

Management of knee articular cartilage injuries in athletes: chondroprotection, chondrofacilitation, and resurfacing

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Abstract Articular cartilage defects of the knee are common among athletes where the physical demands of sport result in significant stresses on joints. Chondral defects are associated with pain and functional impairment that limit sporting participation and may progress to joint degeneration and frank arthritis. Management of established chondral lesions aims to allow athletes to return to high-impact sports and can be considered in terms of protection of existing cartilage, chondrofacilitation, and resurfacing. Repaired and regenerated cartilage must closely resemble and function like normal hyaline cartilage, and this ability may be the most significant factor for the return to sport. Based on our experiences and the available literature, we outline how athletes can best protect their cartilage, how physicians can facilitate intrinsic repair of established lesions, and which methods of cartilage restoration or resurfacing should be used in different situations.

Level of evidence IV.

Keywords Cartilage injury · Return to sport · Knee articular cartilage · Cartilage resurfacing

Who is at risk?

Both acute traumatic injury and chronic repetitive damage to articular cartilage are increasingly recognized in athletes. The overall prevalence of focal chondral defects in the knee is 36 % among all athletes compared with 16 % of the general population [17]. Higher injury rates are noted in competition over practice, athletes with BMI over 30.5, and athletes in certain positions (for example, linebackers) [7]. Increasing participation in recreational sports has also been associated with a rising incidence of cartilage injuries among non-competitive athletes [1]. In addition to being common, these injuries carry a high morbidity. Knee injuries account for 46 % of career-ending injuries in professional soccer with over a quarter resulting from cartilage injuries, and athletes are up to 12 times more likely to develop osteoarthritis than the general population [17].

Natural history of athletic cartilage lesions

The rationale for each treatment approach is based on knowledge of the pathophysiology underlying chondral lesions. Without access to abundant nutrients or progenitor cells, cartilage lacks innate abilities to mount a regenerative response to injury. In partial-thickness defects, there is no involvement of the vasculature. Chondroprogenitor cells in blood and marrow cannot enter the damaged region, and local articular chondrocytes do not migrate to the lesion. As such, the defect is not repaired and will progress.

Full-thickness cartilage injuries that penetrate subchondral bone have the potential for intrinsic repair due to communication with chondroprogenitors in bone marrow. Type I collagen is produced by these differentiating cells, resulting in fibrocartilage rather than the preferred hyaline cartilage

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generated by native chondrocytes [51]. This ‘repair cartilage’ is less robust and has poor wear characteristics.

Athletic activity and chondropenia

The volume and thickness of articular cartilage increase with weight-bearing activity, and there is a positive linear dose–response relationship for repetitive loading activities and articular cartilage function. However, this dose–response curve reaches a threshold, and activity beyond this threshold (such as running over 20 km per day) can result in disturbed cartilage joint homeostasis and chondropenia. Concomitant ligamentous instability, malalignment, and meniscal deficiency can propagate this chondropenic cascade [54].

Acute chondral injury

Chondral defects occur in association with 9–60 % of acute anterior cruciate ligament (ACL) ruptures and 95 % of patellar dislocations [8, 17]. Associated bone bruising results in chondrocyte apoptosis highlighting the importance of the subchondral bone environment. Most acute lesions are single high-grade lesions located on the femur [45].

Chronic chondral defects

Chondral defects can also develop insidiously secondary to joint instability or following meniscal injury in which the chondroprotective function of these structures is lost.

Clinical evaluation and classification

A systematic approach to assessment of chondral lesions in athletes is critical to guide treatment (summarized in Fig. 1). The International Cartilage Repair Society (ICRS) has developed a system of documentation and classification to promote comprehensive evaluation and uniform standards [30]. The systematic method enables understanding of the ‘injury personality’ based on nine variables that influence management: aetiology, defect thickness, lesion size, degree of containment, location, ligamentous integrity, meniscal integrity, alignment, and relevant factors in the patient history. Knee-specific clinical outcome tools [e.g. the modified Cincinnati rating scale, the knee injury and osteoarthritis outcome score (KOOS), and the International Knee Documentation Committee (IKDC) score] and quality of life surveys (e.g. SF36) should be used to measure the patient’s subjective symptoms and to monitor disease progression or response to treatment.

