European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2024; 28: 4080-4104

Unraveling the joints: a narrative review of osteoarthritis

F. PUNTILLO[1], M. GIGLIO[1], A. CORRIERO[1], S. COACCIOLI[2], D.M.M. FORNASARI[3], G. IOLASCON[4], N. LUXARDO[5], S. SARDO[6], A. PALADINI[7], V. SCHWEIGER[8], D. TISO[9], G. FINCO[6]

[1]Department of Interdisciplinary Medicine, ICU Section, University of Bari Aldo Moro, Bari, Italy
[2]European League Against Pain (EuLAP) Zurich, Switzerland
[3]Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Italy
[4]Department of Medical and Surgical Specialties and Dentistry, University of Campania "Luigi Vanvitelli", Caserta, Italy
[5]Department of Surgery, Pain Therapy Centre, ASL Citta di Torino, Ospedale Oftalmico, Turin, Italy
[6]Department of Medical Sciences and Public Health, University of Cagliari, Monserrato, Italy
[7]Department of MESVA, University of L'Aquila, L'Aquila, Italy
[8]Department of Surgery, Odontostomatology and Maternal Sciences, Pain Therapy Centre, Verona University Hospital, Policlinico GB Rossi, Verona, Italy
[9]Department of Nutrition, "Villa Maria" Hospital, Rimini, Italy

ABSTRACT. **– Osteoarthritis (OA) is a chronic and progressive degenerative disease that affects joint structures, such as the hips, knees, and hands, involving the articular cartilage, subchondral bone, ligaments, capsule, and synovium. OA is characterized by a progressive degeneration of the joint structures, resulting in pain and decreased quality of life. Local and systemic risk factors pave the way for OA development. Different phenotypes may be identified, but three main molecular mechanisms define the endotypes: the bone-driven endotype, the synovitis-driven endotype, and the cartilage-driven endotype.**

The hallmark of OA pathophysiology involves more than just mechanical degradation; it includes the release of pro-inflammatory mediators, such as interleukins and TNF-α, which elucidates the significant roles of metabolic syndrome, diabetes, and cellular senescence in its development. OA is distinguished by a clinical presentation that varies significantly between people and is marked by pain, stiffness, and functional impairments. The clinical course can be split into Pre-OA, Early OA, Evident OA, and End-Stage.

Depending on the stage of the disease, OA diagnosis frequently necessitates a complex strategy that combines clinical evaluation to detect joint tenderness, range of motion, and joint swelling or abnormalities, medical history assessment, imaging modalities, and laboratory investigations.

There is no known treatment for OA, and different therapies are usually evaluated based on the stage of the disease to minimize pain and stiffness while maintaining joint function. Treatments are divided into the reduction of modifiable risk factors, pharmacologic therapies, rehabilitation, complementary therapies, interventional pain procedures, and surgery. OA clinical heterogeneity underlines the importance of prevention, early diagnosis, and identifying the phenotype and endotype to tailor the treatment.

Key Words:
Osteoarthritis, Diabetes, Knee osteoarthritis, Hip osteoarthritis, DMOADs, NSAID, Steroids, Total hip replacement.

Introduction

Osteoarthritis (OA) is a chronic and progressive degenerative disease that affects joint structures, including articular cartilage, subchondral bone, ligaments, capsule, and synovium[1]. It is the most prevalent form of arthritis and a major cause of pain and disability in middle age and the elderly[2], with a global prevalence of 596 million[3].

The degradation of articular cartilage structure and function is a significant hallmark of OA[4,5], along with alterations in bone structure and synovitis resulting in clinical complaints, such as joint pain and limitation in mobility, social participation, and poor quality of life[4].

Corresponding Authors: F. Puntillo, MD; e-mail: filomena.puntillo@uniba.it; A. Corriero, MD; e-mail: alberto.corriero@gmail.com

Over the years, the knowledge about OA has evolved significantly towards new concepts of OA phenotypes[6] and endotypes[7]. The difference between phenotype and endotype (Figure 1) lies in the intrinsic molecular mechanism that is well defined in the latter and might be different from the phenotype, which is just a subgroup of clinical characteristics that allows identifying a specific disease[8]. Therefore, OA may include different phenotypes, which can be grouped into primary and secondary phenotypes. Primary phenotypes originate from factors within the joint itself, such as inflammatory synovitis or ligamentous laxity, whereas secondary phenotypes arise from external factors, such as hormonal imbalances. All these phenotypes may share a common endotype, such as inflammation, which is the molecular pathway explaining how the disease develops[8].

OA patients' stratification in specific subsets might prove helpful in building tailored trials and treatments aimed towards a particular phenotype and endotype of the disease, significantly improving the efficacy of the interventions[9].

This review article aims to provide a holistic perspective on OA, spanning from its epidemiology, etiology, and molecular mechanisms to the latest breakthroughs in diagnosis and innovative therapeutic approaches to inspire new insights and avenues for research. We will offer a comprehensive vision of the disease's complexity by delving into the intricate molecular pathways, exploring the genetic predispositions, and unraveling the inflammatory cascades that underlie OA. Furthermore, we will examine the evolving landscape of OA management, emphasizing not only emerging pharmacological interventions and regenerative therapies but also rehabilitation approaches and lifestyle modifications that can effectively counteract this disabling condition in a multimodal and multidisciplinary strategy.

Epidemiology

OA epidemiology varies across different joints, with knee, hip, hand, foot and ankles, and spinal OA presenting unique challenges and considerations. Another joint that can be affected by OA is the shoulder, which is relatively less prone to OA compared to weight-bearing joints like the knee and hip[10]. The lack of a unique OA definition explains why the prevalence and incidence vary greatly among the different studies for each joint.

According to 2019, the global OA population was over 528 million, up 113% from 1990[11]. Precisely, in Italy, the prevalence of OA in 2021 was estimated to be 15.9 %[12]. Notably, 73% of osteoarthritis patients are 55 or older[13]. Furthermore,

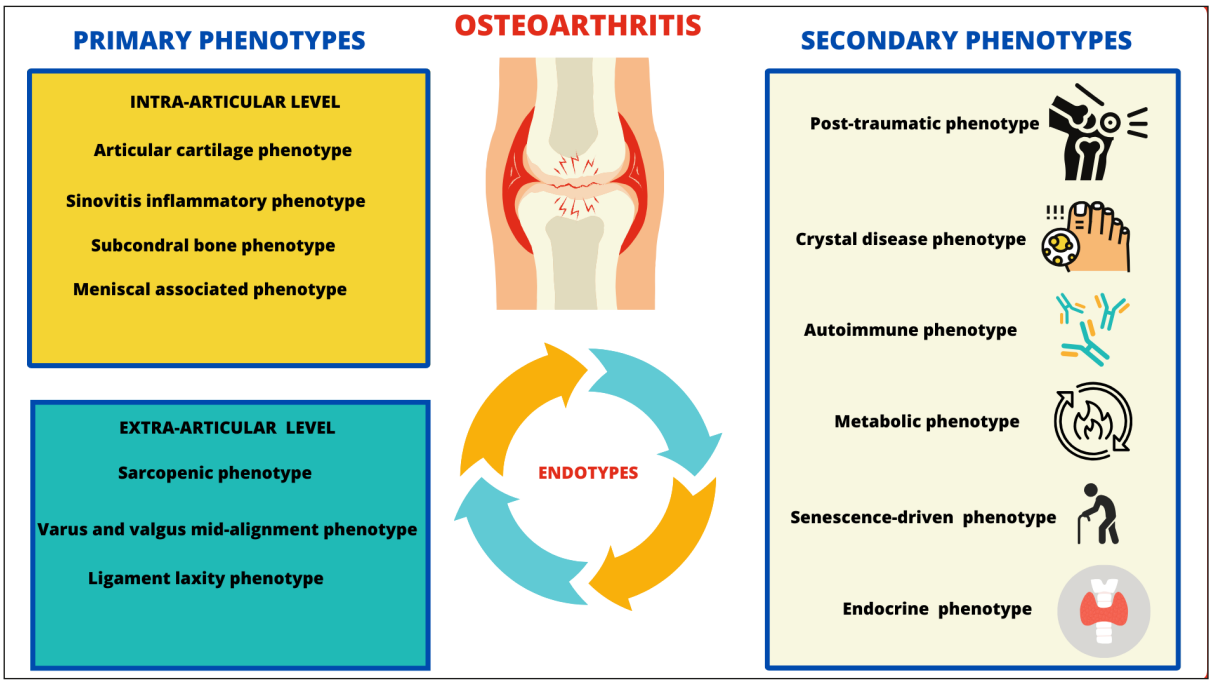

Figure 1. Primary and secondary OA phenotypes.

4081

approximately 60% of those affected by this condition are female[13].

With 365 million instances, the knee joint is the most common. Hip and hand joints follow[14]. The prevalence of knee OA varies among different studies depending on gender, clinical status, race, and geography. In the US Framingham cohort, symptomatic knee OA was 7% in people over 45[15].

The Framingham Osteoarthritis Study conducted between 1983 and 2005 found that knee discomfort and symptomatic knee OA increased with age in people 70 and older. This rise was twice for women and three times for men following age and BMI adjustments (BMI)[16]. It is estimated that the age-standardized and sex-standardized incidence of knee OA is around 250 cases per 100,000 people per year, with a steep increase after age 50[17].

The prevalence of hip OA among persons aged 40 years and above in Spain was examined in a population-based study. The prevalence was determined using the American College of Rheumatology (ACR) clinical and radiographic criteria and was found to be 5.1%[18]. It has been estimated that the lifetime probability of developing symptomatic hip OA ranges from 25% to 32%, considering various factors such as racial and gender-related[19].

Different research studies have found different prevalences of hand OA because of differences in disease categorization and radiographic and clinical symptoms. The Episer study in Spain showed a weighted prevalence of symptomatic hand OA of 7.7%[18], while the British Clinical Assessment Study of the Hand (CAS-HA) showed a weighted -prevalence of radiographic, symptomatic hand OA of 22.4%[20]. The different definitions of OA may explain this consistent difference for each study since, in the latter, there was a radiologic criterium. On the contrary, the diagnosis was based on ACR clinical criteria in the former.

According to the Johnston County Osteoarthritis Project, the incidence of radiographic hand OA among persons aged ≥ 45 years was 60% and symptomatic hand OA was 13% over a 12-year average follow-up period. The weighted lifetime risk of symptomatic hand OA was 40% in the same cohort[21].

According to a systematic review by Murray et al[22], radiographic ankle OA prevalence in individuals aged > 50 is not consistent across studies, with estimates ranging from 0.0% to 97.1%. This heterogeneity's main problem is the different OA definitions considered in each research.

Regarding foot OA, in the American Johnston County Osteoarthritis Project, the prevalence was 22.1% for radiographic foot OA and 5.3% for symptomatic foot OA[23]. In this same study, the incidence of radiographic ankle OA over a mean of 3.5 years was 28.2%, while 4% progressed to symptomatic ankle OA[23].

Spinal OA involves facet joint and intervertebral disc degeneration. Due to diagnostic criteria, prevalence estimates vary substantially among the elderly. Among individuals aged 60 and over, it has been observed that 95% of males and 70% of females exhibit at least one manifestation of arthritis. Cervical spine osteoarthritis is observed in more than 80% of patients aged 55 and above[24], with facet joint arthritis affecting 19% of 45-65-year-olds and 57% of 65-year-olds in the US[25].

Lumbar spine osteoarthritis affects 30% of men and 28% of women aged 55-64 in the US. L4-5 and L5-S1 vertebrae are often affected by their increased load-bearing capacity and joint mobility[26].

Additionally, spine OA epidemiology may vary by ethnicity. This syndrome is less com-

Table I. Osteoarthritis risk factors are subdivided into local and systemic.

Local Factors	Systemic Factors
Intrinsic	Age
Past joint surgery	Female sex
Infection	Diet
Malalignment	Bone density
Dysplasia	Genetics
Extrinsic	Drugs
Past joint injury	Gut microbiota
High BMI	Metabolic syndrome
Physical activity	
Word-relates	

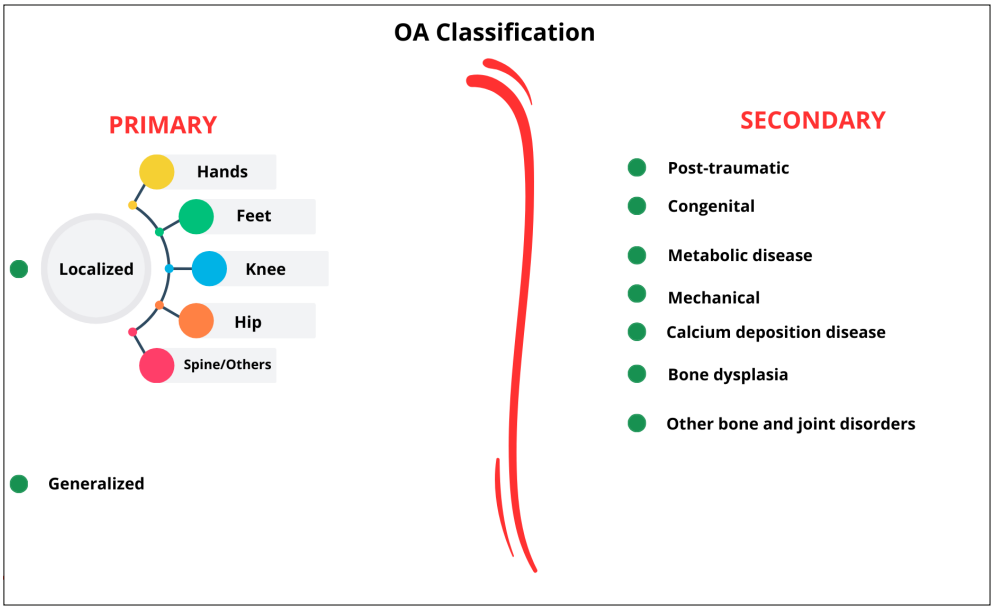

Figure 2. Osteoarthritis classification in primary and secondary subsets.

mon in Asians than Caucasians[24]. Males tend to have more advanced spine osteoarthritis than females[27].

