

# Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation

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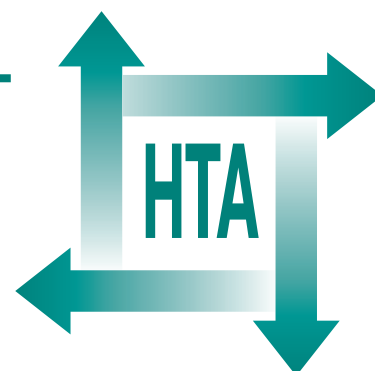
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## *Executive summary*

*Health Technology Assessment 2005; Vol. 9: No. 47*

Health Technology Assessment  
NHS R&D HTA Programme





## Executive summary

### Objective

To support a review of the guidance issued by the National Institute for Health and Clinical Excellence (NICE) in December 2000 by examining the current clinical and cost-effectiveness evidence on autologous cartilage transplantation.

### Proposed service and current methods

Autologous chondrocyte implantation (ACI) is a surgical approach used to treat full-thickness cartilage defects in knee joints. Small samples of normal cartilage with the cells that produce the cartilage (chondrocytes) are removed from the damaged joint. The cells are cultured in special laboratories to increase the number of cells and reimplanted a few weeks later into the areas of cartilage damage. The aim of this procedure is to restore normal hyaline cartilage to the ends of bones and thereby restore normal joint function. The procedure is used mainly for knee joints at present, but has been tried in other joints.

The current standard treatment of cartilage defects is by stimulating repair of the cartilage defect by cells from the underlying bone marrow, usually by the procedure known as microfracture. The hope is that the stem cells from the marrow will differentiate into chondrocytes that will then produce new cartilage. However, the cartilage they produce tends to be an inferior form known as fibrocartilage, which is not as good as the original hyaline cartilage.

Another technique used is called mosaicplasty (or autologous osteochondral cylinder transplantation), whereby cylindrical plugs of cartilage and bone are removed from less weight-bearing parts of the same knee, and transplanted into the damaged area. The problem of damage to the donor sites limits this procedure to smaller lesions.

The expected benefits of ACI consist of short-term relief of symptoms such as pain and long-term prevention of the development of osteoarthritis, and hence reduction in the need for later knee replacement.

### Epidemiology

There are no reliable estimates of the prevalence of cartilage defects in the knee. Lesions are most likely to arise in sportsmen and women as a result of injury, but are often a result of occupational injury. Up to 20% of those sustaining a haemarthrosis following a knee injury may have cartilage damage.

### Methods

This study is an update of a previous review published in this series. Evidence on clinical effectiveness was obtained from randomised trials, supplemented by data from selected observational studies for longer term results, and for the natural history of chondral lesions. Because of a lack of long-term results on outcomes such as later osteoarthritis and knee replacement, only illustrative modelling was done, using a range of assumptions that seemed reasonable, but were not evidence based.

### Results

#### Number and quality of studies

Four randomised controlled trials were included, as well as observational data from case series. The trials studied a total of 266 patients and the observational studies up to 101 patients. Two studies compared ACI with mosaicplasty, the third compared ACI with microfracture, and the fourth compared matrix-guided ACI (MACI<sup>®</sup>) with microfracture. Follow-up was 1 year in one study, and up to 3 years in the remaining three studies. All studies had some methodological shortcomings.

#### Summary of benefits

The first trial of ACI versus mosaicplasty found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. However, the benefit was statistically significant only in the group with medial condylar (i.e. the inside of the leg) defects (just over half of the patients). The other groups (patella and lateral condyle) also did better with ACI, but numbers were too small for

the results to be statistically significant. About half of the biopsies after ACI showed hyaline cartilage. The second trial of ACI versus mosaicplasty found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage. The trial of ACI versus microfracture also found only small differences in outcomes at 2 years. Finally, the trial of MACI versus microfracture contained insufficient long-term results at the time of this review, but the study does show the feasibility of doing ACI by the MACI technique. It also suggested that after ACI, it takes 2 years for full-thickness cartilage to be produced.

### Economic review

Reliable costs per quality-adjusted life-year (QALY) could not be calculated owing to the absence of necessary data. Simple short-term modelling suggests that the quality of life gain from ACI versus microfracture would have to be between 70 and 100% greater over 2 years for it to be more cost-effective within the £20,000–30,000 per QALY cost-effectiveness thresholds. However, if the quality of life gains could be maintained for a decade, increments relative to microfracture would only have to be 10–20% greater to justify additional treatment costs within the cost-effectiveness band indicated above.

### Limitations

The trials published in the literature at the time of this review all compare ACI with a different treatment. Therefore, data on each comparison are limited and no trial data are available for comparing ACI with no treatment. Follow-up from the trials so far has only been up to 2 years, with longer term outcomes being uncertain.

### Conclusions

There is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty. Longer term outcomes are

required. In the absence of hard evidence, 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). However, any results from modelling based on assumptions rather than evidence must be treated with caution.

### Recommendations for future research

The following areas are recommended for additional research.

- In addition to the need for longer term results referred to above, there is a need for study into earlier methods of predicting long-term results. Techniques such as modern methods of magnetic resonance imaging may be useful for assessing quality of cartilage.
- There is also a need for basic science research into the genes and molecules that influence stem cells to become chondrocytes and to produce high-quality cartilage. It may be possible to have more patients developing hyaline cartilage after microfracture. Substances such as cartilage growth factors may have a role.
- Methods of rehabilitation vary, with some centres encouraging weight bearing earlier than others. Research is needed into the most cost-effective method, and the effect of early mobilisation on cartilage growth.

### Publication

Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al.* Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(47).

# NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/65/01. The protocol was agreed in April 2004. The assessment report began editorial review in March 2005 and was accepted for publication in May 2005. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

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Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.

Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.