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RESEARCH ARTICLE

A COMPREHENSIVE STUDY ON OSTEOARTHRITIS: RISK FACTORS, HISTOPHYSIOLOGIES, AND MANAGEMENT

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Abstract

Joints comprise cartilage (articular cartilage), ligaments, capsules, and synovial fluid. The articular cartilage prevents friction and enables smooth movement of bones in a joint. Osteoarthritis is a common clinical condition that is represented as a increasing disease of joint. It affects not only the inner surface of the joint but also other connective tissues in the joint such as cartilage, ligaments, and bone. Thus, this disease affects the entire joint.Osteoarthritis is commonly represented by joint pain, joint stiffness, and inflammation,etc. There are many risks associated with osteoarthritis: ageing, overweight, diabetes, injury, genetic factors, etc.The superiority of osteoarthritis increases with age.It is not an inevitable consequence of ageing .According to WHO data about 528 million people globally were affected with arthritis in 2019 and about 73% of cases were more than 55 years old. Osteoarthritis can affect any joint but the most affected joint is the knee , followed by the hip joint, and hand joint. In this report, we examined many aspects of OA such as;epidemiology, symptoms, risk factors, types of osteoarthritis, and treatment options. This article aims to improve the understanding of this musculoskeletal disorder and also recommends the effective management of the condition.

Introduction:-

Skeletal system consists the bones , tendons, cartilages, and ligaments. Histologically these tissues are comprised of connective tissue made of connective tissue cells, fibers (mainly collagen fibers), glycoproteins, proteoglycans, and glycosaminoglycans.In bones, the cartilaginous and noncartilaginous material is mineralized to make them hard. Histologically Osteoarthritis (OA) may be associated with the cartilage degradation, ligaments or bony change inbetween the joints, thataffect synovium (Alshami, 2014). OA may involve almost any another joint. it mainly affects the feet, hands, hips, and knees joints.(Katz et al., 2021). OA is a major public health problem that affects millions of people worldwide.Although old age individuals have greater risk for OA (Anderson and Loeser, 2010). Age-related variations in the musculoskeletal system increases the tendency to develop Osteoarthritis.but the affected joints and the rigorousness of the OA are associated with other risk factors like anatomical factors, obesity,

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joint injury, and genetics affecting joint mechanics (Anderson and Loeser, 2010). This condition is major cause of joint pain and impaired mobility that causes reduction in the quality of life (Iolascon et al., 2017). It is characterized by progressive growth of the bone marrow, resulting in pain, stiffness and weakness. The situation shows that arthrosis affects not only the articular cartilage but also the entire articular organ, which includes the subchondral bone and the synovium.Osteoarthritis affects each person differently.(NIH, osteoarthritis,2024)

Epidemiology of OA

Osteoarthritis is common disease of old age all over the world . It was estimated that OA was affecting more than 240 million people globally, including about greater than 32 million in the US (Katz et al., 2021).According to the CDC, about 1 in 5 U.S. adults is affected by arthritis (CDC, Arthritis Basics, 2024). In 2019 approximately 528 million people worldwide were affected with Osteoarthritis. With a prevalence of 365 million, knee is the joint most commonly affected by Osteoarthritis which is followed by Hip joint and joint of hand (WHO: Osteoarthritis, 2023).

OA is becoming a global burden among individuals of older age, women, some racial and ethnic groups, and people living in lower socioeconomic conditions. It is also associated with health outcomes. A strong association is also found between obesity, OA and joint injury (Allen et al., 2022).

Types Of Osteoarthritis

Arthritis s considered as the most common type of arthritis. The joints most commonly affected by Osteoarthritis are hands, hips, lower back, knees, and neck. Osteoarthritis may be classified intoprimary, secondary, and tricompartmental(Cleveland Clinic, Osteoarthritis 2023; Seed, 2024).

Primary osteoarthritis

The most common type of OA that develops in joints during a lifetime time by the wear of joints. It is age-related OA.

Secondary osteoarthritis

This type of OA is mainly caused by injury and Trauma. These injuries cause damage to joints that further develop into osteoarthritis. This type of arthritis may be termed post-traumatic osteoarthritis(PTOA) occurs after joint injury and has been widely used in previous models to aid in the overall unde rstanding of OA(Salman et al.,2023).