Plain radiographs can help identify osteochondral lesions, joint space narrowing, patellar maltracking, or lower extremity malalignment. However, magnetic resonance imaging

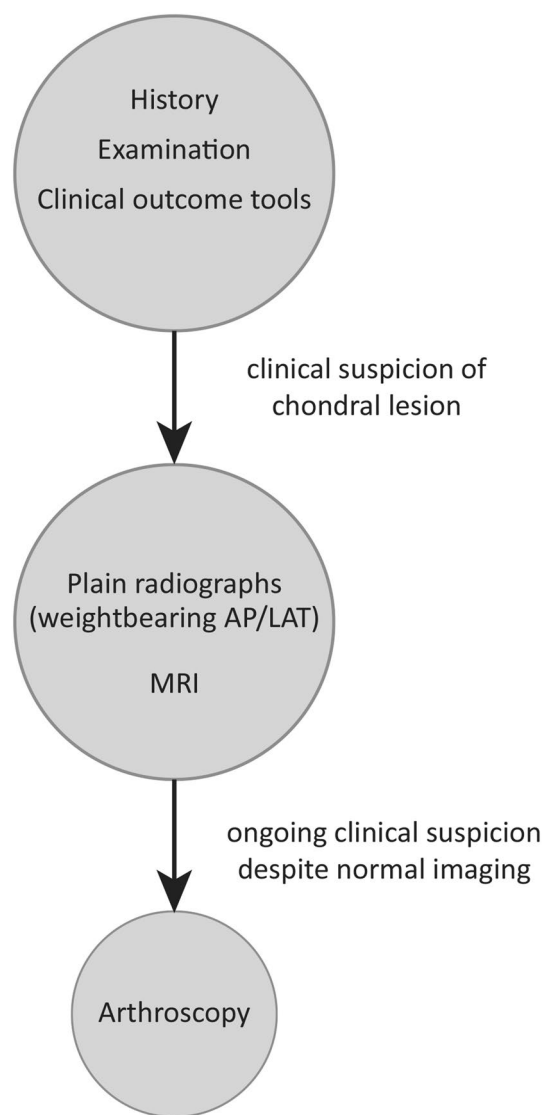


Fig. 1 Approach to diagnosis and clinical evaluation of chondral lesions in athletes. AP anteroposterior, LAT lateral, MRI magnetic resonance imaging

(MRI) is currently the mainstay of diagnostic imaging allowing assessment of chondral lesions and the underlying bony environment. Despite advances in MRI technology, chondral lesions may remain undetected until arthroscopy [16]. A number of systems have been described to classify chondral injury at arthroscopy including the Outerbridge, Bauer and Shri-aree, and the chondropenia severity score (CSS).

Chondroprotection, chondrofacilitation and resurfacing: a framework for management

While avoidance of chondropenia and prevention of injury should always be sought, sport inherently involves

extremes of performance and some chondral injuries are unavoidable. Current treatment options can be considered under three broad categories:

1. *Chondroprotection*: strategies that aim to prevent loss of existing cartilage.
2. *Chondrofacilitation*: strategies that seek to facilitate intrinsic repair of damaged articular cartilage.
3. *Resurfacing*: improvements in chondral surface function are sought through replacement rather than intrinsic repair of cartilage defects. Approaches include autologous chondrocyte implantation (ACI), autografts, allografts, or synthetic products that fill the defect through a variety of techniques.

A vast number of strategies are available in the treatment of chondral injuries, although few are supported by robust clinical evidence. This is reflected in current NICE (National Institute for Health and Clinical Excellence), OARSI (Osteoarthritis Research Society International), and AAOS (American Academy of Orthopaedic Surgeons) guidelines. We have developed a treatment algorithm for the management of chondral injuries based on our experiences of treating athletes and the available literature (Fig. 2).

Chondroprotection: How should athletes protect their cartilage?

Chondroprotective measures should be considered in all patients to prevent disease progression and to protect any surgical repair.

