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A REVIEW ON OSTEOARTHRITIS

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ABSTRACT

For decades, several attempts have been made to better explain the pathophysiology of knee osteoarthritis and natural history. Given the significant amount of research on this subject, controversies are still labeled. This multifactorial disease is affected by social, structural, and external influences, and its patient-to-patient development and/or reaction to therapies differ widely. Numerous treatments have been tested in the past; all existing scientific practices tend to favor low-impact physical exercise although some approaches have reported contradictory results. Different approaches and logistical pathways are under review and some of them have been producing positive early results. This study seeks to provide an summary of the latest information available for knee osteoarthritis in pathophysiology and non-surgical therapies.

Keywords: Osteoarthritis, Pathophysiology, Chronic, Carticosteroids, Diarthrosis.

INTRODUCTION

The most severe type of arthritis is osteoarthritis (OA), only causes of physical disability. This deterioration and chronic articulation disorder impacts about 240 million people globally **[2]** and minimum 27 million human beings in United States **[3,4].** Aged (about 35% of sufferer over 65 years old) woman, sufferer with weight gain and African Americans are the community with the greatest probability of contracting OA **[5,6]** Because of the nation's propensity to live longer and chronic. Such problems are related to the physical disability and disease correlated with this condition, and the negative impact on the social and economic elements of our society. This analysis would address existing findings surrounding knee osteoarthritis patho-physiology, latest clinical guidelines, with a special emphasis on therapy modalities like intra-articular carticosteroids, and recent long release presentations of such materials.

Osteoarthritis in knee:

The knee, human's main diarthrosis, made up of osseous components (thibone, shinbone, and kneecap), cartilage (hyaline cartilage and meniscus), ligaments, and a synovial stratum. The latter is responsible for the development of the synovial fluid, which provides thea vascular cartilage with lubrication and nutrients **[6].** Sadly, due to the heavy usage and discomfort of this articulate, it is a persistent location for painful conditions such as OA **[7].**

Dependent on its etiology, OA is divided into two groups: initially (idiopathic) and secondary (usually attributed to damage or phyical misalignment). The extent of the condition may also be categorized according to the radiographic results of the Kellgren–Lawrence (KL) method mentioned in 1957**[8].** It was thought that Osteoarthritis was primarily a cartilage degenerative disorder, but the new research has shown that Osteoarthritis is a multifactorial phenomenon with several causative determinants such as fracture, mechanical loading, inflammation, reaction of biochemical. The soft tissue is also considered to not be the one affected. The cartilage alone is incapable of inflicting inflammation and discomfort at least in the initial phases of the illness owing to the loss of innervation and vasculature. The cause of pain thus arises mainly from adjustments in the non-cartilaginous materials of the joint, such as the auricular capsule,

synovial membrane, layer of bone below cartilage, ligaments and peri-articular muscles **[6, 9].** As the disease progresses, these properties become impaired and can alter through bone remodeling, osteophyte forming, periarticular muscle contraction, ligament laxity and synovial effusion.

The function of inflammation is not fully known and there is continuing controversy to decide if the inflammatory response causes improvements in the Osteoarthritis, or rather, the inflammation is secondary to improvements in the Osteoarthritis **[9].** Like inflammatory forms of arthritis, inflammation in the Osteoarthritis is persistent and low-grade inflammation, affecting mainly nonspecific immune systems. Synovial inflammation is a typical results in Osteoarthritis which may appear in the initial phase of the illness but may be more frequent in the advanced stages and may be correlated with severity **[1].** For Osteoarthritis, the synovial has been shown to include many messengers that works on blood vessels to enhance inflammatory response, namely plasma proteins (C-reactive protein, presented as a marker for Osteoarthritis development and progress), PGE2 (prostaglandins), LKB4 (leukotrienes), IL1β, TNF, IL15,IL6 and IL17 , TGFβ, NGF ,FGFs, VEGF, , nitric oxide, and complement components **[1,11]** Locally, all of these commodities have been identified as components **[12].**

