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Osteoarthritis – a multifactorial issue

Choroba zwyrodnieniowa stawów – problem wieloaspektowy

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Summary

Osteoarthritis is a progressive disease causing pain and structural and functional changes in the affected joints. The increasing incidence of the disease is associated with society aging and the obesity epidemic. This progressing chronic disease causes disability and loss of independence. Treatment of this disease is focused on pain relief and includes treatment with non-steroidal anti-inflammatory drugs, diet supplements with glucosamine, chondroitin, and injections of hyaluronic acid into the affected joint. A very important part of treatment is physiotherapy as well as non-pharmacological treatment including patient education, body weight reduction, use of orthopedic equipment facilitating motility and kinesitherapy. The article is a review of the osteoarthritis literature, the disease pathophysiology and the ways of treatment.

Streszczenie

Choroba zwyrodnieniowa stawów to postępujący proces chorobowy będący przyczyną bólu, zmian strukturalnych oraz funkcjonalnych w zajętych stawach. Coraz częstsze występowanie tej choroby ma związek z wydłużeniem czasu trwania życia ludzkiego oraz z epidemią otyłości. Ten proces chorobowy jest przyczyną utraty samodzielności. Obecnie leczenie przede wszystkim polega na łagodzeniu objawów bólowych i obejmuje: stosowanie niesteroidowych leków przeciwzapalnych, suplementów diety zawierających siarczan chondroityny, glukozaminę, iniekcje dostawowe z kwasem hialuronowym. Ważnym aspektem terapeutycznym jest stosowanie zabiegów fizjoterapeutycznych. Leczenie powinno obejmować również postępowanie niefarmakologiczne oparte na edukacji zdrowotnej pacjenta, zmniejszenie masy ciała, pomoce ortopedyczne, sprzęt ułatwiający poruszanie się oraz ćwiczenia kinezyterapeutyczne, fizykoterapię. Artykuł stanowi przegląd literatury w zakresie choroby zwyrodnieniowej stawów, jej patofizjologii oraz leczenia.

Introduction

Osteoarthritis is defined as a multifactorial process featuring degradation of articular cartilage, subchondral bone and the capsular ligaments. The disease causes pain and functional changes of the joints [1, 2]. It is the most common cause of disability amongst the elderly, leading to a marked decrease in the quality of life and impeding independent functioning of osteoarthritis patients [2–5]. The prevalence of the disease is related not only to extended life span but also to the obesity epidemic [2, 6]. Changes in the joints indicating an active degenerative process are diagnosed at a radiographic scan in 60% of all individuals past the age of 60 [6]. In ca. 80% of patients in that group there is a pronounced limitation of joint mobility, and in 25% of them it leads to disability [6]. It is estimated that osteoarthritis affects 8 million people in Poland, with 25% of cases involving the knee joint [7].

Osteoarthritis is becoming an important economic problem, as it greatly reduces the ability to work, while expensive treatment is a burden to the state budget [2, 8]. Costs associated with osteoarthritis are related to: drugs, diagnostic examinations, hospitalizations, doctor's appointments, endoprostheses, full-time rehabilitation and sanatorium rehabilitation, and the costs of orthoses [8]. Osteoarthritis is estimated to be in the

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group of 10 diseases most frequently causing disability in the world [6, 9–11]. Nowadays, it is considered to be a lifestyle disease [2, 12], which additionally may become the reason for being made redundant. Chronic pain and disability lead to social isolation, depressed mood, and worsening of the financial situation of the family of the patient [8]. This intensifying health problem becomes a challenge not only for the health care system but also in the job market and insurance market [8]. Now there is a search for novel treatment strategies aiming to delay osteoarthritis progression [12].

The article is a review of the osteoarthritis literature, its pathophysiology and treatment.