Etiology and Risk Factors

OA etiologic factors vary greatly and can be grouped up into systemic and local factors; the latter subdivided into intrinsic and extrinsic ones (Table I). All these factors may concur in a multifactorial etiology setting to the development of OA that is shaped by the interplay between the host and environmental factors.

Age is widely recognized as a prominent risk factor for the development of OA in all sites. The elevated prevalence of OA in older individuals can be attributed to the cumulative impact of many risk factors and age-related alterations in joint structures[28].

Female sex, together with a high BMI (as it places added strain on weight-bearing joints), malignment (e.g., knee malignment[29]), and a previous joint injury are strong risk factors for knee and hip OA[30]. Furthermore, cam deformity and mild dysplasia have elevated the likelihood of developing OA, particularly in individuals aged 55 to 65. However, this association does not hold for the older population aged 65 years and above. On the other hand, severe dysplasia is strongly correlated with hip osteoarthritis and is known to trigger its onset at a younger age, specifically before the age of 50 years[31].

Lifestyle factors like diet and physical activity also play a role in OA. Poor nutrition, especially a diet high in processed foods and low in nutrients, can exacerbate inflammation and weaken joint health[32]. Conversely, regular physical activity can help maintain joint flexibility and reduce the risk of OA, while engaging in physically demanding tasks is considered a significant contributor to hip and knee OA development. Specifically, individuals employed in farming, or the construction industry are more prone to hip OA. Additionally, occupations involving repetitive kneeling and frequent lifting are connected with an increased risk of knee OA[33].

Another crucial contributor is joint trauma and mechanical stress. Repetitive use or injuries to the joint, such as sports-related injuries, can accelerate cartilage degeneration and lead to the development of OA[34]. For instance, several high-impact sports, such as football, handball, hockey, wrestling, weight-lifting, and long-distance running, have been found to have a moderate to substantial correlation with an elevated risk of hip osteoarthritis or knee osteoarthritis, typically exhibiting a dose-response relationship[35,36]. The elevated susceptibility to knee osteoarthritis in those engaged in sports activities can be attributed, in part, to the occurrence of knee injuries. Conversely, the heightened risk of hip osteoarthritis

may be linked to cam impingement, a condition that can manifest during athletic pursuits among teenagers.

Drugs, such as hormone replacement therapy, can also raise the risk of specific OA, such as knee OA, and infections may also play a role in the OA pathogenesis and be a starting point[37,38].

Gut microbiota (GM) and an imbalance of its composition, which we call dysbiosis, have also been proposed as a novel etiologic mechanism that may initiate OA[39]. OA and GM have been linked because the perturbation of GM can compromise the gut barrier, activate the "gut-joint axis," and modulate innate and adaptive immunity through various mediators[40].

Finally, genetics also plays a significant role in OA. There is evidence that specific genes may predispose individuals to the condition, with a more pronounced genetic influence observed in hand and hip osteoarthritis compared to knee osteoarthritis[41]. Specifically, variations in genes (21 independent susceptibility loci identified so far[7]) related to collagen formation, joint structure, and inflammation have all been associated with an increased genetically determined risk of OA that ranges between 30-65 %[42,43].

Classification

Osteoarthritis can be classically categorized into primary (idiopathic) or secondary forms (Figure 2), the latter being associated with identifiable causes[44].

Primary osteoarthritis has the potential to manifest in specific joints, such as chondromalacia patellae, which is a form of mild osteoarthritis commonly observed in young individuals. Primary osteoarthritis is typically classified based on the particular anatomical regions affected, such as the hands and feet, knee, or hip. When primary osteoarthritis affects numerous joints, it is categorized as primary generalized osteoarthritis[44].

Secondary osteoarthritis arises due to many factors that alter the microenvironment of the cartilage or joint structure. The above-mentioned conditions include a variety of factors, such as significant physical injuries, congenital joint ab-

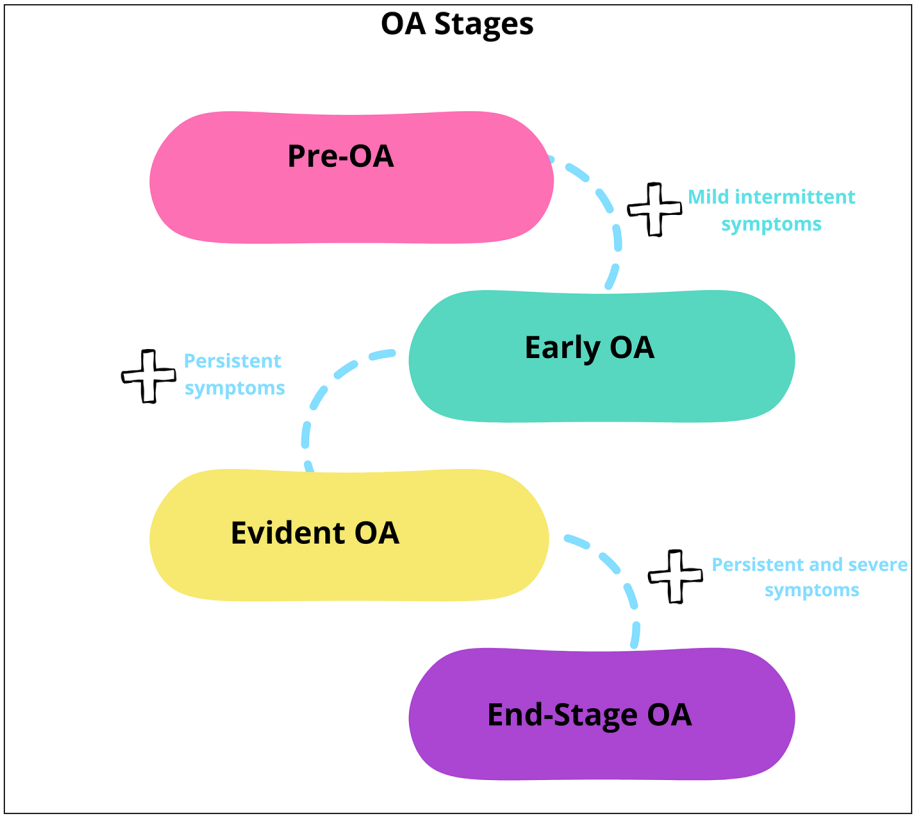

Figure 3. Proposed model of OA progression.

normalities, metabolic disorders like hemochromatosis and Wilson disease, infections that result in postinfectious arthritis, endocrine and neuropathic disorders, and other conditions that disrupt the normal structure and function of hyaline cartilage, including rheumatoid arthritis, gout, and calcium crystal deposition disease[44].

This original classification has gradually evolved over the past two decades into a more patient-tailored classification of OA in phenotypes and endotypes, as introduced above.

Pathophysiology

OA was once regarded as a simply "mechanical" cartilage disruption, but it is now well accepted that it is a "whole joint disease". Cartilages, subchondral bone, and synovium are involved together with extra-articular structures, such as ligaments or infrapatellar fat. Moreover, systemic factors like systemic inflammation, aging, and metabolic syndrome are all involved in OA development[45].

Therefore, an up-to-date and modern view of OA pathogenesis should involve local and systemic pro-inflammatory pathways that interplay with each other, promoting OA progression.

Articular cartilage is formed by tissue fluid (accounting for 65-80% of the wet mass), type II collagen (15-22% of wet mass), and proteoglycans (4-7%)[46], while other collagens (i.e., type V, VI, IX, XI represent only a small part of cartilage components[47]). Collagen fibers form a highly dense meshwork embedded in gel-like negative-charged proteoglycans. Collagen fibers provide tensile strength to the cartilage structure, and aggrecan and other proteoglycans draw water, assuring compressive resistance[48].

Chondrocytes synthesize matrix components and matrix-degrading enzymes in normal conditions, ensuring minimal turnover. Under stimulation, they undergo a proliferative switch. This assures a greater production of catabolic factors by matrix synthesis, mediated by metalloproteinases (MMP) 1, 3, and 13 (which are responsible for collagen degradation) and A Disintegrin and Metalloproteinases with Thrombospondin motifs (ADAMTS) 4 and 5 (which are responsible for aggrecan degradation)[49]. *In vitro* studies suggest that MMP13 could favor the cleavage of chondrocyte-expressed netrin, contributing to pathological vascularization in OA cartilage[50]. During cartilage injury or excessive loading, the fibroblast growth factor signaling (FGF) is activated (mainly FGF2), stimulating MMP13 and ADAMTS 5 expression and potentiating the cartilage matrix's catabolic activity. Also, genetic factors could be involved since collagen II, IX, and X mutations are involved in OA pathogenesis[51]. Moreover, surface shear stress, perpendicular to compressive ones, leads to the so-called "mechano-inflammation" involving PIEZO mechanosensors, leading to actin de-polymerization and increased inflammatory signals due to increased ROS[52]. Toll-like receptor activation induced by inflammation and degradation products promotes the expression of NF-κB transcription. This allows actin de-polymerization and the rise of inflammatory signals cytokines, like IL-1, IL-6, IL-8, IL-12, tumor necrosis factor (TNF)-α, increasing pain, and finally enhancing cell apoptosis[53]. Moreover, the degradation products of collagen type II into the extracellular matrix could activate the complement cascade that can evolve in both cell death and production of matrix-degrading enzymes (such as MMPs) and inflammatory mediators, thus worsening joint pathology[54].

Also, systemic disease could promote low-grade inflammation and catabolic switch of chondrocytes, such as metabolic syndrome and diabetes mellitus type 2. Two major pathways have been proposed for OA pathogenesis and diabetes: the first is oxidative stress resulting from chronic hyperglycemia that causes a spilling of cytokines and advanced glycated end products (AGEs) in joint tissue, that in turn, stimulates a pro-inflammatory and pro-degradative state of chondrocytes through toll-like receptors signaling. Conversely, insulin resistance may influence MMP production and cellular apoptosis in cartilage tissues, mainly *via* leptin activation[55].

This inflammatory process involving the cartilage matrix and the chondrocytes could also be activated in other joint structures, like the synovium or subchondral bone. Blocking this cascade of cytokines secretion, increase in matrix degradation, and oxidative burden with the so-called disease-modifying osteoarthritis drugs (DMOADs) or nutrients, as explained below, is one of the proposed novel strategies to control OA progression and related pain[56].

The synovial membrane is a thin layer surrounding cartilage joints, made by an intima rich of macrophages and fibroblast-like synoviocytes (FLS) that secrete lubricants such as hyaluronic acid (HA) and a subintima that is rich in collagen-type 1[57].

Trauma, mechanical loading, aging, comorbidities such as obesity or diabetes mellitus type 2, and microbial dysbiosis could all contribute to or aggravate synovitis and fibrosis. The hallmarks are the presence and abundance of vascularity, fibrin deposits, hyperplasia and hypertrophy of FLS, infiltration of inflammatory cells like macrophages and lymphocytes[58]. Once activated, FLS secrete cytokines, MMPs, and FGFs that contribute to macrophage and chondrocyte activation and degradation and fibrosis.

Subchondral bone is the third key element of OA development since it represents both a mark and a cause of OA[59]. Subchondral bone supports the avascular cartilage, forming an intermediate layer between the tidemark and the trabecular bone, and it is crucial to joint health[60]. Traditionally, subchondral bone remodeling has been ascribed to the equilibrium between osteoblasts and osteoclasts. In recent years, the pivotal role of osteocytes, the most represented cells in bones, has emerged[60]. In the early phase of OA, osteoclasts will absorb subchondral bone, while osteoblasts will deposit collagens and minerals to align the osteocytes along the principal loading direction in late OA. This uncoupled bone remodeling forms abnormal, weak trabecular bone, gradually contributing to cartilage degeneration. On the other side, cartilage loss can contribute to subchondral bone changes[61] since chondrocytes could participate in subchondral remodeling. Osteoclast disproportionate activity is also linked to netrin-1 pathway, which induces sensory innervation and vascularization of subchondral bone, accounting for persistent pain in OA[62].

The predominant pathogenetic mechanism could help to identify 3 main endotypes. In the bone-driven endotype, uncoupled remodeling and resorption in subchondral bone causes microstructural alterations (early-stage OA) or inhibition (late-stage OA) of osteoclastic bone resorption[63]. In the synovitis-driven endotype, the synovium shows biochemical and histological signs of mononuclear cell infiltration, synovial cell proliferation, and inflammatory cytokines, such as TNF-α, IL-1β, and IL-6[56]. In the cartilage-driven endotype, a failure to maintain cartilage homeostasis leads to an imbalance between extracellular matrix production and breakdown, which is indicative of OA pathogenesis[64]. These pathways are all potential targets for a personalized therapy and are all strategies that are under investigation in clinical and pre-clinical studies.

Metabolic syndrome, also known as the "deadly quartet", has a pivotal role in OA pathogenesis since all components of metabolic syndrome are associated with an increased incidence of OA[65].

In obese patients, adipose tissue macrophages switch from an M2 phenotype to a proinflammatory M1 state that produces cytokines, chemokines, ROS, and adipokines. Adiponectin, leptin, and lipocalin-2, regulate inflammatory immune responses in joints, stimulating both cartilage deterioration *via* chondrocyte activation and synovial inflammation, further increasing cytokine-driven damage[66]. Recent evidence suggests that the infrapatellar fat pad is the major articular adipokine producer in knee OA. Increased cholesterol levels are associated with cartilage disruption, osteophyte formation, and alterations to the subchondral bone. At the same time, high levels of Ox-LDL could also trigger the release of ROS, MMPs, pro-inflammatory cytokines, and activation of NF-κB by synovial macrophages and synovial fibroblasts and chondrocytes[67].

