Introduction

In the orthopaedic practice we still encounter a diagnostic and therapeutic dilemma in managing focal osteochondral defects of the talar dome. The cartilaginous pathology is usually secondary to trauma. However, ischemic necrosis may play a role; others propose a multi-factorial aetiology of osteochondral lesion of the talus. These defects can cause swelling, pain and instability and lead to degenerative changes of the ankle joint. It is possible with newer techniques to diagnose and treat these injuries at an early stage and stop further deterioration. With MRI, it is possible to detect early stage of osteochondritis dissecans of the talus, when the fragment is still in situ. Ankle arthroscopy is a great tool for diagnosing intra-articular changes.

Treatment options include both non-surgical and surgical measures depending on the severity and location of the lesion. The aim of surgery is to repair the chondral defect and decrease the risk of osteoarthritis.

Among surgical options, the most commonly utilized are: cartilage debridement (or shaving), chondroplasty, microfracture and autologous chondrocyte implantation (ACI). In a prospective study we compared the outcomes of chondroplasty versus microfracture and osteochondral autologous transplantation (OAT) in patients with osteochondral lesions of the talus. No significant difference at the final follow-up with American Orthopaedic Foot & Ankle Society (AOFAS) and Single Assessment Numeric Evaluation (SANE) scores; however numeric pain intensity was significantly lower in chondroplasty and microfracture cases as compared to OAT post-operatively. A technique that can be considered as “gold standard” has not been established yet. Among the available options, only osteochondral grafting and ACI have shown the ability to provide a repair of the lesion with hyaline cartilage.

First Generation Autologous Chondrocyte Implantation

Peterson et al. demonstrated that first generation ACI, which involves the use of cultured chondrocytes with a periosteal patch, can result in a repair tissue with hyaline like characteristics mechanically, histologically and histochemically, corresponding well with a good and durable clinical outcome. First generation ACI of the ankle is a two-step procedure. A medial or lateral incision can be performed in a tourniquet-controlled bloodless field depending on the location of the defect. In some instances, a malleolar osteotomy is necessary to obtain access to the defect. With a good exposure of the defect, all the sclerotic bone at the area of the lesion is debrided. If possible, the subchondral bone plate is also shaved and multiple holes are then drilled into the cancellous bone. All damaged cartilage is excised and debrided to make the shoulder of the lesion vertical. Bony defects or the pathologic involvement of the subchondral bone deeper than 5 to 6 mm require concomitant bone grafting. Cancellous bone from the tibia or the iliac crest is harvested and subsequently packed in the bony defect. In the ankle joint the cartilage is very thin so harvesting a sufficient amount of cartilage tissue would result in a large cartilage lesion likely to cause symptoms. For this reason, it is preferred to harvest the cartilage from the non-weight-bearing areas of the knee joint. Sufficient amounts of cartilage are obtained depending upon the size of the defect to be repaired. After enzymatic breakdown of the matrix and isolation of the chondrocytes, the cells are cultured until the
desired cell population is achieved which normally takes two to three weeks. Any ligamentous instability may jeopardize the mechanical properties of the graft. Therefore, reconstruction of the ligaments is advised to achieve a stable joint. Many authors demonstrated in their series satisfactory results over a medium term follow up using first generation ACI in the ankle. However this technique has been considered a demanding procedure, as it’s very difficult to suture in hermetic way a periosteal patch in a narrow joint and manage a liquid culture solution.

**Second Generation Autologous Chondrocyte Implantation**

The use of a three-dimensional scaffold for autologous chondrocyte culture was developed with the aim of improving both the biological performance of chondrogenic autologous cells as well as making the surgical technique easier. A scaffold that is properly sized can be positioned directly into the articular defect under arthroscopic guidance. This technique offers the advantage of enabling the surgeon to avoid an open surgery, as there is no need for harvesting the periosteal flap. However, some technical limitations prevail which include treating posterior lesions. Therefore it must be emphasized that these limits are common to all arthroscopic techniques and could partly be resolved with the development of new arthroscopic tools. For some years, different types of scaffold with different matrices have been tested in animal models but few products have been used in human trials to determine the efficacy in facilitating and promoting cartilage repair. These scaffolds can be divided, according to their chemical nature, into protein based polymers, carbohydrate polymers, and artificial polymers. Combinations of these different polymers are also available.

**Hyaluronan (hyaluronic acid, HA)** is a naturally occurring and highly conserved glycosaminoglycan, which is widely distributed in the body; it has proven to be an ideal molecule for tissue engineering strategies in cartilage repair, given its impressive multi-functional activity through its structural and biological role. Three-dimensional non-woven scaffolds support the in vitro growth of highly viable chondrocytes and promote the expression of the original chondrogenic phenotype. Hyaluronan-based scaffolds for ACI is entirely based on the benzylic ester of hyaluronic acid and consists of a network of 15-20μm-thick fibers with interstices of variable sizes, which has been demonstrated to be a good physical support to allow cell to cell contacts, cluster formation, and extracellular matrix deposition. Chondrocytes, previously expanded on plastic and seeded into the scaffold produce a characteristic extracellular matrix rich in proteoglycans and express typical markers of hyaline cartilage, such as collagen II and aggrecan. The main indications for second-generation cartilage transplantation are symptomatic focal, full thickness cartilage lesion (ICRS Grade III – IV) in the absence of significant arthritis in physiologically young patients (15 – 50 years). The surgical technique originally utilized for the knee has been modified for use in the ankle. Second generation ACI can be carried out through the conventional mini-arthrotomy approach, however, recent advances in scaffold technology have enabled surgeons to perform this technique arthroscopically though this is still a two-step procedure. The first step is arthroscopic evaluation and biopsy and the second being implantation, either using an arthroscopic technique or mini-arthrotomy technique.

