Articular Cartilage Engineering with Autologous Chondrocyte Transplantation

A report by
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Tissue engineering is an emerging discipline that uses a combination of cells, engineering materials and different biochemical factors to improve or replace deficient biological functions. The poor repair capacity of articular cartilage after injury has led to many attempts to improve the repair of injured articular cartilage surfaces during the last 50 years. The first example of clinical cartilage tissue engineering was performed in 1987 when a knee with an articular cartilage defect on the femoral condyle was treated by implanting the patient’s own chondrocytes that had been expanded in vitro and then implanted into the defect in combination with a covering mechanical membrane – the periosteum.1 This, the first generation of chondrocyte transplantations, was initially termed autologous chondrocyte transplantation (ACT). Today, the technique is called either ACT or autologous chondrocyte implantation (ACI) and there exist many modifications of the technique, from the first generation to now second and third generations of chondrocyte transplantation.2-4

The initial surgical technique for ACI has been well described in several reports.5-9 The steps include an initial arthroscopically harvested cartilage biopsy from which chondrocytes can be isolated by enzymatic digestion and, in vitro culture, expanded to several times the initial number of cells. In a clinical setting today, the aim is to implant a density of 30 x 106 cells/ml, or 2 x 106 cells per cm². With the initial technique, implantation consists of an arthroscopy, defect preparation, periosteal flap harvest, fixation of periosteal flap to defect, securing a watertight seal with fibrin glue, implanting the chondrocytes and wound closure.

However, today the periosteum is often replaced by a resorbable membrane such as collagen III membrane ChondroGide® or Restore® (De Puy, Warsaw, Indiana). Second-generation ACI are cell-seeded membranes such as matrix-induced ACI (MACI)5 (Genzyme Biosurgery, Boston, MA) and the third generation includes chondrocytes cultured in 3-D matrices such as hyaluronic acid (Hyalograft-C) (Fidia, Italy).12

In Sweden, ACT in combination with a periosteal graft has been used in approximately 1,500 patients since October 1987 and worldwide variants of ACT/ACI have been tried in around 20,000 patients. The use of ACT is always considered alongside other techniques.

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The Technique

Chondrocytes are isolated from small slices of cartilage harvested transarthroscopically from a minor weight-bearing area in the injured knee. The extracellular matrix is removed by enzymatic digestion and the cells are expanded in monolayer culture. The expansion of chondrocytes in vitro is a selection of a limited number of chondrocyte progenitor clones; the culture process allows the cells to revert to a foetal-like stage in vitro and then implanted into the defect in combination with a covering mechanical membrane – the periosteum.1 This, the first generation of chondrocyte transplantations, was initially termed autologous chondrocyte transplantation (ACT). Today, the technique is called either ACT or autologous chondrocyte implantation (ACI) and there exist many modifications of the technique, from the first generation to now second and third generations of chondrocyte transplantation.2-4

The primary goal of in vitro chondrocyte manipulation is to increase the cell number. Once a suitable number of cells is reached, the increased number of chondrocytes is suspended in culture medium and then implanted into the area of cartilage defect using a membrane over the defect as a method of cell containment. In patients with small cartilage defects, ACT is mostly employed after failure of other techniques after six months. In large defects, ACT (up to 4cm²) may be used immediately as such large defects are difficult to resurface with bone marrow stimulation techniques.

Clinical Follow-ups

In a clinical evaluation of 244 patients with two to 10 years’ follow-up, subjective and objective improvements were seen in high numbers of patients with femoral condyle lesions and osteochondritis dissecans.14 There was a high percentage of good to excellent results (84–90%) in patients with different types of single femoral condyle lesions while other types of lesions had a lower degree of success (mean 74%).

To study the long-term durability of ACT-treated patients, 61 patients who had passed two years post-surgery were followed for at least five years up to 11 years post-surgery (mean 7.4 years). After two years, 50 out of 61 patients were graded good-excellent.14 At the five to 11 years follow-up, 51 of the 61 were graded good-excellent. The total failure rate was 16% (10/61) at mean 7.4 years. All ACT failures occurred in the first two years and patients showing good to excellent improvement at two years had a high percentage of good results at long-term follow-up.

Most reports on the use of ACT from other centres show similar figures...
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with a high degree of success in regard to the total number of improved patients, but the criticism has been that ACT needs to be evaluated versus other cartilage repair techniques in randomised trials. A very comprehensive analysis of the ACT technology was recently presented. The authors stated that, on the basis of the literature, no definite conclusions can be drawn from the clinical effectiveness of ACT, which should be regarded as an experimental procedure. However, on these grounds, almost all other techniques used for treating disabling cartilage defects could be regarded as experimental. The costs of ACT are substantial in comparison with the other techniques and surgeons have reported as good results with these other techniques as have been reported with ACT. Longer term outcomes are required. Economic modelling using some assumptions about long-term outcomes that seem reasonable suggests that ACI would be cost-effective because it is more likely to produce hyaline cartilage, which is more likely to be durable and to prevent osteoarthritis in the longer term (e.g. 20 years). Such speculations are not justified until data from long-term randomised studies become available, with the definitions of a short-term study being minimum two years, mid-term for five years and a long-term study at least 10 years.

