

# Pain in Osteoarthritis: Can Prolotherapy Help?

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**O**steoarthritis (OA) remains the most common joint disease in the world, and to date, has no cure. Approximately 27 million people in the United States (1) suffer from OA, which is characterized by chronic pain, joint stiffness, structural damage, and bone remodeling and is caused by the progressive loss of cartilage. The prevalence of chronic pain in OA has been estimated to range from 8% to more than 60%, depending on the types of populations studied and the methodologies used (2). Economically, the impact of arthritis on lost productive work time for 2003/2004 was estimated to be \$7.1 billion, with 66% of these costs attributed to 38% of workers who had pain exacerbations (3). OA-related annual medical costs in 2007 were \$6,811 per patient for those newly diagnosed and \$6,407 for existing patients. Annual costs of pain-related prescription drugs associated with OA were \$965 each for new patients and \$1,117 for existing patients (4).

Joint pain in OA results from the interactions between

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structural changes, physical impairments, and psychological factors, and researchers have concluded it should be viewed in the context of this composite framework

(5). Treatment, therefore, means addressing the patient's functional stamina, cortical experience of pain, and pain sensitization, as well as the interactions occurring within the joints. Given this, clinicians and pain physicians alike can serve their patients well by gaining a better understanding of the pathogenesis of OA and offering them a treatment option that addresses the underlying cause—the progressive loss of cartilage. Prolotherapy is a regenerative

injection technique that addresses this cause because it has the potential for stimulating cartilage renewal (6). By aiding in healing arthritic joints and relieving pain, prolotherapy is emerging as a promising treatment option for patients diagnosed with OA.

## Structural Changes in OA

OA is characterized by an insidious and progressive disease process in which joints undergo recurring cycles of derangement and sustain damage through a stream of events that alter both joint structure and joint morphology (6,7). While OA is considered a disease of the articular joints, the precipitating factor behind joint degeneration is the progressive loss of articular cartilage. Once full thickness loss is reached, joint space narrowing, subchondral bone remodeling, osteophyte formation, and varying degrees of synovial inflammation begin to develop (7). OA is believed to be the result of both mechanical and molecular events that occur in and around the joint, upsetting the balance between anabolic and catabolic activity and affecting joint integrity. In the case of cartilage, excessive matrix degradation begins to overwhelm matrix synthesis, precipitating full thickness loss of the tissue and subsequent OA progression. Once articular cartilage reaches full thickness loss, joint movement becomes noticeably restricted.

Healthy cartilage has a smooth lubricated surface that facilitates joint movement. However, as cartilage loss increases, the tissue loses this surface, preventing the joint from sliding over bone (8). The loss of the joint's gliding motion not only limits movement, but also causes the spaces between the joint and bone to narrow, exposing the underlying subchondral bone. This precipitates a process of bone remodeling in which the subchondral bone thickens and a poorly mineralized matrix develops. In cases of extensive bone remodeling, the ends of bones can rub together and bone marrow lesions can appear. These bony growths, or osteophytes, form at the margins of joint surfaces and can be detected radiographically. Such remodeling events reflect the pivotal role of articular cartilage in the pathogenesis of OA

and underlie its importance in joint homeostasis.

