Knee articular cartilage defects greater than 4 cm² can be considered large defects. Smaller lesions can also be symptomatic, degenerate and increase in size due to increased stress at the lesion edges, leading to osteoarthritis (OA). However, there is no consensus of opinion on the benefit provided by different treatment options for these types of lesions. Indications for larger defects are less controversial, large defects are usually symptomatic and may have a bigger impact on joint homeostasis. Treatment of large articular defects is therefore mandatory to relieve symptoms and improve knee function, as well as to prevent or delay further joint degeneration.

The peculiar structure of articular cartilage explains its very limited self-repair potential, as well as the challenge in obtaining good results with the biological options currently available. Although cartilage repair procedures have traditionally had limited indication in large defects or OA, they are becoming the focus of increased interest for the provision of pain relief and altering the progression of degenerative diseases. In addition to lesion size, several key factors should be considered for the treatment indication, including lesion depth, joint environment, duration of symptoms, body mass index (BMI), presence of ligament instability, malalignment or general comorbidities. The treatment indication, however, is mainly dictated by the patient’s age. In fact, adolescent patients can obtain satisfactory results with traditional reparative procedures, such as simple fragment refixation or marrow stimulation procedures, whereas more invasive reparative techniques or scaffold-based regenerative procedures are mainly indicated for adult patients. Finally, the chance of a successful procedure decreases in those over 40 years old and patients older than 60 years are precluded from cartilage repair due to their limited self-repair ability and the degenerative environment – both conditions strongly affecting the expected outcomes. Non-operative options are usually the first-choice treatments for maintaining quality of life, whereas knee replacement (preferably unicompartmental) is the most common surgical indication for these patients.
article discusses the specific treatments available according to their indications for large cartilage defects in different age populations.

CHILDREN AND YOUNG ADULTS (<20 YEARS OLD)

Since large cartilage lesions in this group of patients are mainly due to trauma or osteochondritis dissecans (OCD), the presence of a detached fragment is relatively common. The high regenerative potential of young patients makes attempts to preserve a detached fragment mandatory, if feasible. The choice between fragment refixation or removal and marrow stimulation relies on its integrity and vitality.

Fragment refixation

Acute cases require careful curettage of the blood clots and any fibrous tissue, in order to avoid any damage to the subchondral bone at the base of the lesion. In chronic lesions, a more extensive curettage is required to debride the fibrous tissue covering the lesion and the sclerotic subchondral bone; then, it may be necessary to pack cancellous bone at the level of the surrounding osteochondral junction to favour the integration of the refixed fragment.

The fragment can be refixed using different fixation devices (bone pegs, K-wire, pins, compression screws, biodegradable pins). The most superficial part of the fixation device should be kept 2 mm below the level of the cartilage surface in order to avoid mechanical damage on the opposite cartilage surface. In case part of the fragment is severely damaged, this part can be removed and the fragment refixed through an additional autologous osteochondral transplant.

Good clinical results have been reported using these different devices. Moreover, some studies have analysed the histology of refixed fragments. Chondral fragments resulting from acute delamination showed healing into the subchondral bed, with no evidence of fibrous tissue and a normal transitional area with hyaline cartilage at 12 months after surgery. OCD cases also showed normal features of the refixed cartilage and the development of new bone trabeculae at 12 months after surgery.

Marrow stimulation

Even though in older patients marrow stimulation procedures (microfracture or drilling) are usually recommended only for small lesions, in younger patients these techniques may be indicated when a detached fragment is severely damaged or not refixable. Good results can be expected, even for larger articular defects, thanks to the high intrinsic activity of resident bone marrow cells in this patient group. Moreover, these procedures represent a minimally invasive, relatively cheap and technically easy option to perform.

This surgical approach can be performed arthroscopically, taking care to accurately prepare the damaged area, especially in case of chronic lesions. Steadman et al treated a group of 26 patients (average...
ADULT PATIENTS (20 TO 60 YEARS OLD)

The aetiology of articular cartilage defects in patients aged between 20 and 60 years old can be heterogeneous, ranging from traumatic, to degenerative/microtraumatic, OCD sequelae or osteonecrosis, reflecting the clinical history of the patient, different presentation, symptom modality and duration. Regenerative procedures are the preferred method in this age group, in order to maximise the body’s self-regenerative potential and restore the defect with a tissue resembling as closely as possible the original one, aiming to obtain durable clinical benefits.

