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Nonsurgical Management of Cartilage Defects of the Knee: Who, When, Why, and How?

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Abstract

The nonoperative practitioner managing individuals with cartilage defects should use a patient-centered, multifaceted approach that aims to individualize treatment to provide optimal benefit. These include addressing modifiable risk factors for disease progression and instituting interventions such as weight loss, nutrition, physical activity, and potentially regenerative medicine strategies. This review will focus on these nonoperative treatment strategies with a focus on when treatments are necessary, who will benefit from these approaches, why they are specifically appropriate, and, finally, how these treatments directly modify the structure of a patient's cartilage and resulting symptoms.

Keywords
- cartilage
- osteoarthritis
- knee

Cartilage damage can progress in the form of focal lesions or diffuse articular cartilage loss, the latter of which is characteristic of osteoarthritis (OA). Global prevalence of knee OA in 2010 was approximately 3.8%,[1] which translates to an estimated 268 million people.[2] While much of the current evidence to treat cartilage defects is centered around patients with OA due to its widespread and growing impact, nonsurgical treatment of focal cartilage lesions involves similar goals: to improve pain, function, quality of life, and limit structural disease progression. Thus, the focus of this review will be on nonsurgical treatments for OA that can be extrapolated to guide effective management of focal cartilage defects. Altered joint mechanics and intra-articular biological processes are thought to play pivotal roles in the initial breakdown and potentiation of cartilage damage, which is the hallmark of OA. Cartilage lacks innervation and therefore patients are often unable to perceive pain at the point of damage, predisposing them to the development of OA while continuing to load their joints over time. In addition, cartilage also has a poor vascular supply, which limits its reparative capacity, further proliferating degenerative disease. Known risks factors for the development of cartilage defects include being older in age, being female, being overweight or obese, and having a history of prior joint trauma.[3,4] Each of these factors has a multitude of pathophysiological processes that increase the risk for OA development. For example, joints in older individuals have been shown to develop a homeostatic imbalance in catabolic and anabolic activity of chondrocytes, leading to greater cell death in their cartilage.[5] Women are believed to be more highly susceptible than men to developing cartilage defects due to differences in anatomical structures, kinematic loading, joint angles, hormonal influences (i.e., menopause), and an increased risk of joint injuries (i.e., anterior cruciate ligament [ACL] tears).[6] Individuals who are overweight or obese have greater joint compressive and shear forces and more systemic inflammation that progress to cartilage degeneration over time.[7] Patients who have suffered a torn ACL or meniscus have been shown to be four to six times more likely to develop OA, with half of these patients who suffer these injuries experiencing onset within 10 to 20 years from the time of their initial injury.[8,9] Overall, these widespread contributing factors make OA as one of the leading causes of disability worldwide.[4]

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Typically, those with cartilage defects or early knee OA tend to be younger at the time of presentation, which, as the disease progresses, often leads to the need for total joint arthroplasty (TJA). A major concern of TJA is the survival rate of implants, which, if performed in a younger individual in their early fifties, is associated with a likelihood of 35% of cases needing revision surgery during a patient's lifetime.[10] Therefore, optimizing the nonoperative treatment of these patients can slow or obviate the need for TJA. This review will focus on nonoperative treatment strategies with a focus on when treatments are necessary, who will benefit from these approaches, why they are specifically appropriate, and, finally, how these treatments directly modify the structure of a patient's cartilage and resulting symptoms.

Clinical Evaluation

Nonsurgical management options for cartilage defects should involve an individualized approach to treatment that considers patient-specific goals and relevant barriers to adoption that are pivotal to achieving optimal outcomes.[11] The majority of those with cartilage defects present with pain as their primary symptom, typically complaints of pain exacerbated by weight-bearing and improved with rest. Common secondary symptoms include morning stiffness (less than 30 minutes of duration), bony tenderness, and decreased range of motion. The practitioner should evaluate the patient for potential contributors to the development of a cartilage defect, such as being overweight, the presence of a joint malalignment, or a history of prior joint trauma/injury, which may impact the treatment prescribed. Subsequent evaluation requires physical examination with typical findings of joint line tenderness, effusion, and crepitus. The diagnosis can be confirmed using radiographs or magnetic resonance imaging (MRI) for signs of joint space narrowing, osteophyte formation, subchondral sclerosis, or subchondral cysts.[12] Patients who are younger with early indications of or mild-to-moderate cartilage defects will typically show the greatest response to nonsurgical treatments. Older patients with more advanced cartilage loss often become less responsive to noninvasive treatments, leading some to elect TJA in an effort to relieve pain and improve function.[13]