Tricompartmental osteoarthritis

Osteoarthritis affectingthree compartments of knee joints(medial, lateral, and patellofemoral) is termed as tricompartmental osteoarthritis.

Erosive osteoarthritis (EOA)

The hand is the joint usually affected by this type, which is also called EOA. EOA is aform of osteoarthritis that affects joints in the hand. It also can affect thejoints of the feet.

Including this, spondylosis is also a type of OA affecting the spine.

Symptoms and Risk Factors of OA

The most common symptoms related with osteoarthritis is joint pain (during movement, walking, and performing daily activities), decreased movement of joints, joint stiffness after periods of rest, and inflammation in joints (Cleveland Clinic, Osteoarthritis 2023; Seed, 2024).

Risk Factors

The etiology osteoarthritis includes joint damage, obesity, aging, and heredity (Chen et al., 2017). Including this, pre-existing joint disease, metabolic disease (diabetes), and joint damage are known risk factors and are most associated with OA (WHO: Osteoarthritis, 2023). Furthermore, women are more prone of having risk of osteoarthritis (Arthritis, Arthritis Risk Factors, 2024).Generally, it is observed that OA disproportionately affects women, particularly post-menopausal women, due to a addition of biological, hormonal, or lifestyle changes. Research indicates that hormonal changes associated with menopause lead to decreased estrogen levels, suggesting that estrogen may involved in the development of Osteoarthritis (Gokhale et al., 2004). Lower estrogen levels may contribute to increased cartilage breakdown and inflammation of the joint , accelerating onset and increased

Osteoarthritis . Furthermore confirmatory research studies are required to demonstrate the role of low estrogen in the progression of OA.Furthermore, women often have different biomechanical loading patterns than men, which may influence the progression of OA.Some risks for the Osteoarthritis are as follows: (Fig. 1);

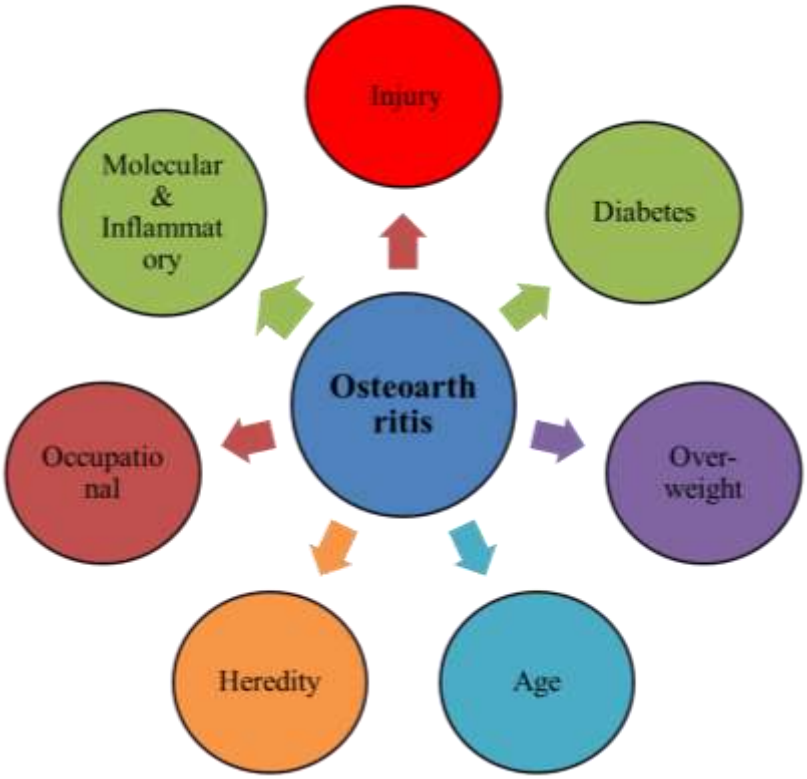

Fig. 1:- Some common risk factors associated with osteoarthritis.