Articular cartilage – its structure and physiological properties

Articular cartilage is a tissue of immense mechanical strength, significant elasticity and limited regenerative abilities [12, 13]. It is devoid of blood and lymph vessels, which underlines its unique mechanism of action [12, 14]. Due to the lack of vascularization, chondrocytes absorb oxygen and nutrients from synovial fluid by simple diffusion [12, 14]. Thanks to high elasticity, cartilage can easily deform due to the shift of loads accompanying movements [14]. An outstanding stability and a low value of friction coefficient are the result of densely packed collagen fibers consisting mainly of collagen II and the matrix composed mainly of proteoglycans [12, 14, 15]. Extracellular matrix of the cartilage accounts for 90% of its mass and consists of water (65–80%), lipids, and proteins [13, 14]. The major proteins found in cartilage matrix are collagens (10–30%) and proteoglycans (5–10%) [13]. One example of proteoglycans is aggrecan, composed of a combination of chondroitin sulfate and keratan sulfate chains [12, 16]. Aggrecan particles bind to hyaluronic acid (one particle of the acid vs numerous particles of aggrecan) forming elaborate multi-million-dalton compounds. Such structure contributes to the maintenance of high internal pressure and osmolarity without edema [12]. Other proteins appear in smaller amounts and fulfill regulatory functions and are responsible for proper metabolism of the cartilage [13]. Chondrocytes are responsible for maintaining balance between matrix production and degeneration, and hence for the process of cartilage tissue homeostasis. Key to the normal functioning of articular cartilage is the interaction between matrix collagen and proteoglycans found therein. Chondrocytes are also responsible for the secretion of both matrix components and enzymes which degrade them. Chondrocytes are sensitive to cytokines, growth factors and mechanical stimuli. Changeable loads move synovial fluid around, improving chondrocyte nutrition and stimulating matrix production. Fixed loads in turn reduce the production of aggrecan and binding proteins [12].

The growth factor protecting articular cartilage is transforming growth factor β (TGF-β), which probably stimulates collagen and proteoglycan synthesis. Also insulin-like growth factor 1 (IGF-1) exhibits anabolic activity. Most cytokines have a catabolic effect on articular cartilage by increasing the expression of matrix metalloproteinase (MMP). Such cytokines include interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α). Cartilage tissue does not contain any stem cells that could transform into tissue able to fill in the defects formed. Limited regenerative abilities of cartilage are related to its very slow metabolism consequential to e.g. lack of vascularization, which prevents inflammatory processes from full development [12]. An inflammatory condition may develop only in the acute stage of the disease and is typically turbulent and accompanied by inflammatory exudate, which – by the thinning out of synovial fluid – additionally reduces its nutrient and lubricating properties, speeding up cartilage degeneration [1]. Degenerative changes of cartilage most often concern the joints prone to heavy loads: knee, hip joints, cervical and lumbar spine [12].

Osteoarthritis – pathomechanism

Osteoarthritis is a degenerative disease affecting one or more joints [4, 9, 17, 18]. The exact mechanism by which this pathological condition occurs remains unknown [2–4, 19]. In the case of primary osteoarthritis, the etiology of the disease is associated with genetic factors. Currently, there are studies aimed at establishing mutations within genes responsible for the structure of articular cartilage [1, 6, 19]. The secondary form of osteoarthritis is a sequel to both acute and chronic injuries [1, 6, 12, 20]. The degree and extent of post-injury destruction of articular cartilage affect the rate of degenerative changes' growth [12]. The disease may also develop as a consequence of defects in the osteoarticular system, both congenital and developmental ones, metabolic disorders (gout), or hormonal disorders (acromegaly) [6, 12].

Risk factors that are not subject to modification in osteoarthritis are age, gender (women are affected more often), inherited susceptibility and race. Risk factors that can be modified are obesity, physical activity, muscle strength and joint injuries [9, 11]. Repetitive superficial joint injuries cause cartilage defects by depleting it of collagen fibers, proteoglycans and other underlying elements [6, 21]. Cartilage tissue in osteoarthritis degenerates due to collagen fiber damage [2, 3, 21]. The joint affected is too metabolically active, which leads to the

generation of a chronic inflammatory state [2]. The disease is also associated with edema and thickening of cartilage consequential to collagen network damage and increase in proteoglycan production by chondrocytes [2, 3]. Disease progression leads to thinning of the cartilage, and water and proteoglycans decrease. Finally, metalloproteinases are activated and proinflammatory cytokine expression is increased [1–3]. The concentration of proinflammatory agents rises, including the levels of IL-6, TNF-α, E_2 prostaglandin, leukotrienes and nitrogen oxide [1, 6, 22]. The subchondral layer witnesses the creation of degenerative cysts and tissue sclerosis [2], while along the chondro-osseous margin osteophytes and chondrophytes form; ligaments gradually lose their elasticity [2, 6, 18].