The primary objective of the nonsurgical management of cartilage defects on a physiological level is to slow the progression of cartilage degradation. The preservation of cartilage thickness/volume has been shown to be associated with improvements in pain, function, and quality of life.[14] The practitioner should therefore incorporate a holistic approach to treatment that involves an assessment of the cartilage injury/damage, individual goals, body habitus, nutritional status, and engagement in physical activity. Although not the focus of this article, analgesic medications, such as nonsteroidal anti-inflammatory medications or intra-articular injections of corticosteroids, may be required to allow for engagement in other facets of the treatment approach. However, recent evidence has suggested that regular intra-articular injections may be deleterious to cartilage health.[15]

Treatment Strategies of Cartilage Defects

Weight loss, nutrition, and physical activity display the strongest evidence to directly enhance cartilage integrity in individuals who possess the aforementioned modifiable risk factors. While all three interventions are in some ways interrelated, they each target different abnormalities of the joint. These include reducing joint loading forces, preserving cartilage morphology, minimizing joint space narrowing, and decreasing biomarkers of cartilage tissue turnover and inflammation, which, in turn, improve the joint environment. The following sections present current evidence to support these strategies for the nonsurgical management of cartilage defects.

Weight Loss

Multiple epidemiological studies have suggested a relationship between obesity and the presence of cartilage defects.[16–18] Classically, obesity has been thought to contribute to the development of knee OA through biomechanical "overloading" of the joint, as suggested by multiple clinical studies. A secondary analysis of the ADAPT (Arthritis, Diet, and Activity Promotion Trial) study[19] of 252 overweight and obese individuals with knee OA used three-dimensional gait analysis to measure peak knee joint loading forces and moments.[7] It is known that higher external knee adduction moment during gait is associated with increased joint compressive forces in the medial compartment of the knee.[20,21] Findings from the ADAPT study revealed that for every kilogram of weight lost, knee joint loading forces decreased by about four times that amount, and external adduction moment also decreased significantly with weight loss.[7] Alternatively, the distinctive biological profile of individuals who are overweight or obese introduces other mechanistic pathways to consider that may contribute to worsening cartilage health in these individuals. Obesity has been associated with altered lipid metabolism and low-grade systemic inflammation that may directly affect cartilage structure.[22] This has also been suggested by studies that identified an association between incidence of hand OA (a nonbody weight-bearing joint) and higher body mass index, inferring a potential biological component of cartilage degradative pathology in these patients.[23] Altered adipose tissue composition in overweight and obese individuals is known to induce low-grade systemic inflammation by upregulating expression and release of proinflammatory cytokines, such as adiponectin, leptin, interleukin (IL) 6, and tumor necrosis factor-α (TNF-α), that may contribute to cartilage degradation and/or disease progression.[22,24]

Weight loss therefore as a treatment strategy for cartilage defects likely has both a biomechanical and a biological effect on joint disease and, in turn, the potential to improve patient-reported symptoms. For example, primary outcomes from the ADAPT study revealed how reductions in joint loading forces after weight loss translated to significantly less knee pain along with improved 6-minute walk distance, stair-climb time, and self-reported Western Ontario and McMaster University Osteoarthritis Index (WOMAC) physical function.[19] Similarly, the IDEA (Intensive Diet and Exercise for Arthritis) trial was an 18-month randomized controlled trial (RCT) investigating the effects of weight loss on 399 overweight and obese older adults with knee OA.[25] Participants were randomly assigned to diet (which involved caloric intake regulation), exercise, and a combination of diet and exercise, with follow-up measurements at 6 and 18 months. Diet interventions included caloric restrictions and partial meal replacements, whereas exercise sessions involved onsite and home-based programs incorporating both aerobic and resistance exercises. After 18 months, weight loss was most successfully achieved in the diet and exercise group (11.4%) followed by diet (9.5%) and exercise (2%), inferring that dietary intervention had a significantly greater effect on weight loss than exercise. These findings were reflected in corresponding decreases in total fat mass in only the diet and exercise (18%) and diet (13%) groups, and knee joint compressive forces were found to be lower across all groups with both diet groups displaying significantly greater changes.[25] In a secondary analysis of the IDEA trial, higher total body and fat mass, specifically total abdominal and thigh fat, were found to significantly increase knee joint compressive and shear forces, further validating the biomechanical effect of obesity on OA and reiterating the efficacy of weight loss to treat OA.[26] These findings that display the marked benefits of substantial reductions in weight and fat mass have led to the assertion that losing 10 to 20% of baseline body weight for overweight or obese individuals with knee OA can aid in achieving optimal clinical and physiological benefits.[27]

