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Clinical expert statement on osteoarthritis: diagnosis and therapeutic choices

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Abstract

Osteoarthritis (OA) is a chronic, progressive disease that affects bones and joint structures. Osteoarthritis is associated with joint pain, cartilage degradation, synovial inflammation, subchondral bone remodeling and osteophyte formation. It mainly impacts the knees, hips, hands, and lumbar spine. Despite its high prevalence, no current treatments can modify the course of OA, with most therapies focused on symptomatic relief. Non-pharmacological approaches such as weight management, exercise, and self-management programs are strongly recommended. Nonsteroidal anti-inflammatory drugs (NSAIDs), both topical and oral, are commonly used but pose risks with long-term use. In contrast, symptomatic slow-acting drugs for OA, such as glucosamine, chondroitin, and avocado-soybean unsaponifiables (ASU), offer a safer alternative, but their effects remain controversial. Newer therapies, including intra-articular glucocorticosteroids, hyaluronic acid, and centrally acting agents such as duloxetine, offer targeted relief. Emerging evidence suggests that ASU may help reduce pain and improve joint function, potentially lowering the need for NSAIDs, with minimal side effects.

Key words: osteoarthritis, symptomatic slow-acting drugs, avocado-soybean unsaponifiables.

Introduction

Osteoarthritis (OA) is a chronic, progressive, heterogeneous disease with various primary and secondary causes. It is one of the most common musculoskeletal disorders, typically affecting the knee, hip, lumbar facet, hand, and temporomandibular joints. It is also one of the major causes of disability [1–3]. Osteoarthritis leads to a gradual deterioration of the structure and function of articular cartilage, especially in middle-aged and older adults [1]. It is associated with chronic pain and various joint issues, including cartilage damage, synovial inflammation, subchondral bone remodeling, and osteophyte formation, resulting in a significant reduction in joint mobility, muscle weakness, and limited active participation in social life [4–7]. The incidence of OA is steadily increasing due to population aging and the global epidemic of obesity, resulting in a significant societal burden and a major public health challenge [2, 8]. Despite high prevalence, there are currently no medical therapies that can modify the course of the disease [2]. Medications recommended by international guidelines for the treatment of OA provide only symptomatic pain relief,

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but their long-term use is associated with significant side effects and toxicity [9, 10]. In addition to medications, the Osteoarthritis Research Society International (OARSI) guidelines recommend dietary weight management (with or without exercise), mind-body exercise, self-management programs, and walking aids [11]. The use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), such as glucosamine, chondroitin, avocado and soybean unsaponifiables (ASU), and diacerein, remains controversial. The 2019 OARSI guidelines conditionally support the use of intra-articular glucocorticosteroids (GCs) and intra-articular hyaluronic acid for the treatment of knee OA [11]. On the other hand, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases strongly recommends pharmaceutical-grade crystalline glucosamine sulfate and chondroitin sulfate as primary SYSADOAs, with diacerein and ASU as alternative options [12].

The pathogenesis and clinical symptoms of osteoarthritis

Osteoarthritis affects the bone, cartilage, synovium, synovial fluid, meniscus, tendons, ligaments, and the joint capsule [13]. In this active disease process, the balance between the destruction (catabolism) and renewal (anabolism) of the extracellular matrix of articular cartilage is disturbed. The characteristic features of OA include the involvement of the entire joint, articular cartilage degradation, bone remodeling, osteoproliferation, and arthrosynovitis. The destruction of articular cartilage and subchondral bone is associated with progressive locomotor disability and pain [14]. Initially, the cartilage surface remains intact due to compensatory mechanisms, but as the disease progresses, changes in the composition and organization of the extracellular matrix occur [1, 15, 16]. Degenerative lesions in the meniscus with loss of type I and II collagen are associated with repetitive mechanical abrasions. On the other hand, cartilage matrix homeostasis is disrupted by proinflammatory cytokines, highlighting the role of inflammation in early OA [17, 18]. Since articular chondrocytes have limited regenerative capacity and low metabolic activity in healthy joints, they temporarily proliferate and differentiate in response to increased matrix synthesis in an attempt to repair damage. Hypertrophic chondrocytes lose their ability to generate new cartilage matrix, which leads to abnormal subchondral bone remodeling at the bone-cartilage interface. Increased protein catabolism creates an imbalance in collagen and proteoglycan synthesis, causing collagen fibers to stop associating with proteoglycans, which in consequence weakens the cartilage and leads to the formation of gaps on its surface. Changes in cartilage composition and structure stimulate chondrocytes to produce more mediators involved in degradation, leading to chondrocyte apoptosis and complete destruction of the articular cartilage [1, 19]. Metalloproteinases released in this process degrade the articular cartilage, which results in the formation of subchondral cysts and osteophytes that stabilize the joint. Moreover, chondrocytes, osteoblasts, and synoviocytes release cytokines such as interleukins (IL) 1, 4, 9, and 13, tumor necrosis factor α (TNF-α), and degradative enzymes (e.g., a disintegrin and metalloproteinase with thrombospondin motifs), initiating further destructive mechanisms [17]. Tumor necrosis factor α stimulates the increased synthesis of IL-6, IL-8, RANTES (regulated upon activation, normal T cell expressed and secreted), and vascular endothelial growth factor, but also the production of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2 synthase, thereby increasing the levels of their respective products [17]. Inflammatory mediators affect surrounding tissues, altering the subchondral bone and synovium. Synovial inflammation induced by cartilage fragments disrupts the synthesis of synovial fluid, reducing its viscosity and elasticity and impairing its ability to lubricate the cartilage. Tissue damage again triggers the release of proinflammatory mediators (IL-1, TNF-α), which stimulate joint protease production. Chronic inflammation sensitizes receptors, leading to further sensitization due to constant stimulation [20]. As a result, even a typical stimulus can trigger pain response. Moreover, the ability of cartilage to repair itself is limited by the low mitotic activity of resident chondrocytes, the absence of blood vessels and nerves, and the lack of mobility [21].

