



Contents lists available at ScienceDirect

Journal of Cartilage & Joint Preservation®

journal homepage: www.elsevier.com/locate/jcjp

Autologous chondrocyte implantation for treatment of articular cartilage defects in the knee and ankle of football (soccer) players ☆



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ARTICLE INFO

Keywords:

Autologous chondrocyte implantation (ACI)
Cartilage
FIFA
Football
Return to play
Soccer

ABSTRACT

Background: Autologous chondrocyte implantation (ACI) continues to evolve into one of the most efficient and common techniques for repair of articular cartilage defects. Significant progress has been made within the last decade regarding its application in the context of professional sports, such as football. This article provides a current overview of the application of ACI in the context of amateur and professional football.

Methods: Clinical studies involving football players and other high-impact sports athletes treated with ACI were reviewed. The scientific and technical development of ACI was evaluated considering latest publications, and analyzed for treatment outcome parameters.

Results: Football players reported good to excellent results after treatment with ACI or matrix-associated chondrocyte implantation (MACI). Activity scores and clinical knee and ankle scores were significantly improved after surgery. Great advances have been made in surgery specific rehabilitation algorithms, leading to shorter return to play times. New surgical techniques have been introduced, reducing the 2-stage design of ACI to only one surgical intervention, accelerating return to play time further while reducing morbidity.

Conclusion: Surgical repair of focal articular cartilage defects via ACI in football players often provides successful return-to-competition and produces long lasting regeneration tissue, enabling players to continue their career on the pre-injury level of play. The technique itself is constantly evolving, addressing initial shortcomings and making it more widespread available to the recreational and professional athlete.

Introduction

Focal articular cartilage defects are amongst the most substantial injuries in the game of football (soccer), often leading to an early career end when left untreated.¹⁻³ Most soccer-related joint injuries occur in the lower extremities, with 16% to 46% occurring in the knee and 17% to 40% occurring in the ankle.⁴ After the anterior cruciate ligament (ACL) and the meniscus, the articular cartilage of the knee is amongst the most frequently injured structures in football players.⁵ Out of the most common 31 injuries in professional football, knee cartilage injuries are responsible for the most absence days per injury, after ACL tears and injuries to the lateral meniscus.⁶ In addition to the injury's athletics implications, they may lead to disabilities during activities of daily living. In 1743,

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<https://doi.org/10.1016/j.jcjp.2022.100059>

Received 10 February 2022; Revised 20 April 2022; Accepted 28 April 2022

Available online 1 June 2022

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William Hunter famously remarked that “ulcerated cartilage is universally allowed to be a very troublesome disease when destroyed, it is never recovered.”⁷ Hunter’s assertion was in the meantime partially disproved, enabling today’s physicians to effectively address cartilage injuries, allowing return-to-play (RTP).⁸

Elite football players are used to high intensity gameplay that is often associated with significant impact forces on load bearing joints and articular cartilage surfaces. While football has continued its athletic evolution to a high velocity game, articular cartilage injuries are observed with increasing frequency in players, especially on the elite level.^{9,10} Collegiate, professional, and world-class football players are expected to have a higher risk of developing osteoarthritis in the knee and ankle than the average athlete. Within the ankle, injuries to the cartilage surface are second only to damage of the collateral ligaments.⁹ Therefore, the need for early diagnosis and treatment is particularly high to prevent such unfavorable outcomes after a professional athletic career. Biomechanical calculations as well as investigations in vivo with large joints and the spine have shown that increased muscle strength loads the joints and articular cartilage surfaces but cannot relieve the resulting impact forces.¹¹⁻¹⁶ Consequently, well trained and developed muscles in the professional soccer athlete cannot prevent the increased loads within the knee and ankle joint, thereby explaining the rise in cartilage injuries despite improvements in injury prevention and conditioning in athletes compared to earlier decades.¹⁷ According to the International Olympic Committee Consensus Statement on Load in Sport and Risk of Injury, high accumulated loads have been shown to be a risk factor for injury in multiple sports, including football.¹⁸

The continuously evolving nature of the game of football intensifies the need for sufficient cartilage repair techniques, even to a higher degree than it was a decade ago.¹⁹ The number of games per season increases constantly, leaving little room for recovery and rehabilitation within the season, which increases the risk of injury.²⁰ For the best of players, the breaks between seasons are shortened by international competitions, such as the World Cup, European Championships, and the Copa America, intensifying the need for efficient and fast surgical procedures that ideally facilitate a rapid return-to-competition time. While the need for prevention of injuries has become more apparent within the last decade and great efforts were made to address it, injury rates remain high in the world of professional football, despite significant progress that has been made, for example with the FIFA 11+ injury prevention program.^{21,22}