The Benefits of Weight Loss on Cartilage

Weight loss has also been demonstrated to directly alter cartilage composition and integrity through imaging studies and biological marker analyses. MRI is used in cartilage research as a means of quantitatively evaluating both the appearance and structural composition of cartilage in vivo. Both T1 and T2 imaging can provide early indications of cartilage stress and signs of cartilage degradation, with lower T1 and higher T2 values associated with greater structural degeneration.[28,29] Gersing et al analyzed T2 relaxation times for 258 overweight and obese individuals at risk of or with mild-to-moderate knee OA who had lost moderate (5–10%) to sizable (>10%) amounts of weight over 48 months.[30] Participants were taken from the Osteoarthritis Initiative (OAI), a national multicenter cohort of individuals with or at risk of knee OA who were prospectively followed over several years. Compared with 258 individuals of stable weight and similar background, the cohort that lost >10% of baseline body weight displayed a significantly smaller increase in T2 relaxation times in the medial compartment of tibiofemoral cartilage. Greater T2 values were also shown to be significantly associated with increases in WOMAC pain and disability.

Biological markers of cartilage turnover, extracellular matrix (ECM) degradation, and inflammation in synovial fluid and serum are capable of dynamically quantifying changes in joint remodeling and disease progression of OA.[31] A secondary analysis of the IDEA trial by Loeser et al investigated the changes in serum biomarker levels of cartilage degradation in response to weight loss in the different intervention treatment groups of the IDEA trial (diet alone, exercise alone, and diet and exercise).[32] C1M, C2M, C3M, and CRPM were measured in serum samples collected at baseline and 18 months. Trademark characteristics of OA include articular cartilage degeneration, osteophyte development, and synovitis driven by inflammatory mediators and proteolytic enzymes such as matrix metalloproteinase (MMP). Activities of these enzymes and inflammatory cytokines often result in structural changes to the ECM, which, in turn, releases measurable fragments. Type I collagen is the most abundant type in the human body forming a variety of connective tissues, including synovial membrane, ligament, and tendon, and C1M is a neoepitope of type I collagen and a byproduct of MMP degradation. Type III collagen is upregulated along with MMP in synovitis during fibrogenesis, indicating greater type III collagen turnover and release of the protein fragment C3M. CRPM is an indicator of chronic inflammation and a component of C-reactive protein, which is initially upregulated during an acute inflammatory response and is broken down by MMP to release CRPM as it accumulates in joint tissue. Lastly, type II collagen is the primary component of the ECM of cartilage and can be measured by fragments of C2M.[33] Findings from the IDEA trial showed that across all groups, C1M, C3M, and CPRM decreased as a result of weight loss, and C1M and C3M were additionally found to be significantly lower at 6 and 18 months in both diet groups compared with the exercise group alone. All three biomarkers were also positively associated with changes in IL-6 levels, indicating less systemic inflammation in the context of weight loss. However, these systemic biomarker changes were not associated with improvements in WOMAC pain or function despite signs of structural enhancement in the joint on MRI.[32]

Nutrition

Changes in diet and nutritional supplementation can aid in mediating processes that alter cartilage composition. Nutrition encompasses a variety of interventions, but in the context of OA it has most often been applied in the context of dietary caloric restriction to lead to weight loss. However, as will be expanded upon in this section, specific dietary choices can also have a significant impact on joint and cartilage health through means entirely independent of weight loss. Typically, many of the dietary recommendations for joint and cartilage health are closely aligned with existing recommendations for the prevention of other chronic conditions such as coronary artery disease and diabetes. With very few exceptions, the dietary recommendations discussed here can be safely implemented by patients regardless of age or comorbidities.

