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Osteoarthritis: Review of Etiopathology, Diagnosis and Management

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ABSTRACT

Osteoarthritis (OA) is the most common type of arthritis in the world characterized by articular cartilage degeneration with inflammatory components in ageing population. It involves about 10% of adult population and is among the most disabling disease condition. It is multifactorial in its etiology with a number of non-modifiable and modifiable risk factors. Ageing is the most important risk factor followed by obesity in probably genetically susceptible individuals. The end result of inflammation and articular cartilage degeneration arising from repeated overloading of joint, mechanical or biochemical imbalance of repair and degeneration affects not only joint cartilage but also subchondral bone and periarticular structures. Patient mainly presents with variable degree of pain, stiffness and functional limitation with or without swelling and deformity. Diagnosis is clinical and plain imaging is useful for documentation, to see the grading and plan the suitable treatment. There are a number of treatment options in practice each having their pros and cons but no single treatment method is superior to all. There is no cure for it but judicious use of non-pharmacological and pharmacological measures, often in combination in tailored fashion help to ease the patient's symptoms. Operative intervention in the form of arthroplasty is reserved for end stage arthritis with disabling symptoms not responding with conservative management. Numerous newer treatment modalities are under different phases of clinical trial to test the efficacy and clinical use. Aim of this narrative review article is to analyze literatures obtained from electronic database and present the synthesized relevant clinical update on etiopathology, diagnosis and treatment modalities of symptomatic osteoarthritis.

Keywords: osteoarthritis; pathophysiology; risk factors.

INTRODUCTION

Osteoarthritis (OA) also known as degenerative joint disease or Osteoarthrosis, is the most common types of arthritis. It constitutes 10% of adult population and by 2030, it has been estimated that about 20% of adults in Europe and North America will have developed OA.[1] WHO has labeled it as priority disease.[2] It is one of the 10 most disabling disease in the industrialized nations.[3] Hip and knee OA ranks as 11th most disabling global burden of disease.[3]. Knee is the most common joint followed by hip and hand joints to be affected by OA. Knee OA constitutes about 85% of burden of disease.[4] Shoulder, elbow, wrist, acromioclavicular joint, ankle and foot joints are less commonly affected joints by OA.

OA is multifactorial disease. Age is the most important risk factors to initiate disease process in the genetically predisposed people with abnormal or excess joint insult due to different biomechanical abnormalities. OA is rare below the age of 40 years and very common, about 50%, after the age of 65 years.[5] What exactly initiates the disease process is not yet clearly understood but, there is clear evidence of inflammation as well as degenerative process that is responsible for cartilage degradation and secondary involvement of synovium, capsule, subchondral bones, Para articular ligaments and muscles. There are a lot of research in the past and present to unveil the etiopathogenesis of the disease. OA is primarily a disease of synovial joint cartilage with progressive disintegration and loss of cartilage and bone giving rise to pain, deformity, disability and addition of morbidity in old age. There are end number of treatment modalities with areas of controversies in the optimum management of this disabling disease. Since there is no Disease Modifying Osteoarthritis Drugs (DMOAD), aim of treatment is to reduce the pain and morbidity. It is wise approach to prevent the disease process or slow down the progress so that fewer numbers of patient need costly operative intervention which are not free of complications. This concise narrative review article attempts to present salient features about etiopathology, diagnosis and management of OA.

METHODS

This narrative review study involved recent and past literature search through Medline, Pub med, Cochrane review, Scopus and Google scholar using key words osteoarthritis, risk factors OA, pathogenesis OA, treatment OA and tried to synthesize the information and result of treatment in narrative way.

Classification

Traditional classification of OA is based on the presence or absence of preexisting disease.

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- **Primary or Idiopathic OA:** There is no obvious cause or preexisting disease pathology. This is the most common type.
- **Secondary OA:** OA develops secondary to insult to the joint such as fracture, cartilage injury, ligament or meniscal injury, deformity, dysplasia, malalignment, infection, metabolic disease etc.