As mentioned above, diabetes mellitus type 2 also plays a role. Hyperglycemia affects chondrocytes, FLS, and subchondral bone and favors pro-inflammatory effects. Insulin resistance and AGEs accumulation favor macrophage infiltration and chemokines liberation, intensifying the inflammatory response at the joint level[68,69]. This link between obesity and osteoarthritis is the substrate that explains the potential role of diet as well as anti-diabetic drugs[65,66].

Another key contributing factor in OA pathogenesis is the so-called "inflammaging"[70]. Senescence changes in adipose tissue, reduced muscle mass, and increased fat mass alter joint loading and are associated with an increase in adipokine and cytokine production, resulting in low-grade systemic inflammation[71]. In addition, senescent chondrocytes, meniscal cells, and the infrapatellar fat in the knee joint can exhibit growth arrest and produce cytokines, such as TGF-β and IL-6, ROS species, growth factors, and MMPs. This occurs mainly in response to mechanical or oxidative injury, advancing tissue destruction[72].

A strong relationship between OA and GM has been emerging in recent years since GM dysbiosis can disrupt the gut barrier and activate the gut-joint axis. This results in the modulation of innate and adaptive immunity through LPS release, short-chain fatty acid modification, macrophage activation, cytokine liberation, regulation of T-cell responses, and B-Cell differentiation[73]. Moreover, GM can influence OA progression by

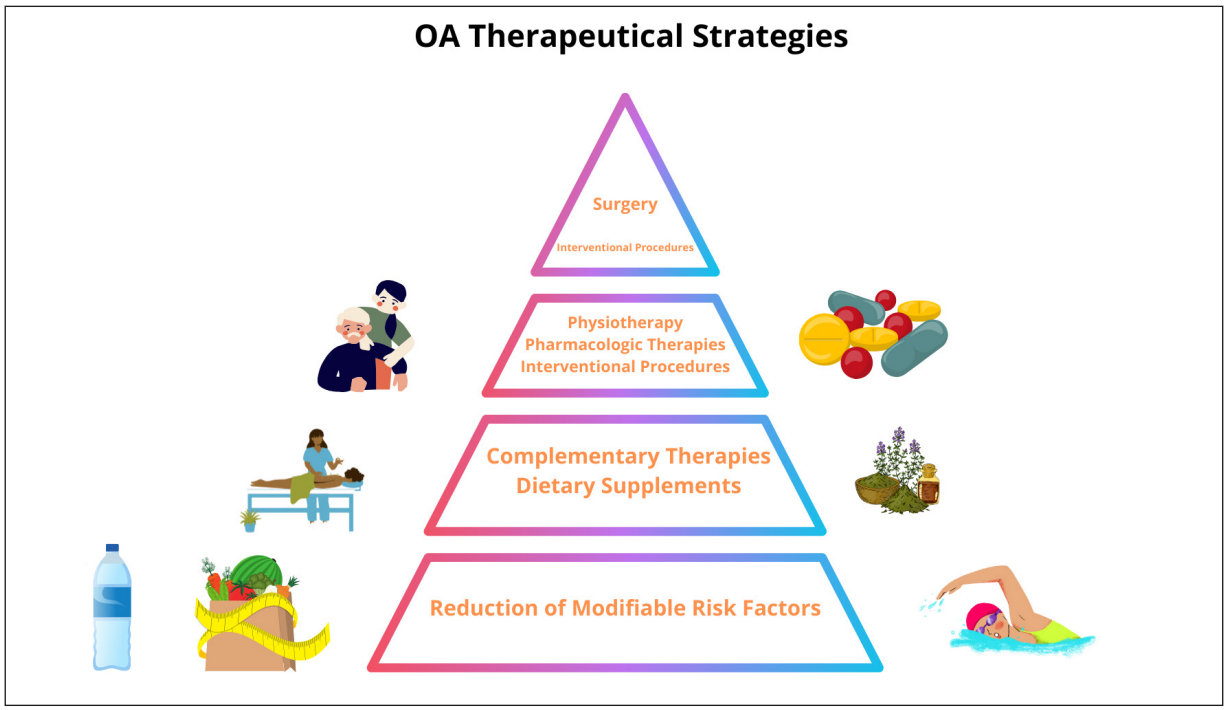

Figure 4. OA treatments.

interacting with other OA risk factors, such as age, sex, obesity, inflammation, and mechanical load. The potential role of GM modulation for OA progression and treatment is an intriguing strategy under investigation[74].

Since OA shows a complex and multifaceted pathogenesis, clinical manifestation may significantly vary among individuals as long as treatment response.

A literature review tried to clarify the clinical phenotype classification and finally underline the existence of six different clusters of variables in knee OA manifestation that defined six different pathogenetic phenotypes[6]: Minimal Joint Disease (MJD), Malaligned Biomechanical (MB), Chronic Pain (CP), Inflammatory (I), Metabolic Syndrome (MS) and Bone and Cartilage Metabolism (BCM).

A combination of low levels of self-reported pain (worse pain in the last week ≤ 3/10) and mild to moderate radiographic OA classifies subjects in the MJD phenotype, in which slow progression over time (2-10 years) has been evidenced. This phenotype represents the only subgroup defined without regard to the disease etiology. The prevalence of these features in the knee OA population ranged between 17% and 47%[75].

Chronic pain phenotype has a 16-19% prevalence in reporting studies. It shows a predominant alteration in the central nervous system and pain neurophysiology in which peripheral spreading and central sensitization are the most important features[76]. Moreover, other factors could foster this clinical phenotype, such as psychological distress, poor coping style, sleep disturbance, fatigue, widespread pain, and illness burden, making it a "whole person" disease rather than a simple joint pathology[77]. The inflammatory OA phenotype, with a prevalence of 16-30%, is characterized by an overspilling of inflammatory cytokines, such as IL-1β, IL-8, IL 6, and C-reactive protein (C-RP), TNF[78]. These patients usually present a higher pain level at baseline and show faster radiographic progression than those with cytokine under expression. The evidence of synovitis at MRI is a strong indicator of this phenotype. The metabolic syndrome phenotype recognizes a subgroup of patients displaying a higher prevalence of metabolic factors (obesity, diabetes, hypertension, and dyslipidemia) and a specific biomarker profile (such as plasma leptin and h-Sensitivity C-RP)[75].

The subgroups of patients with alterations in bone and cartilage metabolism include individuals with higher expression of markers of bone formation and resorption (i.e., high levels of osteocalcin) as well as altered equilibrium in cartilage deposition and catabolism (i.e., elevated levels of C-terminal telopeptide of type II collagen (CTX-II)[78,79].

Table II. Differential diagnosis of osteoarthritis.

Knee OA	Shoulder OA	Hip OA	Hand OA	Multiple Joint OA
Patellar tendinosis	Rotator cuff impingement, tendinopathy, tears	Referred visceral pain	Ganglion cyst	Referred pain or radicular pain
Pes anserine bursitis	Labral tear	Aortoiliac insufficiency	Dupuytren contracture	Avascular necrosis
Patellofemoral pain syndrome	Adhesive capsulitis	Sacroiliac neuropathy	Carpal tunnel syndrome	Gout
Medical plica syndrome	Glenohumeral joint or scapular instability	Lateral femoral cutaneous nerve syndrome	Mallet finger	Pseudogout
Quadriceps tendinosis	Biceps tendinopathy	Snapping hip	Stenosis flexor tenosynovitis	Septic arthritis
Saphenous nerve entrapment	Scapulothoracic weakness	Piriformis syndrome		Osteochondritis dissecans
Popliteal artery aneurysm	Subscapular bursitis	Osteitis pubic		Trauma ligamentous or bone injury
Prepatellar bursitis	AC joint sprain	Sacroiliac joint pain		Stress and osteoporotic fracture
	Sternoclavicular joint subluxation/dislocation			Bone tumors
				Systemic rheumatologic disease: rheumatoid arthritis, psoriatic arthritis, reactive arthritis, hemochromatosis

A recent paper[80] confirmed the clinical utility of the phenotype classification that can successfully allocate patients in almost 84% of cases with an overlap of 20%, providing strength to this personalized approach to OA.

Clinical Presentation

OA is characterized by a clinical presentation that is highly variable among individuals and revolves around pain, stiffness, and functional limitations[81]. A proposed model in a previous study[82] subdivides the clinical course of OA into 4 main stages: Pre-OA, Early OA, Evident OA, and End-Stage OA (Figure 3). The pre-OA is the pre-clinical stage of the disease, where the patient is mainly asymptomatic, and risk factors are already at work to push the progression of the disease further. The symptoms appear in the early OA but are still intermittent. In contrast, in the evident OA, the symptoms become constant and more severe until the end-stage disease, when they reach the maximum level of intensity[82]. Each phase will require adequate therapy and management personalized to the patient's phenotype.

It is essential to underline that during the disease's evolution, there is a clear dissociation between radiologic/imaging findings (e.g., no correlation between the severity of symptoms and the growth of osteophytes) and the clinical picture. This could lead to scenarios in which patients report no symptoms despite showing clear abnormalities in the joint structures[83]. The reason for this dissociation can be found at the molecular level in the function of specific factors such as netrins, which play a key role in the pathophysiology, as previously explained[84].

Pain is the hallmark symptom of OA that prompts patients to consult their primary care physician. It is usually described as intermittent and worsens during and after weight-bearing activities[85]. Throughout OA's course, inflammation outbreaks may occur.

Stiffness is another symptom that may occur, particularly in the morning, after periods of inactivity, and in the evening. Unlike rheumatoid arthritis, where stiffness can last over 30 minutes,

this stiffness typically lasts only a few minutes[85].

Loss of mobility completes the triad of OA symptoms, as patients usually report that their symptoms limit their ability to ascend stairs, walk, and perform household chores. This poor quality of life explains why symptomatic OA may be linked to depression and sleep disturbances, contributing to disability[85].

The physical examination may find joint enlargement caused by joint effusion, bony thickening, or both. This is the macroscopic expression of microscopic changes such as inflammation of synovial tissue, cartilage damage and loss, outgrowth of bone (i.e., osteophytes), sclerosis and cysts of subchondral bone, and weakening and contracture of ligaments and muscles. Notably, a synovial effusion may not only be identified during OA episodes but also as a persistent feature during chronic phases. Furthermore, crepitus is a distinctive clinical feature of OA. It is characterized by a crackling or grating sensation within the joint during movement. This occurs due to uneven surfaces within the joint from cartilage loss and is often palpable or audible during physical examination[85].

Finally, joint deformities can be detected in advanced joint disease. They are caused by injury to cartilage, periarticular bone, synovium, articular capsule, ligaments, and muscles. The joint can lock if loose substances or cartilage fragments enter the joint space[85].

Understanding the clinical presentation of OA is essential for both early diagnosis and developing effective management strategies to alleviate pain and improve the functionality and quality of life for those affected by this widespread joint disorder.

Diagnosis

OA is traditionally considered a clinical diagnosis involving a physical examination assessing joint tenderness, range of motion, and joint swelling or deformities[86]. Nevertheless, it often requires a multifaceted approach that combines clinical evaluation, medical history assessment, imaging techniques, and laboratory tests, depending on the stage of the disease. For the preclinical stage, OA may only be spotted with biomarkers. In contrast, in the early OA stage, intermittent symptoms (sporadic and self-resolving pain), including pain plus magnetic resonance imaging (MRI) and radiographic Kellgren-Lawrence grade (KL) 0-1 (subtle narrowing of the joint space), may help for the diagnosis. When the symptoms become constant (evident OA and end-stage OA), the diagnosis will be clinical with the confirmation of a radiographic KL 2-3[82].

Different biomarkers have been proposed. For instance, the CHECK study[87] assessed 14 different biomarkers that could be grouped up into the following subcategories: cartilage degradation, cartilage synthesis, bone degradation, bone synthesis, synovium degradation, synovium synthesis, and adipokines. Unfortunately, no marker demonstrated enough discriminatory power to accurately predict OA's diagnosis or prognosis. Two markers exhibited a wider range of variation than initially anticipated. The marker C-terminal telopeptide of type II collagen (CTX-II), which indicates the deterioration of cartilage, reveals notable resemblances to markers associated with bone metabolism, implying that CTX-II may also come from bone tissue. In early-stage OA, it is possible for the cartilage breakdown marker known as COMP (Cartilage Oligomeric Matrix Protein) to also be derived from inflamed synovial tissue[87]. Further research is needed to explore additional biomarkers and different subsets of patients.

The radiographic characteristics of OA encompass various aspects of assessment. These include the presence of osteophytes along the margins of the affected joints or on the tibial spines, the occurrence of periarticular ossicles in the distal or proximal interphalangeal joints, the narrowing of joint cartilage accompanied by subchondral bone sclerosis, the identification of small pseudocystic regions with sclerotic walls within the subchondral bone, and the alteration in the shape of bone ends, particularly in the femoral head[88]. The KL grades are the following:

- Grade 0: no reactive changes or joint space narrowing.
- Grade 1: there is uncertainty regarding the shrinking of the joint space and the potential presence of osteophytic lipping.
- Grade 2: there are definitive osteophytes present, indicating the possible joint space narrowing
- Grade 3: there is evidence of moderate osteophyte formation, clear indications of joint space narrowing, and potential bone end deformities
- Grade 4: there is evidence of large osteophytes with pronounced joint space narrowing, extensive sclerosis, and evident deformity[88].

