Therapeutic approaches in the management of knee osteoarthritis (Review)

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Abstract. Osteoarthritis (OA) is a common, frequently met degenerative disease, that generates pain and decreasing functionality; risk of suffering from this disorder increases with ageing. Being a complex disease, treatment is often difficult due to complications. Knee OA therapy demands a strategy that specialists agree with in considering the clinical symptoms and the disease evolution. The initial management of its treatment should be conservative requiring both a pharmacological and a non-pharmacological approach. If this conservative, noninvasive therapy fails, the surgical approach is discussed. The present review focused on the assessment of therapy choices for patients with knee OA, in order to reduce pain and enhance functionality and knee range of motion, underlying benefits and advantages for each choice. Existing data of available treatment for knee OA, both surgical and nonsurgical were analyzed, focusing on the latest results, indications, developments, and level of evidence provided by the literature in the topic.

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Contents

1. Introduction

The most frequently diagnosed type of arthritis is knee osteoarthritis (OA), its incidence continuously growing with increasing life expectancy and obesity. As certain studies revealed, ~10% of men and 13% of women aged 60 or more, have characteristic knee OA (1).

For patients over 70 years old, the incidence increases to 40%. Knee OA is more frequent in women than in men. Not all patients radiographically exhibiting knee OA are symptomatic. Only 15% of subjects radiographically exhibiting knee OA have symptoms, as revealed by a recent study (1). The occurrence of symptomatic knee OA is ~240 cases in 100,000 subjects annually, regardless of age (1).

Knee impairment varies based on its cause. Pain in the area of the knee joint is the most frequent symptom for knee OA. The pain intensity may vary from constant, intermittent (on and off), sharp or dull and from mild to severe. It may also lead to decreased range of motion. Grinding or popping sounds may be noticed in addition to muscle weakness. Frequent symptoms are locking, swelling and knee instability. These impairments, closely connected to pain, commonly lead to difficulties in domestic activities, walking, standing, climbing stairs and have a negative psychological impact on sufferers, leading to a reduced quality of life (2).

The present review highlighted the current data on the therapy recommendations, considering both conservative and

surgical therapy. In this regard, the most known databases (such as Web of Science, Cochrane database and PubMed) were searched in-depth to construct a solid review based on the most recent, valuable, and informative published data in the field. The review intended to summarize and search published data on the topic, between 1957-2021, providing information related to pathogenesis of the knee OA, conservative (non-surgical) treatment, surgical treatment, detailing the most important aspects of this invasive technique, and per total emphasizing the most known therapeutic approaches in the management of knee OA. In this regard, our study was conducted by adding statements from the well-known publishers/scientific databases (i.e., Access Pharmacy, Embase, Google Scholar, Medline, ScienceDirect, Web of Science, Scopus, MDPI, etc.). Additionally, two controlled vocabulary thesauri were used, as follows: terms in Medical Subject Headings (MeSH), for PubMed searching, and Embase subject heading (Emtree), for Embase searching (i.e., the key words mentioned as representative for this paper, including 'knee osteoarthritis', 'gonarthrosis', 'conservative treatment', 'orthopedic surgery', 'prosthesis', or closely related to these terms). From a total of 241 bibliographic references which were selected at the beginning as being suitable for this research, 174 were eliminated for different reasons (duplicates, not in the English language, not enough information, etc.), and the 67 that remained (associated with the topic, relevant, informative, English language, etc.) were cited as references to support the statements in this review.

2. Pathogenesis of the knee osteoarthritis (OA)

The articular cartilage structure comprises proteoglycans, type II collagen, water, and chondrocytes. Normal articular cartilage structure sustains a balance between all components, the synthesis correcting any cartilage impairments. Healthy articular cartilage is maintained in this way. In OA, degradative enzymes also known as matrix metalloproteases (MMPs) are upregulated, causing an imbalance that leads to proteoglycan and collagen loss. At the OA onset, chondrocytes tend to enhance proteoglycan synthesis to balance deterioration and produce tissue inhibitors of MMPs (TIMPs). However, this restorative action is insufficient. The imbalance leads to a reduced quantity of proteoglycans in spite of enhanced synthesis, higher water content, chaotic collagen structure as well as articular cartilage elasticity decline. These modifications determine cartilage fissure and cracking and eventually articular surface abrasion (3).