The development of OA is influenced by various risk factors including genetics, race, advanced age, female sex, hypertension, obesity, physical labor, joint malalignment, poor muscle strength, high-intensity exercise, genetic predispositions, and previous joint injuries [22–24]. These systemic and local factors can affect signaling pathways (e.g., Wnt/β-catenin, Ihh, transforming growth factor β [TGF-β], epidermal growth factor receptor, hypoxia-inducible factor, nuclear factor κ-light-chain-enhancer of activated B cells [NF-κB], and Notch) and the regulation of key functional molecules involved in pain transmission and regulation of chondrocyte homeostasis, survival, and death, ultimately leading to joint pain and pathological cartilage modifications within the synovial joint [25, 26]. The immune system is vital for the pathomechanisms of OA, as both humoral and cellular mediators contribute to cartilage degradation, synovitis, abnormal bone remodeling, and joint effusion [27]. The exact pathological mechanisms of OA remain

unknown. Emerging evidence shows alterations in the epigenetic regulation of catabolic and anabolic gene expression in osteoarthritic chondrocytes and highlights the role of various cell death types and the synovial lymphatic system [28].

Clinical signs and symptoms of OA include chronic joint pain, swelling, stiffness, instability, radiographic evidence of joint space narrowing [1], loss of joint function, mild localized inflammation of the synovial membrane (synovitis), and reduced quality of life [1]. Pain associated with joint damage often appears to be the primary symptom that prompts patients with OA to seek medical attention. However, pain does not always correlate with structural changes in the joint tissues [2].

Epidemiology

Osteoarthritis is the most common joint disorder, affecting more than 7% of the global population (528 million people), with a higher prevalence reported in developed countries (14% in the United States) [29, 30]. It is also the fifteenth leading cause of years lived with disability (YLDs) worldwide, accounting for 2.2% of total YLDs in 2019 [29]. Osteoarthritis predominantly affects the knee (365 million cases, 61% of YLDs lost due to OA), hand (142 million cases, 24% of YLDs), and hip (33 million cases, 5.5% of YLDs) [29, 31, 32].

Osteoarthritis has a significant economic impact, with costs borne by patients, their families, healthcare systems, employers, social security, and national budgets [30]. Direct costs include prescription and over-the-counter drugs, doctor visits, diagnostic tests, hospitalizations, endoprostheses, rehabilitation, and adaptive equipment for disabled individuals (stabilizers, canes, walkers). As much as 37% of these costs are covered by patients. On the other hand, indirect costs are higher and are associated with informal caregiver assistance (60%), loss of workplace productivity (31%), absenteeism (time away from work due to health-related issues), presenteeism (reduced productivity while at work), other caregiver expenses (9%), and early retirement and disability [33, 34]. The cost of OA treatment is also affected by psychosocial and work-related factors, because in addition to pain, patients may experience disability, depression, family and social challenges, job loss, and economic strain [30]. Moreover, patients pay for the treatment of drug side effects such as stomach ulcers, perforations, and gastrointestinal bleeding, often requiring hospitalization [35]. Due to its high prevalence, OA is associated with a significant reduction in quality of life and financial costs worldwide [30]. Therefore, efforts to develop new treatments, such as disease-modifying drugs and community-based interventions, may help mitigate some of the quality of life and productivity losses associated with OA [30].

