INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis. Although the hallmark of the disease is progressive degeneration of the articular cartilage, which causes narrowing of the joint space, OA also causes pain, loss of motion, instability, and physical disability, thus impairing quality of life. The pathophysiology of OA involves a combination of mechanical, biological, biochemical, molecular and enzymatic processes ***(Loeser et al., 2012).***

The pain tends to worsen with activity, especially following a period of rest. OA can cause morning stiffness usually lasts for less than 30 minutes. Patients may report joint locking or joint instability. These symptoms result in loss of function, with patients limiting their activities of daily living. The joints most commonly affected are the hands, knees, hips, and spine, but almost any joint can be involved and is often asymmetric ***(Sinusas, 2012).***

Treatment of OA includes nonpharmacological and pharmacological treatment. Nonpharmacologic therapies include education, exercise, weight reduction, the provision of physical aids, orthosis, heat or cold therapy, transcutaneous nerve stimulation , ultrasound, and acupuncture. The available pharmacologic therapies for pain relief in patients with OA are oral analgesic therapy, topical therapy, and intra-articular (IA) therapy. Oral pain relievers such as acetaminophen are common

first treatments. Nonsteriodal anti-inflammatory drugs (NSAIDs) decrease swelling and pain. Tramadol for more serious pain ***(Rannou and Poiraudeau, 2010).***

Symptomatic slow-acting drugs for osteoarthritis (SySADOA) include agents that are licensed for use as medications and nutritional supplements in favor of relieving the symptoms of OA in the long-term, to decrease the requirement for concomitant symptomatic medications. They include glucosamine sulfate, chondroitin sulfate, and diacerein ***(Dougados, 2006).***

Topical drugs include capsaicin cream, lidocaine and diclofenac gel. IA injections with corticosteroids or with hyaluronic acid can give months of pain relief from OA. IA hyaluronic acid injection is given in the knee, and may help to delay the need for a knee replacement by a few years in some patients. Surgical treatment becomes an option for severe cases, or when medical treatment fails to relieve pain and patients have major loss of function ***(Altman and Barthel, 2011).***

Existing pharmacological interventions for OA remain insufficient. However, pharmacologic treatments have shown moderate symptomatic efficacy over short-term treatment courses, but no relevant effect over the long-term use. In addition, they have adverse events in certain settings and patient populations. Furthermore, there is currently no evidence to

suggest that they can also influence structural disease and thus be disease modifying ***(Kennedyand Moran,2010).***

Over the past two decades, studies have focused on mechanism of actions aimed at slowing or halting the progression of articular cartilage destruction or chondroprotection. No disease modifying osteoarthritis drugs (DMOADs) are approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMEA). Pain relief remains a primary unmet medical need with issues around safety and tolerability, and enhanced efficacy ***(Graverand-Gastineau, 2010).***

The introduction of anticytokine therapy has been the most impressive advance in the field of rheumatology. Expermental evidence in culture and animal models has shown that interleukin-1 (IL-1) plays a pivotal role in initiating and sustaining cartilage destruction and that tumour necrosis factor alpha (TNF-α) synergises with IL-1 in stimulating the degradation and inhibiting the synthesis of cartilage-specific matrix proteins. Thus, anticytokine therapy, particularly if there is combined action against both of these primary cytokines, would theoretically be effective against OA if the disease could be diagnosed early enough to prevent or inhibit cartilage damage before significant joint instability is established ***(Goldring, 2001).***

Data from in vitro human and animal OA explants studies and in vivo animal models of OA provide substantial evidence that blocking IL-1β and TNF-α could be beneficial in counteracting the degenerative mechanisms associated with OA pathology ***(Kapoor et al., 2011).***

A recent study demonstrated that short-term treatment with adalimumab for 12 weeks in patients with inflammatory OA of the knee refractory to conventional treatment resulted in clinical benefit in the majority of patients using the Osteoarthritis Research Society International/Outcome Measures in Rheumatology Clinical trials (OARSI/OMERACT) responder index. The response was also maintained in most patients at the last time of follow up at 22 weeks after treatment had been discontinued for 10 weeks. Major clinical improvement was seen in almost half of the patients that included improvement in function, daily activity, and sleep in addition to objective amelioration of joint effusion ***(Maksymowych et al., 2012).***