Based on etiology there are two categories of OA: primary, non-traumatic or idiopathic; and secondary, mostly due to mechanical misalignment or trauma. In concordance with the radiographic results of the 1957 Kellgren-Lawrence (KL) system, the intensity of the impairment can be classified (4). OA was considered to be particularly a degenerative disorder that affects the cartilage, but previous studies have highlighted the complexity of OA, having several causes such as inflammation, metabolic disorders, trauma, biochemical reactions and mechanical forces (5-9). As evidence has revealed, the cartilage is not the only part affected. The cartilage is not able to generate pain or inflammation due to vasculature and innervation absence, in the early phases of the illness. For this reason, the pain is mostly generated by alterations in the non-cartilaginous joint constituents such as ligaments, the subchondral bone, the joint capsule, peri-articular muscles and the synovium (5,6). With the progression of the disease these parts are damaged, resulting in obvious alterations including weakening of periarticular muscles, bone remodeling, obvious synovial effusion, looseness of ligaments and osteophyte formation (7).

Since inflammation has an insufficiently known influence, it is not precisely known whether the OA modifications are generated by the inflammatory reaction or they generate the inflammation (5). Unlike inflammatory arthritis, OA inflammation is chronic, of low intensity, affecting the natural immunity pathways. A general finding regarding OA, highlighted in the primary phases of the illness, is represented by synovitis (inflammation of the synovial membrane) although with higher prevalence in later stages associated with intensity. The synovial fluid, in OA, has been revealed to include several inflammatory mediators such as leukotrienes (LKB4), growth factors (VEGF, TGFβ, NGF and FGFs), plasma proteins (C-reactive protein, suggested as an indicator for OA development and evolution), cytokines (IL1β, IL6, IL15, IL17, IL18, IL21 and TNF), complement components, nitric oxide and prostaglandins (PGE2) (8,9).

All aforementioned components are capable of generating MMPs as well as certain hydrolytic enzymes (prostaglandin E and cyclooxygenases as well) at the local level, resulting in collagen and proteoglycan damage, thus leading to cartilage breakdown (10). The innate immune cells (mast cells and macrophages) identify particular molecules (injury-associated molecular models) generated by extracellular matrix breakdown that determine the action of white blood cells in the protection process. Nevertheless, this may determine tissue damage due to long term and systemic inflammation (8).

3. Conservative treatment (non-surgical)

Therapies for knee OA, regardless of age, vary from lifestyle changes and treatment to gradually intrusive injectable treatments, several being initiated by primary care physicians.

Non-pharmacologic treatment. Losing weight yields a decrease of the pressure on the knee joint, improving physical function and biomechanics, combined with exercise. Research on biomechanics highlighted that a decrease in weight of 1 kg produces quadruple reduction of the forces acting on the knee (11). For subjects exhibiting OA symptoms, an amelioration of the symptoms has often been observed through weight loss only. Physical exercise decreased pain load [95% confidence interval (CI) of 10 to 15; 12 points/100], ameliorated the quality of life and enhanced physical function (95% CI of 8 to 13; 10 points/100) as revealed by a meta-analysis of 44 randomized controlled trials (RCTs) that evaluated routine exercise programs, land-based, against no exercise program (12). Weight loss is favored by exercise and diet. An extended RCT indicated a 4.9% loss of total body weight in nutrition intervention and 5.7% body weight decrease with a program including diet and exercise for 18 months, in subjects with arthritis (13). Cardiovascular wellbeing and weight loss are stimulated through aerobic exercise (elliptical training

or swimming) concurrently protecting the damaged joint areas (12).