Erythrocytes are also affected, the degradation of the ECM releases some molecules (danger-signals) which are typically recognized as a defense mechanism by the cells that mediate innate immunity (mast cells and macrophages). This sustained and dysprosium level of inflammation can therefore contribute to destruction of tissue. **[1]** Macrophages were found to be active in the production of osteophytes in animal experiments and are a pathological characteristic of OA **[1].**

The body system also has molecular defensive mechanisms indulging various growth factors (transforming growth factor B , , platelet-derived and fibroblast 18), which, sadly, are changed in knee OA patients and can become injurious to the articulate**[1,11].**

Treatment:

OA is a chronic and degenerative disease where the weakened systems are unable to recover and rebuild.

Present treatment modalities are often geared at symptom reduction until the degree of seriousness determines the need of joint replacement surgical intervention **[1].**

Currently, many scholarly and medical associations have established different recommendations to standardize and prescribe the care methods available (Table 1). The Osteoarthritis Research Society International (OARSI) **[13],** American College of Rheumatology (ACR) **[14]** and the American Academy of Orthopedic Surgeons (AAOS) **[15]** publications are amongst these.

Table 1 management recommendations from societies for Knee osteoarthritis

Societies recommendations			
Treatment	**ACR**	**QARSI**	**AAOS**
Water and land based Exercise	Strong recommendation	Appropriate	Strong recommendation
Intra-articular viscosupplementation	No recommendation	Uncertain	Recommended against use
Transcutaneous electrical nerve stimulation	Conditional recommendation	Uncertain	Inconclusive
Weight control	Strong recommendation	Appropriate	Moderate recommendation
Duloxetine	No recommendation	Appropriate	No recommendation
Oral NSAIDs	Conditional recommendation	Without comorbidities: appropriate With comorbidities: not appropriate	Strong recommendation
Chondroitin or Glucosamine	Recommended against use	Not appropriate for disease modification, Uncertain	Recommended against use
Acetaminophen	Conditional recommendation	Without comorbidities: appropriate	Inconclusive
Topical NSAIDs	Conditional recommendation	Appropriate	Strong recommendation
Intra-articular corticosteroids	Conditional recommendation	Appropriate	Inconclusive
Opioids	No recommendation	Uncertain	Recommended only tramadol

Note: Data from these studies **[13–15]**

Abbreviations: OARSI, Osteoarthritis Research Society International; ACR, American College of Rheumatology; AAOS, American Academy of Orthopedic Surgeons; TENS, transcutaneous electrical nerve stimulation; NSAIDs, non steroidal antiinflamatory drug.

Non pharmacological management:

The aim of OA management is to monitor the harmful signals from these joints but, more so, to increase efficiency and quality of life. As the first phase of therapy for knee OA **[3,6,13–15],** non-pharmacological treatments will also be attempted.

Inactivity and disuse are counterproductive to the knee joint's wellbeing, the lack of mechanical stimulus contributes to accelerated cartilage degeneration due to cartilage softening / dilution, reduced glycosaminoglycan quality, weakened joint dynamics and strength **[16,17].** Light-to-moderate physical exercise has many advantages for this patient group, in addition to technical and physiological changes, it also promises a decrease in the incidence of depression, medical problems, crashes, cognitive disorder and self-efficacy **[16,18].**

Table 2 Exercise modalities for knee OA

Balance/proprioceptive	**Aerobic/endurance**	**Stretching**	**Exercise modalities**
			Resistance/strength training
This includes modalities such as Tai Chi, using slow and gentle movements to adopt different weight baring postures while using breathing techniques.	Some studies showed a reduction of 10–12% on the physical disability and the knee pain questionnaires **[16].** Including all activities like cycling, walking, and climbing stairs. They can decrease joint tenderness while improving functional status and respiratory capacity. Cycling is especially attractive to patients given the low impact profile **[16,18].**	This group will specifically help with patient's range of motion and flexibility.	Isometric, isotonic, isokinetic, and dynamic modalities have been Studied. Most of them targeting quadriceps, hip abductors, hamstrings, and calf muscles. They improve strength, physical function, and pain levels, with similar efficacy and outcomes than aerobic exercises.

