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Brief summary on the mechanism, symptoms, epidemiology, management and treatment of osteoarthritis

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Abstract. The most common degenerative joint disorder is osteoarthritis (OA) which impacts hundreds of millions worldwide, with the primary risk factor being age. The disorder is characterized by the breakdown of extracellular matrix (ECM) components, leading to impaired chondrocyte function and cartilage repair. Further, the subsequent inflammation results in pain and even joint disability in severe cases. Conventional treatments focus on symptomatic relief and improvement of joint function, through pharmacological means, physical therapy or surgeries. However, long-term anti-inflammatory or analgesic treatment may result in adverse side effects such as drug dependence. Meanwhile, joint replacement surgery poses risks of permanent disability. This review discusses the underlying mechanisms and risk factors of OA, their relationship to symptoms and disease progression, and current epidemiological trends. Additionally, we focus on new-generation treatments with the application of bioengineering and stem cell therapy. Finally, we address contemporary treatment strategies and the potential for future disease-altering therapies that may be implemented on a large scale.

Keywords: osteoarthritis, bioengineer therapy, stem cell therapy.

1. Introduction

Osteoarthritis (OA) affects 600 million people worldwide as the most common joint disorder. It primarily affects articular cartilage, bones, and the surrounding soft tissues. The normal function of the articular cartilage of the joints is by the chondrocytes which produce and maintain the cartilage through its anabolisms and catabolism. In OA, there is a breakdown of extracellular matrix (ECM) components such as collagen and proteoglycans. This results in a decrease in ECM synthesis, therefore, a loss of chondrocyte function and capability for cartilage repair. During the response to stimulation, inflammatory cytokines are released in the joint, inducing inflammation, and further promoting disease progression. Moreover, the resulting loss of chondrocyte function has been linked to the risk factors of ageing, genetic factors and oxidative stress [1]. The main risk factor for OA is ageing, which is important given the ageing population of the world [2]. Conventional treatment relies on pharmacological therapies to provide symptom relief through the improvement of joint function, allowing patients to resume an active lifestyle, which is essential for maintaining joint stability. However, long-term use of pain medications, especially opioids and NSAIDs, may cause side effects or even drug dependence. As a last resort, arthroplasty (joint replacement surgery) may be considered, restoring a modicum of joint function, at the risk of permanent joint disability. New therapies currently under development would allow the regeneration of cartilage without the risk of major surgery. In this review, we summarize the

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mechanism and the symptoms of OA. Moreover, we focus on the disease progression and outcomes, the relationship of the current trends in epidemiology and rising importance. Importantly, we discuss the contemporary treatments and management of symptoms concerning possible disease-altering treatments that can be implemented in the future.

2. Epidemiology of osteoarthritis

OA can significantly impact the quality of life of affected individuals. The epidemiology of OA is essential given its significant and growing impact on public health worldwide. According to WHO, the World Health Organization, it was estimated that in 2020 one billion were aged 60 or older, comprising just under one-eighth of the global population; it is projected to increase to one-sixth by 2030. In 2019 with 528 million people with OA, approximately seven per cent of the world's population. As the risk for OA increases with age, it is a substantial contributing factor to disability in older adults.

Additionally, OA is more prevalent throughout developed countries, most likely due to longer life expectancies along with greater exposure to risk factors such as obesity and physical inactivity. OA is the most frequently occurring joint disorder in the United States, affecting about 30 million adults. In Europe, over the age of 60, OA impacts women more than men with 18% of women compared to 10% of men, which is expected to rise by 40% for both sexes in the next 20 years. However, OA is less common in Asia than in more industrialized countries, although it is also on the rise due to ageing populations and changes in lifestyle factors.

3. The mechanism and clinical features of osteoarthritis

The underlying mechanism of biomechanical pressures on the hyaline cartilage in joints influences the ECM's combination of chemical and biological factors. Since cartilage's mechanical properties are provided by ECM, this results in the resulting breakdown. Generally, proteoglycans are replaced at a faster rate than collagen proteins. When collagen degeneration increases, it is replaced with type one collagen, which is not as mechanically suited for the role and wears away faster [2]. As the rate of matrix breakdown exceeds the anabolic repair process, the cartilage gradually decreases in depth and eventually reaches the bone in late cases [1]. The secretion of inflammatory cytokines in response to joint injury or chronic mechanical stress intensifies the breakdown of cartilage and other joint tissues, further leading to pain and joint disability. The inflammation and oxidative stress that contribute to chondrocyte dysfunction and matrix breakdown involve the activation of matrix metalloproteinases (MMPs) and aggrecans [3]. These enzymes further degrade the ECM, leading to the release of fragments that can trigger more inflammation and catabolic processes, creating a vicious cycle of damage [2]. In advanced stages of OA, the subchondral bone can change such as sclerosis and cyst formation, further compromising joint integrity. Meanwhile, the formation of osteophytes, bone spurs, and synovitis (inflammation of the synovial membrane) contribute to pain and stiffness.

