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Współczesne poglądy na temat roli i patogenezy choroby zwyrodnieniowej stawu kolanowego

Streszczenie

Choroba zwyrodnieniowa stawów (ChZS) jest najczęstszą chorobą układu ruchu związaną z przewlekłym bólem i niepełnosprawnością. Charakteryzuje się degradacją chrząstki stawowej, zmianami struktury kości podchrzęstnej oraz lokalnym zapaleniem w obrębie stawu. Powszechność występowania oraz wysokie koszty leczenia powodują, że ChZS coraz częściej uznawana jest za chorobę cywilizacyjną. W Polsce cierpi na nią około 8 mln ludzi, z czego u 40% dotyczy stawów biodrowych, a u 25% stawów kolanowych. Jej częstość występowania wzrasta wraz z wiekiem a nadwaga i otyłość sprzyja jej rozwojowi. Szczególnie zagrożone są osoby, które były otyłe w dzieciństwie i w młodym wieku. Do głównych objawów klinicznych zalicza się: ból, obrzęk, sztywność, ograniczenie funkcji i zakresu ruchów, deformacje stawu. Klasyczna radiologia stanowi najbardziej dostępne narzędzie diagnostyczne do oceny ChZS. Najlepsze w diagnostyce wczesnej postaci patologii chrząstki stawowej wydaje się być skojarzenie badania USG i MR.

Do oceny wielkości i miejsca uszkodzenia chrząstki stawu kolanowego obecnie stosowana jest artroskopia. Głównymi komponentami ubogokomórkowej tkanki są chondrocyty oraz bezpostaciowa substancja międzykomórkowa, która zbudowana jest z macierzy chrzęstnej oraz gęsto ułożonych włókien kolagenowych. Chondrocyty to komórki o typowym kulistym lub heksagonalnym kształcie. Stanowią mniej niż 1% objętości dojrzałej chrząstki, otoczone są macierzą około komórkową. Posiadają zdolność do produkcji kolagenu typu II i agrekanów. Najważniejszą cechą chondrocytów uzyskanych od osób z ChZS jest ich nadreaktywność. Najważniejszym czynnikiem samonaprawy jest interakcja pomiędzy kolagenem macierzy a proteoglikanami.

Zapobieganie wystąpieniu ChZS jest bardzo istotne prognostycznie.

Słowa kluczowe: choroba zwyrodnieniowa stawów, chrząstka stawowa, chondrocyty, diagnostyka ChZS.

Current views on the role and pathogenesis of osteoarthritis of the knee

Abstract

Osteoarthritis (OA) is the most common condition of the motor system accompanied by chronic pain and disability. It is characterized by articular cartilage degradation, subchondral bone lesions and a local inflammation within the joint. High costs of treatment and great incidence of OA have led to recognizing this condition as a civilization-related disease. In Poland eight million people suffer from OA. In 40% of the cases the disease is located in hip joints and in 25% knee joints. The prevalence increases with age and overweight and obesity create favorable conditions for the development of the disease. People who were obese in their childhood or adolescence are more likely to suffer from OA. The main clinical symptoms include pain, edema, stiffness, limited function and scope of movement and joint malformation. Radiology is the most available diagnostic technique to assess OA. In early diagnostics of articular cartilage pathology the best option is to combine ultrasonography and magnetic resonance imaging.

Currently, in order to assess the size and location of defects of articular cartilage doctors perform arthroscopy. The main components of this hypocellular tissue are chondrocytes and amorphous intercellular substance which in turn is composed of cartilage matrix and densely packed collagen fibers. Chondrocytes are typically spherical and hexagonal shaped cells. They account for less than 1% of the volume of mature cartilage and are surrounded by pericellular matrix. They have the ability to produce type II collagen and aggrecans. The most important feature of chondrocytes obtained from OA patients is their hyperreactivity. While the most important factor of self-healing is the interaction between collagen matrix and proteoglycans.

Osteoarthritis prevention is prognostically useful.

Keywords: osteoarthritis, articular cartilage, chondrocytes, OA diagnosis.

