

Society for translational medicine-expert consensus on the treatment of osteoarthritis

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Introduction

Osteoarthritis (OA), also known as osteoarthrosis, is the most prevalent form of joint pathology. It is attributed to diverse causes like joint injury, obesity, aging, and genetic predisposition. The result is the degeneration of the articular cartilage, the subchondral bone, and the entire joint organ. The articular cartilage destruction, typical of OA, is associated with joint space narrowing and periarticular hypertrophic changes. Chronic knee pain significantly affects quality of life (1). People suffering from OA are often confused about the management of their condition. Healthcare professionals must provide support and clear advice on the possible ways to regulate symptoms like pain and decreased physical function, which have an impact on self-efficacy and social engagement.

Symptoms and signs (2)

- (I) Pain: pain in the affected joints can occur in the early stage and it is often well localized. The pain tends to worsen with activity but usually is alleviated by rest. Pain and discomfort in the knee joint after prolonged sitting, for example, is an early symptom of knee OA; persistent pain with weightbearing activities and nocturnal pain may occur in severe cases or in the advanced stages; pain intensity is poorly correlated with joint space narrowing (3); ultimately, pain may or may not be triggered by changes in weather.
- (II) Stiffness: joint stiffness or tightness typically occurs after waking up in the morning, although it is relatively mild, lasts for a limited period of time (e.g., 30 minutes), and improves with activity.
- (III) Joint effusion: local inflammation and synovitis often lead to joint effusion, both during the acute exacerbations of OA as well as later in the severe stages of the disease.
- (IV) Tenderness: tissues including muscles and ligaments around the affected joint may suffer from tenderness on palpation.
- (V) Clicking/crepitus: these are usually signs of advanced OA, especially when articular cartilage wear or tear is present. As a result, clicking, catching and crepitus may be heard or felt during joint motion.
- (VI) Limitation of joint movement or function: the affected joints can suffer from various degrees of

reduction in movement, and flexion contractures often occur over time.

- (VII) Joint deformity: in advanced or severe OA cases, joint deformity often occurs due to major osteophyte formation and bony erosion leading to mal-alignment. Varus, valgus and flexion deformities are common in the knee joint.

Radiographic findings (4)

The diagnosis of OA can usually be made on clinical grounds alone. In most cases, standard radiological evaluation can be used to confirm a clinical relevant OA diagnosis. Radiographic evaluation is worldwide used for grading of OA both for research and clinical use. The main radiographic findings include bony hyperplasia at joint margin, osteophyte formation, increased subchondral bone density, and cystic degeneration. In more advanced cases joint space narrowing (or even disappearance) and deformities in the joint alignment may be visible. Modern CT scanning can in some cases be useful as well. However, the sensitivity of X-ray is low to detect the improvement in cartilage remodeling.

MRI

Magnetic Resonance Imaging (MRI) is not a first line diagnostic tool. Nevertheless, it can detect an early degeneration, articular cartilage thinning and destruction, and can also reveal different intra-articular comorbidities, like meniscal tears, ligament injuries, synovial hyperplasia and joint effusion. Moreover, bone edema, associated with OA activity and progression, is detected. T2 sequences, dGEMRIC and sodium MRI offers new possibility of assessing quality & functionality of cartilage tissue. The water content is a reflection of proteoglycan in the extracellular matrix (ECM), and is quantified through these new MRI analyses.

Laboratory tests (5)

Routine and biochemical blood and urine tests typically show normal results. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are within the normal ranges but occasionally may be increased slightly. Serum immune complexes and complements are also normal.