Generally, although symptoms may vary depending on the location, characteristic joint pain, stiffness and subsequent joint disability, especially in the morning or after a period of inactivity. It is noted to improve during physical activity. There may also be a feeling of grinding and popping in the joint known as crepitus. In the most advanced cases, as the cartilage wears down osteophytes (bone spurs) will appear, a sign of late-stage OA, restricting the range of motion through inflammation and resulting in external deformities of the fingers. Inflammation also occurs though less so than in rheumatoid arthritis resulting in swelling warmth and tenderness.

4. The risk factors of osteoarthritis

Common risk factors of OA include obesity and those who have suffered specific joint trauma in the past causing joint misalignment. The risk factors can be in two categories physiological and local (joint level), the strongest risk factor for OA is age, although obesity also plays a role in OA cases in a large proportion of weight-bearing joints such as the hips. Age shows a positive correlation with the degree of symptoms. Obesity is another significant risk factor for OA, particularly in weight-bearing joints such as the hips and knees, although there is mixed evidence for the hip joints. The excess body weight places

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additional stress on the joints, increasing the likelihood of matrix breakdown. Genetics can also play a role in OA development, as certain genetic factors may predispose individuals to OA. Women have a higher chance of developing OA than men, particularly after menopause due to the decrease in hormones that maintain bone density. Hip, knee and hand OA are more commonly diagnosed in women than men. Other indirect factors could also contribute to the higher risk, for example, reduced cartilage volume, bone density and muscle mass in comparison. Acute joint trauma, such as a ligament tear or fracture is common in athletes, and can also increase the risk of developing OA in that joint. Chronic mechanical stress, such as kneeling or squatting, can also contribute to the development of OA in the affected joints.

5. The therapies of osteoarthritis

5.1. Pharmacological treatment and surgery

Treatment options for OA include lifestyle modifications, physical therapy, pain management, and joint replacement surgery in severe cases [1]. Pharmacological therapy is employed as the initial treatment for OA, with different classes of drugs employed depending on the patient's pre-existing conditions and the severity of their OA symptoms. Paracetamol is a typical over-the-counter painkiller used to treat mild to moderate OA pain. It has fewer adverse effects than other pain medications such as NSAIDs (Nonsteroidal anti-inflammatory drugs) or opioids but may be less effective in treating severe pain. Traditionally, NSAIDs, like ibuprofen and naproxen are used, as they are effective in relieving moderate to severe OA pain and inflammation, but they can have gastrointestinal adverse effects, especially when used long-term. While opioids such as tramadol and oxycodone may be administered for severe OA pain, their chronic use is controversial due to their potential for addiction and other negative effects [4]. To avoid such severe side effects, alternative treatments such as topical analgesics, are considered. The usage of these analgesics could treat OA pain with fewer adverse effects than systemic medications. The typical topical analgesics are capsaicin and lidocaine formulations applied directly to the injured joint to deliver regional pain relief with no systemic adverse effects. Intra-articular corticosteroid injections can provide immediate pain relief while also reducing inflammation in the afflicted joint. However, due to potential side effects and diminishing results with repeated injections, their use should be restricted.

Indeed, arthroplasty is another efficient treatment of OA. However, one million knee and hip joint replacements are done every year comprising more than US$27 billion in cost globally given the current impact, it is vital to develop novel treatments that alter disease progression instead of merely alleviating the pain or replacing the joints impacted entirely [5-7]. More importantly, this surgery risks permanent joint disability.

5.2. Bioengineering treatment and stem cell treatment

Bioengineering procedures aim to restore joint function and alleviate pain by repairing or replacing damaged joint tissues. Tissue engineering uses biomaterials like hydrogels and scaffolds to promote the growth and differentiation of chondrocytes, and joint resurfacing procedures involve making small holes in the subchondral bone or transferring healthy bone and cartilage tissue from a donor to encourage the growth of new cartilage and repair the damaged joint surface. While these approaches have shown promise in preclinical studies, their clinical efficacy and long-term results are still being evaluated.

