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RESEARCH ARTICLE

ADVANCES IN NON-SURGICAL MANAGEMENT OF GONARTHROSIS: A SYSTEMATIC REVIEW

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Abstract

Objectives: Knee osteoarthritis (KOA) is typically the result of wear and tear andprogressive loss of articular cartilage and may eventually lead to disability. Treatment forKOA begins with conservative methods and progresses to surgical treatmentoptions when conservative treatment fails. This systematic review aims to highlight the latestadvancements in non-surgical interventions to improve the management of this commonmusculoskeletal disorder.

Methods: A comprehensive search of sources available in both English and Frenchencompassing various databases such as PubMed, Google Scholar, and relevant medicaljournals in addition to recommendations provided by prominent organizations(EULAR, ACR, SFR, SOFMER, OARSI, ESCEO, NICE, PANLAR, AAOS). Inclusion criteria were good quality systematic reviews, meta-analyses, practice guidelinesexcludingsurgicalKOA treatment.

Results: We thoroughly examined a large set of 545 articles and meticulously selected 117 for detailed analysis. This carefully selected set comprised randomized controlled trials, consensus statements, international guidelines, systematic reviews, meta-analyses, cohort studies, and reviews. Qualitative synthesis revealed widely approved nonpharmacological therapies such as information/education programs, weight loss, and physicalactivity. Most agreed on pharmacological therapies were oral and local NSAIDs, Paracetamol, and intra articular corticosteroid injection. Other treatment options were subject to controversy.

Conclusion: Various options are available for the treatment of KOA. However, KOA remains a commonglobal health challenge, affecting millions and compromising the quality of life through pain, functional limitations, and associated morbidities. A comprehensive and personalized approach seems crucial in order to reduce pain, improve knee function over the long term.

Introduction:-

Knee osteoarthritis (KOA), or gonarthrosis, is the leading cause of disability worldwide, [1] and is also a widespread health issue impacting people's daily lives and putting strain on healthcare systems globally. Their physical, psychological and social health was compromised to that of healthy individuals,[2] attributed to the loss of functional

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independence resulting from pain and activity limitations, alongside associated morbidity and mortality concerns. as a result, the quality of life of patients with KNO is reduced. [1]

According to a 2020 meta-analysis of 73 research with 9 440 250 participants. The estimated prevalence of a global KOA prevalence was 23% (95%CI, 20%-26%) in patients older than 40 years (roughly 654 million individuals).[3]Globally, as individuals live longer, the prevalence of KOA is rising and the women are more likely than males to experience KOA.[2]While surgical interventions remain a prominent consideration, the pivotal role of non-surgical approaches cannot be overstated.

In this systematic review (SR), we highlight recent literature and we embark on a thorough exploration of non-surgical treatments for gonarthrosis, drawing insights from reputable scientific societies and meticulously conducted research studies. Our goal is to shed light on the current landscape of non-surgical interventions, aiming to improve the management of this prevalent musculoskeletal disorder.

Method:-

In order to streamline the management of knee osteoarthritis, our working group, led by a chairman (TH), undertook the task of synthesizing data from both national and international scientific literature. We performed an extensive literature review of sources available in both English and French encompassing various databases such as PubMed, Google Scholar, and relevant medical journals. A meticulous analysis was performed to identify studies focusing on the treatment of gonarthrosis, Keywords such as "gonarthrosis," "knee osteoarthritis," and "non-surgical treatment" were used to retrieve articles. Additionally, we systematically reviewed guidelines and recommendations provided by prominent organizations, including the European League Against Rheumatism (EULAR), [4-5] the American College of Rheumatology (ACR),[6] the French Society of Rheumatology (SFR),[7]the French Society of Physical Medicine and Rehabilitation (SOFMER),[8] the Osteoarthritis Research Society International (OARSI),[9]the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO),[10] the National Institute for Health and Care Excellence (NICE),[11]the Pan-American League of Associations for Rheumatology (PANLAR),[12] and The American Academy of Orthopedic Surgeons (AAOS).[13]These guidelines were compiled to present an overview of the current recommendations from various scientific societies, informing our discussion on the management of gonarthrosis. We embarked on a thorough exploration of the references cited in selected articles to unearth additional pertinent literature.

Our attention was drawn to SR, meta-analyses, practice guidelines, randomized clinical trials (RCTs), and articles of exceptional value to practicing clinicians, which we deemed essential for inclusion in our analysis. (to ensure the inclusion of studies of utmost scientific rigor).

The following exclusion criteria were applied: records evaluating surgical therapy, records presented in duplicate, non-English or French Records.

Result:-

In our pursuit of knowledge, we diligently examined a wealth of 545articles. From this extensive pool, we carefully handpicked 117articles for thorough analysis

Figure 1: -This curated selection included RCTs, consensus statements/International guidelines, SR and/or meta-analyses, cohort studies and reviews.

