ARTICULAR CARTILAGE REPAIR IN ATHLETES

CURRENT CONCEPTS AND FUTURE TREATMENTS

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INTRODUCTION

Articular or hyaline cartilage is a specialised tissue of mesenchymal origin that provides a smooth, low-friction environment for proper joint movements. It spreads the applied load onto subchondral bone and absorbs tensile, sheer and compression forces exerted. The hyaline cartilage consists of chondrocytes that are scarcely embedded into the extracellular matrix, which is mainly composed of 65 to 80% water, collagen type II and proteoglycans (Figure 1)[1]. The cartilage itself is avascular, aneural and alymphatic and the nutrients are received by diffusion from the surrounding synovial lining.

The exact incidence of cartilage injuries in the athletic population is unknown, but recently published reports demonstrated evidence of articular pathology in 60 to 70% of patients that underwent knee arthroscopy[2]. Moreover, the frequency of cartilage injuries have increased in both high-level competitive and recreational athletes (Figure 2). The cartilage lesions may be isolated, but usually occur with (traumatic) soft tissue injuries like meniscal tears, ligament and tendon rupture and even joint dislocations. Although metabolically active, the intrinsic healing capacity of cartilage is limited and once damaged it rarely heals spontaneously. Partial-thickness cartilage lesions do not heal at all and full-thickness lesions penetrating the subchondral bone are filled with fibrocartiligineous tissue predominantly composed of collagen type I, that fails to restore the original properties of the native matrix.

The restoration of damaged articular cartilage remains one of the biggest challenges in modern clinical orthopaedics. There is no pharmacological treatment that promotes the cartilage repair and non-operative treatment inevitably may lead to premature osteoarthritis[3]. Current treatment modalities include bone marrow stimulating techniques such as 'microfracture', autologous chondrocyte implantation (ACI) and osteohondral grafts transplantation. These techniques have their benefits and shortcomings. Although effective in relieving pain and improving joint function, these surgical modalities have failed to regenerate true hyaline cartilage. Improvements to the existing methods and innovative approaches are required for optimisation of the short- and long-term results.

CURRENT TREATMENT OPTIONS
Bone marrow stimulation techniques

Bone marrow stimulation techniques (microfracture, abrasion chondroplasty

Zone 1: Tangental zone
Zone 2: Transitional zone
Zone 3: Radial zone
Zone 4: Calcified cartilage

HE 100 x 1

HE 400 x 1
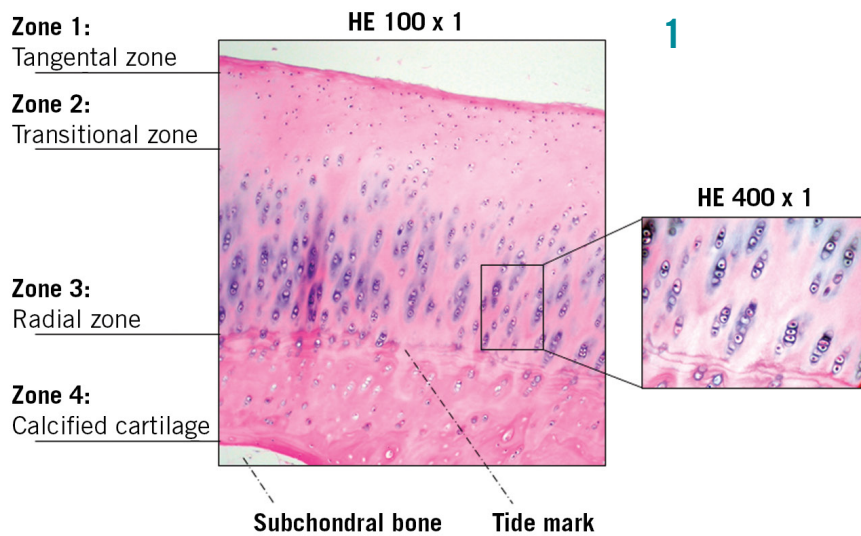
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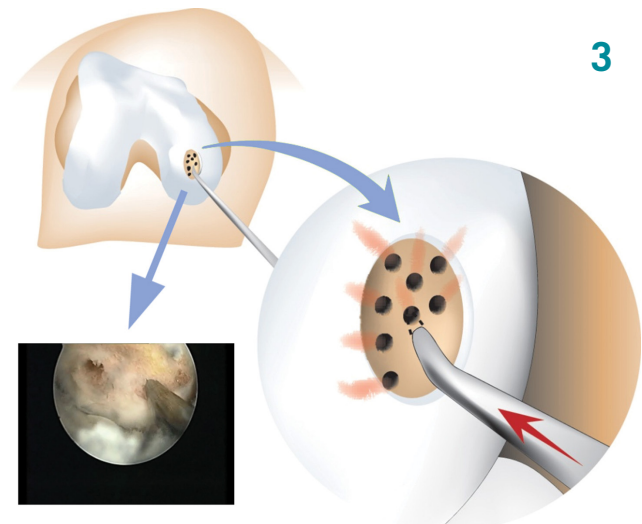
Subchondral bone   Tide mark

