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3D scaffolds in talus chondral lesions – ACI / fibrin glue scaffold versus type I collagen / hydroxyapatite scaffold

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Abstract

Chondral lesions do not heal in adult mature cartilage. Introduced in 1987 for large full thickness cartilage defects treatment, autologous cultured chondrocyte implantation (ACI) with cells in suspension showed promising results. With chondrografts of second and third ACI generation, the scaffold choice became the real issue. One of the disadvantages that has been pointed out about ACI procedure, is the need for a previous cartilage harvesting before implantation.

In order to avoid this two-step surgery a new engineered type I collagen/hydroxyapatite scaffold has recently been developed, which allows to address chondral lesions with a one-step procedure, laying an implant in place that will eventually be fulfilled with new cells arising from the subchondral bone.

In this study we used both a 3D-solid fibrin glue scaffold with chondrocytes included inside the scaffold, and a type I collagen/hydroxyapatite scaffold, on a number of different patients.

In pre-clinical animal studies, both chondrocyte implantation using autologous cultured chondrocytes inside a solid fibrin-glue scaffold and the type I collagen/hydroxyapatite scaffold proved to be a good solution for full thickness cartilage defects treatment.

Seven patients with ages between 32 and 65 years-old were treated with either ACI or the collagen/hydroxyapatite (HA) scaffold. All the four patients treated with ACI procedures had a clinical follow-up of more than five years, whereas the collagen/HA scaffold patients had a mean follow-up of one and a half years. The final result seems to be age dependent.

A second-look surgery was performed in two cases. In both cases it had been used the collagen/hydroxyapatite scaffold. In one case there was a reactive synovitis and in the other an arthrofibrosis developed. In both cases arthroscopy showed complete cartilage coverage of the previous lesion.

All the patients were retrospectively clinically assessed using Weber and Mazur ankle rating scales. Overall results showed good or excellent clinical results in all but one patient (85%), with 5 asymptomatic patients (72%) even in heavy work or in high sports level. The two symptomatic patients belong to the collagen/hydroxyapatite scaffold group.

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1. Introduction

Chondral lesions do not heal in adult mature cartilage. Surgical repair of chondral defects is still imperfect and transient [1,2]. Attempts have been made to restore cartilage by filling the defects with artificial matrix with or without chondrocytes. After having solved the problem of chondrocyte proliferation [3], with second and third generation chondrografts the scaffold choice became the real issue [4-9].

Ideally, scaffolds designed for cartilage by tissue engineering should provide mechanical stability with optimal mechanical and structural properties, perfect biocompatibility, a predictable biodegradation/bioreabsorption rate and, last but not least, should be easy to handle.

On the other hand, three dimensional (3D) scaffolds do increase the efficiency of adhesion and differentiation of cells creating new opportunities for either chondrocytes and/or stem cells.

The result of this field of investigation is well known and the orthopaedic surgeon has at his disposal several 3D chondrografts with common characteristics and similar clinical results (collagen, fibrin, polylactic acid, hyaluronan, among others).

In order to increase the efficiency of cell adhesion and extra-cellular matrix production, emphasis has been placed on development of materials able to direct cell adhesion, differentiation and metabolism. The investigation in the last decade included regulation of pore geometry (coated composites of polymers and ceramics), the creation of “smart scaffolds” (capable of responding to environmental or cellular stimuli “on demand”), the cross-linked surface scaffold modification (with polyethyleneimine for example), or the combination of several elements (with chitosan and/or chitin for example).

Apart from the actual available possibilities, the expectable future research will include the integration of novel hybrid scaffold fabrication techniques (like rapid prototyping or electrospinning), the introduction of hydrogels to increase adhesion and scaffold recovery after compression and the adoption of computational methods in biomaterials design.

Our own actual experience in the treatment of the large full thickness cartilage lesions, includes the use of solid fibrin 3D chondrografts for ACI, starting with the animal model, and ending in human application and the use of a 3D Type I collagen/hydroxyapatite (HA) scaffold with a porous tri-layer composite structure.

2. Patients and Methods

Between 2008 and 2012, seven patients were treated from full thickness cartilage defects in the talus. The four women and three men had a mean age of 43 (between 32 and 65) years. The mean follow-up was 35 (from 12 to 58) months.

All the 7 lesions were traumatic medial defects. Therefore, each scaffold was implanted through a medial malleolar osteotomy, after debridement as far as the surrounding normal cartilage and until subchondral bone was exposed. All the procedures were performed under regional anaesthesia and tourniquet control.

The lesions had a mean area of 1.90 cm² (1 to 3) as measured intra-operatively.

All seven patients received either ACI or Maioregen® for disabling symptoms of pain and swelling after an ankle sprain for a minimum period of six months. Only one had had surgery (drilling and debridement) before referral.