Several reports of controlled trials in patients operated with the use of these scaffolds have been presented and the largest collection of data using the HA scaffold in clinical practice is represented by a multicenter observational study conducted in Italian Orthopaedic Centers since 2001; however many of these studies have been done on the knee joint. Second generation ACI, when used in the ankle with arthroscopic technique, offers several advantages and most important being reduction of the surgical trauma. Arthroscopy bypasses the need of open surgery with malleolar osteotomy and subsequent hardware removal, no separate incision for periosteum harvesting and faster rehabilitation.

An interesting possible improvement may be represented by a proprietary process, which results in an optimised cell culturing process aimed at maintaining chondrocyte homeostasis in the repair of cartilaginous lesions. After years of intensive research, industry has identified a set of gene markers
characterizing chondrocytes with cartilage-forming potential; in pre-clinical animal model, the quality of implanted cartilage has shown a good correlation with the phenotypic chondrocyte markers. A follow-up product in which chondrocytes are seeded on a hyaluronic acid scaffold is currently under development and could represent a step further.

**One-step Surgery: Mesenchymal Stem Cells**

Recent directions in cartilage repair are moving towards the possibility to perform one-step surgery. The need of two operations and the high cost for chondrocytes culture remain the major problem in performing second generation ACI. These considerations prompted us toward the search of different solutions. The use of mesenchymal stem cells (MSCs) and growth factors offer the possibility to avoid the first surgery (biopsy) and subsequent chondrocyte cultivation. Many authors have recognized that nucleated cells found in bone marrow as an useful source of cells for restoration of damaged tissue due to their ability to differentiate into different cells including chondrocytes therefore utilizing MSCs and Platelet Rich Plasma (PRP), it is possible to repair cartilage defects in a one step procedure.

Previous studies have shown in animal and laboratory studies that MSCs have a high proliferation and multi-lineage differentiation potential into adipogenic, osteogenic and chondrogenic cells however only few clinical studies have been done. Once MSCs are cultured in the appropriate microenvironment, they can differentiate to chondrocytes and form cartilage; onset of chondrogenesis requires a chemically defined serum free medium supplemented with dexamethasone, ascorbic acid and growth factors such as TGF-B. The micromass culture or pellet culture system is generally considered a good in vitro model of chondrogenesis; Johnstone et al. cultured MSCs as pellets at the bottom of a tube for 2 weeks in a specific serum free cocktail medium; under these conditions cells organize a cartilaginous matrix by secreting proteoglycans and type II collagen and cells appear as real chondrocytes embedded in their own matrix lacunae. Wakitani et al. used autologous culture of expanded bone marrow for repair of cartilage defects; 24 patients were divided into cell transplanted group and cell free group. After 16 months follow-up, they concluded that MSC were capable of regenerating a repair tissue for large chondral defects. Giannini et al. presented their one step surgery procedure using MSC and scaffold in a prospective study they investigated 48 patients treated with bone marrow concentrated at a minimum follow up of 24 months. Clinical results have been evaluated with AOFAS scoring system; MRI and some biopsies were performed. The AOFAS score improved from 64 to 91 and histologic evaluation showed regenerated tissue in various degrees of remodelling although none showed completely normal hyaline cartilage.

In our institution we also use bone marrow aspirate concentrate (BMAC) for MSC in treating chondral defects: our technique consists of harvesting 60 mL of bone marrow aspirate from the iliac crest with aspiration kit and a centrifugations system following the method recommended by the manufacturer in order to harvest BMAC and from these we are able to increase concentration of BMAC four to six times the baseline value. Using batroxobine enzyme, we can activate the bone marrow concentrated and produce a sticky clot material that we paste into the defect; finally we cover the treated defect with a hyaluronan-based scaffold. Preliminary data from our institution and other Italian authors on MSC implantation with a one-step procedure seem to be promising, showing good clinical outcomes at early follow-up.

**Postoperative treatment and rehabilitation**

Antibiotic and thrombosis prophylaxis are given for 48 hours and 3 weeks respectively. Continuous passive motion is resumed 6 to 8 hour after surgery and is used intermittently throughout the hospitalisation, usually two to three days. The patient is then encouraged to continue with active ROM exercises. A brace is placed and calibrated to allow motion of 15° plantar flexion and 15° dorsal flexion. This is used for six weeks. Following this, the patient allowed to use crutches, with limited weight bearing (= 20 kg) for the first six weeks. Gradual increase is commenced every week until full weight bearing is achieved in week 8 to 10. A gait, as close to normal as possible, is practiced and stair walking before the patient is discharged.
from the hospital.

The rehabilitation continues, under the supervision of a physical therapist, with motion and strength training. Once the brace is removed pool exercises can commence; as full weight bearing is reached gait training is started along with long distance walking and bicycling. Functional exercises in closed chain are also incorporated in the rehabilitation program. Motion and proprioceptive training is continued throughout the rehabilitation, running and Plyometric exercises have to wait for six months.

**Conclusions**

A number of viable options have been made available over the years to address problems concerning cartilage damage and each technique has its advantages and disadvantages. From an initial arthrotomy approach with first generation ACI, now some of the new techniques can be performed arthroscopically. This modification enables surgeons to avoid possible intra-operative problems and decrease in operative time. Joint trauma is significantly reduced as the need for an open procedure and harvesting the periosteal flap is eliminated. Complications, such as graft hypertrophy and ossification are also avoided with the use of the newer scaffolds.

Biotechnology is progressing at a rapid pace and has introduced numerous new products for clinical application. Good clinical outcomes are showing that the use of BMAC and scaffold can be a promising option for the treatment of full-thickness cartilage defects; however, long-term prospective randomized studies are needed to confirm these preliminary results.

**References**