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Editorial

The Effect of Mechanical Loading on Articular Cartilage

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Abstract: The effect of mechanical loading on articular cartilage is the topic chosen for the second editorial of this newly launched journal. The aim of this interesting editorial is to illustrate the cell signaling correlated to the mechanical loading, some aspects of the mechanobiology and the positive and negative effects of the mechanical loading on articular cartilage. The benefits of the mechanical loading on articular cartilage have been shown to have a short- and long-term effectiveness. In this article, the role of mechanical signaling in the maintenance of articular cartilage and how the alterations in normal signaling can lead to joint pathology have been discussed.

Keywords: articular cartilage; osteoarthritis; mechanical loading; cell signaling; mechanobiology

1. Introduction

Articular cartilage (AC) is a specialized connective tissue that covers joint surfaces and facilitates the transmission of loads with a low frictional coefficient, allowing friction-free movement. Nevertheless, AC has very poor healing potential and is prone to both acute injury and degenerative conditions, such as osteoarthritis (OA), that are considered a medical challenge [1,2]. Both aging and mechanical loading influence AC homeostasis and are involved in the pathogenesis of degenerative joint diseases [3,4]. In AC, chondrocytes, which are the only present cells, are surrounded by the extracellular matrix (ECM) comprising a fibrillar network of both collagens and non-collagenous proteins immersed in a viscous water-based substance. The fibers are differently orientated and characterize the three zones of AC: the superficial zone (SZ) with fibers parallel to the articular surface, the intermediate zone (IZ) with fibers in oblique disposition and, finally, the deep zone (DZ) with vertical fibers perpendicular to the articular surface [2]. The DZ ends in a mineralized zone distinguished by the tidemark from the subchondral bone further below [5,6]. The ECM is also composed of large proteoglycan aggregates (PGAs) derived from a single hyaluronic acid (HA) (also called hyaluronan) with about 100 proteoglycans (PG) attached [7,8]. Aggrecan is the major PG of the AC, and it contains three globular domains (G1–G3) and is built by a core protein attached with glycosaminoglycans (GAGs) and oligosaccharide chains [7,8]. The high tensile strength and low compliance of AC is given by GAGs that attract cations and water, resulting in swelling, counteracted by the fibrillar network [7,8]. During the joint loading, the PGAs are compressed and they permit the distribution of the force on the rest of the joint surface, thereby reducing the pressure on the AC [9]. The joint surface is lined with a glycoprotein called lubricin, produced by both chondrocytes and synoviocytes [10–12]. It has boundary lubrication properties, facilitating low friction levels at the interfacing surfaces of AC [10–12]. Loss of lubricin influences the functional properties of synovial joints and could have a role in the pathogenesis of cartilage degeneration [10–12].

2. Cell Signaling and Articular Cartilage Morphology Changes in Response to Mechanical Loading

AC has been considered a post-mitotic tissue with virtually no cellular turnover. This has been based on the fact that the tissue is hypocellular and avascular and relies on diffusion for its nutrient supply. Mechanical loading of AC stimulates the metabolism of chondrocytes and induces the biosynthesis of molecules to preserve the integrity of the tissue [1,2]. Mechanical signals modulate biochemical activity and changes in cell behavior through the so-called mechanotransduction. Compression of cartilage leads to complex changes within the tissue including matrix and cell deformation, hydrostatic and osmotic pressure, fluid flow, and altered matrix water content, ion concentration and fixed charge density [7,9,11,12]. These changes are detected by mechanoreceptors on the cell surface, which include mechanosensitive ion channels and integrins. The activation of these mechanoreceptors initiates intracellular signaling cascades, leading to the tissue remodeling process. Excessive mechanical loading also influences chondrocyte metabolism but, unlike physiological stimulation, leads to a quantitative imbalance between anabolic and catabolic activity resulting in depletion of matrix components [7,9,11,12].