Both professional and recreational football players hope for pain relief, return of functionality and a restoration of joint homeostasis after sustaining a focal articular cartilage injury. While the recreational player may be satisfied with the ability to engage in some kind of athletic activity after a cartilage injury, the professional players strive for a fast return to their previous high-demanding activity level without limitations.⁵ The resulting expectations of a fast, sustainable return in the highly competitive world of professional football, where financial stakes are high and the next playoff game might be just around the corner, create a delicate dilemma for the responsible physician—balancing a quick recovery with the highest possible margin of safety for the regenerated cartilage site.

Autologous chondrocyte implantation (ACI) as a treatment option for articular cartilage lesions was initially introduced in 1994 by Peterson as the first clinical application of tissue engineering.²³ Clinical results have been favorable in the long-term follow-up in the general population and the procedure has undergone a significant and ongoing evolution over several generations.²⁴ The procedure is most commonly used for treatment of focal chondral lesions >2 cm².⁵ This article provides an overview of current evidence of its application in cartilage injuries in the knee and ankle and focuses its impact on RTP rates and times, being the most important outcome for the injured football player.²⁵

Autologous chondrocyte implantation—a medical evolution

ACI has undergone a continual evolution as a restorative technique since its first introduction almost 3 decades ago. Originally proposed as a 2-stage procedure, spanning over a period of normally 6 weeks, it included an arthroscopic surgery followed by a large open arthrotomy. The first stage involving cartilage biopsy that was sent to a laboratory for in vitro cell expansion. This biopsy is most commonly harvested from non-weightbearing areas of the knee, either the intercondylar notch, the proximal aspect of the medial or lateral femoral condyle, or from the rim of the lesion.^{26,23} The second stage requires an arthrotomy exposing the cartilage defect, which is debrided to stable rims with vertical walls, facilitating optimal preconditions for suturing of the graft. The first generation ACI used an autologous periosteal membrane as a graft acquired from the proximal tibia and sutured into place over the defect, protecting the cultured chondrocytes, injected into the construct.²³ This procedure was associated with a large incision, to harvest the periosteal flap and access the cartilage defect, as well as the frequent complication of graft hypertrophy, resulting in mechanical symptoms and the risk of delamination.

These limitations were addressed by the introduction of second generation ACI, using a bioabsorbable collagen membrane instead of a periosteal flap (Fig. 1). This change in technique led to a reduction of graft hypertrophy to 6% and a decline in surgery-associated morbidity, but still required an arthrotomy and suturing of the collagen membrane into the defect.²⁷

Further evolution occurred by the introduction of third generation ACI, replacing the collagen membrane by biodegradable membranes or scaffolds to temporarily support the chondrocytes until their replacement by neocartilage matrix components synthesized by the implanted cells. The matrix-induced autologous cultured chondrocytes implantation (MACI) was approved by the FDA in 2017 in the United States and is currently the only FDA-approved cell-based cartilage repair treatment option (Fig. 2).²⁸ While still approved in the United States, MACI was suspended by European Medicines Agency in 2014 because of manufacturing site closure in Europe, leaving Spherex, a culture expanded aggregation of autologous chondrocytes, and Invossa as treatment options in Europe and Korea, respectively.^{29,30} The previously mentioned options use either a biomatrix seeded with chondrocytes or cell clusters that can be administered arthroscopically and further reduce surgical invasiveness and perioperative morbidity.³¹ Its cell carrier more evenly distributes the cells with a density of 500,000 to 1,000,000 cells per cm² over the defect area and is easier to implant than its predecessor.³² Fibrin glue can be used for fixation of the cell-seeded membrane, reducing surgical exposure, and the subsequent risk

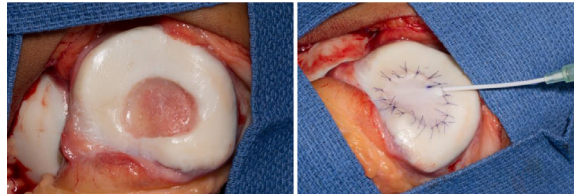


Fig. 1. A traumatic patella defect addressed with a second generation autologous chondrocyte implantation (ACI) repair with sewned in collagen patch.