Figure 1: Light micrograph of articular hyaline cartilage (100 × Haematoxylin & eosin [HE]). Hyaline cartilage has a complex structure formed by several different layers of cells. Its primary components are water, collagen type II and proteoglycans. In the uppermost zone (tangential zone) the chondrocytes are small and round and the collagen fibres are oriented parallel to the surface. In the deeper zone (radial) the chondrocytes are larger and arranged in vertical columns (smaller quadrant 400 × magnification) and the collagen fibres also have more vertical orientation. The deepest zone contains calcified cartilage which separate hyaline cartilage from subchondral bone.

Figure 2: Arthroscopic view of a knee joint of a professional football player showing exposed bone (yellow) due to full-thickness cartilage defect located on a medial condyle.

Figure 3: Picture and arthroscopic view of microfracture being performed. Surgeon penetrates the subchondral bone with special awl to allow the migration of mesenchymal progenitors and formation of blood clot within the defect.

and subchondral drilling) involve surgical penetration of subchondral bone to allow the migration of mesenchymal progenitors and formation of a blood clot within the defect[4]. These stem cells govern the regeneration process of fibrocartilaginous tissue repair. The resulting volume and quality of repair tissue is variable and differs substantially from normal hyaline cartilage in its durability, organisation and structure which is predominantly composed of collagen type I. Microfracture (MFX) is preferred over abrasion chondroplasty and subchondral drilling as it is less destructive to the subchondral bone, it provides a controlled method of depth penetration and its specially designed angled awls

enable perpendicular orientation of MFX holes (Figure 3). MFX is widely accepted as a first line treatment for lesions up to 2 cm[2]. Favourable outcome predictors are smaller lesions, younger patients and shorter duration of symptoms prior to surgery[5,6]. The postoperative rehabilitation protocols are crucial for successful MFX procedures and consist of 6 weeks non-weight-bearing and passive motion exercises in order to improve the quality or repair tissue. Full return to training and competition can be achieved in a period of 6 to 8 months. Although MFX are low-cost and low-morbidity procedures with good short-term results, most of the studies showed gradual deterioration of results and a decline of

sporting activities at final follow-up[7,8]. It has been shown that bone marrow stimulation techniques have a strong negative effect on subsequent cartilage repair with autologous chondrocyte implantation and therefore should be used judiciously in larger cartilage defects that could require future treatment with autologous chondrocyte implantation[9].

Autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) marked the beginning of new era in orthopaedic surgery. For the first time a tissue engineering solution has been successfully applied in orthopaedic patients. This laid the foundation for the

development of a new concept known as regenerative orthopaedics[10]. It was first performed by Peterson in 1987 and later Brittberg and co-workers published their initial results in the *New England Journal of Medicine* in 1994[11]. Original ACI is a two-step procedure. During the first step the cartilage is biopsied from the non-weight-bearing part of the knee joint articular surface, enzymatically digested and expanded in monolayer culture. During the second step the autologous chondrocytes are injected under an autologous periosteal flap, sutured on the cartilage defect. Despite the initial enthusiasm and promising clinical results, limitations of the classical or first generation ACI procedure included graft failure, followed by delamination and tissue hypertrophy[12].