Treatment

General treatment

Exercise therapy (ET) (strongly recommended)

The growing body of evidence has shown that exercise interventions may improve pain, function and quality of life in patients with knee OA (6). Low-intensity aerobic activities are highly recommended: walking and cycling represent first line activities together with swimming and water aerobics. The main purpose of ET is to improve periarticular strength (e.g., quadriceps femoris muscle, hip abductors and external rotators and calf muscles); improving ROM and augmenting proprioception represent other goals of an ET program. In a RCT, it has shown that all modes of aerobic exercise (lower limbs with and without weight bearing and upper limb) combined with resistance training may lead to reduced pain and improved function in mild to moderate knee OA (7,8). Besides, Moderate quality evidence suggests that exercise reduces pain; improves physical function, has small benefits for depression, little or no effect on anxiety. There is low quality evidence that exercise improves self-efficacy and social interaction (9). In the scenario of isolated patellofemoral arthritis, walking (120–140 steps per minute) and cycling are highly recommended since more challenging sports, such as mountain-climbing and stair-climbing, should be avoided. However, assessment and correction of the modifiable risk factors may bring additional treatment effects on pain and function (8). Obese patients and patients with severe, multi-joint arthritis should perform low-load exercises (10-12).

Mind-body intervention—Tai Chi (strongly recommended)

Mind-body intervention are highly recommended. Studies have suggested that mind-body intervention/exercises, particularly the Tai Chi, may be a promising treatment option for patients with KOA. For instance, investigators found that Tai Chi (13-16) a popular mind-body exercises, can significantly reduce KOA pain. Similar finding has also been observed in Baduanjin (15-17), another popular mind-body intervention.

Activities modification (generally recommended)

Weight reduction. The aim of such a program would be to achieve a normal BMI with the goal to reduce the weight being transferred through the joint to reduce symptoms and further joint destruction. A healthy weight loss program should aim for at least 5% of body weight reduction by

its end or to reduce 0.25% of body weight weekly within a 20-week timeframe; at the end of this, the ideal body weight should be maintained through proper exercise and diet (18). Female patients should also avoid wearing high-heeled shoes (19) (*generally recommended*). Patients engaging in high-intensity exercise or heavy physical work should reduce or avoid such exercise or work.

Patient education and supervision (strongly recommended)

Both verbal and written information on OA should be provided for patients and a close connection with them, in terms of scheduled follow-ups, should be established (20,21). Research has found 1a level of evidence for the effect of patient education on pain in knee and hip OA. Education techniques have benefits also in improving function, increasing coping skills, improving psychological outcomes and fewer visits to primary physician and improved quality of life (22-24).

Non-pharmaceutical therapies

Such treatments, including hydrotherapy, thermotherapy, cryotherapy, acupuncture and moxibustion, transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), photobiomodulation therapy (PBMT), and massage have been used because of their capabilities of increasing local blood circulation, alleviating pain and/or inflammation, increasing muscle structure and muscle force, and increasing functionality.

Hydrotherapy/balneotherapy

Hydrotherapy can be applied for multiple-joint OA (*strongly recommended*) and isolated knee OA (*limitedly recommended*). Hydrotherapy is suitable for the treatment of OA and other symptoms similar to OA in multiple joints (25,26). However, its role in treating isolated knee OA remains unclear due to the limitations in multiple study designs and poor overall evidence (27,28).

Thermotherapy (moderately recommended)

Thermotherapy can improve the local blood supply to the joint affected by OA. By increasing collagen fibers, it can improve joint function, increase pain threshold, improve muscle metabolism, and thus achieve an overall analgesic effect. However, thermotherapy may cause increased fluid exudation into the periarticular area and exacerbate the symptoms when used in the acute phase. Therefore, use of

thermotherapy is recommended only in the remission stage of the disease (29,30).

Cryotherapy (moderately recommended)

Cryotherapy can relieve pain by alleviating local inflammation (31,32) and reducing the conduction velocity of nerve impulses (33). It is especially suitable for the treatment of OA in the acute phase.

Acupuncture and moxibustion (strongly recommended)

Many studies have shown that acupuncture and moxibustion can improve knee function and relieve pain (34,35). A recent meta-analysis found that acupuncture had more total effective rate, short-term effective rate, and less adverse reactions than western medicine in treating KOA based on high-quality outcomes (36). In another systematic review on laser Acupuncture, a less commonly used acupuncture modality, indicated that the laser acupuncture can effectively reduce knee pain in patients with KOA at short term, but the effect obtained likely fades away during the subsequent follow-up period (37). Interestingly, a Network Meta-Analysis on efficacy comparison of five different acupuncture methods showed that acupuncture with heat pain (fire needle) or electrical stimulation might produce better improvement in all acupuncture methods to OA of the knee (38). In addition to acupuncture, a recent meta-analysis on moxibustion suggest that it is effective for pain reduction and symptom management in KOA compared to sham moxibustion and oral drugs (39). Therefore, acupuncture, particularly the electroacupuncture, as well as moxibustion are recommended for treatment of OA.