The most affected part of the knee joint in knee OA is the mid-section. The effectiveness of unloader knee braces in knee OA has been demonstrated by published data and in spite of the fact that 92% of these studies recommended their use, 94% of total research was not randomized or according to advisory opinion (12-14). A thorough analysis of six RCTs that compared the impact of applying a medial unloader knee brace in treating mid-section arthritis with that of a control orthosis, revealed a minor statistically significant advantage supporting the brace in pain release (95% CI of 0.13 to 0.52; standard mean difference (SMD) 0.22. Due to poor evidence, these results have uncertain clinical significance (15).

Treatment with physical strengthening exercises has as an effect, improvement of leg muscle activities particularly the quadriceps, decreasing load and knee joint stress in movement (16). A number of 26 RCTs evaluating different programs of strengthening work at the onset of knee OA were systematically reviewed and revealed moderate amelioration of physical function, pain and wellbeing (17).

Pharmacologic treatment. Several types of analgesics are used in therapy, their selection depending on multiple factors. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogenous group of substances, chemically unrelated, that have similar therapeutic activities and side effects. In treating OA, NSAIDS administered orally are most frequently indicated, being prescribed to 65% of OA subjects in the US (18). The efficiency of various doses and formulations of nonsteroidal anti-inflammatory medications used in 74 RCTs to relieve OA pain was evaluated in a previous network meta-analysis, revealing diclofenac 150 mg/day as the most efficient treatment for pain relief and physical condition improvement (19). Nevertheless, there are serious cardiovascular, gastrointestinal, and renal risks in oral intake of nonsteroidal anti-inflammatory medications. Daily intake of nonsteroidal anti-inflammatory medications revealed a 4-fold increase in the risk of upper gastrointestinal bleeding, in a 280-RCT meta-analysis, showing a major growth of vascular events by one third when administering a Cox-II inhibitor (20,21). Due to their lower risk compared with oral preparations, topical NSAIDs are widely used for relieving OA pain (22). The use of topical agents is recommended by several guidelines and systematic reviews and meta-analyses indicate ketoprofen and diclofenac topical formulations to be helpful in knee OA therapy (23).

Cox-I and Cox-II are suppressed by nonspecific Cox-inhibitors (diclofenac, ibuprofen, aspirin and meloxicam) with minor selectivity in reducing prostaglandin synthesis. With high affinity for Cox-II, the selective Cox-II inhibitors (rofecoxib, celecoxib and valdecoxib) were approved due to their superior side effect profile, in gastrointestinal endoscopic trials. Compared with other NSAIDs they present reduced side effects with regard to the gastrointestinal tract and were demonstrated to be efficient in reducing OA pain. Relevant data indicate the use of NSAIDs in OA therapy, with efficient results, consistent with high-standard patient-focused evidence. However, there are adverse reactions in the renal, gastrointestinal, and cardiovascular systems that may question the use of NSAIDs in OA treatment. The literature recommends using paracetamol for level A OA, however in relieving pain NSAIDs are more efficient (24).

The efficiency and safety of opioid oral therapy gives rise to concerns. Opioids as well as nonsteroidal anti-inflammatory medicines have similar action in relieving pain in OA patients (23). Medicines obtained from opium, opiates, comprise natural products including codeine, morphine, and several semi-synthetic compounds. Opioids trigger pain control circuits from the midbrain through the rostral ventromedial medullary tract towards the spinal cord dorsal horn and restrain the transfer of nociceptive information from the spinal cord dorsal horn, thus presenting analgesic action. Opiates are categorized as follows: short-acting opioids, long-acting opioids, and partial agonists. All aforementioned categories proved efficient in relieving pain and are supported by level 3 evidence. Nevertheless, their analgesic effect is limited, these drugs producing frequent side effects, severe in certain cases with long term use. Continuous daily intake of opioid analgesics produces tolerance and physical dependence to certain extent (25).