Diagnosis

Although OA has a high prevalence, its diagnosis can be challenging because there is no single sign, symptom, or test that can identify the disease. Instead, the diagnosis is based on several factors, including the patient's age, medical history, and symptoms [36, 37]. Osteoarthritis can be diagnosed based on pathological and radiographic findings as well as clinical symptoms, depending on the qualitative and quantitative nature of the analyzed joint. The diagnosis is usually made on the basis of the following clinical symptoms: knee pain on most days in the previous month, osteophytes of the joint margins on radiography, synovial fluid findings typical for OA, patient age ≥ 40 years, morning stiffness ≤ 30 minutes, and crepitus on active joint movement, or radiographic, ultrasound or magnetic resonance imaging (MRI) findings in the presence of an atypical clinical picture [38]. In the case of advanced changes in several joints, the clinical picture becomes more diverse in functional terms. The physical examination focuses on the presence of swelling, crepitus, limited range of motion, joint tenderness, and mild inflammation. Other indicators include muscle weakness, first around the joint and then elsewhere a given kinematic chain, as well as joint instability, deformity, bony lumps, unequal leg lengths, and altered gait [39].

In knee OA, symptoms often include pain, especially when going downstairs or during weight-bearing activities, with morning stiffness lasting less than 30 minutes. In the advanced stages of the disease, hard bony enlargement and crepitus may be observed [37]. Another red flag is the presence of knee effusion. Patients with such suspicion require puncture and drainage with fluid analysis, followed by referral to a specialist for further evaluation. Radiography (A-P view) is used to confirm the diagnosis by showing joint space narrowing, increased sclerosis of the acetabular roof, and osteophytes. On the other hand, hip OA presents with hip pain and radiographic findings of joint space narrowing or osteophytes [36]. Additional diagnostic criteria may include the presence of an architectural defect in patients aged ≤ 50 years, the absence of morphological abnormalities on plain radiographs, initial limited internal hip rotation, morning stiffness of short duration, and age over 50 years. For hand and finger OA, symptoms include pain, visible bony enlargement, and family history. Radiographic evidence shows osteophytes and sometimes joint space narrowing [36].

Radiographic methods are applied to assess cartilage degeneration and skeletal changes using the semi-

quantitative Kellgren-Lawrence score, Ahlbäck classification, and Knee Osteoarthritis Grading System [40]. The Kellgren-Lawrence score is the most popular and has been used for over 40 years also in clinical trials. In this grading system, OA is scored on a scale of 0 to 4 based on the presence of definite osteophytes (grade ≥ 2) or, in more severe grades, the progressive occurrence of joint space narrowing, sclerosis, cysts, and deformity [31]. However, not all patients with radiographic evidence of OA show clinical symptoms, and not all patients with joint symptoms have radiographic features of OA. Therefore, the diagnosis of OA requires a combination of pathological, clinical, and radiological methods [40].

When assessing joint pain, there are several serious pathologies that need to be excluded because they may require urgent care or a different approach to treatment [41]. Part of this process involves differentiating OA from other types of arthritis and determining whether a patient has primary OA or secondary OA associated with another disease or condition. Rheumatoid arthritis, gout, and lupus can mimic the symptoms of OA [42]. Infections (meningism, fever, history of immunosuppression or intravenous drug use) should be excluded based on radiography, MRI, and complete blood count, while inflammatory arthritis (rheumatoid arthritis, giant cell arthritis, polymyalgia rheumatica) should be excluded based on blood tests for erythrocyte sedimentation rate, C-reactive protein, and rheumatological markers as well as rheumatology consultation [41]. For accurate diagnosis of OA and appropriate treatment, falls resulting in fractures should also be excluded, especially in patients with concomitant osteoporosis or evidence of a tumor. If fractures are suspected, recommended tests include radiography and computed tomography, as well as referral to an orthopedic surgeon to confirm the diagnosis. On the other hand, when a tumor is suspected, especially in patients with a history of cancer, unexplained weight loss, significant night pain, or severe fatigue, radiography and MRI are necessary to exclude the diagnosis [41]. In addition, abnormal intensity and/or duration of hip pain may indicate the presence of rapidly destructive coxarthrosis or a subchondral bone microfracture, which are both considered red flags for hip OA [36]. On the other hand, red flags for hand and finger OA include the involvement of several joints, swelling, joint pain that occurs at rest and during movement, even without exertion, and the presence of psoriasis. These symptoms require referral to a specialist. In the absence of red flags, a clinical examination should be performed to determine the location of pain and the presence of any deformity. Finally, laboratory tests help exclude other diseases and assess inflammatory markers to confirm systemic inflammation, while synovial fluid analysis can determine the cause of joint swelling [39, 40].

If patients report joint pain at rest and during movement that lasts more than 6 weeks or is unresponsive to treatment, the assessment of psychosocial risk factors for developing chronicity (yellow flags) should be considered [42]. The presence of psychosocial risk factors can have a significant impact on diagnosis and management. Individuals with such risk factors will benefit from reassurance and education to reduce the risk of chronicity. Psychosocial risk factors should be reassessed after 6 weeks of treatment [42].