Kellgren and Lawrence classification is based on the radiological features and has been divided into following types.[6]

Grade 0	No radiographic features of OA
Grade 1	Doubtful joint space narrowing and possi ble osteophytic lipping
Grade 2	Definitive osteophytes and possible joint space narrowing
Grade 3	Multiple osteophytes, definitive joint space narrowing, sclerosis and possible bony deformity
Grade 4	Large osteophytes, marked narrowing of joint space, severe sclerosis and definitive deformity of bone ends

Risk factors

Unmodifiable Risk factors

- **Age**: Increase in age is the most common risk factor of OA changes.[8] With age, there is proportionate rise in both radiographic and symptomatic OA. But all OA changes in the joint may not be symptomatic.
- For knee osteoarthritis, strong evidence indicates a variety of moderate to strong risk factors, including female sex, obesity, and previous knee injury.[7,8] Knee malalignment is also a moderate to strong risk factor and knee extensor muscle weakness is likely to be a weak risk factor.
- **Sex**: Female are more prone to develop OA than male in about 2:1 ratio. Female sex becomes more important risk factor for Knee OA than male.[8]
- **Genetics**: OA is considered to have polygenetic susceptibility as a number of genetic predisposition have been found in the current research. It is considered to be contributing 40-80% in the development of OA especially in hip and hand.[9]
- **Ethnicity**: Some ethnic groups are more prone to get it than others. European and Americans suffer more commonly than Asian and African population.

Modifiable Risk Factors:

- **Obesity:** Increased Body Mass Index (BMI) has strong evidence of having increased risk of developing symptomatic OA.[8]
- **Injury to the joint:** Injury to the joint cartilage, intraarticular fracture, meniscal or ligamentous structures have been found to be associated with increased risk of development of secondary OA. Previous knee injury, and malalignment are moderate to strong risk factor for knee OA.[10]
- **Level and nature of physical activity:** People who need to do repeated kneeling, squatting, excess walking on up and down stairs are at increaed risk to OA changes.[10] Similarly, occupations such as farmers, factory workers or army personnel which involves repeated act of above activities are at increased risk.[11] Excess physical activities such as heavy physical training or sports such as football, basketball, Rugby etc have been found to have increased prevalence of OA.[11] It may be due to excess cartilage loading or injury to menisci and ligaments.
- **Muscle strength:** Decreased muscle mass or strength is associated with increased risk of OA.
- **Metabolic disease:** DM, thyroid disorder, RA and gout have been found to increase the risk of arthritis.
- **Malalignment of the Limb:** Congenital, developmental or acquired condition of limb malalignment, deformity or limb length discrepancy act as predisposing factors for development of OA. Hip dysplasia and cam deformity are strong risk factors for hip OA.[12,13] Association between OA and other comorbid conditions such as atherosclerosis, cardiovascular events, DM, dyslipidemia, and depression have been found in different studies.[14] There is slightly increased risk of cardiovascular incidence among patients with OA. Similarly, patients with the above medical comorbidity have increased chance of worsening symptoms of OA.[15-17]

Pathogenesis

Pathogenesis of osteoarthritis is a complex process arising from imbalance between cartilage repair and degeneration on the background of mechanical, inflammation and metabolic factors.[18-20] It ultimately leads to cartilage loss, synovial hypertrophy and effusion, subchondral bone, capsule, ligament and muscle affection. With age, there is relative dysfunction of chondrocytes in its reparative function which is also known as chondrosenescence.[21] Cartilage healing process is very slow. Once there is injury or fibrillation of the cartilage tissue layer, the reparative process takes long time. When it is combined with cartilage injury due to trauma or mechanical imbalance or repeated loading predisposed with other mechanical and genetic factors, there starts secretion of proinflammatory mediators such as interleukin, TNF-α from chondrocytes and synoviocytes.[22] Cytokines and metalloproteinases are released into the joint which are responsible for cartilage degradation.[22]