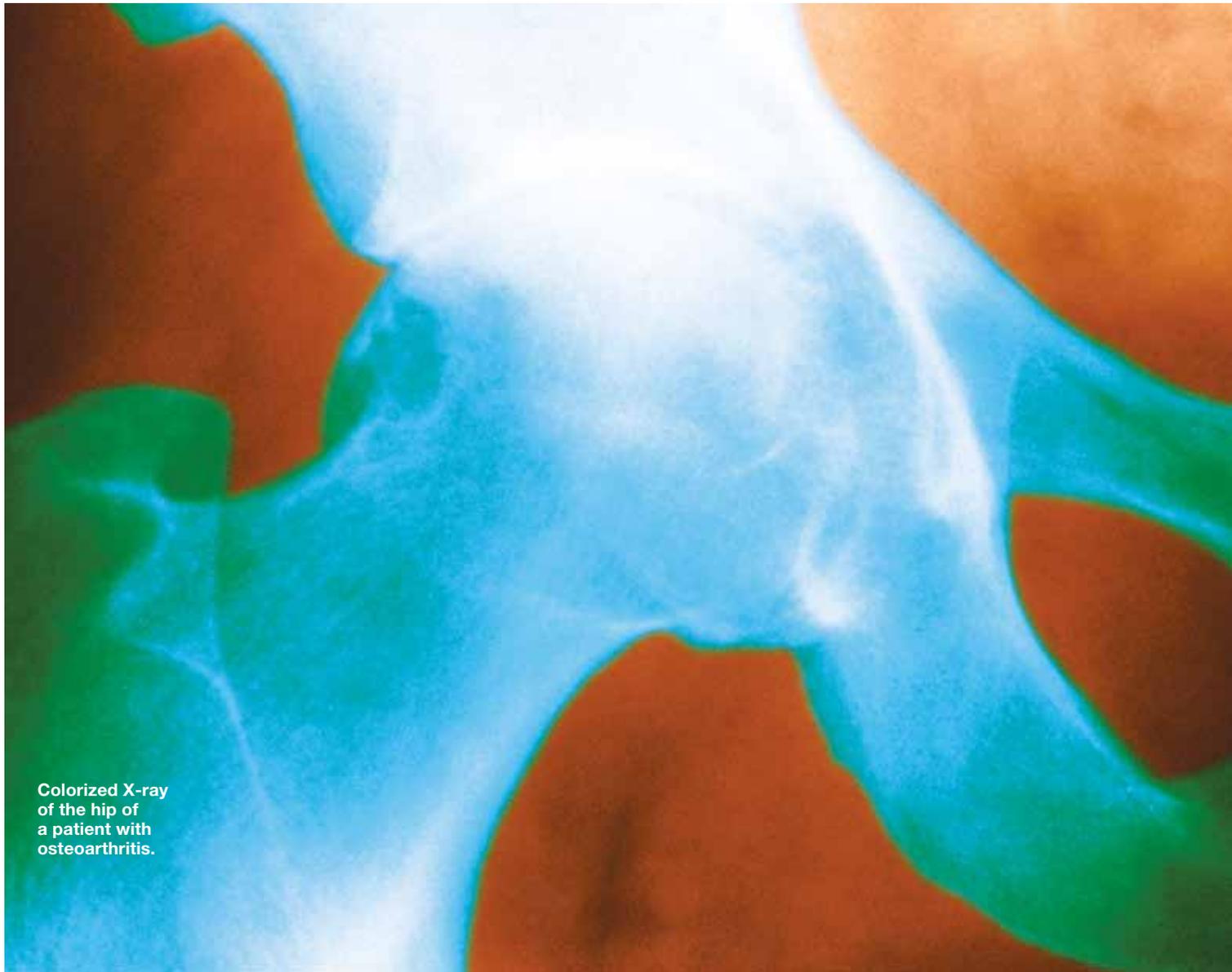
### Role of Cartilage in OA

Despite its central role in the development and progression of OA, articular cartilage is not a source of OA pain since the tissue does not contain nerve fibers. The sources of nociception in OA are the synovium, subchondral bone, periosteum, joint capsule, and periarticular ligaments and muscle, which are all highly innervated (9). As the disease progresses, pathological changes in the joint structures stimulate the nociceptive fibers and mechanoreceptors that elicit pain; in knee or hip OA, pain can also arise from bone marrow lesions and synovitis/effusion (10).

Cartilage is unique because it contains only one cell type—the chondrocyte. Chondrocytes are responsible for both the synthesis and breakdown of the tissue's cartilagi-

nous extracellular matrix. Thus, their loss to cell death equates to a decline in actual cell numbers, which is most apparent in the tissue's superficial zone at the joint surface where changes in cartilage first occur (11).

Chondrocytes are normally quiescent, but during the early stages of OA, they undergo a change in phenotype, characterized by cell proliferation and cluster formation and increased production of matrix proteins and matrix-degrading enzymes. However, these matrix components are not as viable or the same as those made by normal adult chondrocytes (12). The impaired cartilage properties also appear to trigger subsequent damage to the collagen network and negate attempts at matrix repair (13). Although the precise mechanisms are not known, abnormal mechanical stimulations are thought to generate dysfunctional chondrocytes, furthering the breakdown of the cartilage



Colorized X-ray of the hip of a patient with osteoarthritis.

extracellular matrix and leading to degradation of articular cartilage (See Figure) (14).