Treatment

Regardless of the socioeconomic factors, several recommended rehabilitation and pharmacotherapeutic interventions – focused on pain relief, reducing stiffness, maintaining functionality, and improving quality of life – make it possible to consider surgery as a last resort [43]. Available therapies allow effective use of joint function at a certain level of damage based on its functional potential. Several guidelines have been developed, including by the OARSI, the American College of Rheumatology (ACR), and the American Academy of Orthopedic Surgeons, to standardize and recommend optimal treatments for OA [11, 44–46]. These guidelines cover a range of nonpharmacological and pharmacological options [40]. Comprehensive management of OA includes educational, psychosocial, behavioral, and physical interventions, as well as oral, topical, or intra-articular medications [11, 44–46]. Treatment decisions should be based on the patient's beliefs, preferences, medical condition, and presence of comorbidities (e.g., gastrointestinal bleeding risk, hypertension, and cardiovascular disease) that may affect treatment choice and risk of side effects [47]. The assessment of the effectiveness of rehabilitation and treatment for patients with OA should be based on pain reduction, reduction of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), reduction of stiffness, and overall improvement in joint function and mobility, as well as improvement in quality of life. Figure 1 shows nonpharmacological and pharmacological treatment in patients with OA.

Nonpharmacological treatment

The most recent (2019) ACR guidelines recommend exercise, tai chi, and self-management programs as initial treatments [47]. Exercise is strongly recommended for patients with knee, hip, and hand OA, with the strongest evidence for effectiveness in knee and hip OA. Although aerobic exercise has been the most widely studied, no specific type of exercise appears to be superior. In addition, the best frequency, duration, and intensity of exercise have not been established. Specific

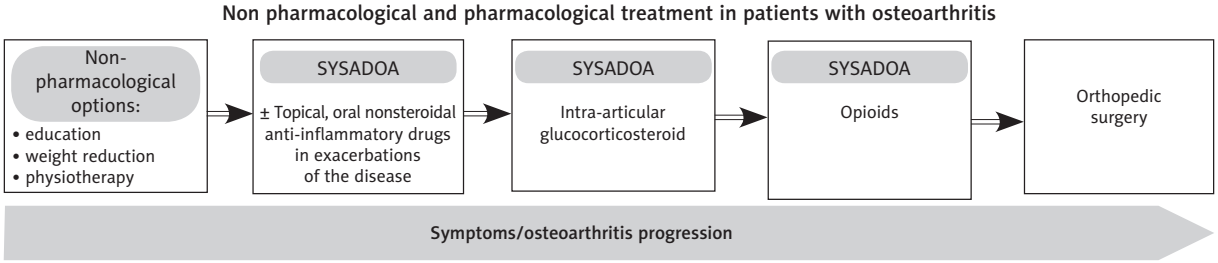

Fig. 1. Nonpharmacological and pharmacological treatment in patients with osteoarthritis. Treatment options are presented hierarchically, with subsequent steps introduced if previous interventions are ineffective. Arrows indicate the flow of treatment progression based on patient response.

SYSADOA – symptomatic slow-acting drug.

exercises such as strengthening with isokinetic weight machines or resistance training, neuromuscular training for muscle weakness and functional instability, and aquatic exercises for joint motion and aerobic fitness are all beneficial. However, although aquatic exercise appears to be beneficial, it is recommended conditionally due to issues with accessibility, cost, and risk of injury in frail patients [11]. For polyarticular OA, structured land-based exercise and arthritis education are core interventions. Supervised exercise programs, often led by physical therapists, are more effective, especially when combined with self-efficacy and weight loss programs. The ACR also strongly recommends the traditional Chinese mind-body practice of tai chi for patients with knee and/or hip OA. The benefits of tai chi, which stem from a holistic impact on balance, strength, fall prevention, self-efficacy, and depression, last for at least 24 weeks. In contrast, the effects of physical exercise may last for up to one year [47].

Weight loss is another strong recommendation from the ACR for overweight or obese patients with knee and/or hip OA. Even a 5% weight loss significantly improves knee and hip pain, and the benefits increase with increasing weight loss [47]. In contrast, according to the OARSI guidelines, dietary weight management is unlikely to significantly reduce hip OA symptoms, but may be recommended as part of a healthy lifestyle for patients with a body mass index of 30 kg/m^2 or higher [11]. Dietary weight management is conditionally recommended for patients with polyarticular OA without comorbidities, or with gastrointestinal or cardiovascular disease, or with widespread pain or depression, but not for frail individuals [11]. Moreover, structured land-based exercise, combined dietary weight management and exercise, and mind-body exercises such as tai chi and yoga are recommended for patients with knee OA and considered effective and safe regardless of comorbidities. Mind-body exercises (tai chi or yoga) are conditionally recommended by the OARSI for hip OA irrespective of comorbidities, given their proven efficacy and safety in patients with knee OA [11]. On the other hand, balance exercises, yoga (for knee OA), and cognitive behavioral therapy (for knee, hip, and/or hand OA) are conditionally recommended by the ACR for the management of OA symptoms [47]. Self-management activities focused on positive thinking, problem solving, goal setting, education about the disease, joint protection strategies, fitness and exercise methods and objectives, and the benefits and side effects of medications are also strongly recommended for patients with knee, hip, and/or hand OA [47]. According to the OARSI guidelines, education about OA should be part of standard care, and clinicians should provide ongoing information about disease progression and self-care while promoting optimism about treatment outcomes [11].

