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TREATMENT STRATEGIES FOR ATHLETIC OSTEOARTHRITIS: BALANCING SURGERY AND REHABILITATION

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Abstract: Osteoarthritis (OA) is a degenerative chronic process that primarily affects the elderly, but there are also reports of OA in the young and sports-active population. Symptoms of OA usually include pain, joint stiffness, and crepitation. Physical, radiologic, and laboratory tests are required for diagnosis. The main goal of OA treatment is to restore normal function to the joint affected by OA.

Methods: A literature search on PubMed was used to collect facts about the relationship between sports and OA and possible treatment methods. All forms of articles were considered in the literature search. Articles that were not written in English were not included. Literature from the library of the Faculty of Medicine in Mostar was an additional source of information.

Results: OA occurs more frequently in people who play or have played professional sports. On the other hand, daily exercise has a positive effect on cartilage metabolism. Most articles reported the occurrence of OA in former professional athletes. The joint most commonly affected by OA was the knee. Injuries were a predictive factor for the occurrence of OA, and most studies talk about anterior cruciate ligament injuries. Running and football were the most commonly studied sports. Treatment options include conservative treatment, surgical methods, and biological therapy.

Conclusion: Frequent strain and injury in athletes can cause cartilage damage and potentially lead to the development of OA. The benefits of exercise far outweigh the risks of developing OA. In addition, some studies report a significant stimulating effect of exercise on cartilage cell metabolism. Treatment of OA consists of the use of analgesics, intra-articular therapy, and physiotherapy. Surgical methods are considered when conservative approaches are unsuccessful. Biological therapy and similar treatments are the new potential treatments.

Keywords: Athletes; cartilage; osteoarthritis; treatment

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INTRODUCTION

Osteoarthritis (OA) is a degenerative chronic process that mainly affects older people, but there is also data linking OA and sport. Literature reports provide information about the effect of demanding sports as a predictive factor for the development of OA (1-5). Other risk factors include age, obesity, previous injury, and genetic predisposition (6-9). A study by Amoako and Pujalte reports that the incidence of OA-related disability increased by 64% between 1990 and 2010. It is an extremely serious health and socioeconomic problem (10). OA affects cartilage, synovium, joint capsule, and bone (11, 12). The most commonly affected joints are Knee, hip, and interphalangeal joints (10). In athletes, the knee is most commonly affected, immediately, followed by the ankle and shoulder (4). Before describing cartilage pathology, it is important to understand the physiology and histology of normal cartilage. As a tissue, cartilage is avascular and not innervated. It is composed of an intercellular substance containing glycosaminoglycans and proteoglycans bound by collagen and elastic fibers. The proteoglycans form proteoglycan aggregates by binding to long chains of hyaluronic acid. The components of the intercellular matrix synthesized by the chondrocytes located in the lacunae provide defense against mechanical stress (3, 13, and 14). The early stage of OA is characterized by chondrocyte hypertrophy and the formation of chondrocyte clones, which may contain up to 50 cells in clusters. In the later phase, the cartilage becomes hypocellular and lacunae depletion, loss of Type 2 collagen, loss of proteoglycans, and mineralization of the matrix occur. Changes are also observed in the synovium, including inflammation, hypertrophy and Activation of macrophages, accumulation of fibroblasts, and release of inflammatory mediators (Figure 1). The released inflammatory cytokines can alter the metabolism and histologic appearance of the cartilage (15, 16). Understanding the bimolecular process of OA development is of great importance for the complete understanding of this clinical entity. The role of some signaling pathways in the development of OA has already been observed. For example, the Wnt/ β catenin, transforming growth factor (TGF) β /Smad, and Ihh signaling pathways have effects on bone and cartilage morphogenesis. *In vitro* studies in chickens have shown that overexpression of β -catenin leads to reduced expression of the cartilage-specific genes Sox9 and Col2. Increased expression of MMP and BMP genes was also observed with increased activation of the Wnt/ β -catenin signaling pathway, leading to increased cartilage degradation. In addition, a significant increase in ADAMTS5 levels in articular cartilage, another important cartilage-degrading enzyme, was observed in mouse models with Ihh activation. On the other hand, the absence of TGF- β signaling is associated with cartilage damage, and TGF- β is also known to be involved in early osteophyte formation. We will also highlight the role of FGF-2 mentioned by Xia et al. who report the release of FGF-2i during cartilage matrix loading and its involvement in activating the MAPK signaling pathway and stimulating the expression of MMP-13, the main enzyme for Type II collagen degradation (17, 18). This information enables a new targeted therapy based on biomolecular processes. Regarding cartilage regeneration, we know that it is difficult and that only partial regeneration is possible. Therefore, newer treatments that attempt to regenerate cartilage lesions have become the subject of research (18). An extremely important component of joint health is the subchondral bone. This is indicated by studies that have

