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A review on current evidence for the treatment of Osteoarthritis

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ABSTRACT: Osteoarthritis (OA) is a common Joint inflammatory disease. This disease may be 11th most leading joint arthritis in the adult population worldwide. Osteoarthritis traditionally was known as a disease of articular cartilage but lack of inflammatory response. Earlier newer treatments were available, unchecked Osteoarthritis caused remarkable lack of ability and mortality. Now it's time to accepted that primary diagnosis and therapy which is essential and useful. Improvement in therapy of OA has made it possible to extremely influence signs and symptoms as the period that the lack of inflammatory response. Earlier and more efficient treatment becomes visible to significantly improve the prospects of this disease. In this article, the traditional and new methods for treatment of osteoarthritis, their limitations and benefits were reviewed. A new method for treatment of OA includes nonsteroidal anti-inflammatory drug (NSAIDs) and corticosteroids. These steroid hormones class of drugs and dietary supplements are incorporated with micro and nanocarrier-mediated drug delivery systems, including polymeric particles, liposomesand hydrogels, which can be delivered by Intra-articular drug delivery systems. The main goal of this review studied that the intra-articular drug delivery system is convenient delivery system in future to deliver drugs for treatment of osteoarthritis with longer retention time and high efficacy with less side effect.

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INTRODUCTION:

Osteoarthritis (OA), popularly known as degenerative joint disease, degenerative arthritis or osteoarthrosis. OA is the most common musculoskeletal disease affecting the whole synovial joint [1]. It is believed that cartilage is not the sole organ being affected by OA. The other organs that are affected by OA are ligaments, synovial and bone, which undergo metabolic and structural modifications as the disease progresses. As age increases prevalence of OA increases significantly [2], which results in clinical manifestation of significant

pain, reduced range of motion and increased disability [3].

OA is actually one of the most common, costly and disabling forms of joint found at the end of long bones in articulating joints and in the intervertebral disc [4], whose main function is to provide a smooth, lubricated surface for articulation and to facilitate the transmission of loads with a low frictional coefficient [5]. Osteoarthritis is a multifactorial process in which mechanical factors have a central role and is characterized by changes in structure and function of the whole joint [6]. The current concept holds that osteoarthritis involves the entire joint organ, including the subchondral bone, menisci, ligaments, periarticular muscle, capsule, and synovium (Fig 1).

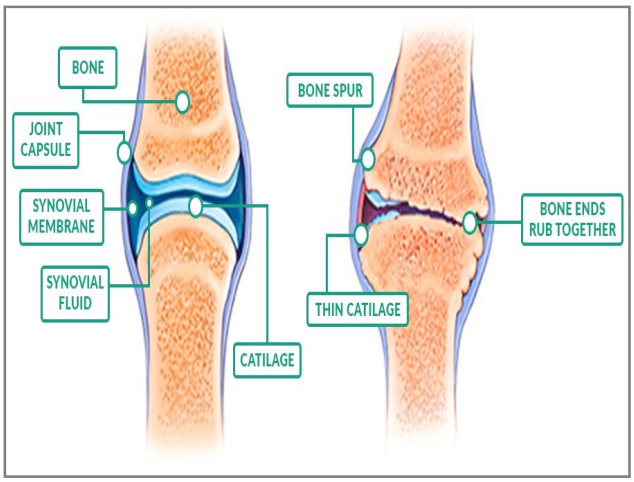

Fig 1. Diagram showed difference between normal and Osteoarthritis Knee [7].

Global Status of OA:

OA is the leading cause of chronic disability globally in individuals older than 70 years and has been designated a 'priority disease' by the World Health Organization (WHO) (report WHO/ EDM/PAR/2004.71). OA is one of the ten most disabling diseases in industrialized countries. In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability [8]. The prevalence of OA is set to increase in parallel with the increase in the number of people aged 60 years and older and the rise in obesity across the world. In the United States alone OA is the highest cause of work loss and affects more than 20 million individuals, costing the US economy greater than US$100 billion annually [9,10]. OA represents one of the top 5 healthcare costs in Europe [8]. The number of people in the UK with knee OA is estimated to increase to 6.5 million by 2020 [11].

Scott and Kowalczyk [12] reported that a cohort study found that radiologic features of knee osteoarthritis were very common in adults: 13 % of women 45 to 65 years of age (an incidence of 3 % per year). In Saudi Arabia, Al-Arfaj and Al-Boukai [13] in their cross-sectional study found radiographic knee osteoarthritis in 53.3 % males and 60.9 % females. Approximately 18 % of women and 10% of men suffer symptoms due to osteoarthritis [14]. Although OA is present by histologic or radiographic criteria in nearly 80.0 % of people by the age of 80 years, only half have symptoms (Hochberg *et al*., 1989) and these are often variable and intermittent. There is a modest correlation between the presences of symptoms.