Osteoarthritis – clinical symptoms, diagnostics

The main symptom of osteoarthritis is pain in the joints [2, 6, 17, 18, 24]. In the early stage, pain occurs upon movement, walking or change of position. In the more advanced disease, pain accompanies the smallest movement or follows extended periods of immobilization (e.g. after a night sleep) [18]. Pain is associated with changes in structures, such as the periosteum, subchondral bone, synovial membrane, ligaments, muscles and tendon attachments [6]. With disease progression, joint mobility becomes reduced, periarticular tissues lose their elasticity, muscular atrophy occurs, and there is a gradual stiffening of affected joints which leads to disability [2, 3, 7, 18, 20]. The symptoms of an inflammatory condition occurring within a joint include swelling, redness, and increased skin temperature [1, 6].

A degenerative disorder may affect various joints, most frequently the spine, knee and hip joints, shoulder joints and the joints in the hand/arm [2, 7]. The knee joint, after the spine and hip joint, is the third most common location of degenerative changes [7]. By a biopsy of the synovial membrane one can detect the presence of a proliferative ependymal layer or lymphocytic infiltration [6]. Recently, it has been observed that the changes are accompanied by neutrophil activation, as expressed by their increased activity in blood serum [6].

Laboratory analyses are a highly important part of osteoarthritis diagnostics, e.g. an increased level of C-reactive protein (CRP) may indicate an inflammatory process within joints. An analysis of synovial fluid in turn demonstrates changes characteristic of inflammation, including a slight decrease in viscosity, increased protein concentration, and raised neutrophil rate. Some calcium pyrophosphate dihydrate crystals and hydroxyapatite crystals or fragments of degenerated cartilage may also be detected [6]. Radiographic imaging is the key in the diagnosis of osteoarthritis [6]. The most common classification of osteoarthritis dependent on radiographic findings is the five-point Kellgren-Lawrence grading scale [11, 24]. The scale considers the following features: presence of osteophytes, periarticular ossification, joint space narrowing, subchondral sclerosis and deformities of the articular surface of the bones [11]. More and more appreciated lately is ultrasound diagnostics, whereas critical to the diagnostic process is MRI scanning.

Osteoarthritis – treatment recommendations

The process of treating osteoarthritis includes nonpharmacologic treatment, pharmacologic treatment and surgery [25]. Therapeutic procedures are subject to various factors, such as age, coexistent diseases, pharmacotherapy followed, presence of local inflammation, the degree of pain intensity, damage of articular structures and degree of disability [25]. The standards of therapeutic conduct in osteoarthritis are updated by experts at scientific associations, such as the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR) and the Osteoarthritis Research Society International (OARSI). In 2012 the previous guidelines referring to therapies in osteoarthritis of the hand, hip, and knee were updated. Recommendations were developed by expert teams from numerous fields: rheumatology, orthopedics, geriatrics, psychiatry, primary care physicians and physiotherapists. The target of osteoarthritis therapy was to reduce pain and increase osteoarthritis patient life quality. Amongst nonpharmacologic therapies recommended by the ACR were: education of the patient and his family, encouragement to maintain everyday activity, including exercises suited to individual abilities of a given patient, joint protection against harmful mechanical factors, decrease in body weight and physiotherapy, including local use of thermal agents, and psychotherapy, along with participation in self-help programs [25]. The patient should also be provided with orthopedic devices [N5, N8]. Pharmacological management typically includes the application of paracetamol (acetaminophen). As it causes less adverse effects on the gastrointestinal tract, it is a weaker and safer medicine than the classical non-steroidal anti-inflammatory drugs (NSAIDs) [25, 26]. It may be used either in monotherapy or in combination with an NSAID if its use alone is insufficient [25]. In patients at risk of developing an ulcerous disease, it is recommended that proton pump inhibitors be administered [25, 26]. Non-steroidal anti-inflammatory drugs should not be administered to a chronic renal disease patient.

