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Review Article

Current Management in Osteoarthritis

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Abstract

Osteoarthritis (OA) is a process of destruction of joint cartilage, subchondral bone and other joint structures, leading to anatomical damage to the joint, impaired movement and pain. Secondary changes may be accompanied by synovitis, caused by degradation products of cartilage and bone. There is a disturbance in balance between the synthesis of articular cartilage components and their degradation.

Osteoarthritis is the most common chronic disease of the joints. It causes joint pain, stiffness, distortion and impairment of function, leading to disability. The disease occurs in the elderly, but it is not a consequence of aging.

Optimal treatment requires early diagnosis and removal of risk factors. Early diagnosis may be treatment non-pharmacologically, according to NICE's treatment in chronological order, and may still benefit from physical therapy. Late diagnosis requires more invasive treatments, including alloplasty, and prognosis is poorer. Diagnosis must be based on clinical examination and supported by imaging.

Obesity is the main modifiable risk factor for OA. Other factors are hyperglycemia, diabetes, and hypercholesterolemia, injuries of knees and hips and meniscus damage. Unmodifiable risk factors are female gender, age, joint malformations, trauma.

Pain and stiffness are symptoms of OA. Joint pain occurs after joint movement and disappears after rest. As the disease progresses, the pain appears already after small joint movements and finally during sleep. The main goals of treatment are patient education, pain reduction, function optimization, and the degenerative process modification. The current treatments OA are non-pharmacological methods, topically capsaicin and topically NSAIDs, paracetamol, then oral NSAIDs and, finally, arthroplasty.

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Introduction

Osteoarthritis (OA) is a process of destruction of joint cartilage, subchondral bone as well as other joint structures, leading to their anatomical damage, impaired movement and pain. The changes may be accompanied by synovitis, caused by the breakdown products of damaged cartilage and bone. There is a disturbance between cartilage synthesis and degradation.

The American College of Rheumatology (ACR) classified OA as a heterogenous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins" [1]. The American Academy of Orthopedic Surgeons (AAOS) offered a more detailed definition. OA is the result of both mechanical and biological events that destabilize the normal coupling of degradation and synthesis of articular cartilage and subchondral bone. Although it may initiated by multiple factors including genetic, developmental, metabolic, and traumatic, OA involves all the tissues of the diarthrodial joint. The disease presents as morphological, biochemical, molecular and biomechanical changes as well as cells and matrix, leading to the loss of cartilage and sclerosis of subchondral bone, forming osteophytes and subchondral cysts. It is characterized by pain, stiffness, loss of motion, crackling, sometimes the presence of fluid in the joint and local inflammation in various degrees of intensity" [2].

Both definitions highlight the fact that OA is not considered a degenerative disease of "wear and tear", but is a result of active biochemical, biomechanical and intercellular processes. Wear-and-tear from overuse does not cause OA, however biomechanical changes in the joint, not necessarily due to over-use of the joint, may cause OA. In the pathophysiology of OA, the presence of cartilage damage is of no particular importance, lather; it is considered a disease of the entire joint structure. The local destruction of articular cartilage, subchondral bone sclerosis, osteophyte formation, periarticular muscle weakness, weakened ligaments, slight synovitis of the joint, degeneration of menisci and involvement of the sensory nervous system, these all factors influence the progression of the disease.

OA is among the 30 reason of living with a disability and includes the even-increasing percentage of the population due to the obesity pandemic, as well as aging of the population [3]. The disease usually affects the elderly, but is not a consequence of an aging organism. Obesity is the main modifiable risk factor of the disease - mostly knee OA in women, but also hip OA and hand OA. Two different mechanisms may explain the role of obesity in the progression of OA. Firstly - it increases the weight, which increases the mechanical pressure on the joint and secondly, the increase in insulin-like growth factor type I and vistalin, according to Sellam and Berenbaum these metabolites, which are increased in obese patients, also propagate OA [4]. Peripheral bone fractures, knee and hip trauma, and damaged menisci, are associated with OA due to chondrocyte apoptosis. Direct risk factors

include malformation of joints and past fractures, indirect include female gender, age, hyperglycemia, diabetes and hypercholesterolemia.