Ultrasound may also help identify and surveil osteoarthritic joints, detecting early changes with high accuracy in most cases[89].

Different groups have proposed different comprehensive diagnostic criteria for OA for different stages and joints, such as knee OA[90,91]. Luyten et al[91] proposed three classes of criteria for the diagnosis of early OA of the knee: (1) The assessment of pain, symptoms/signs, self-reported function, and quality of life can be conducted through the utilization of tools such as the Knee injury and Osteoarthritis Outcome Score (KOOS). A score of 85% or lower in at least two of these four categories indicates a certain level of impairment; (2) The clinical examination should include the presence of either joint line tenderness or crepitus; (3) a KL of 0 or 1. Conversely, The Italian Society for Rheumatology clinical practice guidelines[90] for the diagnosis and management of knee, hip, and hand osteoarthritis recommended the diagnosis of early knee OA when either of the following criteria are verified : (1) two mandatory symptoms such as knee pain in the absence of recent trauma or injury plus short joint stiffness lasting for less than 10 minutes at the start of the movement; (2) knee pain and 1 or 2 risk factors; (3) three or more risk factors in the presence of at least one mandatory symptom. Besides, the standard radiograph may be compatible with a KL 0.

Finally, in the context of diagnosis, it is crucial to consider a comprehensive range of potential differential diagnoses (Table II)[92-94]. In fact, laboratory tests are utilized to rule out other possible causes of joint pain and inflammation. Blood tests may be performed to assess for inflammatory markers, such as C-reactive protein or erythrocyte sedimentation rate. These markers can help exclude predominantly inflammatory forms of arthritis, like rheumatoid arthritis[95].

We believe early diagnosis is paramount to initiating appropriate interventions, including lifestyle modifications, rehabilitation, and medications. Therefore, the therapists' goal should focus on early OA detection, where most OA features can still be counteracted with a better outcome than later disease stages. Tools like the homeostasis Model Assessment (HOMA) index[96] and waist circumference measurement[97] may help detect patients exposed to an increased risk.

In summary, OA diagnosis involves clinical exams for joint tenderness and deformities, imaging (X-rays, MRI, ultrasound) for structural changes, and lab tests to exclude other conditions. Early detection relies on symptoms, risk factors, and imaging findings. Biomarkers lack sufficient accuracy for routine use.

Treatment and Management

Currently, treatment for OA aims to manage pain and mobility limitation[98]. It should be noted that pharmacological and non-pharmacological interventions have limited supporting evidence, whereas drug treatment is associated with adverse events (AEs) on the gastrointestinal (GI), cardiac, and renal systems, particularly for NSAIDs, the most prescribed drugs for OA patients[99].

These premises underline the importance of focusing on the early OA and the pre-OA by addressing the modifiable risk factors. Furthermore, research should pursue the development of disease-modifying osteoarthritis drugs (DMOADs), many of which are being studied but not yet approved by any regulatory agency[100]. A DMOAD refers to a pharmacological substance that has the ability to impede or reverse the advancement of structural deterioration in the joint. As a result, this intervention can potentially bring about positive changes in symptoms, such as alleviating pain or enhancing physical functionality. Hence, including structural and symptomatic advantages is necessary to classify an agent as a DMOAD[101]. A DMOAD would be particularly helpful in secondary OA where even the joint replacement would not permanently treat the condition as it may only reproduce later in a different site or even in the same[102].

Treatments can be classified into reduction of modifiable risk factors, pharmacologic therapies, rehabilitation, complementary therapies, interventional pain procedures, and surgery (Figure 4). It is important to emphasize that in Figure 4 there is no hierarchy within the categories; one or more options may be useful at different points in the course of a given patient's illness, even if working on the risk factors must be prioritized in the pre-OA and in the early OA. Pharmacological and non-pharmacological interventions form the backbone of OA treatment in all disease stages, while surgery will remain the gold standard for the end-stage disease[82]. In the context of the effectiveness of available OA interventions, particularly in pain relief, the placebo effect should be carefully considered[103].

Whenever possible, the phenotype and endotype underlying the specific OA should be considered to tailor the therapy to the patient.

Reduction of Modifiable Risk Factors

Exercise interventions

Reducing obesity and, therefore, exercising are key elements in preventing and improving OA. A

systematic review and network meta-analysis conducted by Uthman et al[104] examined 60 RCTs and concluded that exercise interventions were associated with significant pain relief and improvement in functional outcomes. Additionally, this study proposed therapies that integrated exercises targeting muscular strength, flexibility, and cardiovascular fitness[104]. This positive influence depends on the systemic amelioration resulting from decreased adipose tissue as well as from the decreased load that a lower BMI will impose on weight-bearing joints[105]. Moderate aerobic and anaerobic exercise are recommended. Aerobic sports, such as swimming, walking, and dancing will positively impact glucose homeostasis and significantly decrease systemic arterial pressure, insulin resistance, and visceral fat. Furthermore, aerobic exercise is particularly helpful because it enhances the browning process of adipocytes thanks to irisin's release by muscle cells, which in turn helps to reduce body fat[106]. On the other hand, anaerobic sports, such as weight-lifting (1-2 kg) and ankle weights (1 kg) will raise lean mass and muscle strength, as well as the number of mitochondria within the muscle cells[107,108]. Different exercises will be available for each joint. For instance, Deyle et al[109] recommended a specific physical treatment for knee OA.

Diet

Diet is another potential modifiable risk factor, although there is a lack of data regarding the impact of fruits or herbs on OA outcomes. Regardless, certain foods, such as those in a Mediterranean diet, may play their part in OA prevention and treatment in synergy with other medications by their antioxidative mechanisms[110].

Dietary supplements

Many dietary supplements are available. Among these, there are collagen hydrolysate, passion fruit peel extract, Curcuma longa extract, Boswellia serrata extract (BSE), bromelain, curcumin, Pycnogenol, L-carnitine, undenatured type II collagen, HA, avocado soybean, methylsulfonylmethane, diacerein, glucosamine and chondroitin[111].

Boswellia serrata extract

BSE contains boswellic acids (BAs), which are specific nonredox inhibitors of 5-lipoxygenase (5-LOX)[112]. By blocking 5-LOX, BAs reduce the production of leukotrienes, specifically 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotrine B4 (LTB-4) levels, which are potent chemotactic factors that in turn lead to increased permeability[113]. This effect ultimately translates into less WBC at the site of the trauma or inflammation, like an osteoarthritic joint.

Additionally, BAs have an impact on the cellular defense system, affecting the release of cytokines. Therefore, it can be observed that BAs can impede the activation of NFκB, a transcription factor synthesized by neutrophil granulocytes. Specifically, BAs activity decrease proinflammatory cytokines, including TNF-α, IL-1, IL-2, IL-4, IL-6, and IFN-γ[114].

Another beneficial effect of BAs is their ability to lower glucosamine degradation, which is important in maintaining cartilage in good shape[115]. They also inhibit the human leukocyte elastase, which underlines their potential immunoregulatory role and anti-inflammatory effects[116].

A meta-analysis[111] has shown that BSE effectively lowered pain and improved disability in OA, especially in the short term. For instance, in a randomized, double-blind, placebo-controlled trial, the oral supplementation of BSE for 8 weeks (333 mg x 3/die) significantly decreased knee pain, increased knee flexion, and walking distance, reporting only minimal side effects, such as epigastric pain or nausea, which regardless did not comport the withdrawal from the study[117].

Bromelain

Bromelain is a mixture of proteolytic enzymes derived from pineapple and has been shown to possess anti-inflammatory effects through down-regulation of the NF-κB and MAPKs-signaling pathways[118], which may be beneficial in OA[119].

Curcumin and curcuma longa extract

A recent meta-analysis about the effect of Curcumin and Curcuma longa Extract in the management of OA demonstrated a potential to reduce pain, enhance joint function, and improve joint stiffness. Furthermore, the inclusion of Curcumin and Curcuma longa Extract did not increase adverse events[120]. Curcuma longa Extract can be considered a DMOAD targeting synovitis[121].

Glucosamine and Cchondroitin

Glucosamine and chondroitin sulfate may be beneficial in some OA phenotypes. As recommended by the 2019 ACR guidelines[122], chondroitin supplementation may be useful for the OA affecting the joints of the hand. Conversely, a recent meta-analysis encompassed 8 studies and used a sample size of over 4,000 individuals diagnosed with knee OA, concluding that there is a

lack of substantial data supporting glucosamine and chondroitin's significant efficacy in OA treatment[123].

Collagen supplements

Collagen supplementation can reduce the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and/or the Visual Analog Scale (VAS), thus improving OA symptoms, as shown in a meta-analysis[124]. According to Oesser and Seifert[125], collagen hydrolysate can potentially enhance collagen production in chondrocytes, specialized cells responsible for synthesizing, maintaining, and arranging the extracellular matrix (ECM). Alterations in the ECM composition elicit collagen turnover, activating chondrocytes and subsequent production and ongoing remodeling. The authors concluded that oral administration of collagen hydrolysate has the potential to accumulate within cartilage and effectively trigger a substantial increase in the creation of ECM macromolecules by chondrocytes[126]. Undenatured type II collagen is another treatment option that survives digestion with the three-dimensional structure needed to interact with the lymphoid tissue surrounding the small intestine (e.g., Peyer's patches). This is believed to affect the gut immune system, inducing oral tolerance to turn off the immune response targeting type II collagen in joint cartilage[127].

Undenatured type II collagen significantly improved knee function in OA subjects by day 180, compared to placebo and to glucosamine hydrochloride plus chondroitin sulfate, and was well-tolerated[128].

Hyaluronic acid

HA is an anionic, non-sulfated glycosaminoglycan present widely in connective tissues and synovial fluid[129]. It may be supplemented in OA either orally or intraarticularly[130,131].

HA supplements may assist osteoarthritis patients, although data is scarce. A study[132] found that symptoms of knee osteoarthritis improved after three months of HA supplementation in obese people. The researchers found that joint fluid HA concentrations rose, and inflammatory cytokines decreased after treatment. However, this study only enrolled 40 patients.

Another study found that oral HA had similar effects[133]. The 72 knee osteoarthritis patients who received oral HA had lower pain levels and better sleep than the placebo group. They also took fewer painkillers.

Intra-articular HA appears well-tolerated and effective for mild-to-moderate knee OA patients who fail first-line pharmaceutical treatment[134-136].

Vitamin D

Vitamin D supplementation may influence bone reabsorption and can be classified as DMOAD targeting the subchondral bone[121].

These therapies pave the way for chondroprotection, which must act simultaneously as structural support (replacing structural components, i.e., collagen and HA) and a systemic anti-inflammatory action (BSE, curcumin), especially during maintenance treatment.

Intra-articular injections

Intraarticular corticosteroids are a further step in OA management, particularly useful during the flare. Usually, intraarticular corticosteroids provide 4 to 8 weeks of relief. They work well for knee osteoarthritis[137] but not shoulder[138] or hand osteoarthritis[139]. Corticosteroids and lidocaine are usually injected together. Lidocaine might provide rapid relief, confirming the injection was accurate at the proper site. Symptoms may flare up in the first 24 hours and then improve around 48 hours. Repeat injections in the same joint are allowed but usually limited to four per year[140].

Platelet-rich plasma injections may prove useful for alleviating pain, enhancing knee function, and improving quality of life, particularly in younger patients and cases of mild OA[141].

Intra-articular injection of mesenchymal stem cells (MSCs) is a newer intra-articular treatment that may be associated with more effective pain alleviation than cell-free techniques, but further studies are required[142]. Non-pharmacologic intra-articular treatment, such as intra-articular HA, is also available[131]. Intra-articular HA viscosupplementation aims to alleviate pain, improve joint function, and potentially slow down the progression of OA. It has been proven to relieve pain in mild knee OA for up to 24 weeks[143]. However, this therapeutic approach should be reserved for patients who have not received enough pain relief from topical or oral medications and physical therapy. It does not cause significant side effects, and even minor adverse effects like local soreness and swelling usually subside after a few days[144].

Pharmacologic therapies

First-line treatments for osteoarthritis (OA) include NSAIDs and acetaminophen, followed by opioids, serotonin-norepinephrine reuptake inhib-

itors (SNRIs), and intra-articular medications like steroids. It must be underlined that these medications do not modify the disease's natural course or prevent long-term disability. On the other hand, numerous DMOADs have been investigated and are currently in phase-3 and phase-4 studies[121].

Paracetamol

Paracetamol is cheap, safe, and effective[145]. A 2006 Cochrane study[145] found that acetaminophen treats mild osteoarthritis better than placebo and as well as NSAIDs but with fewer gastrointestinal side effects. Patients should take 650 to 1000 mg of acetaminophen four times a day for OA symptoms. The Food and Drug Administration (FDA) advises against taking more than 4000 mg of acetaminophen daily to avoid liver damage[145]. Besides, it must be noted that some scientific organizations have recently indicated that the use of paracetamol and opioids for the treatment of OA is either conditionally advised or not suggested at all[146].

NSAIDs

The next step is NSAIDs, as they are more effective than acetaminophen in the treatment of OA[145]. No NSAID is clearly better than another, so inexpensive, generic medications such as ibuprofen, naproxen, and diclofenac are considered suitable options[145]. Selective cyclooxygenase (COX) 2 inhibitors or nonselective NSAIDs plus a gastroprotective drug should be taken with care in those with gastrointestinal illness[147].

NSAIDs dampen the inflammation by inhibiting the enzyme COX; thus, they provide relief by lowering the systemic and local inflammation, which is a hallmark of OA pathogenesis, but they do not exert chondroprotection[148]. Ideally, an NSAID should influence all the 3 main OA endotypes (bone-driven, synovitis-driven, and cartilage-driven), but this does not really happen. Some NSAIDs may also harm the ECM. For instance, naproxen, indomethacin, and ibuprofen inhibit the synthesis of chondroitin sulfate/dermatan sulfate[149]. Topical NSAIDs have been strongly recommended for knee OA while conditionally recommended for hand OA by the 2019 ACR Guidelines[146].