Cane use is highly recommended for ambulation and joint stability in patients with knee and/or hip OA. In addition, the ACR recommends specific treatments for specific joints, such as tibiofemoral knee braces, which limit pain and improve walking speed in patients with knee OA, or hand orthoses, which reduce pain and enhance function in the first carpometacarpal joint affected by OA [47]. Other interventions such as patellofemoral braces, hand orthoses, kinesiotaping, acupuncture, thermal therapies, paraffin, and radiofrequency ablation are also conditionally recommended based on individual patient needs and preferences [47].

Nonpharmacological treatment options for various forms of OA according to the OARSI and ACR guidelines are presented in Table I.

Pharmacotherapy

Nonsteroidal anti-inflammatory drugs, used topically or systemically, are the basis of pharmacotherapy for OA. Topical NSAIDs should be used before oral NSAIDs, based on the principle that medications with minimal systemic exposure are preferable [48]. Topical NSAIDs are strongly recommended for patients with knee OA and no comorbidities, or for those with concomitant gastrointestinal or cardiovascular comorbidities and

Table I. Nonpharmacological treatment options for various forms of OA according to OARSI and ACR guidelines (adapted from [11, 47])

Treatment/ guideline	Hand OA	Knee OA		Hip OA		Generalized OA
	ACR	OARSI[a]	ACR	OARSI[a]	ACR	OARSI[a]
Physical exercises	Strongly recommended	Basic treatment	Strongly recommended	Basic treatment	Strongly recommended	Basic treatment
Balance exercises	–	Basic treatment	Conditional recommendation	Basic treatment	Conditional recommendation	Basic treatment
Weight control	–	Basic treatment	Strongly recommended	3/4[b]	Strongly recommended	1B/3/4[c]
Self-management and self-control programs	Strongly recommended	1B	Strongly recommended	1B/2	Strongly recommended	1B
Tai chi	–	Basic treatment	Strongly recommended	1B	Strongly recommended	1B[d]
Yoga	–	Basic treatment	Conditional recommendation	1B	–	1B[d]
Cognitive-behavioral therapy	Conditional recommendation	1B	Conditional recommendation	2/4[e]	Conditional recommendation	3/4[f]
Cane	–	1B	Strongly recommended	1B	Strongly recommended	1B[g]
Orthosis of the first carpometacarpal joint	Strongly recommended	–	–	–	–	–
Orthoses for other joints of the hand	Conditional recommendation	–	–	–	–	–
Tibiofemoral brace	–	1B	Strongly recommended	–	–	–
Patellofemoral brace	1B	Conditional recommendation	–	–	–	–
Kinesiotaping	(I CMC joint) Conditional recommendation	–	Conditional recommendation	–	–	–
Acupuncture	Conditional recommendation	4	Conditional recommendation	4	Conditional recommendation	4
Radioablation	–	–	Conditional recommendation	–	–	–
Thermal treatments	Conditional recommendation	–	Conditional recommendation	4	Conditional recommendation	4 (warmth)
Paraffin treatments	Conditional recommendation	–	–	–	–	–

[a] *Categories of recommendations in the OARSI guidelines: strong positive recommendations (level 1A), positive conditional recommendations (level 1B and 2), conditional (level 3), and negative recommendations (level 4).*
[b] *Conditional recommendation (level 3), except for patients with frailty, in whom the recommendation is negative (level 4).*
[c] *Weight loss in combination with or without physical exercise was conditionally recommended in all patients with generalized OA, except patients with frailty syndrome, in whom weight control without exercise is a level 3 recommendation and with exercise is a level 4 negative recommendation.*
[d] *The recommendations cover mind-body techniques in general.*
[e] *Positive (conditional) recommendation only in patients with generalized pain or depression (level 2).*
[f] *Conditional recommendation (level 3) in all patients except those without comorbidities, in whom the recommendation is level 4.*
[g] *Refers to gait aids in general.*
ACR – American College of Rheumatology, OA – osteoarthritis, OARSI – Osteoarthritis Research Society International.

frailty, due to their modest benefit and minimal and mild adverse effects (primarily minor, transient local skin reactions) [11]. The ARC guidelines also conditionally recommend topical NSAIDs for patients with hand OA [47]. However, their use in hip OA is unlikely to be effective due to the depth of the joint under the skin [47].

