

How to Cite:

Ahmed, H. S., & Al-Ghafoor, S. A. A. (2022). Knee osteoarthritis: Diagnosis and medical concerns. *International Journal of Health Sciences*, 6(S3), 12252–12263.
<https://doi.org/10.53730/ijhs.v6nS3.8974>

Knee osteoarthritis: Diagnosis and medical concerns

Hind Shakir Ahmed

Department of Chemistry/ College of Education for Pure Science (Ibn Al-Haitham)/ University of Baghdad, Baghdad-Iraq

*Corresponding author email: hindshakir82@gmail.com

Shahad Adil Abd Al-Ghafoor

Department of Chemistry/ College of Education for Pure Science (Ibn Al-Haitham)/ University of Baghdad, Baghdad-Iraq

Abstract---Osteoarthritis (OA) is recognized as a main public health difficult. It is one of the major reasons of reduced function that diminishes quality of life worldwide. Osteoarthritis is a very common disorder affecting the joint cartilage. As there is no cure for osteoarthritis, treatments currently focus on management of symptoms. Pain relief, improved joint function, and joint stability are the main goals of therapy. The muscle weakness and muscle atrophy contribute to the disease process. So, rehabilitation and physiotherapy were often prescribed with the intention to alleviate pain and increase mobility. Medical therapy provides modest benefits in pain reduction and functional improvement; however, non-steroidal anti-inflammatory drugs, tramadol, and other opioids have significant potential harms. Joint replacement may be considered for patients with moderate to severe pain and radiographically confirmed osteoarthritis. This article highlights on overview of osteoarthritis and focuses on biomechanics, etiology, diagnosis and treatment strategies, conservative treatment including the physical therapy management. This information should assist health care practioners who treat patients with this disorder.

Keywords---osteoarthritis, Knee osteoarthritis, classification, molecular disorder, risk factors, clinical findings, treatment.

Introduction

Osteoarthritis

Osteoarthritis (OA) is the most common progressive musculoskeletal condition that can affect joints, but it mainly affects the hips and knees as predominant weight-bearing joints¹. Knee osteoarthritis (KOA) is characterized by structural modifications to primarily articular cartilage and the subchondral bone, but also Hoffa's fat pad, synovia, ligaments and muscles, leading to the concept of observing OA as a whole joint disease². Because of the higher prevalence of asymptomatic OA, it is approximated that 250 million people all over the world suffer from OA³. The prevalence of KOA increased significantly over the last decades and continues to rise, partially because of the increasing prevalence of obesity and other risk factors, but also independently, of other causes⁴. Osteoarthritis should be suspected in patients with pain in the fingers, shoulders, hips, knees, or ankles, particularly if they are older than 40 years⁵. Other diagnoses should be deliberated in patients with erythema, inflammation, or pain that rises or changes considerably⁶. The distinction diagnosis comprises collagen vascular disease, gout and pseudogout, trauma, septic arthritis, ankylosing spondylitis, and psoriatic arthritis. Common symptoms and signs of OA⁷ are illustrated in table 1.

Table 1
Signs and symptoms of OA⁷

Table 1 – Common symptoms and signs of OA
<p>Symptoms</p> <ul style="list-style-type: none"> • Joint pain • Joint stiffness • Crepitus • Alteration in joint shape • Functional impairment <p>Signs</p> <ul style="list-style-type: none"> • Crepitus • Restricted movement • Tenderness (joint line, periarticular) • Bony swelling • Soft tissue swelling • Limp • Deformity • Muscle atrophy/weakness • Increased warmth ± effusion • Instability
<p>OA, osteoarthritis. Adapted from O'Reilly S, Doherty M. In: Brandt KD, Doherty M, Lohmander SL, eds. <i>Osteoarthritis</i>. 2nd ed. 2003.¹²</p>

