the progression of OA. Subchondral bone ischemia is a causal factor in OA development, which may have several possible consequences. Firstly, nutrients and oxygen supply from the subchondral bone to the overlying articular cartilage would be reduced from regions of ischemia. More than 50% of the glucose, oxygen and water requirements of cartilage are provided by perfusion from the subchondral vessels. In addition, inspection of the osteo-chondral junction of long bones reveals that osteocytes and osteocyte canaliculi, which are also likely conduits of nutrients, are intimately associated with the articular cartilage. [10] Studies have shown that in the pathogenesis of OA subchondral bone remodeling plays an important role. Loss of subchondral bone trabeculae results in cartilage breakdown by enhancing cartilage deformation upon joint loading. Reduction in the arterial inflow and obstruction of the venous outflow have been shown to impair bone blood flow and to lower the cellular nutrient and oxygen supply. This mechanism has been described schematically in the images below. The suggested mechanism as to how venous stasis in the subchondral bone contributes to cartilage degradation in MetOA has been the following. Episodes of venous stasis in OA may lead to loss of osteocyte viability in regions of the bone. This is likely to be especially the case in the highly vascular subchondral region of long bones. [11] Venous stasis may also result in a decrease in nourishment to the overlying cartilage, as proposed by Imhof et al. Loss of osteocyte viability in the subchondral bone would lead to increased bone turnover in order to repair damaged and necrotic bone tissue, which in turn may result in altered architecture of the subchondral bone and perhaps to articular degeneration because of compromised structural support for the cartilage.

Dyslipidemia and OA

Dyslipidemia and OA initially focused on showing that elevated levels of serum cholesterol are a risk factor for OA development. A positive association between serum cholesterol levels and OA (knee and hand), independent of

obesity, has been reported in 1003 women aged 45–64 from Chingford, UK.[12] Furthermore, a study of femoral heads samples collected from 23 patients with OA and two healthy controls revealed that levels of total fatty acids and arachidonic acid were also significantly ($P < 0.01$) increased in patients with OA, and were linked with increasing incidence and severity of the disease.

Obesity and MetOA

Various epidemiological studies explain the role of obesity in the lower limb osteoarthritis. However, recently various studies have shown clear role of obesity even in the other joints such as hip and hands. One obvious mechanism of obesity in OA to weight bearing joint is mechanical stress applied to joints. However, physical stress cannot be the only reason in such patients and systemic mediator has to have role. This comment is very much supported by meta-analysis where, obesity and overweight are independently linked to 2-fold increased risk of hand osteoarthritis. [13] In consideration of the above facts, authors have also explained the mechanism and role of systemic mediators in obesity which are mainly responsible for MetOA. Adipose tissues in obese patients are considered to be only energy storage sites, but these also release mediators, such as, adipokines such as adiponectin, leptin, and visfatin may act on both weight-bearing and non-weightbearing joints. In MetOA, these mediators released from chondrocytes and synoviocytes and are responsible for immune and inflammatory responses. [14]

Role of adipokines Association of adipokines with obesity and its inflammatory nature has shown interest in research to understand the pathophysiology behind the OA associated with metabolic syndrome. Researchers have started believing that adipokines plays a crucial role in homeostasis of cartilage and bone.

Role of adiponectin

Serum adiponectin level results in radiographic progression of osteoarthritis. At the knee, the release of adiponectin by the infrapatellar fat pad may diffuse into the knee joint. Adiponectin has more of catabolic effects on several tissues/ cells involved in the initiation and progression of OA. Adiponectin and adiponectin receptors have been identified in human chondrocytes. Adiponectin exert a proinflammatory function as it stimulates NOS2, MCP-1, MMP-1, -3, -9 and-13, IL-6, IL-8, PGE2, and vascular endothelial growth factor (VEGF) production from chondrocytes and cartilage. Adiponectin can induce vascular cell adhesion molecule 1 (VCAM-1) expression in human chondrocytes, suggesting its role to perpetuate cartilage degradation by modulating molecules responsible for leukocyte infiltration at inflamed joints. In addition, adiponectin levels in OA synovial fluid was correlated with aggrecan degradation. [14] Hence from above it is clearly indicated that adiponectin plays crucial role in providing inflammatory environment in OA. Franchin et al., produced similar results where authors have shown link between adiponectin and cartilage degradation. Authors conclude that OA develops in the highly metabolic and inflammatory environment of adiposity. This has been attributed to adiponectins, universally present with truncal obesity, rather than simply with overweight. The adiponectins were reported to stimulate the production of IL-6, IL-8 and prostaglandin E2 (PGE2) by human synovial fibroblasts, suggesting its potential contribution to the pathogenesis, joint degradation, and inflammatory process. The adipokine is found in the synovial fluid of human OA. Lago et al. established that adiponectin may trigger cartilage destruction through up-regulation of MMPs and pro-inflammatory mediators.