Topical NSAID use is recommended past the age of 75 [25]. Intraarticular glucocorticosteroids are recommended only in the case of strong pain not resolving with treatment. Not more than a few injections per year should be performed into one joint [26, 27]. Weak opioids, such as tramadol, codeine, or dihydrocodeine, may be used alternatively in patients not responding to NSAIDs or whenever NSAIDs are contraindicated. In knee and hip osteoarthritis patients past the age of 75, it is recommended that intraarticular injections with hyaluronic acid be performed (the therapy is not recommended in the treatment of hand osteoarthritis) and that tramadol or duloxetine be administered. Tramadol, regarded as a weak opioid, is recommended whenever NSAIDs prove ineffective or contraindicated. It may be used as a monotherapy or in combination with paracetamol and an NSAID in the case of severe pain. In the case of unusually intense pain, use of a strong opioid, such as morphine, is recommended, but non-cancer patients' rules apply. Strong opioids may be included in treatment only when nonpharmacologic and pharmacologic therapies prove ineffective in alleviation of symptoms, and when the patient does not qualify for a joint endoprosthesis. Glucosamine sulfate and chondroitin sulfate, although well tolerated by patients, were not included in the ACR 2012 recommendations due to ambiguous data obtained from literature analyzed by the experts. Alloplasty is recommended in severe osteoarthritis or after the failure of conservative treatment [25]. For instance, progressing osteoarthritis involving restriction of mobility, escalation of pain, and deformations of the joint, is the basis for qualifying the patients for, e.g. total knee alloplasty [7]. Knee joint alloplasty involves the introduction of foreign elements, which replace the degenerated knee, into the body [27]. It is a commonly accepted method of treatment of advanced degenerative disease [27, 28]. Knee implants are selected so as to match the patient's clinical situation, age, gender, biological activity and hormonal activity state of the bone tissue [27]. Knee plasty may be performed through classic or arthroscopic access [11]. Regrettably, the high demand for surgical treatment and insufficient financial means in this section of health care have resulted in long queues of patients awaiting surgical procedures [20]. In some leading centers, the waiting time for arthroplasty is several years.

Rehabilitation and physiotherapy

Lately, more and more attention has been paid to rehabilitation and physiotherapeutic interventions. Certain exercises improve muscle strength, joint mobility and articular cartilage nutrition [20]. In the study by Iwaniszczuk et al. [20], the effect of certain physiotherapeutic methods on the range of joint mobility improvement and pain decrease in hip osteoarthritis patients was evaluated. The study group included 30 randomly selected patients qualified for treatment at a day rehabilitation department. Osteoarthritis related to both hip joints in all patients. The efficacy of physiotherapeutic treatment in hip osteoarthritis was confirmed. Currently more and more focus is on the use of extracorporeal shockwave therapy (ESWT) in the treatment of knee osteoarthritis. Wang et al. [29] demonstrated that ESWT has a chondroprotective effect in knee joint disease in rats. In another study by Zhao et al. [30], 70 patients were observed, of whom 34 were administered ESWT and 36 received placebo. The objective of the study was to evaluate ESWT in knee osteoarthritis. The group undergoing ESWT showed less pain and improvement in knee joint function.

Selected therapeutic methods

Hyaluronic acid is a natural component of synovial fluid, which imparts elasticity and is responsible for proper functioning of articular surfaces [2, 3, 15]. It is a polysaccharide composed of glucuronic acid and *N*-acetylglucosamine [12, 15]. Hyaluronic acid extruded to synovial fluid by synoviocytes serves as a support structure for proteoglycans in cartilage [12, 18]. Viscosupplementation is a therapy involving intraarticular infusion of drugs affecting viscosity of synovial fluid (e.g. hyaluronic acid). It is becoming a more and more frequent element of osteoarthritis treatment, mainly due to the lack of adverse effects compared with prolonged NSAID use [2, 18, 31]. The most significant aspect of hyaluronic acid activity is its influence on normalization of rheological properties of synovial fluid, decrease in conduction and excitability of pain receptors, and inhibition of IL-1 proinflammatory activity [2].