Clinical Symptoms

Classical symptoms of OA include pain and stiffness of joint. Pain appears after joint movement and disappears after rest. At the disease progresses, pain appears with small joint movements at rest, and finally at night. Because cartilage does not contain nerves, it does not project pain, but joint pain is caused by damage to adjacent structures such as periostium, interarticular ligaments, pressure on subchondral bone, bone marrow edema, tension of joint capsule, changes in the synovium, tendons and fascia. Additionally, pain conduction to the CNS is disrupted.

Stiffness may occur in the morning or after a period of immobilization during the day. Morning stiffness disappears after a period shorter than 15 minutes. Stiffness after rest or immobilization usually disappears after a few minutes.

Impaired movement and function of joints progresses with disease duration and is associated with joint surface damage, decreased joint space, muscle contraction or decreased its strength, which leads to joint instability and blocking of movement due to osteophytes and floating bodies.

OA may be associated with depression and disruption of sleep, influencing the disability and quality of life. It is necessary to exclude other joint diseases such as inflammatory or metabolism arthritis, gout and other crystalopathies, septic joint inflammation.

In the physical exam you may find:

- Joint swelling during acute disease activity or its chronic course
- Joint stiffness during activity. Limited passive movement may be the first and only symptom of OA
- Joint deformity or subluxation due to cartilage loss, damage of subchondral bone, formation of osteophytes and cysts, which leads to incorrect joint alignment, its instability and limb shortening
- Incorrect gait and posture of the patient during standing and walking
- It is necessary to examine the bursas and extraarticular tissue. It is important to note if any change in position is accompanied with pain or it is secondary pain, eg., hip joint pain may radiate to the knee joint. In this case, manipulation of the knee joint itself does not cause pain, however movement in the hip joint may cause pain in the knee joint. Hip joint pain maybe secondary to lumbar pain. A precise physical examination is necessary to exclude these causes

Medical Imaging in OA

Diagnosis of OA is often possible by patient history and physical exam, however some joint may require additional imaging studies to exclude other disease, eg., a vascular necrosis, Paget's disease, inflammatory arthropathies and fractures, especially in locations such as tarsal bones, elbows or shoulders. Radiological imaging is necessary to confirm the diagnosis of knee or hip OA. Degenerative changes in x-ray imaging show joint destruction, and OA is defined as a process of destruction of joint cartilage, subchondral bone and other joint structures, so is therefore needed in order to diagnose OA in imaging tests. Confirmation of degenerative changes is based on diagnosing narrowed joint space, subchondral sclerosis and the presence of osteophytes and cysts.

MRI examination technique portrays all tissues involved in the disease process: damaged cartilage, fluid in the joint, bone marrow edema, slight synovitis, damage to menisci and ligaments.

Arthroscopy is used to visualize cartilage, synovium, osteophytes and damaged menisci. Biochemical cartilage markers and bone turnover markers may be present in patients not suffering from OA, and may result in misdiagnosis. Other methods such as medical imaging are more accurate.

Typical placement of OA changes are in knee, hips, hands joint, cervical and lumbar spine, the first MTP joint. These placements explain the fact that joint developed when our ancestors moved on four limbs and due to the change function of these joints as well as its overload. The DIP, PIP and MCP joint OA occurred due to the development of active hand manipulation, however after trauma, changes may localize in every joint. Active hand manipulation may result in biomechanical changes of joint which may result in OA. Not all hang manipulations undergo biomechanical changes however 'wear-and-tear' change may occur in over-active hand manipulations, which does not lead to OA.