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Introduction

Osteoarthritis (OA) is the most common condition of the motor system accompanied by chronic pain and disability. It is characterized by articular cartilage degradation, subchondral bone lesions and local inflammation within the joint [1]. High costs of treatment and high incidence of OA have led to recognizing this condition as a civilization-related disease [2]. An analysis of incidence of OA shows that 4% of the population below 25 years of age suffer this disease. In the population below 35 years it is 5%, in people over 65 years – 70% and in the population aged between 75-79 years as much as 85%. Epidemiological studies show that in Poland eight million people suffer from OA and in 40% of the cases the disease is located in hip joints and in 25% in knee joints. In the United States it is osteoarthritis that is the cause of 95% of medical interventions connected with joint diseases. Treatment costs (medical advice, imaging, rehabilitation equipment, hospitalization, rehabilitation and health resort treatment) rise together with the costs of treating adverse outcomes of commonly used medicine which include stomach ulcer or bleeding from the gastrointestinal tract [3]. There are many theories which aim at explaining the mechanism of joint degeneration development. The prevalence increases with age and overweight and obesity create favorable conditions for the development of the disease. People who were obese in their childhood or adolescence are more likely to suffer from OA. Decreasing weight by 5 kg reduces the risk of developing symptomatic OA by 50%. Main clinical symptoms include pain, edema, stiffness, limited function and scope of movement and joint malformation [4-6].

OA diagnosis

Radiology is the most available diagnostic technique to assess OA. The evaluated symptoms include osteophytosis, joint space narrowing, subchondral cysts, subchondral sclerosis and enthesophytes. A predictor in a knee joint is the width of the space between medial condyle of femur and medial tibia. Lack of articular space serves as a reliable sign of cartilage loss and is the main indication to perform a knee joint replacement surgery [7,8].

Current imaging diagnostics of an early stage of articular cartilage pathology is mainly based on ultrasonography and magnetic resonance imaging (MRI). Ultrasonography detects fibrillar microstructure of tendons and ligaments, fascicular structure of nerves and bipennate muscles [9]. Ultrasound imaging has many advantages among which there is a relatively easy access with no need of prior preparation of the patient and the possibility of dynamic assessment of the cartilage depending on the situation of the joint. It allows for the assessment of grade I chondromalacia in which the cartilage is soft with no discontinuity of the bone surface and grade IV chondromalacia where deep fissures exposing subchondral tissue are visible. The biggest disadvantages of ultrasonography include no possibility to assess endostea and subjective evaluation of the examiner [10,11]. In early diagnostics of OA in a knee joint, MRI plays a vital role as it provides precise imaging of articular cartilage with the ability to measure its thickness but it also allows for assessing intra-articular structures and bones. Cartilage lesions are depicted as defects with irregular contours. The classification of chondromalacia is as follows. Grade I – softening of articular cartilage, grade II – softening of articular cartilage with fibrillation, fissuring and blisters, grade III – when lesions extend down to 50% of cartilage depth it is classified as grade IIIa and when the lesions reach over 50% it is classified as grade IIIb. If defects are visible through the whole depth of the cartilage and the subchondral bone is exposed- it is classified as grade IV. The disadvantages of this method include high costs and a relatively long examination during which the patient must stay completely still [12,13]. The best option in cartilage diagnostics seems to be a combination of ultrasound imaging and MRI. This solution allows a clinician to precisely plan further treatment.

Currently, in order to assess the size and location of defects or the condition of articular cartilage doctors perform arthroscopy. Among many grading systems, the most common is a four-grade Outerbridge classification. The classification of chondromalacia is as follows: grade I: distinctly soft unbroken surface of the cartilage, grade II: fissures on the surface that reach less than half of its depth, grade III: deeper fissures but not to the level of subchondral bone and grade IV: exposed subchondral bone. Arthroscopy depicts diffused and focal lesions which may appear in isolation or they can co-exist with lesions of other intra- and extra-articular surfaces.

Currently, arthroscopy is believed to be a valuable method employed in articular cartilage assessment. It allows for assessing a macroscopic condition of its surface, its flexibility, color and situation of the lesion. One of the advantages of this method is the possibility to perform surgery during the examination [14-16].