Together with degradation of extracellular cartilage matrix and cartilage itself, synovial hypertrophy and hypervascularity occur. The mechanical and

biochemical property of hyaline cartilage changes and it loses its elasticity and ability to repair. This cascade can progress leading to further disintegration, fibrillation and loss of joint cartilage, subchondral bone changes and reactive new bone formation at the joint margin. Late changes can be in the form of marked loss of cartilage, subchondral bone cyst and sclerosis, capsular contracture, joint deformity, muscle wasting, synovial hypertrophy and recurrent effusion. So, osteoarthritis is not only a passive age related degeneration but an interplay of inflammation, ageing, mechanical and metabolic imbalance of the joint tissue resulting in cartilage loss in the joint and pan articular affection to the surrounding tissues. Many recent studies have shown the presence of synovitis in OA patients and demonstrated a direct association between joint inflammation and disease progression in contrary to traditional theory of purely age related cartilage degeneration disease.[3,24-26]

Clinical Presentation

Patient with OA classically presents with pain and stiffness of the involved joint with variable degree of functional limitation in the advanced stage. Patient is typically above 45 years of age and more commonly 5^{th} to 6^{th} decade of life. Females and obese people are more likely to develop and present with this condition. Knee joint is the most commonly affected joint. Pain is the most common and early presentation of all the osteoarthritic patients. Pain is generally mild to moderate and intermittent to start with. It is of weeks to month duration, exacerbates with loading to the joint or extreme movement to the joint. Knee pain is more while trying to get up from sitting position or trying to squat or sit cross legged. Pain increases with walking upstairs or downstairs or kneeling position. Pain at knee is mostly on medial or anteromedial side and can extend to anterior, posterior or all around depending upon the extent of disease and parts of joint involved. Since medial compartment OA is the most common and initiating part of OA knee, features are mostly on the medial side. Joint effusion, synovitis, development of Baker's cyst can have pain all around or posterior side of the knee joint. Hand affection has typically multiple DIP joints pain, stiffness and swelling. Less commonly, PIP and MCP joints are involved. Hip joint pain is felt in the anterior groin deep inside. It may be felt in the lateral aspect, gluteal region or even thigh and referred pain in the knee.

Morning stiffness lasting typically <30 minute is another characteristic feature of OA and differentiates from joint stiffness of RA where it lasts more than 1 hour. Bilateral affection of hand and knee OA are common but severity often varies and one side is more affected than others. Stiffness of hand joints such as DIP joints are more common. Pain and stiffness improve with movement of joint, walking or warmth. Swelling can be present in the joint due to effusion, synovitis or new bone formation. Formation of bony nodules in the DIP joints are classical of OA hand and is known as Heberden's nodules. Less commonly, similar nodules found in OA of PIP joints are known as Bouchard nodule. There can be deformity in the DIP joint with flexion or medial or lateral deviation especially in erosive type of OA. Deformity in the knee can be varus, flexion or combined. Hip can have milder degree of adduction, internal rotation and flexion deformity at late stage. Affection of other joints can also have similar presentation with pain, stiffness, swelling or deformity in variable combination and extent.

Examination

Tenderness is present at the joint line in the affected joint. Typical medial joint line tenderness is suggestive of knee OA. Hip OA may have anterior groin tenderness. Examination of the patient at the involved joint often reveal variable degree of fullness. Tense effusion of the knee can be easily appreciated with inspection and palpation of thickened synovium and fluid collection. Other joint effusion are less common and difficult to appreciate clinically. Knee can have Baker's cyst as part of manifestation of OA. Local temperature is often normal. Bony osteophytes may be palpable in the joint margin in superficial joints. Crepitus may or may not present on joint movement. There might be deformity commonly in the knee, DIP joint and hip. Terminal range of motion is painful and may be restricted. Assess for the functional limitation, mood disorder and coexisting medical morbidities to plan the selective and suitable treatment options.