Clinical evaluation is based on pain assessment, using the Visual Analogue Scale (VAS) or the 5-point Likert's scale (no pain, mild, moderate, severe, very severe pain). To evaluate pain and disability, the Western Ontario and McMaster Universities (WOMAC) index [5], is used, especially to evaluate pain and function of the knee and hip joints. In this index pain is evaluated using a questionnaire made of 17 questions, regarding every day activity, and through the Lequesne's functional index, which includes pain and deterioration of function [6].

Treatment

OA is considered a chronic disease, and by 'effective' it is meant that the disease may 'regress', which is not possible in OA. Recommendations are placed in order to inhibit disease progression.

Optimal treatment requires early diagnosis and exclusion of risk factors which may worsen prognosis. The main aim of treatment is to:

- Educate patient
- Reduce pain
- Optimize joint function
- Modify the OA process

The current recommendations regarding treatment is presented in table 1 in accordance to each societies use of a given medications. The societies responsible for the recommended treatment used in OA are:

AAOS: American Academy of Orthopedic Surgeons

ACR: American College of Rheumatology

OARSI: Osteoarthritis Research Society International

NICE: National Institute for Healthy and Care Excellence

EULAR: European League Against Rheumatism

DRUG	AAOS	ACR	OARSI	NICE	EULAR
Acetaminophen	Yes	Yes	Yes	Yes	Yes
NSAID	Yes	Yes	Yes	Yes	Yes
Opioids	Yes	Yes	Yes	Yes	Yes
SSRI (selective serotonin reuptake inhibitor)	No	Yes	Yes	No	No
Glucocorticosteroids (GCS) intraarticular	Yes	Yes	Yes	Yes	Yes
Hyaluronic acid	No	Yes	Yes	No	Yes
Gluosamine	No	No	No	No	Yes
Chondroitin	No	No	No	No	Yes

Table 1: Current medications recommended by AAOS, ACR, OARSI, NICE, EULAR [9-17].

European League Against Rheumatism (EULAR) created the recommended treatment of knee OA [7], hip OA and hand OA as well as nonpharmacological treatment of OA [8-11], American College of Rheumatology (ACR) for OA Osteoarthritis Research Society International (OARSI) for hip and knee OA [12-16], National Institute for Healthy and Care Excellence (NICE) for OA [17].

Current OA treatments according to NICE in chronological order are:

- Non - pharmacological treatment
- Topical capsaicin and NSAID
- Paracetamol
- Oral NSAID in the lowest therapeutic dose for the shortest period of time
- GCS intraarticular
- Opioids
- Alloplasthy

Non-pharmacological treatment

A professional approach in explaining the diagnosis and prognosis, explanation of the goal of physical therapy and providing a detailed explanation of the benefits and inconvenience of different treatment methods plays an important role. This conversation decreases the amount of doctor visits, and helps the patient independently reduce pain and limit joint movement. Regular phone consultations and group education is important. It is recommended to use physical therapy as first line of treatment, regardless of age, comorbidities, pain severity and disability. Each patent should have an individual treatment plan and should be reassured that a change in attitude, eg., regular physical therapy, reduced body mass, use of appropriate footwear, will bring an effect. It should be taken into account the patent age, their occupation, recreation method, patient expectation and degree of disability, as well as additional illnesses, such as renal or cardiovascular diseases, which are contraindicated in the use of oral NSAIDs. It should be remembered that depression increases perceived pain.

Joint are constructed in such a way that in order to function properly, they must be in motion regularly. The best exercises are aerobic exercises and increased activity, which improved mood and sleep, decreased obesity and positively impacts other diseases eg., diabetes, congestive heart failure and hypertension. Exercising the quadriceps and gluteus muscles decreases muscle tension, improve balance and decreases tendencies to fall. Patients should be advised on how long to walk, when walking should be stopped to rest, which decreases mechanical load and decreases pain. It should be stressed that exercises should be the standard treatment of OA. Rehabilitation includes: aerobic, exercises with limited pain, muscle strengthening exercises as well as orthopedic equipment - walking-sticks, crutches, orthopedic insoles, correct footwear as well as limb-axis correctors, elastic bands and tools to aid in everyday activities.

