

Osteoarthritis: A review of pathophysiology, market analysis and current commercial and emerging products

Abstract

Osteoarthritis is a progressive musculoskeletal disease characterized by chronic cartilage degradation, inflammation, joint dysfunction, and pain. More than 600 million people worldwide are affected by osteoarthritis, making it a leading cause of disability. Demographic and societal trends, including an aging population and an increasing incidence of injury-related joint damage, are contributing to a growing demand for osteoarthritis therapeutics. In 2025, the global osteoarthritis therapeutics market was valued at approximately USD 5.49 billion and was projected to grow at a compound annual growth rate of 8.88%. This review summarizes current knowledge of the complex pathophysiology of osteoarthritis, examines major market trends, and evaluates existing commercial therapies as well as emerging clinical and preclinical candidates. This review first discusses what the healthy articular joint looks like and then describes the pathological changes that occur in articular cartilage, subchondral bone, synovium, and surrounding tissue during osteoarthritis progression. An analysis of disease and market trends offers insight into the growing prevalence of osteoarthritis and expanding commercial market. Current therapeutic approaches, including pharmacological treatments, viscosupplementation, and medical devices, are also discussed. Finally, emerging clinical trials and preclinical studies highlight an ongoing need for strategies that can enable long-term remodeling and healing of the osteoarthritic joint environment.

Keywords: osteoarthritis, articular cartilage, subchondral bone, intra-articular therapy, regenerative medicine, mesenchymal stem cells, hyaluronic acid hydrogel, orthobiologics

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Abbreviations: ADAM, a-disintegrin and metalloproteinase; ADAMTS, a-disintegrin and metalloproteinase with thrombospondin motifs; ADSCs, adipose-derived stem cells; BMAC, bone marrow aspirate concentrate; BMLs, bone marrow lesions; BSM, bone substitute material; CEFFE, cell-free fat extract; CAGR, compound annual growth rate; COX, cyclooxygenase; DALYs, disability-adjusted life years; ECM, extracellular matrix; FAs, focal adhesions; HA, hyaluronic acid; IGF, insulin-like growth factor; IL-4, interleukin-4; IL-10, interleukin-10; IOBP, IntraOsseous BioPlasty; MMPs, matrix metalloproteinases; MSCs, mesenchymal stem cells; MFAT, microfragmented adipose tissue; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa B; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; PDGF, platelet-derived growth factor; PRP, platelet-rich plasma; RFA, radiofrequency ablation; SVF, stromal vascular fraction; TIMPs, tissue inhibitors of metalloproteinases; TGF- β , transforming growth factor beta 1; TNF- α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; YLDs, years lived with disability

Introduction

Osteoarthritis is a chronic and debilitating bone and joint disease that is characterized by cartilage degradation, joint inflammation, and osteophyte formation that eventually presents as joint pain, gait disturbance, and disability.^{1,2} Although primarily thought of as a joint disease, osteoarthritis also impacts the function of ligaments, tendons, and bone.¹ Osteoarthritis was long classified as a degradative disease that was a product of gradual wear and tear, but is now understood to also be impacted by inflammatory processes that alter the natural joint.³ This multifaceted disease causes various morphological changes, including fraying tendons, ligaments, and muscles;

synovial inflammation; and fibrotic, thickened connective tissue capsules.¹ Osteoarthritis is one of the most disabling disease globally, especially in developing countries.^{4-6,7} The therapeutic market size for osteoarthritis continues to grow, and current commercial therapies include pharmacologies for pain relief, viscosupplementation, and bone graft substitutes.⁸⁻²² In the clinical and preclinical space, there are a variety of developing injections and cellular therapies aiming to reprogram the intra-articular space and stimulate cellular and extracellular repair.²³⁻³⁹ This review will cover the pathophysiology of osteoarthritis, market size and trends, as well as the current and upcoming products to provide a clear overview of osteoarthritis from an industry perspective.