A potential treatment option to reduce pain and perhaps alter disease progression is administration of anti-inflammatory cytokines derived from autologous blood. IA injections of platelet-rich plasma (PRP) have been shown to reduce pain and improve quality of life scores for patients with degenerative conditions of the knee. Another blood-derived technology that takes advantage of anti-inflammatory cytokines present in whole blood is Orthokine. This product has demonstrated

varying degrees of success in reducing pain in OA patients ***(Woodell-May et al., 2011).***

The potential approaches to using stem cells in the treatment of OA include their application in tissue engineering and their use alone in treatment protocols. The use of stem cells alone in the treatment of OA depends upon the injury response cascade. After injury or onset of disease, an inflammatory response usually occurs. By providing the host with an enhanced number of stem cells in the biological regenerative phase, an acceleration of the functional repair of the tissue can occur. This treatment concept would either use mesenchymal stem cells (MSCs) for the direct repair of articular surfaces or for their trophic or immunomodulating function ***(Goldberg, 2012).***

Gene therapy can be used in OA as a drug delivery system to modify or restore the balance between anabolic and catabolic factors, or to modulate the proinflammatory mediators. Gene therapy holds considerable potential for improving OA, as high concentrations of biologics can be achieved in the joint and sustained over time. Various ex vivo or in vivo strategies using nonviral and viral vectors can be considered. Since OA can affect a single knee, local gene therapy holds promise as an affordable and effective treatment strategy ***(Chevalier and Kemta-Lepka, 2010).***

AIM OF THE WORK

The aim of this work is to review the pathogenesis of osteoarthritis in order to throw light on the possible implication of the promising biological therapy in the treatment.

OSTEOARTHRITIS

Osteoarthritis (OA) is a gradual loss of articular cartilage, combined with thickening of the subchondral bone (SB), bony outgrowths (osteophytes) at joint margins, and mild, chronic nonspecific synovial inflammation ***(Berenbaum, 2008).***

Although the etiology of OA is incompletely understood, the accompanying biochemical, structural, and metabolic changes in articular cartilage have been well documented. It is now known that cytokines, mechanical trauma, and altered genetics are involved in its pathogenesis, and these factors can initiate a degradative cascade that results in many of the characteristic alterations of the cartilage in osteoarthritis ***(Di Cesare et al., 2009).***

Moreover, OA results from a complex system of interacting mechanical, biological, biochemical, molecular and enzymatic feedback loops. The final common pathway is joint tissue destruction resulting from the failure of cells to maintain a homeostatic balance between matrix synthesis and degradation. As the disease advances, the degradative process eventually exceeds the anabolic process, leading to progressive joint tissue lesions ***(Martel-Pelletier and Pelletier, 2010).***

Risk factors involved in pathogenesis of OA

OA has a multifactorial etiology, and can be considered the product of an interplay between systemic and local factors. A person may have an inherited predisposition to develop OA but may only develop it if an insult to the joint has occurred. The relative importance of risk factors may vary for different joints, for different stages of the disease, for the development as opposed to the progression of disease ***(Zhang and Jordan, 2010).***

Joints become susceptible to injury and subsequent OA when local factors in the joint combine with systemic vulnerabilities. Local factors include joint deformity, previous injury that has damaged important protective structures, and malalignment. Local factors can powerfully determine the risk of OA and leave a joint vulnerable to normal daily activity. Systemic vulnerabilities to OA probably act through local mechanisms for the most part ***(Felson, 2004).***

Major factors that affect the degree of risk for developing OA include age, joint location, obesity, genetic predisposition, joint malalignment, trauma, and gender **(Adatia et al., 2012).**

Age: Age is the major risk factor for OA, the aging changes in joint tissues that contribute to the development of OA include cell senescence that results in development of the senescent

secretory phenotype and aging changes in the matrix, including formation of advanced glycation end products (AGEs) that affect the mechanical properties of joint tissues ***(Anderson and Loeser, 2010).***

However, there are important differences between an aged joint and one with OA. The ageing changes observed in the cells and extracellular matrix of joint tissues likely increase the susceptibility of older adults to OA when other osteoarthritis risk factors are also present ***(Anderson and Loeser, 2010).***

The links between aging and the development of OA are becoming more apparent. The aging chondrocyte's ability to produce and repair the extracellular matrix is compromised due to a decline in growth factor activity, as well as a decline in the chondrocyte's response to stimulation with growth factors ***(Goldring and Goldring, 2010).***