Dietary Modifications

Dietary modifications that change the consumption of certain types and amounts of fatty acids display mild evidence for the maintenance of healthy cartilage morphology. It has been shown that higher intake of total and saturated fats is strongly associated with progressive joint space narrowing in individuals with knee OA, whereas higher intake of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) resulted in less joint space width loss. Additionally, PUFAs have been identified as precursors of eicosanoids, which play a role in mediating and regulating inflammation.[34]

The type of PUFA consumed appears to impact whether there is a contribution to inflammation or inhibition. Omega-6 PUFAs such as linoleic acid, which is derived from vegetable oils, seeds, and nuts, can facilitate the formation of arachidonic acid (AA), another omega-6 PUFA abundant in red meats. AA can be further processed to become inflammatory mediators such as prostaglandins, leukotrienes, and thromboxanes that contribute to acute and chronic inflammation. Omega-3 PUFAs, such as α-linoleic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are commonly found in leafy vegetables, linseeds, flaxseed oil, walnuts, and fish oils.[23] Omega-3 PUFAs are believed to reduce inflammation through competitive inhibition of AA as an enzyme substrate, decreasing AA metabolism and production of AA-derived inflammatory mediators in exchange for less potent EPA- or DHA-derived inflammatory products.[23] Additionally, dietary omega-3 PUFAs have been shown to downregulate the expression of inflammatory cytokines (such as IL-1β, TNF-α, and IL-6), decrease the production of reactive oxygen species, and induce secretion of anti-inflammatory resolvins.[35] (Omega-3 fish oil supplementation is further discussed below.) These findings support the broader implementation of other anti-inflammatory dietary interventions that have been shown both in vivo and in vitro to decrease biological markers of inflammation, cartilage degradation, and oxidative stress associated with OA.[36–38]

Traditional Western diets commonly consist of red meats and dairy products that are sources of omega-6 PUFAs and saturated fats, which are often substituted for foods high in omega-3 PUFAs.[23,39] Due to its high content of MUFAs, mostly from olive oil, the Mediterranean diet has therefore been suggested to be beneficial to joint health.[40] Mediterranean-style cuisine is typically comprised of whole grains, beans, fruits, vegetables, fish, white meats, and olive oil.[39] To date, the evidence for olive oil and the Mediterranean diet in promoting joint health is limited. A study using a rat model of knee OA demonstrated that olive oil supplementation along with physical activity resulted in a significant increase in levels of lubricin, a chondroprotective glycoprotein.[40] Additionally, a recent RCT incorporated the Mediterranean diet as a treatment intervention for knee OA and investigated changes in serum biomarkers associated with the disease.[41] These included proinflammatory IL-1α and cartilage oligomeric matrix protein (COMP), a type II collagen protein that binds collagen fibers in the ECM of chondrocytes. Both of these markers decreased significantly after 16 weeks compared with controls. Another study by Veronese et al specifically evaluated the association between the Mediterranean diet and OA symptoms in individuals taken from the OAI.[42] They found that those with greater adherence to a Mediterranean diet had significantly improved WOMAC scores for knee pain and disability. Of note, patients in the study with close adherence also displayed a higher quality of life on the 12-Item Short Form Survey. While further studies are needed, there is a growing body of evidence to support that specific dietary modifications may have a positive impact on cartilage health independent of weight loss.

Supplements

A wide variety of nonprescribed dietary supplements for cartilage and joint health are currently available to patients. The majority of studies indicate that dietary supplements are most effective in patients with mild-to-moderate symptoms and less severe radiographic disease. Glucosamine, chondroitin sulfate, fish oil, curcumin, and calcitonin are the most widely studied for cartilage health.