The exact therapeutic action of hyaluronic acid has not been fully accounted for. Presumably, intraarticularly injected acid has antiinflammatory action and stimulates the production of hyaluronic acid by synovial membrane's fibroblasts [2, 18, 32]. Intraarticular injection of hyaluronic acid temporarily relieves the suffering of knee osteoarthritis patients [31].

Many studies have recorded the slowing down of disease progression and quality of life improvement in viscosupplemented patients [3]. An example of such a study is that of Gądek et al. [2], in which there participated 4519 osteoarthritis patients with the mean age of 54.2 (SD 13.2). Each of the qualified patients received 3 intraarticular injections of 20 mg of sterile hyaluronic acid over a period of 30 days. Very good and good drug tolerance was observed in 68.8% and 29.6% of the pa-

tients, and only in 1.6% were some adverse reactions, such as swelling, exudate, itching, redness and pain, recorded. It seems that some of the symptoms were induced by the injection itself. No serious adverse events were reported. The substance used in the study proved safe, effective and well tolerated by the study population. Due to rare adverse events during sodium hyaluronate administration, it is indicated in the treatment of osteoarthritis in patients who do not tolerate NSAIDs, i.e. in the elderly, or in cases where NSAIDs are contraindicated due to, e.g., gastric ulcers [2, 18].

Another study by Hładki et al. [3] included 138 knee osteoarthritis patients treated at an orthopedic or trauma surgery center (mean age 59.4 years). The patients had their medical history taken, and knee joint radiographic scanning and ultrasound examinations were performed. Those qualified for the study received 3 intraarticular injections of the medication one week apart. The preparation contained 20 mg of sterile sodium hyaluronate in 2 ml of solution. At 1 month and 6 months after the end of treatment, patients' condition was reassessed. The study demonstrated that viscosupplementation with the above drug is effective in reducing clinical symptoms of mid-stage osteoarthritis. As a result of the injection, a significant decrease in pain was noted both at rest and when moving vertically or laterally. In addition, a marked limitation or even recession of morning stiffness of the joint was observed following treatment.

A metaanalysis of hyaluronic acid use published in 2013 confirmed the safety and efficacy of the therapy when administered to patients with knee osteoarthritis [32].

Glucosamine is an amino sugar, one of the components of proteoglycans in articular cartilage [5, 12, 33]. It is isolated from crustacean chitin [33]. It protects cartilage by inhibiting the catabolic effect of IL-1. The onset of therapeutic action of glucosamine is slower than in the case of NSAIDs, but clinical research shows that it alleviates disease symptoms to a much greater extent than placebo and comparably to NSAIDs [12]. Glucosamine administered orally supplements its deficiency in the system and stimulates the biosynthesis of hyaluronan and proteoglycans required for articular cartilage reconstruction [1, 5].

Chondroitin sulfate is a long nonbranched polysaccharide composed of alternating glucuronic acid and *N*-acetylgalactosamine. Chondroitin sulfate is found in proteoglycans that form articular cartilage [12]. It demonstrates anabolic activity by intensifying the synthesis of proteoglycans in chondrocyte cultures [12, 33]. Summing up the findings of numerous studies involving chondroitin sulfate, glucosamine or a combination of both substances used to treat osteoarthritis, little improvement when compared with placebo was observed. A thorough insight into the mechanisms of action of glucosamine and chondroitin sulfate could serve as the basis for developing osteoarthritis therapy guidelines [33].

Today, the ACR does not recommend the use of chondroitin sulfate and glucosamine due to there being little evidence in favor of their advantageous effect. Treatment should take into account individual needs of the patient and must be modified to suit the patient's condition as the disease progresses [25]. An optimal therapeutic action should combine nonpharmacologic and pharmacologic modalities. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire use allows the monitoring of disease course and efficacy of the treatment applied. We need to stress that osteoarthritis is a disease that require cooperation of many specialists: rheumatologists, orthopedists, primary care physicians, psychologists, nursing staff and social workers [24].