Consider training alternatives to high-impact joint loading

Exercise and activity modification are important chondroprotective measures that are supported by robust evidence and key guidelines [14, 38, 61]. Mechanical loading is an important regulator of chondrocyte metabolism and cartilage health. Oscillatory loads at low frequencies have been shown to be beneficial, while high strain rates and extended immobilization may lead to matrix degradation [35]. While competitive activity cannot be altered, diversification in training to include low-impact activities such as cycling and swimming may be practical.

Incorporate injury prevention warm-ups

Structured training programmes for injury prevention such as the FIFA 11+ warm-up are effective in reducing the rates of injuries in athletes of all ages, levels of ability participating in different sports [37].

Restore stability

The abnormal kinematics, contact pressures, and repeated episodes of instability in patients with ACL insufficiency increase risk of further chondral pathology. ACL reconstruction should therefore be performed within 8 weeks of injury [21].

Consider meniscal repair for simple, peripheral tears

In the absence of menisci, joint contact forces increase by twofold–threefold predisposing to articular cartilage degeneration [52]. Encouraging results have emerged following repair of simple longitudinal meniscal tears in the periphery and complex multiplanar tears extending into the central third [60]. However, meniscal repair is possible only in a minority and may not be achievable in the presence of considerable meniscal damage. Caution should be taken, especially in high-level athletes, where failure of repair requiring a second surgical procedure would result in prolonged absence from sport.

In athletes at the end of their competitive career, meniscal allografts can play a role in halting the progression of chondropenia, although long-term success rates are not available, and this procedure is not recommended as a prophylactic measure in patients without chondral damage [52].

If osteotomy is required counsel patient on poor prognosis of competitive sporting return

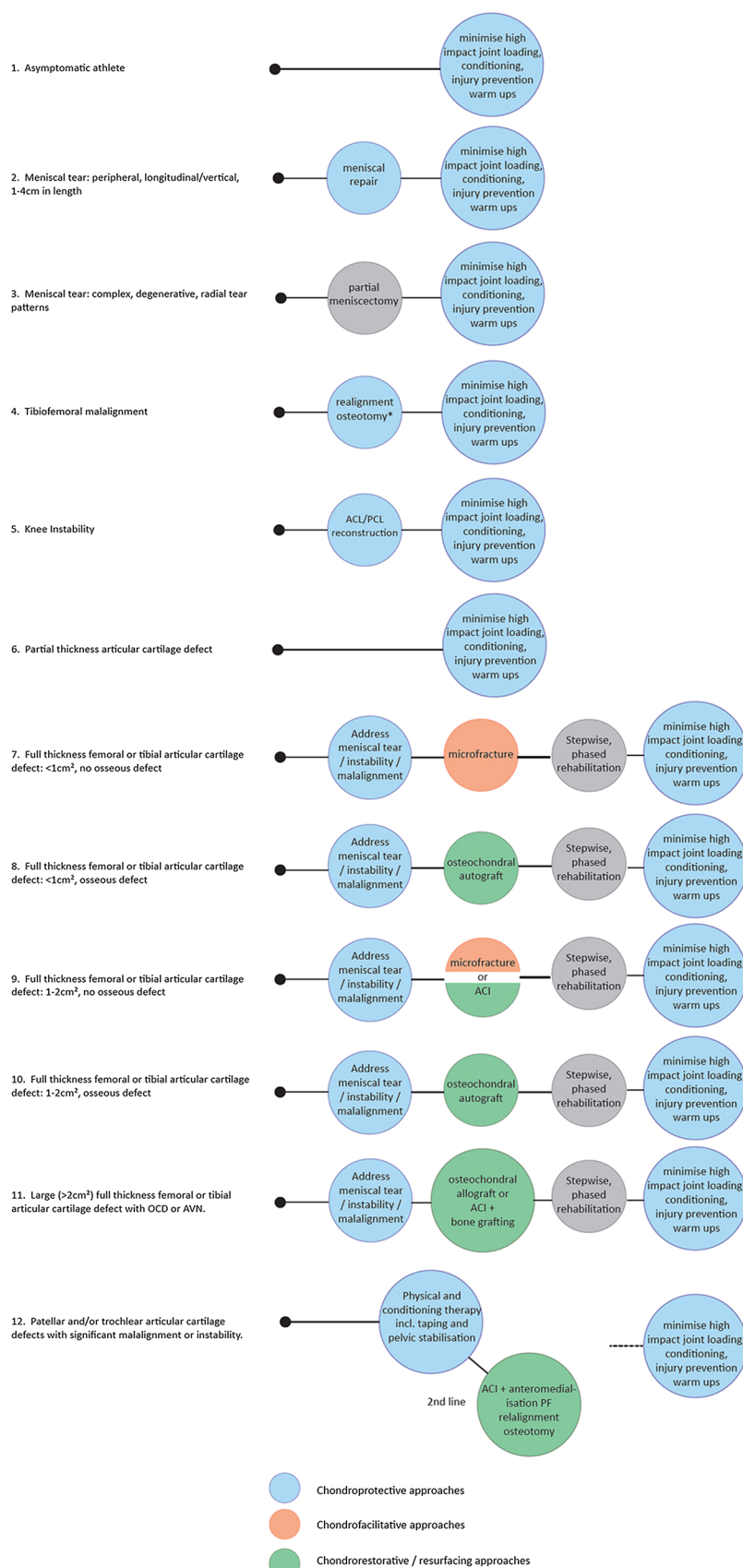
Tibial or femoral osteotomies aim to correct abnormal loads on the articular surface of the knee, resulting from tibiofemoral axis deformity. Young motivated patients are able to resume strenuous activities, although activities are limited in the majority and return to competitive sport is not likely [5].