Investigation and Diagnosis

Diagnosis of the OA can be solely based on the clinical history and examination findings. Investigation either imaging or blood are not typically needed. They are helpful in doubtful cases, to rule out other conditions and plan the treatment. Its value also lies in the documentation and see the progression.

Plain X ray is the most common and first imaging investigation that can be advised. The characteristics X- ray signs of OA are decreased joint space, osteophytes formation, subchondral sclerosis and cyst. There is no proportionate clinical correlation with the extent of X-ray findings in osteoarthritis. USG, CT scan and MRI are not recommended routinely. USG may be helpful to see effusion but does not help in the diagnosis. MRI may be useful to see meniscal pathology or loose bodies but rarely needed. Needle aspiration of the joint fluid may be indicated in tense, large painful effusion to reduce the pain or to send the sample when there is doubt about the diagnosis. Fluid aspirated in OA is straw

color or clear or mildly turbid. It can be sent for cell count which is typically <2000 per microliter. It can be sent for crystal analysis to differentiate from suspected acute gout or other crystal forming arthropathy. Fluid may be sent for Gram stain, AFB stain and culture if infective pathology is the close suspicion.

Blood investigations are largely normal and is not needed for diagnosis. But, it may be advised as part of general assessment and for treatment planning.

Treatment

Till date, OA is considered to have no definitive cure. There is no disease modifying agents like used in Rheumatoid Arthritis yet in the practice. Aim of treatment is to relieve pain, restore the functional status and slow down the progression of the disease. There are broadly non pharmacological, pharmacological and operative options available for the treatment of OA. They are often used in combinations and tailored as per the suitability and patient's conditions.

Non pharmacological Treatment

- **Reduction of weight:** Weight reduction in obese patient has been consistently shown to have positive response in terms of improvement in pain and function, especially for knee OA with effect size of 0.35. Hip and other joints have not shown to have consistent lyproven benefit. [27]

- **Physical therapy and exercise:** Combined low impact light exercise and muscle stretching and strengthening exercise are recommended as evidence has shown effect size up to 0.5.[28,29] It is especially useful for knee and hip osteoarthritis. Long term compliance to the exercise program is the major concern for majority of the patients. Dietary modification to reduce the obesity combined with above exercise regimen have been shown to have better improvement of pain and function in hip and knee OA.

- **Self Education:** Education regarding the disease nature, treatment plan, its course, modification of life style and options of self-management are important measures to ease the pain and functional impairment in OA patients. It also helps to limit the use of NSAID.

- **Use of brace and walking aids:** They are often recommended as part of first line treatment in indicated cases. Walking aid can help support, balance and offload the joint to some extent in hip or knee OA. Different types of braces are available in the market for knee OA. They may be beneficial to some patients but lack consistently proven value. Valgus knee brace is said to have reduce the pain but clinical evidence is not strong.[30] Use of raised insole has not been found useful in most of the patients. First carpometacarpal joint OA patient has been found to be benefitted with brace.

- **Thermotherapy:** Application of hot or cold for patient with OA have been shown to have variable outcomes in different studies. Some have shown reduced pain, swelling and improvement in ROM. They can be tried as part of first line therapy. Heat is useful for stiffness and cold application for pain.

- **Acupuncture:** Role of acupuncture in treatment of OA is controversial. It can be tried with short term benefit in some patients for acute pain but there lacks the evidence for long term positive outcome with its use.[31]

Pharmacological Therapy

Paracetamol and NSAIDs: Pharmacological treatment in the form of different drugs alone or in combinations is recommended along with non-pharmacological measures as first line of treatment to reduce the pain. Paracetamol is often the first line and historically used medicine with relatively better safety profile but with low potency (effect size 0.2).[32] So it can be prescribed alone or in combination with other NSAID in mild to moderate pain in the dose of 500mg 4 times a day (maximum <3 gm/day). Liver function is to be tested and monitored for its use. NSAID is often recommended for patients with moderate to severe pain or patient not suitable or not responding to paracetamol alone. It has been shown to improve both pain and function with varying effect size but better than paracetamol. Diclofenac, Ibuprofen, Ketorolac, Naproxen are some commonly used non selective NSAIDs. Selective COX-2 inhibitors such as Celecoxib can be used with lesser Gastrointestinal (GI) side effect.