Autologous chondrocyte implantation (ACI)

ACI is the most documented regenerative method for the surgical treatment of large articular defects in young to middle-aged patients. However, ACI has notable disadvantages due to the need for two different surgeries – the first operation for the arthroscopic harvest of articular cartilage and, after cell isolation and culture, the second for the implantation of cultured chondrocytes.

The first generation ACI technique involved the injection of a cell suspension under an autologous periosteal flap that had been previously sutured to the edge of the surrounding cartilage to cover the defect. Beris et al treated a group of 42 patients for large symptomatic chondral defects of the knee (mean size 5.3 cm²), showing significantly improved clinical and functional scores at 8-year follow-up. Minas et al reported the results of over 200 patients treated for very large lesions (mean size 8.4 cm²) and observed durable outcomes at long-term follow-up and a 71% graft survivorship at 10 years follow-up. Interestingly, the authors reported an increased risk of failure in patients with larger lesions and in those previously treated with microfracture for the same defect. Moreover, level one studies reported no clear difference in outcomes between ACI and microfractures at 60 months follow-up for the treatment of large lesions.

Despite these good and durable clinical results using first generation ACI, a relatively high rate of graft hypertrophy, together with the need for an open and technically demanding surgery prompted the use of newer techniques in which the cultured cells are seeded into three-dimensional matrices (mainly type I/III collagen or hyaluronan). Some of these second generation techniques simplified the overall approach and even allowed for arthroscopic implantation. Further modifications include combination with autologous bone implants to address deeper lesions that are very frequently associated with large size defects or OCDs. These matrix-assisted ACI (MACI) procedures have also been successfully used for the treatment of large lesions, with positive results at long-term follow-up. Bigger focal defects can be treated up to 12 cm² in size; however,
large lesions often occur in a degenerative joint environment, which is a relative contraindication for MACI procedures. In fact, MACI did not show superior mid-term results to those of microfracture when the onset of symptoms was more than 3 years before the operation\textsuperscript{34}. Saris et al showed in a level one study that MACI produced superior results and a lower failure rate at 24 months follow-up in 137 patients treated for large lesions of the knee (mean size 4.8 cm$^2$). This superiority, however, was not reflected by MRI appearance of the repair tissue\textsuperscript{35}.

Finally, some findings also highlighted poorer but still effective and durable results in patients older than 40 years, suggesting the possibility to extend the treatment indication to this age group, where the regenerative approach has traditionally been excluded\textsuperscript{3}.

Beside some controversial findings, ACI procedures seem to produce better tissue repair quality and longer-lasting results than microfracture and currently there is an overall consensus for the treatment of large lesions with such a biological approach.

\textbf{Osteochondral autograft transfer (OAT)}

OAT techniques, including mosaicplasty, rely on viable osteochondral grafts to fill an articular defect through a single-step surgery\textsuperscript{36}. Despite being reported to offer overall good and durable clinical results at long-term follow-up, their use for the treatment of large lesions is questionable, due to technical limitations, graft availability and issues related to donor site morbidity\textsuperscript{37}. Thus, while OATs represent an affordable choice for the treatment of small defects (usually not larger than 2.5 cm$^2$) requiring a limited number of plugs, autologous one-step procedures are not indicated for large lesions\textsuperscript{38}.

The mega-OATS technique was proposed as a salvage procedure for large osteochondral lesions of the knee. It involves the harvest of a significant part of the posterior knee condyle as a source of osteochondral graft, which is then prepared with a specific device\textsuperscript{39}. The few available studies report a significant clinical improvement at mid-term follow-up, with satisfactory outcomes in terms of knee function\textsuperscript{40,41}. Paired with this, a few cases of positive MRI features were reported in terms of vitality of the graft and also partial remodelling of the posterior condyle. However, the loss of the posterior femoral condyle makes a certain degree of donor site morbidity unavoidable and the use of this procedure should be restricted to salvage procedures in young patients with large knee osteochondral defects and limited treatment alternatives\textsuperscript{42}.