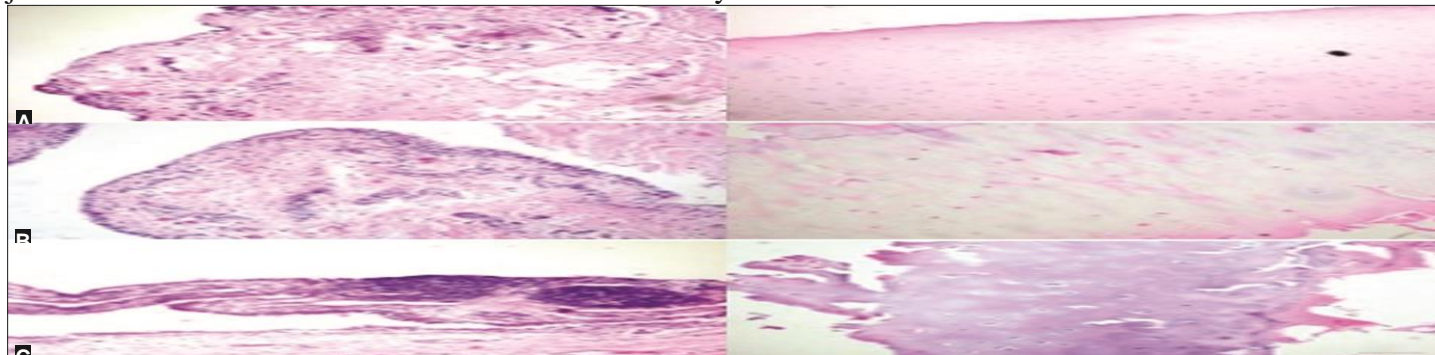


FIGURE 1 Synovial membrane (first column) and cartilage (second col)

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Concluded that patients with subchondral marrow edema and OA are 9 times more likely to require total joint arthroplasty than patients without edema (19). Lesions involving the bone marrow below the subchondral bone are poorly circumscribed defects that are seen on Magnetic resonance imaging (MRI) in 80% of people with symptomatic OA. The histopathologic features of these lesions, which include fat necrosis, fibrosis, and microfractures of the trabecular portion of the bone, occur at sites of increased stress (20). Symptoms of OA usually include joint pain, although this need not be severe, joint stiffness, crepitations due to uneven joint surfaces, and edema due to joint effusion (6). To make a diagnosis of OA, it is necessary to collect detailed anamnestic data and to summarize the results of physical, radiological, and laboratory examinations. A plain radiograph is the first choice in radiologic diagnosis. It can show osteophytes, subchondral necrosis, cysts, and joint space irregularities, including narrowing of the space between the articular surfaces. A better method than an X-ray examination is conventional MRI, but this cannot provide any information about the tissue composition. For this reason, GEMRIC (Gadolinium-Enhanced MRI of Cartilage) is the best choice for diagnosing OA in its early stages (21). Ultrasound is a simple and inexpensive method and is therefore also frequently used for diagnosis (1). The main goal of treating OA is to restore normal function to the joint affected by OA. This is important for athletes pursuing a professional career (7). Medical treatments primarily include physical rehabilitation therapies, followed by pharmacological treatments and surgical interventions (22). Aspects of the treatment of an osteoarthritic joint are discussed later in the text. With this review of the literature, we have attempted to determine the influence of sporting activity on the occurrence of OA and the optimal treatment methods of control patients (A), and patients with mild (B) and severe (C) OA. Hematoxylin and Eosine staining. Magnification $\times 40$, scale bar 40 μm . (Used and adapted with permission of Prof. Violeta Šoljić, MD, PhD.).