Chondroprotective strategies with limited evidence

Glucosamine and chondroitin sulphate are widely used in the treatment of chondral injury or degeneration although their mechanism of action is not fully understood. While there have been conflicting reports of benefit in terms of symptomatic relief, these strategies have shown no significant benefit in terms of disease modification and are not recommended in current OARS, AAOS, or NICE guidelines [14, 38, 61].

Arthroscopic knee washout alone should not be used as a treatment for osteoarthritis because clinically useful benefit in the short or long term has not been demonstrated. A number of RCTs [6, 31] have been published since Moseley's [50] landmark study in which 180 patients were randomly assigned to surgical debridement or sham procedure showed no significant difference in measures of pain or function. Pooled results show no benefit for lavage and or debridement over placebo.

Fig. 2 A treatment algorithm for the management of articular cartilage defects in athletes based on protection of existing cartilage, chondrofacilitation and chondrorestoration/resurfacing. *ACI* autologous chondrocyte implantation, *PF* patellofemoral, *OCD* osteochondral defect, *AVN* avascular necrosis. *astrick* athletes undergoing tibiofemoral realignment osteotomy should be counselled on the poor prognosis of competitive sporting return



Chondrofacilitation: How should the physician facilitate intrinsic repair of established chondral lesions in athletes?

Non-operative strategies seek to promote regeneration of functional hyaline cartilage through the delivery of growth factors or by tempering inflammation. Surgical methods aim to facilitate regeneration of native hyaline cartilage through stimulation of MSCs. Despite widespread popularity non-operative strategies including viscosupplementation with hyaluronic acid, the addition of growth factors [such as platelet-rich plasma (PRP) or bone marrow aspirate concentrate (BMAC)] and the addition of an electromagnetic field are not yet supported by robust evidence. Chondrofacilitation through microfracture should be considered for lesions $<2\text{ cm}^2$ that do not have an underlying osseous defect.

Microfracture

[Indications: Full-thickness lesions $<2\text{ cm}^2$. *Contraindications:* Larger lesions, underlying osseous defect].

Perforation of the subchondral bone generates conduits to the vascularized bone marrow allowing migration of MSCs and the potential for intrinsic repair. The main drawback is the limited durability of the repair tissue, which is predominantly fibrocartilage rather than hyaline cartilage. The perforations created with microfracture can result in bone compaction and fracturing around holes that are largely sealed off from adjacent bone marrow. Nanofractures are created with thinner awls (1 mm) that protrude to a controlled depth of 9 mm. Preservation of trabecular architecture with this technique has been confirmed using high-definition CT.