Obesity

Obesity increases the risk for OA (Cleveland Clinic, Osteoarthritis 2023; Seed, 2024). Obesity was found associated with the development of Osteoarthritis in no weight-holding joints and weight-holding joints. It is also suggested that weight loss in OA may play a very important role in improvements in inflammatory pain and reducing in progression of structural damage to joints (King et al., 2013). A dose-response interaction was identified between the mass index of body (BMI) and clinical consequences in knee osteoarthritis. Including this, approaches for managing KOA are also suggested to vary according to obesity severity. High physical activity was also found to be associated with low BMI and also participated in controlling the clinical consequences of KOA (Raud et al., 2020).

Diabetes

Numerous common risk factors have been found linked with Diabetes mellitus (DM) and osteoarthritis (OA). Moreover, Diabetes Mellitus and Osteoarthritis occurs in the same population and the coexistence of Diabetes Mellitus in people wit Osteoarthritis is associated with the development and progression of the disease .Diabetes Mellitus is also associated with more sever osteoarthritic pain (Alenazi et al., 2023).

Age

Aging causes changes at physiological and structural levels. It is accompanied by many biochemical and molecular changes that affect cells, subcellular organelles, tissue and organs. These changes are also associated with mitochondrial changes, nuclear changes, epigenetic and transcriptional changes, and also changes in the matrix present out of the cells. The process of aging affects the mechanics of connective tissues (Philip et al., 2016). Ageing is found as the common factor contributing to obesity. According to WHO fact sheet, in 2019, on an average 73% of people with OA were of age 55 years or older, and 60% were female. Although ageing and OA are linked processes but independent. Aging cause molecular changes in chondrocytes, extra-cellular matrix, synovium, and

subchondral bone. Ageing causes structural changes in articular tissues (articular cartilages) and the development of osteoarthritis (OA). Several age related-processes such as age-related inflammation, cellular senescence, mitochondrial dysfunction, and oxidative stress, etc., contribute to the progression of Osteoarthritis through several factors that increase the destruction of joint tissue and repair the damaged matrix (Loeser et al., 2016). Including this, disruption in cell signaling due to oxidative stress and other ageing associated factors also affects the ability to maintain the extracellular matrix of cartilage and cell death (Loeser, 2017).

Occupational Factors

Jobs and working styles that are more repetitive causing joint stress, or heavy weight lifting can increase the likelihood of developing OA.Laborers carrying weightmanually are prone to develop joint injuries anda higher possibility to develop incidence of knee and hip osteoarthritis.

Hereditary

OA is also found to be associated with genes that cause defects in cartilage that cause fast deterioration of joints. Retrospective real-time PCR (RT-qPCR) studies at the cellular and tissue levels identified two significant markers (COL6A3 and ACTG1) associated wit h OA (Li et al., 2020). Scientific studies also showed that CEMIP (KIAA1199 also called Cell migration-inducing protein) was found overexpressed in murine and human OA cartilage along cartilage dedifferentiation (Deroyer et al., 2019). Many reports indicate the overexpression of β2 integrins in OA (Hu et al., 2022).

Cartilage Degeneration

The main structural components of joints are articular cartilage, ligaments, joint capsule, and synovial fluid. Out of these, articular cartilage playsan important role in preventing friction between bones during movement. Structural changes in cartilage may cause joint pain, stiffness, and decreased function. Thus, cartilage degradation, damage or any structural changes in cartilage due to injury or any other factor may participate in the progression and development of OA. This degeneration also results in several key changes in articular cartilage such as; **loss of proteoglycans,** development of fissures, and erosion, exposing underlying subchondral bone. These changes not only cause pain due to increased friction but can also lead to further joint damage.**Joint space narrowing**can also be a sign of OA progression(Jewell, 2019).

Inflammatory factors

Inflammatory factors involves in Osteoarthritis, causing pain and further injury to joints.Pro-inflammatory cytokines and the tumor necrosis factor (TNF-α), are generally found at progressive levels in the joints Osteoarthritis patients. The presence of these cytokines not only promotes cartilage breakdown but also triggers pain-signaling pathways.Synovial inflammationsynovitis), oxidative tension (as a result of increased levels of oxygen species in the joints),and chondrocyteloss are also found associated with OA. It is suggested that chronic, low-grade inflammation in Osteoarthritis facilitates of symptoms and disease progression. It is assumed that oxidative tension, inflammatory mediators, and biochemical injuries affect the chondrocyte's vviability,and It stimulates hypertrophic differentiation as a pro-inflammatory and pro-catabolic response.Liu-Bryan and Terkeltaub, 2015).