METHODS

By searching the literature on PubMed, we have collected facts about the relationship between sports and OA and possible treatments. All forms of articles were included in the literature search. Articles that were not written in English were not considered. The keywords we used were athletes, cartilage, OA, and treatment. Literature from the library of the Faculty of Medicine in Mostar was an additional source of information.

RESULTS

OA is more common in people who play or have played professional sports (6). On the other hand, daily exercise has a positive effect on cartilage metabolism (23). Most articles have reported the occurrence of OA in former elite male athletes. The joint most affected by OA was the knee. Injury was a predictive factor for the occurrence of OA, and most studies focused on anterior cruciate ligament (ACL) injuries. Running and football were the most commonly studied sports. Treatment options included conservative treatment, various surgical methods, and biological therapy.

OA and sports

Studies suggest that OA in people who are active in sports is a consequence of frequent strain or injury that occurs during sports (24). Finnish athletes were found to be 2 times more likely to be hospitalized for OA than non-athletes (25). Frequent injuries lead to the development of a local inflammatory condition related to cartilage degradation (26). In addition, trauma can lead to changes in joint kinematics that stress the cartilage. In the study by Madaleno et al. discussing this, we found that after ACL repair or meniscectomy, patients experienced changes in the translation between the tibia and femur that caused a load shift to a region that is normally less loaded. Such changes ultimately led to a thinning of the cartilage (8). The study by Stiebel et al. shows that trauma-induced OA accounts for 12% of all OA in patients (11). The cause of this phenomenon is explained not only by biomechanical but also by biochemical processes. In the acute phase after trauma, reduced synovial density,

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suppression of collagen and proteoglycan synthesis, as well as pronounced inflammatory mediators and matrix-degrading enzymes, have been observed. Subchondral bone lesions have also been observed (12). Therefore, some believe that the formation of a callus at the site of subchondral bone damage decreases compliance and causes a greater compressive load on the cartilage (26). It has also been observed that when an ACL lesion is associated with a meniscal lesion, there is a significantly higher risk of developing OA (27). Immobilization and sparing are considered an additional risk factor for the development of OA when associated with trauma (3). In addition to injury, body mass index (BMI), muscle strength, and genetics are also considered important predictive factors (26, 27). It is thought that former athletes gain body weight in retirement, which places additional mechanical stress on the joint (8). The influence of increased BMI on the occurrence of OA may additionally be explained by biochemical proinflammatory processes associated with metabolic syndrome (9). On the other hand, observations in children show that children who played sports were twice as likely to have problems in the articular cartilage of the tibia as children who were less active (8). Professional athletes begin their careers in childhood, during the development of the musculoskeletal system. This may lead to the development of CAM morphology in the hip joint, which is associated with the development of OA. In addition, the articular cartilage of an adult is more resistant to trauma than the epiphyseal plate of a child (28). Injuries in children can also lead to the development of angular deformities (29). The study by Jang et al. report that the type, intensity, and duration of sport often play a role in the occurrence of OA (30). Several studies report a relationship between squatting and knee OA (8, 11, and 30). Numerous studies report that long-distance runners, weightlifters, and wrestlers have a higher risk of developing OA than basketball players or archers (1, 31). One study conducted on former soccer players found that 66% of them had knee OA on X-ray, most of which was mild to moderate (32). Another study, this time conducted on a young, athletically active population, showed a higher incidence of osteophytes in the joints and therefore a higher likelihood of OA occurring. Interestingly, although this was an extremely young population (mean age 28.5 years), age was still a significant predictive factor, although this could also be due to prolonged sports (33). A study in mice that had run uphill and downhill showed increased serum levels of inflammatory mediators and the observation that running downhill can cause more damage than running uphill. In addition, lower levels of anti-inflammatory cytokines such as IL-10 were also observed in these mice (34). Tibiofemoral and patellofemoral OA have been observed in former runners according to a study published by Gouttebarger et al. (35). A review of the literature found that more skilled, faster skiers and those who have competed in more races have a higher risk of development OA (36). Studies of sports instructors found a higher incidence of OA compared to the control group (31). Longterm intense running of 40 km/day for 1 year (animal studies) reduced proteoglycans in the cartilage composition and caused remodeling of the subchondral bone, but did not accelerate the degenerative changes (23). Hip dysplasia as a predictor for the occurrence of OA has been observed in professional dancers, and the study hypothesizes that the cause is greater flexibility of the joint (23). The most commonly affected joints in sports are the knee, ankle, and shoulder (4). Degenerative changes in the proximal interphalangeal joints have been reported in climbers (37). There is evidence that physical activity has a positive effect on cartilage and prevents the development of OA. It reduces the risk of cartilage loss and reduces stress on the cartilage by increasing muscle strength. Exercise, if not excessive, prevents the loss of proteoglycans and also improves joint stabilization by increasing muscle strength (7, 35, and 38). It has been found that the synthesis of glycosaminoglycans is regulated by compressive forces that promote an increase in synthesis. A decrease in proinflammatory cytokines, caspase-3, and MMP-13 and an increase in anti-inflammatory cytokines