Workout exercises should be adjusted to the needs / tolerance and desires of each participant, high stress behaviors should be minimized, and long-term commitment should be maximized to improve success **[18,19].** Multiple workout modalities have been found to have a positive influence on knee OA patients (Table 2), workouts should be done three days a week, and the participant shoulder should be tested for reaction **[6].**

Aquatic (water-based) treatments offer an option for patients who are hesitant to participate in land-based activities owing to the reduced pressure on the joint. Many patients can best withstand aquatic therapy and decrease symptom exacerbation (sometimes encountered when weight-bearing exercises are started). Many clinicians use this procedure as a pathway to tackle terrestrial modalities until the individual has overcome fear of moving **[16,17].**

Weight control plays a significant part in the treatment of symptoms and it has been recognized that the advantage of exercise is potentiated by weight reduction **[16].** Obesity can predispose patients to suffer from knee OA, it has molecular and mechanical deleterious results. The very adipose tissue is a reservoir of inflammatory factors. The cytokines adipokine, IL6, TNF alfa and C-reactive protein are elevated in the plasma of obese patients and have been linked with homeostasis and degeneration abnormalities in cartilage **[1,9].** During ambulation, the knee joint needs to sustain 3-5 times the body weight, while minor weight adjustments reflect a large variance in joint forces **[20].** Because of the procedure used (bariatric surgery vs lifestyle modifications), the probability of knee OA decreases by around 10% per kilogram of body weight (the same proportion occurs in the opposite direction of the increase) **[21].** Such results were also observed in the Framingham report, where a weight drop of 12 lbs resulted in a 50 percent decrease in the likelihood of knee OA **[22].** Not only is the total weight decrease significant, but research also take into consideration improvements in the percentage of body fat; each point reduction reflects a 28 percent increase in function and a 9.4 percent gain in Western Ontario and McMaster**[23].**

Patients that benefit from thermal modalities with certain non-pharmacological treatments however there is little data to support the usage of transcutaneous electrical nerve stimulation (TENS) or clinical ultrasound **[3].**

Pharmacological management:

The vast number of OA patients are aged, and others may have several comorbidities. Therefore particular consideration should be paid to the potential reactions and harmful consequences that may be caused by clinical drugs in this community. Historically, the most widely used drugs have been the cyclooxygenase inhibitors (acetaminophen and NSAIDs). Yet considering the harmful effects of these drugs on the gastrointestinal, renal, cardiac and hematological side, their long-term usage is minimal. Acetaminophen has been found to be better than NSAIDs and not preferable to placebo for pain relief, contributing to some recommendations for abstaining from using it as an appropriate medication treatment technique for mild to extreme OA **[15].** Topical NSAIDs have been found to be better, with a similar or marginally greater effectiveness than systemic NSAIDs **[13,24].** Brief follow-up trials revealed that they were superior to placebo in pain management during the first week of therapy but struggled to demonstrate advantage after 2 weeks **[24].**

Recently there has been a increasing concern of the effects of excessive drug use. Research still tend to offer proof that opioids for enhancing OA discomfort or WOMAC ratings are not preferable to NSAIDs, and the dangers of their usage far exceed the advantages **[25,26].** Tramadol, a serotonin and norepinephrine reuptake inhibitor with mild μ opioid receptor agonist effects, has demonstrated some promise in the diagnosis of extreme to moderate OA if an individual becomes refractory to certain medications and the usage of an opioid becomes suggested. The drug has a significantly reduced incidence of misuse and respiratory failure relative to other opioids **[27,28].**

Duloxetine is a US Food and Drug Administration (FDA)-approved serotonin and norepinephrine reuptake inhibitor for the diagnosis of diabetic peripheral neuropathy and fibromyalgia. Recent trials have shown that this drug is safer if used for longer than 10 weeks than placebo to manage pain and boost function in patients with OA **[29,30].**

Interventional management:

Throughout the past many substances administered by intra-articular (IA) injections were investigated. The theory behind this is that local procedures would have less systemic harmful consequences and a more immediate result would be to inject the drug within the joint.