A novel and encouraging option used to trigger injured cartilage regeneration is considered platelet-rich plasma (PRP). PRP, autologous agglomeration of human platelets in a small pool of plasma, comprises several growth factors secreted by platelets, favoring mesenchymal tissue healing. It is helpful in the therapy of articular cartilage degenerative lesions and OA. The efficiency of several types of intraarticular injections for knee OA has been evaluated in numerous studies. Corticosteroids and hyaluronic acid (HA) efficiency in treating painful knee OA was evaluated in systematic research by Rodriguez-Merchan. HA was demonstrated to be more efficient than corticosteroids in reducing pain, as 3-5 weeks of injections with HA had a pain alleviating effect duration of 5-13 weeks while corticosteroids had a pain alleviating effect duration of only 2-3 weeks (26). Randomized clinical research conducted by Raeissadat *et al* compared the long-term effect of intra-articular PRP and HA injections on the clinical results and the wellbeing of patients suffering from knee OA. After 12 months, both groups exhibited significantly improved bodily pain and WOMAC pain score; the PRP group exhibiting better results than the HA group ($P<0.001$) particularly in Kellgren stages 1 and 2. The study revealed the higher efficiency of PRP in alleviating pain in patients suffering from OA (27).

Stem cells are used in sustaining the self-healing process of damaged knee joint cartilage affected by OA. Mesenchymal stem cells (MSC) that split into chondrocytes are present in the joint fluid. The stem cell therapy consists of harvesting PRP and MSC from the patient receiving medical treatment. In order to increase cartilage, buildup MSC are separated through centrifugation and other purification steps included in the process. The existent clinical data on the stem cell therapy efficiency compared with pharmacological therapy for OA are insufficient. Taking into account the current stage of clinical trials concerning autologous stem cell therapy for knee OA, there are concerns about dosing, type of MSC, timing of intervention, mode and route of MSC delivery in clinical trials (28).

4. Surgical treatment

Arthroscopic lavage and debridement. Knee debridement and lavage (rough cartilage shaving or smoothening of the damaged

meniscus) are arthroscopic techniques. Theoretically, OA arthroscopy alleviates symptoms eliminating debris as well as inflammatory cytokines that generate synovitis (29,30). Loose cartilage flaps and torn meniscal parts are eliminated through debridement. The efficiency of arthroscopy in knee OA therapy is questionable (31). There is little evidence for the beneficial results of arthroscopy, although it is extensively used. Moseley *et al* compared arthroscopic lavage and debridement with sham surgery in a controlled trial and the arthroscopic techniques exhibited no advantage over the sham surgery (32,33). The patient selection prior to knee arthroscopy was considered significant by Dervin *et al*. Patients with obvious meniscus damage or cartilage flaps may be candidates for surgery (34).

In another study, arthroscopic debridement was demonstrated to temporary reduce symptoms for middle-aged patients with knee OA (35). There was an increased potential for amelioration in those patients with less advanced arthritis (as evidenced by radiography, less damage to the articular cartilage, and younger age at surgery) (36). Surgery exhibited improved results including short duration of pain and mechanical symptoms and mild to moderate radiographic phases of arthritis (37).

Osteotomies around the knee. In the therapy of unicompartmental OA associated with varus or valgus deformation, the agreed method consists of osteotomies around the knee. This is a procedure used at the beginning of the 19th century (38). Moreover, already frequently performed at the beginning of the 20th century, osteotomies gained recognition following the findings of Gariépy, Jackson, Coventry, Waugh and others, published in the late 1950s and 1960s (39-42). In unicompartmental knee OA, osteotomy became a standard therapy alternative. The Coventry typical osteotomy consisted of closed-wedge valgization, comprising a fibula osteotomy performed near the tibial tuberosity (42). The choice of open-wedge osteotomy without applying bone graft, with no damage risk for the peroneal nerve as well as development of new plates (particularly angular stability plates) determined the orientation towards osteotomy around the knee in the last decade, particularly for younger subjects (43,44). The weightbearing axis of the lower extremity is modified through osteotomies around the knee (45). The affected section is relieved, the weight load being transferred from the damaged area through moderately overcorrecting a varus or valgus axis to alleviate pain and delay the degenerative process and joint replacement (46,47).

Adequate patient selection as well as proper evaluation of all three knee sections are essential for a favorable postoperative outcome (48,49).