Few studies indicate that adipokines stimulates production of chemokines, cytokines and matrix-degrading enzymes both in synovial fibroblasts and in chondrocytes. Adiponectin expression was correlated with grade of OA progression in obese patients. The adipokine stimulates the production of chemokines and cytokines, and human synovial fibroblasts increase the protein secretion of proMMP-1, MMP-3, MMP-10 and MMP-12 in response to adiponectin. The adipokine upregulates numerous MMPs in human chondrocytes including MMP-1, -3, -13.21 6.3. Role of leptin Leptin increases the production of metalloproteinases (MMPs) enzymes such as MMP-1, -3, -9 and -13 and decreases the production of basic fibroblast growth factors (FGF). The role of leptin on cartilage metabolism in OA patients can be detected from these evidences. In various study reports, an increased level of leptin is found in cultured chondrocyte suffering from OA. Leptin increases key mediators such as tumor necrosis factor-alpha (TNFa), interleukin (IL)-1b, IL-6, IL-8 that are responsible for cartilage degradation. It has been shown that leptin had proinflammatory and catabolic effects on chondrocyte proliferation. Leptin reduced proliferation of OA chondrocytes after the 48-h treatment. Nitric oxide (NO) is a proinflammatory mediator which promotes apoptosis, chondrocyte phenotype loss, as well as MMPs activation. The combination of leptin and interferon-g can activate the production of type 2 nitric oxide synthase (NOS2) in cultured chondrocytes. Leptin, alone or in synergy with IL-1b, has also been reported to enhance the production of inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2) and cyclooxygenasse (COX)-2 in human OA cartilage and chondrocytes.[15]

Linked of obesity with all other metabolic disease conditions Metabolic OA has been recently individualized based on recent data showing an increased incidence of OA in patients with metabolic syndrome. Moreover, recent epidemiological studies have strengthened this hypothesis by showing an increased incidence of OA in patients with metabolic syndrome (MetS). MetS, also known as syndrome X, is defined as a condition mixing several independent risk factors for cardiovascular (CV) events, including insulin resistance (identified by type 2 diabetes, impaired fasting glucose or impaired glucose tolerance) plus any two of the following: hypertension, elevated plasma triglycerides, decreased high-density lipoprotein cholesterol, obesity, proteinuria. Indeed, estimation of the prevalence of diabetes reaches over 10% of the population in industrialized countries, coexisting with obesity in specific geographic patterns because of a convergence of prevailing social norms, community and environmental factors, socioeconomic status and genetic risk factors among ethnically similar groups.

Diabetes and MetOA

Several epidemiological and experimental data support the hypothesis that diabetes could be an independent risk factor for osteoarthritis (OA), leading to the concept of a diabetes-induced OA phenotype. Berenbaum has explained the reason of diabetes or high blood sugar levels posing a risk for advancement of cartilage decay in MetOA. Various mechanisms are responsible to induce OA related to diabetes. Important mechanisms are highlighted as below: It has been shown that in hyperglycemia there is decreased in dehydroascorbate transport in to the chondrocyte, which compromise the synthesis of type II collagen and increase synthesis of ROS (reactive oxygen species). These are closely associated factors of cartilage degradation in diabetes. Another component of this pathoanatomy is AGE (advanced glycation end product). Advanced glycation end products (AGEs), the products of nonenzymatic glycation and oxidation of proteins and lipids, accumulate in several diabetic tissues such as the vasculature due to

hyperglycemia. AGEs have been shown to accumulate in cartilage leading to matrix stiffness, becoming more sensitive to mechanical stress. AGEs can also bind to membrane receptors called RAGE (for 'receptor for age glycation end products') present on many cell types including chondrocytes. Once bound to RAGE, AGEs trigger the activation of different signaling pathways leading to the over expression of proinflammatory and prodegradative mediators and to some alterations in the chondrocyte differentiation phenotype. Thus to summarize, increased concentration of glucose in diabetic cartilage matrix environment would lead to enhanced cartilage degradation and faster rate of progression of OA. In another longitudinal cohort study by Schett et al., authors have shown US (ultrasonography) that elevated circulating levels of interleukin-6 and tumor necrosis factor-a are responsible for inflammation which are more frequent and severe in the joints of diabetic subjects than non-diabetic individuals. In same cohort study, authors have also associated sensory and motor polyneuropathy as a common complication of type 2 diabetes mellitus which can increases risk of OA due to muscle weakness and loss of vibratory sense. [16] In a similar cohort study, authors have put forward the concept of metabolic OA where OA is a part of metabolic syndrome. This explains the view of OA as a degenerative joint disease based on continuous mechanical overload to a metabolic etiopathogenesis. The link between OA and type 2 diabetes suggests that alterations in glucose metabolism directly affect joint integrity independently of body weight and creates room for hope that adequate control of glucose metabolism hampers development of OA. Above findings are independent of age and BMI and suggests that longstanding diabetes per se is detrimental for knee and hip joints, leading to progressive destruction and joint failure.

Atherosclerosis and MetOA

The elevated levels of serum cholesterol as a risk factor for OA development have been depicted by various epidemiological data. In a clinical study, authors have reported positive correlation between elevated serum cholesterol and OA. Authors have observed lipid accumulation in chondrocyte and thus commented that altered lipid metabolism plays a part in the development of OA. Additionally, proteomic analyses of osteoarthritic cartilage and isolated chondrocytes have demonstrated that a substantial proportion of proteins related to lipid metabolism, such as peroxisome proliferator-activated receptors (PPAR), and apolipoproteins, are differentially expressed in osteoarthritic tissue. Moreover, in study authors have commented that cartilage in patients with weight and non-weight bearing OA expressed lecithin-like oxidized LDL receptor 1, while same was absent in cartilage of patients without OA. [17]

Conclusion

Emerging evidence supports that people with metabolic syndrome are more susceptible to develop osteoarthritis. OA and metabolic syndrome in aging are linked by age and obesity factors, such as cumulative joint loads, systemic inflammation, and abnormal lipid metabolism. Hyperglycemia may also directly impact OA. Atherogenic effects related to hypertension could change the microvasculature of subchondral bone and could have an effect on the development of knee OA. In this review, we have discussed the common links between OA and metabolic syndrome in older adults along with the metabolic and physical impairments commonly present in this population. We suggest that metabolic OA should be a new facet of the definition of MetS, supported by its strong associations and shared mechanisms with other MetS components.

Further research, however, is needed to accepted components of MetS.

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