Molecular factors

The recent studies have revealed that a protein receptor activin-like kinase 3 (ALK3) has been found associated with the formation of cartilage, bone formation, and the skeletal development after birth **(**Ruan et al., 2023). Moreover, Runx2 expression is also being suggested participating in pathogenesis of OA (Chen et al., 2019).

Autoimmune Diseases

Immune cell activation is also found with the progression of OA. It is found that complement activation and pro-inflammatory cytokines are also associated with cartilage destruction and synovitis. Some Damage involves molecular patterns (DAMPs), and pattern recognition receptors have been found to contribute to cartilage degradation in models of animal studies (Liu-Bryan et al., 2013). Among these, T cells and activated macrophages also play a role in OA development and inflammation (Lopez et al., 2017). Synovial macrophages have also been shown to contribute to the development and progression of OA. Activated macrophages and their subtypes (M1/M2 ratio) are found linked with OA severity. The interactions between chondrocytes and macrophages plays a role in the initiation and progression of OA through the release of growth factors, inflammatory cytokines, matrix

metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs), that lead to structural changes in the cartilage via degradation (Zhang et al., 2020).

Diagnosis of OA

The diagnosis of osteoarthritis (OA) involves a thorough clinical assessment, including a review of the patient's medical history and a physical examination. Imaging techniques, such as X-rays or MRI scans, may also be used to confirm the diagnosis and assess the extent of joint damage. As osteoarthritis advances, individuals may experience bone loss, joint swelling, and joint stiffness . American College of Rheumatology has established diagnostic criteria for osteoarthritis, which rely on a combination of patient history, physical examination, laboratory results, and imaging findings such as X-rays. These criteria are based on history, physical examination and laboratory findings, and Radiographic findings.To meet the ACR criteria for knee osteoarthritis, a patient typically must exhibit knee pain and some other features identified by clinical, laboratory, and laboratory analysis (Table 1; Altman et al., 1986; ACR-Endorsed Criteria: as on 1986 ACR Classification Criteria of the Knee, 2024).

Table 1:- Idiopathic osteoarthritis of the knee joint (Altman et al., 1986; 1986 ACR Classification Criteria of the Knee).

S.No.	Investigation	Criteria for classification
1	Clinical	Knee pain, along with at least three out of the following six criteria Age > 50 years, Stiffness < 30 minutes, Crepitus**,** BonyTenderness, Bony enlargement, Absence of palpable warmth in the joint
2	Clinical and laboratory	Knee Pain + at least 5 of the 9: Age > 50 years, Stiffness < 30 minutes, Crepitus**,** BonyTenderness, Bone enlargement, absence of palpable warmth, ESR < 40mm/hour, RF<1.4, SF OA RF: Rheumatoid Factor; SF OA: synovial fluid signs of OA (Clear, viscous, or White Blood Cell count < 2,000/mm^3)
3	Clinical and radiographic	Knee Pain + at least 1 of the 3: Age > 50 years of age , stiffness < 30 minutes, Crepitus +Osteophytes

Generally, blood tests are not performed to diagnose the OA but these blood tests may be used to find any infections that may be responsible for secondary OA. The formation of bone spurs is also an important feature of osteoarthritis.Arthrocentesis or analysis of synovial fluid is a biochemical test used to diagnose OA to find if gout, any infection, or any other factor is associated with inflammatory arthritis. Furthermore, Arthroscopy is also a viewing technique to check the abnormalities within joints, and injury of the cartilage and ligaments of the joint (WebMD, How do I know if I have osteoarthritis? 2024).

Threatment and Management of OA

OA has resulted from age-related reduction in the capacity of connective tissue cells in the body to maintain homeostasis. Aging also affects the cartilage matrix, and advanced glycation further affects the mechanical properties of the joint tissues (Anderson and Loeser, 2010). It was also observed that radiologic features of the knee the osteoarthritis are commonly seen in adults (Scott and Kowalczyk, 2008).