Joint Arthroplasty. For the treatment of knee OA, joint arthroplasty is considered to be safe, well-accepted, and also cost-effective. Due to the irreversibility of the procedure, undergoing a joint arthroplasty procedure is advisable only in cases in which different treatment procedures are contraindicated or have failed. The prosthetic components last ~15-20 years whereas the durability of unicompartmental arthroplasties is usually shorter. Considering this aspect, in patients younger than 60, arthroplasties should be avoided if possible. Unloading osteotomy or unicompartmental knee arthroplasty (UKA) may be considered if OA is limited to a single compartment, however, in different situations, total knee arthroplasty (TKA) with or without patellar resurfacing is recommended.

UKA. Following the studies of Marmor, published in the 90s, considerable attention was directed towards UKA (50). When only one section of the knee, the patellofemoral, medial tibiofemoral or lateral compartment, is affected by OA, UKA is recommended. Throughout the most frequent UKA, the medial tibiofemoral section is replaced with two metallic prosthetic devices, and a polyethylene inlay is inserted between them. A lateral compartment kept in good condition in relation to the cartilage and meniscus is the first requirement for successful medial UKA (51). The stability of the prosthesis is conditioned by the intact cruciate ligaments, the implant not being restricted in the sagittal plane (52).

Significant malalignment of the member represents a contraindication. The progression of OA and persisting manifestations may be determined by overcorrection of the contralateral section, which has to be prevented (53). Similarly, clinical inefficiency of the UKA as well as increased probability of revision are linked to under correction (54). A less invasive surgical method is among the benefits of UKA (55). The extensor system is not deteriorated, and the patella is not everted, allowing a faster recovery and earlier release from hospital. It maintains the bone stock, increased physiological function and regular knee kinematics (56). The result and survival associated to medial UKA have been enhanced by using modern surgical methods and implants (55). The durability of the medial UKA is ~10 years fluctuating significantly from 80.2 to 98% (57,58).

TKA. TKA has demonstrated significant effectiveness in the therapy of advanced knee OA, involving several compartments, when usual therapies fail, having as an outcome consistent amelioration in the patient mobility and quality of life (59). At present, it is the first therapy option for end-phase knee OA. Survival rates of up to 98% at 15 years were highlighted as the long-term outcome of TKA (60). Survival rates <76% at 10 years were frequently observed for younger subjects (61). Although TKA is efficient in the therapy of end-phase knee OA, postsurgical pain appears or lasts in one out of eight patients; however, they do not exhibit radiological or clinical malfunctions (62). Infections, femoropatellar problems, stiffness of the knee and loosening of components represent the most serious complications. The comorbidities of patients influence the condition of the knee and the total freedom of movement following surgery (63). Understanding the complications has allowed the treatment to be substantially improved. Subjective factors (related to the patient) in the evaluation of TKA results have proven their importance, and are necessary to consider when patients are advised before TKA. The femoropatellar joint represents a main problem in persistent postoperative pain. Patella resurfacing has not demonstrated efficiency, and the options for using patella resurfacing have not been clearly determined (64,65). The initial noninfectious recommendations for TKA revision continue to be issues concerning the femoropatellar joint and the extensor mechanism (66). To

enhance the results of total knee replacement, in the last few years, improved strategies have been developed, under the influence of or related to occasionally disappointing results. The strategies aforementioned include development of the implant design (anatomic and biomechanical), improvement of the fixation technique, minimally invasive surgery (MIS), intraoperative control with computer-assisted surgery (CAS), and improved instrumentation (67).

5. Conclusions

Although it is among the most common and studied diseases of the knee, OA does not have a defined pathophysiology or a single effective method of treating symptoms and related damage. An effective treatment for patients with knee OA, in the early stages of the disease, is exercise. Different non-surgical procedures have a fluctuating efficiency, the results being determined by numerous factors (equipment, provider, patient) and, based on the particular clinical situation, their use must be carefully selected. Biological fixation is an attractive option to increase the durability of TKA, particularly for young subjects, due to improvements in biotechnologies and biomaterials with increased osteo-conductive characteristics.

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BU, CMV, DMT, AA, OM, TAM and CH searched and selected articles from scientific databases. ACN, TB, JMP and SB made substantial contributions to the conception of the study, and they also drafted the manuscript and were major contributors in writing the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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