Healthy physiology

To develop a comprehensive understanding of the pathophysiology behind osteoarthritis, it is first necessary to examine the characteristics of healthy physiology in the joint and subchondral bone. Articular cartilage is a type of hyaline cartilage that lines the articulating ends of bone to provide protection and cushioning from the mechanical load that is experienced by the joint during everyday physiological movement.³ While the bone-cartilage interface is lined with calcified cartilage, there is a transition to softer cartilage moving away from the bone.³ Cartilage is weakly vascularized and has no innervation, contributing to its limited regenerative capacity after damage.⁴⁰⁻⁴³ Weak vascularization creates a hypoxic environment where chondrocytes, the main cells of the cartilage, are forced to rely on diffusion and glucose transporter proteins to get adequate nutrients.^{3,42} Chondrocytes make up less than 1% of the total cartilage matrix. Besides these cells, molecules like type II collagen, fibronectin, aggrecan, and hyaluronic acid along with highly hydrated proteoglycans contribute to the cushioning ability of the cartilage.^{3,41} Within the extracellular

matrix, there is a pericellular matrix that is a specialized protective layer composed of type VI and type IX collagen in addition to the aforementioned components.³ The pericellular matrix engulfs clusters of chondrocytes to provide more structural support to ensure the longevity of the cartilage.³

Healthy cartilage matrix is characterized by a balance of matrix synthesis and degradation, and the regulation of the matrix is done by protein families including metalloproteinases (MMPs), a-disintegrin and metalloproteinase (ADAM), a-disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and tissue inhibitors of metalloproteinases (TIMPs).³ Dysregulation of these proteins can lead to excessive cartilage degradation. Additionally, chondrocytes themselves can recognize mechanical stimulation and stress through integrin signaling. Upon experiencing mechanical load, extracellular matrix-bound integrins will cluster on the cell membrane and prompt the assembly of focal adhesions (FAs). These FAs lead to the activation of signaling pathways and focal adhesion kinases that facilitate an adequate cellular response.⁴¹

The synovial capsule also plays a large role in reducing friction at the joints. Synovial joints are surrounded by a synovial capsule, which is comprised of dense connective tissue and internally lined by the synovial membrane.^{1,3} This capsule is highly innervated, but lacks good vascularization.³ The synovial membrane secretes lubricin and hyaluronic acid to lubricate the joint and reduce friction, and the loose organization of the capsule allows the diffusion of plasma into the synovial fluid.^{1,44} There are two main cell types in the synovium. While type A synoviocytes are debris-clearing macrophages, type B synoviocytes are secretory fibroblast-like cells that also can help to elicit immune responses.⁴⁴ The synovial capsule is also externally lined by fat pads, which are increasingly thought to be involved in synovial function.¹ However, the relationship is still unclear.¹

Changes to the subchondral bone are also implicated in the development of osteoarthritis.⁴³ Subchondral bone is the bone right underneath the articular cartilage, which includes the proximal cortical subchondral bone plate and the cancellous bone trabeculae. Not only does the subchondral bone provide mechanical support to the articular cartilage, but it is a source of nutrients and mesenchymal stem cells that are thought to play an active role in both cartilage regeneration and degradation.⁴³

Diseased pathophysiology

Previously referred to as osteoarthrosis, this debilitating bone and joint disease was renamed osteoarthritis in the late twenties century to reflect the recognition that inflammation deeply contributes to cartilage degradation, subchondral bone remodeling, and disease progression.³ Osteoarthritis symptoms include cartilage degradation, osteophyte formation, synovial inflammation, fibrotic capsule thickening, chronic pain, and swollen joints.¹ Molecularly, this disease is characterized by cell stress, inflammatory responses, and extracellular matrix degradation, as shown in Figure 1.¹ Various phenotypes of osteoarthritis have been identified, including inflammatory, metabolic, hormonal, and mechanical overloading, where the primary drivers of osteoarthritis differ.^{1,41} However, there is not a clear consensus on the different phenotypes, with various groups emerging in the literature, underlining how this disease is not well understood.^{1,41} Osteoarthritis is most common in the knee and hip joints, which consequently represent the largest market size for osteoarthritic therapies.^{1,5}