OA is developed from addition of risks while aging and obesity play important roles (Fig. 1). The pathophysiology of OA is still developing, from assumed as a multifactorial disease that extends beyond cartilage damage, affecting the entire joint and interfering with its normal function. (Martel-Pelletier et al., 2016). Osteoarthritis (OA) may cause significant discomfort and functional impairment. Though, some symptoms may be mild but some symptoms may need immediate medical attention. Persistent or worsening joint pain, particularly after physical activity or with prolonged use, may be considered a signal for the development of the disease.During the management of OA, regular monitoring of the symptoms is essential, and patients should seek advice if there are changes in functionality.Early interventionsare assumed to play a remarkable role in maintaining symptoms effectively and potentially.

Treatment of osteoarthritis of hip and knees should focus on managing joint inflammation and stiffness, maintenance and improvement in mobility, or optimizingthe patient's functioning and improving the quality of life

while managing the development of the joint damage. There are innovations for a combination of nonpharmacological / pharmacological strategies for the management of OA (Hawkeswood and Reebye, 2010).

Fig. 2:- Treatment approaches for osteoarthritis. Physical therapy comprises ex: Treatment approaches for osteoarthritis. Physical therapy comprises exercises, while advanced therapies comprise biological therapies, gene therapies, and regenerative therapies.

The commonly used treatment options for the treatment of OA include; treatment to manage pain (for example using Acetaminophen, and NSAIDs),physical therapy by performing exercises, occupational therapy, Transcutaneous electrical nerve stimulation(TENS), surgical or other procedures like (Cortisone injections, injections of hyaluronic acid, Realigning bones, knee osteotomy) and joint replacement etc . (Mayo Clinic: Osteoarthritis, Diagnosis and Treatment, 2021).

To manage osteoarthritis (OA), both strong and conditional recommendations have been made. For hand OA, conditional recommendations include joint protection techniques, use of assistive devices, thermal applications, trapeziometacarpal joint splints, nonsteroidal anti-inflammatory drugs (NSAIDs), and other pain management medications. Similar strategies are applied for knee and hip OA management.

For knee OA, nonpharmacologic interventions strongly recommended include physical exercises such as aquatic, aerobic, and resistance training, as well as weight loss for overweight individuals. Certain nonpharmacologic approaches are conditionally recommended as well. In addition, pharmacologic treatments are conditionally suggested for the initial management of knee OA, with opioid analgesics considered for specific patient conditions. (Hochberg et al., 2012).

Being diagnosed early, and using a treatment plan is a good approach to reducing the progression of disease and function optimizations. The overall treatment strategies include non-pharmacological interventions likephysical exercise, weight management, and assistive devices. Medications, including anti-inflammatory drugs, may be used for pain management. In severe cases, joint replacement surgeries may restore movement, reduce pain, and improve quality of life (WHO: Osteoarthritis, 2023).

Emerging Therapies And Future Directions In Osteoarthritis

The guidelines for OA treatment recommend therapy in the following order (Crofford, 2013; Goldring and Berenbaum, 2015):

(1) Behavioral interventions
(2) Use of simple analgesics
(3) Use of NSAID, including COX-2 inhibitors
(4) Injections of hyaluronic acid or corticosteroid (Intraarticular)
(5) Total joint replacement.

Research into new treatments for OA is ongoing, focusing on both pharmacological and non-pharmacological approaches.

1. Biological Therapies

Biologic agents targeting specific inflammatory pathways have shown promise in OA management. Research has identified that osteoarthritis is very complex disease where inflammatory mediators are secreted by synovium, cartilage, and bone (Berenbaum, 2013). It has been identified that pro-inflammatory cytokines, such as interleukin-1 (IL-1β) and tumor necrosis factor-alpha (TNF-α), plays a very important role in the pathogenesis of OA by interfering with the metabolism of chondrocytes (Chen et al., 2015).Thus, inhibition of Interleukin-1 is assumed to be a possible critical target for the treatment of OA. The use of interleukin-1 receptor antagonist (IL-1Ra) anakinra demonstrats its efficacy in the management of rheumatoid arthritis, and it also suggested to use of anakinra in the treatment of OA (Iqbal and Fleischmann, 2007). However, the clinical trial of anakinra in 170 patients did not demonstrate improvements in the symptoms of OA as compared with the placebo (Chevalier et al., 2009).Including this, clinical trials using IL-1β inhibitor canakinumab caused reduction in total joint replacements and a reduction in the osteoarthritis joint problems reported as adversing events (Conaghan, 2021).Similarly, agents targeting TNF-α are being investigated, as they may modulate inflammatory responses that exacerbate joint degeneration.

