Knee osteoarthritis: Current status and research progress in treatment (Review)

RUIZHI GENG[1,2*], JIAYI LI[1,3*], CHEN YU[1,4], CHAOQUN ZHANG[1,2], FEI CHEN[1,2], JIE CHEN[1,5], HAONAN NI[1], JIAXU WANG[1,2], KAIQIANG KANG[1,2], ZIQI WEI[1,3], YONGQING XU[1,2] and TAO JIN[1,2]

[1]Graduate School, Kunming Medical University, Kunming, Yunnan 650500; [2]Institute of Traumatology and Orthopedics, 920th Hospital of Joint Logistics Support Force of The People's Liberation Army, Kunming, Yunnan 650051; [3]Department of Anatomy and Histology, and Embryology, Kunming Medical University, Kunming, Yunnan 650500; [4]Department of Orthopedics, The First People's Hospital of Yunnan Province, Kunming, Yunnan 650034; [5]School of Public Health, Kunming Medical University, Kunming, Yunnan 650032, P.R. China

Received March 7, 2023; Accepted August 11, 2023

DOI: 10.3892/etm.2023.12180

Abstract. Knee osteoarthritis (KOA) is a common chronic articular disease worldwide. It is also the most common form of OA and is characterized by high morbidity and disability rates. With the gradual increase in life expectancy and ageing population, KOA not only affects the quality of life of patients, but also poses a burden on global public health. OA is a disease of unknown etiology and complex pathogenesis. It commonly affects joints subjected to greater loads and higher levels of activity. The knee joint, which is the most complex joint of the human body and bears the greatest load among all joints, is therefore most susceptible to development of OA. KOA lesions may involve articular cartilage, synovium, joint capsule and periarticular muscles, causing irreversible articular damage. Factors such as mechanical overload, inflammation, metabolism, hormonal changes and ageing serve key roles in the acceleration of KOA progression. The clinical diagnosis of KOA is primarily based on combined analysis of symptoms, signs, imaging and laboratory examination results. At present, there is no cure for KOA and the currently available therapies primarily focus on symptomatic treatment and delay of disease progression. Knee replacement surgery is typically performed in patients with advanced disease. The current study presents a review of epidemiological characteristics, risk factors, histopathological manifestations, pathogenesis, diagnosis, treatment modalities and progress in KOA research.

Correspondence to: Professor Yongqing Xu or Professor Tao Jin Institute of Traumatology and Orthopedics, 920th Hospital of Joint Logistics Support Force of The People's Liberation Army, 212 Daguan Road, Kunming, Yunnan 650051, P.R. China
E-mail: xuyongqingkm@163.net
E-mail: 1415456167@qq.com

*Contributed equally

Key words: arthroplasty, cartilage, conservative treatment, cyclooxygenase 2, cytokine, disease progression, glucocorticoid, inflammation, non-steroidal anti-inflammatory agent, synovitis

Contents

1. Introduction

Knee osteoarthritis (KOA) is a multi-etiological, chronic disabling disease that affects the entire knee joint, which is the most common site of involvement in OA (1). KOA is classified as primary or secondary depending on etiology. The pathogenesis of primary KOA is complex and involves numerous factors, such as mechanical stress, inflammation, metabolism, immunity and genetics, with age, genetics, body weight, sex and race being risk factors (2,3). By contrast, secondary KOA is primarily caused by either trauma, congenital articular dysplasia or iatrogenic injury. The pathological changes of KOA are not passive degenerative or wear-and-tear lesions but active changes caused by an imbalance between articular tissue damage and repair (4). They are typically accompanied by lesions in articular or subchondral bones, ligaments, synovium, joint capsule and periarticular muscular structures (5). The primary clinical manifestations are pain and limited mobility, which reduce the quality of life of patients (6). Surveys have indicated a higher incidence of KOA symptoms in the Chinese population aged ≥60 (19.4%) (7), with the incidence rate in women (10.3%) being higher than that in men (5.7%) (8). The ageing population has led to an increase in the proportion of