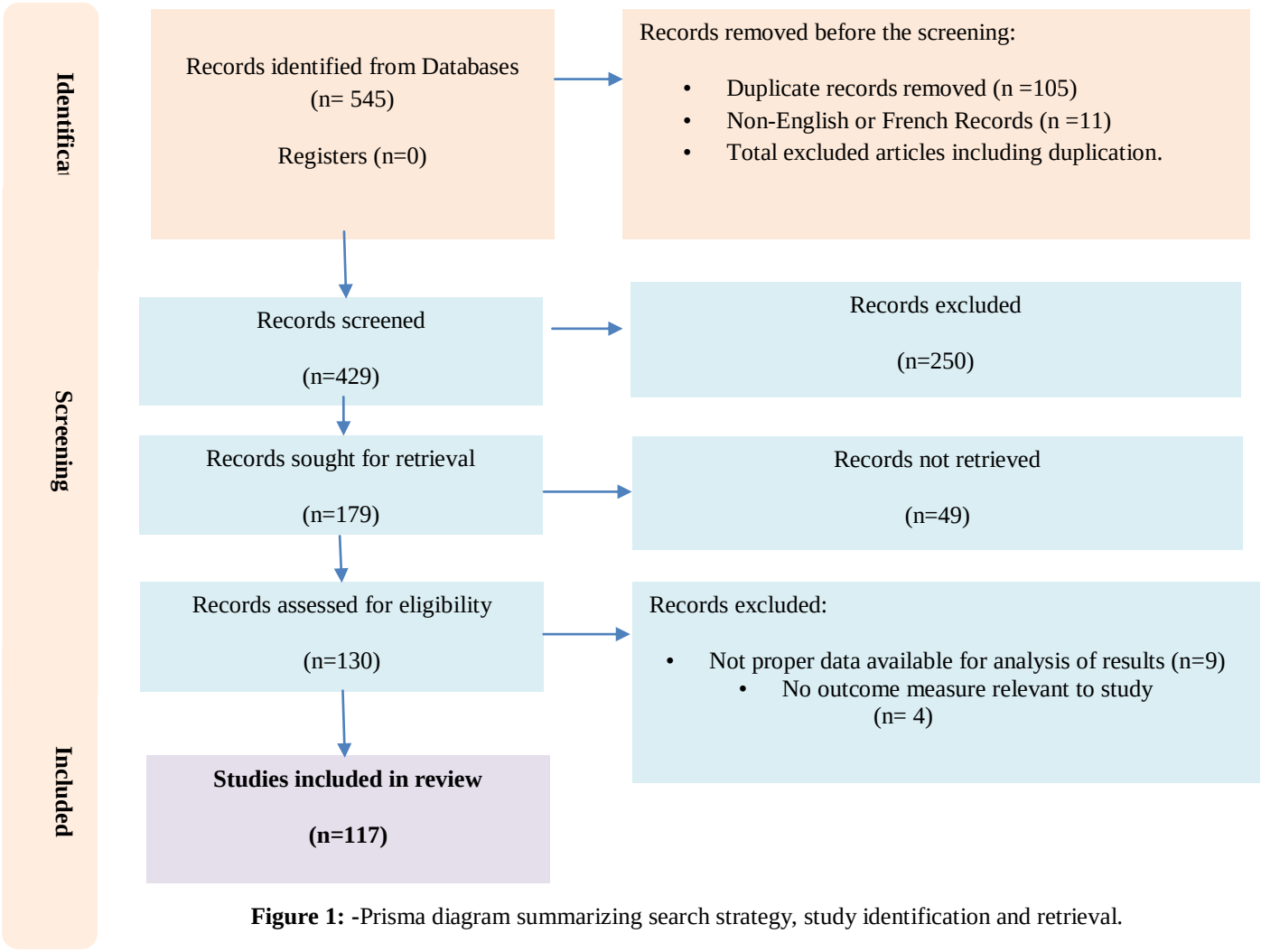

Figure 1: -Prisma diagram summarizing search strategy, study identification and retrieval.

ConservativeManagement:

- **General treatment principles:**

A multidisciplinary approach is necessary for the management of KNO. It is imperative to emphasize thatthere is now no cure for this disease,[14]but we can effectively control the symptoms. After going over the basic guidelines provided by the different organizations, we found three broad guidelines for managing gonarthrosis that were consistently included in all the sources, as shown in**Figure 2.**

1. ***Management of** KOA **should include pharmacological and non-pharmacological measures:***

This first concept highlights how critical it is to manage KOA holistically, using both pharmacological and non-pharmacological interventions. Therefore, various professional societies, support this beneficial combination. It lessens the severity of pain and delays the course of the illness, which eventually reduces the necessity for surgery. This all-encompassing strategy acknowledges that KOA is a complex condition with multiple contributing factors and requires a multifaceted treatment strategy for optimal outcomes.

2. ***Long-term patient adherence to these measures is crucial and requires regular consultations and evaluations:***

The second principle highlights the critical role of long-term patient adherence to prescribed pharmacological and non-pharmacological measures for effectively managing KOA. Achieving and maintaining patient adherence can be challenging and requires continuous support, education, and regular follow-up consultations. These measures allow healthcare providers to assess treatment efficacy, monitor disease progression and adjust management strategies accordingly.