Electrical stimulation and TENS (limitedly recommended)

TENS is a non-pharmacologic and non-invasive peripheral stimulation technique that is used to relieve nociceptive, neuropathic, and musculoskeletal pain (40,41). During TENS pulsed electrical currents are delivered across the intact surface of the skin to activate underlying nerves (42). The goal of conventional TENS is to stimulate selectively large diameter, low threshold non-noxious afferents (A-beta) in dermatomes related to the pain. This should inhibit activity in second order nociceptive transmission neurons in the central nervous system, and is achieved by increasing TENS pulse amplitude to generate a strong, comfortable, non-painful paraesthesia beneath the electrodes (42). However, as shown in six studies with good level of evidence, electrical stimulation and TENS

had no significant effect in alleviating pain, improving function, or strengthening periarticular muscles in OA patients (29,43-45).

NMES (moderately recommended)

NMES can be defined as the application of a series of intermittent electrical stimuli to a group of intramuscular nerve branches that determine visible skeletal muscle contractions with the aim of restoring muscle function (46). The best-evidence analysis showed moderate evidence in favor of NMES alone or combined with exercise for isometric quadriceps strengthening in elderly with OA (47). In addition, there is increasing evidence that NMES has a significant effect on improving periarticular muscles structure and strength (48-51), decreasing pain (52) and improving OA patients' health status (49). As muscle weakness is a risk factor for OA development and progression, improving periarticular muscles structure and function might alleviate joint contact forces, thereby reducing the mechanical risk factor of OA development and/or progression.

PBMT or low-level laser therapy (LLLT) (limitedly recommended)

PBMT, also known as LLLT, is a form of light therapy that utilizes non-ionizing forms of light sources, including lasers, LEDs, and broadband light, in the visible and infrared spectrum. PBMT is a nonthermal process involving endogenous chromophores eliciting photophysical (i.e., linear and nonlinear) and photochemical events at various biological scales. This process results in beneficial therapeutic outcomes including but not limited to the alleviation of pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration (53,54). There is increasing evidence showing positive effects of PBMT in patients with OA. PBMT has been shown to increase knee-extensor muscle activation and knee-extensor torque in elderly with knee OA after an 8-week intervention program (51). PBMT has also been shown to reduce pain in knee OA (55,56) and to improve microcirculation in the irradiated area (55). However, a systematic review and meta-analysis (57) evaluated the effectiveness of PBMT on symptoms and function in patients with knee OA, and concluded that the best available current evidence does not support the effectiveness of PBMT as a therapy for patients with knee OA. Therefore, additional high quality randomized clinical trials need to be performed before a final conclusion can be reached

regarding the use of PBMT to treat OA. Nevertheless, there is new evidence from OA experimental models (58) that PBMT promotes cartilage recovery and reduces the progression or maintenance of spinal cord sensitization, suggesting a potential role of PBMT in reducing cartilage degradation and long-term central sensitization associated with chronic OA (59).

Electromagnetic fields (limitedly recommended)

Current evidence suggests that electromagnetic field may provide moderate benefit for OA sufferers in terms of pain relief (60).

Massage (limitedly recommended)

For non-acute knee and hip OA, massage, combined with multiple exercise techniques, can reduce pain and improve functions (28,58,61). A meta-analysis including 352 patients found low- to moderate-quality evidence that massage can produce greater effect than nonactive therapies in reducing pain and improving certain functional outcomes in patients with arthritis (62).