To overcome these limitations, improvements to the original method were introduced. Second generation ACI includes use of bi-layer collagen membrane instead of periosteal flap (Figure 4). Further developments of the ACI have brought third generation procedures which combine three-dimensional, biodegradable scaffolds with cultured chondrocytes (Figure 5)[13]. An indication for ACI procedure includes larger lesions measuring from 2 to 10 cm^2 and is currently suggested as first-line treatment for professional athletes and the younger, more active population[14]. Similar to other cartilage restoring procedures, rehabilitation is crucial for successful ACI and consists of early range of motion exercises with restricted weight-bearing[15]. Return to the activities of daily life can be expected within 4 months, but return to training and competition is expected within 1 year following the procedure.

Osteochondral transplantation

The concept of osteochondral transfer was popularised in late 1990s by Bobic[16] who used single plugs and Hangody et al[17] who used multiple plugs (so called "mosaicplasty") to treat cartilage defects. The concept is quite simple: cylindrical plugs of subchondral bone and overlying cartilage are harvested from the non-

Figure 4: Second generation autologous chondrocyte implantation. a) Chondral defects on patella and trochlea, debrided and ready for implantation; b) Same knee after the procedure. Defects are covered with collagen membrane and the suspension of autologous chondrocytes has been injected underneath the membrane.

Figure 5: Third generation autologous chondrocyte implantation. Trochlear defect in a professional basketball player implanted with three-dimensional collagen scaffold seeded with autologous chondrocytes. The construct is fixed with fibrin glue within the defect.