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is chondroprotective and anti-apoptotic (7). In people with OA, a reduced perception of pain has been associated with exercise (6). Research shows that treadmill running increases the expression of proteins in the bone that are responsible for morphology and prevents lesion progression in a rat model with ACL resection (7).

Methods of treatment

Non-surgical treatment methods

The aim of therapy is to restore the joint's functionality, and for athletes, this means a return to play. The main role in non-pharmacological treatment is the aforementioned training, including aerobic exercises, strength exercises, and flexibility exercises (2, 6, and 35). Exercise has been shown to play a small to moderate role in reducing pain and improving function in OA in the hip, and we find slightly stronger evidence when it comes to OA in the knee (22). The previous studies have found an association between muscle weakness and the occurrence of OA (39). The role of physiotherapy, particularly manual therapy, is controversial, as a recent study found no significant role for physiotherapy in improving function or relieving pain (22). Electromagnetic field stimulation and transcutaneous electrical nerve stimulation have been shown to be effective in relieving pain, improving quadriceps strength, and increasing joint function (40, 41). As for supplements such as glucosamine and chondroitin, recent studies have shown the effect of 800 mg/day of chondroitin sulfate to be similar to that of celecoxib and better than placebo in improving function and reducing pain, whereas chondroitin, which is not pharmaceutical grade, has not been shown to be effective in a large number of studies. Variations in composition and preparation as well as purity are thought to be the cause (42). Pharmacological treatments primarily include paracetamol (for mild forms), non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular treatments with corticosteroids and hyaluronic acid, and Platelet-rich plasma (PRP) (12, 43, and 44). The results of a meta-analysis conducted by Murphy et al. indicate that paracetamol is one of the least effective treatment options for non-surgical therapy (22). Of the NSAIDs, diclofenac and etoricoxib showed the greatest efficacy (22). Duloxetine, a serotonin reuptake inhibitor, has been shown to be effective for knee pain, although there are no significant results for hip pain (45). Tramadol is the drug of choice for pain relief when other analgesics do not help, while non-tramadol opioids are not recommended due to a variety of side effects that outweigh the benefits (22). One study reported that opioid therapy for pain is no better than non-opioid therapy (46). Strontium ranelate modulates osteoprotegerin, RANK ligand, and MMP activity, inhibiting bone resorption. It is thought to have a direct effect on cartilage by stimulating proteoglycan synthesis *in vitro* (45). Caution should be exercised when use corticosteroids as they have a cytotoxic effect on chondrocytes (6). Repeated administration of 40 mg corticosteroids resulted in a greater loss of cartilage volume than in a control group of patients receiving saline. This suggests that intra-articular corticosteroids are only used for a short period of time (42). The effect of hyaluronic acid is based on its anti-inflammatory effect, its analgesic properties, and its role in elasticity (6, 47). Research shows that concentrated growth factors can promote cartilage healing (48). PRP is the body's own blood with a higher than physiological concentration of platelets, that contain growth factors important for the healing process (42). PRP is thought to have a stimulating effect on the proliferation of synoviocytes and chondrocytes as well as mesenchymal cells. It has also been observed to inhibit the expression of nfkB, MMP enzyme, and disintegrin and to increase the synthesis of collagen and proteoglycans (7). A meta-analysis conducted by Khan et al. found that intra-articular injection of PRP was significantly associated with reduced pain and improved function compared to hyaluronic acid or saline injections (42). Intraarticular administration of botulinum toxin, mentioned in several studies, blocks the release of substances P and neuropeptides associated with inflammation