Major concerns over use of NSAIDs are gastrointestinal and cardiovascular side effects.[32] So, they are prescribed as short duration and low dose as possible to minimize the systemic side effect. Intermittent use may be a wise decision. But there is need to balance the effective dose and at the same time minimize GI and cardiovascular side effect. NSAID is often co-prescribed with proton pump inhibitor to minimize gastritis and GI bleed. Topical NSAID is safe and probably as effective as oral NSAID.[33] It can be combined with oral analgesics or can be used topical alone. Topical preparation of diclofenac and capsaicin have been shown to be beneficial and safe especially for superficial joint arthritis.

Opioids: Routine use has been recently discouraged because of its limited efficacy, side effect of drowsiness, constipation, nausea, vomiting and drug dependence. It is recommended to use for short term in suitable group of patients who are not responding

or contraindicated to NSAIDs.[34] Despite controversy and limited evidence of its role, it is one of the increasingly prescribed medication for OA patients.

Duloxetine: It is serotonin and norepinephrine reuptake inhibitor, used as antidepressant and anti-anxiolytic agents. It has been shown to improve pain and function clinically in patient with OA when used for more than 3 months. So it can be used in resistant cases who can tolerate it.[35,36]

Amitriptyline and Gabapentin: Role of low dose tricyclic antidepressant such as amitriptyline and centrally acting GABA mimetic agent such as Gabapentin in OA is not established and hence routine use cannot be justified.

Glucosamine sulphate, Chondroitin and Hyaluronidase: Role of chondroitin sulphate and Glucosamine are controversial. Some studies have shown some benefit in relieving pain with Glucosamine sulphate.[37-39] But, larger trial failed to establish its benefit in the long run.[40]Intraarticularinjection of Hyaluronic acid has been used as visco supplementation in OA in different trials and long term beneficial role is controversial.[41,42]According to both the Osteoarthritis Research Society International 2012 guideline and the American College of Rheumatology 2013 guidelines, routine intraarticular injection has neither been discouraged nor recommended.[43] Some study has shown short term benefit but local pain at the injection site is a frequent complication.

Glucocorticoids: Oral steroids are not recommended but intraarticular injection of Glucocorticoid has been shown to improve short term pain and function. Its use in the form of injection Triamcinolone 40 mg or methyl prednisolone 40 to 80 mg in larger joint and 10 mg in smaller joint can be used for patient with painful joint and not responding to other medications. It may be effective in reducing acute symptoms in most of the patients but effect lasts for few weeks to few months only. Recommendation varies about the dosing, frequency and role of Ultrasonogram guidance as evidenced in different studies. Frequent use is discouraged as it has been shown to cause cartilage injury and risk of infection.[44]Aspiration of painful, effusion is more effective before injecting intraarticular steroid. It is often used in combination with injection Xylocaine to minimize acute pain at injection site.

Platelet Rich Plasma: It has been shown to be beneficial in some studies but results are controversial. Mesenchymal stem cell therapy is yet to prove its efficacy and clinical use.[45-47] Use and benefit of bisphosphonates, Vitamin D, A, C, Herbal preparation, or, calcium are controversial in the treatment of osteoarthritis.

Newer Drugs: Disease Modifying Osteoarthritis Drugs (DMOAD) are under different phases of trial and yet to see their clinical efficacy and application. Some of them are antibody against Nerve Growth Factor, Inhibitors of Interleukin and mesenchymal stem cell therapy. These agents may be expected to modify the disease course, halt, or slow down or even reverse the disease process by cartilage regeneration if proven successful in the clinical trial.