Glucosamine and Chondroitin Sulfate

Glucosamine and chondroitin sulfate are commonly used supplements purported for their benefits in joint health. They are amongst the most popular dietary supplements taken in the United States, with sales in 2008 approaching 2 billion dollars.[43] Despite widespread use, their mechanism of action and clinical efficacy on joint health has been a topic of much debate. Multiple molecular targets have been implicated, including signal transduction pathways, the oxidative stress response, and protein synthesis and folding.[44] In vitro animal models of cartilage stress have shown that glucosamine and chondroitin sulfate lead to enhanced proteoglycan synthetic activity.[45] Though multiple mechanisms of action for glucosamine and chondroitin sulfate have been proposed, the majority of trials that have measured the clinical effects of glucosamine and chondroitin sulfate have focused on evaluating whether or not they are able to slow cartilage degradation over time.

The largest study to date is the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), a 24-month double-blind placebo-controlled study that randomized 662 participants with OA to groups taking glucosamine (500 mg, three times daily) and chondroitin sulfate (400 mg, three times daily) alone, the combination of glucosamine and chondroitin sulfate, and celecoxib (200 mg daily) or placebo. At 12 and 24 months, there was no significant difference in the medial tibiofemoral mean joint space width in both groups compared with placebo, implying a lack of significant benefit to cartilage health from glucosamine and chondroitin sulfate.[46] In a secondary analysis of the GAIT study, Sawitzke et al evaluated the effects of the different supplements on WOMAC pain and function but found that no treatment group achieved a clinically important difference in WOMAC outcomes compared with placebo.[47] In its entirety, this study suggests that these supplements neither significantly alter the rate of cartilage breakdown nor meaningfully impact patient symptoms of OA. However, a recent systematic review by Gallagher et al found that three out of four high-quality studies for chondroitin sulfate and two out of three high-quality studies for glucosamine displayed a significant decrease in cartilage loss when compared with placebo.[48] That being said, studies on these supplements are limited, and further investigation is necessary to provide more definitive findings.

Fish Oil

Omega-3 fatty acids, which are commonly found in Mediterranean diets, can also be found in dietary supplements of which fish oil has been found to be the most beneficial.[49] While much of the data in support of fish oil is related to cardiac health,[50,51] there is also evidence that fish oil is beneficial for joint health based on the aforementioned role of omega-3 fatty acids in the competitive inhibition of the AA oxidation pathway (see the Dietary Modifications section). Multiple in vitro studies found that exposing inflammatory-induced chondrocytes to omega-3 fatty acids reduced the genetic expression and activity of inflammatory mediators and cartilage degradative enzymes such as various ILs, aggrecanases (ADAMTS [a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13]), MMPs, cyclooxygenase-2 (COX-2), and TNF-α.[49,52,53] Additionally, omega-3 fatty acids have been shown both in vitro and in vivo in animal models to decrease the release of glycosaminoglycan (GAG), a primary component of proteoglycans that comprise the ECM of chondrocytes.[54,55] These findings suggest that omega-3 supplementation may have a beneficial effect on cartilage morphology. A recent study by Hill et al evaluated the impact of fish oil supplementation on radiographic progression of cartilage loss in humans.[56] The trial compared high- and low-dose supplementation of fish oil over the course of 2 years. While the trial found no significant differences in cartilage thickness between groups, the overwhelming majority of participants who were analyzed through MRI in both high- and low-dose groups (89 and 97%, respectively) showed either no change or an increase in cartilage volume with minimal side effects. Fish oil supplementation has also been evaluated for its efficacy in symptomatic OA. A recent systematic review found that three out of four studies using fish oil as a supplement in individuals with knee OA found significant beneficial effects on patient-reported WOMAC symptoms.[57]

Physical Activity

Physical activity has long been acknowledged for its myriad of benefits, including joint health. Aerobic and resistance exercise have particularly been identified in the literature as showing the greatest benefit. A recent meta-analysis by Juhl et al including 48 RCTs on exercise in patients with knee OA found that aerobic or resistance-based training programs were the most efficacious and displayed similar outcomes for pain reduction in individuals with OA.[58] In spite of this, many patients may be reluctant to pursue regular exercise for fear of causing damage or further degradation to cartilage.[59,60] However, cartilage is mechanosensitive and requires appropriate amounts of loading to maintain its structural integrity. Reduced loading conditions involving prolonged immobilization or paraplegia that are characteristic of sedentary lifestyles have been associated with atrophic cartilage.[61,62] Quadriceps and overall muscle weakness are also common in this patient population and a major risk factor for the potential progression of cartilage disease.[63] Therefore, any exercise prescription for patients with OA should include both aerobic and resistance components.