Oral nonselective NSAIDs are conditionally recommended by the OARSI guidelines for patients with hip

OA or polyarticular OA without comorbidities and for patients with widespread pain and/or depression, as well as for individuals with knee OA without comorbidities. They are also recommended for patients with gastrointestinal comorbidities in combination with proton pump inhibitors or selective COX-2 inhibitors due to their beneficial effect on pain and functional outcomes [11]. However, oral NSAIDs are not recommended for patients with frailty and those with cardiovascular comorbidities due to increased cardiovascular risk [49–52]. On the other hand, the ACR guidelines strongly recommend oral NSAIDs for knee, hip, and hand OA, as they are the primary pharmacological treatment with proven short-term efficacy in numerous trials. When oral NSAIDs are used despite potential risks, they should be administered at the lowest possible dose for the shortest duration, ideally with proton pump inhibitors to provide gastric protection [11]. Moreover, patients should be monitored for potential adverse gastrointestinal, cardiovascular, and renal effects [47].

The chronic use of NSAIDs is associated with a risk of kidney failure due to nephrotoxicity. In addition, NSAID use is linked to hemostatic disorders, liver function impairment, porphyria, water and electrolyte disorders, and high risk of thromboembolic events. Acute and chronic use may also cause gastrointestinal toxicity, and acute use may lead to hematologic toxicity [53]. However, in certain situations, clinicians must weigh these risks against therapeutic necessity and accept the potential for complications. Nonsteroidal anti-inflammatory drugs should be used with caution in elderly patients due to possible drug interactions and adverse effects. Caution is also advised in individuals with cancer and other serious life-threatening medical conditions due to a higher risk of gastrointestinal bleeding and opportunistic infections that may go undetected in the early stages due to fever suppression [53]. Moreover, NSAIDs should be avoided during the third trimester of pregnancy, because they can adversely affect uteroplacental blood flow and fetal kidney function and cause premature closure of the ductus arteriosus [54].

Acetaminophen is conditionally recommended for knee, hip, and hand OA, although its effectiveness is limited and may be no better than placebo in the long term [47]. Regular monitoring for hepatotoxicity is required, especially at the maximum daily dose of 3 g. Duloxetine is also conditionally recommended for knee, hip, and hand OA, with effects likely to be similar across these joints [47].

Intra-articular GCs are strongly recommended by the ACR for knee and hip OA under ultrasound guidance and conditionally recommended for hand OA (due to a lack of specific evidence). However, the optimal preparation or dosage has not been specified [47]. On the other hand, intra-articular GCs are only conditionally recommended by the OARSI for acute (1–2 weeks) or short-term (4–6 weeks) use for pain relief [11]. For longer-term symptom improvement lasting over 12 weeks, intra-articular hyaluronan is conditionally recommended due to its favorable safety profile [11]. Intra-articular hyaluronic acid injections are conditionally recommended against for knee and first carpometacarpal joint OA and strongly recommended against for hip OA [47]. In general, intra-articular GCs injections are conditionally recommended over other intraarticular treatments, such as hyaluronic acid, due to higher-quality evidence supporting their efficacy [47]. Concerns have been raised about potential cartilage loss from certain GCs preparations or frequent injections, but the clinical significance remains unclear [47, 55].

A range of centrally acting agents, including pregabalin, gabapentin, serotonin norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants, are used in managing chronic pain, but only duloxetine has gained enough evidence to be recommended for OA. Duloxetine in monotherapy or in combination with NSAIDs shows efficacy in treating OA; however, due to tolerability issues and side effects, no recommendations have been made for other centrally acting agents [47].

Tramadol is conditionally recommended by the ACR for patients with knee, hip, and hand OA, as recent studies demonstrated modest benefits in long-term management of non-cancer pain (3 months to 1 year) [47, 56]. Tramadol or other opioids may be appropriate for patients with OA when NSAIDs are contraindicated, other therapies are ineffective, or surgery is not an option [47]. Tramadol is conditionally recommended over non-tramadol opioids, which are generally recommended for patients with knee, hand, and/or hip OA. However, such opioids may be used when alternatives have been exhausted. Due to high risk of toxicity and dependence, opioid therapy is recommended at the lowest possible dose for the shortest possible duration [47].

In the ACR guidelines, topical capsaicin is conditionally recommended for knee OA due to small effect sizes. However, it is not recommended for hand OA due to the lack of direct evidence and the risk of eye contamination and for hip OA due to the depth of the joint under the skin. Similarly, intra-articular botulinum toxin injections and prolotherapy are conditionally recommended against for knee and hip OA. Platelet-rich plasma and stem cell injections are strongly recommended against for knee and hip OA. Tumor necrosis factor inhibitors and IL-1 receptor antagonists are also strongly recommended against for knee, hip, and hand OA [47].

Colchicine, fish oil, and vitamin D are conditionally recommended against for OA [47]. Limited studies sug-

gest minimal benefits and potential adverse effects of colchicine. Fish oil, despite its popularity, lacks evidence of efficacy in OA, while vitamin D trials show small or no effects on OA symptoms. Moreover, bisphosphonates, glucosamine, methotrexate, and hydroxychloroquine are strongly recommended against in knee, hip, and hand OA.