Diagnosis and Epidemiology

The diagnosis of osteoarthritis is largely made by obtaining a detailed history and conducting a complete physical examination. Ancillary diagnostic tests may occasionally be necessary when the diagnosis remains uncertain. The diagnosis of OA relies on clinical symptoms, physical findings, and radiographic findings. Not all persons who have radiographic OA have clinical disease. Conversely, not all persons who have joint pain demonstrate plain radiographic findings of OA. Thus, there is often discordance between X-ray findings and symptoms of OA⁸. A thorough history and physical exam (with a focused musculoskeletal exam) should be performed on all patients, with some findings summarized above. Osteoarthritis can be diagnosed with confidence if the following are present: 1) pain worse with activity and better with rest, 2) age more than 45 years, 3) morning stiffness lasting less than 30 minutes, 4) bony joint enlargement, and 5) limitation in range of motion. A differential diagnosis should include rheumatoid arthritis, psoriatic arthritis, crystalline arthritis, hemochromatosis, bursitis, avascular necrosis, tendinitis, radiculopathy, among other soft tissue abnormalities⁹. It has been found that by age 70 to 74 years, about 33% of men and 40% of women will have OA with clinical and X-ray features¹⁰. The lifetime risk of developing symptomatic KOA is about 45%, rising to 66% in obese persons¹¹. Osteoarthritis is diagnosed by physical examination and, when necessary, x-rays, *magnetic resonance imaging* (MRI), and arthroscopy. However, these diagnostic tools have low sensitivity and specificity. Figure 1 shows a healthy knee and a knee joint affected with OA¹².

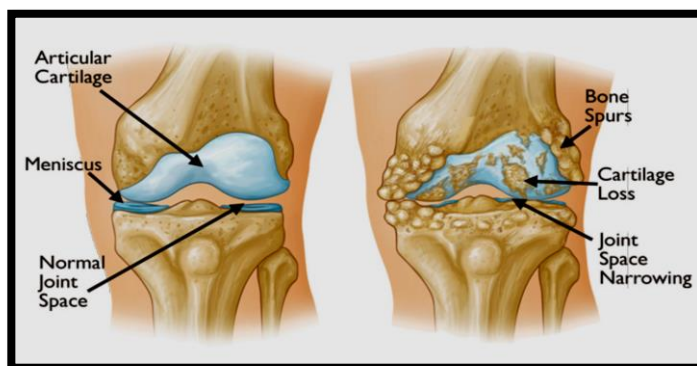


Figure 1. A healthy knee and a knee joint affected with OA¹²

Etiology and Pathogenesis

The exact etiology of OA is unclear. Numerous influences (such as genetics, trauma, and obesity) interrelate to cause this illness. Any incident that modifies the environment of the chondrocyte has the possible to cause OA¹³.

The OA has historically been classified as:

- Primary OA is the most common subset of the disease and is diagnosed in the absence of a predisposing trauma or disease but is associated with the risk factors.

- Secondary OA occurs with a preexisting joint abnormality.

Predisposing conditions include trauma or injury, congenital joint disorders, inflammatory arthritis, avascular necrosis, infectious arthritis, Paget disease, osteopetrosis, osteochondritis dissecans, metabolic disorders (hemochromatosis, Wilson's disease), hemoglobinopathy, Ehlers-Danlos syndrome, or Marfan syndrome¹⁴.

Pathophysiology

The cause of OA is an interaction of risk factors, mechanical stress, and abnormal joint mechanics. The combination leads to pro-inflammatory markers and proteases that eventually mediate joint destruction. The complete pathway that leads to the destruction of the entire joint is unknown¹⁵. Usually, the earliest changes that occur in OA are at the level of the articular cartilage that develops surface fibrillation, irregularity, and focal erosions. These erosions eventually extend down to the bone and continually expand to involve more of the joint surface. On a microscopic level, after cartilage injury, the collagen matrix is damaged, causing chondrocytes to proliferate and form clusters. As more of the collagen matrix is damaged, chondrocytes undergo apoptosis. Improperly mineralized collagen causes subchondral bone thickening; in advanced disease, bone cysts infrequently occur. Even rarer, bony erosions appear in erosive OA¹⁶.

Radiographic Classification of Knee Osteoarthritis

A self-reported physical disability or assessment questionnaire most frequently used to evaluate the effect of exercises for OA. The most popular specific questionnaire for KOA is the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire which measures pain, stiffness, and functional limitation¹⁷. Knee OA develops progressively over years and progresses in stages. Generally, the severity of KOA is divided into five stages: first stage (stage 0) resembles to normal healthy knee and the final stage (stage 4) corresponds to the most severe illness. The most frequently used systems for grading KOA are the International Knee Documentation Committee (IKDC) system, the Ahlback system, and the Kellgren & Lawrence (KL) grading system. The KL grading scale was approved by the World Health Organization as the reference standard for cross-sectional and longitudinal epidemiologic studies¹⁸. The KL grading system is still considered the gold standard for initial assessment of KOA severity in radiographs. Figure 2 shows the KL grading system. The KL grading system categorizes KOA severity into five grades (grade 0 to 4). The KL grading scheme for quantifying KOA severity from X-ray images is defined as follows¹⁹:

- Grade 0: absence of radiographic features (cartilage loss or osteophytes) of OA.
- Grade 1: doubtful joint space narrowing (JSN), osteophytes sprouting, bone marrow edema (BME), and subchondral cyst.
- Grade 2: visible osteophytes formation and reduction in joint space width on the antero posterior weight-bearing radiograph with BME and subchondral cyst.

- Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bone deformity.
- Grade 4: large osteophytes, marked JSN, severe sclerosis, and definite bone deformity.

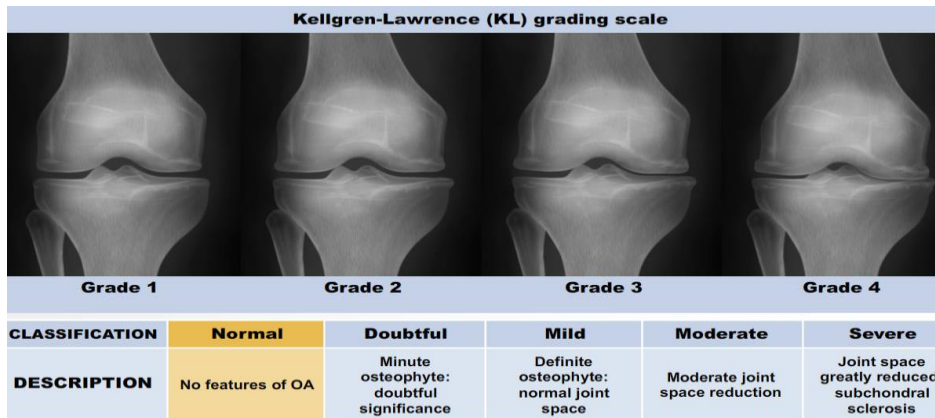


Figure 2. The Kellgren and Lawrence grading system to assess the severity of KOA¹⁹

Risk Factors

Endogenous risk factors for KOA include age, sex, family history, ethnic origin (OA is more common in people of European descent), and post-menopausal changes. Exogenous risk factors include macrotrauma, repetitive microtrauma, being overweight, repetitive joint surgery, and lifestyle factors (e.g alcohol and tobacco use). While protective factors are exercise, healthy diet, and occupational injuries (Figure 3)²⁰.

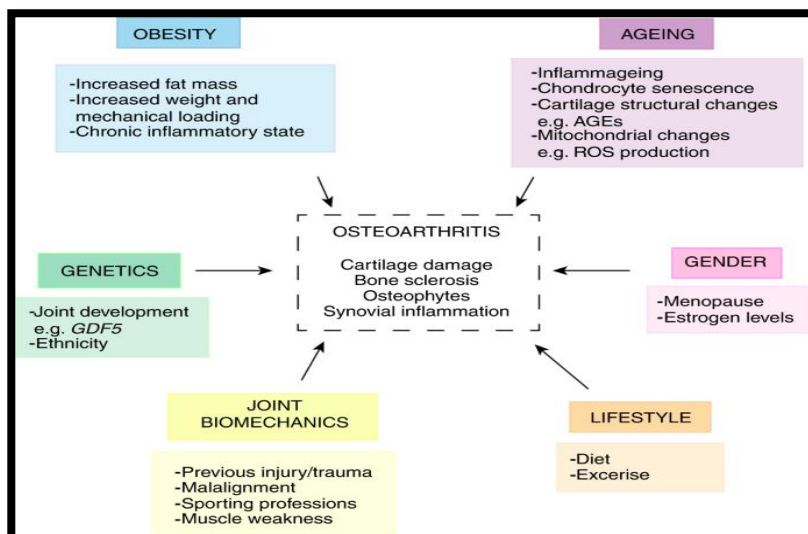


Figure 3. The risk factors for OA²⁰

Physical disability resulting from pain and loss of functional ability reduces the quality of life and increases the risk of disease. Although there is a wide range of palliative devices and medications available that can relieve pain and improve quality of life, no pharmaceutical product can stop or reverse the onset of OA²¹. In general, mild-to-moderate activity is not likely to lead to OA in normal joints. Vitamin D intake may also affect OA. Low dietary intake or serum levels of vitamin D are associated with increased rates of progression²².