Integrins are transmembrane proteins that activate internal cell signaling by binding chemical molecules, such as cytokines and growth factors. They are very important in cartilage structuring as they are involved in the interaction between chondrocyte and ECM by forming bonds between them and collagen type II, VI and fibronectin [13,14]. It has been shown that stretch-activated ion channels and integrins lead to the release of interleukin (IL)-4 by human articular chondrocytes in response to mechanical stimulation [13,14]. IL-4 stimulates the expression of aggrecan, and decreases matrix metalloproteinases (MMP)-3 [15]. IL-4 possesses anti-inflammatory properties, underlined by the enhancement of the breakdown of mRNA for the transcription factor of nuclear factor kappa B (NFκB) and the suppression of both IL-1 and tumor necrosis factor alpha (TNF-α) expression [16]. IL-1 and TNF-α reduction is due to IL-10 which suppresses the translocation of NFκB, working in addition to IL-4 [17]. Moreover, the IL-10 expression has been found enhanced following a single bout of resistance exercise in patients with OA, and this has been included among the beneficial effects of exercise on OA [18]. When articular lesions occur, due to both acute and long-term overloading, various peptides from matrix components, e.g., fibronectin fragments (FN-fs), are released, indicating a damaged ECM. The repair process begins with the removal of broken structures before laying down new ones [14]. FN-fs bind to integrins and toll like receptors (TLR) and, via NFκB, lead to an increased expression of proinflammatory cytokines such as IL-1, -6, -8 and TNF-α as well as MMPs, disintegrin and MMP with thrombospondin motifs (ADAMTS), leading to further destruction and breakdown [14,18]. Matrix breakdown products from fibromodulin and decorin (members of the small leucine-rich PGs, SLRP) and collagen or COMP (cartilage oligomeric protein) can activate integrins, TLRs and the complement system, resulting in the same catabolic effect [19]. TLRs are upregulated by IL-1 and TNF-α, which, through the NFκB signaling pathway, lead to growing quantities of MMPs, nitric oxide (NO) and prostaglandin E2 (PGE2) [20]. Moreover, the NFκB pathway has been also shown to inhibit the TLRs and lubricin expression. Lastly, receptors for advanced glycation end-products (RAGEs) have been found on the chondrocytes [21]. The stimulation of RAGEs triggers the NFκB pathway and the biosynthesis of IL-6, IL-8, TNF-α, MMPs and ADAMTS [21].

There are clinical studies on patients showing reduced thickness (>10%) of AC in the knee joint, in the absence of normal joint loading [22], and also in partial loading following an ankle fracture in the knee of the affected leg [23]. Animal models provide supplementary details on this issue [24]. Indeed, knee joint immobilization leads to reduced GAG content, especially from the SZ [25,26], with unchanged collagen content [25]. The AC is softer due to either reduced stiffness of the collagen network, or a decrease in PG content with unchanged conditions [26,27]. These findings suggest that the lack of mechanical stimulation results in thinner and softer AC, which is also more susceptible to trauma, as collagen damage occurs earlier in thin cartilage [28]. Moreover, *in vitro* studies showed that collagen fibrils are more susceptible to degradation when in a sagging state and compared to

the one under tension [28]. In rats, the unloaded, passive movements were responsible for cartilage atrophy development, which was caused by an increase in MMPs and ADAMTS [29]. This increase in breakdown enzymes during unloading could be due to the decreased expression of IL-4 or IL-10, which determine their suppressive effect on NFκB, as such resulting in catabolism. Atrophy seems only partially reversible and remobilization does not fully restore the stiffness [27] or the GAG content in the areas of the joint without weight bearing [26,27]. In the animal model, moderate loading demonstrates increased PG content in the DZ only, with unaltered content of collagen [24,30]. A magnetic resonance imaging (MRI) study on players failed to show a significant difference in the AC thickness between lifelong and highly active players and physically inactive controls [31,32]. However, increases in the total surface area of the tibia and patella cartilage were found, suggesting how AC adapts to increased mechanical stimulation [31,32]. As the area and thereby the volume expands, exercise could be speculated to preserve the optimal (normal) thickness and thus the deformation capacity as well, and due to the larger surface area the AC is able to withstand a greater amount of loading and stress [9]. A difference has been noticed in the deformation capacity in groups of different training status (professional weight-lifters, bobsleigh sprinters and untrained controls) [33]. Furthermore, increased thickness of the patella cartilage, but not the rest of the knee, was found, with the surface area being equal to controls [34]. The cartilage of the patella shows a "dose-dependent" deformation with increased loading and range of motion, while the tibia and especially the femur cartilage do not [33]. Thus, it seems that a tendency towards increased patellar cartilage thickness in athletes performing power sports and a tendency towards larger tibia and patellae surface areas of endurance sports exist, but these findings should be confirmed in larger samples. Patellofemoral pain (PP) is a common and debilitating disorder. Elevated cartilage stress of the patellofemoral joint is hypothesized to play an important role in the pain onset. The knowledge of normal patellar tracking is essential for understanding the knee joint function and for diagnosis of patellar instabilities. The PP has been associated with the mechanical environment during stair climbing, but the contribution of loading to this condition is not clearly understood. It was hypothesized that the loading conditions during stair climbing induce higher patellofemoral pressures, a more lateral force distribution on the trochlea, and a more lateral shift and tilt of the patella compared to walking at early knee flexion [35]. Stair climbing thus leads to more challenging patellofemoral contact mechanics and kinematics than level walking at early knee flexion. The increase in patellofemoral pressure, lateral force distribution and lateral tilt during stair climbing provides a possible biomechanical explanation for the patellofemoral pain frequently experienced during this activity [35]. Patellofemoral joint contact areas should be measured under loaded conditions to account for cartilage deformation and changes in patellar alignment that may occur with load. This is particularly relevant when trying to understand potential mechanisms of PP. Understanding the complex interaction between cartilage contact area, joint contact forces, and resulting cartilage stresses in the patellofemoral joint might be helpful in defining the mechanisms responsible for pain and establishing more effective treatment strategies [36].