Physical therapy includes: criotherapy, heat-therapy, Transcutaneous Electrical Nervous Stimulation (TENS), laserotherapy, ultrasound therapy, magnetotherapy, ionoforesis.

Pharmacological methods

Therapy should be started with topical NSAID and creams with capsaicin, as no gastrointestinal adverse effects occur. NSAID may be administered in the form of creams, gels, sprays 3 x daily, as many times, pain is due to periarticular changes and not intraarticular ones.

Capsaicin is an alkaloid derived from chilli peppers (genus *Capsicum*). Capsaicin is a agonist of the Transient Receptor Potential Vannilloid Type 1 (TRPV1). The initial effect of capsaicin is the activation of nocyceptors in the skin, resulting rash after the release of vasoactive neuropeptides (substance P). One week after the application of a capsaicin with a high concentration of 8% within the skin, ion channels are opened for calcium ions. A rapid inflow of these ions into the cell and reversible mitochondrial damage has been observed. The result is prolonged atrophy of peripheral cutaneous nerves. Changes in the nocyceptors of the skin and peripheral nerves are reversible after 12 weeks. The mechanism of action of capsaicin also involves the removal of the neurotransmitter substance P from the peripheral nerve terminals. As a consequence, there is a reversible depletion of substance P and reducing the transmission of pain from peripheral nerve fibers to the CNS.

In order to reduce pain, acetaminofen should be administered in doses of 1 g 3 - 4 x daily. Acetaminofen blocks Cyclooxygenase (COX)3. It is a safe drug to use as it does not interact with the drugs often used by elderly patients, except for large doses of warfarin. Rarely, gastrointestinal adverse effects may occur. If acetaminofen does not achieve the desired effect, oral NSAIDs may be used for a short period of time. NSAIDs are the most commonly use drugs in the population; around 30-50 mln people use NSAIDs on a daily basis. They are effective anti-inflammatory and anti-analgesics, as they inhibit COX via acetylation, however they contain many adverse effects.

Arachidonic acid rising after cellular damage via phospholipase A2 from phospholipid cell membranes, which undergo enzymatic reactions mainly through two processes: Cyclooxygeneses (COX) and lipooxygenases (LOX). COX pathway results production of prostanoids (prostaglandin, prostacyclin and thromboksane), LOX pathway- leukotriens. Prostanoids are synthesized via synthesis of prostaglandin endoperoxidase, which is composed of COX and peroxidase. Via COX, hydroendoperoxidase PGG2 arises, which after peroxidation changes to endoperoxidase PGH2. Both endoperoxidases are, through the use of free oxygen radicals, increase the action of COX by positive feedback. The two forms of COX - COX1 i COX2 - work in different ways. COX1 is an enzyme which sustains homeostasis under normal condition in the organism, as well as through the release

of prostaglandins - has a protective effect on gastric mucosa. COX2 is induced through damaged tissue, endothelial cells, macrophages and fibroblasts during the inflammation in the form of enzyme, which take part in inflammatory processes, pain transmission and thermoregulation. Prostaglandins relax the smooth muscles of blood vessels, tromboxan A2 works as vasoconstrictor, and prostacyclin work as antiagregates and vasodilators. Due to the various chemical composition of NSAIDs, we can divide them into salicylates (acetylosalicylic acid, salicylamide), and derivatives of indole acetic acids (indomethacin, acemethacin, tolmethin), derivatives of phenylacetic acids (acyclofenak, diclofenak, fenclofenak), derivatives of phenylopropioic acids (ibuprofen, naproxen, phenbufen, phenoprofen, ketoprofen), derivatives of fenamic acids (mefanamoic acid, meclofenamoic acid), derivatives of enolic acids (oxycam - piroxycam, izoxycam, tenoxycam) and pyrazolidine - phenylbutazone, oxyphenbutazone.