Autologous Chondrocyte Implantation (ACI) is a new type of cartilage transplantation that includes extracting healthy cartilage cells from the non-affected portion of the patient's joint, cultivating them in a laboratory, and then implanting them into the injured area to encourage cartilage regeneration. To encourage the growth of new cartilage and repair the damaged joint surface, joint resurfacing procedures, such as microfracture surgery and osteochondral allograft transplantation, involve making small holes in the subchondral bone or transferring healthy bone and cartilage tissue from a donor. Instead of transplanting cartilage directly, utilizing stem cells' regenerative capacity to restore damaged joint tissues is a promising strategy for treating OA. For the treatment of OA, various stem cell types have been investigated, including MSCs (mesenchymal stem cells), which although previously extracted from bone marrow, a variety of other tissues, including adipose tissue, and synovial fluid can also be

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used. They differentiate into chondrocytes and release substances that encourage the regeneration of cartilage and lessen inflammation. MSCs can be injected directly into joints or used in conjunction with biomaterials for tissue engineering purposes.

With the development of induced pluripotent stem cell (iPSCs) strategies, another type of assessing stem cells displays the advantages in the treatment of OA. Adult somatic cells can be reprogrammed to iPSCs, which can then be used to create new pluripotent cells, then differentiate into diverse cell types including chondrocytes. iPSC-derived chondrocytes can be employed as a cell source for ACI or other tissue engineering techniques promoting cartilage repair. Stem cell therapy remains a promising approach for treating OA. However, there are still challenges to be addressed, such as optimizing cell sources, delivery strategies, and safety profiles, before stem cell therapy can be widely used in clinical settings. Moreover, apart from novel bioengineering stems cell therapies, for example, new disease-modifying osteoarthritis drugs (DMOADS), can be used in addition to conventional treatment, and have the potential to provide more long-term and non-surgical solutions for OA by addressing underlying tissue damage and promoting joint repair. By addressing the underlying causes use of DMOADs can lead to continued improvements in joint function and pain relief, enhancing the quality of life for patients with OA. However, these approaches are still in clinical trials and may not be accessible or suitable for all patients.

5.3. Other non-pharmacological treatment

Non-pharmacological interventions, such as physical therapy, exercise, weight management, and the use of assistive devices, are also of use in improving the quality of life for people with OA. Regular exercise, including low-impact activities like swimming, cycling, and walking, can help maintain joint flexibility and muscle strength, ultimately reducing pain and stiffness. Weight management is crucial, as excess weight(obesity) puts additional stress on weight-bearing joints, exacerbating OA symptoms. Additionally, non-pharmacological interventions such as supplementing with glucosamine and chondroitin sulphate have also been used to treat OA symptoms, although their efficacy and safety profiles are still under investigation [4].

6. The outcome of osteoarthritis

Pain, stiffness, and limited mobility often lead to a lower quality of life in patients with OA. Without therapy, the progressive nature of OA may lead to worsening symptoms and further functional decline, negatively affecting daily activities and overall well-being. With therapy, many patients can manage their symptoms and maintain a relatively high quality of life. However, for some, especially those with advanced OA, conservative treatments may not provide adequate symptom relief and surgical options, such as joint replacement or joint fusion, may be considered to improve function and alleviate pain. Successful surgeries can significantly improve the quality of life for patients with severe OA, but they come with potential risks and complications [8-11].

7. Conclusion

Osteoarthritis is a widespread and debilitating joint disorder with a significant global impact. The disease's progression is primarily attributed to the breakdown of ECM components and the subsequent decline in chondrocyte function, leading to cartilage damage and inflammation. The ageing global population is expected to lead to an increased prevalence of OA, necessitating more effective treatment strategies. Current pharmacological treatments primarily focus on symptom relief and improving joint function, but pain medications when used long-term can cause deleterious side effects, and joint replacement surgeries carry inherent risks. Therefore, there is an urgent need for the further development of novel, disease-altering therapies that can both alleviate symptoms and address the underlying pathophysiology of OA. Emerging treatments, such as regenerative medicine techniques and targeted gene therapies, hold significant promise for the future management of OA. By better understanding the mechanisms involved in OA progression and exploring innovative therapeutic approaches, it is possible

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to develop more effective interventions that could improve the quality of life for millions of people suffering from this debilitating condition.

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