older people with OA. Therefore, OA has become a major healthcare and economic burden (9). Currently available pharmacological therapies such as NSAIDs are palliative as they are mainly aimed at symptomatic relief of inflammation and pain and the delay of disease progression (10). There are presently no drugs that halt disease progression or reverse pathological changes in the entire joint and most patients with end-stage KOA require surgical treatment (11,12). The definition of KOA, as well as identification of risk factors and pathophysiological mechanisms, are being improved and developed as researchers investigate pathogenesis of the disease (13). However, the scientific, rational and effective treatment of KOA remains a challenge in clinical practice (14). The present study reviews the epidemiological characteristics, risk factors, histopathological manifestation, pathogenesis, diagnosis, treatment modalities and the latest KOA research.

2. Epidemiology

KOA primarily occurs in ≥50-year-old individuals (15). It is a chronic degenerative joint disease that clinically manifests as pain, joint deformity and limited mobility that typically causes disability (16). With the acceleration of population ageing and the increase in the proportion of obese individuals, KOA is the 11th leading cause of disability worldwide and ranks 38th among disability factors that affect life expectancy (17). In developed regions, such as North America, Western Europe, Japan, Australia and New Zealand, the prevalence of KOA is ~22.0% in men aged ≥80 and 30.3% in elderly women; in the Western Pacific region, the corresponding prevalence rates are 13.0 and 20.5%, respectively, with prevalence increasing considerably in individuals aged ≥45 (14.1% for men and 22.8% for women) (18). The prevalence of KOA in China is ~18% (19,20). Prevalence rate is notably higher among women than men, especially in the population aged ≥60 years (10.0% for men and 37.3% for women) (19,20). The median age of KOA diagnosis is 55 years (21). With rapid increase in the elderly population of China, the incidence of KOA has risen. Besides causing physical pain and dysfunction, KOA leads to an increase in anxiety, helplessness, depression and social barriers at both social and psychological level; this affects daily life, social function and quality of life of patients, brings economic burdens and pressure to families and social healthcare and poses a challenge to social health (22). The pain and disability caused by KOA posed economic burdens worldwide, with the cost amounting to 1.0-2.5% of the gross national product in developed countries (23).

3. Risk factors

Age. In the United States, Osteoarthritis is the second leading cause of incapacity in men >50 years of age (24). The disease is also one of the main causes of disability (24) and affects the quality of life and economic status of patients. Therefore, greater emphasis on the prevention and treatment of KOA in older people is important to decrease disability rates and improve quality of life in the elderly population.

Genetics. Family history is a risk factor for KOA. In a previous study, the heritability frequencies of femoral, tibial, patellar and total cartilage volumes were estimated to be 61, 76, 66 and 73%, respectively (25). Given the relatively high heritability of tibial cartilage volume and greater susceptibility of the elderly to tibial fractures, attention should be paid to the protection of the tibia during middle and older age. KOA is also associated with abnormalities in the *COL2A1* gene, which is associated with type II collagen synthesis. One-third of the mutations in the COL2A1 gene are dominant negative mutations, affecting glycine residues in the α1 chain G-X-Y repeat sequence. These mutations disrupt the triple helix structure of collagen and are common in type II achondroplasia and hypochondroplasia (26). Which suggests that KOA is influenced by genetics (27).

Body mass index. High body mass index is a risk factor for KOA. A previous study reported a 35% increase in KOA risk with every 5-unit increase in body mass index (28). This is primarily attributed to the fact that greater body weight increases the weight-bearing pressure of the knee joint, thereby increasing the probability of KOA.

Sex. Sex differences exist in the incidence rates of KOA. In rural Tianjin, the prevalence of KOA was higher in women than in men (14.1% vs. 6.5%) (29-32). The causes of sex differences in KOA incidence remain unclear and may be associated with estrogen levels (33).

Race. Race affects the incidence of KOA. Through the investigation of the prevalence of KOA among the elderly population in an urban area in China and the white population in the United States, it was shown that the prevalence rates of radiological and clinical KOA in Chinese women were 46.6 and 15.4%, respectively, which were considerably higher than the rates in white American women of the same age group, 34.8 and 11.6% respectively. The radiological and clinical KOA prevalence rates in elderly Chinese men were 27.6 and 7.1% (34), respectively, similar to those in white American men, 30.8 and 6.9% respectively (35).