Fig. 2. A traumatic patella defect addressed with matrix-induced autologous chondrocyte implantation (MACI) using a technique with fibrin glue fixation of a pre-seeded patch.

of scarring and arthrofibrosis.³³ Five-year follow-up for MACI results demonstrated notable clinical improvements in comparison to microfracture in randomized prospective studies.³² Revision rates in this period are relatively low at 9% to 10%, while the most common reason for revision surgery remains symptomatic overgrowth of the neocartilage.³² While this technique is the most advanced widely available cartilage repair procedure, its limitations remain the 2-stage design, donor-site morbidity, the length of 4 or more weeks between procedures which further delays return-to-play, the relative invasiveness of the (mini-) arthrotomy, the high logistic and monetary burden, and finally the resulting repair tissue is not hyaline cartilage.²⁴

These limitations are partly addressed by novel single-stage cartilage repair techniques.^{34,35} One of the procedures was coined Instant MSC Product Accompanying Autologous Chondron Transplantation, that was introduced in 2013 in the treatment of 35 patients for a symptomatic cartilage defect on the femoral condyle or trochlear groove within a clinical trial.³⁶ As culture expanded chondrocytes cannot be used for a one-stage design, this technique is replacing them by multipotent mesenchymal stromal (stem) cells, which were introduced >30 years ago and gained interest for their *in vitro* ability to differentiate into different lineages, including cartilage and *in vivo* capability for immune modulation and the secretion of growth factors.³⁷ As these cells are readily available and have a fast turn-over time in the laboratory, the procedure promises to potentially cut costs, accelerate RTP time, and alleviate logistical challenges, while being safe and producing favorable clinical results.³⁸ Further clinical trials are underway, investigating its application in a larger cohort and comparing outcomes against other cartilage restoration techniques.³⁹

ACI for treatment of focal articular cartilage defects of the knee

ACI is indicated for the treatment of chondral defects of the knee with a size >2 cm²; large osteochondral defects >2 cm² in combination with bone grafting if the depth of the defect is >8 mm; and for all types of chondral and osteochondral defects with previously failed other types of cartilage repair.⁴⁰ Several randomized controlled trials have demonstrated ACI has superior clinical outcomes and better structure repair compared to scar formation after microfracture in the general population.^{41,42,38} Results for cartilage restoration techniques in football players are described in several cohort studies, which underline the beneficial impact of ACI on outcome parameters within the last decade.⁴³⁻⁴⁵ Microfracture historically was the most widespread technique and showed a statistically significant improvement from baseline in functional outcome, pain scores, and Tegner activity levels after at least 1-year follow-up among professional football players.⁴⁶ ACI however produced superior results in comparison to microfracture, with an even higher good to excellent treatment success in professional football players, better functional outcome, and enhanced pain scores.^{45,47} This paradigm shift is impacting the clinical use of the procedures. While microfracture is still the most frequently used technique across FIFA Centers of Excellence, ACI and other cell-based solutions are quickly gaining ground.¹⁰

ACI seems to be especially effective in athletes and football players, as significantly better results were found in this group regarding IKDC, KOOS, and Lysholm score, when compared to the non-athletic population.⁴⁷ Players who were treated with ACI for smaller defect sizes (5.0 ± 0.5 cm²) had good or excellent results at final follow-up, while players with significantly larger defect sizes (8.5 ± 1.9 cm², *P* < .05) reported less favorable postoperative results.⁴⁵ Good to excellent results have been reported in 85% to 92% of players at 2 years, with femoral condyle lesions generally producing better results than defects of the patellofemoral joint.⁴⁸

It should be noted that ACI, used as a salvage procedure after failed bone marrow stimulation, produces significantly worse results as compared to its initial use for an untreated lesion.⁴⁹ This effect might be due to a previous alteration of the subchondral bone through a marrow stimulation technique, leading to compromised graft incorporation.⁵⁰ Additionally, Minas et al noted that they

frequently observed an intralesional osteophyte when performing secondary ACI, leading to inferior clinical function or even the need for revision surgery.⁵⁰

A recent study by Zaffagnini et al evaluated the clinical outcome in terms of rate and level of return to sports in a group of competitive athletes who underwent matrix-assisted autologous chondrocyte transplantation.⁵¹ They reported a satisfactory clinical subjective outcome with stable high clinical scores in the long-term follow-up. Interestingly, only about 60% of the athletes reached the highest goal of returning to sport at preinjury level, but this rate varied significantly according to specific patient and lesion characteristics.⁵¹