Aerobic Exercise

Aerobic exercises, including walking, cycling, and swimming, have been associated with beneficial effects on cartilage structure in those with cartilage defects.[62,64] A study by Munukka et al monitored MRI T2 relaxation times, dGEMRIC (a negatively-charged MR contrast agent that allows researchers to estimate concentrations of GAG) index changes, and self-reported leisure time physical activity (LTPA) in 76 postmenopausal women with mild knee OA.[65] Physical activity primarily consisted of regular walking exercise over the course of 12 months. Findings revealed a strong linear relationship between levels of LTPA and dGEMRIC index in the posterior regions of the medial and lateral tibiofemoral cartilage. Similarly, Multanen et al investigated the effects of a high-impact 12-month aerobic and step-aerobic jumping exercise program on function, cardiovascular fitness, and tibiofemoral and patellofemoral cartilage integrity in an identical patient population.[66,67] In the intervention group, T2 relaxation times for patellofemoral cartilage decreased significantly after 12 months compared with controls, indicating enhanced morphology of the patellofemoral cartilage. Knee extensor strength, balance, and maximal aerobic capacity also improved in this group. However, tibiofemoral cartilage displayed no significant changes, which may have been due to the specific type of aerobic exercise used in the study.

Low-impact activities, such as swimming and cycling, can remove physiological barriers to exercise for sedentary individuals with cartilage defects. Aquatic exercise is a recommended treatment option by the Osteoarthritis Research Society International and the American College of Rheumatology.[68] Water exerts a buoyant force and hydrostatic pressure that are posited to effectively offload weight-bearing joints and facilitate a safe environment to move in such a way that could otherwise not be performed on land.[69]

Cycling is another exercise modality that reduces weight-bearing stress on joints. A recent study found that peak loading forces during cycling were substantially lower compared with walking (50–163% cycling vs. 252% walking). Therefore, cycling at moderate power levels was recommended to reduce tibiofemoral contact forces in individuals with cartilage defects.[70] A study by Salacinski et al used a group cycling program as an intervention and discovered marked improvements in preferred gait velocity and visual analog scale pain scores during the 6-minute walk test.[71] The study concluded that cycling may not only be a viable option for individuals with mild-to-moderate knee OA but can also improve pain while walking, which is a common burden in this patient population. Another recent RCT studied the impact of a 3-month swimming exercise program to a more well-established cycling intervention in 48 older individuals with OA.[72,73] At the conclusion of the exercise program, both groups displayed similar improvements. Significant reductions in IL-6 levels translated to better outcomes in WOMAC scales for joint pain, stiffness, and functional limitations along with higher scores on the 36-Item Short Form Survey for mental and physical quality of life. Additionally, functional improvements were observed through increased knee extensor and flexor strength and distance covered during the 6-minute walk test. With only minor to no adverse events reported across studies, aerobic exercise displays a strong safety profile and a high efficacy to enhance cartilage health and patient function.

Resistance Exercise

Resistance exercise, which places a greater emphasis on muscle strengthening, is another form of physical activity that displays benefits for cartilage defects and resulting symptoms. Although often considered an aerobic exercise, aquatic exercise can also be tailored to a form of resistance training because of its properties that create resistance to movement due to hydrostatic pressure. A recent trial investigated the efficacy of an aquatic resistance training program to alter cartilage structure and symptoms associated with cartilage defects.[74,75] Eighty-four postmenopausal women with mild knee OA were randomized to either control or exercise groups for 4 months, and tibiofemoral cartilage was visualized using MRI T2 relaxation times and dGEMRIC indices. After 4 months, a significant decrease in T2 values in the posterior region of the medial femoral condyle was observed, which is indicative of greater collagen fiber integrity. However, a corresponding decrease in dGEMRIC index in the same region of cartilage points to a loss of GAG content and potentially contradictory study findings. The authors hypothesized that this could be due to variable response rates between the collagen-interstitial environments and GAG to aquatic exercise, which requires further study. Nevertheless, the program also resulted in an increase in cardiorespiratory fitness and walking speed with a concurrent decrease in overall fat mass, inferring cardiovascular and functional benefits from aquatic resistance training.