In this study, the treatment of full thickness cartilage lesions involved the use of one of two kinds of scaffolds: Either (a) a solid fibrin 3D chondrograft embedding autologous cultured chondrocytes for ACI or (b) a nanostructured biomimetic scaffold with a porous 3D tri-layer composite structure (Maioregen®): The upper layer, consisting of Type I collagen, has a smooth surface; an intermediate layer that consists of a combination of Type I
collagen (60%) and HA (40%); and a lower layer, a mineralized blend of Type I collagen (30%) and HA (70%). The goal of this structure is to recreate the entire osteochondral unit anatomy.

The 3D Type I collagen/hydroxyapatite (HA) scaffold surgery is a one-step procedure.

The ACI surgery (a) is a two-stage procedure. The first involves the harvesting of cartilage cells, followed by isolation, culture and proliferation of chondrocytes.

The cartilage harvesting is performed through a knee arthroscopy, under tourniquet control. Specimens of cartilage (250-300mg) are taken using a 5-mm gouge from the superomedial or superolateral trochlear zone, a non-weight-bearing area. The biopsy material is then transported to the laboratory for chondrocyte culture. The culture includes the enzymatic isolation of chondrocytes, the in vitro culturing and expansion of chondrocytes (primoculture/2-3 subcultures) for 3-4 weeks in the nutrient medium at 37°C and 5% CO2 atmosphere. This procedure allows to achieve 5 - 10 million of cells per ml of chondrocyte suspension.

After quality control, viability and proliferation tests, and inverted light microscopy evaluation, the chondrocyte suspension is embedded in fibrin glue (Tisseel®), forming a soft solid chondrograft, easy to handle. The second stage involves implantation of this chondrograft.

Two of the patients were surgically accessed by arthroscopy, six and eight months after the first surgery. Both of them were from the MaioRegen® group, and they both had significant ankle synovitis. The macroscopic examination of the implanted area revealed that in both cases cartilage defects were filled in with cartilage indistinguishable from the surrounding tissue with a complete marginal integration, but having a slightly softer surface than the surrounding cartilage.
Rehabilitation was divided into two phases. Phase I (immediately post-operatively until the 6th week) involved non-weight-bearing with active and passive exercises. The phase II (after the 6th week post-operatively) included progressive weight-bearing and more aggressive physiotherapy and included cycling and swimming.

All seven patients treated by the previously described methods, were retrospectively clinically assessed using the subjective patient satisfaction (from ‘extremely pleased’ to ‘worse than before surgery’), and the Mazur’s ankle score.

3. Results

These patients clinical outcomes were improved in all the clinical scoring systems used and they were well correlated with the patients own perception of improvement.

Overall results showed good or excellent clinical results in all but one patient (85% pleased or extremely pleased), with 5 asymptomatic patients (72%) even in heavy work or in high sports level. The two symptomatic patients were female patients and belong to the type I collagen/hydroxyapatite scaffold group: One case of only mild pain related with long standing periods, and one case of moderate pain in walking activities, severely worsening with weight-bearing sports.

All malleolar osteotomies united clinically and radiologically. Assessment using a Mazur’s ankle score gave a mean pre-operative score of 51/100 (37 to 66), with improvement at one year to a mean of 84/100 (51 to 98).

The range of movement post-operatively at one year was 30° to 45° of plantar flexion and 0° to 20° of dorsiflexion.

There was no association between outcome and duration of symptoms, previous surgical debridement with drilling or the size of the defect.

None of the harvested knees was symptomatic.

4. Discussion and Conclusion

Cartilage damage is a common problem in a symptomatic joint after an acute or chronic trauma. Chondral lesions do not spontaneously heal in adult mature cartilage and the surgical repair of these defects is still imperfect and transient. Clinical experience with autologous chondrocyte transplantation for this purpose now exceeds 20 years [10,11], and the results are well documented in literature [4-9]. After solving the problem of chondrocyte proliferation, with second and third generation chondrografts the scaffold choice became the real issue [4].

Three dimensional scaffolds designed by cartilage tissue engineering do increase the efficiency of adhesion and differentiation of cells creating new opportunities for chondrocytes and can provide mechanical stability; they also have a proved biocompatibility with a predictable biodegradation/ bio-reabsorption rate and they are easier to apply.

At the present moment, and, with the actual available possibilities, either the solid fibrin-glue scaffold and 3D tri-layer composite Type I collagen/Hydroxyapatite [12] (Maioregen) seem to be a good tool in the treatment of the large full thickness cartilage lesions, as proved either by the animal study and the good clinical results at 2 to 5 years, with the majority of patients free of symptoms, some of them even in heavy work or in high sports level. However, the tissue quality is still questionable, in spite of the hyaline-like cartilage production in most of the cases.

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