ACI for treatment of focal articular cartilage defects of the ankle

The ankle is one of the most commonly injured joints in football and contributes to a majority of the injuries sustained on the field.⁹ Osteochondral lesions of the talus, that can be sustained through an ankle strain, often have substantial impact on quality of life and athletic performance, resulting in the inability of an athlete and football player to train and compete.⁵²

The use of ACI in the treatment of ankle, and more specifically talus lesions, is not as widespread and well investigated as in the knee since most of the talar lesions are of osteochondral nature and therefore involve the subchondral bone to varying degrees. According to the *Proceedings of the International Consensus Meeting on Cartilage Repair of the Ankle* "ACI can be considered in primary or revision procedures for large lesions greater than 1 cm², with or without cysts."⁵³

Nam et al reported at a mean follow-up of 38 months an improvement in Tegner activity level from 1.3 ± 1.0 (mean \pm SE) preoperatively to 4.0 ± 1.6 ($P < .002$) postoperatively. The Finsen score (modified Weber score) showed significant improvement in the total score ($P < .001$). There was also overall significant improvement of the American Orthopedic Foot and Ankle Society ankle hindfoot score from 47.4 ± 17.4 preoperatively to 84.3 ± 8.1 postoperatively ($P < .001$). At repeat arthroscopy, complete coverage of the defect was seen in all patients.⁵⁴

Lenz et al treated lesions with a mean size of 204 mm² and found a significant improvement in mean AOFAS score from 60 preoperatively to a mean of 84 at 12 years postoperatively and the 12-year FAAM score for Activities of Daily Living was 89% (range, 62%-99%).³³ These studies, however, were not conducted in an athletic population and are testament to the efficiency of ACI in talus lesions in the general population, while the outcome in terms of sport activity is rarely documented.

A study by Giannini et al examined 46 patients 12 months after arthroscopically guided MACI. In this case series, 29 patients were sport active before the onset of symptoms (25 at recreational level, 4 professionals). Of those, 16 played contact sports (football, basketball) and 13 noncontact sports (volleyball, tennis, swimming, and other). At follow-up, 20 out of 29 continued sport activities at the primary level, and 3 out of 29 at a lower level. All professional athletes continued their career.⁵⁵

Newer techniques for the treatment of focal articular cartilage lesions have emerged, such as the use of particulated juvenile articular cartilage allograft, avoiding a 2-stage procedure.⁵⁶ While the technique showed promising results, comparable to ACI, in a regular population, there are no current data available on its performance in athletes and particularly in football players.

Advances in rehabilitation after ACI

Rehabilitation after articular cartilage repair is essential for optimal function and return to preinjury game levels. Postoperative rehabilitation protocols vary among surgeon's and institution's preferences but can generally be divided into several phases aiming at protection of the graft by a gradual increasing weightbearing and active range of motion. This progressive design may enhance graft maturation, remodeling, and integration.⁵⁷

Focal articular cartilage defects of the knee and ankle are often accompanied by concomitant injuries, such as meniscus lesions or ligamentous ruptures.⁵⁸ In other instances, a preexisting malalignment might have contributed to the emergence of the injury.^{59,28} A systematic review of 5 different case series calculated that the incidence of severe articular cartilage lesions in patients with acute ACL rupture is 16% to 46%.⁶⁰ These concomitant pathologies must be addressed at the time of surgery to facilitate the best possible outcome for the athlete.

The rehabilitation period has traditionally been prolonged after chondrocyte implantation, as early rehabilitation protocols focused on protection, rather than accelerated rehabilitation.⁶¹ More current, more aggressive concepts allow for partial weightbearing within the first week of surgery, improving cartilage healing, knee function, and sports participation after chondrocyte implantation.⁶² For these protocols, less pain was reported at 3 months, while similar KOOS scores were obtained at 5 years' follow-up.⁶³ Additionally, the implementation of low-load activities during the first 3 months after surgery seemed to positively influence the clinical outcome after 2 years.⁶⁴ The high standard of rehabilitation facilities and the availability of experienced physicians and physio therapists in professional sport organizations creates a perfect environment for a more aggressive rehabilitation approach after cartilage surgery. The almost unrestricted amount of time professional athletes can dedicate to rehabilitation procedures further facilitates this approach.⁶⁵