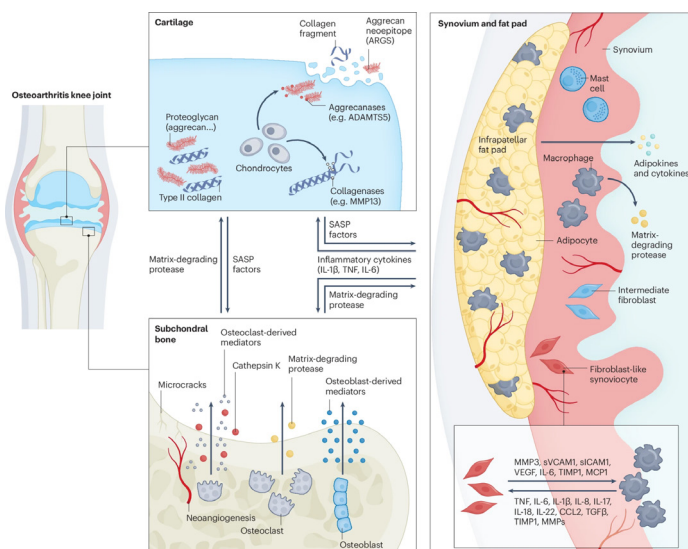


Figure 1 Schematic of Pathological Changes in Osteoarthritis.¹

This image shows an overview of the pathological changes to cartilage, subchondral bone, and synovium during osteoarthritis.

Within the articular cartilage, the balance between matrix synthesis and matrix degradation is disrupted due to a dysregulation of several matrix-associated proteins. Several MMPs, like MMP-1 and MMP-13, are upregulated, leading to excessive extracellular matrix degradation.³ For example, MMP-13 degrades type II collagen, a main component of the cartilage matrix. As MMPs cleave matrix fibronectin, the fibronectin fragments bind with chondrocyte fibronectin receptors to signal damage that upregulates inflammatory signaling through the nuclear factor kappa B (NF-κB) and mitogen-activated kinase (MAPK) pathways. ADAMTSs also experience abnormal activation, with ADAMTS-4 and ADAMTS-5 playing a role in degrading aggrecan, another crucial matrix component.^{3,41} The shift towards MMP and ADAMTS activation favors catabolism, where degradation outweighs rebuilding and the cartilage gradually weakens.³

Besides protein dysregulation, chondrocyte populations shift towards inflammatory subtypes that contribute to the overall chronic inflammation of the joint.¹ As chondrocytes try to repair damaged cartilage, they start to exhibit more fibroblast-like expression that results in excessive cartilage fibrosis.¹ This leads to an upregulation of type I collagen that further degrades native cartilage to replace healthy cartilage with fibrotic tissue.¹ Additionally, there appears to be a loss of integrin homeostasis that normally allows chondrocytes to respond to mechanical stimulation.³ Overall, there are several phenotypic cellular changes associated with osteoarthritis.

Both the subchondral bone and synovium experience changes and can cause pain before visible cartilage degradation begins.¹ Synovitis can accompany osteoarthritis where inflammatory macrophages are upregulated, and overactive type B synoviocytes can cause hyperplasia, the thickening of the capsule's connective tissue.¹ Additionally, inflammation can facilitate angiogenesis that increases immune cell infiltration into the synovium and exacerbates a chronic inflammatory immune response.¹ Changes in the subchondral bone microenvironment also precede cartilage changes.¹ Cartilage erosion is highly associated with areas of subchondral bone defects, like MRI-diagnosable subchondral bone lesions, indicating the impact of

bone density on articular cartilage health.⁴² Increased porosity and decreased bone density leads to abnormal mechanical loading that causes increased bone turnover, and subsequent irregular remodeling can cause bone sclerosis.⁴² The innervation of bone is thought to be associated with the early osteoarthritic pain, since cartilage itself is not innervated.⁴² Besides the synovium and subchondral bone, the health of nearby ligaments, tendons, and muscles can exacerbate osteoarthritis development, and likewise the onset of this disease can lead to the degradation of these structures.^{1,3}

Market size and trends

Impacting over 600 million individuals, osteoarthritis remains a major cause of disability in developed countries.^{3,4} The prevalence of osteoarthritis increased 132% from 1990 to 2020.⁵ The rising global burden of osteoarthritis is associated with the increasing prevalence of obesity and high body-fat levels, and there is also increased risk of osteoarthritis following joint injury.^{3,4} Females experience higher incidence of osteoarthritis, potentially due to fluctuations in estrogen levels that impact bone and cartilage development and pregnancy-related joint stresses.^{4,5} Figures 2a and 2b illustrate the increasing prevalence of osteoarthritis with age, as well as its higher prevalence among females.⁵