Trauma. KOA is associated with articular injuries, including articular surface fractures, joint dislocation and ligament and meniscus injury (36). These traumatic injuries increase the incidence of KOA to different extents. For example, there a near 7-fold and 8-fold increase in the odds for the development of KOA post ACL injury and ACL reconstruction have been reported (37).

Other risk factors. Humid, cold and dark living environments (38-40), joint load (41) and professional sports training (42) are risk factors for KOA.

KOA occurs as a result of combined effects of multiple factors, but there is currently no consensus on the exact risk factors. Specifically, age, genetics, body weight, sex, race and trauma have been recognized as risk factors by a number of studies, but opinion is divided on the roles of diet, smoking and exercise, which require further investigation (43-46). This article summarizes the risk factors, pathogenesis and treatment of KOA in the form of graphs (Fig. 1).

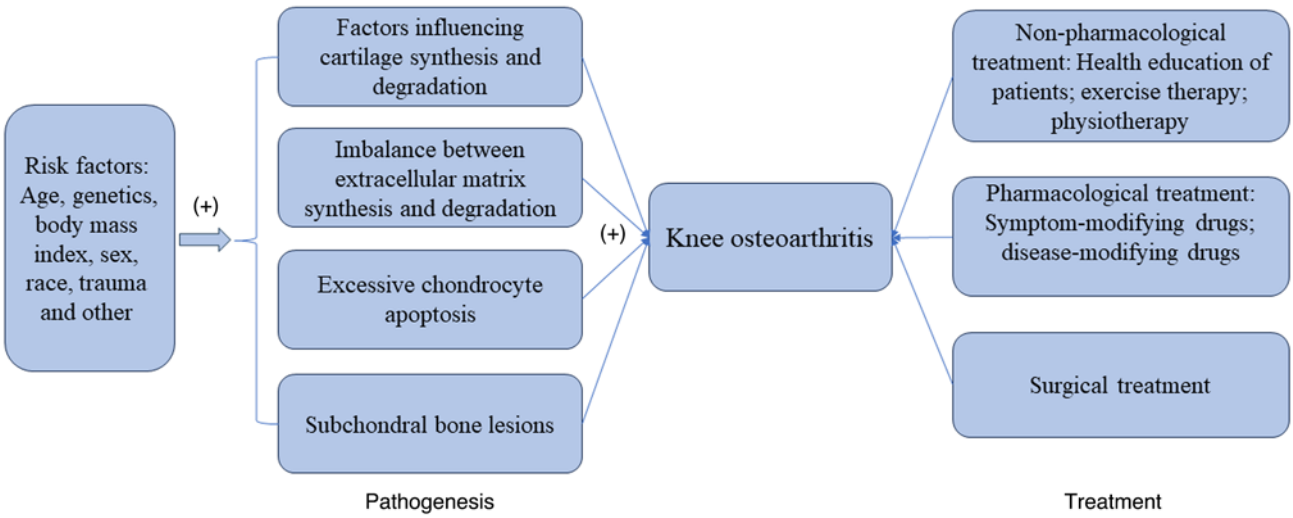

Figure 1. Pathogenesis and treatment of knee osteoarthritis.

4. Histopathological manifestation

The primary histopathological characteristics of KOA include degradation and degenerative changes of the articular cartilage matrix. However, these are not limited to articular cartilage and may even involve the entire joint. Other manifestations include articular cartilage softening, fibrosis, ulceration, and the loss of articular cartilage, synovial hyperemia, swelling and hyperplasia, subchondral bone sclerosis and eburnation and osteophyte and subchondral cyst formation (47,48).