\textbf{Osteochondral allograft transplantation (OCA)}

Osteochondral allografting allows the replacement of a damaged osteochondral unit with viable tissue, while avoiding the issues related to donor-site morbidity; thus, it is a suitable option for the treatment of a large surface area. The different storage methods (fresh, fresh-frozen and cryopreserved) are important factors, since chondrocyte viability directly correlates with the clinical success of OCA transplantation\textsuperscript{5,35} and it has been shown that fresh OCAs stored at physiological temperatures have the highest chondrocyte viability\textsuperscript{43}. Fresh osteochondral grafts can be harvested and implanted through free-hand technique or as described above for Mega-OATS implantation\textsuperscript{44}.

This procedure is common in the United States, where the use of allografts is widespread. Excellent results have been reported in 122 patients by Levy et al with 82% survivorship at 10 years, decreasing to 66% at 20 years follow-up. Patients over 30 years old who had two or more previous surgeries were associated with graft failure\textsuperscript{44}. On the other hand, Gracitelli et al showed that, while previous bone marrow stimulation was correlated to a higher re-operation rate after osteochondral allografting, no influence was observed on graft survivorship or functional outcomes\textsuperscript{45}. Raz et al also confirmed the benefits of OCA after up to 22 years follow-up, with an acceptable survival rate of 59% at final-follow-up\textsuperscript{46}. Finally, limited and controversial data are available on more active patients, in terms of their return to previous sports or physical activity\textsuperscript{7,19}.

\begin{quote}
Encouraging findings have been recently documented in a one-step surgical procedure in which multi-potent stem cells in a bone marrow concentrate are used to treat large full-thickness chondral defects
\end{quote}
While the outcomes for OCA are good and durable, this procedure is still difficult to implement in most countries due to high costs and difficulty in finding fresh donors\(^5\). Thus, in many countries it is mainly restricted to salvage procedures in young patients with no other options.

**Bi-layered scaffolds**

In recent years, advances in the field of biomaterials have enabled the introduction of new strategies for the treatment of large articular defects. Some of the biopolymers, applied as scaffold, have been used ‘cell-free’, using the properties of the biomaterial itself to improve marrow stimulation-induced reparative processes in a single operation\(^6\). While some of them have also been tested seeded with bone marrow concentrate.

Improved knowledge of the primary role of subchondral bone in large articular defects has led to the development of bi-layered scaffolds which mimic the biological and functional requirements for the growth of both bone and cartilage. In fact, the results of the previously-mentioned cartilage regenerative techniques were limited when applied to more complex articular lesions, where the subchondral bone is frequently involved\(^7\). Among the few osteochondral scaffolds approved for clinical use, one is more specifically targeted for the treatment of large osteochondral defects.

MaioRegen™ (Fin-ceramica, Faenza, Italy) is the most widely documented osteochondral scaffold, a nanostructured implant consisting of different ratios of collagen and hydroxyapatite organised in three layers. After promising preliminary findings, the positive results offered by this biomaterial have been confirmed up to a mid-term follow-up. Twenty-seven patients were evaluated at 5 years’ follow-up, confirming that the improvement in clinical scores was stable over time. MRI evaluation revealed some abnormalities, but ongoing improvement. However, no correlation was found with the clinical outcome\(^8\). Several studies further confirmed the effectiveness and versatility of this approach for the treatment of different kinds of articular defects of the knee. Among these, Delcogliano et al published a study on 19 patients affected by large (5.2±1.6 cm\(^2\)) cartilage defects, showing encouraging results after 2 years\(^9\). Comparable results at short-term follow-up were also reported by Berruto et al in a larger group of 49 patients affected by large (4.4±1.3 cm\(^2\)) lesions and treated by this scaffold implantation – a significant improvement was observed in all clinical scores, paired with encouraging MRI findings of the regenerating tissue. Interestingly, lower activity levels and older age were significantly correlated with worse outcomes, suggesting that this regenerative approach is less effective in older patients, with limited regenerative potential\(^10\). Similar age limitations were shown, despite the overall benefit offered by this procedure, in the treatment of unicompartmental OA in relatively young patients, where the osteochondral scaffold implantation was applied as a salvage procedure alternative to metal resurfacing. This study also underlined the importance of addressing all comorbidities in order to obtain the best clinical result\(^11\).

Even though some issues have been raised on the quality of the repair tissue offered by this approach\(^12\), it still represents a viable option for the treatment of large osteochondral defects in a young population, where limited options are suitable\(^13\). However, the indication should be planned carefully and an age limit has been highlighted. Future studies should focus on a possible improvement with different cell types to ameliorate the regenerative potential and possibly favour healing of more difficult cases such as larger lesions in older patients.