NSAIDs can also be split into their ability to inhibit certain COX isoenzymes: selective COX1 (ASA) in cardioprotective dose 75 - 150 mg, non-selective COX1 (higher affinity to COX1 than COX2 [ibuprofen, diclofenac, ketoprofen, naproxen, ASA in the classical dose, piroxicam, indomethacin]), COX2 preference ([a greater affinity towards COX2 then COX1 [nimesulide, meloxicam]), selective COX2 (coxibs - showing over 200 times greater affinity to COX2 then COX1 [celecoxib, etoricoxib]).

NSAIDs are used in rheumatology as anti-inflammatory drugs. In oncology they are the first line on the analgesic ladder and used as addition to higher levels on the analgesic ladder. Acetylsalicylic acid is used in cardiology in acute coronary syndromes and profilacticaly in cardiovascular risk factors due to their platelet anti-aggregation properties. All NSAIDs have adverse effects: Gastrointestinal - symptoms of dispepsia and damage to gastric and duodenal endothelium (erosions, ulcers, GI bleeding, perforation), cardiovascular symptoms - heart insufficiency and increased cardiovasculatory risk, renal symptoms - renal insufficiency, renal papilla necrosis, they may also cause liver damage, hemolytic anemia, granulocytopenia, functional impairment of platelets, ototoxicity, hypersensitivity reactions (skin changes, aspiration asthma).

A lot of hope has risen with the introduction of coxibs, which would ensure less adverse effects from the GI tract, however more adverse effects would occur in cardiovascular system, as well the same probability of renal insufficiency while using standard NSAIDs.

Choosing NSAIDs. The best choice is using topical NSAIDs due to their lack of GI and cardiovascular adverse effects. Oral NSAIDs should be used for the shortest period of time in the lowest therapeutic dose. If possible, it should be avoided using drugs that potentiate the adverse effects of NSAIDs and reduce their dosage. NSAIDs with a short half-life should be used as they are safer (ex. ketoprofen, diclofenac). Patients after acute coronary attacks should not use NSAIDs 6 months post attack, however patients who take cardiogenic doses of ASA, should take NSAIDs while maintaining a 2-hour delay between drugs, and cannot take ibuprofen. In patients with a high cardiovascular risk and who do not take ASA, the drug of first choice is naproxen. In patients who use ASA, the preferred drug is ketoprofen. In patients with a high GI risk and a small cardiovascular risk, coxibs should be used (celecoxib, etoricoxib) combined with a PPI. In patients with a low GI and cardiovascular risk who need long-term therapy, diclofenac may be used, and in short-term therapy - nimesulid [18]. Authors of metaanalysis in clinical trials using over 58 000 OA patients, report that using 150 mg/day diclofenac or etoricoxib 60 mg/day results in almost 100% certainty of clinical improval. [19].

NSAIDs are the most commonly used drugs in pain, inflammation and fever, however are 3 to 5 times more likely to give severe GI adverse effects such as bleeding and perforation, which is caused by inhibiting COX1 enzyme. After discovering this mechanism of action, drugs that do not inhibit COX1, but inhibit COX2, were created. They are called coxibs. These drugs have a lower toxicity and fewer GI adverse effects. In 2004, rofecoxib was withdrawn due to increased cardiovascular adverse effects. EMA reported that coxibs are contraindicated in patients with coronary artery disease, cerebrovascular disease and peripheral artery disease. Due to lack of concrete information of cardiovascular adverse effects after NSAIDs and not enough literature regarding this, the SOS (Safety of non-steroidal anti-inflammatory drug) project was created, which is available on www.sos-nsaids-project.org. This project encompasses published metaanalytical clinical trials and observations, as well as current epidemiological analysis in a 35 mln population, mostly from the European population taking NSAIDs. Based on the SOS report Castellsaque et al., published upper GI adverse effects based on metaanalysis of 28 randomized cases, which sums up to 24 mln patients. In total sixteen NSAIDs (aceclofenac, celecoxib, ibuprofen, rofecoxib, diclofenac, meloxicam, ketoprofen, nimesulid, sulindac, tenoxicam, indomethacin, naproxen, piroxicam, difunisol, ketorolac and azapropazon) were used in the metaanalysis [20], and conducted that the least upper GI occurred in the following: aceclofenac, celecoxib and ibuprofen, however the most adverse effects occurred in: piroxicam, ketozolac and azapropazone. Mild risk occurred in: Ketoprofen, diclofenac, meloxicam, nimesulid and naproxen.