Articular hyaline cartilage structure

Mature articular cartilage has no blood or lymphatic vessels. Main components of this hypocellular tissue are chondrocytes and amorphous intercellular substance which in turn is composed of cartilage matrix and densely packed collagen fibers. Matrix is composed of proteoglycans which consist of protein core with covalently attached chondroitin and keratan sulfate chains [17]. The most important cartilage proteoglycan is aggrecan which interacts with hyaluronic acid thanks to globular domain in core protein. Collagen proteins that create fibers are an important element of extra-cellular matrix . They account for 70% of dry mass of cartilage [18,19]. Type II collagen fibers are distributed evenly and together with type XI collagen they form a net of fibers which in turn interacts with type IX collagen [20]. With cartilage maturation, the concentrations of type I and III collagen decrease. Among structural proteins we can find chondronectin, fibronectin, tenascin-C, C- and N-terminal collagen propeptides and GLA proteins. A vital component of this group is matrix GLA protein (MGP) – a small molecule protein that is vitamin K dependent [21]. This protein probably protects cartilage matrix against calcification and regulates differentiation of chondrocytes. This protein is secreted by proliferative chondrocytes and smooth muscles of the vascular wall [22]. It also acts as inhibitor of bone morphogenetic protein 2 (BMP-2) which is believed to be the main osteogenic factor. A considerable reduction of MGP concentration in serum may be a cause of articular cartilage calcification accelerating degeneration [23-25].

Enzymatic proteins include matrix metalloproteinases (MMPs) whose enzymatic activity is Zn^{2+} and Ca^{2+} ions dependent. They play a vital role not only in degradation of extracellular matrix but also in angiogenesis [26,27]. In cartilage we can find mainly MMP-1 which is responsible for degradation of type I, II and III collagen; MMP-2 (gelatinase A) and MMP-9 (gelatinase B) which degrade type IV and V collagen and MMP-3 (stromelysin) that degrades proteoglycans and collagens. MMPs secretion is regulated at the level of transcription by growth factors, cytokines, hormones, cell cell or cell extracellular matrix interactions as well as by physical factors e.g. ultraviolet radiation [28]. Metalloproteinases are produced as inactive pro-enzymes (pro-MMP). Degradation of extracellular matrix leads to destroying the barrier which strongly affects cellular migration under normal and pathological conditions. The main MMP inhibitor is glycoprotein TIMP-1. Its expression is regulated by cytokines, mainly by interleukin-1 (IL-1), tumor necrosis factor (TNF- α), tumor growth factor (TGF- β), interleukin-6 and interleukin-10 (IL-6, IL-10). Another MMP inhibitor is non-glycosylated protein produced by fibroblasts TIMP-2 which can bind to progelatinase though it is not susceptible to the action of cytokines. Moreover, TIMPs regulate cell migration, inhibit angiogenesis and induce or prevent programmed cell-death [28-31]. Among other inhibitors of metalloproteinases we can find: plasminogen activator inhibitors (PAI-1, PAI-2), cysteine proteases and TNF-stimulated gene 6 protein (TSG-6) [17].

Chondrocytes are typically spherical and hexagonal shaped cells derived from mesoderm. They account for less than 1% of the volume of mature cartilage and are surrounded by pericellular matrix [32]. They have the ability to produce type II collagen and aggrecans which makes them easily identifiable e.g. in tissue cultures. Access to oxygen and nutrients from synovial fluid is possible through simple diffusion [19]. Chondrocytes are specific as they have the ability to produce and secrete both the components of the matrix and enzymes that deteriorate it. The synthesis is regulated by locally produced cytokines. Plasma membrane of chondrocytes is rich in integrin receptors for fibronectin (α5β1), type II and VI collagen (α1β1, α2β1, α10β1), laminin (α6β1), as wells as for vitronectin and osteopontin (αvβ3). The receptors are essential to regulate articular cartilage turnover. The role of growth factors such as insulin-like growth factor 1 (IGF-1) and transforming growth factor β (TGF– β) is to prevent cartilage degradation by interacting with the above mentioned receptors. However, stimulation of chondrocytes through IL-1 and TNF-α leads to a higher secretion of enzymes degrading cartilage and to an inhibition of proteoglycan and type II, IX and XI collagen syntheses [17]. Synergic action of IL-1 and IL-17 has been observed in stimulating production of nitrogen oxide and prostaglandin E_2 [33]. A less intensive, though still a similar effect to IL-1 in stimulating gene expression for cyclooxygenase 2, induced nitrogen oxide synthase, IL-6 and MMP-3 has been found in IL-18 [30]. It has been reported that concurrent stimulation of type I and III collagen synthesis leads to the production of osteophytes. In normal conditions catabolic action of IL-1 is inhibited by interleukin-1 receptor antagonist (IL-1 RA), IGF-1 and TGF-β which in turn inhibit the expression of receptors. Soluble receptors (Stef-R) lead to the inhibition of TNF-α. In such conditions catabolism is slow and the ability of chondrocytes to degrade the matrix is physiological. The most important for the normal function of cartilage is the balance between the degradation and synthesis of cartilage matrix. Chondrocytes show major histocompatibility complex (MHC) class I and II antigen expression as well as the ability to present antigens to lymphocytes T. Natural killer (NK) cells whose activity is stimulated by IL-2 produced by lymphocytes T take part in destroying chondrocytes. Thus, chondrocytes may serve as the aim of immunological response but they also may actively participate in the induction of immunological reactions which destroy cartilage [17,19].