Mobility assistive devices (moderately recommended)

Mobility assistive devices are designed to reduce weight bearing on the affected joints. Canes, crutches, and other walking aids may be used. Patients should be encouraged to wear soft, flat, thick-soled and casual shoes. It is recommended to use walking aids and auxiliary equipment both at work as well as during activities of daily living. Canes are particularly suitable for patients with isolated knee or hip OA. A cane or crutch may be used by a patient with unilateral limb disease on the contralateral healthy side, whereas a walking frame or a wheeled walker is more suitable for patients with bilateral diseases. Notably, the use of crutches may occasionally cause secondary injuries such as brachial plexus and radial nerve traction injuries, lymphatic carcinogenesis, arteriosclerosis, wrist sprains, and lateral chest wall abrasions (26,63–65). For patients with hip or knee OA, soft, flat, thick-soled, and casual shoes are highly recommended by the current literature (66,67).

Unloading Knee braces, regular knee braces and knee pads (moderately recommended)

According to the type of deformity associated with knee OA (i.e., varus or valgus), corresponding biomechanical interventions are recommended to alter a non-anatomical mechanical axis. For instance, unloading knee braces,

regular knee braces, knee pads, and foot orthoses may be applied to balance the load between the medial and lateral tibial plateau, which have been shown to be effective in reducing pain, joint stiffness, and medications use and dosage (26,68–73).

Lateral wedge insoles (not recommended)

Lateral wedge insoles to correct varus mal-alignment of the knee may be used according to patients' symptoms; however, relevant clinical evidence is still lacking.

Functional diets, herbs and antioxidants supplements

Apart from indirect action of functional foods and herbs that help in reducing body weight and improving OA, there is an increasing interest on the direct and beneficial role of a balanced nutrition on the management of OA (74). Consumption of diets, fruits and herbs rich in antioxidants including vitamin A (Carotenoids), vitamin C (Ascorbate) and Vitamin E (tocopherol) limits damaging effects of reactive oxygen species (ROS) and therefore moderately improves OA (75). Diets rich in vitamin K mainly Phylloquinones (vitamin K1) help in mineralization of bones and cartilage. Herbs from Indian medicine (Ayurvedic) as well as Chinese and Taiwanese herbs like Du-huo-ji-sheng-tang have been reported to have moderate efficacy on OA (76). A recent randomized clinical trial reports the beneficial use of cucumber extracts against Glucosamine-Chondroitin for the reduction of pain intensity and improvement of physical conditions of patients suffering from moderate OA. Fishoil (omega 3) has been recommended for OA patients as well. However, evidence from quality clinical studies are missing despite some support from animal studies (77,78).

Pharmaceutical treatment: when non-pharmaceutical options fail, pharmaceutical treatments should be applied according to the severity of joint pain

Topical medications (strongly recommended)

Before the use of oral medications, topical drug therapy is recommended. Topical drugs include pastes, creams, gel pastes, and ointments, gels, and liniments containing non-steroidal anti-inflammatory drugs (NSAIDs). They can effectively relieve mild and moderate joint pain. Topical NSAIDs to treat OA pain have comparable efficacies to their oral counterparts, having fewer adverse reactions. The combined use of both oral and topical NSAIDs may be considered for patients with severe osteoarthritic pain (79).

Table 1 Evaluation of risk factors of NSAIDs

No.	Patients at high risk of upper gastrointestinal adverse reactions	Patients at high risk of cardiovascular and renal adverse reactions
1	Elderly patients (>65 years)	Elderly patients (>65 years)
2	Long-term use	History of cerebrovascular diseases (history of stroke or transient ischemic attack)
3	Oral use of corticosteroids	History of cardiovascular disease
4	History of peptic ulcer and hemorrhage	History of kidney disease
5	Use of anticoagulants	Co-administration of angiotensin-converting enzyme inhibitors and diuretics
6	History of alcoholism	In the perioperative period of coronary artery bypass grafting (NSAIDs should be avoided)

NSAIDs, non-steroidal anti-inflammatory drugs.

Systemic analgesics (80)

Systemic analgesics may be administered as oral, injection or suppository.

(I) Principles of drug administration:

- ❖ Any potential risk should be assessed before the administration of systemic analgesics, in particular the potential risk of GI bleeding and allergic reactions;
- ❖ The dosing of systemic analgesics should be tailored to the patient's conditions;
- ❖ The minimum effective dose should be used when possible, in order to avoid drug overdose especially in the scenario of concomitant use of similar drugs;
- ❖ After 3 months of treatment, routine blood and stool tests, fecal occult blood test and liver and kidney function tests should be performed in order to detect any abnormalities deriving from the use of a new medication.