In a second study published using SOS data, by Arfe et al., the risk of hospitalization due to heart failure in patients using NSAIDs in 2000 to 2010. Out of 92 163 hospitalizations due to heart failure, 16 000 patients were currently using NSAIDs [21]. The greatest risk was observed after using ketozolac, etoricoxib, indomethacin, rofecoxib, piroxicam, diclofenac, ibuprofen, nimesulid and naproxen. However meloxicam, ketoprofen and aceklofenac did not increase the risk of heart failure.

A third publication by Varos-Lorenco et al., using SOS data studied the risk of an acute heart infarct after using NSAIDs [22]. Based on the metaanalysis from 25 clinical studies, it was reported that 100 000 event of acute heart infarct, the lowest risk was after following: naproxen, celecoxib, ibuprofen, meloxicam, rofecoxib, diclofenac, indomethacin, etodolac and etoricoxib.

In the SOS project, the least amount of ischemic strokes were observed after following: ketoprofen, meloxicam, celecoxib, naproxen and etoricoxib.

In a study of Rafani et al., from 2016, on the topic of GI adverse effects, the least risk occurred after ketoprofen and ibuprofen, on the basis of 2804 serious registered adverse effects after pharmacological treatment, in which 374 cases included severe GI adverse effects from the Italian health data [23]. The most severe adverse effects occurred after diclofenac, nimesulide and ketozolac.

Intraarticular GCS - it is recommended to administer GCS to the same joint 2 - 3 x/months, due to the risk of cartilage necrosis or subchondral bone necrosis. Methylprednisolone, betamethasone, triamconolone is used - they work as analgesics and improve joint function up to a few weeks.

Analgesic opioids should be used in cases where pain reaches over 5 in the VAS scale, because it prevents the development of neuropathic pain. Weak opioids - tramadol in the dose 50-100 mg 2 - 3 x daily, it should be used in patients with severe pain only, and for a short period of time. Strong opioids - fentanil in plaster (Durogesic) from every 72 h - also for the shortest possible time. Adverse effects after opioid use includes - nausea, vomiting, sleepiness, constipation, dizziness, depression of respiratory center.

"Nutraceutics" are natural pro-health products. These products considered joint improvement products and delaying the onset of OA, are available in pharmacies or supermarkets under the name SYSADOA (symptomatic slow release drugs for OA). These products are increasingly popular and achieve great popularity world-wide. Favorable properties of glucosamine and chondroitin is that they are the basic compounds that make up glucosoaminoglycans in cartilage, and supplementation of these compounds improve the integrity of matrix cartilage. However, there is no sustainable argument for the improvement of pain in OA. The mechanism of action, in vitro as well as in vivo of these compounds is still controversial, however their safety is rarely questioned. In general, the results from randomized studies regarding the progression of OA are favorable towards glucosamine sulfate in a dose of 1500 mg/day, however metaanalysis does not confirm their superiority [24]. Metaanalitical results regarding pain management mostly come from low quality studies and show that chondroitin sulfate may helps in mild to moderate pain [25].