Evaluation of articular tissue degradation rate

Collagens. Twenty different types of collagen proteins found in the human body have been described in the literature, of which the most abundant are collagens I–XII. Cartilage collagen forms a network of tiny fibers giving cartilage its shape and determining its tensile strength [13, 34]. Type II collagen is the basic collagen of cartilage matrix. It is estimated that it accounts for 90% of all collagen proteins [13, 34, 35]. As much as 85–90% of organic bone is type I collagen [13]. A product of type II collagen degeneration, CTx-II (*C*-terminal crosslinked α chains telopeptide type II collagen), is produced as a result of breakdown of type II collagen chains, forming cartilage matrix, and subsequently excreted by kidneys [13, 35]. Urine CTx-II level may indicate the rate of degradation of articular cartilage [13, 29, 31]. CTx-I (*C*-terminal crosslinked L chains telopeptide type I collagen) in turn is considered a marker of bone turnover. According to literature findings, the level of plasma CTx-II correlates with body weight and increases together with BMI increase. Many researchers have tried to evaluate the utility of using CTx-II urine concentration in osteoarthritis as an index of articular cartilage damage level [13]. The level of CTx-II is observed to be related to the rate of degenerative changes in articular cartilage [34]. Urine and synovial fluid CTx-II concentration plus CTx-I level and CRP determination may provide a complete picture of the intensity of degenerative changes and intensity of inflammatory processes in osteoarthritis, which could facilitate the diagnostic process and application of suitable treatment [13, 34, 35].

The study by Garnero et al. [36] conducted with the participation of 67 knee osteoarthritis patients (mean age

– 67, mean disease time – 8 years) and 67 control patients revealed that urine CTx-II concentration may be a useful marker in knee osteoarthritis. Urine CTx-II level was found to be a potentially better index of joint degenerative change progression rate than serum CRP since CTx-II concentration changes are detectable at an early stage of the disease, when inflammation markers are normal [34].

Osteoarthritis and lifestyle

Osteoarthritis significantly lowers the quality of life. Patients find it difficult to perform basic activities of daily life, which take up more and more time as the disease progresses, and may result in loss of independence [9]. The liaison between the osteoarthritis patient and the healthcare system should center on the nurse who teaches the patient how to cope with the new situation [37]. In the study of Sierakowska et al. [37], the study population included 100 patients diagnosed with osteoarthritis in line with ACR criteria, treated full-time and at an outpatient clinic. Degenerative changes in the study group mainly involved the joints of the spine (51%) and hands (49%). Knee and hip joint degeneration was observed in a comparable group of patients. According to the patients, the most oppressive health issue accompanying osteoarthritis was pain (82% of those polled) and limitation of mobility (47%). The evaluation of symptoms regardless of patient's age demonstrated pain intensification and mobility restriction with disease period extension, interlinked with its progressive and irreparable nature. More than 46% of the respondents in whom the disease had lasted more than 10 years required constant and systematic 24-hour care. Additionally, BMI in 46 patients indicated overweight and in 35 obesity. Only 14 patients followed the diet recommended for osteoarthritis. Respondents' behavior observed in the cited study reflects a lack of knowledge and lack of ability to cope with the disease, suggesting that professional preparation of patients for self-care is requisite, whereas elective and targeted education should constitute an important element of nonpharmacologic treatment.

In a study by Kuciel-Lewandowska et al. [38], 52 osteoarthritis patients were analyzed. The analysis of health behavior and lifestyles revealed a low proportion of patients actively spending their leisure time. Moreover, the studied patients did not relate a healthy lifestyle to a diet or physical activity. In their conclusions, the authors drew attention to the necessity of undertaking more effective educational actions in this group of patients.

Conclusions

Symptomatic treatment of osteoarthritis involves predominantly pain alleviation, inflammatory state reduction, and stimulation of articular cartilage regenerative processes. In line with the 2012 ACR guidelines, treatment of the osteoarthritis patient should also involve nonpharmacologic therapy based on health education, psychological support, body weight reduction, orthopedic aids, devices facilitating movements, rehabilitation and physiotherapy. Furthermore, it is important to take medical history data with attention to detail, including but not limited to any concurrent diseases, e.g. renal disease, gastrointestinal system disease, and circulation system disease, which will be of utmost importance when starting pharmacologic treatment. In patients with severe osteoarthritis or whenever conservative treatment fails, surgical intervention may become a solution.

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