Clinical Findings

Clinically, KOA in primary care is usually managed with analgesics and non-drug options, such as exercise. Exercise has been shown to improve function, strength, walking speed, self-efficacy, and reduce pain and the risk of other chronic diseases²³. Plain radiographs are commonly used to classify OA subjects for clinical studies and JSN is often used as a measure of disease progression²⁴. Although plain radiography currently exists, the 'gold standard' for assessing OA progression, it is fraught with problems with the accurate reproducibility of joint space width measurements, particularly in subjects with OA²⁵. Among the clinically practical drugs, some of them have adequate results in relieving pain and improving joint function, while a significant part of them do not have obvious consequences²⁶. Clinical guidelines concerning the use of some pharmaceutical preparations are often inconsistent. This difference may be due to variances between clinical trials, in which biologically heterogeneous subjects are involved²⁷. Furthermore, the criteria for inclusion of clinical trials running from 2016 to 2021 to explore the influences of a specific drug on KOA did not take into account the molecular features of the contributors²⁸. Thus, an important research gap in matching drug mechanisms with patients' molecular features remains and needs to be filled. Indeed, KOA patients show early molecular and compositional fluctuations before the disease shows any clinical indicators. The International Arthritis Research Society (OARSI) validated a new definition of OA, focusing on molecular abnormality as the primary disorder followed by anatomical and/or physiological disturbances, and which highlights the molecular characterization of the pathological mechanisms responsible for KOA²⁹. In fact, a large amount of KOA-related molecules can be detected in body fluids reveals the pathogenesis of KOA³⁰.

Biochemical analysis of body fluids is often used in hospitals and clinics for effective diagnosis of disease because it contains many valuable information about the disease, which provides the possibility of diagnosing and assessing KOA at the molecular level. Here, rendering to the progressive change of representative molecules in body fluids, it has been proposed a new molecular classification of KOA (that is, pre-, early-, progressive-, and final-stage KOA), emphasizing its role in KOA prediction, diagnosis, and evaluation of treatment usefulness. These classification criteria may permit molecule-based diagnosis and treatment system, for example, to simplify enrollment of biosimilar patients in clinical trials and to support the therapeutic effectiveness of disease-modifying medicines in a given patient population³¹.

Knee Osteoarthritis: A Molecular Disorder

Traditionally, KOA has been considered a disorder of the articular cartilage. However, KOA is a complete joint disease, or even a systemic disorder because it can be affected by many local and systemic risk factors. The main pathogenesis of KOA involves molecular crosstalk between articular cartilage, synovium, subchondral bone, meniscus, tendons, muscle, and the infrastructural fat pad (IFP)³². For example, accumulation of M1 macrophages in the synovium leads to the secretion of proinflammatory cytokines, which facilitates the formation of inflammation microenvironment and aggravates cartilage degradation and synovitis³³. A variety of cytokines and adipokines secreted by IFP also participate the local inflammation and contribute to the development of KOA³⁴. In turn, the debris released from degenerated cartilage can also boost the inflammatory response within the joint. Such cross-linked molecular dysregulation is the basis of the visibly pathological events, making a strong case to outline its profile in KOA³⁵.

Certainly, besides extensive molecular crosstalk, the opportunity to evaluate molecular fluctuations is obtainable by the molecular mediator of pregnancy, in which synovial fluid (SF), blood and urine are included³⁶. The SF is a gold typical fluid for identification of KOA molecules due to its intimate relationship with different joint tissues and its significant role in transmitting and receiving molecular signals in the joint cavity. Blood and urine are simply withdrawn and reserve a cluster of molecules reflecting KOA pathogenesis³⁷. Given the widespread use of humoral tests, it would be anticipated to characterize the molecular profile of KOA patients by analyzing SF, blood, and urine. Identifying the molecular profiles, including the local and systemic inflammatory cytokines, would help reveal the major inflammatory mechanisms and stratify KOA patients with different molecular characteristics. This strategy could facilitate the diagnosis of inflammation-driven subtype of KOA and the development of molecular based treatment strategies.

Laboratory Findings

The typical clinical presentation of OA does not require laboratory testing. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually normal. Complete blood count is normal. The rheumatoid factor and antinuclear antibodies are usually negative. Note that these antibodies may be low positive and of no significance in elderly patients and in some chronic cases. The SF analysis may be conducted to help exclude other diagnoses. In OA, the white blood cell (WBC) count is usually less than 500 cells per mm² (0.5×10^9 per L) and is composed predominantly of mononuclear cells. In inflammatory aspirates, the WBC count is usually greater than 2,000 cells per mm² (2.0×10^9 per L), and the predominant cell type is usually the neutrophil. Laboratory tests should only be performed if secondary causes of arthritis are clinically suspected³⁸.