Basic science studies support early return of range of motion for improved cartilage healing.⁶⁶ Animal studies reported improved chondrogenesis, proteoglycan and glycosaminoglycan synthesis in cartilage as well as decreased collagen breakdown after early resumption of range of motion using continuous passive motion.⁶⁷ Furthermore, early range of motion prevents disuse atrophy and prevents knee stiffness, thereby improving postoperative outcomes.⁶⁸ These enhancements in rehabilitation protocols lead to a direct improvement of rate of sports participation and return-to-play-time.⁶² Through continued decreasing invasiveness of newer-generation ACI, faster postoperative joint mobilization can be achieved, accelerating neuromuscular recovery, and restoration of joint biomechanics.¹⁹

After usually 6 weeks of protected weightbearing, full weightbearing can be progressively reached within 2 to 6 weeks, depending on surgeon's preferences.⁶² A randomized controlled trial even reported that it was safe to resume full weightbearing at 6 weeks compared to 8 weeks.⁶⁹ Professional and sub elite football player are most often subject to individualized rehabilitation programs with stepwise on-field rehabilitation and reintegration into sport-specific movement patterns, resulting in accelerated return-to-play times when compared to recreational athletes.⁶² The majority of available literature reports return-to-play times for the professional sub-group of 6 to 12 months, significantly reducing the average time to return-to-sport from 18 months, as reported for first generation ACI technique, without compromising durability and return rate in even highly competitive players.^{61,62} It remains to be seen if weightbearing protocols should differ based on the location of the cartilage lesion, as very little literature is available that takes this parameter into account.

Every rehabilitation protocol is criteria based and highly individualized, depending on concomitant injuries and surgeries and the athlete's strengths measurements pre- and postoperatively. However, the following timeline provides a generalized guide based on above evidence:

Weeks 4 to 6: Partial Weightbearing (15-20 kg, crutches); ROM: free/0°/90°

Weeks 7 to 8: Progressive increase to Full Weightbearing; Full ROM

Weeks 9 to 11: Full Weightbearing; Full ROM; Intensive hypertrophy training; Intensive training on maximum flexion

From Week 12: Sport-specific exercises; Maximum quadriceps strength training; Reactive training

Discussion

ACI is a well-established and successful technique for the restoration of full-thickness articular cartilage lesions in the knee and ankle of football players.¹⁷ While most of the available data consists of cohort studies and case series, few randomized controlled studies are also available and were included in this article.^{70,32,69} While Mithoefer et al provided a comprehensive overview on the topic 10 years ago, substantial new evidence has been added in the meantime, further illuminating the use of ACI in football players and adding to the growing body of evidence.¹⁹ Recent studies demonstrated that football players achieved significantly better results in all outcome parameters when treated with ACI than non-athletes.⁴⁷ This is valuable and encouraging information for the surgeon in the decision-making process, as treatment of cartilage lesions is still highly individualized and better results can be expected in patients with higher level of sports activities.⁷¹ Since ACI is in clinical use for almost 3 decades now, long-term outcome data is available for up to 25 years postoperatively.^{72,73}

The technique is in successful use for articular cartilage repair in athletes and specifically in football players.⁷⁴ It provides a longstanding structural repair, which tolerates the high impact loads imposed on the football player's knee and ankle.¹⁰ Chondrocyte implantation in this specific population provides lasting functional improvement, demonstrating the biomechanical abilities of the resulting repair cartilage tissue in withstanding exceptional pressure and shear forces in vivo. While microfracture possibly allows for faster recovery, clinical deterioration over time is likely and a growing body of literature demonstrates less predictable long-term clinical outcomes mostly attributed to the problematic durability of fibrocartilage tissue.^{75,76,41} Osteochondral Allograft Transplantation is an integral part of the cartilage repair paradigm and has shown favorable results in clinical outcome scores and potentially allows for a fast RTP.^{77,78} The implantation of fresh osteochondral allografts provides a well described and tested treatment option for focal chondral lesions because it provides immediate structural integrity to the joint surface by transplanting structural bone and viable hyaline articular cartilage into the defect.⁷⁸ While the procedure is commonly adapted in the United States, especially for the repair of large chondral defects, it is not widespread applied in most of Europe and Asia due to unavailability of allografts.⁷⁹ ACI, however, is applied in American and European countries alike and provides good and stable clinical results that are accompanied by a slightly delayed RTP time.⁴³ Given the frequency of articular cartilage injuries in professional football, the increased risk for the development of knee osteoarthritis and the short time span of an average athletic pro career, ACI seems to be a more sustainable option for both, the athlete himself and the professional football clubs.⁸⁰ The available data confirms that early improvement after ACI is sustained for a long period of time, as shown by the significant improvement in almost all outcome parameters.⁷⁰ Especially players with large cartilage lesions (>2 cm²) seem to profit significantly from the treatment with ACI.⁸¹ Not only the long-term survival rate has been proven in recent studies, but it was shown that the greatest improvements in clinical scores occurred within the first 2 years of surgery, building a plateau thereafter.^{70,69} Therefore, surgical debridement of the focal lesion during the season, combined with a biopsy for a possible off-season ACI procedure, may lead to a decrease in loss of playing minutes and follows faster return to competition within a single noninternational team football season.⁵ Return to football is significantly better if cartilage repair is performed within 12 months after injury, leaving the athlete's physician room for an individualized treatment algorithm.^{82,83} Further delayed surgery is associated with significantly inferior cartilage morphology, inferior patient-reported-outcomes and RTP rate.^{84,82}