(II) Drugs and their usage

- ❖ Nonsteroidal anti-inflammatory drugs (NSAIDs) (strongly recommended): NSAIDs include non-selective NSAIDs and selective COX-2 inhibitors. Efficacy and adverse effects of oral NSAIDs may vary in different patients. Any drugs should be carefully selected by referring to its indications and after assessing any NSAIDs-associated and district related risk factors, including gastrointestinal, liver, kidney, and cardiovascular (*Table 1*). In the scenario of elevated risk factors for gastrointestinal complication risk, selective COX-2 inhibitors should be used. Alternatively, non-selective

NSAIDs combined with H2 receptor antagonists, proton pump inhibitors, misoprostol, or other gastric mucosal protective agents should be used. If the patient is at high risk for developing cardiovascular disease, the use of selective COX-2 inhibitors should be used cautiously. The co-administration of two NSAIDs should be avoided because it does not increase the therapeutic effect but may increase the collateral side effects.

- ❖ Acetaminophen (generally non-recommended): in a recent meta-analysis, acetaminophen was shown to have minimal short-term benefit for people with OA (81). In addition, there is increased concern for acetaminophen toxicity (82).
- ❖ Other analgesics (generally recommended): for OA patients in whom NSAIDs are ineffective or poorly tolerated, tramadol, opioid analgesics, or compound opioid/paracetamol analgesics may be used (83). However, opioid abuse in chronic non-cancer pain is problematic—long-time daily use not to be recommended for OA pain, for most patients (84,85).

Intraarticular injections

(I) Corticosteroids

- ❖ In patients having failed standard NSAIDs treatment, intraarticular injection of glucocorticoids is a feasible (26,85,86) next step treatment, which might achieve significant and fast pain relief. However, long-term use is not recommended, and repeated use should be avoided, as they may become less effective leading to more severe

cartilage destruction. Generally, injection should not be repeated more than 3–4 times annually.

(II) Viscosupplementation

- ❖ The therapeutic efficacy of sodium hyaluronate remains very controversial (83,86–88). It is recommended that viscosupplementation with sodium hyaluronate should be applied in patients who are not responsive.

(III) Growth factors or platelet-rich plasma (PRP)

PRP, i.e., an autologous blood derivative rich in growth factors, may be used for intra-articular injection if the triple injections fail (HA + corticosteroids + lidocaine). A few trials have shown that PRP is superior to placebo in terms of symptomatic relief and functional recovery (89,90). Anyway, currently available randomized controlled trials against viscosupplementation were unable to detect a clear superiority of PRP compared to HA, thus preventing endorsement of this blood-derived product as a first line treatment for OA.

- ❖ Level of evidence: non-recommended.
- ❖ Intra-articular injection of PRP is a relatively new treatment approach, and its long-term efficacy requires further investigations (91–94).

(IV) Mesenchymal stem cell (MSC) therapy (under clinical investigation).

The poor self-healing ability of articular cartilage advocates for triggering regeneration through different pathways, including stem cell therapy. Conventional and current surgical treatment procedures for OA are incapable of reversing the damage of articular cartilage. To overcome these hurdles, cell-based therapies are currently being investigated to repair and regenerate the structure and function of articular tissues. In particular, in clinical practice, the use of MSCs has been tested. MSCs can be obtained from different sources [bone marrow (BM), synovial fat pad, adipose tissue, peripheral blood, placental tissue] and can be concentrated or expanded in laboratory for subsequent intra-articular delivery. The most commonly adopted strategies involve the use of bone marrow concentrate (BMC), bone marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs). In the former case, BM is harvested and concentrated by centrifugation to obtain a product rich in MSCs; in the latter, after a liposuction from the abdominal area or buttocks, the lipoaspirate is treated usually by adding collagenases to digest the ECM and, after filtration or centrifugation, the final output is obtained, containing AD-MSCs together with endothelial cells,

pericytes, macrophages and other cellular types, all playing a therapeutic role within the joint (95).