OA may present in patients as radiographic OA, symptomatic OA, or both. Evidence of radiographic OA is demonstrated by changes in osteophytes (bone spurs or bony overgrowths), with signs of subsequent joint space narrowing and bony sclerosis signaling disease progression. Symptomatic OA is generally defined by the presence of pain, aching, or stiffness in a joint showing radiographic OA (15). While radiographs have remained the preferred imaging tool in OA, they should not be used alone to establish a diagnosis since many patients with solid clinical evidence of OA may have normal radiographs and vice versa. However, radiographic findings can be helpful in determining the prognosis of patients with OA. As degeneration progresses, the breakdown of cartilage and underlying bone within the joint leads to pain and joint stiffness and the development of symptomatic OA. Additional symptoms include restricted joint mobility, deformity, and swelling, the latter of which can be caused by bony remodeling, excessive osteophytosis, or joint subluxation, as well as by a phenomenon

called crepitus, which is a grinding, crackling, or grating sensation felt in the joint.

**Pain in OA**

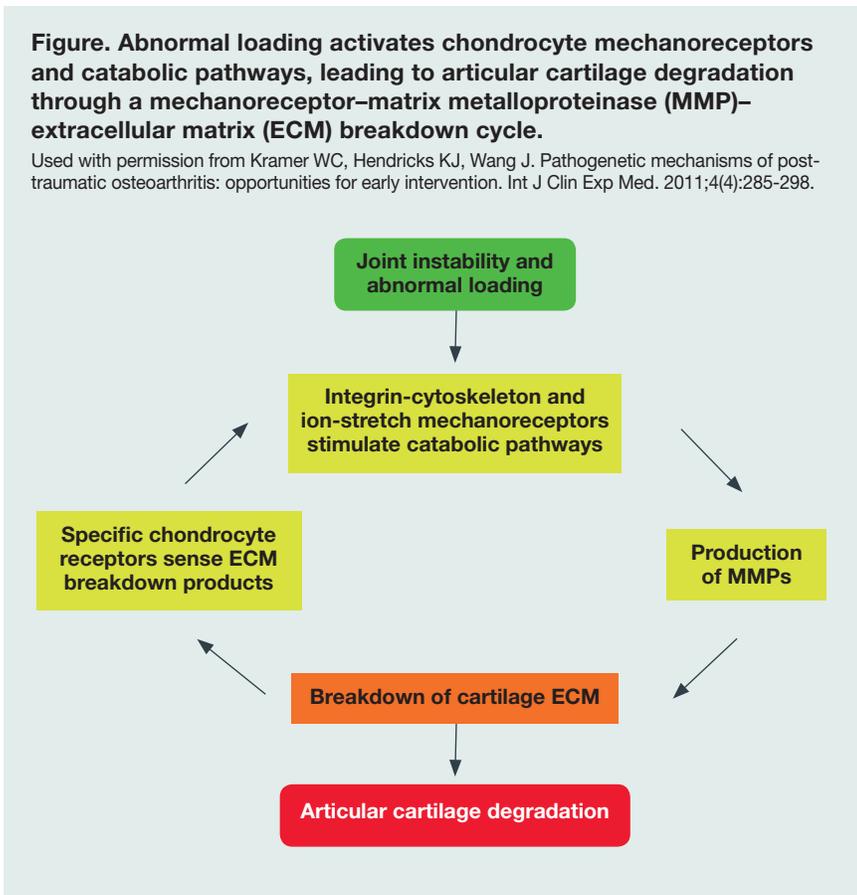
OA pain typically progresses through three stages, although not all patients go through each distinct stage (10). Joint pain is generally referred to as mechanical (Stage 1), meaning it occurs with and is exacerbated by physical exertion, especially weight-bearing activity, and is relieved by rest. As OA progresses, pain may become more persistent and begins to manifest itself at rest (Stage 2), usually doing so with an insidious onset. This unremitting pain is often described as deep, aching, and not well localized, and over time, leads to joint stiffness, loss of function, and an inability to perform daily activities (Stage 3). However, patients with the same degree of structural damage can experience widely different levels of pain, most likely because of differences in joint forces and joint stress during functional activities.

In knee OA pain is usually most severe over the joint line (10). Knee joint pain is felt anteriorly, and the location and pattern of pain indicate which of the compartments is affected. Pain is anteromedial in medial compartment tibiofemoral joint OA, and joint-line tenderness is felt anteriorly on either side of the patella tendon when the knee is flexed. Pain is anterior and behind the patella in patellofemoral joint OA and can occur in the presence of patellofemoral compression, joint deformity, quadriceps wasting and weakness, or hip muscle weakness. Pain is worsened by prolonged sitting, by standing up from low chairs, and by climbing or descending stairs.