5. Pathogenesis

Factors influencing cartilage synthesis and degradation. During development of KOA, the balance between cartilage synthesis and degradation is primarily affected by pro-degenerative cytokines, such as interleukins (ILs) and tumour necrosis factor-α (TNF-α), and pro-anabolic factors such as insulin-like growth factor 1 (IGF-1), transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMPs) (49). Pro-degenerative factors primarily include IL-1β, -6, -15, -17 and -18 and TNF-α, with IL-1β and TNF-α being strong activators of cartilage extracellular matrix (ECM) degradation. Pro-anabolic factors include IGF-1, members of the TGF-β family, BMP-2 and -7, IL-4 and -10 and anti-inflammatory or regulatory cytokines secreted by the synovium, cartilage or other tissues, including fibroblast growth factor 2 and IL-4, -6, -10 and -14 (50-52). Free radicals are also associated with cartilage destruction and matrix degradation in KOA. For example, reactive oxygen species can inhibit the proliferation of articular chondrocytes, promote their apoptosis and cause an imbalance in synthesis and degradation of collagen and proteoglycans (PGs) in the cartilage matrix, thereby inducing cartilage injury (53).

Imbalance between ECM synthesis and degradation. ECM, synthesized and secreted by chondrocytes, is primarily composed of water, collagen and PGs. These components form a complex network structure that provides nutrients and support to chondrocytes and serves as a site for physiological activity of chondrocytes (54). A previous study showed that cartilage injury in KOA occurs primarily in the form of ECM degeneration (55), which manifests as an imbalance between degradation and synthesis. Signaling pathways associated with degradation comprise MAPKs, NF-κB, the Wnt/β-catenin and Notch signaling pathways and toll-like receptors (56).

Excessive chondrocyte apoptosis. A small amount of apoptosis occurs in normal cartilage and is generally limited to the surface layer. It is an essential physiological process for growth, development, functional regulation and maintenance of internal environment stability in cartilage (57,58). However, excessive apoptosis of cartilage is a pathological process and one of the pathogenic mechanisms of KOA (59). In a previous study, flow cytometry data showed that ~5% of normal chondrocytes and 22% of OA chondrocytes undergo apoptosis. Staining of cartilage sections revealed that apoptotic cells existed on the surface and middle cartilage layers, with PGs notably decreased in apoptotic regions, and the number of apoptotic cells was positively associated with KOA severity (60). Chondrocyte apoptosis in KOA is primarily regulated by the mitochondrial, death receptor and endoplasmic reticulum stress response pathways (61,62). A previous study investigated the widely recognized Fas pathway among death receptor pathways, and the NO pathway among the various mitochondrial pathways (62-66). Genes involved in regulation of apoptosis mainly include the BCL-2 and interlukin-1β-converting enzyme (ICE) gene families and the p53 and c-myc genes.

Subchondral bone lesions. Subchondral bone hardening and osteophyte formation, known as bone remodeling, are characteristic manifestations of KOA (67). Studies have shown that subchondral bone lesions appear during the early stage of KOA and may occur earlier than cartilage degeneration (68). Although there is a lack of consensus in this aspect, it has been widely recognized that subchondral bone lesions promote cartilage degeneration (68-70).

6. Diagnosis

KOA is primarily diagnosed based on clinical symptoms, signs, imaging examinations and laboratory examinations.

Symptoms. KOA primarily manifests as knee joint pain that is aggravated by fatigue or weather changes and cold and wet weather, and relieved after rest or the application of heat. Patients typically experience either dull and needle-like pain or joint soreness (71). The pain originates from tissue around the knee joint, such as subchondral bone microfractures, synovitis, joint capsular strain caused by osteohypertrophy and increased intraosseous venous pressure (72). In the early stage of disease, pain is only felt during continuous loading or overuse of the joint. When joint weakness or movement disorders develop during middle-to-late stages of the disease, pain occurs with mild exertion or during rest or night-time (73). Patients also experience limited joint mobility upon waking in the morning, known as morning stiffness, which usually lasts <30 min (74) and is limited to the affected joints.