Protective properties of articular cartilage can be found e.g. in IL-11, IL-13, IL-4 and IL-10 [34,35].

Cartilage damage

Knowledge of the structure and physiology of cartilage allows for understanding its function and pathomechanism responsible for its damage in OA. It has been reported that the most important feature of chondrocytes obtained from OA patients is their hyperreactivity [36,37]. As mentioned above, IL-1 and TNF-α play the key role. It has been shown that stimulated chondrocytes are also a source of chemokines: monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), macrophage inflammatory protein β (MIP-1 β), and regulated on activation normal T-cell expressed and secreted (RANTES) [38]. Their receptors are also produced and they include: CCR1, CCR-2, CCR-3, CCR-5, CXCR-1, CXCR-2 [39]. More attention should be paid to the role of vascular endothelial growth factor (VEGF) which takes part in angiogenesis and ossification that are in fact processes observed in hypertrophic cartilage. Enomoto et al. showed that immunoactivity of VEGF positively correlated with cartilage degradation. They also reported increased expression of VEGFR-1, VEGFR-2 i NRP-1 receptors in OA patients while they showed that concentration of these molecules in healthy patients was on the verge of detectability [40].

In recent years there has been a need to find a sensitive and precise biochemical marker which could reflect metabolic changes in subchondral bone. We should emphasize the usefulness to employ multiple marker assays at the same time [41]. Lis reports that a low concentration of already mentioned MGP may corroborate the development and progression of OA and correlate with cartilage matrix deterioration. It is a negative predicator which accelerates progression of degenerative changes [42]. Lis reports that the determination of MGP concentration in serum may be very useful in OA diagnosis. Among the assayed markers those taken under consideration are cartilage oligomeric matrix protein (COMP) and type II collagen degradation products (CTxII i C2C) [38,41,43]. Vilim claims that the determination of COMP concentration is useful only in the early stage of the disease [44]. In line with this conclusion is Lis who believes that the assay performed at a later stage has no real clinical value [41,43]. Conrozier et al. showed a strong correlation between the concentration of collagen degradation products in serum with joint space narrowing in patients with OA [45,46]. Whereas Garnero reports that low concentration

of the assayed substances which is connected with advanced cartilage damage may lead to misinterpretation [32]. On the other hand, Lis claims that low concentrations of both COMP and C2C may be good predictors of disease progression. [41,43]

More and more often bone sialoprotein (BSP) is seen as a useful biochemical marker of changes in subchondral bone turnover. Carlinfante et al. reported that BSP is a sensitive marker of changes in bone turnover. This glycoprotein controls mineralization of bone through strong interaction with hydroxyapatite [13]. Synovial fluid seems to be a good diagnostic material in which high concentration of BSP reflects the damage of bone tissue [47,48].

Marker YKL-40 is recognized as an antiapoptotic factor and it participates in proliferation and angiogenesis. Johansen et al. showed increased concentration of this marker within synovial fluid in OA patients [49]. It has been proven that chondrocytes, synovial or tumor cells secrete YKL-40. It has also been found that the concentration of protein in serum positively correlates with the degree of articular cartilage damage [50]. While Kawasaki et al. reported that YKL-40 concentration is more of a reflection of articular tissue inflammation than cartilage metabolism [51].

Osteopontin (OPN) is one of proteins commonly present in extracellular fluids and extracellular mineralized matrix [52]. Apart from the attributed chemotactic function of immunological cells the role of the inhibitor of inflammatory reaction has been demonstrated through limiting the production of nitrogen oxide, prostaglandin E_2 and IL-1. Pulling et al. reported a considerable expression of mRNA in damaged cartilage [53].

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