Osteoarthritis - From New Insights into Disease Pathogenesis to Contemporary Personalized Therapeutic Strategy

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Osteoarthritis (OA) is the most common joint disease and the leading cause of disability worldwide [1]. OA affects the whole joint and the pathology includes progressive degradation of cartilage, synovial inflammation, changes in the subchondral bone [2]. OA is characterized by complex pathogenesis, may manifest with different localization i.e., knee, hip, spine, hand, etc. At present, there is not approved disease-modifying drug for the treatment of OA and the global results from the pharmacological treatment are not satisfactory. Complex therapeutic approaches that include measures directed towards diverse underlying pathogenic processes in OA probably have the potential to retard the disease progression [1]. Target and individualized treatment in every clinical case are the base of the concept of personalized treatment. Identification of different disease phenotypes of OA is in the research agenda and would facilitate the assessment of disease prognosis and the choice of an appropriate individualized therapeutic strategy.

Knee OA is a major localization of the pathological process. In a proportion of the patients (approximately 50%), knee OA is associated with obesity and is influenced by the action of mechanical, inflammatory and metabolic factors. It has been found that obesity and the associated conditions (hyperglicemia, dyslipidemia and hypertension) are risk factors for the development of knee OA, which leads to the hypothesis that drugs, which influence the inflammatory and metabolic processes in obesity, may also have the potential to slow the progression of OA [1]. An increased risk of OA in obese patients was suggested to be not only a consequence of altered biomechanics in weight-bearing joints but also due to the effect of systemic mediators e.g., adipokines that are derived primarily from the dysfunctional adipose tissue and have also been associated with incidence and severity of hand OA [3, 4]. Results from in vitro studies suggest that adipokines, including leptin, adiponectin, visfatin, and resistin could promote chondrolysis [3, 5]. In a large study (Kroon et al., 2019), which includes 6408 participants (with 22% prevalence of knee and/or hand OA), it has been found that serum leptin levels were associated with OA, while adiponectin levels were not associated with OA [6]. In 200 patients with symptomatic knee OA, higher serum levels of resistin were associated with knee synovitis and structural abnormalities assessed via magnetic resonance imaging (MRI). Thus, it has been suggested that obesity may promote OA not only by increasing weight loading on joints but also by systemic effects and triggering of different inflammatory pathways [7].

Candidate biomarkers and opportunities for new therapeutic interventions in OA based on new insights in diseases pathogenesis

The major target of the pathologic process in OA is the articular cartilage, which in normal conditions is composed of an extracellular matrix, containing mainly collagen type II, the proteoglycan aggrecan and a leading cell type – chondrocytes. In OA, there is an accumulation of shorter proteoglycans, decreased synthesis of type II collagen, increased production of collagen type X. A constant feature is the up-regulation of cartilage degrading enzymes - matrix metalloproteinases (MMPs) i.e., MMP-1, 3, 7, 9, 13, ADAMTS metalloproteinases. The target molecules for ADAMTS metalloproteinases are aggrecan and for collagenase-1 and 3 (MMP-1, MMP-13) - collagen type II, respectively. Interleukin-1β and tumor necrosis factor-α (TNF-α) are key players in the induction of the catabolic processes in OA. They are produced by chondrocytes, osteoblasts, cells forming the synovial membrane, and mononuclear cells and are detected to be elevated in synovial fluid, synovial membrane, cartilage, and the subchondral bone. Increased expression of transforming growth factor – β (TGF-β) and insulin-like growth factor (IGF) has been observed in human articular cartilage and in the subchondral bone in OA patients and the adipokine leptin has been proposed to induce TGF-β and IGF expression [8]. It has been observed that in vivo injection of leptin in knee joints of rats produces catabolic effects on articular cartilage with increased production of MMP-1, 3, 9 и 13. A positive association between leptin level and markers of articular degradation such as urinary C-terminal telopeptide of collagen type II has been observed [9]. Different molecules have been analysed as biomarkers that reflect cartilage damage in OA i.e., serum cartilage oligomeric protein, serum level of different MMPs (MMP 1,3,13, etc.), different metabolic products of collagen type II i.e., urine

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C-terminal telopeptide of collagen type II, type II collagen cleavage product, etc [2, 9]. Candidates for biomarkers in OA are most likely to be structural molecules or fragments linked to cartilage, bone or synovium and may be specific to one type of joint tissue or common to them all. They may be markers of tissue degradation or synthesis and may be measured in synovial fluid, blood or urine [2]. Due to the complex pathogenesis of OA, probably the activity and prognosis of the disease could not be assessed using a single biomarker but via measurement of complex of different biomarkers. This could potentially lead to personalized approach and complex individualized therapeutic strategy.

Currently, pharmacological treatment in OA includes the administration of non-steroidal anti-inflammatory drugs, analgesics, symptomatic slow-acting drugs (glucosamine, chondroitin, avocado, soy bean, and intraarticular hyaluronic acid). Although there are data that some compounds such as glucosamine and chondroitin may retard OA progression, at present, there is no approved drug with disease-modifying properties in OA.