Signs. A physical examination should be performed to determine whether symptoms are associated with joints. It usually consists of joint palpation, testing of the active and passive range of motion of joints and assessment of pain using the pain index. Common signs include the following: i) Tenderness and tactile pain in the knee joint and joint edges, with tender points mostly located near the joint line, joint capsule and insertion points of the collateral ligament. This may be associated with muscle spasms, bursitis and tendonitis (71); ii) hypertrophy and swelling of the knee joint resulting from osteophyte formation leading to osteohypertrophy with or without aseptic inflammatory exudation from the synovial membrane within the joint, which may be accompanied by an increase in local skin temperature of the knee joint (75); iii) obviously palpable articular crepitus sounds during active or passive joint flexion and extension, primarily related to articular cartilage detachment and degeneration of joints such as the patella and femur, which result in uneven articular surfaces that rub against each other and the presence of cartilage fragments in the joint (5); iv) limited joint range of motion and movement abnormalities, which may be related to pain, exudate adhesion, flexion contracture, muscle spasms, cartilage loss, degeneration, mechanical obstruction caused by cartilage or the menisci or intra-articular loose bodies (76) and v) joint varus deformity or valgus deformity (77).

Imaging examinations. X-ray is the first-choice imaging modality in the diagnosis of KOA. In general, anteroposterior and lateral radiographs of the knee joint, particularly the weight-bearing views, are required for the comparison of bilateral knee joints (78). In the early stage of disease, X-ray findings are usually negative, with small osteophytes occasionally seen on the superior and inferior patellar edges. Advanced disease manifests as narrowing of the joint space, bone sclerosis, cystic changes, osteophyte formation along joint edges, subchondral ossification or cystic changes, or joint deformation (79). Further disease progression leads to the occurrence of manifestations such as subchondral bone osteosclerosis, subarticular cysts, bone resorption and intra-articular loose bodies (80). The Chinese Medical Association Guidelines for the Diagnosis and Treatment of OA (2018 edition) summarized the three typical X-ray manifestations of OA, namely asymmetric joint space narrowing in the affected joints, subchondral bone sclerosis or cystic changes and osteophyte formation along joint edges (39).

Computed tomography (CT) and magnetic resonance imaging (MRI) are primarily used for differential diagnosis. CT possesses limitations, such as for certain minor soft tissue injuries, CT images may not be sensitive enough and is less commonly used in clinical practice (81). It is primarily used to locate loose bodies or debris in the joint, and to determine patellofemoral joint structure (82). MRI can show lesions in the cartilage, bone marrow and soft tissue of the knee joint, provide indications of early cartilage and synovial lesions and reveal structural abnormalities in periarticular tissues such as ligaments and menisci (83). It also enables the evaluation of bone resorption around the knee joint. With semi-quantitative and quantitative analysis of cartilage, the degree of lesions can be evaluated in a more accurate manner, which provides early diagnostic value (84). Quantitative T2-weighted MRI may serve as an indicator for early KOA diagnosis and evaluation of disease condition (85-89), but it is of limited use in the guidance of clinical treatment of KOA (90) as it is difficult to distinguish inflammatory arthritis OA with MRI.

Ultrasound examinations are of use in detecting joint exudation, cartilage lesions and popliteal cysts and in guiding punctures and injections in joints and the surrounding soft tissue (91). Radionuclide bone imaging assists in determining the metabolic status of osseous tissue, which contributes to early diagnosis (92).

Laboratory examination. At present, no specific clinical laboratory markers of KOA are known (30). A previous study showed that ESR is associated with joint function limitation, whereas CRP is associated with severe KOA (93). However, further research is required to ascertain whether ESR and CRP serve as indicators for disease diagnosis and monitoring (93). Serum IGF-1 expression and matrix metalloproteinase (MMP)-3 expression are associated with osteophyte formation and articular index in patients with KOA, respectively (94,95).