Like knee OA, hip OA presents with pain, stiffness, and restricted movement. However, in hip OA the most severe pain radiates distally from the originating joint (10). Pain caused by hip OA usually presents at and is maximal deep in the anterior groin, but may spread to the anteromedial or upper lateral thigh, and occasionally to the buttocks. Some investigators speculate that femoroacetabular impingement (FAI) may account for most cases of idiopathic hip OA, partly because it usually presents as groin pain (15). FAI occurs with repetitive abutment between the proximal femur and the acetabular rim and is due to abnormal hip mor-

**Figure. Abnormal loading activates chondrocyte mechanoreceptors and catabolic pathways, leading to articular cartilage degradation through a mechanoreceptor–matrix metalloproteinase (MMP)–extracellular matrix (ECM) breakdown cycle.**

Used with permission from Kramer WC, Hendricks KJ, Wang J. Pathogenetic mechanisms of post-traumatic osteoarthritis: opportunities for early intervention. *Int J Clin Exp Med.* 2011;4(4):285-298.



phology or excessive hip motion. Repeated abutment leads to degeneration of the labrum and damage to circumferential cartilage. Hip-referred pain sometimes occurs at the knee, but unlike knee-originating pain, it is usually more generalized, involves the distal thigh, and tends to lessen with rubbing. Both active and passive hip movements may be painful. Pain can be exacerbated by rising from a seated position or walking (10). The earliest movement to be restricted is often internal rotation with the hip flexed, but in severe disease movements may be globally restricted.

The origin of pain in OA is not completely understood, but excessive neuronal activity in the pain pathway is responsible for the generation and ultimate exacerbation of the joint pain that patients experience (16). The generation of pain evolves through the activation and transmission of nociceptive fibers and mechanoreceptors in and around the joint compartments. With OA progression, inflammatory mediators accumulate in the joint and trigger a self-perpetuating cycle of pain generation. Overall, the recurring cycles of pain generation make normal joint movements such as walking a painful sensation (17).

### **Disease Progression and Pain Exacerbation**

The synovium appears to be involved in the inflammatory process in OA, and synovitis is a possible pain generator (9,18). As full-thickness cartilage loss begins to occur, the subchondral bone becomes exposed, and unmyelinated free nerve endings present in the structure can and most likely do generate pain. In a study of 182 individuals with knee OA (305 knees), Moision and colleagues identified a relationship between the percent of denuded bone and pain, specifically that between subchondral bone plate exposure and prevalent and incident knee pain (19). Bone marrow lesions and increased bone remodeling can be detected by MRI or bone scans in areas of cartilage loss in people with OA and are associated with pain as well as disease progression (11,17). Recent studies into the clinical relevance of OA features (20), such as subchondral bone edema-like lesions or bone marrow lesions, have shown that these lesions can change measurably in a matter of weeks, as seen on MRI, and tend to enlarge with time and with disease severity.

### **Psychological Impact of Chronic Pain**

Chronic pain, such as that occurring in OA, often becomes a pathological source of disability and distress to patients (9) and often results in catastrophizing and avoidance

behavior. Traditional cognitive behavioral therapy (CBT) emphasizes changing maladaptive cognitions, including the magnification, rumination, and helplessness involved in catastrophizing, to improve emotional and physical functioning. Patients' acceptance of pain in their CBT treatment has been identified as an important factor in improving outcomes (21).

Pain catastrophizing and pain-related fear, in particular, have been strongly and consistently associated with pain severity and disability in patients with knee OA (22). Likewise, low self-efficacy and helplessness have been identified as predictors of disability in OA patients. In some cases, educational interventions, such as pain-coping skills training, have had positive effects on outcomes (23-25). Despite these positive results, another study showed that individuals with lower preoperative radiographic OA severity were more likely to experience high pain following joint replacement surgery (26). This paradoxical finding indicates that risk factors for chronic pain following such surgery remain mostly unknown and underlies the complexities involved in pain perception. Pain is a highly charged and emotional experience that is hard to describe and even more difficult to quantify. Today many pain specialists are focusing on cell-based therapy in hopes that its more biologically relevant basis may make it a more effective treatment for resolving pain. Multiple small exploratory autologous and allogeneic cell therapy-based clinical trials with both pain and structure endpoints are currently underway (clinicaltrials.gov) for the treatment of OA (7).