Topical capsaicin may also be an option for certain OA subsets, such as in the hand, knee, hip, or shoulder[150].

Opioids

Opioids are the next step if the previous has failed, considering side effects such as chronic constipation and respiratory depression. It is recommended that opioids are supplied at low dosages and subjected to diligent monitoring to assess the risk of developing dependence[151].

SNRI

Coming from the hallmark of central sensitization[152] among OA mechanisms of pain, drugs such as SNRI that affect the spinal cord and periaqueductal grey may improve the clinical outcome. The first RCT comparing duloxetine to placebo was conducted by Chapell et al[153]. Average pain ratings improved significantly. Another trial[154] found that duloxetine with an NSAID relieved OA pain better than NSAID alone. This study helped the FDA to approve duloxetine for persistent knee OA.

Disease-Modifying Osteoarthritis Drugs

Interleukin 1 Inhibitors, such as anakinra, TNF-α inhibitors, such as adalimumab and inflximab, and senolytic molecules, such as fisetin, are the main DMOADs that target the synovium[155-158].

Recombinant fibroblast growing factors such as sprifermin, proteinase inhibitors, Wnt signaling inhibitors such as Lorecivivint, AMPk modulators such as metformin, and platelet-rich plasma are the main DMOADs that target the cartilage[159-161]. Finally, strontium ranelate, bisphosphonates such as zoledronic acid, transforming growth factor beta, parathyroid hormone, and cathepsin K inhibitors such as MIV-711, are DMOADS aiming towards the subchondral bone[163-167]. Several drugs, including sprifermin and MIV-711, have effectively prevented cartilage loss or preserved subchondral bone in individuals with OA[159,167]. Lorecivivint significantly improved osteoarthritis patients' WOMAC discomfort, function, and joint space width, and metformin improved pain[161,162]. Conversely, proteinase inhibitors, bisphosphonates, and monoclonal antibodies, such as IL-1β and TNF inhibitors, have not demonstrated efficacy in the treatment of OA[155-157]. The main challenge for managing DMOADs and designing future clinical trials remains the need to personalize the therapy for the specific subset of the disease and the translation from pre-clinical to clinical.

Complementary Therapies

Many complementary therapies have been investigated, such as acupuncture, self-management and education, Tai Chi, balneotherapy, and psychotherapy[168-172]. Despite the widespread use of these treatments, the evidence supporting their effectiveness is of low quality.

Rehabilitative Approaches

Therapeutic exercise should be a key treatment for osteoarthritis[173]. There is a strong need for rehabilitation studies on osteoarthritis of the hip, hand, foot/ankle, shoulder, and spine.

Physical supports, such as bracing, may prove useful in some joints, such as knee OA. Unloading knee braces have the potential to offer symptomatic treatment for individuals with medial and lateral knee OA. Sleeves equipped with a peripatellar device or taping techniques have shown potential benefits in managing patellar OA and have the potential to offer a degree of thermal insulation and alleviate discomfort. Neutral knee braces are useful for multicompartmental knee braces. Finally, lateral and medial wedge insoles have demonstrated potential efficacy in managing OA[174].

Carpometacarpal OA of the thumb base can be managed using semirigid and rigid splints to immobilize the affected joint[175].

Physical modalities, such as laser therapy, ultrasound therapy, and electrotherapy, may also be added to other management strategies for OA patients[176-178].

Interventional Pain Procedures

Several interventional techniques, such as radiofrequency ablation (RA) and electrical neuromodulation, are emerging to reduce joint pain. In some cases, these techniques can be guided by ultrasound as an alternative to fluoroscopy, reducing the impact of X-ray exposure on the patient and physician.

According to the 2019 ACR Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee, RA is only indicated on a case-by-case basis for patients with knee OA[146]. Many studies have shown possible analgesic advantages with various ablation procedures. However, this suggestion is conditional due to the heterogeneity of techniques and controls used and a lack of long-term safety evidence[146].

Regarding hip OA, Mariconda et al[179] reported that continuous radiofrequency (CRF) alleviates pain *via* determining joint neurolysis and may be useful in patients who fail to respond to other lines of treatment.

A recent meta-analysis showed that radiofrequency may prove useful. Musculoskeletal pain covers many districts, from the shoulder to the sacroiliac joint to the spine and the knee[180]. Notably, pulsed radiofrequency in chronic shoulder pain provided analgesia comparable to conservative medical three months after the treatment[181]. Regarding the spine district, when compared to sham treatments or epidural nerve blocks, conventional radiofrequency denervation resulted in reductions in low back pain originating from the facet joints in individuals with the best diagnostic block response throughout the first 12 months[182].

Surgery

Surgical intervention should be exclusively allocated to individuals who have exhibited unresponsiveness to alternative treatment modalities, which equals OA end-stage disease[183]. The widely acknowledged criterion for surgical intervention is the persistence of discomfort and functional impairment despite using non-invasive therapeutic approaches. Various surgical techniques have been explored for the treatment of OA[183]. However, none have achieved the same level of effectiveness as a complete joint replacement, which is considered the most productive surgical strategy, exhibiting favorable patient outcomes in cases of hip, knee, and shoulder joint replacement procedures[184-186]. Total hip replacement (THR) has been renamed "the operation of the century", featuring millions of yearly THRs, with over 95% of patients satisfied with the functional results[187].

Modern surgery techniques allow patients to put the joint under load shortly after surgery. Multimodal pain management is recommended[188], and the hospital stay averages 2-3 days. Among surgical complications, infections, failed prosthesis, wound dehiscence, and deep venous thrombosis represent key elements of post-surgical management that must be actively prevented. For instance, active exercises and early, frequent walking can prevent thrombosis, while pulmonary physiotherapy may prevent atelectasis[189].

A recent longitudinal study that evaluated the quality of life and all the domains of the WOMAC score in patients that had undergone THR or total knee replacement before the surgery and at one year from the surgery reported consistent improvements in all domains concerning physical function as well as those concerning social relationship[190].

Prevention

OA prevention is paramount in preserving joint health and enhancing the quality of life. While some risk factors, like genetics and aging, are beyond our control, there are numerous effective strategies for mitigating the risk of developing OA and countering the low-grade systemic inflammation that is a catalyzer of many diseases.

Maintaining a healthy weight is perhaps the most critical aspect of OA prevention, as the modifiable risk factors section explains. Exercise helps prevent OA through several mechanisms[191]:

1) Strengthening muscles: regular exercise strengthens muscles around the joints, particularly the quadriceps, providing better support and reducing joint stress.
2) Improving flexibility: stretching exercises increase joint flexibility, reducing stiffness and improving range of motion.
3) Weight management: aerobic exercises help maintain a healthy weight, reducing the load on weight-bearing joints.
4) Cartilage health: physical activity stimulates the production of synovial fluid, which nourishes cartilage and reduces friction.

Diet is another key factor in osteoarthritis prevention. A diet rich in antioxidants, omega-3 fatty acids, and essential vitamins supports joint health by reducing inflammation and enhancing cartilage integrity. Conversely, a diet high in processed foods, sugary beverages, and trans fats can exacerbate inflammation and accelerate joint deterioration[32,192].

Proper hydration ensures the synovial fluid is not depleted and may benefit OA prevention and management, even reducing pain[193].

Finally, abstaining from smoking and limiting alcohol intake can reduce the risk of cartilage damage and inflammation[194,195].

Future Strategies: Role of Inflammation Markers in Osteoarthritis

Inflammation markers, such as the neutrophil-to-lymphocyte ratio (NLR), hold significant potential for the early detection and management of OA. NLR is an easily measurable, cost-effective biomarker that reflects systemic inflammation, a critical factor in the pathogenesis of OA. Studies have demonstrated that elevated NLR levels are associated with various inflammatory conditions and can indicate diseases possibly correlated with OA, such as osteoporosis, and subsequent femoral fractures[196-198].

Research has indicated that patients with advanced OA exhibit significantly higher NLR values compared to those with mild OA and healthy controls. This was highlighted in studies where patients with symptomatic knee OA had NLR values that correlated with clinical severity and patient-reported outcomes, such as the WOMAC and the VAS[199,200]. This correlation suggests that NLR could be utilized as a diagnostic tool to identify early inflammatory changes in OA, potentially before significant joint damage occurs.

Moreover, NLR, in conjunction with microRNA-141, has been shown to enhance diagnostic accuracy and predict the severity of OA[200]. This combined approach could improve the identification of high-risk individuals and allow for timely interventions to slow disease progression.

To fully realize the benefits of NLR in OA detection and management, future research should focus on large-scale, longitudinal studies to validate its predictive value and establish standardized thresholds for clinical use. Integrating NLR monitoring into routine practice could enable earlier and more precise interventions, ultimately improving patient outcomes and quality of life[199].

Conclusions

OA is a ubiquitous and debilitating illness that causes pain, decreased quality of life, and high health-care costs that are doomed to increase further due to an increase in the elderly population combined with a rising epidemic of obesity. As we learn more about the pathophysiology of OA, we open the door to novel therapeutic options. Given the disorder's numerous paths, a multidisciplinary approach to treatment and prevention is expected to be the future treatment of OA.

The main challenge is the OA clinical heterogeneity, so efforts must be concentrated on prevention and early diagnosis, which offers the most consistent window of opportunity, and on identifying the phenotype and endotype of the specific patient to personalize the treatment. The validation of new biomarkers will help in this matter.

As this tailored approach enters the daily clinical practice, trials learning from the past failed trials will focus on specific subsets of the disease, helping to develop new drugs such as DMOADs to address the unmet demands of patients with OA.

Conflict of Interest

The authors declare that they have no conflict of interest.

ORCID ID

Filomena Puntillo: 0000-0001-7274-6467
Mariateresa Giglio: 0000-0002-4901-0045
Alberto Corriero: 0000-0002-9760-9394
Stefano Coaccioli: 0000-0001-9972-1366
Diego Maria Michele Fornasari: 0000-0002-9668-3103

Giovanni Iolascon: 0000-0002-0976-925X
Nicola Luxardo: None.
Salvatore Sardo: 0000-0001-7664-8928
Antonella Paladini: 0000-0002-1219-9315
Vittorio Schweiger: 0000-0001-9833-4997
Domenico Tiso: 0000-0001-5001-3668
Gabriele Finco: 0000-0002-3059-9865

Authors' Contributions

Conceptualization, A.C., F.P., M.G., and G.F.; writing–literature review and original draft preparation, A.C., F.P., and M.G.; writing–review and editing, A.P., D.M.F., D.T., G.I., G.F., N.L., S.S. and V.S.; figure preparation, A.C.; supervision, F.P and G.F. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

The authors express their sincere gratitude to the URGO Foundation, which is working with healthcare professionals to promote awareness campaigns and training sessions on treating acute and chronic pain. Additionally, we would like to extend our appreciation to our colleagues and AISD members for generously sharing their valuable insights from their clinical experience.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

The APC for the publication of this paper was founded by Fondation d'Entreprises URGO.

AI Disclosure

We hereby certify that no AI tools or automated writing systems were used in the creation of this research paper. All content, including the text, analysis, and conclusions, were generated by the authors through traditional research and writing methods.

References

1) Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A Disease of the Joint as an Organ. Arthritis Rheum 2012; 64: 1697-1707.
2) Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58: 26-35.
3) GBD 2021 Gout Collaborators. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Rheumatol 2023; 5: e508-22.
4) Cucchiarini M, de Girolamo L, Filardo G, Oliveira JM, Orth P, Pape D, Reboul P. Basic science of osteoarthritis. J Exp Orthop 2016; 3: 22.
5) Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, Zheng MH. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. Arthritis Res Ther 2013; 15: 223.
6) Dell'Isola A, Allan R, Smith SL, Marreiros SSP, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord 2016; 17: 425.
7) Zengini E, Hatzikotoulas K, Tachmazidou I, Steinberg J, Hartwig FP, Southam L, Hackinger S, Boer CG, Styrkarsdottir U, Gilly A, Suveges D, Killian B, Ingvarsson T, Jonsson H, Babis GC, McCaskie A, Uitterlinden AG, van Meurs JBJ, Thorsteinsdottir U, Stefansson K, Davey Smith G, Wilkinson JM, Zeggini E. Genome-wide analyses using UK Biobank data provide insights into the genetic architecture of osteoarthritis. Nat Genet 2018; 50: 549-558.
8) Mobasheri A, Saarakkala S, Finnilä M, Karsdal MA, Bay-Jensen AC, van Spil WE. Recent advances in understanding the phenotypes of osteoarthritis. F1000Res 2019; 8: F1000 Faculty Rev-2091.
9) Mobasheri A, van Spil WE, Budd E, Uzieliene I, Bernotiene E, Bay-Jensen AC, Larkin J, Levesque MC, Gualillo O, Henrotin Y. Molecular taxonomy of osteoarthritis for patient stratification, disease management and drug development: biochemical markers associated with emerging clinical phenotypes and molecular endotypes. Curr Opin Rheumatol 2019; 31: 80.
10) Shoulder Osteoarthritis | NHS Lanarkshire [Internet]. [accessed on October 6, 2023]. Available from: https://www.nhslanarkshire.scot.nhs.uk/services/physiotherapy-msk/shoulder-osteoarthritis/.
11) WHO. Osteoarthritis [Internet]. [accessed on October 6, 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/osteoarthritis.
12) Italy: prevalence of osteoarthritis 2021 [Internet]. Statista. [accessed on October 5, 2023]. Available from: https://www.statista.com/statistics/1316657/prevalence-of-osteoarthritis-in-italy/.
13) GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1204-1222.
14) Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, Lin J, Guo A. Prevalence Trends of Site-Specific Osteoarthritis From 1990 to 2019: Findings From the Global Burden of Disease Study 2019. Arthritis Rheumatol 2022; 74: 1172-1183.

15) Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham osteoarthritis study. Arthritis Rheum 1987; 30: 914-918.

16) Nguyen USDT, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing Prevalence of Knee Pain and Symptomatic Knee Osteoarthritis: Survey and Cohort Data. Ann Intern Med 2011; 155: 725-732.

17) Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995; 38: 1134-1141.

18) Blanco FJ, Silva-Díaz M, Quevedo Vila V, Seoane-Mato D, Pérez Ruiz F, Juan-Mas A, Pego-Reigosa JM, Narváez J, Quilis N, Cortés R, Romero Pérez A, Fábregas Canales D, Font Gayá T, Bordoy Ferrer C, Sánchez-Piedra C, Díaz-González F, Bustabad-Reyes S; EPISER2016 Project Working Group. Prevalence of symptomatic osteoarthritis in Spain: EPISER2016 study. Reumatol Clin (Engl Ed) 2021; 17: 461-470.

19) Murphy LB, Helmick CG, Schwartz TA, Renner JB, Tudor G, Koch GG, Dragomir AD, Kalsbeek WD, Luta G, Jordan JM. One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. Osteoarthritis Cartilage 2010; 18: 1372-1379.

20) Myers H, Nicholls E, Handy J, Peat G, Thomas E, Duncan R, Wood L, Marshall M, Tyson C, Hay E, Dziedzic K. The Clinical Assessment Study of the Hand (CAS-HA): a prospective study of musculoskeletal hand problems in the general population. BMC Musculoskelet Disord 2007; 8: 85.

21) Qin J, Barbour KE, Murphy LB, Nelson AE, Schwartz TA, Helmick CG, Allen KD, Renner JB, Baker NA, Jordan JM. Lifetime Risk of Symptomatic Hand Osteoarthritis: The Johnston County Osteoarthritis Project. Arthritis Rheumatol 2017; 69: 1204-1212.

22) Murray C, Marshall M, Rathod T, Bowen CJ, Menz HB, Roddy E. Population prevalence and distribution of ankle pain and symptomatic radiographic ankle osteoarthritis in community dwelling older adults: A systematic review and cross-sectional study. PLoS One 2018; 13: e0193662.

23) Jaleel A, Golightly YM, Alvarez C, Renner JB, Nelson AE. Incidence and progression of ankle osteoarthritis: The Johnston County osteoarthritis project. Semin Arthritis Rheum 2021; 51: 230-235.

24) Sarzi-Puttini P, Atzeni F, Fumagalli M, Capsoni F, Carrabba M. Osteoarthritis of the spine. Semin Arthritis Rheum 2005; 34 (6 Suppl 2): 38-43.

25) Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol 2013; 9: 216-224.

26) Laplante BL, DePalma MJ. Spine osteoarthritis. PM R 2012; 4 (5 Suppl): S28-36.

27) Uhrenholt L, Charles AV, Gregersen M, Hartvigsen J, Hauge EM. Histological Osteoarthritic Changes in the Human Cervical Spine Facet Joints Related to Age and Sex. Spine 2018; 43: E689-96.

28) Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2008; 34: 515-529.

29) Brouwer GM, van Tol AW, Bergink AP, Belo JN, Bernsen RM, Reijman M, Pols HA, Bierma-Zeinstra SM. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis Rheum 2007; 56: 1204-1211.

30) Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015; 23: 507-515.

31) Saberi Hosnijeh F, Kavousi M, Boer CG, Uitterlinden AG, Hofman A, Reijman M, Oei EHG, Bierma-Zeinstra SM, van Meurs JBJ. Development of a prediction model for future risk of radiographic hip osteoarthritis. Osteoarthritis Cartilage 2018; 26: 540-546.

32) Xu C, Wang S, Ti W, Yang J, Yasen Y, Memetsidiq M, Shi SQ. Role of dietary patterns and factors in determining the risk of knee osteoarthritis: A meta-analysis. Mod Rheumatol 2022; 32: 815-821.

33) Ezzat AM, Li LC. Occupational physical loading tasks and knee osteoarthritis: a review of the evidence. Physiother Can Physiother Can 2014; 66: 91-107.

34) Migliorini F, Maffulli N, Pintore A, Ernst J, Eschweiler J, Hildebrand F, Betsch M. Osteoarthritis Risks and Sports: An Evidence-based Systematic Review. Sports Med Arthrosc Rev 2022; 30: 118-140.

35) Vigdorchik JM, Nepple JJ, Eftekhary N, Leunig M, Clohisy JC. What Is the Association of Elite Sporting Activities With the Development of Hip Osteoarthritis? Am J Sports Med 2017; 45: 961-964.

36) Driban JB, Hootman JM, Sitler MR, Harris KP, Cattano NM. Is Participation in Certain Sports Associated With Knee Osteoarthritis? A Systematic Review. J Athl Train 2017; 52: 497-506.

37) Hou WY, Zhu CY, Gu YF, Zhu L, Zhou ZX. Association of hormone replacement therapy and the risk of knee osteoarthritis: A meta-analysis. Medicine (Baltimore) 2022; 101: e32466.

38) Levy O, Iyer S, Atoun E, Peter N, Hous N, Cash D, Musa F, Narvani AA. Propionibacterium acnes: an underestimated etiology in the pathogenesis of osteoarthritis? J Shoulder Elbow Surg 2013; 22: 505-511.

39) Ramires LC, Santos GS, Ramires RP, da Fonseca LF, Jeyaraman M, Muthu S, Lana AV, Azzini G, Smith CS, Lana JF. The Association between Gut Microbiota and Osteoarthritis: Does the Disease Begin in the Gut? Int J Mol Sci 2022; 23: 1494.

40) Corriero A, Giglio M, Soloperto R, Inchingolo F, Varrassi G, Puntillo F. Microbial Symphony: Exploring the Role of the Gut in Osteoarthritis-Related Pain. A Narrative Review. Pain Ther 2024; 13: 409-433.

41) van Meurs JBJ. Osteoarthritis year in review 2016: genetics, genomics and epigenetics. Osteoarthritis Cartilage 2017; 25: 181-189.

42) Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, Ozaki K, Takigawa M, Tanaka T, Nakamura Y, Jiang Q, Ikegawa S. A functional polymorphism in the 5′ UTR of GDF5 is associated with susceptibility to osteoarthritis. Nat Genet 2007; 39: 529-533.

43) Kerkhof HJ, Lories RJ, Meulenbelt I, Jonsdottir I, Valdes AM, Arp P, Ingvarsson T, Jhamai M, Jonsson H, Stolk L, Thorleifsson G, Zhai G, Zhang F, Zhu Y, van der Breggen R, Carr A, Doherty M, Doherty S, Felson DT, Gonzalez A, Halldorsson BV, Hart DJ, Hauksson VB, Hofman A, Ioannidis JP, Kloppenburg M, Lane NE, Loughlin J, Luyten FP, Nevitt MC, Parimi N, Pols HA, Rivadeneira F, Slagboom EP, Styrkársdóttir U, Tsezou A, van de Putte T, Zmuda J, Spector TD, Stefansson K, Uitterlinden AG, van Meurs JB. A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. Arthritis Rheum 2010; 62: 499-510.

44) Hart DJ, Spector TD. The classification and assessment of osteoarthritis. Baillières Clin Rheumatol 1995; 9: 407-432.

45) Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, Carr AJ. Osteoarthritis. Lancet 2015; 386: 376-387.

46) Eyre DR, Wu JJ, Fernandes RJ, Pietka TA, Weis MA. Recent developments in cartilage research: matrix biology of the collagen II/IX/XI heterofibril network. Biochem Soc Trans 2002; 30: 893-899.

47) Knudson CB, Knudson W. Cartilage proteoglycans. Semin Cell Dev Biol 2001; 12: 69-78.

48) Goldring MB, Marcu KB. Cartilage homeostasis in health and rheumatic diseases. Arthritis Res Ther 2009; 11: 224.

49) Xia B, Di Chen, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. Calcif Tissue Int 2014; 95: 495-505.

50) Akoum J, Corvol MT, Tahiri K, Anract P, Biau D, Borderie D, Étienne F, Rannou F, Nguyen C. Netrin-1 Secreted by Human Osteoarthritic Articular Chondrocytes Promotes Angiogenesis in Vitro. Cartilage 2022; 13: 94-104.

51) Kannu P, Bateman JF, Belluoccio D, Fosang AJ, Savarirayan R. Employing molecular genetics of chondrodysplasias to inform the study of osteoarthritis. Arthritis Rheum 2009; 60: 325-334.

52) Segarra-Queralt M, Piella G, Noailly J. Network-based modelling of mechano-inflammatory chondrocyte regulation in early osteoarthritis. Front Bioeng Biotechnol 2023; 11: 1006066.

53) Barreto G, Manninen M, K Eklund K. Osteoarthritis and Toll-Like Receptors: When Innate Immunity Meets Chondrocyte Apoptosis. Biology (Basel) 2020; 9: 65.

54) Silawal S, Triebel J, Bertsch T, Schulze-Tanzil G. Osteoarthritis and the Complement Cascade. Clin Med Insights Arthritis Musculoskelet Disord 2018; 11: 1179544117751430.

55) Veronese N, Cooper C, Reginster JY, Hochberg M, Branco J, Bruyère O, Chapurlat R, Al-Daghri N, Dennison E, Herrero-Beaumont G, Kaux JF, Maheu E, Rizzoli R, Roth R, Rovati LC, Uebelhart D, Vlaskovska M, Scheen A. Type 2 diabetes mellitus and osteoarthritis. Semin Arthritis Rheum 2019; 49: 9-19.

56) Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017; 19: 18.

57) Smith MD. The normal synovium. Open Rheumatol J 2011; 5: 100-106.

58) Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. Nat Rev Rheumatol 2022; 18: 258-275.

59) Baker-LePain JC, Lane NE. Role of Bone Architecture and Anatomy in Osteoarthritis. Bone 2012; 51: 197-203.

60) Zhu X, Chan YT, Yung PSH, Tuan RS, Jiang Y. Subchondral Bone Remodeling: A Therapeutic Target for Osteoarthritis. Front Cell Dev Biol 2020; 8: 607764.

61) Hu Y, Chen X, Wang S, Jing Y, Su J. Subchondral bone microenvironment in osteoarthritis and pain. Bone Res 2021; 9: 1-13.

62) Zhu S, Zhu J, Zhen G, Hu Y, An S, Li Y, Zheng Q, Chen Z, Yang Y, Wan M, Skolasky RL, Cao Y, Wu T, Gao B, Yang M, Gao M, Kuliwaba J, Ni S, Wang L, Wu C, Findlay D, Eltzschig HK, Ouyang HW, Crane J, Zhou FQ, Guan Y, Dong X, Cao X. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. J Clin Invest 2019; 129: 1076-1093.

63) Hu W, Chen Y, Dou C, Dong S. Microenvironment in subchondral bone: predominant regulator for the treatment of osteoarthritis. Ann Rheum Dis 2021; 80: 413-422.

64) Man G, Mologhianu G. Osteoarthritis pathogenesis – a complex process that involves the entire joint. J Med Life 2014; 7: 37-41.

65) Askari A, Ehrampoush E, Homayounfar R, Arasteh P, Naghizadeh MM, Yarahmadi M, Tarbiat N, Eghbali SS. Relationship between metabolic syndrome and osteoarthritis: The Fasa Osteoarthritis Study. Diabetes Metab Syndr 2017; 11 Suppl 2: S827-S832.

66) Wang T, He C. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine Growth Factor Rev 2018; 44: 38-50.

67) Sampath SJP, Venkatesan V, Ghosh S, Kotikalapudi N. Obesity, Metabolic Syndrome, and Osteoarthritis-An Updated Review. Curr Obes Rep 2023; 12: 308-331.

68) Qiao L, Li Y, Sun S. Insulin Exacerbates Inflammation in Fibroblast-Like Synoviocytes. Inflammation 2020; 43: 916-936.

69) Li Q, Wen Y, Wang L, Chen B, Chen J, Wang H, Chen L. Hyperglycemia-induced accumulation of advanced glycosylation end products in fibroblast-like synoviocytes promotes knee osteoarthritis. Exp Mol Med 2021; 53: 1735-1747. Erratum in: Li Q, Wen Y, Wang L, Chen B, Chen J, Wang H, Chen L. Author Correction: Hyperglycemia-induced accumulation of advanced glycosylation end products in fibroblast-like synoviocytes promotes knee osteoarthritis. Exp Mol Med 2022; 54: 862-865.

70) Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1966-1971.

71) Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12: 412-420.

72) Martin JA, Buckwalter JA. The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repair. J Bone Joint Surg Am 2003; 85-A Suppl 2: 106-110.

73) Sun C, Zhou X, Guo T, Meng J. The immune role of the intestinal microbiome in knee osteoarthritis: a review of the possible mechanisms and therapies. Front Immunol 2023; 14: 1168818.

74) Hao X, Shang X, Liu J, Chi R, Zhang J, Xu T. The gut microbiota in osteoarthritis: where do we stand and what can we do? Arthritis Res Ther 2021; 23: 42.

75) van der Esch M, Knoop J, van der Leeden M, Roorda LD, Lems WF, Knol DL, Dekker J. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. Osteoarthritis Cartilage 2015; 23: 544-549.

76) Zhen G, Fu Y, Zhang C, Ford NC, Wu X, Wu Q, Yan D, Chen X, Cao X, Guan Y. Mechanisms of bone pain: Progress in research from bench to bedside. Bone Res 2022; 10: 44.