3. ***Screening, treating comorbidities, and personalized treatment are integral components:***

The third principle underlines the importance of considering comorbidities as well as customized treatment plans designed to suit individual patient characteristics and preferences. Screening for comorbid conditions such as obesity, diabetes, cardiovascular disease, depression and others is essential, as these conditions can impact the course and management of KOA and may necessitate additional interventions. Addressing these comorbidities and tailoring treatment plans to the specific needs of each patient are integral components of effective KOA management.

Strongly recommended
Conditionally recommended
Conditionally recommended against

STRENGTH OF RECOMMENDATIONS

Strongly recommended against
Inconclusive, not determined
Not reported

Professional societies / General principles	SFR[7] and SOFMER[8]	EULAR[4,5]	ACR[6]	AAOS[13]	ESCEO[10]	OARSI[9]	NICE[11]	PANLAR[12]
Management of knee osteoarthritis should include pharmacological and non-pharmacological measures	●	●	●	●	●	●	●	●
Long-term patient adherence to these measures is crucial and requires regular consultations and evaluations.	●	●	●	●	●	●	●	●
Screening, treating comorbidities, and personalized treatment are integral components.	●	●	●	●	●	●	●	●

Figure 2: - Overview of Treatment General Principles for Knee Osteoarthritis from Key Professional Organization.

- **Non-pharmacological treatment:**

One of the mainstays of KOA care is non-pharmacological therapies, which include a range of approaches that have been approved by many professional associations that have developed guidelines for OA management **(Figure 3)**. In order to address KOA management in a holistic manner, these recommendations provide a core range of non-pharmacological therapies.

Information/Education programs:

A key component of non-pharmacological therapy is information and education programs, providing patients with essential knowledge about osteoarthritis and self-management strategies. A recent review has demonstrated that patient education positively impacts the treatment of KOA and leads to improved treatment outcomes, including decreased pain and enhanced physical function.[15-16]. However, patient education should not be offered as the sole treatment and research suggests that the combination education with exercise therapy may yield even better results.[17]

Weight loss:
Osteoarthritis involves gradual wear and tear on the joint surfaces and often affects the joints that bear our weight. Weight loss alleviates pressure on the knee joint, enhancing physical function and biomechanics, particularly when combined with exercise. Biomechanical research indicates that a 1 kg weight loss results in a fourfold reduction in the forces exerted on the knee.[18]International guidelines seem to agree on the necessity of a weight loss for overweight and obese individuals, addressing it through dietary modification and adapted exercise programs enhances physical function and decrease pain.[19]

Obesity plays a significant role in the development of the metabolic syndrome (MS), and individuals with MS have more than double the risk of developing gonarthrosis.[20]The magnitude of weight lost has a favorable correlation with the therapeutic benefit,[10]and a recent network meta-analysis shows that to achieve a 50% drop in each Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score subscale, a 25% weight reduction from baseline is required. However, physical exercise is necessary to preserve the lean body mass and to prevent sarcopenia.[21]

Tailored exercise program /physical activity/physical therapy sessions:
Tailored exercise programs, physical therapy sessions and adapted physical activity (APA) were the center of interest of the majority of professional organizations. Their goal was to reduce both the associated risk factors (chronic inflammation, metabolic syndrome, excess weight, and sarcopenia) and the symptoms most troubling to the patient.[22]Structured land-based exercise programshave been shown to be an appropriate intervention for people with KOA, [23]improving their functional mobility and quality of life, and has at least short-term benefit in terms of reduced knee pain and physical activity.[24]A SR with meta-analysis that applyingaquaticexercisesessions in treatment of KOA showed a statistically significant difference in the WOMAC stiffness, the Visual Analogue Scale (VAS), and the Timed Up and Go Test .[25]In essence,an effective physical therapy sessions aims to decrease pain while enhancing knee range of motion, productivity and isometric quadriceps strength for all patient with KOA.[26,27-28]

Tai chi/Yoga:
Mind-body exercise including Yoga or Tai Chi, were not the focus of most scholarly societies while several studies demonstrated their beneficial effect and safety.[29]Traditional Chinese exercise like Tai Chi has proven its effectiveness not only on physical function but also on mental health of patients with KOA.[26]Additionally a 2024 SRconcluded that, due to its accessibility, practicality, and potential benefits, yoga may serve as a supportive therapy for individuals with osteoarthritis. However, it is essential to emphasize that the practice of Yoga should be undertaken under the guidance of an expert to ensure optimal benefits and improvements in health and overall quality of life.[30]

Lateral wedge insoles (LWI):
Concerning the utilization of LWI and knee brace (KB) in femorotibial KNO, there has been a contentious debate among the different professional organizations, ranging from recommended to strongly recommended against. LWI are a simple and economical treatment strategy for KOA, certainly it has been demonstrated that they can improve femorotibial angle ,[31]but several studies have shown its ineffectiveness in KOA.[32]15 studies extracted from 13 RCThave revealed that they don't yield relieving pain neither improving function.[33]On the other hand,recent clinical evidence supports that LWI and KB either independently or together are fruitful in KNO and help to improve pain and function,[34]especially when the patient is treated with conventional physiotherapy followed by LWI.[35]These results indicated that LWI should be analyzed in more details.