Hosseini and coauthors [28] have reviewed the literature to describe the amount of pressure intervals needed for no damage, softening, collagen loss and visual damage, respectively, which all seem to overlap. AC from pigs enclosing the subchondral bone exhibits that destruction arises in stages depending on loading intensity. The earliest damage is represented by the cartilage softening without collagen loss, the next step is collagen loss without visible damage and, finally, macroscopic destruction appears [28]. In dogs, overloading shows diminished GAG content both in the SZ and IZ, along with cartilage softening due to change in the organization of the collagen network [24]. Moreover, subchondral bone remodeling with chondrocyte loss, especially in the SZ, was observed, and the calcified zone was enlarged by a tidemark duplication in the superficial direction, thus marking the irreversible transition to OA [24]. With the destruction of SZ, damage propagates through the IZ and DZ, ultimately leaving behind a thin lining of AC yielding the radiological characteristics of OA with joint space narrowing, osteophytes and subchondral sclerosis [37].

3. Mechanobiology and Physical Activity

Mechanobiology is an emerging field of science between biology and engineering that investigates the role of movement and biomechanics in determining morphology and cell function. It is based on the concept that physical forces and changes in cell or tissue mechanics contribute to development, physiology, and disease. The main function explored is the mechanotransduction, the molecular mechanism by which cells respond to mechanical stimuli. The development of AC *in vivo* [38], indeed, is influenced by mechanical stimuli, since they have both anabolic and catabolic effects on chondrocytes [39,40]. Understanding the mechanically-induced chondrogenesis of mesenchymal stem cells (MSCs) is of great interest for cartilage tissue engineering research, with the aim to produce cartilage with functionally competent mechanical properties. It has been demonstrated that mechanical stimulation induces the differentiation of undifferentiated stem cells in chondrocytes [41,42]. Dynamic compressive loading is one of the most employed systems of mechanical stimulation in MSC-based cartilage regeneration [43], although it is less potent than growth factor treatment in initiating MSC differentiation. However, different factors, such as a pre-differentiation period and some specific loading parameters, could enhance mechanically-stimulated MSC-based chondrogenesis [38]. Moreover, differentiated MSCs are able to maintain a stable chondrogenic phenotype. The bioreactor system gives a multifactorial mechanical stimulation based on compression-shear loading and further enhances mechanically-induced chondrogenesis. The multifactor system is more potent than the single-factor system in inducing matrix biosynthesis in MSC-derived chondrocytes [44]. Even without exogenous growth factors, this kind of stimulation enhances collagen type II and aggrecan expression, and increases GAG production. Authors also reported the enhanced production of endogenous TGF-β following the mechanical stimulation [45]. These findings open the door to the possible manipulation of the MSC fate in tissue engineering-based therapeutic strategies, which should be certainly taken into account and thoroughly studied. Another important field in dynamic mechanical loading is represented by continuous passive motion (CPM). CPM is currently a part of patient rehabilitation regimens after a variety of orthopedic surgical procedures. The most commonly prescribed parameters within a CPM regimen are initiated on the first postoperative day, with an initial range-of-motion of 0 to 30 degrees and a frequency of one cycle per minute, for 6 to 8 h daily over six weeks. The lack of consistent standardized reporting of postoperative CPM protocols provides an impetus to researchers and clinicians to more clearly define and describe their use following knee articular surgery [46]. While CPM can enhance the joint healing process, the direct effects of CPM on cartilage metabolism remain unknown. Recent *in vivo* and *in vitro* observations suggest that mechanical stimuli (continuous passive motion) can regulate AC metabolism of lubricin, a putative lubricating and chondroprotective molecule found in synovial fluid and at the AC surface [47]. These findings are supported also by other studies where the authors described that mild physical activity improves lubrication by promoting lubricin synthesis and prevents cartilage degeneration in rats. It has been also demonstrated that physical activity increases joint mobility and lubricin expression in aged rats. Moreover, the beneficial effects of physical activity on the AC of rats with glucocorticoid-induced osteoporosis have also been evaluated by our research group [11,12,48].