Studies also demonstrated that IA interventions are usually more successful than NSAIDs and other conventional pharmacological procedures, but they have reported that a proportion of the gain may be secondary to the impact of IA placebo **[2].**

Corticoid injections:

Corticoids (CS), by acting directly on nuclear receptors, elicit their immunosuppressive andanti-inflammatory effects, interrupting the inflammatory cascade at multiple levels. They decrease the action and production of IL-1, leukotrienes, prostaglandins, and metalloproteinases **[9,11].** And these are believed to be some of the mechanisms of pain relief and enhance joint mobility in knee OA. Currently, the FDA-Immediate Release (IR) corticosteroids available for IA use are: Methylprednisolone Acetate (MA), Triamcinolone Acetate (TA), Triamcinolone Hexacetonide (TH), Betamethasone Acetate (BA), Betamethasone Sodium Phosphate (BSP), and Dexamethasone **[9].** In the past, attempts have been made to determine which is the best option. Dosages equal to or greater than 50 mg of prednisone (equal to 40 mg of TA and MA) tend to be correlated with a longer pain relief duration of 12–24 weeks compared with a brief pain relief of 2–4 weeks recorded with lower doses **[31–36]** There could be minor variations in pain relief between the licensed IR corticosteroid formulations, but existing research is equivocal. Yavuz et al reported that MA may provide superior pain relief for the first 6 weeks relative to the other corticosteroids used (TA, BDP), but they both offer comparable pain relief from week 6 to 12 **[36].** Pyne et al have indicated that TA works quicker and provides stronger pain relief in the first 3 weeks than MA, but the impact of the latter does not start instantly, because it migrates **[37].**

A new comparative research by Buyuk et al found that both MA and TH were similarly successful up to week 24 with a second week peak of action 34 supporting similar results by Lomonte et al **[38].** Several studies have attempted to explain issues relevant to the use of IA CS, such as the basic mechanism of action, length, choice of CS, signs, impact on cartilage structure / in. Any of these experiments were extremely diverse in nature, presenting conflicting findings and hindering effective consensus-building. This is expressed in the numerous organization recommendations, which endorse their usage in the OARSI and ACR guidelines **[13,14].**

Although the AAOS found the relevant data to be inconclusive to advocate for or against them **[15]** .In the past an effort was made to classify the correct applicants. Regardless of the anti-inflammatory results, one of the first findings was that those with knee effusion, synovitis, and decreased synovial membrane thickness (shown by ultrasound) will be the most effective category of those. A placebo-controlled study demonstrated positive correlation **[31],** but there was no clear link from other trials **[39–41].** Despite this inflammatory pattern, the synovial fluid often underwent cytological studies. Dieppe et al indicated that cell counts were not linked to the probability of reaction **[42]** but McCabe et al recently reported that patients with large synovial white blood counts (ranging from 251/µL to 1000/µL) will have a greater answer than patients with lower numbers **[43].**