Appropriate and comfortable shoes:
The biomechanical therapy for osteoarthritis of the knee RCT aimed to assess whether biomechanical footwear was more effective than standard footwear in reducing knee pain in individuals with KOA.A total of 220 participants were randomly allocated to either the biomechanical footwear group or the control group. The use of biomechanical footwear led to a statistically significant improvement in pain after 24 weeks of follow-up. However, the clinical significance of this improvement remains uncertain.[36]Another RCT was conducted with the aim of comparing flat flexible shoes with stable supportive shoes for the symptoms of KOA, it found that stable supportive shoes were more effective than flat flexible shoes. This contradicted the initial hypothesis, as stable supportive shoes showed greater improvement in knee pain during walking.[37]

Walking aids

Walking aids, including canes, are important and beneficial for individuals with KOA. Although there is limited clinical trial evidence supporting this, cross-sectional studies indicate that walking aids, particularly canes,[38]are commonly used by people with KOA, especially those with severe knee pain. However, the effectiveness of canes compared to other assistive devices remains inconclusive based on conflicting results from available RCTs.[13-38]On average, individuals with osteoarthritis use nearly 10 devices, with high satisfaction rates across all categories of 87%.[39]Using assistive devices such as a walking stick, walker, or crutches is recommended as a preventive measure. When using a walking stick, it should be held in the contralateral hand and adjusted to the level of the greater trochanter, with the elbow bent at an angle of 25 to 30 degrees.[40]

Thermal therapy:

The delivery methods of thermal interventions vary widely in published reports. Heat increases the flexibility of collagen tissue by promoting the viscous flow of collagen fibers, and enhances blood circulation and stimulates free nerve endings and peripheral nerves through mechanisms effectively aiding in pain control.[41]Cryotherapy can be used to reduce pain, inflammation and edema. Superficial cooling can relieve muscle spasms and increase the pain tolerance. Vasoconstriction and reduced metabolic activity led to decreased local blood flow, aiding in swelling control and pain reduction. However, cold therapy should be avoided in patients with Raynaud's phenomenon, cold hypersensitivity, cryoglobulinemia, or paroxysmal cold hemoglobinuria due to potential adverse effects.[43]Recently, focal thermal therapy at acupressure points was found as a viable conservative treatment for KOA. In fact, the pressure applied at the acupressure points enhances the benefits of topical thermal therapy alone.[44]Another recent works underlined the beneficial role of thermal therapies in decreasing OA pain.[45]Additionally, many studies have investigated the impact of thermal techniques on preventing and rehabilitating musculoskeletal disorders. The OARSI guidelines endorse such treatments for KOA.[40,46-47]

Work adaptation /Ergonomic measures/Assistive devices:

Adaptations are important and beneficial for people with KOA.[39]Cross-sectional studies confirm that adaptations at home and/or work are important and commonly used by people with KOA.[48-49]Assistive devices can help alleviate pain and enhance participation in both home and work environments. Examples include devices for dressing assistance, height-adjustable chairs, raised toilet seats, handrails for staircases, or suitable walking aids(cane, walker). Furthermore, a recent study demonstrates the importance of ergonomic measures in preventing musculoskeletal diseases and disorders and specially KOA.[50]Holding a cane, whether ipsilateral or contralateral of the painful knee, has proven effective in reducing the load and stress on a lower limb affected by KOA.[51]

While pain receptors in the osteoarthritis knee joint can be stimulated by both mechanical and chemical stimuli,[52]current research shows that putting too much load on the joint can lead to knee pain.[53]KB for osteoarthritis are designed to reduce the load on the joint, which helps to ease pain and improve symptoms.[54]Many of these devices are intended to unload one compartment of the knee by applying force to one side, thereby reducing pressure on the opposite side. These unicompartmentoffloaders have proven beneficial for patients with unicompartmental tibiofemoral osteoarthritis.[55]These braces have demonstrated an immediate reduction in sagittal plane knee moments and quadriceps muscle activity.[56]

Acupuncture:

Despite numerous trials investigating acupuncture for osteoarthritis, its efficacy remains controversial. Recently, a study demonstrated that acupuncture in KOA has been shown to reduce pain, stiffness, and dysfunction compared to no treatment. Acupuncture can be considered as an alternative therapy when conventional treatments prove ineffective or if patients experience adverse reactions that hinder their continuation of treatment. Both manual acupuncture and electroacupuncture are recommended for a duration of 4–8 weeks to improve the health status of patients with KOA.[57]Another study found that acupuncture may offer lasting, clinically significant pain relief and functional improvement for up to 5 months after treatment compared to usual care, and up to 6 months after treatment compared to diclofenac.[58]

Transcutaneous electrical nerve stimulation (TENS):

A recent study demonstrated that activeTENS led to greater improvements inVASscores compared to sham TENS. Additionally, TENS proved superior to other interventions alone for the pain subgroup of the WOMAC in both the medium and long term. Furthermore, TENS combined with other interventions showed superiority for function in

the medium and long term compared to other interventions.[59]Accordingly, TENS combined with ultrasound, sodium hyaluronate, massage, functional training and other treatment options is effective for treating KOA.[60]