7. Research in KOA treatment

The Guidelines for the Diagnosis and Treatment of OA (2018 Edition) published in China first proposed the concept and strategy of stepwise treatment. Basic treatment, including patient education, exercise therapy, physical therapy and action support therapy, is applicable to all patients with OA. Appropriate basic treatment regimens can be selected for patients with early-stage KOA. For those with aggravated disease, secondary pharmacological treatment can be administered with the appropriate drug administration routes and drug types selected based on affected sites and risk factors of the patient. If basic and pharmacological treatment prove ineffective, surgical treatment can be performed. The surgical plan should be developed by taking the lesion site and degree, general condition and willingness of the patient into consideration (39). At present, the treatment principle for KOA is combined use of non-pharmacological and pharmacological

therapies, with surgery only performed when necessary. Treatment of symptomatic KOA should be aimed at the following: i) Control 0of symptoms; ii) improvement of limited joint function; iii) enhancement of quality of life; iv) reduction of disability rate and v) avoidance of excessive medication. In 2000, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommended the following treatment options for patients with KOA: Non-pharmacological, pharmacological and surgical treatment options (96).

Non-pharmacological treatment

Health education of patients. KOA-related knowledge can be provided to patients through health education to promote positive and optimistic attitudes towards the disease. Measures such as maintenance of good lifestyle habits, regular exercise, avoidance of weight-bearing activities and body weight reduction contribute to the enhancement of self-management and exert good preventive and stabilizing effects during the rehabilitation stage. Therefore, health education is essential for treatment of KOA.

Exercise therapy. Exercise therapy, which possesses advantages such as ease of operation, lack of adverse reaction (including liver and kidney damage and gastrointestinal irritation), effective pain relief and improvement of joint function, is by various guidelines as the first-choice treatment method for KOA (97). Various exercise training regimens have been reported to have therapeutic effects on KOA. Aerobic exercise is the most widely used and can reduce pain and improve physical function (98). Strength training is the most effective exercise therapy against muscle weakness (99). The research basis for exercise training in patients with KOA has been stated in recommended regimens for non-pharmacological treatment of arthritis proposed by the EULAR in 2013 (53). Forms of exercise therapy recommended by various guidelines on KOA treatment published worldwide primarily include aerobic and aquatic exercise and muscle strength training (97).

Physiotherapy. Clinical application of physiotherapy improves blood circulation, provides anti-inflammatory and analgesic effects, and assists in the alleviation of symptoms (100). Physiotherapy techniques primarily used in the treatment of KOA include hot compression, aquatic therapy, acupuncture and electromagnetic and ultra-short-wave therapy (101,102).

Pharmacological treatment. EULAR has classified pharmacological agents for KOA treatment into two primary categories, namely symptom- and disease-modifying drugs (103-105). Traditional Chinese medicine and Chinese herbal medications can also be used for the treatment of KOA (106). Modern pharmacological studies have shown that Yanghe decoction has the effect of preventing chondrocyte apoptosis and exerts an anti-inflammatory action during KOA treatment (107,108).

Symptom-modifying drugs. Acetaminophen is the most representative analgesic and the primary drug used to control symptoms in patients with mild-to-moderate KOA. It causes less gastrointestinal irritation, has a good safety and tolerability profile and is less likely to cause gastrointestinal bleeding, which makes it suitable for use in elderly patients. However, its analgesic effects are relatively weak, making it more suitable for patients with early-stage KOA or milder symptoms. In 2000, the ACR and EULAR recommended acetaminophen as the first-choice therapy for the treatment of OA, but large doses or long-term use may lead to liver or kidney damage (109).

Non-steroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory effects by decreasing the synthesis of prostaglandins through the inhibition of cyclooxygenase (COX) and are used as first-line therapy in KOA treatment (110). NSAIDs include salicylic and phenylpropionic acid, acetic acid derivatives, fenamates, enolic acids, naphthalenones and COX inhibitors, with acetylsalicylic acid, ibuprofen, naproxen, indomethacin and sulindac commonly used in clinical practice (111). Traditional NSAIDs produce toxic side effects due to the lack of selectivity towards COX-1 or COX-2 (112). To address this, second-generation NSAIDs, a class of COX-2 selective inhibitors, have been designed to avoid adverse reactions associated with traditional NSAIDs, including gastrointestinal complications, cardiovascular events, renal toxicity, the exacerbation of hypertension and fluid retention (113). Representative drugs include celecoxib and rofecoxib. Studies have demonstrated that celecoxib enables an increase in PG content of the cartilage matrix, cartilage repair and delay of cartilage degeneration (114,115). However, COX-2 selective inhibitors increase risk of cardiovascular disease (116). Therefore, consideration of various factors and rational drug use is necessary for the clinical application of NSAIDs.