The knowledge about the role of TNF-α in OA and the eventual presence of synovitis in patients with severe hand has led to the speculation that TNF-α blockers may be an effective strategy. However, the attempt to influence TNF-α in OA has not proved efficacy in reduction OA symptoms. In patients with hand OA, adalimumab did not show any effect on pain as compared to placebo [10, 11] or on synovitis and BMLs evaluated via MRI [10]. In a 1-year, double-blind, randomised, multicentre trial that included 90 with patients symptomatic erosive inflammatory hand OA randomised to etanercept (n=45) or placebo (n=45), etanercept did not relieve the pain. In a small group of patients with available MRI findings (n=20), greater decrease in bone marrow edema-like lesions (BML) scores was observed in the etanercept group, without a difference in the MRI-detected synovitis [12].

Initially, improvement of symptoms has been reported in patients with erosive OA treated with hydroxychloroquine in a limited number of patients [13-15]. However, in a large placebo controlled trial with 12-month duration that included 248 patients with hand OA, it has been observed that hydroxychloroquine is not more effective than placebo for pain relief [16].

The knowledge about the crucial role of subchondral bone in the initiation and progression of OA has led to a hypothesis about a possible role of bisphosphonates in the treatment of OA. The subchondral bone supports the overlying articular cartilage and distributes the mechanical loads across joint surfaces. Thus, the development of subchondral bone stiffening leads to increased load to the articular cartilage and could promote cartilage damage. MRI visualizes subchondral BMLs, which have been found to correlate with clinical symptoms and with structural progression in OA. Of note, BMLs have also been observed even in normal knees without clinical symptoms or articular cartilage pathology that suggests the hypothesis that early subchondral damage may precede the disease manifestation [17]. The administration of risedronate has led to a decrease of urinary excretion of C-terminal telopeptide of collagen type II, that is a marker of cartilage damage, but an improvement of clinical symptoms and/or radiograph progression has not been registered. There are data that treatment with zolendronic acid decreases the number of BMLs in the subchondral bone [18].

The association between OA and obesity also reflected by the link between adipokines and cartilage function, has stimulated the hypothesis about the role of metformin in the complex therapeutic approach in OA. Metformin possesses glucose-lowering effects and additionally it modulates the action of inflammatory and metabolic factors that leads to weight loss, reduction of the inflammation and plasma lipid level [1]. There are data from clinical studies that metformin may retard OA progression via modulation of inflammatory and metabolic factors. In a randomized clinical trial in patients with symptomatic, radiologically confirmed knee OA, in patients treated with metformin and meloxicam, a significant reduction in the serum levels of IL-1β, IL-8 and TNF-α has been detected [19] as well as superior improvement of pain and function [20] as compared with patients treated with meloxicam alone for a period of 12 weeks. During a 10-year follow-up, it has been observed that in patients with OA and type 2 diabetes, who have received combined treatment with COX-2 inhibitor and metformin, the joint replacement surgery rates were lower as compared with patients treated only with COX-2 inhibitor [21]. In a recent study (Wang et al., 2019), it has also been reported an observation about slowing of OA progression during a 4-year follow-up period in patients with radiologically confirmed knee OA (Kellgren-Lawrence grade ≥2), who have had concomitant obesity with BMI ≥30kg/m² and have taken metformin. 56 patients received therapy with metformin at baseline, and on the visits of the 1st and 2nd year from the follow-up and 762 have not reported about metformin use at any visit for the 4-year period of follow-up. The cartilage volume of femoral condyle and tibial plateau were assessed using MRI at baseline and at the follow-up in the 4th year. The rate of medial cartilage volume loss was lower in metformin users compared with non-users (0. 71% vs. 1.57% yearly) and the difference (0.86% yearly) was statistically significant (p = 0.02) after adjustment for age, gender, BMI, pain score, Kellgren-Lawrence grade, self-reported diabetes, and weight change during the 4 years of follow-up. These results suggest that the presence of long-term positive effect of metformin in patients with OA and obesity and disease-modifying potential of the drug that requires confirmation in future randomized studies [1]. More recently, in fundamental research, in mice with induced OA via destabilization of the medial meniscus, it has been observed that administration of intragastric and intraarticular metformin led to less cartilage damage under scanning electron microscopy vs mice receiving intragastric and intraarticular saline. In vitro experiments have demonstrated that the anabolic and anti-catabolic effects of metformin could be a result of its effect on the activation of adenosine monophosphate-activated protein kinase [22].

The advances in our understanding of OA pathogenesis are expected to reveal new opportunities for the determination of different phenotypes of the disease based on clinical and laboratory findings. Probably the successful therapeutic approach will be a combination of different pharmacological interventions based on disease phenotype. In this regard, basic research projects
that evaluate the effect of new disease-modifying therapeutic strategies on histological changes of joint structures in animal models are the future step forward.

REFERENCES