Cognitive behavioral therapy (CBT):

CBTwas recommended for patients with widespread pain and/or depression by OARSI.[9]Accordingly, findings from a study indicate that the benefits of CBT associated with treatment may last over time. This supports its potential as a promising alternative or complementary intervention for patients with KOA, particularly in addressing pain and insomnia.[61]Hence, a recent meta-analysis showed that combining exercise and CBT appears to be an effective method for reducing KOApain.[62]

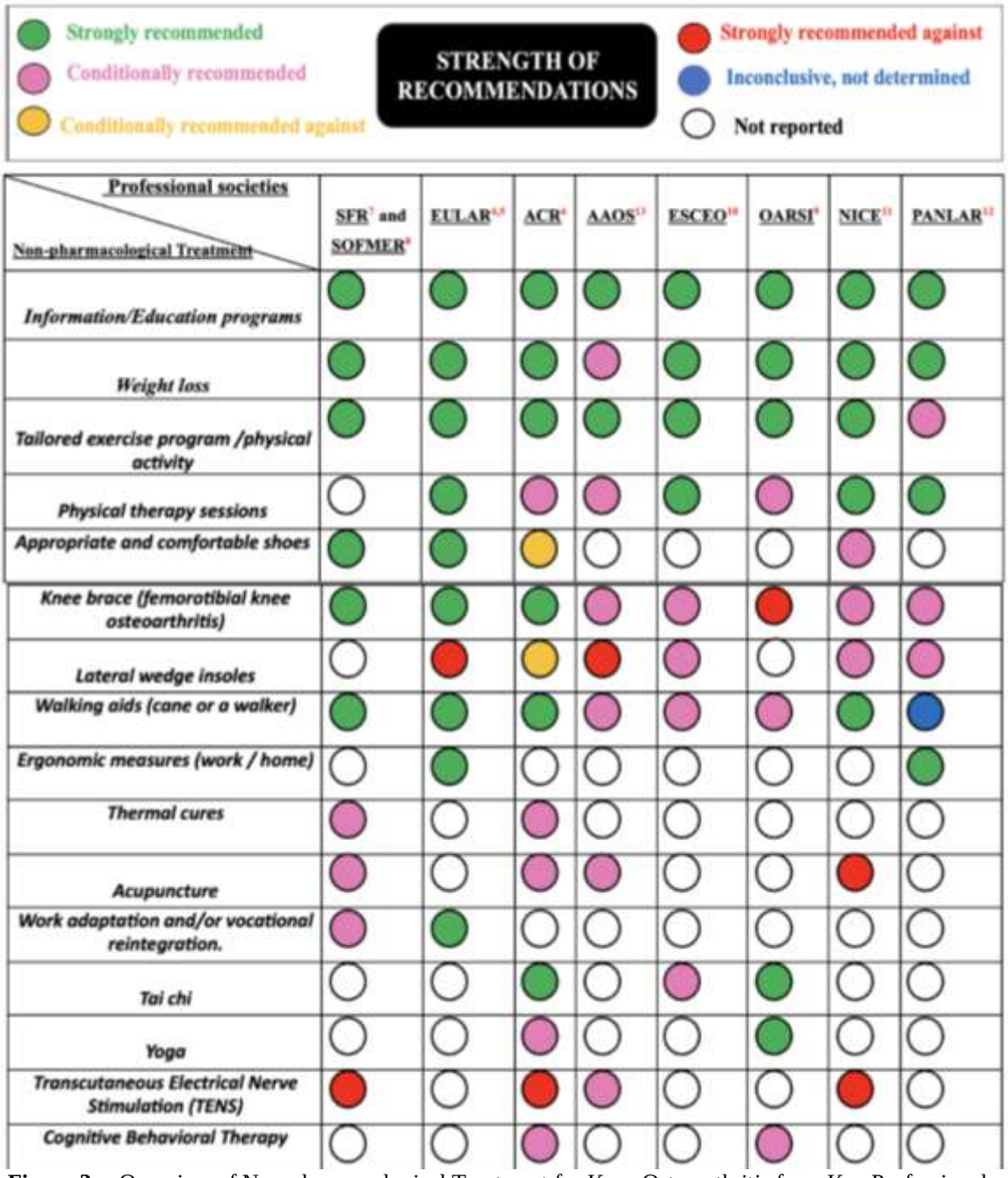

Figure 3: - Overview of Non-pharmacological Treatment for Knee Osteoarthritis from Key Professional Organization.

- **Pharmacological treatment:**

Acetaminophen/Paracetamol:
Published research has shown that paracetamol remains a primary analgesic, often prescribed as a first-line treatment for the majority of patients with knee osteoarthritisdue to its relative safety compared to NSAIDs.[63]And It is important to regularly monitor for hepatotoxicity, especially when acetaminophen is taken consistently at the recommended maximum dosage of 3 grams daily in divided doses.[6]

Clinical trials investigating KOA have found that the effect sizes of acetaminophen are very small, indicating that few individuals treated experience significant benefits.[64]Furthermore, longer-term treatment with acetaminophen does not provide better results than treatment with placebo for most individuals. Members of the Patient Panel have observed that acetaminophen is generally ineffective for most individuals.