More traditional land-based resistance exercises, such as lunges, squats, and balance training, have also been widely studied. Roos et al used MRI-based T1-enhanced dGEMRIC analyses of tibiofemoral cartilage changes in patients at risk of developing knee OA following randomization to a 4-month physiotherapist-led resistance training program targeted at improving strength and neuromuscular control in the lower extremities.[76] The study found that T1 dGEMRIC relaxation times increased significantly in the exercise group compared with controls, inferring an increase in cartilage GAG concentrations. Another trial used a leg press machine and adjusted the amount of repetitions, sets, and percentage of participants' one-repetition maximum to designate participants to high resistance, low resistance, or control groups.[77] Both exercise groups displayed marked improvements in walking speed, balance, coordination, knee extensor, and flexor strength compared with controls. This translated to significantly less WOMAC pain and greater WOMAC physical function scores.

Other study protocols have focused on quadriceps muscle strengthening that has long been understood to contribute to the onset and worsening progression of cartilage defects when weak, especially in women.[78,79] Additionally, weak quadriceps musculature is highly associated with greater pain and less function.[80] The aforementioned meta-analysis by Juhl et al found that quadriceps-specific exercises resulted in significantly greater pain reduction than general lower limb exercises.[58] A single session of quadriceps strengthening can lead to a significant decrease in intra-articular levels of COMP in joint synovial fluid while observing no appreciable change in other biomarkers of inflammation and cartilage turnover, suggesting a biological benefit to cartilage health.[81] Other studies evaluating quadriceps strengthening more longitudinally over the course of 3 months have also demonstrated improved femoral cartilage thickness[82] and greater molecular weight of hyaluronic acid and viscosity of joint synovial fluid (both indicators of joint health). Additionally, a concurrent decrease in levels of chondroitin sulfate, a major GAG and primary component of articular cartilage, would suggest less cartilage tissue turnover.[83] These findings provide potential evidence for a healthier joint environment as a result of sustained quadriceps strengthening exercises. Overall, the available evidence suggests that both regular aerobic and resistance exercise can have physiological and symptomatic benefits in individuals with cartilage defects and/or knee OA.

Regenerative Medicine

Regenerative medicine strategies in knee OA have more recently been studied extensively with the goal of creating a novel tissue that has similar mechanical and biological properties to native cartilage. By far, the two most common types include stem cell therapies and autologous growth factor related treatments. Although these treatments display potential, significant difficulties remain with their incorporation into treatment strategies. For example, articular cartilage defects also commonly involve damage to the subchondral bone, which is not typically addressed through stem cell therapies that focus treatment purely on cartilage alone. Of note, the inflammatory environment of an injured or osteoarthritic joint can also potentially impact the repair and regenerative potential of these therapies. While developments in stem cell therapy display the potential to regrow cartilage, the current body of work is comprised of poor-quality evidence with widespread heterogeneity, a lack of reproducibility, and gaps in translating in vitro and preclinical findings to patient care.[84,85]

By far, the most widely studied growth factor related treatment is platelet-rich plasma (PRP). PRP is produced by high-speed centrifugation of blood that leads to a supernatant with a platelet concentration well above baseline. These platelets have α-granules that contain a multitude of bioactive proteins and growth factors such as transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), and insulinlike growth factor (IGF-1).[86] There are very few clinical trials of this treatment for knee OA and all with marked differences in sample preparation, centrifugation speed, dosage, and frequency of injections. However, PRP has displayed some efficacy in treating pain, function, and morphology of the regenerated tissue in comparison to