New cartilage restoration techniques, such as Instant MSC Product Accompanying Autologous Chondron Transplantation /RECLAIM have the potential ability to further shorten RTP time and introduce cell-based cartilage repair techniques to a broader market, by reducing morbidity, costs, and logistic burden.³⁸ It could constitute a sufficient tool for in-season cartilage repair in professional athletes and enhance the availability of the technique to sub elite players, letting them participate in the advantages of the technique on a higher scale. While clinical trials are ongoing, it remains to be seen how repair cartilage tissue resulting from this single-stage technique will perform in vivo in the demanding circumstances of competitive football.

While ACI is an efficient treatment option, its deployment must be accompanied by critical evaluation of concomitant injuries or malalignment. Ligamentous instabilities are frequently associated with cartilage injuries in the knee and the ankle and must be addressed at the time of surgery to facilitate healthy joint biomechanics, allowing the cartilage repair site to heal. By choosing a single-stage approach, multiple surgical procedures and connected comorbidities with prolonged rehabilitation can be avoided. It has

been shown that addressing simultaneously both, cartilage lesion and concomitant injury, does not negatively affect the return-to-play rate.⁸⁵ In the presence of a concomitant meniscus tear it is crucial to suture and refixate the tissue where possible, as a partial or full meniscectomy is known to be a contributor to progression of osteoarthritis and negatively affects the healing potential of the cartilage lesion.³ While a debridement of a meniscus lesion might lead to an earlier RTP, its mid- and long-term effects are less favorable and should therefore be avoided if possible.⁸⁶

Ligamentous injuries, especially ruptures of the ACL, are common among professional soccer players and show a high association with focal cartilage defects of the knee. If concomitant with a cartilage injury, it is crucial to address the instability-causing pathology first, before repairing the cartilage defect. Then, the clinical short-term outcomes after ACI at the knee joint in combination with ACL reconstruction are good and similar to the results after isolated ACI in ligament intact knees.⁸⁷

It is important to note, that there are several disadvantages of the ACI technique as of today. Almost all centers use a 2-stage approach, resulting in the need for 2 surgeries with ex vivo expansion of the chondrocytes. This delays the final rehabilitation of the patients, and in some cases results in quadriceps atrophy and deconditioning of the affected extremity. While this can usually be prevented in the professional setting, it remains a challenge in amateur athletes with limited access to physical therapy between surgical cases. In addition, this procedure is very costly, and is continuously challenged by payers in most countries.

Conclusion

Recently available long-term data suggests that first- and third-generation ACI methods are equally effective treatments for isolated full-thickness cartilage defects of the knee and ankle. The technique provides a high probability for football players with focal articular cartilage defects to return to sports activity. The return-to-play time has been significantly shortened due to enhanced surgical techniques and more aggressive rehabilitations protocols without compromising the return rate, the level of activity achieved upon return, and the long-term stability and integrity of the cartilage repair construct.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

M.H. and D.B.F.S. designed the research. M.H. performed the literature search. M.H. wrote the manuscript in consultation with D.B.F.S., R.J.H.C., A.J.K. A.J.K. provided picture material. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Funding information

The authors would like to acknowledge the support from the Foderaro-Quattrone Musculoskeletal-Orthopaedic Surgery Research Innovation Fund. Martin Husen acknowledges the funding from Deutsche Forschungsgemeinschaft (DFG), grant number: 466023693.

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