Inflammatory mediators, such as interleukin-1 (IL-1β) and tumor necrosis factor-alpha (TNF-α), also contribute to the production of matrix metalloproteinases (MMPs). These enzymes play a key role in the degradation of the extracellular matrix, further exacerbating joint damage in conditions like osteoarthritis.

The collagenases MMP-1 and MMP-13 play a key role in the development of OA (Mehana et al., 2019). Thus, the drugs inhibiting metalloproteinases are being developed in development, with the aim of slowing disease progression.Synthetic MMP inhibitors also have therapeutical potential to be used in the treatment of OA (Mukherjee and Das, 2024).

2. Regenerative Medicine

In the Unavailability of disease-modifying drugs, regenerative therapy, which involves changing the structure of damaged articular cartilage, is being investigated as a treatment for OA. MSCs are an important source of cells for the treatment of OA. Including this, MSCs possess immunomodulatory and anti-inflammatory capabilities make favorable conditions for the regeneration of injured articular cartilage. Moreover, mesenchymal stem cells (MSCs) based treatment is also becoming a promising approach for the treatment of OA (Gherghel et al., 2023). MSCs are known to have multipotent capabilities and may be differentiated into other cell types under specific conditions. These MSCs may be used in cartilage regeneration and these therapies may be effective for cartilage repair (Mamachan et al., 2024).

3. Gene Therapy

Gene therapy is an innovative approach being explored for OA treatment. This strategy involves delivering genes that encode anti-inflammatory cytokines or growth factors directly to the affected joints. By modifying the underlying mechanisms of OA, gene therapy could offer a disease-modifying option, rather than merely alleviating symptoms.Several human trials have been initiated, using transgenes encoding interferon-β, interleukin-1 receptor antagonist, transforming growth factor-β1, NKX3.2 transcription factor or variant interleukin-10 (Evans et al., 2023).

4. Lifestyle modification and Digital tools

Innovations in non-pharmacological interventions are also emerging. Digital health technologies, including telehealth platforms and mobile applications, are enhancing patient management. Proper diet and lifestyle modifications are emerging as potential approaches to reduce the progression of OA. Digital tools also offer flexibility and cost-effectiveness. Digital tools facilitate remote monitoring of symptoms, personalized exercise

programs, and patient education, empowering individuals to take an active role in their care. It has been observed that digital self-management programs may offer improvement in physical and pain function in patients with knee and hip OA.But their effectivity is not clear in disability and health-related quality of life (Safari et al., 2020).

The future of OA treatment is likely to embrace personalized medicine. Factors such as genetics, lifestyle, specific test results, and specific clinical characteristics will help to decide treatment decisions for improved outcomes and reduction in adverse effects.

Conclusion:-

Osteoarthritis is a common musculoskeletal disease that requires various treatments. Early diagnosis, lifestyle changes and personalized treatment plans are crucial to improving patients' quality of life. The cause of this disease is multifactorial; aging, genetic predisposition, joint injuries, obesity, and inflammation play an important role in the progression of the disease. Osteoarthritis often affects stiff joints such as the knees, hips, hands, and spine.The treatment options are based on pain management, diet and exercise, and surgical procedures. These approaches are categorized as pharmacological and nonpharmacological approaches. New treatments such as biological drugs and innovative therapies may offer better treatments in the future. Continued research, increased awareness, lifestyle modification, and patient care are recommended to reduce the burden of OA.Due to the heterogeneous nature of OA, individualized treatment plans may play a key role in OA management. Ongoing research to explore the pathophysiology of OA and the development of novel therapeutic agents offers more effective management strategies in the future with reduced adverse effects.

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Conflicts Of Interest:

No.

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