A recent systematic analysis demonstrated that microfracture provided effective short-term functional improvement, particularly in younger patients with smaller lesions [42]. However, these positive results tended to decline with time, likely reflecting differences in mechanical properties between hyaline and fibrocartilage [22]. Extending clot stability through improvements in clot adhesion using polysaccharide polymers, biodegradable hydrogels, or 3D scaffolds (e.g. AMIC) may improve effectiveness of microfracture in future [28, 63]. Concomitant use of PRP or BMAC may improve outcomes over microfracture alone [18, 39].

Chondrofacilitative strategies with limited evidence

Viscosupplementation

[Indications: Not currently recommended by the authors for discrete chondral lesions in athletes].

Hyaluronic acid is a major component of synovial fluid that reduces inflammatory reactions and enhances proteoglycan production [62]. A number of systematic reviews have concluded that intra-articular hyaluronic acid (IAHA) results in small but significant clinical benefit in terms of pain and function for knee OA, although well-designed studies showed small effect sizes [2, 56]. Overall, meta-analyses report conflicting results, and hyaluronic acid is not currently recommended by OARSI, AAOS, or NICE [14, 38, 61].

Growth factors including PRP and BMAC

[Indications: Not currently recommended by the authors in isolation for discrete chondral lesions in athletes].

Platelet-rich plasma (PRP) has been used safely with proposed healing properties attributed to the increased concentrations of autologous growth factors and secretory proteins that may enhance tissue regeneration [19]. While the few studies evaluating platelet aggregates in the treatment of chondral lesions or OA report decreased pain in the post-injection period compared to hyaluronic acid [34, 57], they do not allow for comparative analysis of clinical effectiveness. There is currently insufficient evidence for PRP to be recommended in key guidelines, and well-designed RCTs are required to establish the clinical value of PRP in this setting.

Bone marrow aspirate concentrate (BMAC) improves cartilage repair compared with microfracture in animal models although clinical evidence is currently limited [18]. BMAC may be particularly useful in the treatment of certain osteochondral lesions of the tibia plateau where the use of osteochondral allografts is limited by awkward size or location.

Electromagnetic field therapy

[Indications: Not currently recommended by the authors in isolation for discrete chondral lesions in athletes].

Pulsed electromagnetic fields have been shown to increase proteoglycan synthesis and decrease levels of inflammatory cytokines in animal models. Electromagnetic field therapy reduces recovery time after knee arthroscopy and may therefore be a useful surgical adjunct [65].

Chondrorestoration: indications for different resurfacing methods in athletes

While chondrofacilitative strategies seek to support and augment the body's ongoing attempts to produce hyaline cartilage from the site of injury, chondrorestoration and resurfacing approaches originate from outwith the lesion

itself through transplantation (allogenic or autologous) or implantation of autologous chondrocytes. While level IV studies have evaluated a number of these procedures, many use different techniques, outcome measures, and differing lengths of follow-up precluding definitive comparison. As such, current AAOS, OARSI, and NICE guidelines conclude that the evidence for superiority any specific technique over another is inconclusive and advocate that treatment strategies should be devised on an individual basis. The multiple options currently widely used suggest that a definitive evidence-based treatment has yet to be established. Below we outline the key chondrorestorative options, their indications, and available results.

Osteochondral autograft transplantation

[Indications: Osteochondral lesions $<2\text{ cm}^2$. *Contraindications:* Larger defects].

Osteochondral implantation provides replacement of mature hyaline cartilage together with underlying subchondral bone. Osteoarticular transfer system (OATS) (Arthrex), COR (Mitek), and mosaicplasty (Smith and Nephew) are commercially available systems. Defects of up to 2.5 cm^2 have been successfully addressed in young athletes although long-term results in an athletic population are still unclear. In a 17-year prospective multicenter study, good to excellent results in 91 % of femoral, 86 % of tibial, and 74 % of patellofemoral mosaicplasty in athletes were reported [26]. Equivalent results have been reported in athletes with osteochondral transfer and ACI, although improvements occurred more rapidly with osteochondral transfer [29]. A prospective, randomized study reported significant superiority of osteochondral transfer over microfracture at 3 years [24].