### **Prolotherapy: an Under-recognized Treatment Option for Unresolved Pain in OA**

Prolotherapy, also known as proliferative therapy, regenerative injection therapy, or platelet rich plasma (PRP) therapy, is emerging as a promising treatment option for musculoskeletal and arthritic pain. Prolotherapy injections target multiple potential pain generators in and around painful joints and are typically administered into joints and surrounding ligaments of the spine, pelvis, and peripheral joints to tighten unstable joints. Prolotherapy has shown success in a number of case series, including patients with diagnosed OA (6, 27-39).

In Hackett-Hemwall prolotherapy, a small amount of a proliferant solution such as hypertonic dextrose, sodium morrhuate, or polidocanol is injected into the painful entheses of ligaments or tendons, as well as at trigger points

and adjacent joint spaces. This produces an inflammatory response involving fibroblastic and capillary proliferation, along with growth factor stimulation, that induces healing and strengthening of the damaged or diseased structure (40-42). When OA is advanced, cellular prolotherapy, which utilizes cellular and extracellular matrix components of the blood, fat, or bone marrow, is recommended. This cell-based technique consists of intra-articular injections of the PRP portion of the blood or progenitor cells from a lipoaspirate or bone marrow aspiration (43). The goal of this type of prolotherapy treatment is not only pain relief but also regeneration of joint structures including articular cartilage.

Prolotherapy has shown success in alleviating pain and improving function in OA (31,44-47). Rabago and his group recently conducted two studies, one a single-arm uncontrolled study (44) and another, a three-arm randomized controlled trial (RCT) (45), using dextrose prolotherapy in the treatment of symptomatic chronic knee OA. In the single-arm trial, they compared pain and disability scores for participants before and after receiving prolotherapy; in the randomized controlled trial, they compared the effects of prolotherapy with blinded saline control or at-home exercise therapy. Outcomes in both studies showed significant improvements in WOMAC scores at one year post treatment compared to baseline; in the RCT, knee pain scale scores in the dextrose prolotherapy group were also significant compared to at-home exercise or saline-control injections. Reeves and Hassanein (46,47) previously conducted two prospective, randomized, double-blind, placebo controlled trials that showed the efficacy of dextrose prolotherapy in relieving OA pain. In a knee OA study, dextrose prolotherapy resulted in statistically and clinically significant improvements in pain, swelling, buckling, and flexion range of motion at six months, as compared with a control solution, according to Visual Analogue Score ratings (46). In a finger/thumb OA study (47), participants assigned to prolotherapy treatment achieved significant improvement in pain with movement of fingers, compared with the control group.

Overall, dextrose prolotherapy treatment, as reported in these studies, resulted in safe, significant, and sustained improvements in quality-of-life, function, stiffness, and pain measures for OA. Studies using cellular proliferants for prolotherapy have also demonstrated efficacy in OA. In one study of patients with knee OA, PRP prolotherapy significantly improved pain, function, stiffness, and quality of life at six months following intra-articular infiltration of plasma

rich in growth factors (PRGF) (48). These results were confirmed in a separate study involving 115 knees with articular degeneration in which significant improvements in pain, function, and quality of life were documented at 6 and 12 months following treatment (49). Another study involving 15 knees showed no change in MRIs, although statistically significant changes in pain, function, and activities of daily living were observed at one year (50).

More recent research in prolotherapy has involved the use of mesenchymal stem cells (MSCs) from adipose tissue and bone marrow, which can differentiate into various connective tissue types including cartilage (51-53). While no RCTs have been conducted, smaller studies using autologous bone marrow MSCs had positive outcomes; overall improvements in pain, functional status of the knee, and walking ability, as well as in cartilage quality, were reported (54,55). In our own clinic, intra-articular autologous bone marrow injections in combination with dextrose prolotherapy showed statistically significant improvements in VAS scores, stiffness, and range of motion, even in patients with severe OA who had been advised to have joint replacement surgery (6,56).

## Conclusion

Pain is a highly charged and emotional experience that is hard to describe and even more difficult to quantify, and the pain experienced in osteoarthritis is no exception. Osteoarthritic pain is a complex issue for patients and their health care providers, the latter of whom have relatively few effective treatment options to offer in terms of pain resolution and return of function. Prolotherapy is an injection technique that aids in healing arthritic joints and relieving pain and is emerging as a promising treatment option in OA.

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