Many potential variables such as knee tenderness, baseline discomfort, BMI, class, and anxiety or depression have failed to show accurate response predictors **[40,44-47].** In the other side, a small degree of radiographic changes in the KL system (0–1) tend to be correlated with a stronger response compared with patients with extreme radiographic changes (3–4) **[45].** Multiple IA knee injection methods have been identified in the past, including the anterolateral and anteromedial (with the knee flexed 60–90 degrees), as well as the mid-lateralandsuperolateral strategies (with the knee extended) **[35].** Reports conclude that utilizing ultrasonic guidance for the superolateral technique offers the greatest way to reliably administer the CS into the knee joint. Use the ultrasound on average offers 96.7 per cent precision, versus 81 per cent for landmarks. In fact, improved pain management may be demonstrated in the effective application of the ultrasound instructions relative to other therapies **[48-50]**. While problems are uncommon (about 1 in 3000) [**11]** the usage of this therapy is still a concern. Facial flush and intermittent flares are self-limited and can be observed in the first 3 days **[35].** A research evaluating frequent radiographic shifts, 40 mg TA vs placebo injections every 3 months over a 2-year span showed little difference,46 but a new randomized controlled trial using MRI reported signs of cartilage volume loss **[51].** Work on CS and knee cartilage integrity has often provided conflicting findings, some research indicate that the cartilage function is not changed, whilst others say that CS may cause chondrocyte degradation and increase the need for joint replacement **[4,9,35,36,51].** One of them found that cartilage damage could be caused by oxidative stress that could be minimized by the incorporation of vitamin C **[52].**

A portion of the IA CS is systemically absorbed, with the risk of causing hypoglycemia and transiently influencing the hypothalamic-pituitary-adrenal (HPA) axis in up to 25 percent of patients **[34,53].** The levels of cortisol may decrease after injection, but they return to baseline after 1–4 weeks.

Intended-discharge triamcinolon acetonide :

A molecule named FX006 was developed and approved by the FDA by the end of 2017 in an effort to extend the pain relief benefit, and also to decrease adverse effects, avoiding the high peak plasma concentrations seen with the use of IR. FX006 has TA (20 to 100 µm) in the microsphere. Such microspheres consists of Poly-Lactic-Co-glycolic acid (PLGA), a substance that is biocompatible and eventually degrades into carbon dioxide and water **[54-56].**

In 2014 Kumar et al published their first animal study using this drug. They found that there was an extension of the analgesic effect, improvement in inflammation, pannus formation, cartilage degradation and resorption of the bone, without evidence of the role of the HPA axis **[54].** A double blind-multicenter Phase-2 analysis involved 228 patients who were randomized for 12 weeks to obtain various doses of FX006 or 40 mg IR TA. They found the analgesic effect of FX006 was extended and increased with an optimum dose of 40 mg compared to that of the IR. It was found that the analgesic effect was superior at 2 to 12 weeks, and substantially superior at 5–10 weeks. Other measured results such as stiffness, feature, WOMAC scores, and change scale impression showed the FX006's dominance, particularly up to week eighth. Authors observed a decrease of plasma peak CS levels by eight times **[57].**

A subsequent study attempted to determine the optimum dose of FX006, compared three groups (16 mg, 32 mg and placebo) over the course of 24 weeks and found that the average daily pain was substantially improved by the concentration of 32 mg for the first 11-13 weeks, but only a minimal difference was observed after 13 weeks **[55].** Current research on FX006 are ongoing, some of the preliminary findings indicate that this alternative could reliably cost-effectively provide 12 weeks of pain relief. But these should be carefully examined until the final reports have been published **[58].** Some authors also suggest that PLGA may not be the best microspheric component and indicate that polyester amide (PEA) may have a safer profile and better release of the contained compound.

Non-corticoid interventional therapies:

In recent years, new drugs and treatments have been used as an alternative to the IA CS targeting at various causes other than inflammation. While these products are promising, some work is still needed to evaluate their efficacy, applicability and safety profile.