Operative Intervention

Operative intervention of the arthritic joint is the last resort when patient is not responding with other measures of conservative treatment. Among widely used options of total joint arthroplasty, uni-compartmental arthroplasty, osteotomy and arthrodesis, judicious choice depends upon the joint involved, age, severity, patient's expectation, surgeon factor and disabling symptom.

Arthroplasty: Operative treatment in the form of total joint arthroplasty is the most suitable and widely used option for end stage arthritis with disabling pain who fail to respond to conservative management. This is one of the highly successful and cost effective options especially for end stage knee and hip osteoarthritis, on long run with acceptable limit of complications and revision rate.[48]

It has been considered as safer options than other pharmacological treatments when GI, CVS, Renal risks are considered. Even the mortality rate is lower than the conservative treatment options when all the risks of long term use of drugs are considered. Despite good proven outcome in 80% - 90% of the arthroplasty patient of knee and hip OA, only 15% of the end stage arthritis patients are willing to undergo arthroplasty.[49] Overall complication rate is about 5% in knee and hip arthroplasty with 10 year survival of the prosthesis of knee arthroplasty is about 96% in carefully selected patients.[50] Uni-compartmental replacement of knee can be an option for isolated early stage medial compartmental OA of knee in non -responders to non-operative treatment but its wider use has been overtaken by total joint replacement option.

Osteotomy: High tibial osteotomy for realignment of the knee may be recommended for isolated medial compartment OA of knee in relatively younger adult patient. Osteotomy can be medial open wedge or lateral closed wedge and needs fixation and protection till osteotomy site unites. It redistribute the proportionate load distribution in both medial and lateral compartment of arthritic knee so that pain disappears and disease process is expected to halt or slow down. About 70%-80% success rate has been shown at 10 years.[51]

Arthroscopy: Regular use of arthroscopy in the management of isolated OA knee is not recommended and there is no short or long term benefit from it. But, if OA is associated with loose bodies or symptomatic meniscal tear which needs

partial meniscectomy, it can be used to relieve the pain or mechanical symptom.

Arthrodesis: It is least preferred and least used operative option for refractory type of end stage arthritis. It is not suitable for larger weight bearing joints such as knee or hip due to wide availability of better choice of arthroplasty but may be opted for smaller joints in hand and ankle joint arthritis.

SUMMARY

Osteoarthritis is the most common type of arthritis and prevalence is rising due to increased ageing population and obesity. It is characterized by age related degenerative changes in articular cartilage combined with inflammation in genetically susceptible individual due to excess mechanical imbalance or repeated loading. Patients are largely concerned about the pain and functional limitation. Diagnosis is clinical and plain imaging gives the extent of arthritis. Treatment is tailored with the combination of non-pharmacological and pharmacological measures most of the time with variable success rate. Non pharmacological options of weight reduction in obese patients, light exercise, muscle stretching and strengthening exercise, life style modification and self-education are the most important recommendation to ease the symptoms. They are beneficial when practiced alone or combination with medications. Judicious use of short term or intermittent NSAIDs are often the choice of medications to relieve the pain and stiffness and choice of medication depends upon the suitability, response of the patient and tolerance. Controversy exists about the efficacy and clinical result of each modality of conservative treatment options and none is superior or beneficial to all the patient category. Surgical treatment is reserved for selective cases of resistant types of end stage arthritis. Arthroplasty is the most common and suitable option among surgical treatment but joint involved, extent of arthritis, patient's conditions and expectation are other determining parameters for the satisfactory outcome besides surgical factor. Newer drugs are under different phases of trial and clinical success is yet to see.

Limitations

Nature of this article is narrative review and there exists wide variations in the study design and their results in the literature. Its beyond the scope of this article to go into details of each component. Meta-analysis of individual point of interest and further Randomized Controlled Trial (RCT) studies on controversial topics are recommended.

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