The burden of OA is projected to increase, due in part to obesity and population aging [15]. While the prevalence of OA increases with age [16], there is a growing recognition that OA affects people at younger ages. Recent US data demonstrated that half of people with symptomatic knee OA are diagnosed by age 55 [17]. It is estimated that in adults over the age of 30, up to 6 % of adults are symptomatic of knee arthritis and around 3% are symptomatic of hip arthritis [18,19]. The prevalence of osteoarthritis increases with age, and with an aging population [20], the effect of this disease will represent an ever-increasing burden on health care. Osteoarthritis of the hip and knee is the most common cause of difficulty in walking [21]. It has a huge impact on the economy, with absence from work and early retirement exceeding 2 % of the gross domestic product [22]. It is estimated that over 1 million total hip replacements are performed worldwide each year [23], and in the United States alone it is predicted that between 1995 and 2020 an additional 19 million people a year will be affected by arthritis [24]. OA is the most common form of arthritis. It is among the most prevalent and disabling chronic conditions in the United States.

The prevalence increases with age, and by the age of 65, approximately 80 percent of the US population is affected. More than half of those with arthritis are under 65 years of age. Nearly 60 % of Americans with arthritis are women. Indian data in this regard is lacking.

It is difficult to estimate the prevalence of osteoarthritis because there are no universally applicable criteria for its diagnosis. Radiographic and symptomatic knee OA in adults 45 years or older was prevalent in 19 and 7 % of Framingham subjects, respectively, and in 28 and 17 % of Johnston county subjects, respectively. The overall number of US adults affected by OA in any joint clearly

has increased during recent decades due to aging of the population and the increasing prevalence of obesity.

Status of OA in India:

Osteoarthritis OA is the second most common rheumatological disease and it is the mostly common joint disease with a prevalence of 22 to 39 % in India. OA is occur more common in female as compare than male, but the prevalence increases significantly with age in human being [32]. Around 45 % of female below the age of 65 years has shows symptoms while radiological proof is found in 70 % of above the 65 years. OA of knee is a major reason of mobility impairment, which is basically found in among females. OA was also estimated to be the 10th foremost cause of nonfatal trouble [30-32].

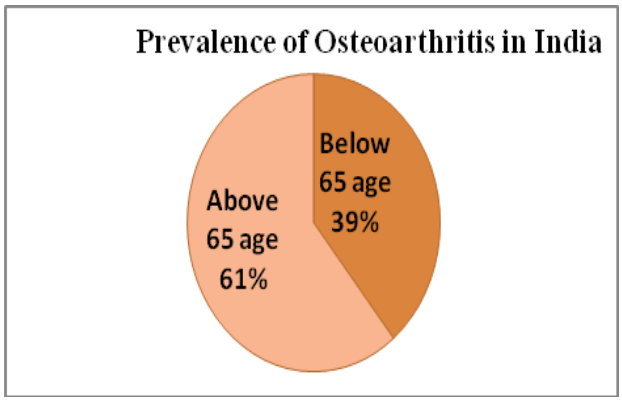

Fig 2. Prevalence of Osteoarthritis in India.

Pathophysiology of OA:

With normal aging, cartilage breakdown begins in joint areas with little or no contact. As destruction advances, it moves gradually into the more heavily loaded areas. At this point, biomechanical factors such as loading patterns, tibiofemoral contact time, and motions about the joint generate shear and frictional stresses [25]. Cartilage softens and fibrillates. Aging or injury to the knee joint increases joint laxity and permits excess or aberrant motion about the knee, a process that exacerbates progression of OA.

OA is viewed as a metabolically active, dynamic process, including both cartilage destruction and repair. These processes may be initiated by several biochemical and mechanical insults [27, 28]. The first OA change occurring in articular cartilage include a decrease in the superficial proteoglycan content, deterioration of superficial collagen fibrils, and an increase in the water content.

The loss of proteoglycans and collagen results in diminished cartilage stiffness [28]. Subsequently, the chondrocytes increase the synthesis of cartilage matrix proteins, the destruction of components in the extracellular matrix accelerates, and the thickness of cartilage may even increase. At the same time, calcified cartilage and subchondral bone become thicker in a response to the increased formation and resorption of the subchondral bone [29].