However, for individuals with limited pharmacologic options due to intolerance or contraindications to NSAIDs, acetaminophen may be suitable for short-term and occasional use.

Finally, KOA guidelines differ in their recommendations regarding the use of paracetamol **(Figure 4)**. A more comprehensive approach is necessary for managing this condition, taking into account the patient's profile, disease stage, and pain management during physical activity, to determine its appropriate use.[65]

Weak opioids (Tramadol-codeine):
Concerning week opioids (tramadol, codeine), these drugs are often used for short term use even though it is controversial. For some, and for severely symptomatic patients, the last pharmacological options include short-term weak opioids, such as tramadol, which have been shown to provide significant analgesic benefit in KOA by older studies.[10] Opioids have been found to significantly reduce pain intensity and have a small effect on function. Previous meta-analyses have indicated that non-tramadol opioids provide modest benefits for osteoarthritis pain and function, but they are associated with heightened safety concerns, particularly among individuals aged 60 and older.[66-67]

Meta-regression analysis indicated that increasing opioid doses beyond 20–50 mg did not significantly enhance pain relief but posed higher safety risks.[68]

Accordingly, many advice against the use of either oral or transdermal opioids in individuals with osteoarthritis due to the potential for chemical dependency associated with opioid medications.[69-71]Moreover, there is compelling evidence suggesting that opioids offer limited or no meaningful benefit for osteoarthritis symptoms.[72]

Strong opioids:
The prescription of strong opioids should be reserved for patients with contraindications to knee surgery, in cases of failure or contraindication to other treatments, taking into consideration comorbidities, and after informing them of the potential side effects.[69]

A recent study found that strong opioids led to significant healthcare costs without providing substantial pain relief. They also resulted in increased cognitive deficits and a slight rise in the number of patients experiencing severe to total dependency after 36 months of treatment.[73]In this regard, a SR of clinical practice guidelines concluded that strong opioids are recommended against.[74]

Indeed, many experts acknowledge that opioids have serious side effects. They recommend reserving their use for short-term scenarios or when no other options are available.[75]

Duloxetine:
Although various centrally acting agents have been utilized for managing chronic pain, only duloxetine has sufficient evidence to support its recommendation for use in osteoarthritis.[6]OARSI recommend duloxetine as a second line treatment option for KOA for people with depression or widespread pain disorder.[9]

Non-steroidal anti-inflammatory drugs:(NSAIDs)
NSAIDs are the initial pharmacologic treatment for osteoarthritis. Multiple placebo-controlled trials have consistently shown that NSAIDs provide greater pain relief compared to placebo but should be used at the lowest effective dose for the shortest necessary duration to manage pain and to avoid the potential risks of gastrointestinaland cardiovascular events associated with all NSAIDs.[9,76-77]Accordingly, in a 2020 meta-analysis, oral NSAIDs were associated with less pain and improved function at 2 weeks, with effects diminishing over 26 weeks. Traditional NSAIDs showed the largest improvements in pain, with 24%and 64% greater improvement than celecoxib and intermediate cyclooxygenase inhibitors, respectively, at 2 weeks, and 33% and 44%, respectively, at 12 weeks.[78]

In a network meta-analysis conducted in 2020, topical NSAIDs were found to improve function compared to acetaminophen, however, the pain response was similar. Topical NSAIDs exhibited a better safety profile, with lower rates of gastrointestinal adverse events.[79]Its preferred and advisable to consider topical NSAIDs before resorting to oral NSAIDs.[80]

However, a recent study indicates that prolonged use of NSAIDs for managing KOA could result in exacerbated symptoms and increased likelihood of progressing to total knee replacement, without causing structural changes in the knee joint over a period of 4 to 5 years.[81]

Capsaicin:
A study reviewed five double-blind RCTs and one case-crossover trial investigating the efficacy of topical capsaicinshowed moderate efficacy compared to placebo for reducing VAS pain scores and found that applying topical capsaicin four times daily is moderately effective in reducing pain intensity for up to 20 weeks. This effect was noted in patients with at least moderate pain and clinically or radiologically confirmed osteoarthritis, and the treatment was well tolerated.[82]

Topical capsaicin gel at low doses (<1%) is also known for its favorable safety profile and was shown to be an effective treatment for KOA. The most common adverse effect is a localized burning sensationwhich tends to diminish with continued use.[83]

Intra articular corticosteroids injection:
Patients who cannot take NSAIDs or do not respond to them may consider intra-articular corticosteroid injections, which generally offer pain relief for a few weeks.