However, age-related changes within the chondrocyte, including cellular senescence and a reduced responsiveness to growth factors, and external factors affecting chondrocyte aging, such as angiogenic growth factors accumulation and oxidative stress may work in combination to disrupt cartilage homeostasis. These changes will make the cartilage matrix more vulnerable to damage and lead to the onset of OA ***(Leong and Sun, 2011).***

Obesity: Obesity plays an important role through mechanical forces and inflammation in predisposing to OA development. Interventions designed to promote dietary weight loss and exercise in obese people who have OA have demonstrated clinically significant improvements in symptoms and disease risk factors ***(Messier, 2009).***

Genetic predisposition: OA is a highly heritable disease, its heritability varies by the type of joint. Fifty percent of the hand and hip OA is attributable to inheritance. Emerging evidence suggests that persons with genetic mutations in proteins that regulate the transcription of major cartilage molecules are at high risk of OA ***(Felson, 2010).***

Malalignment: Joint alignment is one risk factor for OA that has been commonly investigated. Malalignment of the lower leg, in either the valgus or varus direction, has been found to influence the distribution of load across the articular surfaces of the knee joint, these increases in compartment loading that are thought to increase stress on articular cartilage and other joint structures, subsequently leading to degenerative changes ***(Tanamas et al., 2009).***

Malalignment has consequences beyond the direct effects on cartilage, including alteration in other knee-related tissues, such as bone-marrow lesions, that further propagate OA. These changes in the cartilage and other local tissues about the knee

lead to further malalignment, and it is this vicious cycle that is the major determinant of the rate of structural progression of OA of the knee ***(Hunter et al., 2009).***

The malalignment that cause OA generally occurs in the knee joints in the frontal plane. The normal balance of varus-valgus is commonly malaligned. If there is a degree of malalignment, it can lead to progression of OA and to pain and disability. Due to malalignment, the normal pressure points at the weight bearing joints shifts or the pressure falls on a much smaller surface area of weight bearing joints, which leads to increased wear and tear and OA. Malalignment (mostly in knee joints) develops over many years as a result of anatomical change in bones and joints ***(Felson et al., 2013).***

Trauma: Osteoarthritis may occur in cases when the joint has been damaged previously or if a joint was not correctly healed after an accident. Joint injuries may occur because of intense sports or different activities that imply an intense use of the joint. Osteoarthritis in young adults is most commonly a result of a previous injury to the knee ***(Gelber et al., 2000).***

Injuries to the anterior cruciate ligament (ACL) and menisci frequently occur in athletes. Although ACL ruptures occur less commonly in the general population, meniscal lesions are common both in athletes and in the general population. There is sufficient evidence that on long-term

follow-up, these lesions are associated with the development of knee OA, leading to pain and functional impairment in the young or middle-aged adult ***(Lohmander et al., 2007).***

Gender: Women not only are more likely to have OA than men, they also have more severe OA. The definite increase in OA in women around the time of menopause has led investigators hypothesize that hormonal factors may play a role in the development of OA ***(Zhang and Jordan, 2010).***

Biomechanical factors: Biomechanical factors have been suggested to be risk factors for OA as well as an important factor affecting disease progression. Biomechanics refers to the forces acting upon and within biological structures, including the effects produced by these forces. It is generally agreed that the pathomechanical component of OA is the result of two major categories of factors: (i) those that increase the regional load across articular cartilage, and (ii) those that affect the material properties and the remodelling process of articular cartilage ***(Jackson et al., 2004).***

Biomechanical factors play important roles in the health and function of the diarthrodial joint. Impact loading can cause acute damage to the joint. In vivo and in vitro studies have shown static compression suppresses matrix biosynthesis, and cyclic and intermittent loading stimulate chondrocyte metabolism ***(Guilak et al., 2004).***

Under physiologic conditions, joints of the body are subjected to millions of loading cycles resulting in forces of up to 10 times body weight passing through the joints. Under normal circumstances, such loads have no adverse effects on the cartilage or other joint tissues. Abnormal loads can lead to alterations in the composition, structure, metabolism and mechanical properties of articular cartilage and other joint tissues. Abnormal loading may be caused by a variety of factors such as obesity, immobilisation, joint instability, overuse or trauma ***(Guilak, 2011).***

All joints are exposed to biomechanical loading but most scientific data result from the lower extremity, especially from the knee joint, because it is the most commonly affected joint by OA. Over the last two decades it has been shown that altered joint biomechanics of the knee, such as loss of cruciate ligaments, removal of menisci, posttraumatic cartilage damage, changes in bone alignments, unloading through casting, and overloading through intense exercise may cause disease initiation and progression of cartilage degradation ***(Egloff et al., 2012).***