Most recommendations do not support the use of nutraceuticals to manage pain in OA. NICE, takes into account the high cost of use against effect, concluded that these products should not be used. Hyaluronic Acid (HA) is a glucosaminoglycan with a large molecular weight, which is part of the composition of many tissues, including synovial matrix and cartilage. The viscous-elastic properties of HA and in moisturizing joint and hydrating tissue. The main source of HA in joints are from synovial cells. The main reason for using HA in OA would be to increase the concentration of HA, which is usually lowered in the synovium in which disease processes have begun, as well as to improve the joint lubrication (so-called visco-supplementation). Randomized clinical trials report that products with HA used in OA of knee joints decreases pain and are better than placebo after 3 months after injection, however the improvement is minimal [26]. Most recommendations, excluding NICE, show limited recommendations in using HA in OA. Most products require weekly intraarticular administration, from 3 to 5 times, in order to observe the benefits of reduced symptoms. Adverse effects are rare, but more pronounced than after intraarticular GCS.

Not Recommended

- NICE does not recommended the use of glucosamine and chondroitin, because it does not regenerate cartilage, however chondroitin does have analgetic properties by blocking bradykinin via the B2R receptor and prevent the decrease of pain threshold, preventing peripheral sensitization
- NICE does not recommended the use of intraarticular HA, as well as athroscopic treatment (lavage or debridement), except in cases of mechanical joint blocking by foreign bodies. The presence of foreign bodies in the joint, seen on X-ray, is not an indication to use the above treatment
- NICE not recommend the use of oral NSAID before using non-pharmacological treatment or paracetamol and topical NSAIDs

Surgical Methods

Alloplasty should be used before long-term disability of the joint occurs, and decrease in quality of life as a result of this. If joint blocking due to a foreign body is excluded, corrective osteotomy, synovectomy, debridement, joint lavage and arthroscopy should not be performed.

Joint blocking which is not caused by a foreign body should be treated using other methods listed in NICE, according to chronological order.

New therapy in OA

Experimental therapy based on inhibiting the production of cytokines and metaloproteinases which damage cartilage, and administration of growth factors, which inhibit protease activity are considered, as well as gene therapy.

Sprifermin (recombinant human Fibroblast Growth Factor [FGF]) in phase I of clinical studies has achieved reduced pain and reduced loss of cartilage [27].

Tanezumab - a monoclonal antibody against β-Nerve Growth Factor (NGF- β) reduces chronic pain in OA of the hip and knee joints [28]. It was observed that in OA, there is a decreased concentrations of morphogenic bone protein 7 (BMP-7). Intraarticular injection of this protein or OP-1 (osteogenic protein 1) reduces OA in animal studies, and is currently in phase I of clinical studies in human [29]. In addition, studies using the regulation of cytokine and metaloproteinase production, which participate in cartilage breakdown is currently under way, as well as gene therapy which is based on applying intraarticularly a protein which improves cartilage synthesis. Even though proteases weaken cartilage, but more damage is caused by mechanical cause, that is why therapy should be aimed at decreasing joint load and returning its correct biomechanics and cartilage rebuilding should be a long term plan. Blocking certain enzymes or cytokines that take part in joint destruction or stimulation of products that rebuild cartilage do not stop disease progression. The most important factor is to remove mechanical causes. Cartilage repair is caused by IGF-1 and TGF-β, which stimulate biosynthesis of proteoglycans and collagen and decrease the number of IL-1 receptors on chondrocytes.

Administration of autologous platelet rich plasma, which contain growth factors such as TGF-β 1, PDGF, VEGF, IGF-1, HGF - which provide positive results in the initial period OA [30].