Ultimately, the concentration of proteoglycans decreases and collagen fibrillation declines due to diminished repair capabilities of chondrocytes. This process leads to splits of the cartilage extending down to bone. The degenerated cartilage with the disrupted collagen network cannot regenerate, and this pushes the OA tissue to the point of no return [29]. On the other hand [31], postulated that the repetitive impulsive loading my first induce trabecular micro fractures in the subchondral bone. According to this theory, subsequent remodeling increases the stiffness and thickness of the subchondral bone in an attempt to dampen impact forces. As a consequence, the overlying cartilage may become overloaded and break down resulting in cartilage degeneration and loss.

Stages of OA:

The progression of Osteoarthritis in knee is measured by following four stages (Fig3).

***Stage I (Minor)*:**

Small amount of disruption. There is already 10% cartilage loss.

***Stage II (Mild)*:**

Joint-space narrowing. The cartilage gets start to breakdown and occurrence of Osteophytes.

***Stage III (Moderate)*:**

Notable joint-space narrowing. This joints gets expand and becoming swollen and reddened.

***Stage IV (Severe)*:**

Joint space largely reduced. Almost 60 % of cartilage already lost and occurrence of Large Osteophytes.

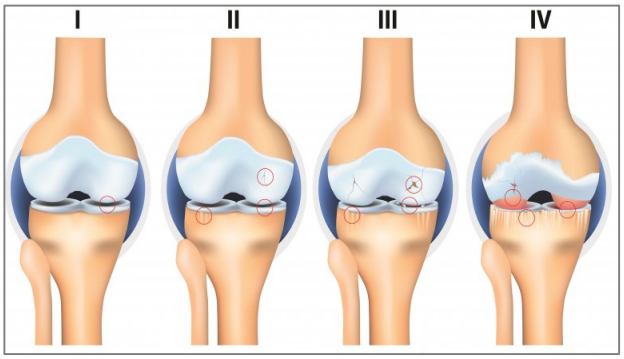

Fig 3. Illustration of different Stages of OA in knee joint [31].

Causes of OA:

Several causes which are responsible for occurrence of Osteoarthritis are degeneration of the cartilages due to ageing, excessive strain on the joint, any kind of injury to the joint, are the frequent causes of arthritis, mechanical stress (obesity), endocrine and metabolic disorders (diabetes, calcium deposition disorders) and other articular diseases (gout and pseudogout, rheumatoid arthritis). The traumatic causes are injury to joints or ligaments and postsurgical. The infective causes are septic arthritis and lyme disease. The metabolic reasons are haemochromatosis and Wilson's disease, gout, calcium crystal deposition and alkaptonuria. The other miscellaneous causes are haemophilia, osteonecrosis [33-35].

Risk factors of OA:

The risk factors for Osteoarthritis are age older than 50 years, obesity, Trauma/injury to joints, genetics (significant family history), reduced levels of sex hormones, muscle weakness, repetitive use (ie, jobs requiring heavy labor and bending), crystal deposition, acromegaly, hemoglobinopathies (e.g. sickle cell disease and thalassemia) and neuropathic disorders leading to a Charcot joint (e.g. syringomyelia, tabes dorsalis, and diabetes) [36].

Symptoms of OA:

The clinical symptoms are moderate to severe pain at the affected joint, joint stiffness observed especially after long spans of rest to the affected joint, restricted and painful movements of the joint, crunching or crackling noise when the joint moves (crepitation), localized tenderness in severe cases, Swelling and increased local temperature at the affected site [35,36].

Drug used for treatment of OA:

For the treatment for Osteoarthritis most commonly Analgesia, antipyretics, NSAIDS, Opioid analgesics were used to reduce the inflammation and severe pain in joints and also help to reduce swelling. Other drugs like steroidal drugs and Dietary Supplement are also used to support the immune system and its helps to develop autoimmune system.

Delivery system available for OA:

Now a days, most frequently drug delivery system is design for better efficacy and avoid frequent injection, because of that intra articular drug delivery system (DDS_s) are designed, in which drug may remain in OA joints for a long time and sustain release drug are clinically. Intra-articular drug delivery is a method to apply drug substances or therapeutic composites into the joint cavity. Important to note, drug biodistribution following delivery is quite different from systemic administration or local injection into many other tissues or organs. The diarthrodial joint is surrounded by a highly vascularized synovial membrane that efficiently filters most solutes and drugs in the intrasynovial joint space; with an intra-articular concentration that is generally proportional to plasma concentrations [38].To apply drugs into joints, the most simple and straight-forward method is direct injection. Such method is attractive since relatively high drug concentrations can be delivered directly at the main desire site and the systemic side effects are minimized compared to oral delivery [39-40]. Therefore, aspirating and injecting the knee or other joints is a common technique for both diagnostic and therapeutic purposes. However, the downside of direct injection of drugs includes: the lack of accessibility of the joint, infection, post-injection flare, crystal-induced synovitis, cutaneous atrophy and steroid arthropathy [41-43]. Moreover, a more important concern is how long the drug can stay at the desired place. Although post-injection rest is required in order to increase the residence time of the administered substance [44], depending on the chemical structures of drugs, some active compounds are rapidly cleared from the joint, thus requiring numerous injections, which could cause infection or joint disability [45]. Therefore, direct injection is the simplest method to intra-articularly deliver drugs but not the most effective one.

However, current preparations of intra-articular drug delivery often require frequent injections that have a high financial burden, impaction to patient's quality of life, rapid degradation and clearance of injected pharmacologic agents, and also increase the risk of complications [46]. Micro- and nanocarrier-mediated drug delivery systems, including polymeric particles, liposome, and hydrogel, are well-established as methods for sustained release in intra-articular applications.

These systems could prolong drug retention time, reduce the clearance of drug into joint cavity, and increase patient compliance as well as therapeutic effect of pharmaceutical agents. This process guaranteed a longer effect of the drug in the action site and consequently, a reduced risk of infection due to numerous injections [47]. Sustained therapeutic drug concentrations can also be achieved with intra-articular slow-release drug delivery device, rather than repeated injections.

Table 1. Drugs used for treatment of OA.

Drugs	Category	Uses
Acetaminophen	Analgesics and Antipyretics	Pain relievers and Fever reducer
Ibuprofen	NSAIDs	Reduce fever and inflammation
Aspirin	NSAIDs	Pain , Fever and inflammation
Codeine	Opioids	Treat pain
Oxycodone	Opioid analgesics	Relieve moderate to severe pain
Morphine	Opioid analgesic	Reduce the pain
Diacerien	Anthraquinone	Treat joint diseases such as OA
Glucosamine	Dietary supplement	Help to rebuild cartilage and treat arthritis.
Carticosteroid	Steroid hormones	Provide relief the inflamed areas of the body
Hyaluronic acid	Integral membrane proteins	Treat OA of the knee via injecting it into the joint
S-Adenosyl methionine	SAMe	Treating OA
Buprinorphine	Mixed opioid agonist-antagonist	Treat dependence of narcotics
Fentanyl	Opioid Analgesic	Relieve severe ongoing pain
Chondroitin sulfate	Dietry Suppliment	Alternative medicine to treat OA

It has been shown that sustained intra-articular drug concentration can be realized through coupling the desired drug to liposomes, microparticles, or hydrogels. The main goal in the future is to increase the residence time of the drug in the joint as well as improve its diffusion within the target tissue [48]. Various literatures survey such as X. Chevalier was reviewed of 28 clinical trials a significant short term reduction in pain and improvement in self-assessment with intra-articular corticosteroid injection as compared to placebo injection. Mason L *et.al,* was presumed that corticosteroid inhibit accumulation of inflammatory cell lines, reduce PG synthesis, inhibit leukocyte secretion from synovial cells and reduces interleukin secretion by the synovium. Bellamy N *et.al*. studied about Hyaluronic acid (HA) intra-articular injection is FDA approved for knee OA. Arroll B *et.al* , was investigated that Hyaluronic acid(HA) intra-articular injection when compared to glucocorticoids intra-articular injection it was found that benefits from each injection was similar, at some point of time there were greater benefits of HA, although these benefits were not sustained for long periods.

CONCLUSION:

OA is a degenerative joint disease and the response to treatment is unpredictable. It has been proven that near the beginning treatment may lead to the reduction in Cartilage damage and an improvement of incapacity in the long-term. Traditional therapies and conventional therapies may be used such as NSAIDs, corticosteroids, and Dietary supplement which may lead to decrease the severity of OA, but sometimes cause sustained reduction and can have side effect and therefore cannot be used for long time. Hence, the treatment of OA can be successful with early diagnosis and using new drugs at the same time.

Micro- and nanocarrier-mediated drug delivery systems, including polymeric particles, liposome, and hydrogel, are well-established as methods for sustained release in intraarticular applications therefore; it may have better impacts and fewer side effects in comparison with free drug. The main goal in the future is to increase the residence time of the drug in the joint as well as improve its diffusion within the target tissue.

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