77) Cruz-Almeida Y, King CD, Goodin BR, Sibille KT, Glover TL, Riley JL, Sotolongo A, Herbert MS, Schmidt J, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB. Psychological profiles and pain characteristics of older adults with knee osteoarthritis. Arthritis Care Res (Hoboken) 2013; 65: 1786-1794.

78) Otterness IG, Swindell AC, Zimmerer RO, Poole AR, Ionescu M, Weiner E. An analysis of 14 molecular markers for monitoring osteoarthritis: segregation of the markers into clusters and distinguishing osteoarthritis at baseline. Osteoarthritis Cartilage 2000; 8: 180-185.

79) Berry PA, Maciewicz RA, Cicuttini FM, Jones MD, Hellawell CJ, Wluka AE. Markers of bone formation and resorption identify subgroups of patients with clinical knee osteoarthritis who have reduced rates of cartilage loss. J Rheumatol 2010; 37: 1252-1259.

80) Dell'Isola A, Steultjens M. Classification of patients with knee osteoarthritis in clinical phenotypes: Data from the osteoarthritis initiative. PloS One 2018; 13: e0191045.

81) Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. The Lancet 2011; 377: 2115-2126.

82) Im GI. The Concept of Early Osteoarthritis and Its Significance in Regenerative Medicine. Tissue Eng Regen Med 2022; 19: 431-436.

83) Fukui N, Yamane S, Ishida S, Tanaka K, Masuda R, Tanaka N, Katsuragawa Y, Fukui S. Relationship between radiographic changes and symptoms or physical examination findings in subjects with symptomatic medial knee osteoarthritis: a three-year prospective study. BMC Musculoskelet Disord 2010; 11: 269.

84) Schubert T, Denk A, Mägdefrau U, Kaufmann S, Bastone P, Lowin T, Schedel J, Bosserhoff AK. Role of the netrin system of repellent factors on synovial fibroblasts in rheumatoid arthritis and osteoarthritis. Int J Immunopathol Pharmacol 2009; 22: 715-722.

85) Firestein GS, Budd RC, Gabriel SE, Koretzky GA, McInnes IB, O'Dell JR. Firestein & Kelley's textbook of rheumatology. 11th ed. Philadelphia: Elsevier, Inc; 2020: 1547-1561.

86) Expert Guide to Rheumatology Arthur Yee Expert Guide to Rheumatology, Stephen Paget American College of Physicians No of pages: 500 £31.95 1930513 550 1930513550 [Formula: see text]. Nurs Older People 2005; 17: 35.

87) Wesseling J, Boers M, Viergever MA, Hilberdink WK, Lafeber FP, Dekker J, Bijlsma JW. Cohort Profile: Cohort Hip and Cohort Knee (CHECK) study. Int J Epidemiol 2016; 45: 36-44.

88) Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res 2016; 474: 1886-1893.

89) Iagnocco A, Palombi G, Valesini G. Role of ultrasound in osteoarthritis. Rev Esp Reumatol 2001; 28: 301-306.

90) Ariani A, Manara M, Fioravanti A, Iannone F, Salaffi F, Ughi N, Prevete I, Bortoluzzi A, Parisi S, Scirè CA. The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. Reumatismo 2019; 71: 5-21.

91) Luyten FP, Bierma-Zeinstra S, Dell'Accio F, Kraus VB, Nakata K, Sekiya I, Arden NK, Lohmander LS. Toward classification criteria for early osteoarthritis of the knee. Semin Arthritis Rheum 2018; 47: 457-463.

92) Ferrazzo KL, Osório LB, Ferrazzo VA. CT Images of a Severe TMJ Osteoarthritis and Differential Diagnosis with Other Joint Disorders. Case Rep Dent 2013; 2013: e242685.

93) Wenham CYJ, Grainger AJ, Conaghan PG. The role of imaging modalities in the diagnosis, differential diagnosis and clinical assessment of peripheral joint osteoarthritis. Osteoarthritis Cartilage 2014; 22: 1692-1702.

94) Zhang R, Yang X, Wang J, Han L, Yang A, Zhang J, Zhang D, Li B, Li Z, Xiong Y. Identification of potential biomarkers for differential diagnosis between rheumatoid arthritis and osteoarthritis via integrative genome wide gene expression profiling analysis. Mol Med Rep 2019; 19: 30-40.

95) WebMD. How Osteoarthritis Is Diagnosed [Internet]. WebMD. [accessed on October 23, 2023]. Available from: https://www.webmd.com/osteoarthritis/know-if-you-have-osteoarthritis.

96) Rogers-Soeder TS, Lane NE, Walimbe M, Schwartz AV, Tolstykh I, Felson DT, Lewis CE, Segal NA, Nevitt MC; Multicenter Osteoarthritis (MOST) Study Group. Association of diabetes mellitus and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis. Arthritis Care Res 2020; 72: 98-106.

97) Wang X, Xie L, Yang S. Association between weight-adjusted-waist index and the prevalence of rheumatoid arthritis and osteoarthritis: a population-based study. BMC Musculoskelet Disord 2023; 24: 595.

98) Driban JB, Harkey MS, Barbe MF, Ward RJ, MacKay JW, Davis JE, Lu B, Price LL, Eaton CB, Lo GH, McAlindon TE. Risk factors and the natural history of accelerated knee osteoarthritis: a narrative review. BMC Musculoskelet Disord 2020; 21: 332.

99) Leifer VP, Katz JN, Losina E. Chapter 1: The Burden of OA-Health Services and Economics. Osteoarthritis Cartilage 2022; 30: 10-16.

100) Oo WM, Yu SPC, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs 2018; 23: 331-347.

101) Katz JN, Neogi T, Callahan LF, Block JA, Conaghan PG, Simon LS, Kraus VB, Hochberg MC. Disease modification in osteoarthritis; pathways to drug approval. Osteoarthr Cartil Open 2020; 2: 100059.

102) Roemer FW, Kwoh CK, Fujii T, Hannon MJ, Boudreau RM, Hunter DJ, Eckstein F, John MR, Guermazi A. From Early Radiographic Knee Osteoarthritis to Joint Arthroplasty: Determinants of Structural Progression and Symptoms. Arthritis Care Res (Hoboken) 2018; 70: 1778-1786.

103) Iolascon G, Moretti A. Myths and Truths about Placebo Effect in Rehabilitation for Musculoskeletal Pain. Adv Ther 2021; 38: 4995-5001.

104) Uthman OA, Windt DA van der, Jordan JL, Dziedzic KS, Healey EL, Peat GM, Foster NE. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013; 347: f5555.

105) King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res 2013; 138: 185-193.

106) Wang D, Zhang X, Li Y, Jia L, Zhai L, Wei W, Zhang L, Jiang H, Bai Y. Exercise-Induced Browning of White Adipose Tissue and Improving Skeletal Muscle Insulin Sensitivity in Obese/Non-obese Growing Mice: Do Not Neglect Exosomal miR-27a. Front Nutr 2022; 9: 940673.

107) Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005; 64: 544-548.

108) Nejati P, Farzinmehr A, Moradi-Lakeh M. The effect of exercise therapy on knee osteoarthritis: a randomized clinical trial. Med J Islam Repub Iran 2015; 29: 186.

109) Deyle GD, Allison SC, Matekel RL, Ryder MG, Stang JM, Gohdes DD, Hutton JP, Henderson NE, Garber MB. Physical therapy treatment effectiveness for osteoarthritis of the knee: a randomized comparison of supervised clinical exercise and manual therapy procedures versus a home exercise program. Phys Ther 2005; 85: 1301-1317.

110) Buck AN, Vincent HK, Newman CB, Batsis JA, Abbate LM, Huffman KF, Bodley J, Vos N, Callahan LF, Shultz SP. Evidence-Based Dietary Practices to Improve Osteoarthritis Symptoms: An Umbrella Review. Nutrients 2023; 15: 3050.

111) Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. Br J Sports Med 2018; 52: 167-175.

112) Safayhi H, Mack T, Sabieraj J, Anazodo MI, Subramanian LR, Ammon HP. Boswellic acids: novel, specific, nonredox inhibitors of 5-lipoxygenase. J Pharmacol Exp Ther 1992; 261: 1143-1146.

113) Ammon HPT. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomedicine 2010; 17: 862-867.

114) Cuaz-Pérolin C, Billiet L, Baugé E, Copin C, Scott-Algara D, Genze F, Büchele B, Syrovets T, Simmet T, Rouis M. Antiinflammatory and antiatherogenic effects of the NF-kappaB inhibitor acetyl-11-keto-beta-boswellic acid in LPS-challenged ApoE-/- mice. Arterioscler Thromb Vasc Biol 2008; 28: 272-277.

115) Reddy GK, Chandrakasan G, Dhar SC. Studies on the metabolism of glycosaminoglycans under the influence of new herbal anti-inflammatory agents. Biochem Pharmacol 1989; 38: 3527-3534.

116) Safayhi H, Rall B, Sailer ER, Ammon HP. Inhibition by boswellic acids of human leukocyte elastase. J Pharmacol Exp Ther 1997; 281: 460-463.

117) Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. Phytomedicine 2003; 10: 3-7.

118) Insuan O, Janchai P, Thongchuai B, Chaiwongsa R, Khamchun S, Saoin S, Insuan W, Pothacharoen P, Apiwatanapiwat W, Boondaeng A, Vaithanomsat P. Anti-Inflammatory Effect of Pineapple Rhizome Bromelain through Downregulation of the NF-κB- and MAPKs-Signaling Pathways in Lipopolysaccharide (LPS)-Stimulated RAW264.7 Cells. Curr Issues Mol Biol 2021; 43: 93-106.

119) Pothacharoen P, Chaiwongsa R, Chanmee T, Insuan O, Wongwichai T, Janchai P, Vaithanomsat P. Bromelain Extract Exerts Antiarthritic Effects via Chondroprotection and the Suppression of TNF-α-Induced NF-κB and MAPK Signaling. Plants (Basel) 2021; 10: 2273.

120) Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W, Chen H. Efficacy and Safety of Curcumin and Curcuma longa Extract in the Treatment of Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trial. Front Immunol 2022; 13: 891822.

121) Li S, Cao P, Chen T, Ding C. Latest insights in disease-modifying osteoarthritis drugs development. Ther Adv Musculoskelet Dis 2023; 15: 1759720X231169839.

122) Guidelines for Osteoarthritis Treatments | Arthritis Foundation [Internet]. [accessed on October 21, 2023]. Available from: https://www.arthritis.org/diseases/more-about/guidelines-for-osteoarthritis-treatments.

123) Meng Z, Liu J, Zhou N. Efficacy and safety of the combination of glucosamine and chondroitin for knee osteoarthritis: a systematic review and meta-analysis. Arch Orthop Trauma Surg 2023; 143: 409-421.

124) García-Coronado JM, Martínez-Olvera L, Elizondo-Omaña RE, Acosta-Olivo CA, Vilchez-Cavazos F, Simental-Mendía LE, Simental-Mendía M. Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. Int Orthop 2019; 43: 531-538.

125) Oesser S, Seifert J. Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell Tissue Res 2003; 311: 393-399.

126) Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. Curr Med Res Opin 2006; 22: 2221-2232.

127) Bagchi D, Misner B, Bagchi M, Kothari SC, Downs BW, Fafard RD, Preuss HG. Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. Int J Clin Pharmacol Res 2002; 22: 101-110.

128) Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. Nutr J 2016; 15: 14.

129) Laurent TC, Fraser JR. Hyaluronan. FASEB J 1992; 6: 2397-2404.

130) Oe M, Tashiro T, Yoshida H, Nishiyama H, Masuda Y, Maruyama K, Koikeda T, Maruya R, Fukui N. Oral hyaluronan relieves knee pain: a review. Nutr J 2016; 15: 11.

131) Santilli V, Paoloni M, Mangone M, Alviti F, Bernetti A. Hyaluronic acid in the management of osteoarthritis: injection therapies innovations. Clin Cases Miner Bone Metab 2016; 13: 131.

132) Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, Wilton P, Martinez-Puig D, Wu W. The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatol Int 2015; 35: 43-52. Erratum in: Rheumatol Int 2015; 35: 53.

133) Jensen GS, Attridge VL, Lenninger MR, Benson KF. Oral Intake of a Liquid High-Molecular-Weight Hyaluronan Associated with Relief of Chronic Pain and Reduced Use of Pain Medication: Results of a Randomized, Placebo-Controlled Double-Blind Pilot Study. J Med Food 2015; 18: 95-101.

134) Jevsevar D, Donnelly P, Brown GA, Cummins DS. Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence. J Bone Joint Surg Am 2015; 97: 2047-2060.

135) Strand V, McIntyre LF, Beach WR, Miller LE, Block JE. Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials. J Pain Res 2015; 8: 217-228.

136) Richette P, Chevalier X, Ea HK, Eymard F, Henrotin Y, Ornetti P, Sellam J, Cucherat M, Marty M. Hyaluronan for knee osteoarthritis: an updated meta-analysis of trials with low risk of bias. RMD Open 2015; 1: e000071.

137) Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ 2004; 328: 869.

138) Glenohumeral Joint Osteoarthritis - Clinical Practice Guideline (CPG) | American Academy of Orthopaedic Surgeons [Internet]. [accessed on October 22, 2023]. Available from: https://www.aaos.org/quality/quality-programs/upper-extremity-programs/glenohumeral-joint-osteoarthritis/.

139) Meenagh GK, Patton J, Kynes C, Wright GD. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. Ann Rheum Dis 2004; 63: 1260-1263.

140) Bettencourt RB, Linder MM. Arthrocentesis and therapeutic joint injection: an overview for the primary care physician. Prim Care 2010; 37: 691-702, v.