In this regard, encouraging findings have been recently documented in a one-step surgical procedure in which multi-potent stem cells in a bone marrow concentrate are used to treat large full-thickness chondral defects. The procedure looks promising, even for less favourable cases which would otherwise be doomed to a metal resurfacing procedure.

**OLDER PATIENTS (>60 YEARS OLD)**

Large defects of the articular surface in patients of older age are usually part of a more complex degenerative environment, likely to be encompassed by the definition of OA, which is a primary cause of chronic disability in the elderly. As discussed above, most cartilage repair surgical options present decreased effectiveness when applied to degenerated joints and lower outcomes are correlated with ageing. In fact, these patients present with an already altered homeostasis that strongly impairs the regenerative processes.

Thus, only conservative choices are indicated in this patient group, which is characterised by a low regenerative potential, with the aim of improving quality of life by reducing temporary symptoms and improving joint function. This can be

> **The high regenerative potential of young patients makes attempts to preserve a detached fragment mandatory, if feasible**
considered the first-line approach either in the early or more advanced OA phases, in order to delay metal resurfacing procedures that may be too demanding for the patient both from a physical and psychological point of view.

**Physical therapies**

Non-pharmacological therapies, such as exercise and rehabilitation, have been reported to have beneficial effects in the short-term for pain reduction and physical function improvement, even though data from the literature are limited and there is no clear evidence for any particular method of exercise. Physical therapy has also been shown to be effective in OA patients and, despite very few studies being available, this approach has been included into the Osteoarthritis Research Society International recommendations for the management of knee and hip OA. The optimal physical strategy, as well as its dosage in terms of intensity, frequency and duration, however, still has to be determined.

**Injective therapies**

Injective treatments are very popular among patients and physicians. Classic and new substances can be applied directly into the affected joint. Some of them act as biomechanically active spacers or via their immunomodulatory properties. Corticosteroids are well-known for their strong anti-inflammatory properties, able to interrupt the immune cascade at different levels. Intra-articular injections of corticosteroids were originally described in 1951 by Hollander et al, with the rationale of maintaining a prolonged concentration of drug in the synovial space, thus maximising the anti-inflammatory effect with minimal risks of systemic side-effects. This approach was reported to be effective in the short-term on pain reduction and global assessment versus placebo, but its benefit seemed to decrease after the fourth week of follow-up, while hyaluronic (HA) had longer-lasting effects. Since the prolonged use of corticosteroids might accelerate tissue atrophy and joint degeneration and since the long-term benefits seem to be limited, their use as chronic treatment is questionable.

Viscosupplementation is based on the rationale that HA concentration highly decreases in the OA knee, therefore HA intra-articular injections have been proposed to provide lubrication and shock absorbency to the joint, some evidence even suggests biologic disease-modifying properties. Among the many HA preparations available on the market, they can be broadly classified into low and high molecular weight HA. The correlation between molecular weight and clinical efficacy is still controversial, but HA lower than 500 kilodalton was reported as ineffective in improving pain and function. While clinical findings suggest that HA injections may be an effective treatment for OA, randomised studies failed to show superiority of any product. As a result, American Academy of Orthopaedic Surgeons does not recommend viscosupplementation for the treatment of mild-to-moderate OA.

Platelet-rich plasma (PRP) is a blood derivative that has recently garnered much interest for its supposed anabolic and anti-inflammatory properties. Pre-clinical studies showed promising findings, with positive effects on the entire joint homeostasis and there is an overall support among the published clinical literature on PRP intra-articular administration. However, the superiority of PRP versus HA injections has not clearly been proven yet and the best formulation and application modalities are still under investigation in order to optimise the treatment of joints affected by OA.

**CONCLUSIONS**

The treatment of large articular lesions in young knees remains a challenge for surgeons, with patients subjected to pain and at risk for further joint degeneration. Several procedures have been proposed to address large defects in order to improve symptoms and prevent OA-related changes. The indication for the right technique is driven by some key factors including patient age, but also by the availability of the procedure due to legal and economical issues. In this respect, cell-free scaffold-based procedures or one-step cell-based procedures are emerging as promising options for restoring a biologically and functionally effective tissue even for challenging large osteochondral lesions.

References

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