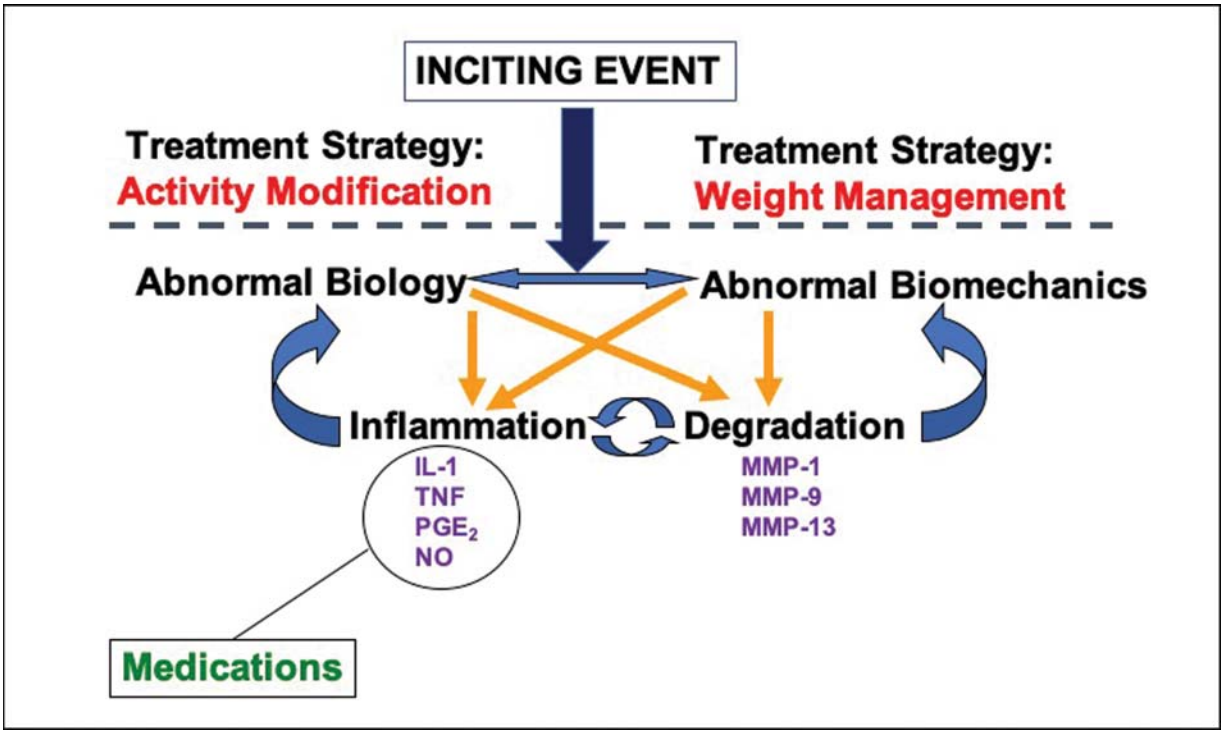

Fig. 1 Summary diagram of the treatment strategy for cartilage defects. Cartilage disease progression involves a complex interplay between biological and biomechanical factors that causes a cycle of inflammation and degradation. Initial treatment involves the management of pain and inflammation through the use of anti-inflammatory medication. However, other more global treatment strategies involve activity modification through aerobic and resistance exercise that can have beneficial effects, as can weight management strategies such as dietary modifications and nutritional supplements. IL-1, interleukin-1; MMP, matrix metalloproteinase; NO, nitric oxide; PGE, prostaglandin; TNF, tumor necrosis factor.

standard-of-care corticosteroid or hyaluronic acid injections.[87] It also appears as though optimal effects of PRP occur in younger patients with milder cartilage disease. Additionally, PRP has been administered in association with MSCs (mesenchymal stem cells) or BMCs (bone marrow cells) as an adjunct to improve outcomes of these procedures. Shapiro et al in a single-blind RCT of BMC with PRP observed a significant improvement in pain compared with placebo.[88] However, a study by Bastos et al found that adding PRP to MSC injections for knee OA did not provide significant benefits. Further studies are required in this domain.[89]

Conclusion

Clinicians should always use a patient-centered approach when designating nonsurgical treatment options for patients with cartilage defects (►**Fig. 1**). Prior to making recommendations, it is critical that clinicians consider how patients may respond to interventions based on their comorbidities and attitudes toward treatment. Weight loss, nutrition, and physical activity demonstrate promising evidence for managing cartilage defects. Regenerative medicine strategies, such as stem cells and PRP, have potential but require further longitudinal study. As we are faced with a global population that is becoming older, earlier treatment of cartilage defects will be pivotal to optimizing patient outcomes and improving quality of life in this vast and growing proportion of the population.

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Conflict of Interest
None declared.

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