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and has an antinociceptive effect that some authors have found to be equivalent to that of corticosteroids, while others have found it to have a short-term effect (48). Of critical clinical importance were studies reporting that intra-articular treatment was more effective in relieving pain than oral medications, of which hyaluronic acid showed the greatest efficacy (42). It is worth mentioning the studies indicating the beneficial effect of metformin in the treatment of OA. The mechanism is not entirely clear, but it is thought to have a chondroprotective effect through the AMPK signaling pathway (49). *Surgical methods of treatment* if conservative methods are not helpful, surgical methods are used. These include arthroscopy, osteotomy, and partial or total arthroplasty (50). During arthroscopy, we can perform a lavage to wash out the decay products in the joint (51). This method is limited by its short duration of action (52, 53). We can arthroscopically remove the superficial layer of damaged cartilage with a rotating knife and smooth the uneven joint surfaces. This method is called arthroscopic debridement (53). Quality studies have reported poor performance of these procedures (42). Another possible treatment is microfracture, which aims to cause bleeding through small fractures of the subchondral bone so that connective tissue cartilage forms over time through the arrival of pluripotent stem cells (10). A Norwegian study reports that 76% of National Football League players returned to active sports (54). Mosaicplasty is a procedure in that autologous bone with cartilage is transplanted from a less stressed site to the site of the defect (55,56). Previous reports indicate that these procedures have similar benefits to microfracturing and that return to sport occurred within 6.5 months in 93% of cases (55). Another method is the implantation of autologous chondrocytes. In this procedure, cartilage is harvested from a less stressed area and grown *in vitro*. Once the appropriate number of chondrocytes has been obtained, they are injected into the cartilage defect. The cartilage defect is then covered by suturing the periosteum (57). A study by (Saltzman and Riboh) found that 83% of professional soccer players were able to play again after this procedure (19). Autologous chondrocyte implantation (ACI) has produced good results in the knee. Romeo and colleagues report the case of a young baseball player who underwent ACI of the humeral head and was fully mobile and pain-free after 12 months (58). When we talk about arthroplasty, its durability is questionable. Therefore, in younger patients with cartilage defects in the knee, a corrective osteotomy is recommended to correct the existing deformity that could lead to the development of secondary OA (12). Complications of this procedure may include infection, nerve injury, DVT, or failure to heal (59). Initial results are usually favorable, but degeneration usually progresses, reducing the effectiveness of the surgical approach. About 60% of those who undergo this treatment have a satisfactory result after 10 years, and 20%–50% undergo total arthroplasty (12). Another less commonly used method is arthrodesis (60). In this method, the joint is ankylosed to achieve joint stability. An external fixator, intramedullary nails, or a plate and screw are used (61). It is the method of choice only for severe advanced cases, as the functional results are limited. For example, it is reserved for patients who have a significant lesion of the brachial plexus or other nerves in OA of the GH joint (62). *Future aspects of treatment* one of the new treatment approaches is gene therapy that codes for cartilage growth factors or anti-inflammatory cytokines. These genes can be transferred *in vivo* or *ex vivo* if cells are removed from the patient and the modified cells are returned to them. In 2017, *in vitro* gene therapy with TGF-beta using a retrovirus was approved (32). Biological methods include the use of monoclonal antibodies such as anakinra (IL-1 receptor antagonist) and caspase inhibitors such as non-selective Z-VAD-FMK and selective Z-DEVD-FMK, which have also been investigated (63). Tofacitinib and TD-198946 have also been the subject of research. Tofacitinib is an inhibitor of the JAKS/STAT signaling pathway, which is responsible for the gene expression of proinflammatory cytokines and MMPs. TD-198946 increases the expression of Runx1, which is