Current Studies on Pharmacological and Regenerative Therapies in OA

Regenerative therapy, including autologous chondrocyte transplant are promising alternatives in treatment because they show great potential in cartilage repair [29]. Tissue engineering is the most

promising new therapy as damaged cell may be replaced by new cells, inhibiting further joint destruction. Tissue engineering includes the use of cells, scaffoldings and bioactive factors to increase the regenerative properties of tissues, promote migration of cells, transplantation, proliferation and differentiation of desired cells. Engineering methods of tissue are in the form of cartilage - bone transplants, periosteal transplantation, as well as autologous chondrocyte transplantation. Chondrocyte transplantation is based on obtaining a sample of healthy cartilage, from which chondrocytes are isolated and multiplied. At the same time, the cartilage loss is developed. The second stage is based on obtaining a sample of periosteum from the anterior surface of the tibial bone, which is placed in the area of cartilage loss, and underneath it, the chondrocyte sample. The following conditions must be met in order to use this method: young age and a small, localized area of cartilage loss [31].

Cell therapy offers long-term effects in cartilage repair and regeneration, improvement of symptoms and delay in the progression of OA. Current cell therapy aims to use not only mature cells, but Mesenchymal Stem Cells (MSCs) too. Early results show that therapy based on MSCs decreases pain and improves joint function. Restoration of healthy cartilage in patients with OA is a challenge for researchers and clinicians. Techniques, which cause adult MSCs to differentiate into cells in the chondrocyte line and may be used to regenerate as well as sustain joint cartilage, instead of chondrocytes. These methods use MSCs as progenitor cells to create cartilage implants to repair cartilage or as trophic bioactive factors that stimulate endogenous repair in the joint. Directional gene therapy can aid the use of MSCs. MSCs may be indirectly administered, intraarticularly or as a transplant, which ensures a three-dimentional reconstruction of correct mechanical properties. The use of MSCs eliminates the need for cartilage biopsy, which helps avoid adverse effects due to potential damage of the surface of the donor. Extensive microenviromental analysis was conducted which favor MSCs chondrogenesis in vitro. The culture medium is conditioned using growth factor, including fibroblast growth factor with or without transforming growth factor β, which increases positive selection of chondro progenitor cells. Damage of tissue in progressive OA may be associated with functional changes in MSCs population The ability to proliferate, chondrogenic ability and adipogenic ability of MSCs obtain from patients with OA are decreased. Direct intraarticular injection is possible in early stages of the disease, as damage is localized in the cartilage layer, however if the subchondral bone is revealed over large surfaces, scaffolding or matrix may be needed to support MSCs. After the administration of MSCs, obvious regeneration of the medial meniscus was observed, and transplanted cells were discovered in the newly-formed tissue. Degeneration of joint cartilage, formation of osteophytes and subchondral bone sclerosis was decreased in healing joints as well. In none of the joint, no traces of ligament repair was observed. The precise of mechanism leading to the settlement of transplanted MSCs is not known, however it is certain that these cells secrete many bioactive compounds, which have immunogenic and regenerative properties. Bioactive factors secreted by MSCs inhibit tissue scaring and apoptosis, and stimulate angiogenesis and increase tissue mitosis of stem cells and progenitor cells [32].

Synthetic scaffolding used in the repair of cartilage are produced by using α-hydroxypolyesters, eg., polyglycolic acid. Natural scaffolding - biomaterials (eg., type I collagen, HA) - provide a more natural microenviroment for MSCs compared to synthetic scaffolds [32].

MSCs used as transport carrier of medium for genes seem susceptible for the transduction of different viral vectors, including adenovirus, retrovirus, Herpes simplex virus and others. The use of MSCs in combination with bioactive substances, natural or synthetic, may have a potential clinical significance and most-likely will be important in the future use of MSCs in cartilage repair [32].

Conclusion

Despite many recommendation EULAR, OARSI and NICE, it is important to stress that the treatment of OA is not effective. The most important treatment - education, physical therapy, reduced body mass and elimination of mechanical factors causing disease - they are often overlooked, and the most popular treatment remains pharmacotherapy, especially oral NSAIDs. Long term use of oral NSAIDs, especially in the elderly population, results in frequent bleeding from the GI tract, which are often fatal.

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