Limitations include the potential for incongruity and graft height mismatch that can result in early wear [33]. Poor graft integration has been reported, and microfracture of the gaps and insertion of BMP-7 in a collagen matrix have been used to combat this [10].

Osteochondral allograft transplantation

[Indications: $>2\text{-cm}^2$ full-thickness chondral defect with or without osseous defect or AVN].

Osteochondral allograft transfer (OALT) procedures overcome many of the challenges of matching chondral topography and donor-site morbidity that limit autologous techniques. Several studies have shown that transplanted bone readily becomes incorporated by the host with good articular cartilage function. Ninety-one percentage success rates at 5 years, 85 % at 7.5 years, and 75 % at 10 years with femoral and patellofemoral allografting have been reported [9, 20]. Although these techniques have better

durability than microfracture, there is still a time-dependent decrease in graft survival rates [23]. Concerns about graft sterility, rejection, viral transmission, supply constraints, and cost are limiting factors. As with autologous osteochondral plugs, graft subsidence, lack of peripheral integration, and peripheral chondrocyte death may also occur. If the problem of graft incorporation is overcome, good to excellent outcomes are generally achieved with accelerated return to sport [55].

Autologous chondrocyte implantation

[Indications: Focal lesions $1\text{--}10\text{ cm}^2$, failed microfracture, or osteochondral grafting. *Contraindications:* Reciprocal (kissing lesions), osteoarthritis, and inflammatory arthritis. $>8\text{ mm}$ depth of bone loss].

ACI involves the harvesting of chondrocytes from a healthy non-weight-bearing portion of the knee followed by implantation of culture-expanded autologous chondrocytes under a periosteal flap (first-generation ACI) or a collagen membrane (second-generation ACI), or onto a membrane carrier or porous scaffold prior to implantation (third-generation ACI). MACI has not yet received approval from the United States Food and Drugs Administration (FDA), but is widely available in Europe.

Good to excellent results have been reported in 85–92 % of patients at 2 years, with femoral condyle lesions generally producing better results than defects in the patellofemoral joint [53]. Comparable positive functional results have been reported between second-generation ACI (using porcine-derived type I/III collagen as a cover) and third-generation ACI (MACI) at 1 and 2 years [3]. Sustained improvements seen in large, symptomatic, full-thickness lesions of the distal femur treated with ACI have been reported in the majority of patients at up to 10 years [49]. When performed in elite athletes, ACI resulted in a successful return to high-impact sport with excellent durability at 5 years and beyond [44, 48].

Equivalent functional results have been reported with ACI and microfracture at 5 years [32]. A further study reported functional improvement in 88 % of mosaicplasty patients, compared to 68 % in the ACI group [13]. Conversely, superior ICRS scores with second-generation ACI over mosaicplasty (good or excellent results in 88 vs. 69 %) have been reported in a randomized controlled trial [4]. Equivalent improvements have also been reported following both ACI and osteochondral transfer although recovery was much quicker with osteochondral transfer [29].

The identification of molecular markers known to represent a subset of chondrocytes associated with hyaline cartilage formation has provided a means to selectively expand type II collagen-producing chondrocytes. Implantation of these expanded, characterized chondrocytes compared with

microfracture in a randomized study has shown improved repair tissue at 12 months, but direct comparison to unselected ACI chondrocyte implantation has not yet been reported [58].

The main disadvantage of these techniques is the long time for tissue maturation and consequent return to sport. Further limitations include the requirement for multiple surgical procedures, donor-site morbidity, the expense and potentially harmful modification of cells in culture, and the repair tissue is not hyaline cartilage.

Neocartilage implantation

[Indications: Full-thickness chondral defects of any size. *Contraindications:* Must be performed following bone grafting if osseous defect present].

NeoCart (Histogenics) uses autologous chondrocytes exposed to hydrostatic pressures on a three-dimensional matrix to encourage the production of hyaline ECM. Phase two RCTs have demonstrated that this technique is safe and associated with greater clinical efficacy over microfracture at 2 years [12].

Cartilage autograft implantation system (CAIS)

[Indications: Full-thickness chondral defects of any size. *Contraindications:* Must be performed following bone grafting if osseous defect present].