Treatment

The primary goals of treatment are improved function and quality of life. Treatment should be tailored to the needs of the individual patient. Patient education, rehabilitation, exercise, modification of activities of daily living, pharmacotherapy, alternative medicine and surgery are all treatment modalities

that should be considered. Radiographic findings are included as part of the American College of Rheumatology diagnostic criteria for OA³⁹. Because of the low association with disease, radiographic studies beyond simple radiographic images should only be obtained if the physician is looking for specific pathological sequelae. Laboratory evaluation should only be performed as clinically indicated. New advances in treatment should be critically reviewed and compared to older treatments. Short- and long-term effects and outcomes must be compared. Since no drug has been demonstrated to be curative, the risks and benefits of treatment must be clearly explained to patients⁴⁰. Alternative treatments abound, but many have not been proven effective. In patients whose symptoms persist despite appropriate treatment (patient education, pharmacological intervention, exercise, modification of activities of daily living, physical therapy), referral to an orthopedic surgeon should be considered⁴¹.

Pharmacotherapy of OA involves oral, topical, and/or intra-articular options. Acetaminophen and oral non-steroidal anti-inflammatory drugs (NSAIDs) are the most popular and affordable options for OA and are usually the initial choice of pharmacologic treatment. The NSAIDs are usually prescribed orally or topically and, initially, should be started as needed rather than scheduled. Due to gastrointestinal toxicity, and renal and cardiovascular side effects, oral NSAIDs should be used very cautiously with close monitoring long term. Topical NSAIDs are less efficacious than their oral counterparts but offer fewer gastrointestinal and other systemic side effects; however, they often cause local skin irritation⁴².

Intra-articular joint injections can also be an effective treatment for OA, especially in a setting of acute pain. Glucocorticoid injections have a variable response, and there is ongoing controversy regarding repeated injections. Hyaluronic acid injections are another option, but their efficacy over placebo is also controversial. Notably, there is no role for oral glucocorticoids. Duloxetine has modest efficacy in OA; opioids can be used in those patients without an adequate response to the above and who may not be candidates for surgery or refuse it altogether. Cyclooxygenase-2 (COX-2) agents are a potentially beneficial therapeutic addition (Figure 4); however, it has not been shown to be any more effective than NSAIDs or acetaminophen, nor does it appear to be any safer than acetaminophen, nor is it more expensive⁴³.

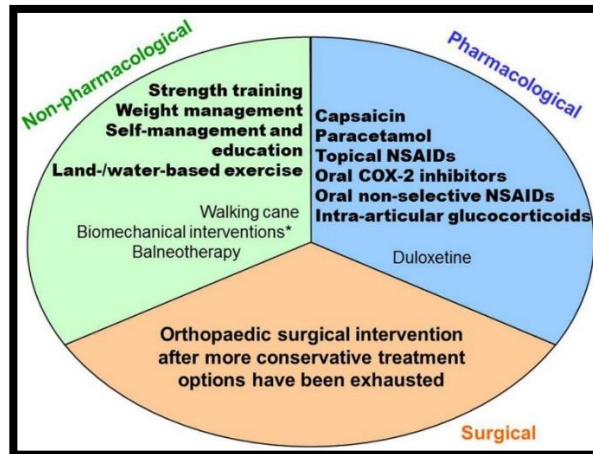


Figure 4. Non-surgical management of KOA⁴³

It is important to note that patients vary greatly in their response to treatment, and there is a large component of trial and error in selecting the agents that will be most effective. In those patients specifically with knee or hip OA who have failed multiple non-pharmacologic and pharmacologic treatment modalities, surgery is the next option. Failure rates for both knee and hip replacements are quite low, and they can provide pain relief and increased functionality. The timing of surgery is key to predict success. Very poor functional status and considerable muscle weakness may not lead to improved postoperative functional status versus those undergoing surgery earlier in the disease course⁴⁴.

Conclusions

Knee osteoarthritis is a major public health concern worldwide and one of the foremost causes of chronic disability in older adults. It is a condition commonly encountered in primary care. Preventive care is dependent upon identification of risk factors for development of incident KOA. The symptoms are often associated with significant functional impairment, as well as signs and symptoms of inflammation, including pain, stiffness and loss of mobility. Conservative treatment has documented for reducing pain and disability. Evidence suggests that stretching, and strengthening exercise decrease pain and improve muscular strength, functional ability and psychological well-being.

Funding

This review received no external funding.

Acknowledgments

None.

Conflict of Interest

The authors declare no conflict of interest.

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