In a SR and meta-analysiscomparing intra-articular corticosteroids and placebo injections for KOA,intra-articular corticosteroid injections provide noticeable pain relief and functional improvement compared to placebo only in the short term for patients with KOA.[84]A more recent formulation of steroid injection, triamcinolone acetonide extended release, appears to have fewer systemic effects compared to traditional steroid injections.[85]

However, other researchsuggests that corticosteroid injections may not provide better pain relief than placebo after three months, and might be less effective than physical therapy after one year.[86]Some studies indicatepotential negative effects of intra-articular steroid injections on cartilagethough their clinical significance is unclear.[87]

Hyaluronic acid: (HA)
Efficacy of intraarticular injection of HA in patients with KOA isn't clear. Evidence from several meta-analyses of RCTssupports HA injections in the therapeutic arsenal for symptomatic KOA,[88-91]demonstrating efficacy versus placebo.[91-93]

A meta-analysis of high-quality placebo-controlled studies showed a modest benefit on pain and function at 3 months.[88]HA injections' efficacy appears similar to oral NSAIDs,[93-94]although a greater placebo effect with intra-articular administration cannot be ruled out.[95]

Further RCTsand two meta-analyses, have questioned HA injections'efficacy.[96-99]One of the meta-analyses included only two studies of Hylan-GF20, limiting its conclusions ,[99]while theRutjes et al. study, which questioned both efficacy and safety, has been criticized,[98-100]which underlines the importance of considering potential iatrogenic effects of any intra-articular procedures.

Accordingly, a recent review of the efficacy and safety profiles of different intra-articular therapies reported uncertain long-term effectiveness due to lack of long-term data and methodological flaws despite reporting short-term benefits in KOA.[101]

From an economic and healthcare perspective, using HA for managing KOA offers economic advantages, reduced reliance on opioids and corticosteroids as rescue medications, and a delayed need for total knee arthroplasty.[102]Younger patients with milder clinical symptoms, radiological findings and a lower or normal body mass index arethe ideal candidates for intra-articular hyaluronic acid therapy.[103]

Platelet-rich plasma (PRP):
The literature on this subject is very active, and the injection protocols vary widely which makes it challenging to analyze the literature comprehensively.[7]

A recent review compared the efficacy and safety of PRP, bone marrow aspirate concentrate (BMAC), andHAinjections for treating KOA, including27 studies with 1042 patients receiving intra-articular PRP injections, 226 BMAC injections, and 1128 patients receiving HA injections. PRP injections resulted in significantly better post-injection WOMAC, VAS, and Subjective International Knee Documentation Committee scores compared to HA injections.[104]

Another recent SR examined PRP's effectivenessin managing KOA, ending that PRP alleviates pain, enhances joint function, increases range of motion, and improves mobility.[105]However, the variability in PRP protocols necessitates further research to identify the most effective PRP configuration.

On the other hand, a study aimed to evaluate the benefits of PRP injections administered to patients with KOA over a six to eight-week period through WOMAC score concluded that a trend of reduction in this score was observed. However, they largely indicate a placebo effect from the injections.[106]

Intra articular HA remains a controversial option in patient with KOA recommended against in the several recommendations.[6,9]

Mesenchymal stem cell (MSC):
MSC is rather new treatment option. In fact, a recent SR included twelve articles involving 539 patients treated with a single intra-articular injection of MSCs for KOA. It concluded that a single intra-articular injection of MSCs is a safe, reliable, and effective treatment option for Kellgren-Lawrence grade I—III KOA.[107]Thus far, MSCs may be a promising therapeutic due to their demonstrated regenerative capabilities. though the best MSC source remains debated.[108]

However, another review included 50 clinical studies and 30SR and meta-analyses found that due to the lack of efficacy of stem cells, the risk of potential complications, and the limited quality of evidence from current studies prevent recommending stem cell products for patients with KOA, and that the clinical application of stem cell therapies remains unsupported and should be approached with caution until more robust evidence becomes available.[109]

Furthermore, another recent review of the efficacy and safety profiles of different intra-articular therapies including stem cells reported uncertain long-term effectiveness of these therapie due to lack of longterm data and methodological flaws despite short-term benefits in KOA.[110]Consequently, the ACR and OARSI recommend against intra-articular MSC injections.[6-9]

Symptomatic slow acting drugs (SYSADOAs):
Diacerein:
A meta-analysis of 12 RCT revealed that diacerein is as effective as NSAIDs in reducing pain (WOMAC, VAS scores), making it a viable alternative for KOA patients unable to use NSAIDs.[111]

It worth noting that the safety of diacerein has been questioned due to reports of severe diarrhea and rare hepatotoxicity.[112]In addition to that, Recent studies indicate that diacerein users have over twice the risk of adverse

events compared to placebo, regardless of concomitant osteoarthritis treatment, mainly gastrointestinal issues like diarrhea, abdominal pain, and colitis, as well as urine discoloration.[113]

Chondroitin-glucosamin:
A recent metanalysis of eight RCTs, confirmed thatcombining glucosamine and chondroitin effectively treats KNO and is superior to other treatments, cost-effective and well-tolerated.[114]

A newer meta-analysis found that chondroitin sulfate (CS) significantly reduces pain and improves physical function, while glucosamine sulfate (GS) significantly reduces joint space narrowing, demonstrating notable therapeutic benefits.[115]

These findings suggest a potential positive effect of this SYSADOAs in patients with KOA.

