Cartilage repair: autologous chondrocyte implantation

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ABSTRACT Riparazione delle lesioni condrali: impianto di condrociti autologhi

In presenza di lesioni condrali, un'opzione terapeutica è offerta dall'ingegneria tissutale, e principalmente dall'impianto di condrociti. L'uso di "scaffold" porosi e riassorbibili consente la migrazione, l'adesione e la proliferazione dei condrociti e la conseguente rigenerazione del tessuto cartilagineo. Le tecniche disponibili per il trattamento delle lesioni condrali si dividono in due gruppi principali: cellulari e acellulari. Nelle prime possono essere utilizzate anche cellule ottenute o meno da coltura. L'impianto di condrociti autologhi nel trattamento dei difetti condrali ha fornito buoni risultati, ma la sua applicazione è tuttora ostacolata dalla limitatezza delle risorse disponibili e dalla complessità della procedura. Le microfratture rappresentano il "gold standard" e sono la tecnica più diffusa per il trattamento di lesioni condrali di piccole dimensioni (<4 cm²).

Le tecniche di bioingegneria continuano a offrire nuove idee per la rigenerazione della cartilagine articolare e una possibile alternativa all'impianto di condrociti è costituita dalle cellule staminali mesenchimali. Il futuro della riparazione delle lesioni condrali dovrà basarsi su una diagnosi accurata, che utilizzi nuove tecniche di "imaging" della cartilagine mediante risonanza magnetica per misurare dimensioni e profondità di una lesione, nonché i biomarcatori nel liquido sinoviale; saranno inoltre necessari studi clinici di buona qualità per valutare gli "outcome" e decidere la migliore terapia per ciascuna indicazione.

Autologous chondrocyte implantation (ACI) has gone a long way since the Nineties, when Pater-son and Brittberg [1] reported the first midterm outcomes. Since then, the technique has been modified. Being an avascular and hypocellular tissue, cartilage has a very limited capacity for self-repair.

Tissue engineering is a therapeutic option, mainly based on chondrocyte transplantation. The first-generation ACI technique was associated with problems with cartilage hypertrophy and ossifications resulting from the use of periosteum. Subsequently, the second-generation technique known as MACI introduced seeded membranes and biomaterials. Third-generation techniques, which are very limited at the present time, propose chondroinductive or chondroconductive scaffolds with allogenic cells and methods to improve mechanical conditions so that a suitable tissue can be developed before surgery. Finally, fourth-generation techniques are based on polymers such as elastin, or hydrogels, to obtain a homogeneous three-dimensional distribution of the cells.

Porous and resorbable scaffolds allow cell migration, adhesion and proliferation promoting and regulating chondral activity. Biomechanical properties of the structure provide resistance to load bearing. Different types of organic components are available, including agarose, alginate, hyaluronic acid, fibrin, collagen and synthetic polymers such as polyglycolic acid (PGA), polylactic acid (PLA) and its co-poly-

mers, lactic-glycolic acid.

Repair techniques for the treatment of chondral injuries can be cell-based or non-cell-based. In a cell-based repair technique cultured or non-cultured cells could be used. An example of a non-cell-based technique is abrasion or joint lavage; a cell-based technique is MACI, but also microfracture can be considered as belonging to this group, since regeneration of the injury relies on cells derived from epiphyseal cancellous bone.

Autologous chondrocyte implantation for cartilage defects has achieved good results, but limited resources and the complexity of the procedure have hindered wider application. A hyaline cartilage biopsy is performed, then the cartilage tissue is digested, cultured, the cells are expanded and subsequently implanted in the patient after a period of time. Once an adequate quantity of cells has been obtained, in a second intervention, which can be performed after 6 weeks, the lesion is cleaned, taking special care not to damage the subchondral bone, and the cultured chondrocytes are deposited in the lesion together with the chosen scaffold. Initially the technique shows good results comparable with other techniques in the short and medium time. Cartilage tissue engineering broadly involves the use of three components: cell source, biomaterial/membranes, and/or growth stimulators, either alone or in any combination. Tissue engineering principles are currently being applied to clinical medicine in the form of autologous chondrocyte implantation (ACI)

or similar techniques. Despite refinements in technique, current literature fails to support a clinical benefit of ACI over older techniques such as microfracture, except perhaps for larger (>4 cm) lesions. Modern ACI techniques may be associated with lower revision rates. The notion that ACI-like procedures produce hyaline-like cartilage in humans remains unsupported by high-quality clinical research [2].

Although these procedures have been implemented with varying degrees of success, no consensus exists on the gold standard of treatment. There is no clear evidence to suggest which one is best.

The innovative aspects of this technique have attracted considerable attention in the literature, with over 800 articles in Medline [3], including multicenter studies. The Cartilage Repair Registry [4] showed that 78% of the injuries treated with ACI improved and that targets were met in 81% of single femoral lesions. Goyal et al [5] analyzed 7 papers with level I and II evidence, noting that there is no evidence that scaffolds are better than periosteum. Limits of these studies are the few number of cases, the different injury characteristics and the young age of the patients. However, they found evidence that MACI facilitates the rehabilitation of patients.