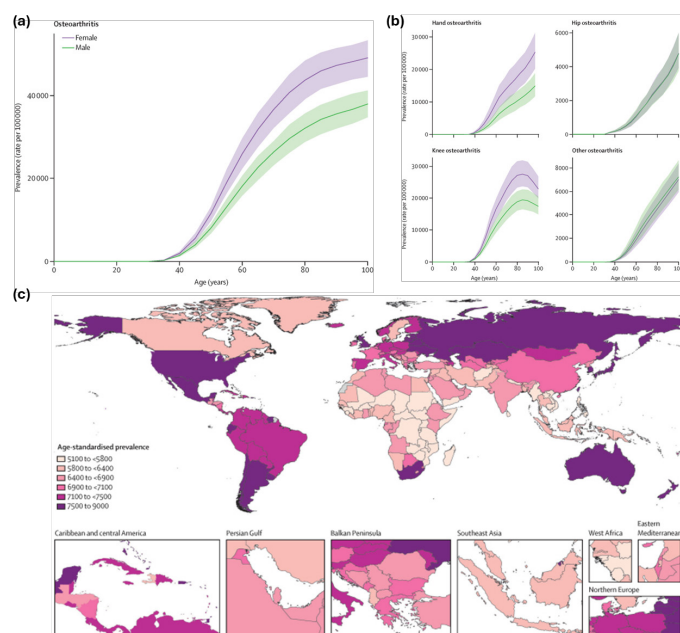


Figure 2 Global Prevalence of Osteoarthritis in 2020.⁵

This image displays the prevalence of osteoarthritis overall by age and sex at various joints, as well as the regional age-standardized prevalence of osteoarthritis.

As of 2021, osteoarthritis was the 14th leading contributor to years lived with disability (YLDs) across all ages, and there was a 24.9% increase in YLD count from 2010 to 2021.⁶ Osteoarthritis most frequently occurs at the knee, followed by the hand and hip, with the knee accounting for 365 million cases globally and 61% of YLDs associated with osteoarthritis. Figure 2c displays the age-standardized prevalence of osteoarthritis globally in 2020, with countries like the United States, Russia, Australia, South Africa, and Argentina displaying the highest rates.⁵ The global average annual cost of osteoarthritis for individual treatment is between \$700 – \$15,600.⁷ In the United States alone, the direct medical cost is estimated at \$72 billion USD, and the indirect costs of osteoarthritis are estimated at around \$12.7 billion.⁷

There are several global trends that are associated with rising osteoarthritis rates. The growing geriatric population majorly contributes to an increasing market size for many bone and cartilage related diseases due to their disproportionate effects on older individuals, including osteoarthritis.⁸ The rising incidence of sports injuries and accident-related damage also drives osteoarthritis rates, as osteoarthritis is associated with prior joint injury.^{3,4,8} Countries with greater development and higher socio-demographic status also experience a high burden of osteoarthritis.⁷

The 2025 therapeutic market size for osteoarthritis was 5.49 billion USD globally, with North America representing the largest market and the Asia Pacific representing the fastest growing market.⁸ The compound annual growth rate (CAGR) from 2026-2033 is estimated to be 8.88%.⁸ As shown by Figure 3, there are various products targeting osteoarthritis, including supplementation and plasma therapy.⁸ There is also expected to be a rise in cartilage-resurfacing products, represented by the “Other” category in Figure 3. The largest companies in this market include Stryker, Zimmer Biomet Holdings, and Medtronic.⁸

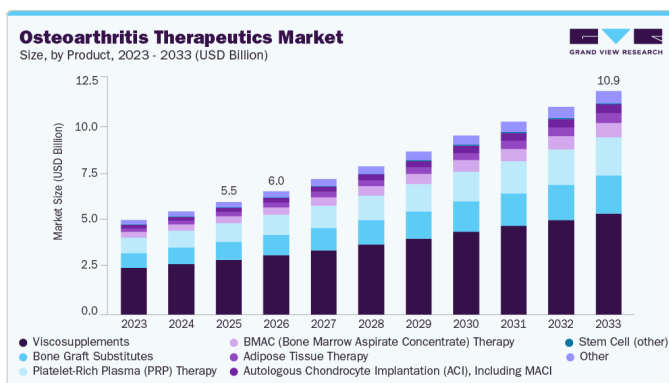


Figure 3 Osteoarthritis Therapeutics Market Growth Overview From 2023 to 2033.⁸

This image shows the projected growth of the osteoarthritis therapeutic market, and is split into different therapeutic sectors like viscosupplements, cell therapy, bone graft substitutes, etc.