Inhibition of inflammation and alleviation of symptoms can be achieved through aspiration of joint effusion and subsequent injection of corresponding medications (117). Steroid hormones (118) and hyaluronic acid (119) are commonly used as intracavitary injection drugs. The intra-articular injection of glucocorticoids enables inhibition of abnormal connective tissue proliferation, reduction of synovitis, significant alleviation of joint pain and improvement of joint function (120). However, it is important to note that repeated injections of intra-articular glucocorticoids over a long period of time can lead to cartilage loss (121). Hyaluronic acid attenuates joint pain, increases joint mobility, decreases synovitis and promotes anabolism of chondrocytes in patients with OA, but the exact mechanisms of action require further investigation (122). Both glucocorticoids and hyaluronic acid effectively relieve joint pain and swelling but should not be used repeatedly due to the damaging effects of injections on cartilage, such as scratching of the cartilage by the syringe needle (123,124). Additionally, intra-articular injections of autologous platelet-rich plasma for treatment of KOA have demonstrated good therapeutic effects (125,126) and possess good prospects for application in clinical practice.

Antidepressants (127) such as duloxetine provide antidepressant, central pain-suppressing and anxiolytic effects. Topical medications such as capsaicin (128), diclofenac diethylamine cream (129) and methyl salicylate (130) relieve the symptoms of joint pain to a certain extent. A study has also shown that statins decrease the incidence of KOA and delay its progression (131). Other studies have demonstrated that salmon calcitonin not only improves symptoms of KOA, but also exerts cartilage-protecting effects (132,133).

Disease-modifying drugs. As the basic substance in the synthesis of polyglucosamine and hyaluronic acid, glucosamine is an important component required for PG synthesis in

articular cartilage matrix. It acts selectively on articular cartilage, promotes PG and hyaluronic acid synthesis, maintains morphology and structure of the cartilage ECM and serves an important role in articular cartilage repair and synovial fluid production (134). Other effects include inhibition of the generation of free oxygen radicals, collagenases, prostaglandin E_2 and phospholipase A_2, which protect articular cartilage and contribute to the delay of OA progression (135). In European countries, glucosamine sulphate is the first-choice prescription drug for the treatment of KOA and is thought to be delay or reverse pathological changes of OA (136). However, adverse reactions such as nausea and vomiting, abdominal distension and diarrhea and bone aches and pain may arise during clinical application of glucosamine sulphate.

Chondroitin sulphate is glycosaminoglycan that promotes the anabolism of chondrocytes, stimulates PG and hyaluronic acid synthesis and inhibits ECM degradation by enzymes, which contribute to relief of joint pain and improvement of joint function (137).

Diacerein is an anthraquinone is extracted from Da Huang (Radix et Rhizoma Rhei). It inhibits inflammatory factors and MMPs, promotes the synthesis of growth factors and stabilizes lysosomal membranes, thereby achieving anti-inflammatory, analgesic and cartilage-protecting effects (138). A previous study demonstrated that the combined use of glucosamine and diacerein improves meniscal damage (139). Diarrhea may occur as a rare adverse reaction.

MMPs may degrade type II collagen and PGs in the ECM, which results in cartilage destruction (140). Tetracyclines (141) inhibit MMP-1 release from type B synoviocytes, as well as nitrous oxide production. This leads to the reduction of damage to knee articular cartilage by inflammatory mediators, which contributes to the improvement of disease in patients with KOA (141). The development of MMP inhibitors has gained increasing research interest in the field of pharmacological therapies for OA (142).

Antioxidants (143) such as superoxide dismutase (144), vitamins C, D and E can provide cartilage-protecting effects by blocking free oxygen radical pathways (145-148). Other drugs such as calcitonin (149) and statins (150) alleviate the disease condition of patients with KOA.