Figure 6: Osteochondral transplantation. a) Osteochondral cylinders are punched out with specially designed harvest instruments; b) Osteochondral cylinder ready to be transplanted to the defect.
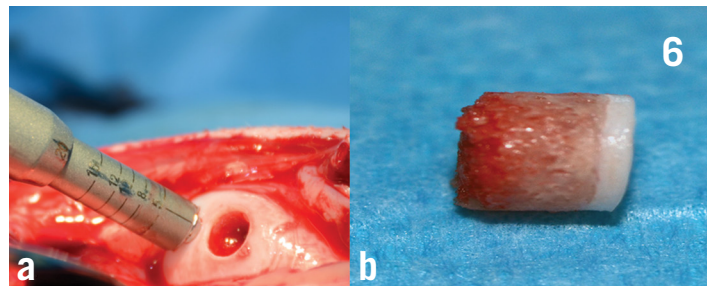
Figure 7: Implantation of a gene plug. a) An adaptation of standardised mosaicplasty instrumentation was used to create a chondral defect on the weight-bearing surface of the medial condyle in sheep; b) Care was taken not to penetrate the subchondral plate. The defect measured 6.2 mm in diameter; c) Aspirated bone marrow is immediately mixed with adenoviral suspension; d) Genetically modified bone marrow forms clot - gene plug; e) Press-fit implantation of the gene plug into the defect; f) The plug is stable and well-placed within the defect. The joint is rinsed with saline and ready to be closed.
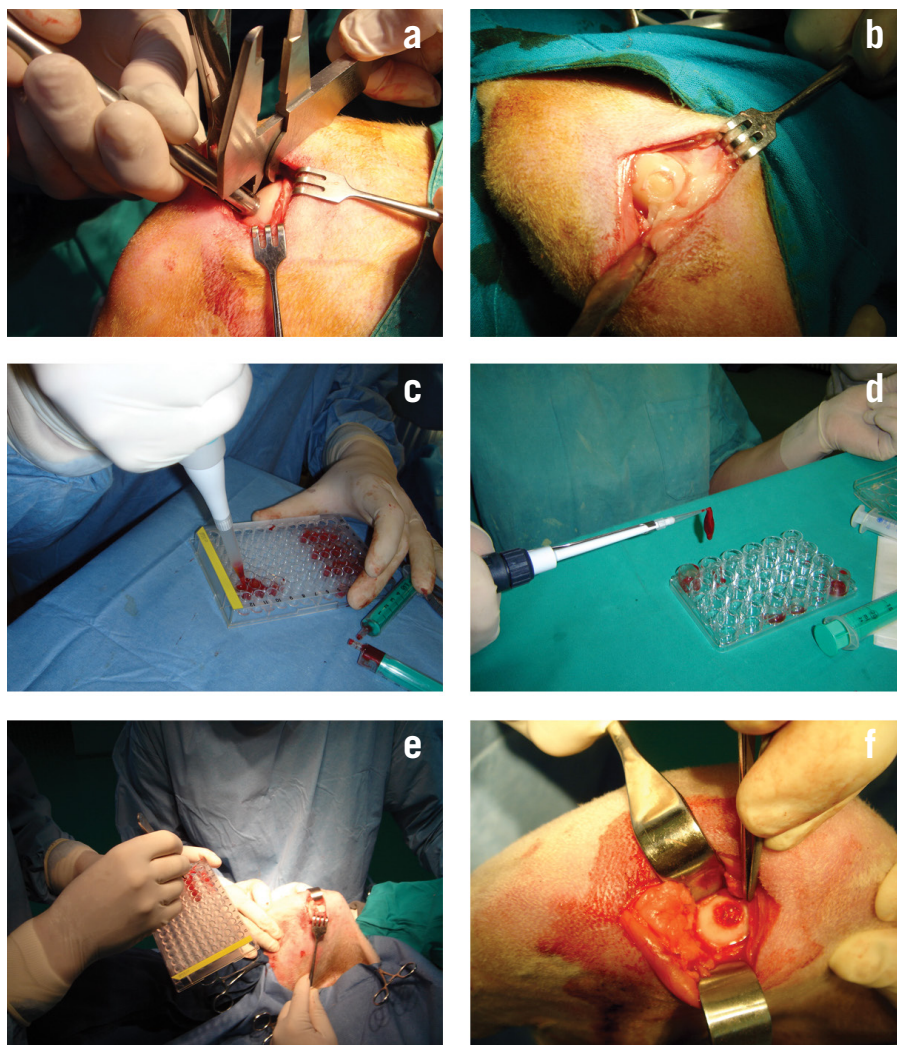
weight-bearing portion of the patient's joint (autograft) or cadaveric source (allograft) and then inserted into the defect (Figure 6). The transplanted tissue is native hyaline cartilage and the subchondral bone serves the purpose of anchoring the plugs within the defect. The main indications for osteochondral transplantation are larger lesions (greater than 2 cm^2), especially those with significant loss of subchondral bone such as osteochondritis dissecans (OCD), focal osteonecrosis or periarticular trauma with bone loss. It is also commonly used as revision or salvage of other cartilage restoring procedures. Although the surgical technique is relatively straightforward and the procedure itself is low-cost, it is not without problems:

- Harvesting autografts results in donor-site morbidity
- Allograft cost and availability are main obstacles for daily clinical application.

The overall survival rate at 10-year follow-up, with good and excellent clinical results, has been reported to be somewhere between 80 and 90% for autografts and 80% for allografts.

> *Restoration of damaged articular cartilage is one the biggest challenges in modern clinical orthopaedics*