Current products

Topical, oral, and intra-articular pharmacologics

To relieve pain and inflammation, there are many topical and oral analgesics that are indicated for use in osteoarthritis therapy. Topical analgesics include nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, and capsaicin. Topical NSAIDs inhibit cyclooxygenase (COX) enzymes involved in prostaglandin-mediated inflammation. Commercial topical NSAID formulations used for osteoarthritis include diclofenac sodium gel, diclofenac diethylamine, eltenac, ketoprofen, and ibuprofen.^{22,23} Salicylates, derived from acetylsalicylic acid, are believed to work through local analgesic and counterirritant effects from COX inhibition and nociceptor desensitization.²² Although generally well tolerated when used topically, salicylates can be associated with adverse effects, including tinnitus, nausea, vomiting, tachycardia, and acute salicylate poisoning. Capsaicins also provide pain relief by facilitating nerve desensitization by irritating nerves over time. Although capsaicin-induced sensory nerve changes are largely reversible after discontinuation, complete recovery may not always occur. Overall, topical analgesics generally have fewer systemic adverse effects than oral analgesics, but they may provide less pain relief than oral medications in some patients.²²

Several oral pharmacologic therapies are also commercially available for osteoarthritis. Oral NSAIDs work through the same COX-inhibitory mechanism as topical NSAIDs, but are associated with gastrointestinal, renal, and cardiovascular side effects. Acetaminophen, another commonly used oral analgesic, activates serotonergic descending pain pathways and inhibits prostaglandin synthesis. However, acetaminophen can cause hepatotoxicity, especially with sustained use or overdose. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has conflicting recommendations for use in osteoarthritis. Due to its ability to relieve depressive symptoms, the Osteoarthritis Research Society International

(OARSI) recommends duloxetine for osteoarthritic patients with comorbid depression. Tramadol, a synthetic opioid with serotonin and norepinephrine reuptake inhibiting activity, is used less commonly.

Intra-articular corticosteroids are injected into the joint space for short-term pain relief. Corticosteroids can interact with cellular receptors to modulate gene transcription and protein synthesis, which decreases immune cell activation and inflammatory cytokines. Injections are most commonly recommended for larger joints like the hip and knee. By contrast, intra-articular injections are used more selectively for osteoarthritis of the hand.²³ Table 1 displays a comparison of commercial pharmacologies used in osteoarthritis care.

Table 1 Summary of current commercially available pharmacologic therapies for osteoarthritis.^{22,23}

Product	Product type	Mechanism of action	Related adverse events
NSAIDs	Topical, Oral	COX inhibition	Elevated blood pressure, gastric/duodenal ulcers, nausea, nephrotoxicity
Salicylates	Topical	COX inhibition and counterirritation	Tinnitus, nausea, vomiting, tachycardia, drowsiness, muscle necrosis, acute salicylate poisoning
Capsaicin	Topical	Counterirritation	Pain, erythema, edema, swelling, nausea, vomiting
Acetaminophen	Oral	Activates serotonergic descending pain pathways and inhibits prostaglandin synthesis	Allergy, hepatotoxicity, thrombocytopenia
Duloxetine	Oral	Serotonin and norepinephrine reuptake inhibitor	Hepatotoxicity, elevated blood pressure, mania, hypomania, seizures
Tramadol	Oral	Serotonin and norepinephrine reuptake inhibitor	Thromboembolism, nausea, dizziness, respiratory depression, dysphoria, constipation, agitation, seizures
Intra-articular corticosteroids	Intra-articular	Regulates gene transcription and protein synthesis to decrease immune response and inflammation	Accelerate cartilage loss, hormonal changes, elevated blood pressure, cytotoxicity

Viscosupplementation

Viscosupplements comprised 48.42% of the total osteoarthritis therapeutic market in 2025.⁸ These intra-articular injections supplement the joint with hyaluronic acid derivatives to restore the shock-absorbing function of natural hyaluronan in the synovial fluid.^{9,10} This is meant to combat the observed loss of hyaluronan concentration and molecular weight in the synovial fluid of patients with osteoarthritis.¹⁰

Commercial viscosupplements are all hyaluronic acid/hyaluronan-based injections, but they vary in molecular weight, source, crosslinking, composition, and recommended frequency of injections.¹⁰ Common formulations include hylan g-f20 products, sodium hyaluronate products, and hyaluronan products.¹¹ Hylan g-f20 is a crosslinked product with a high molecular weight of 6,000 kDA, and it is mainly distributed by Sanofi as Synvisc or Synvisc-One. Synvisc requires three injections over time, while Synvisc-One is more convenient with just one injection.¹¹ Hylan g-f20 has been shown to reduce pain and inflammation, and to promote the synthesis of protein in the extracellular matrix. The cross-linkage of this product allows for a longer-lasting gel, and its use effectively delays knee replacement in patients. However, there are concerns of immunogenicity as this product is derived from rooster comb hyaluronic acid.¹¹