Compare uncultured concentrated cells, cultured cells include a high-purity stem cells that can fulfill their potential for tissue regeneration, and possess paracrine and immune-modulating effects through growth factor and cytokine release (96). There have been a few clinical trials of OA treatment using cultured autologous peripheral blood stem cells (97), allogenic (98) or autologous (99) BM-derived stem cells, autologous adipose tissue-derived MSCs (AD-MSCs) (100) and allogenic human umbilical cord blood MSCs (101), the results confirmed through meta-analysis a modest improvement in function and pain (WOMAC score) of the knee joint without causing adverse events. Further MRI studies in the long term are needed to demonstrate a reduction in cartilage defects by regeneration of hyaline-like articular cartilage. As Caplan, the father of MSCs mentioned, the stem cell therapy for KOA could be a promising option, while the clinical evidence is lacking so far (102).

Symptomatic slow-acting drugs for OA (SYSADOAs)

This drugs category includes diacerein, glucosamine, avocado soybean, unsaponifiables (ASU) and chondroitin. While it has been shown that they have certain roles in protecting cartilage and relieving symptoms, their clinical treatment efficacy on OA remains very controversial (26,83,87,93,94). For example, in a recent study, pharmaceutical-grade chondroitin sulfate was found to be superior to placebo and similar to celecoxib (103). Nonetheless, methodological issues make it difficult to consider the results to be conclusive (104). Diacerein is an IL-1 inhibitor, and its oral treatment for OA might last up to 3 months.

Antidepressants

Duloxetine can effectively alleviate the persistent pain in OA patients and thus can be used as an oral medication for OA. Notably, it has high incidences of side effects such as nausea and developing dry mouth (26,87,88,91,93–95).

Surgical treatment

High tibial osteotomy for treating knee OA (moderately recommended)

For patients with isolated symptomatic medial or lateral compartment knee OA, osteotomies (e.g., high tibial osteotomy or distal femoral osteotomy) to correct eventual misalignment could be performed, with the aim

of unloading the affected compartment. The results are especially good for medial knee OA and replacement surgery can be delayed following osteotomy (105). Osteotomy was suggested to be considered for younger patients, which could be often combined with arthroscopic procedures if indicated. Furthermore, to protect cartilage, some concurrent procedures may be associated with osteotomy, such as ligaments reconstructions in case of symptomatic instability, meniscal transplantation in case of previous meniscectomy and chondral/osteochondral treatments if focal defects are present. The indication to this specific approach should be carefully evaluated based on the patient's age, gender, occupation, functional requirements, and other factors (88). Arthroscopic surgery alone, including debridement, partial synovectomy and meniscus, was not supported by clinical evidence in the literature. However, Arthroscopic surgery may be beneficial in treating severe mechanical problems or inflammation. Sometimes arthroscopic examination is useful to find the best surgical treatment for the patient as well (106).

Joint replacement surgery

- (I) Total joint replacement (*strongly recommended*)
 - ❖ Joint replacement surgery may be recommended for patients with advanced stages of shoulder, hip, knee, and ankle OA, in whom pain, stiffness, and function have not improved after conservative treatment with medical or non-medical interventions. For patients with persisting or worsening symptoms, associated or not with functional limitation, joint replacement surgery is highly efficient and cost-effective and can significantly improve the patients' quality of life.
- (II) Unicompartmental Knee Replacement (*generally recommended*)
 - ❖ In case of unicompartmental knee OA in stable joints in patients without major axial deviation and no history of rheumatic disease, unicompartmental knee replacement is a feasible and effective treatment option, which allows a faster recovery and less morbidity for the patient.

Joint replacement surgery is rated as a safe and effective procedure for patients with advanced OA (2). However, in the future, infections may be even more problematic than today due to antibiotic resistance. Infections and other risk

factors must always be considered as well.

Conclusions

The diagnosis of OA can be made clinically according to the patient's signs and symptoms, and affirmed with radiological investigations. There are numerous non-operative measures, non-pharmacological and pharmacological, that can help control the patients' symptoms. However, if these should fail, with persistent pain and functional limitation, operative intervention may be an option, but the patient should recognize that this does carry the risks of potential surgery complications.

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Footnote

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