FUTURE TREATMENTS
Mesenchymal stem cells

By definition, mesenchymal stem cells (MSC) represent a heterogeneous group of undifferentiated cells residing within terminally differentiated tissues and organs. They play a major role in repair and regeneration of tissues such as bone, cartilage, muscle, tendons and fat (Figure 7). When local cellular homeostasis becomes disrupted (e.g. injury, apoptosis), these cells undergo terminal differentiation and replace lost or injured cells from the local tissues and organs. Another remarkable property of these cells is that they secrete bioactive signals which suppress the local immune system, inhibit scar (fibrosis) formation and apoptosis, enhance angiogenesis, as well as stimulating mitosis and differentiation of other stem cells. In other words, not only those MSC can differentiate into chondrocytes and lay extracellular matrix to rebuild cartilage, but they also govern and regulate homing and differentiation of other cells. At least in theory, one could harvest these cells, modify them to become terminally differentiated as needed (e.g. for cartilage regeneration - chondrogenic differentiation of progenitors), seed them on a three-dimensional scaffold and transplant them back to the patient. Indeed, first clinical results for the transplantation of MSC seeded on collagen type I hydrogel has been reported in 2004 by Wakitani and co-workers[18]. They reported two patients with patellar defect treated with collagen gel/MSC construct and covered with periosteal flap. Subsequently the procedure has been performed in 41 patients and neither tumours nor infections were observed between 5 and 137 (mean 75) months of follow-up.

Bioactive signals that enhance cartilage repair

Cartilage repair is a complex cascade of events controlled by bioactive molecules that provide signals at local injury sites allowing

progenitors and inflammatory cells to migrate and trigger the healing process. It is therefore only logical to try to use these bioactive cues to enhance key features of chondrogenesis such as cellularity of the repair tissue, the differentiation of MSC into chondrocytes and the production and maintenance of a cartilaginous matrix rich in type-II collagen and proteoglycans[19]. Growth factors are important molecules to enhance these processes. Growth factor-ß1 and -ß2 (TGF-ß1 and -ß2) have been shown to be potent stimulators of chondrogenic differentiation of mesenhcymal progenitors. Fibroblast growth factor-2 (FGF-2) and insulin-like growth factor-1 (IGF-1) strongly stimulate cell proliferation and bone morphogenetic protein-7 (BMP-7) and cartilage-derived morphogenetic protein are particularly important for extracellular matrix synthesis. Another possibility is to use transcription factors such as SOX trio (SOX 5, 6 and 9) which directly modulate expression genes responsible for chondrogenesis. Finally, inhibition of cartilage degrading or catabolic signals have also been explored and main targets include blocking the action of interleukin-1 and 17 (IL-1 and IL-17) and tumour necrosing factor.

Gene therapy for cartilage repair

As mentioned above, chondrogenesis is a precisely orchestrated process which involves many growth factors and signalling molecules. By modifying the local cellular environment, it is possible to enhance formation of more natural cartilage tissue within the defect. As these bioactive molecules are difficult to administer effectively, gene transfer strategies have emerged as an attractive option for sustained synthesis and release of these agents at the site of repair[20]. To accomplish this task, two main strategies have been explored. The direct or *in vivo* approach delivers therapeutic DNA directly into the joint. In this case synovial lining cells are the main site of gene transfer. Depending on the vector, cells around or within the defect may also be genetically modified. During indirect or *ex vivo* delivery, cells are recovered, genetically manipulated outside the body and then returned to the defect. Delivery of the genetic material to the living cell can be accomplished by use of either viral or non-viral vectors. While viral vectors are much more effective, they raise several safety concerns. Numerous preclinical animal studies have confirmed the effectiveness of these approaches in joints and several phase I and II clinical gene therapy studies provide reason for cautious optimism (Figure 7)[21].

CONCLUSION

In summary, optimal cartilage reparation or restoration procedure to be used in competitive and recreational athletes should regenerate native hyaline cartilage, with minimal complications and short recovery time. Knowledge and understanding of the available surgical techniques is critical to the appropriate use of these interventions. Those should be tailored to the individual athlete's needs and defect characteristics according to described algorithms. This, so-called *a la carte* approach is crucial for optimal results and quick return to training and competition. Generally speaking, smaller cartilage lesions can be treated with microfractures, while in all other cases cell-loaded or cell-free scaffold is the preferred method of treatment. In revision or salvage cases, osteochondral autografting should be used. Finally, novel treatments that employ stem cells, growth factors and gene therapy will continue to evolve, providing the treating clinician with better options and patient with better outcomes.

> ## The treatment of articular cartilage defects in athletic population should be highly individualised according to the so called 'a la carte' doctrine

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