Sodium hyaluronate is the salt form of hyaluronic acid, and has many commercially available products including Euflexxa, Durolane, and Gelsyn-3.¹¹ There are crosslinked and non-crosslinked versions, produced either from animal extract or fermentation techniques. They are effectively able to reduce pain, but animal-derived versions are

at risk for causing allergic reactions and inflammation. Synolis VA from MDBiologix combines hyaluronic acid with sorbitol to slow hyaluronic acid degradation.¹²

Lastly, hyaluronan is a high molecular-weight polysaccharide that is derived from hyaluronic acid and is found in the endogenous extracellular matrix. This protein directly interacts with surface receptors on cells to influence immune responses, and has been linked to both downregulation and upregulation of immune responses. Hyaluronan also has viscoelastic properties that help to better absorb shock and alleviate joint pain. The main hyaluronan commercial products are Orthovisc, Monovisc, and Hymovis, which differ in injection frequency, molecular weight, and crosslinking.¹¹ Figure 4 shows a comparison of various viscosupplement formulations in terms of impact on patient pain and functionality.¹⁰ While viscosupplements are a more accessible method of obtaining pain relief, a major shortcoming is a lack of long-term relief or treatment for the physical damage present in patients.

Bone graft substitutes

Osteoarthritic patients often develop abnormalities in the subchondral bone of impacted joints, causing issues like osteophyte formation and bone marrow lesions (BMLs).¹³ To correct abnormal bone remodeling that can occur secondary to cartilage degradation in osteoarthritic joints, osteotomy may be recommended to realign or reshape damaged bone, improve joint mechanics, and alleviate pain.¹⁴ Meanwhile, to correct BMLs, there are several bone graft substitutes on the market.

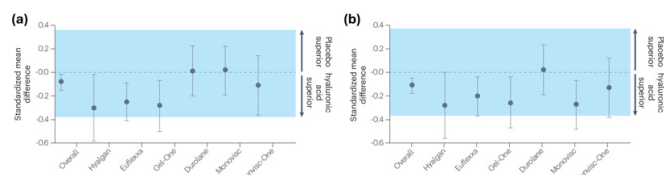


Figure 4 Comparison of Viscosupplements.¹⁰

This image shows a comparison of different commercial viscosupplements based on their effect on pain and patient function based on clinical trial results.

Zimmer Biomet Subchondroplasty® Procedure (Figure 5a) allows for the minimally invasive filling of BMLs with their AccuFill® Bone Substitute Material (BSM). AccuFill® BSM is a mixture of amorphous calcium phosphate and dicalcium phosphate dihydrate that crystallizes at 37° C after implantation in the subchondral bone. The bone mimetic crystalline mixture supports the development of osteoclasts, osteoblasts, and osteocytes, to effectively remodel weakened subchondral bone. The AccuFill® BSM is administered through the openings of a cannula, avoiding the need for extensive surgery and facilitating quick patient recovery. This product has been able to reduce pain and improve function in osteoarthritis patients.¹⁵

Arthrex's IntraOsseous BioPlasty® (IOBP) Technique (Figure 5b) involves decompression of the subchondral lesion to alleviate intraosseous venous hypertension and application of a three-component bone graft substitute.^{16,20,21} The graft substitute formulation combines a demineralized bone matrix with platelet-rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) to stimulate bone regrowth and repair.¹⁶ PRP serves as an autologous source of growth factors like VEGF, TGF-β1, IGF, and PDGF, and its use in repairing bone defects has been shown to promote angiogenesis, stimulate osteoblast and osteoclast activity, and encourage the migration and chondrogenic differentiation of mesenchymal progenitor cells.^{17,18} BMAC, typically autologously harvested from the iliac crest, contains mesenchymal stem cells and supporting growth factors that aid in subchondral bone repair.¹⁹ The IOBP Technique has been reported to reduce joint pain and delay invasive procedures like arthroplasty.²⁰