Pathology of osteoarticular cartilage

Normal cartilage: The cartilage is avascular, aneural, and alymphatic so nutrients and hormones need to diffuse from the synovial fluid through the matrix to reach the cells. Individual chondrocytes are very metabolically active, but the low cell density means a low overall metabolic rate within the articular cartilage ***(Hendren and Beeson, 2009).***

Articular cartilage is a highly organized connective tissue, comprising a single type specialized cell (the chondrocyte) within an extracellular matrix (ECM). Although relatively thin, it has great durability and can provide normal joint function throughout an entire lifetime. A variety of complex interactions between the matrix and the chondrocytes maintain a fine balance between synthesis and degradation of articular cartilage ***(Hendren and Beeson, 2009).***

The cartilage matrix consists of macromolecules in which collagen and proteoglycans (PGs) are the main representatives. These components are highly ordered from the cartilage surface to the deepest layers. Cartilage is divided into four zones with different functions: the superficial, middle or transitional, deep or radial, and calcified cartilage zones. Interestingly, there is no sharp boundary between the first three zones ***(Martel-Pelletier et al., 2008).***

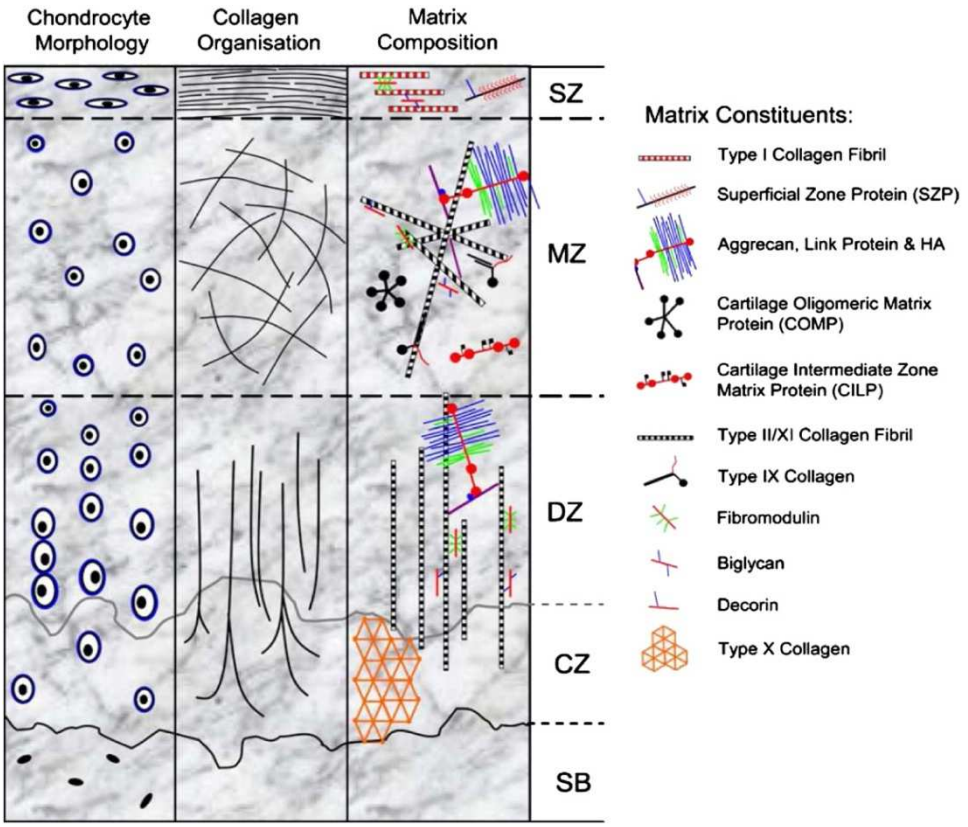

Fig.1. Schematic summarizing the macromolecular organization of mature articular cartilage. The tissue consists of four distinct zones: superficial (SZ), middle (MZ), deep (DZ) and a zone of calcified cartilage matrix (CZ), below which is the subchondral bone (SB). Each zone is distinct in terms of cell morphology (left), collagen fiber organization (middle) and the biochemical composition of its extracellular matrix (right) ***(Hayes et al., 2007).***

The outer surface area of articular cartilage can be divided into two zones, which is in contact with the synovial fluid and provides an essentially frictionless surface. The superficial zone