CAIS (Johnson and Johnson) uses particulated autologous cartilage harvested from an unaffected area of the knee that is implanted on a 3D resorbable scaffold. In short-term clinical studies, CAIS resulted in improved subjective patient scores and MRI evidence of defect filling [15]. An RCT comparing microfracture and CAIS demonstrated similar tissue repair but improved functional scores with CAIS [11].

Cartilage allograft implantation

[Indications: Full-thickness chondral defects of any size. *Contraindications:* Must be performed following bone grafting if osseous defect present].

DeNovo NT (Zimmer) uses 1-mm² cubes of allograft juvenile chondrocytes suspended in their native ECM that are implanted using fibrin glue. Early human outcome studies have demonstrated good results with the formation of hyaline-like cartilage [43]. Concerns of donor-recipient disease transmission necessitate strict screening protocols.

Osteochondral graft substitutes

[Indications: Not recommended by the authors].

The Trufit plug (Smith and Nephew) is a bilayered cylindrical implant composed of a bone and cartilage phase,

designed to match the layers of cartilage and subchondral bone. Despite short-term satisfactory clinical outcomes in small series [64], controversy about its long-term utility persists due to limitations in bony incorporation and the popularity of these systems is declining.

Rehabilitation and return to sport after knee articular repair

Rehabilitation aims to enable full sporting return, prevent reinjury, and minimize the progression to osteoarthritis. An individualized approach should be taken, and it should be recognized that not all athletes will return to pre-injury levels of function.

Rehabilitation must be adapted to the biology of the surgical repair and each athlete's sport-specific demands. This can be achieved by a stepwise approach consisting of an initial protection and joint activation phase, a progressive joint loading and functional restoration phase, and finally an activity restoration phase. The length of rehabilitation depends on an individual's performance at each stage. A key benefit of osteochondral grafting is that early weight-bearing can be tolerated due to graft stability. This is not the same with ACI/MACI or microfracture, where the repair construct has to be given time to embed in the subchondral bone. Combined procedures (ACL reconstructions, high tibial osteotomy, and meniscal allografts and repair) do not adversely affect the return-to-sport rate after cartilage repair [59], although rehabilitation may need to be modified taking into account the concomitant lesion.

Data for the return to activity of athletes with articular cartilage injuries have been reported for treatment with ACI [47], microfracture [46], autologous osteochondral transfer [25], and osteochondral allografting [36]. Several prospective studies have shown that 33–96 % of athletes return to sport after ACI, with 60–80 % of them returning to the same level [40]. Average return to sport times for ACI is 18–25 months [40]. Return to competition has been reported in 59–66 % of athletes after microfracture, with 57 % returning to their pre-operative level of performance [42]. Athletes were able to return to sports 8–17 months after microfracture [46]. Sporting return has been reported in 91–93 % of athletes after osteochondral transfer [24] at an average of 6.5–7 months [40]. Eighty-eight percentage of athletes returned to partial activity and 79 % returned to full activity after osteochondral allograft transplantation in the knee at an average of 9.6 months [36]. While a number of studies have reported a drop in function starting 24 months following microfracture and osteochondral transfer, no functional decline has been seen with ACI [40].

Irrespective of the technique used, the time to sporting return is higher for younger and more competitive athletes

[27]. Factors including no prior surgical interventions, higher pre-injury and post-surgical level of sports, and short pre-operative duration of symptoms correlate with a higher rate of return to sports [41]. Defect-specific factors, such as smaller lesion size and isolated medial femoral condyle lesion location, also correlate with better clinical results.

Conclusions

There are a huge number of established and emerging strategies aimed at preventing chondropenia and protecting chondral surfaces, stimulating the regeneration of native functional hyaline cartilage using growth factors and anti-inflammatory therapies, and restoring chondral surfaces using surgical techniques. Chondral lesions represent a wide spectrum of disorders for which there is no single satisfactory all-encompassing treatment. An individualized or algorithmic approach to treatment is therefore advocated, which aims to give athletes the best chance to return to full sporting activity, prevent reinjury, and minimize the progression to osteoarthritis under the high mechanical demands of athletic activity.

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