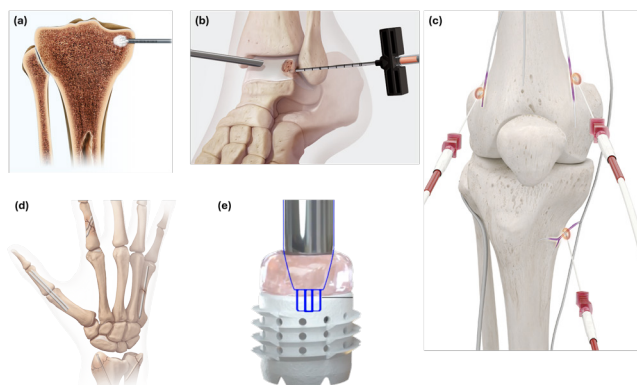


Figure 5 Schematic Examples of Current Commercial Medical Products for Osteoarthritis.^{15,21,24,26,27}

This image shows examples of current commercial medical products for osteoarthritis therapy. (a) Subchondroplasty® procedure from Zimmer Biomet. (b) IntraOsseous BioPlasty® (IOBP) Technique from Arthrex. (c) Genicular radiofrequency nerve ablation from Stryker. (d) Interphalangeal fusion from Arthrex. (e) S-Core® Soft Tissue Anchoring System from Subchondral Solutions, Inc.

Commercial medical products

Several other device-based therapies are used to alleviate osteoarthritis-related pain. Stryker offers radiofrequency ablation systems (Figure 5c) for pain management, including genicular radiofrequency ablation for knee osteoarthritis. In this procedure, radiofrequency is applied to sensory nerves around the knee to disrupt signal transmission.^{24,25} Arthrex offers several fixation products for interphalangeal fusion procedures (Figure 5d) used to treat painful osteoarthritis of the hand and wrist, including bioabsorbable Trim-It™ Drill Pins and Bio-Compression Screws, and the titanium QuickFix™ Cannulated Screw System.²⁶ While fusion can alleviate instability and deformation of the joint, it comes at the cost of mobility and functionality. Additionally, the S-Core® Soft Tissue Anchoring System (Figure 5e) from Subchondral Solutions, Inc. features a multitude of implants to repair subchondral bone damage.²⁷ The implant allows for fixation of soft tissue to bone to structurally reinforce a variety of joints including the knee, hand, foot, elbow, and shoulder.²⁷

Overall, the current commercially available osteoarthritis pharmacologics and therapeutics are mainly focused on treating the symptoms and impacts of osteoarthritis, and do not treat the primary cause of the disease. Many therapies are aimed at pain relief and preserving mobility for as long as possible, with the overarching goal of extending the time before patients require more invasive interventions like knee replacement.

Products in clinical trials and pre-clinical development

Hydrogel injections

In contrast to currently available short-term viscosupplementation of lubricating agents, hydrogel injections like Arthrosamid® and Noltrex™ seek to bring long-term results through just a single administration.^{45,47} Hydrogels can provide a long-term source of joint cushioning to relieve joint pain, and are currently being investigated to treat knee osteoarthritis.⁴⁷ The Arthrosamid® hydrogel is a simple formulation of 2.5% crosslinked polyacrylamide in water, and early results show benefits lasting over 2 years.^{45,46} While the treatment is currently approved in the European Union, clinical testing for FDA approval is ongoing and FDA regulation is the next step.⁴⁵ Similarly, Noltrex, which is already approved for veterinary use in the United States, seems to also be moving toward clinical studies with their polyacrylamide, Ag⁺-loaded hydrogel.^{47,48} Hydrogels could be a promising long-term solution for friction reduction and pain relief, but formulations must have low immunogenicity to prevent amplifying the existing inflammatory environment.

Emerging cell therapies

There are many different regenerative cell therapies that are currently being explored as treatments for osteoarthritis.