Slow-acting drugs for osteoarthritis

Symptomatic slow-acting drugs in OA (SYSADOAs) include ASU, glucosamine sulfate, chondroitin sulfate, diacerein, and similar compounds. Chondroitin sulfate is strongly recommended against in knee and hip OA, but conditionally recommended for patients with hand OA [47]. Compared with NSAIDs, SYSADOAs are not only safer but also offer comparable symptomatic relief and superior efficacy in modifying OA structure [57]. Injections of hyaluronic acid into the joints are aimed at improving the viscosity and elasticity of synovial fluid, resulting in reduced pain and increased joint mobility [58]. However, there are currently no clear data confirming the effectiveness of intra-articular hyaluronic acid injections for OA, while there is stronger evidence for ASU.

Avocado-soybean unsaponifiables are obtained from the unsaponifiable residues of avocado and soybean oils, mixed in a 1 : 2 ratio. They are produced in France under the brand name Piascledine [59]. This product has a unique composition characterized by the presence of alkyl furans, alkyl triols, and squalene, among others [60]. It is becoming a valuable component of connective tissue treatment, particularly for OA, due to its favorable activity and low risk of side effects. Avocado-soybean unsaponifiables have been demonstrated to improve the quality of life of OA patients by relieving pain, increasing joint mobility, and reducing inflammation. Preclinical studies have shown that ASU exert chondroprotective, anabolic (by promoting the synthesis of cartilage extracellular matrix molecules), and anticatabolic (by reducing the degradation of matrix components) effects [61, 62]. The chondroprotective effect is associated with the preservation of glycosaminoglycan and hydroxyproline content in a model of cartilage destruction [63]. In the culture of human articular chondrocytes stimulated with IL-1β, ASU hampered the production of several inflammatory mediators, including IL-6, IL-8, and macrophage inflammatory protein-1β, and suppressed *COX-2* and *iNOS* gene expression [64, 65]. Moreover, ASU were found to stimulate collagen synthesis in articular chondrocytes, to partially counteract the harmful effects of IL-1β on synovial cells and rabbit articular chondrocytes, and to inhibit IL-1β stimulation of stromelysin and collagenase [64, 66, 67].

Studies have demonstrated that ASU-related anti-inflammatory effects extend beyond chondrocytes and fibroblasts to monocyte/macrophage-like cells [68, 69]. By modulating the proinflammatory response in synovial macrophages and other cell types involved in joint inflammation in OA, ASU can help reduce inflammation at different sites within the joints affected by OA [68]. The ability of ASU to downregulate the gene expression of IL-1β and TNF-α in chondrocytes and monocytes indicates their potential to slow the process of cartilage degradation. By reducing matrix metalloproteinases (MMPs) 2 and 3 and increasing tissue inhibitors of metalloproteinase levels, ASU can reverse the catabolic effects of IL-1β in human fibroblasts [70]. This action helps prevent cartilage matrix degradation by inhibiting collagenase production in synovial cells. Specifically, MMP-3 degrades proteoglycan, fibronectin, and various collagens and activates other metalloproteinases, thus playing a significant role in cartilage destruction. Avocado-soybean unsaponifiables also enhance plasminogen activator inhibitor-1 expression, preventing the conversion of plasminogen to plasmin, which is involved in the activation of metalloproteinases [60–62, 65]. In addition, ASU show anabolic effects on cartilage metabolism, restoring aggrecan synthesis and increasing the expression of TGF-β isoforms, TGF-β1 and TGF-β2, in IL-1β-stimulated chondrocytes and plasminogen activator inhibitor-1 in normal chondrocytes [65, 71]. These factors stimulate proteoglycan and collagen synthesis in chondrocytes and inhibit cartilage destruction by IL-1.

Numerous clinical studies have demonstrated the benefits of ASU in OA treatment, including a significant reduction in supplemental NSAID use, pain, and functional impairment in patients with knee and hip OA [72–75]. Two randomized, double-blind, placebo-controlled studies have confirmed the efficacy and safety of ASU (Piascledine) in the treatment of knee and hip OA [73, 74]. In these studies, a daily dose of 300 mg of ASU compared with placebo significantly reduced NSAID intake, with patients reporting fewer days on which they needed pain medication. On the other hand, an open prospective observational study conducted in Poland and involving over 4,000 patients with varying OA severity reported a gradual improvement in functional performance and pain reduction over 6 months [76]. Median rest pain (Visual Analogue Scale score) decreased from 1.8 at visit 0 to 0 at visit 3. The percentage of patients taking analgesics or anti-inflammatory drugs decreased by 58% after 6 months of treatment. Moreover, approximately 50% of participants reported no pain by the end of the study. The number of patients requiring regular use of analgesics and NSAIDs also decreased, and no serious side effects were noted. Mild to moderate gastrointestinal disorders, such as diarrhea, nausea, flatulence, or abdominal pain, were the most common adverse effects, observed only in a few patients [76].