Randomised Studies

to date, six clinical randomised trials have been published. These studies could be seen as short-term and mid-term studies.

Knutsen et al. studied 80 patients who needed local cartilage repair because of symptomatic lesions on the femoral condyles measuring 2–10cm². The patients were randomised into ACT or microfracture treatment and followed at 12 and 24 months. At two years, both groups had significant clinical improvement. According to the short-form 36 (SF-36) physical component score at two years post-operatively, the improvement in the microfracture group was significantly better than that in the autologous chondrocyte implantation group.

Horas et al. performed a prospective clinical study to investigate the two-year outcomes in 40 patients with an articular cartilage lesion of the femoral condyle who had been randomly treated with either transplantation of an autologous osteochondral cylinder or implantation of autologous chondrocytes. Both treatments resulted in a decrease in symptoms. However, the improvement provided by the autologous chondrocyte implantation lagged behind that provided by the osteochondral cylinder transplantation.

Bentley and associates studied a total of 100 patients with a mean age of 31.3 years (16 to 49) and with symptomatic chondral and osteochondral lesions of the knee that were suitable for cartilage repair, and randomised to undergo either ACT or mosaicplasty; 58 patients had ACI and 42 mosaicplasty. Most lesions were post-traumatic and the mean size of the defect was 4.66 cm². The mean duration of symptoms was 7.2 years and the mean number of previous operations, excluding arthroscopy, was 1.5. The mean follow-up was 19 months. Functional assessment using the modified Cincinnati and Stanmore scores and objective clinical assessment showed that other companies (88%) had excellent or good results after ACT compared with 69% after mosaicplasty. Arthroscopy at one year demonstrated excellent or good repairs in 82% after ACI and in 34% after mosaicplasty. This prospective, randomised, clinical trial showed significant superiority of ACT over mosaicplasty for the repair of articular defects in the knee.

Dozin et al. studied 47 patients who were randomly assigned to ACI or mosaicplasty and subjected to arthroscopic debridement of the lesion at the time of enrolment. Notable was the fact that 14 patients (31.8%) experienced substantial improvement following the initial debridement and, being clinically cured, received no further treatment. Among the 23 patients (52.3%) who could effectively be evaluated, a complete recovery was observed upon clinical examination in 88% of
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the mosaicplasty-treated patients and in 68% of the ACI-treated patients (p = 0.093).

Finally, there are two randomised studies comparing two types of ACT: ACT with collagen membrane versus MACI for osteochondral defects of the knee21 and a prospective, randomised study comparing periosteum-covered ACT versus type VIII collagen-covered.22 There were no differences in the outcome when comparing collagen-covered ACT versus MACI even though MACI was technically more attractive.21 In the other22 of those studies, there were no statistical differences between the clinical-outcome of collagen-covered ACT versus periosteum-covered ACT at two years. A significant number of patients who had the periosteum-covered ACT required shaving of a hypertrophied graft. The authors conclude that there is no advantage in using periosteum.

Other Joints Besides the Knee
The ankle, shoulder, elbow, hip and wrist23–26 are other locations that have been tried in smaller numbers of non-randomised patient studies. With the development of arthroscopic techniques,27,28 the use of ACI will be increased also in those smaller joint compartments.

The Future
We will see more and more different cell-containing resorbable scaffolds being used for arthroscopic implantation; some scaffolds with cells cultured for several weeks (mature grafts) and others seeded with cells just one to two days prior to surgery (immature grafts) or even just at implantation time. The repair is dependent on fast integration of the implant and immature constructs have poorer mechanical properties but integrate better than either more mature constructs or cartilage explants. There has been a recent increase in interest in the direct isolation of chondrocytes and implantation in scaffolds alone or with mesenchymal stem cells, as well as spheroid cultures where the cartilage spheroids could be used for implantation.29

The idea of resurfacing osteoarthritic joints with engineered cartilage constructs is tempting. However, in a recent study Tallheden et al.30 found that from osteoarthritic donors the accumulation of proteoglycans was in comparable amounts to those from ACT donors, whereas total collagen was significantly lower in all of the re-differentiated osteoarthritic chondrocytes. The collagen structure is the key to the structure of cartilage, which means that poor collagen production may endanger the final repair results in that osteoarthritic patient category.

Summary
An analysis of the literature provides no evidence so far for regular regeneration of hyaline cartilage in animal experiments and today’s treatments for cartilage resurfacing are still less than satisfactory, and rarely restore full function or return the tissue to its native normal state. Successful repair of injured cartilage will depend on future advances in the understanding of the biology of cartilage and further technological developments in engineering. The rapidly growing field of tissue engineering holds great promise for new generations of better and more functional cartilage tissue substitutes, but emphasises the need for cell biologists, engineers and surgeons to work closely together. With their combined knowledge, it may be possible to repair the entire diarthrodial joint more extensively with biological approaches. Not only the cartilage surface, but the subchondral bone, the menisci and the cruciate ligaments will be the future focus for such a tissue engineering approach.