Avocado-soybean unsaponifiables (ASU)
Several studies showed improvement in pain, stiffness and physical function ASU [116-118]. However, some negative results concerning the effect of ASU on disease progression werefound in some studies[119,120]. A single article has warned of possible adverse effects affecting the gastro intestinal system, skin, liverandplatelet aggregation [121]. In another hand, recent safety meta-analyses of a specific proprietary ASU product have shown no significant differences in safety when compared to placebo treatment, according to limited trial evidence that included the use of concomitant NSAIDs. [113, 122]

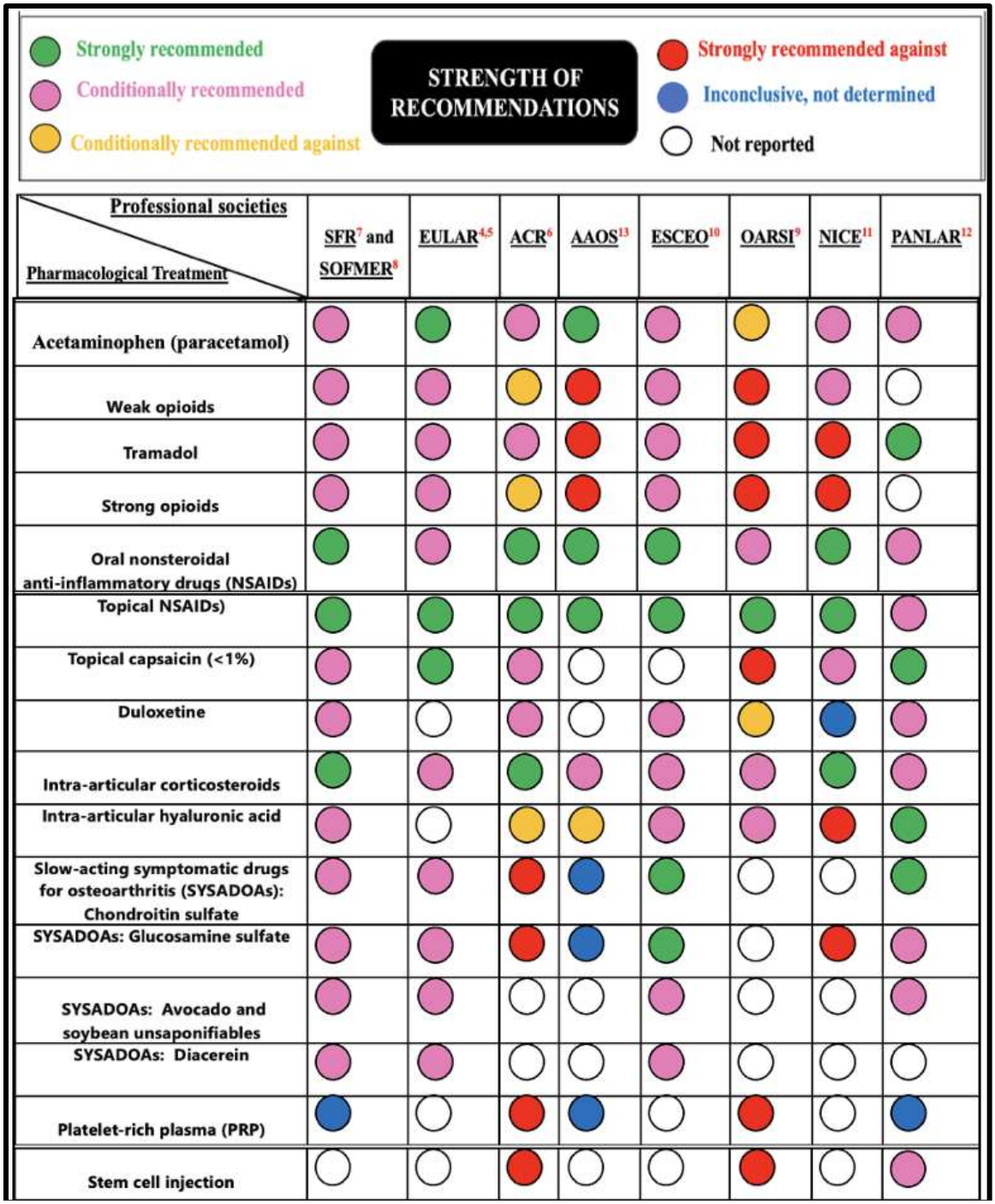

Figure 4: - Overview of pharmacological Treatment for Knee Osteoarthritis from Key Professional Organization.

Conclusion:-

In conclusion, knee osteoarthritis (KOA) represents a significant global health challenge, affecting millions and compromising the quality of life through pain, functional limitations, and associated morbidities.

The non-surgical management of knee osteoarthritis remains a crucial issue for improving patients' quality of life. This SR synthesized data from recent studies, providing a comprehensive overview of current approaches and their efficacy.

While numerous non-surgical options are available and show promising results, a holistic and individualized management approach remains paramount. Interdisciplinary collaboration is essential to offer patients optimal care, reducing pain and sustainably improving knee function.

Declarations

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Theauthors declare no conflict of interest.

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