Viscosupplementation with hyaluronic acid:

Hyaluronic acid (HA) is a normal glycosaminoglycan synthesized into the synovial fluid by type B synovial cells. chondrocytes, and fibroblasts are also secreted into synovial fluid. It provides viscous lubrication, has startling absorbing properties and, in addition, potential anti-and anti-functions have been described **[6,9,11].** The concentration and molecular weight of the HA decrease considerably in the osteoarthritic knee **[9,11]** and this is why some suggested viscosupplementing the joint in an effort to restore the HA benefits. The latest effectiveness evidence is conflicting **[6,9,11,60]** and, as a result, public guidelines differ. The AAOS does not recommend its use **[15]** the ACR has no guidelines on it **[14]** the OARSI has a "uncertain recommendation" **[13]** and a recent European consensus has confirmed that HA is well tolerated and successful for low and moderate OA **[61]** Eventually, this therapy may be more successful in patients with higher knee pain levels, younger and with lower KL score **[60].**

Regenerative medicine:

IA injections of autologous conditioned serum (ACS), platelet-rich plasma (PRP), and mesenchymal stem cell (MSC) were tested to avoid and reverse degeneration associated with OA **[9,11,62,63].** Their modes of action are the suppression of cytokine-mediated inflammatory reactions and the activation of anabolism and differentiation of chondrocytes by growth factors and stem cells in it. Such approaches are effective and, in terms of pain reduction and knee function, some trials have documented them to be healthy, well tolerated and in some cases superior to IA placebo and HA **[9,11,62,63].** This is still a emerging area, so further work is needed to identify so standardize such products 'optimum methods of recovery, storage, and preparation.

DISCUSSION

Osteoarthritis is a complicated, multifactorial condition of the joints which mainly affects the knees.

Many theories were proposed however there is still no simple etiology or explanation of its normal path. Based on these ideas, a broad range of therapies have been established and evaluated, some more effective than others, but all of them are essentially directed at minimizing discomfort, improving function and preventing the need for surgical joint replacement. Both existing recommendations conclude the initial efforts to manage effects will be applied through water or land-based activity, gradually progressing into such treatments such as topical or oral narcotics. If they are not successful, instead a patient may obtain IA therapies which tend to have some degree of advantage over oral therapies with some placebo effect contribution. Of such treatments, one of the more researched was IA CS, although it seems that the latest evidence might not be straightforward provided that attempts are still underway to elucidate the exact mode of operation, analgesic potency, meaning and protection profile. Recent articles have struggled to provide patients with a detailed and consistent response on utilizing IR CS. Some authors reported that the prevalence of joint effusion, synovial membrane thickness, high BMI, psychological influences, and tenderness of the knee may be an indication, but there is no definitive evidence on this **[31, 39-47].** White blood cells that count in the synovial fluid, and low degree of radiographic improvements on the KL score can be correlated with a better result, but this is not a definitive answer. Part of the contradictory data is due to the studies design's high variability which makes it challenging to compare them. With technology and ultrasound advancements nowadays, we will try to use this method wherever possible to improve the rate of acceptable IA positioning of the injected drug. On October 2017, the FDA approved an extended-release presentation for TA in microspheres, called FX006, which in principle would have a longer lasting pain relief and fewer harmful effects compared to IR CS, provided the significant reduction in serum levels of CS **[64,65].** Several experimental models have already been shown to support the cartilage base, and some initial tests have also indicated any satisfactory protection profile, however there are still concerns as to the length past 13 weeks. The fact is, this fresh introduction of an old drug would take further work to explain any questions about the signs and extent of the IR option's benefits. Yet, despite its pharmacodynamic properties, it seems it may play a role if there is a question regarding repression of the HPA axis and hyperglycemia.

The field of regenerative medicine is developing many non-CS IA therapies which show promising effects, but it will take further awareness and standardization of their therapies.

CONCLUSION

While being one of our population's most researched and common diseases, knee osteoarthritis also requires a straightforward pathophysiology or a single most successful therapy to address the resulting symptoms and degeneration.

Early-stage activities are a successful therapy for such conditions, and are advised by all professional societies.

Many non-surgical procedures have uncertain efficacy and their performance depends on several factors (provider, device, patient) and their usage must be specifically chosen depending on the particular clinical condition.

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