Minas et al. [6] showed with the ACI technique good and excellent results in over 75% of 210 patients up to 10 years after surgery. ACI provided durable outcomes with a survivorship of 71% at 10 years and improved function in 75% of patients with symptomatic cartilage defects of the knee at a minimum of 10 years after surgery.

Goyal et al. [7] reviewed fifteen level I and II studies, 6 long-term and 9 short-term, involving microfracture techniques. The use of microfractures for the treatment of small lesions in patients with low postoperative demands resulted in good clinical outcomes at short-term follow-up. Beyond 5 years post-surgery, treatment failure after microfracture could be expected regardless of lesion size. Younger patients showed better clinical outcomes. Negrin and Vécsei [8], in a literature review, analyzed 399 patients aged between 16 and 60 years, with 1 to 10 cm² cartilage defects. Microfracture and ACI groups were matched according to patient baseline characteristics. In all cases, microfracture was performed

according to Steadman, whereas three generations of ACI were applied. When all were combined, non-significant superiority of ACI over microfracture was shown, but this superiority decreased over time. Both series of meta-analyses (combining either all ACI techniques or only second and third generations of ACI) suggest that the treatment effects resulting from ACI and microfracture converge over the years.

Microfracture is the most widely used technique for small chondral lesions (<4 cm²) and is the gold standard against which all other techniques are compared. It should be performed with an appropriate icepick, creating stable, vertical edges; the calcified layer of the cartilage must be debrided, and perforations made every 2 or 3 mm to ensure good anchorage of the clot. Bleeding brings about a greater surface and quality of repair tissue, stimulating the hematopoietic and mesenchymal stem cells (MSCs) to form new tissue, even though the blood partly clots and mostly disappears with the arthroscopic lavage and synovial fluid dilution. To maintain the blood clot and the bone marrow cells in the lesion, scaffold-guided regenerative medicine has been proposed, using chitosan (BST-CarGel®, Piramal, Laval, Canada), a natural polymer scaffold, as a patch which is reabsorbed, leaving all the blood products and MSCs in the area of the injury, protected from the synovial fluid, in order to form hyaline cartilage. In a clinical trial better results were found with the CarGel® technique compared with the standard microfracture technique [9].

Bioengineering techniques continue to provide new ideas for the regeneration of articular cartilage. Recently the use of MSCs instead of chondrocytes was proposed. It appears that MSCs in bone marrow aspirate may differentiate towards chondrocytes or osteoblasts, without requiring laboratory culture, and can easily be delivered in suitable biomaterials; growth factors added to biomaterials may facilitate the differentiation of cells from the bone marrow. MSCs can be harvested by a small puncture of the iliac crest of patients. In contrast to chondrocyte transplantation, this procedure creates no additional harvest defect in the knee joint of the patient. Incorporation of MSCs in suitable tissue engineering scaffolds and culture in chondrogenic medium can produce cartilage-like tissue.

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The future of cartilage repair should be based on an accurate diagnosis, using new MRI techniques for imaging cartilage to estimate the size and depth of lesions and synovial fluid biomarkers, and good clinical trials to assess outcomes and decide the best therapy for each indication.

Bibliography

1. Brittberg M, Lindahl A, Nilsson A et al (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 331:889-895
2. Mollon B, Kandel R, Chahal J, Theodoropoulos J (2013) The clinical status of cartilage tissue regeneration in humans. *Osteoarthritis Cartilage* Sep 7 [Epub ahead of print]
3. Bekkers JE, Inkleaer M, Saris DB (2009) Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med* 37[Suppl. 1]:148-155
4. Mandelbaum BR, Browne JE, Fu F et al (1998) Articular cartilage lesions of the knee. *Am J Sports Med* 26:853-861
5. Goyal D, Goyal A, Keyhani S et al (2013) Evidence-based status of second- and third-generation autologous chondrocyte implantation over first generation: a systematic review of level I and II studies. *Arthroscopy* Sep 26 [Epub ahead of print]
6. Minas T, Von Keudell A, Bryant T, Gomoll AH (2013) The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. *Clin Orthop Relat Res* Aug 24 [Epub ahead of print]
7. Goyal D, Keyhani S, Lee EH, Hui JH (2013) Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy* 29:1579-1588
8. Negrin LL, Vécsei V (2013) Do meta-analyses reveal time-dependent differences between the clinical outcomes achieved by microfracture and autologous chondrocyte implantation in the treatment of cartilage defects of the knee? *J Orthop Sci* Aug 10 [Epub ahead of print]
9. Stanish WD, McCormack R, Forriol F et al (2013) Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. *J Bone Joint Surg Am* 95:1640-1650