Physical activity covers not just sports but also simple everyday movements. Physical exercise can play a crucial role in the treatment of cartilage diseases, optimizing both physical and mental health, enhancing energy, decreasing fatigue and improving sleep. An exercise program for patients with cartilage diseases aims to preserve or restore a range of motion of the affected joints, to increase muscle strength and endurance, and to improve mood and decrease health risks associated with a sedentary lifestyle [49]. Regular exercise has a great importance in maintaining good health, balance and posture, while inactivity represents a risk factor for different chronic diseases [50,51]. Regular physical exercise is normally suggested in cases of non-communicable chronic and neoplastic disease for its specific effects in reducing risk factors, and it also has an anti-inflammatory effect that is well known, as inflammation is the principal component of many chronic diseases [52]. Numerous epidemiologic studies have demonstrated that regular physical activity reduces risk for colon cancer, probably for

endometrium and postmenopausal breast cancers, and possibly for premenopausal breast, prostate, lung, and pancreas cancers. Thus, exercise, as a modifiable health behavior, has a strong potential for primary cancer prevention. Current recommendations call for at least 30–60 min of moderate to vigorous activity daily (aerobic (64% and 79%) and muscle-strengthening (79% and 81%) programs) as recommended by the American College of Sports Medicine (ACSM) and the American Cancer Society (ACS) [53,54].

Physical activity is also increasingly gaining importance in cancer treatment and is now considered to be feasible, safe, and even recommended in almost all stages of the disease. Different studies show that disease and treatment-related symptoms, such as fatigue, sleep disorders, and depression, which sometimes limit quality of life in cancer patients over years, can be reduced by physical activity. Physical activity is widely recognized as a means for the primary prevention of chronic diseases as well as in patients' treatment and rehabilitation. Recent evidence confirms previous findings suggesting that moderate physical activity is very important for the primary prevention of chronic diseases, it decreases all causes of mortality and it is one of the determinants for physical and psychological well-being [55].

4. Conclusions

AC is able to adapt to the amount of mechanical loading as well as to the rest of the musculoskeletal system, where moderate use leads to hypertrophy while immobilization causes atrophy, both primarily due to changes in the content of PGs. Slightly in divergence to other parts of the musculoskeletal system, mechanical overloading of cartilage causes substantial damage to the collagen network and, due to lack of regenerative capacity, this leads to irreversible destruction and is thus the most apparent triggering cause of OA. Conversely, biomechanical stimulus generated by dynamic compression during moderate exercise can reduce the synthesis of proteolytic enzymes, regulating the metabolic balance and preventing the progression of the disease. Moderate adapted or tailor-made physical activity and normal mechanical joint loading is extremely important in a healthy joint. Moderate and adapted exercise promotes the correct movement of our bodies, preventing weakening of the joints and alterations in the AC. For this reason, physical activity should be considered as a complementary and optional non-pharmacological treatment in patients with OA as recommended in national and international guidelines, including EULAR and OARSI, for the treatment of this severe disease. Moreover, mechanical stimulation should be certainly taken into account in manipulation of the MSC fate in tissue engineering–based therapeutic strategies for the reconstitution of a healthy AC with natural mechanical properties.

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