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downregulated in OA cartilage (64). Future therapeutic targets provide insights into the role of the orphan nuclear receptors ERRalpha and ERRgamma that play a role in the regulation of growth factors and inflammatory cytokines (65). Fasinumab is another drug that has shown safety and efficacy in phase 3 trials (66). The effect of sprifermin, a recombinant FGF-18, has also been discussed. The authors found that it was better than placebo when it came to cartilage thickness measured by MRI after 2 years (66). The role of oxidative stress has also been observed when mitochondrial respiratory dysfunction caused cartilage degeneration (63, 67, and 68). The process involves a decrease in the activity of complexes 2 and 3, a decrease in the electrical potential of the mitochondrial membrane leading to membrane damage and swelling of the mitochondria, and Cytochrome c is released, which induces apoptosis (63). Based on this theory, attempts have been made to treat OA with antioxidants such as Vitamins C, K, and D. Low levels of these vitamins are thought to be associated with the occurrence of OA (70). Several studies that have been conducted on this topic have produced minimal and inconclusive results (10, 23, and 71).

DISCUSSION

In reviewing the literature, we looked at the relationship between sports and the incidence of OA. Animal studies mostly showed a correlation between the incidence of OA and the amount of exercise, but a positive effect of exercise on joint health was also observed (23, 24, and 35). It is not meaningful to extrapolate these data to humans, but the results provided interesting hypotheses (24). As far as human studies are concerned, much of the literature is based on professional and retired athletes (4, 72, and 73). Previous injuries are associated with the occurrence of OA (29). There is one study in which the above athletes had no reported previous injuries, but this is only relative, as it is possible that they may have gone unnoticed. Since cartilage has no innervation, an injury limited to cartilage may not have caused symptoms (3). One of the facts is that most of the studies included mostly men (71). We found one study of Australian female runners that linked running to degeneration of the patellofemoral joint. However, this study did not take into account previous knee injuries (31). Women have a higher risk of developing OA than men (39, 69). However, this difference is mostly observed in the sixth decade of life (74). That there is no gender-specific difference was demonstrated in a study of athletes at the Olympic Games in Rio de Janeiro (4). However, one study has shown that age is an important predictive factor in younger age groups. The cause could be prolonged stress on the joint (33). The main symptom of OA is pain, but athletes usually have a higher pain threshold and often do not admit to the pain out of a desire to return to play. Authors led by Madaleno believe that this may be an additional cause for the development of degenerative processes in the cartilage of athletes (8). When other methods fail, surgical treatment is considered (50). Pain as a leading symptom may persist after surgery and may also be neuropathic, caused by nerve damage during surgery (45). Surgery is a very precise technique and inadequate intraoperative examination can lead to failure of the operation. This has led to increasing attention to the development of a new software navigation system. OrthoPilot is one such system that does not require CT (75). There is no pharmacological therapy that could prevent the progression of the disease (12). This is still being researched (68). Therefore, surgical methods are the treatment of choice when conservative methods fail (6). It is hypothesized that biomarkers for inflammation may correlate with imaging of synovitis, which may lead us to the search for the best treatment method (46). We think it would be good to have studies that compare levels of OA biomarkers in active athletes with levels of active training. Drugs aimed at altering inflammatory pathways at the molecular level offer a glimpse into a brighter future for the treatment of OA. Some of them have been shown to be effective in clinical trials (66). Mesenchymal stem cell

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therapy has shown promising results in the treatment of cartilage lesions. However, as such, it is not routinely used and needs further research, and there is a limitation for larger lesions (76). The treatment of OA should be adapted to the course of the disease, according to the patient's symptoms and expectations (6).

CONCLUSION

Frequent strain and frequent injury in athletes can cause cartilage damage and potentially lead to the development of OA. The benefits of exercise are far greater than the risks of the development OA. In addition, some studies report a significant stimulating effect of exercise on cartilage cell metabolism. The conclusion is that the most important thing for joint health is to get the right amount of exercise. The treatment of OA aims to restore the function of the affected joint and consists of the use of painkillers, intra-articular therapy, and physiotherapy. Surgical methods are considered when conservative approaches are not successful. The treatment of OA in young, active patients remains a challenge for orthopedic surgery. Initial treatment that includes exercise, NSAIDs, and a high intake of nutritional supplements, may alleviate symptoms but may not significantly change the nature of the disease. When used for the appropriate indications, surgery offers a potential solution for return to sport.

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