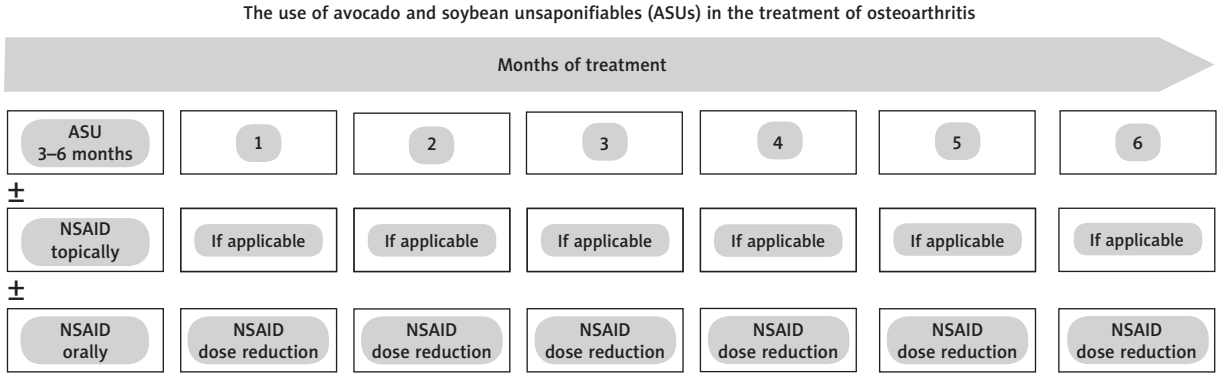

Fig. 2. The use of avocado and soybean unsaponifiables (ASU) in the treatment of osteoarthritis.

ASU – avocado and soybean unsaponifiables, NSAID – nonsteroidal anti-inflammatory drug.

In another study, only 43% of patients taking Piascledine continued to take NSAIDs at day 90, compared with 70% in the placebo group ($p < 0.001$). Moreover, the mean cumulative NSAID dose between days 45 and 90 was significantly lower in the Piascledine group compared with the placebo group (372 ±742 mg and 814 ±1.026 mg, respectively; $p < 0.01$) [73]. Similarly, Appelboom et al. [74] observed that the amount of analgesics taken decreased nearly 3-fold in the Piascledine group, from 143 ±48 mg diclofenac equivalent [mg dicl eq] on day 0 to 45 ±52 mg dicl eq on day 90 (whereas in the placebo group it decreased from 136 ±55 to 81 ±63 mg dicl eq).

Another study also demonstrated an improvement in overall functional disability (based on the Lequesne functional index), with significant effects visible after 2 months of treatment and persisting for 2 months after treatment [75]. Another randomized, double-blind, placebo-controlled study suggested that ASU might reduce the progression of joint space narrowing, implying its structure-modifying effect [77]. Another large randomized controlled trial including 399 patients with hip OA showed that 3-year ASU-E treatment reduced radiological progression assessed on the basis of measuring joint space width, which implied a structure-modifying effect [78]. Since the benefits of ASU persisted for 8 months after treatment, it appears that it has the potential as a symptomatic slow-acting drug for OA [75]. The results of clinical studies confirm that ASU effectively reduce pain and improve joint function in OA patients, while decreasing the need for NSAIDs, thereby minimizing associated risks. However, patients should be informed of potential allergic reactions and liver complications. Particular caution should be exercised in patients with previous or current hepatic or biliary dysfunction or with conditions that may increase the risk of gallstones or liver damage, as well as in patients taking concomitant anticoagulants due to the rare risk of thrombocytopenia [79]. Figure 2 shows use of ASU in the treatment of OA.

Summary

The prevalence of OA is increasing worldwide due to population aging and the obesity epidemic, posing a major public health challenge and significant economic burden. Current treatments only provide symptomatic relief, often leading to side effects and high healthcare costs, including direct expenses for medications, doctor visits, and surgery, as well as indirect costs from lost productivity and caregiver support. The ACR and OARSI guidelines recommend various nonpharmacological strategies such as exercise, tai chi, and weight management, as well as pharmacological therapies including oral NSAIDs for pain relief, but used with caution due to potential adverse effects. It appears that an ASU with chondroprotective and anti-inflammatory properties shows promise in relieving pain, improving joint function, and reducing NSAID use in patients with knee and hip OA, with only mild and infrequent side effects.

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Conflict of interest: Piotr Leszczyński – cooperation with Angelini Pharma Polska, Sandoz, Berlin-Chemie, KRKA, Reig Jofre, Mylan. Przemysław Lisiński – cooperation with Angelini Pharma Polska. Brygida Kwiatkowska – cooperation with Angelini Pharma Polska, BK KRKA, Sandoz. Tomasz Blicharski – cooperation with Angelini Pharma Polska. Jarosław Drobnik – cooperation with Angelini Pharma Polska. Katarzyna Pawlak-Buś – cooperation with Angelini Pharma Polska, Sandoz, Berlin-Chemie, KRKA, Reig Jofre, Mylan.

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