141) Moretti L, Maccagnano G, Coviello M, Cassano GD, Franchini A, Laneve A, Moretti B. Plate-

let Rich Plasma Injections for Knee Osteoarthritis Treatment: A Prospective Clinical Study. J Clin Med 2022; 11: 2640.

142) Zhang Y, Yang H, He F, Zhu X. Intra-articular injection choice for osteoarthritis: making sense of cell source—an updated systematic review and dual network meta-analysis. Arthritis Res Ther 2022; 24: 260.

143) Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19: 611-619.

144) Chavda S, Rabbani SA, Wadhwa T. Role and Effectiveness of Intra-articular Injection of Hyaluronic Acid in the Treatment of Knee Osteoarthritis: A Systematic Review. Cureus 2022; 14: e24503.

145) Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006; 2006: CD004257.

146) Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken) 2020; 72: 149-162. Erratum in: Arthritis Care Res (Hoboken) 2021; 73: 764.

147) Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ 2012; 345: e4934.

148) Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs 1996; 52 Suppl 5: 13-23.

149) Dingle JT. The effects of NSAID on the matrix of human articular cartilages. Z Rheumatol 1999; 58: 125-129.

150) Guedes V, Castro JP, Brito I. Topical capsaicin for pain in osteoarthritis: A literature review. Reumatol Clin 2018; 14: 40-45.

151) Hunter DJ, Lo GH. The management of osteoarthritis: an overview and call to appropriate conservative treatment. Rheum Dis Clin North Am 2008; 34: 689-712.

152) Ohashi Y, Uchida K, Fukushima K, Inoue G, Takaso M. Mechanisms of Peripheral and Central Sensitization in Osteoarthritis Pain. Cureus 15: e35331.

153) Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, Brown JP. A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain Due to Osteoarthritis of the Knee. Pain Pract 2011; 11: 33-41.

154) Brown JP, Boulay LJ. Clinical experience with duloxetine in the management of chronic musculoskeletal pain. A focus on osteoarthritis of the knee. Ther Adv Musculoskelet Dis 2013; 5: 291-304.

155) Chevalier X, Goupille P, Beaulieu AD, Burch FX, Bensen WG, Conrozier T, Loeuille D, Kivitz AJ, Silver D, Appleton BE. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009; 61: 344-352.

156) Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N, Bird P, Jones G. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis - the HUMOR trial. Osteoarthritis Cartilage 2018; 26: 880-887.

157) Güler-Yüksel M, Allaart CF, Watt I, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Schaardenburg D, van Krugten MV, Dijkmans BA, Huizinga TW, Lems WF, Kloppenburg M. Treatment with TNF-α inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. Osteoarthritis Cartilage 2010; 18: 1256-1262.

158) Zheng W, Feng Z, You S, Zhang H, Tao Z, Wang Q, Chen H, Wu Y. Fisetin inhibits IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through activating SIRT1 and attenuates the progression of osteoarthritis in mice. Int Immunopharmacol 2017; 45: 135-147.

159) Eckstein F, Hochberg MC, Guehring H, Moreau F, Ona V, Bihlet AR, Byrjalsen I, Andersen JR, Daelken B, Guenther O, Ladel C, Michaelis M, Conaghan PG. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. Ann Rheum Dis 2021; 80: 1062-1069.

160) Schnitzer T, Pueyo M, Deckx H, van der Aar E, Bernard K, Hatch S, van der Stoep M, Grankov S, Phung D, Imbert O, Chimits D, Muller K, Hochberg MC, Bliddal H, Wirth W, Eckstein F, Conaghan PG. Evaluation of S201086/GLPG1972, an ADAMTS-5 inhibitor, for the treatment of knee osteoarthritis in ROCCELLA: a phase 2 randomized clinical trial. Osteoarthritis Cartilage 2023; 31: 985-994.

161) Kou H, Qing Z, Zhao G, Sun X, Zhi L, Wang J, Chen X, Guo H, Zhang R, Ma J. Effect of lorecivivint on osteoarthritis: A systematic review and meta-analysis. Heliyon 2023; 9: e18682.

162) Alimoradi N, Tahami M, Firouzabadi N, Haem E, Ramezani A. Metformin attenuates symptoms of osteoarthritis: role of genetic diversity of Bcl2 and CXCL16 in OA. Arthritis Res Ther 2023; 25: 35.

163) Yu DG, Ding HF, Mao YQ, Liu M, Yu B, Zhao X, Wang XQ, Li Y, Liu GW, Nie SB, Liu S, Zhu ZA.

Strontium ranelate reduces cartilage degeneration and subchondral bone remodeling in rat osteoarthritis model. Acta Pharmacol Sin 2013; 34: 393-402.

164) Cai G, Aitken D, Laslett LL, Pelletier JP, Martel-Pelletier J, Hill C, March L, Wluka AE, Wang Y, Antony B, Blizzard L, Winzenberg T, Cicuttini F, Jones G. Effect of Intravenous Zoledronic Acid on Tibiofemoral Cartilage Volume Among Patients With Knee Osteoarthritis With Bone Marrow Lesions: A Randomized Clinical Trial. JAMA 2020; 323: 1456-1466.

165) Lee H, Kim H, Seo J, Choi K, Lee Y, Park K, Kim S, Mobasheri A, Choi H. TissueGene-C promotes an anti-inflammatory micro-environment in a rat monoiodoacetate model of osteoarthritis via polarization of M2 macrophages leading to pain relief and structural improvement. Inflammopharmacology 2020; 28: 1237-1252.

166) Sun Q, Zhen G, Li TP, Guo Q, Li Y, Su W, Xue P, Wang X, Wan M, Guan Y, Dong X, Li S, Cai M, Cao X. Parathyroid hormone attenuates osteoarthritis pain by remodeling subchondral bone in mice. Elife 2021; 10: e66532.

167) Conaghan PG, Bowes MA, Kingsbury SR, Brett A, Guillard G, Rizoska B, Sjögren N, Graham P, Jansson Å, Wadell C, Bethell R, Öhd J. Disease-Modifying Effects of a Novel Cathepsin K Inhibitor in Osteoarthritis: A Randomized Controlled Trial. Ann Intern Med 2020; 172: 86-95.

168) Manyanga T, Froese M, Zarychanski R, Abou-Setta A, Friesen C, Tennenhouse M, Shay BL. Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis. BMC Complement Altern Med 2014; 14: 312.

169) Kroon FPB, van der Burg LRA, Buchbinder R, Osborne RH, Johnston RV, Pitt V. Self-management education programmes for osteoarthritis. Cochrane Database Syst Rev 2014; 2014: CD008963.

170) Kang JW, Lee MS, Posadzki P, Ernst E. T'ai chi for the treatment of osteoarthritis: a systematic review and meta-analysis. BMJ Open 2011; 1: e000035.

171) Protano C, Fontana M, De Giorgi A, Marotta D, Cocomello N, Crucianelli S, Del Cimmuto A, Vitali M. Balneotherapy for osteoarthritis: a systematic review. Rheumatol Int 2023; 43: 1597-1610.

172) Helminen EE, Sinikallio SH, Valjakka AL, Väisänen-Rouvali RH, Arokoski JP. Effectiveness of a cognitive–behavioural group intervention for knee osteoarthritis pain: a randomized controlled trial. Clin Rehabil 2015; 29: 868-881.

173) Collins NJ, Hart HF, Mills KAG. Osteoarthritis year in review 2018: rehabilitation and outcomes. Osteoarthritis Cartilage 2019; 27: 378-391.

174) Rannou F, Poiraudeau S, Beaudreuil J. Role of bracing in the management of knee osteoarthritis. Curr Opin Rheumatol 2010; 22: 218.

175) Buhler M, Chapple CM, Stebbings S, Sangelaji B, Baxter GD. Effectiveness of splinting for pain and function in people with thumb carpometacarpal osteoarthritis: a systematic review with meta-analysis. Osteoarthritis Cartilage 2019; 27: 547-559.

176) Dombrowski A, Imre K, Yan M, Kalnins P, Gouge L, Silver D, Zwickey H. Treatment of Osteoarthritis With Low-level Laser Therapy, Acupuncture, and Herbal Therapy: A Case Report. Integr Med (Encinitas) 2018; 17: 48-53.

177) Wu Y, Zhu S, Lv Z, Kan S, Wu Q, Song W, Ning G, Feng S. Effects of therapeutic ultrasound for knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil 2019; 33: 1863-1875.

178) Letizia Mauro G, Scaturro D, Gimigliano F, Paoletta M, Liguori S, Toro G, Iolascon G, Moretti A. Physical Agent Modalities in Early Osteoarthritis: A Scoping Review. Medicina (Kaunas) 2021; 57: 1165.

179) Mariconda C, Megna M, Farì G, Bianchi FP, Puntillo F, Correggia C, Fiore P. Therapeutic exercise and radiofrequency in the rehabilitation project for hip osteoarthritis pain. Eur J Phys Rehabil Med 2020; 56: 451-458.

180) Farì G, de Sire A, Fallea C, Albano M, Grossi G, Bettoni E, Di Paolo S, Agostini F, Bernetti A, Puntillo F, Mariconda C. Efficacy of Radiofrequency as Therapy and Diagnostic Support in the Management of Musculoskeletal Pain: A Systematic Review and Meta-Analysis. Diagn Basel Switz 2022; 12: 600.

181) Pushparaj H, Hoydonckx Y, Mittal N, Peng P, Cohen SP, Cao X, Bhatia A. A systematic review and meta-analysis of radiofrequency procedures on innervation to the shoulder joint for relieving chronic pain. Eur J Pain 2021; 25: 986-1011.

182) Lee CH, Chung CK, Kim CH. The efficacy of conventional radiofrequency denervation in patients with chronic low back pain originating from the facet joints: a meta-analysis of randomized controlled trials. Spine J Off J North Am Spine Soc 2017; 17: 1770-1780.

183) de l'Escalopier N, Anract P, Biau D. Surgical treatments for osteoarthritis. Ann Phys Rehabil Med 2016; 59: 227-233.

184) Gandhi R, Perruccio AV, Mahomed NN. Surgical management of hip osteoarthritis. CMAJ Can Med Assoc J 2014; 186: 347-355.

185) Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, Rasmussen S. A Randomized, Controlled Trial of Total Knee Replacement. N Engl J Med 2015; 373: 1597-1606.

186) Singh JA, Sperling J, Buchbinder R, McMAKEN K. Surgery for Shoulder Osteoarthritis: A Cochrane Systematic Review. J Rheumatol 2011; 38: 598-605.

187) Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet 2007; 370: 1508-1519.

188) Goode VM, Morgan B, Muckler VC, Cary MP, Zdeb CE, Zychowicz M. Multimodal Pain Management for Major Joint Replacement Surgery. Orthop Nurs 2019; 38:150-156.

189) Chen AF, Stewart MK, Heyl AE, Klatt BA. Effect of Immediate Postoperative Physical Therapy on Length of Stay for Total Joint Arthroplasty Patients. J Arthroplasty 2012; 27: 851-856.

190) Mezey GA, Paulik E, Máté Z. Effect of osteoarthritis and its surgical treatment on patients' quality of life: a longitudinal study. BMC Musculoskelet Disord 2023; 24: 537.

191) Kong H, Wang XQ, Zhang XA. Exercise for Osteoarthritis: A Literature Review of Pathology and Mechanism. Front Aging Neurosci 2022; 14: 854026.

192) Xu C, Liu T, Driban JB, McAlindon T, Eaton CB, Lu B. Dietary patterns and risk of developing knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2021; 29: 834-840.

193) ul-Haq F, Yaqoob U, Mehmood M, Siddiqui AA, Usama SM, Hussain SZM, Khan MMA. Characteristics of back pain in young adults and their relationship with dehydration: a cross sectional study. F1000Research 2022; 9: 159.

194) Joseph GB, McCulloch CE, Nevitt MC, Foreman S, Liu F, Lane NE, Link TM. Associations between alcohol, smoking, and cartilage composition and knee joint morphology: Data from the Osteoarthritis Initiative. Osteoarthr Cartil Open 2019; 1: 100006.

195) Magnusson K, Mathiessen A, Hammer HB, Kvien TK, Slatkowsky-Christensen B, Natvig B, Hagen KB, Østerås N, Haugen IK. Smoking and alcohol use are associated with structural and inflammatory hand osteoarthritis features. Scand J Rheumatol 2017; 46: 388-395.

196) Qu Y, Chen S, Han M, Gu Z, Zhang Y, Fan T, Zeng M, Ruan G, Cao P, Yang Q, Ding C, Zhang Y, Zhu Z. Osteoporosis and osteoarthritis: a bi-directional Mendelian randomization study. Arthritis Res Ther 2023; 25: 242.

197) Liu YC, Yang TI, Huang SW, Kuo YJ, Chen YP. Associations of the Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio with Osteoporosis: A Meta-Analysis. Diagnostics 2022; 12: 2968.

198) Cianni L, Perna A, Pietramala S, De Fazio A, Oliva MS, Bocchi MB, Covino M, Ziranu A, Vitiello R. Correlation between Neutrophil-to-lymphocyte ratio and Euthyroid Sick Syndrome in elderly patients with proximal femur fractures. Eur Rev Med Pharmacol Sci 2022; 26 (1 Suppl): 9-15.

199) Chawla A, Paraoan V, Rabiu R, Clark T, Powell S, Grammatopoulos D, Armitage C, Penedo A, Havard A, Metcalfe A, Barlow T, Khatri C. Determining the stress biomarker profile in patients undergoing total knee replacement and the relationship with outcome at 12 months. Knee 2019; 26: 1379-1385.

200) Cai C, Zhang R, Xu X, Li G, Gou H. Diagnostic values of NLR and miR-141 in patients with osteoarthritis and their association with severity of knee osteoarthritis. Exp Ther Med 2021; 21: 1-1.