Surgical treatment. Surgical treatment is recommended for patients with advanced KOA who respond poorly after 6 months of conservative treatment, and whose condition severely affects daily living (103,151). However, the effects of surgical treatment may be influenced by factors such as pain, joint function, anatomical factors and patient's physical function (152). Current surgical treatment methods for KOA include knee arthroscopy (153), bone marrow stimulation (154) and osteotomy (155-157) and joint replacement (158), fusion (159) and arthroplasty (160). For patients with early-to-mid-stage KOA, joint arthroscopy is a better option as it provides the advantages of a smaller wound and rapid recovery (153). Artificial joint replacement, which is the terminal treatment for KOA, may be considered for patients with advanced KOA who experience joint ankylosis, severe damage to joint structures and intense pain (158). However, there is need for further exploration into the prevention and treatment of postoperative complications following artificial joint replacement (159). Osteotomy techniques such as high tibial osteotomy are primarily used for the treatment of KOA with varus and valgus deformities (161).

8. Conclusion

KOA is a common chronic disease in orthopedic practice and one of the primary causes of disability and pain in older people (162). Although etiology and pathogenesis of KOA have not yet been fully elucidated, research on its pathogenic mechanisms has shifted from the macroscopic level, including looking at biomechanics, articular cartilage and subchondral bone lesions to the microscopic level, including investigation of inflammatory cytokines and neural mechanisms (140). However, current research remains limited (9). For example, certain progress has been made in the investigation of KOA-associated inflammatory cytokines (163) from the single-factor perspective, but the complex mechanisms of association among multiple factors have not yet been determined (164). Given the lack of early symptoms and signs and specific diagnostic indicators in imaging and laboratory examinations, differential diagnosis of KOA in clinical practice is of importance. Clinicians are required to make judgments based on analysis of risk factors, symptoms, signs and results of imaging and laboratory examinations. Identifying specific diagnostic markers via measurement of markers in the peripheral blood, joint fluid and other body fluids of patients may facilitate early detection, diagnosis and treatment of KOA. However, the combination of various factors, such as risk factors, symptoms, signs, imaging and laboratory findings is required for confirmed diagnosis and staging to provide a basis for clinical treatment.

Numerous factors, including risk factors, psychosocial factors, symptoms, signs, imaging and laboratory findings, should be taken into consideration for the determination of KOA treatment regimens as disease characteristics and general conditions differ between individuals. Prevention should take priority, followed by individualized and standardized treatment via formulation of treatment regimens suited to every patient to maximize clinical effects. KOA treatment is currently limited to symptomatic therapy such as anti-inflammatory treatment, analgesia and limited functional improvement. In previous studies, researchers have developed pharmacological agents to promote cartilage repair and regeneration (165,166), inhibit cartilage degradation (167), promote cartilage matrix secretion (168), specifically inhibit inflammatory factors and pathways (169) and maintain the joint cavity environment (170,171). However, the majority of these drugs are still undergoing clinical trials. In addition, sociopsychological support should also be provided to patients during treatment process to assist in the recovery of social function. With the continuous improvements in understanding of the pathogenesis of KOA, it is anticipated that drugs that directly target pathogenic factors of the disease will emerge in the future and create new breakthroughs in disease treatment. It is anticipated that KOA may be prevented, controlled or cured through active intervention rather than passive treatment. Future research efforts should be directed towards the prevention of KOA, etiological treatment, maximum recovery of joint

structure and function and the limitation or even reversal of KOA progression.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Yunnan Provincial Clinical Orthopedic Trauma Medical Center (grant no. ZX20191001) and the Science and Technology Plan Project of The Science and Technology Department of Yunnan Province (grant no. 202101AY070001-296).

Availability of data and materials

Not applicable.

Authors' contributions

YX and TJ conceived the study. RG and JL designed the study and drafted, reviewed and edited the manuscript. CY, CZ, FC and JW wrote the manuscript. JC, HN, KK and ZW analysed the literature. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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