Platelet-rich plasma (PRP) therapy

As described earlier, PRP is rich in growth factors and can stimulate the activity of several osteogenic, chondrogenic, and stem cell populations.^{17,18} Although PRP is currently used commercially for subchondral bone defects, its application as an intra-articular injection is also under extensive clinical investigation.²⁸ PRP injections are being evaluated across multiple joints, including the knee, shoulder, and thumb, and have been reported to provide pain relief for up to 18 months in patients with severe knee osteoarthritis.^{29–32} Meta-analysis suggests PRP may be more effective than other intra-articular injection

options, such as corticosteroids or hyaluronic acid derivatives. However, there is an overall lack of standardized protocols, leading to inconsistencies in variables like leukocyte content, blood volume harvested, and PRP administered.²⁹ Previous and ongoing clinical trials aim to better define the therapeutic potential of PRP in osteoarthritis. These include studies comparing PRP to hyaluronic acid injections in the knee, trials investigating the efficacy of different combinations of PRP and hyaluronan, and studies trying to evaluate difference between leukocyte-rich and leukocyte-poor PRP.^{30,33,34} The breadth of ongoing clinical investigation reflects growing interest in PRP-based therapies, a trend further supported by the expanding PRP market.⁸

Bone marrow aspirate concentrate (BMAC) therapy

BMAC, which is also administered through intra-articular injection, provides mesenchymal stem cells, hematopoietic progenitors, and growth factors to the damaged joint to drive tissue repair.^{19,35} BMAC injections have been investigated for several years now, and recent studies show that it may be associated with a reduction of BMLs, as well as improvements in pain and function in knee osteoarthritis over a 12-month period.³⁵ While BMAC has not been as widely pursued as PRP injections, several recent completed and ongoing clinical trials are assessing the efficacy of BMAC injections in the knee, including studies comparing BMAC to corticosteroid injections.^{36–38}

Adipose tissue therapy

Another widely researched area in osteoarthritis therapeutics is adipose tissue-based therapy. The cartilage repair potential of adipose tissues has been investigated in many cellular and cell-free products.³⁹ Microfragmented adipose tissue (MFAT) is thought to provide a natural scaffold that supports cartilage repair and chondrocyte migration, reducing inflammatory markers like TNF- α and providing long-term pain relief. Stromal vascular fraction (SVF) is a mixture of vascular-derived cells that promote type II collagen production. While there is short-term efficacy, more investigation is required to understand SVF's full therapeutic potential. Adipose tissue has emerged as an accessible source of stem cells, prompting further studies into the use of adipose-derived stem cells (ADSCs) for osteoarthritis. Additionally, dedifferentiated adipocytes (DFAT) have the ability to differentiate into chondrogenic, osteogenic, and vascular lineages, giving them the potential to promote tissue regeneration. There are several non-cellular adipose therapies like ADSC extracellular vesicles and cell-free fat extract (CEFFE), although these require additional processing for decellularization.³⁹ Combination adipose-based therapies are also being explored, including current studies evaluating MFAT in combination with hyaluronic acid.⁴⁰

Pre-clinical research: Tribosupplementation

Tribosupplements are an umbrella term for cartilage lubricants, which are currently being widely explored preclinically. Fluid additives and cartilage-bound supplements represent the two broad categories of tribosupplements currently being investigated.¹⁰ Fluid additives are designed to reduce cartilage-to-cartilage contact by enhancing the synovial fluid, while cartilage-bound therapies aim to bolster the strength of the articular cartilage surface.¹⁰ Tribosupplements of both subcategories can exist as linear polymer, hydrogel, or particle formulations.¹⁰ The exploration into broader biomaterials and polymer platforms can expand the possibilities for osteoarthritis therapies. However, the use of exogenous materials in these approaches must be rigorously evaluated for biocompatibility, immunogenicity, and toxicity, a drawback not shared by autologous therapies.^{49–52}

Conclusions

Osteoarthritis is both marked by wear and tear processes and chronic inflammation, and there are changes to the subchondral bone, synovial fluid, cartilage composition, and chondrocyte populations.^{1,3} Current commercial products aim to restore the integrity of the joint and surrounding structures to relieve pain and revive function.^{3,22,23,8–21} There is a growing therapeutic market around osteoarthritis, with particular interest into cellular therapies like platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and adipose-derived tissue-based therapies.^{17,35,39} There are no effective cures to osteoarthritis at this time, and the goal of many current therapies is to delay the need for invasive surgeries like knee or hip replacement. The numerous active and completed clinical trials surrounding osteoarthritis demonstrate the substantial industry-wide effort to develop novel and superior therapeutics, with many studies investigating the effects of combination products that utilize multiple new technologies.^{30–34,36–38,40} The market for osteoarthritis therapeutics will continue to grow over the next decade as the global geriatric population rises, and new therapies may continue to emerge as researchers develop a better understanding of the pathophysiology of osteoarthritis.⁸

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Conflict of interest

Authors declare that there is no conflict of interest.

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