Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee

Introduction

Chondral defects in the knee are very common. Although they can occur at any age, they are rare in paediatric patients but tend to be seen with increasing frequency from the teenage years onwards. In younger patients they often occur as a consequence of trauma. They are not unusual following patellar dislocation, for example. The condition of osteochondritis dissecans in which there is separation of an osteochondral fragment from the knee joint surface, usually from the medial femoral condyle is another relatively common cause in younger patients. In middle aged patients chondral defects are most often associated with a degenerative process in the joint and can be considered a pathological process that in a proportion of patients will progress to symptomatic osteoarthritis of the knee.

Articular cartilage has very limited healing capacity. Loss of the normal hyaline articular cartilage is usually a permanent event – the joint can heal the defect, but with fibrocartilage which is an inferior joint surface without the specialised biomechanical and biological characteristics of healthy hyaline articular cartilage. Chondral lesions may be asymptomatic, particularly if small and if the area of the surface is away from a main weight-bearing part of the joint. In general, larger lesions on the main weight-bearing surfaces are more likely to be associated with painful symptoms. In general they cause activity related pain, sometimes associated with other mechanical symptoms such as swelling, crepitus and locking.

In patients with troublesome pain which does not respond to non-operative therapy there are a number of treatment modalities available. Until 20 years ago the options were limited – microfracture, realignment osteotomy or some form of arthroplasty were the only choices. Mosaicplasty and autologous chondrocyte implantation (ACI) were developed in the late 1990s and have attracted a lot of scientific and clinical interest as alternative surgical modalities. Realignment osteotomies and arthroplasty are really only appropriate for advanced chondral deterioration with osteoarthritic change established in the knee. Neither procedure would be appropriate for a smaller symptomatic chondral lesion in a knee with normal alignment.

The main options for more localised symptomatic chondral lesions are therefore microfracture, mosaicplasty or ACI. For technical reasons the chondral lesions accessible to these techniques are either on the femoral condyles or in the patellofemoral joint. The limited access to the medial and lateral tibial plateau renders most defects in those locations unsuitable for these treatment modalities. Microfracture has two main advantages: it is cheap and technically straightforward to perform. Of the three treatment options it has been the most widespread in clinical practice for these reasons, but also because it has been available for much longer. Mosaicplasty is a technically more demanding procedure to perform but most experienced knee arthroscopic surgeons could be easily trained to carry out the procedure. It can usually be performed arthroscopically, except for lesions in the

patellofemoral joint where for technical reasons to do with access an arthrotomy of the joint is often required. The procedure is more expensive than microfracture although the difference is small. The defect size is also limited by the need to harvest donor articular cartilage and the more of these required the greater the chance of donor site morbidity.

ACI is the technique which has excited the greatest academic interest but it also the technique that has been used least frequently. It involves an initial procedure to harvest chondrocytes and a subsequent procedure to reimplant them usually undertaken about 6 weeks later. It is the most expensive of the three options. The surgical complexity of the procedure, particularly when it was first introduced and the cost are two reasons that account for the limited use of the technique in clinical practice.

Natural history of chondral lesions

The natural history of chondral lesions in the knee is not well-established. These lesions are common incidental findings in arthroscopic knee surgery undertaken for other indications. The presence of a chondral lesion is therefore not invariably associated with pain. Some of these can be considered as an early stage in the development of generalised osteoarthritis of the knee. However chondral lesions are very common whereas the requirement for total knee joint replacement is not so it is difficult to predict which chondral lesions would progress to the point of symptomatic arthritis requiring knee arthroplasty. It is also well-recognised that symptomatic chondral lesions can become asymptomatic for reasons that are uncertain.

Clinical trials

Clinical trials comparing the 3 surgical modalities above have appeared regularly in the last decade. Most have compared some form of ACI to microfracture. Trials featuring mosaicplasty have been fewer. No trial has been conducted comparing one of the treatment modalities to nonoperative treatment. This is a problem because the assumption has been that nonoperative treatment is inferior to doing something operatively, which may not be the case.

Since the last NICE document evaluating ACI in 2005 there is therefore a better evidence base to inform the decision making process regarding the use of ACI in clinical practice. A broad interpretation of the literature is as follows. ACI and mosaicplasty are associated with better clinical results than microfracture. Both ACI and mosaicplasty are effective in relieving pain in the majority of patients. ACI appears to have a modest advantage over mosaicplasty with a modest improvement in the success rate and long term survival.

Randomised trials are always a challenge to design and complete with adequate patient numbers and duration of follow-up. The difficulties involved are abundantly clear in the published trials in this area. The list of criticisms is a long one but some of the main points to make are:

1. There is no trial using a nonoperative treatment arm or a “sham” surgery arm.
2. The patient numbers in the trials are small.

3. The follow-up is short in many studies.
4. The main outcome measures used in many trials are the IKDC score, the Lysholm score, the Tegner knee score and Knee Injury and Osteoarthritis Outcome score.
5. These are clinical outcome questionnaires and some were designed mainly for evaluation of knee ligament injury and surgical reconstruction. They are obviously not intended to assess the quality of a regenerated joint surface.
6. There is no reliable way of determining the quality of the articular cartilage generated by the surgical interventions.
7. The techniques of ACI have evolved over the past decade and the various generations of the method may not be comparable with each other.
8. Although there appears to be an advantage for ACI over microfracture some trials did not demonstrate superiority.
9. Inclusion criteria were very variable and in some trials very non-specific.

Economic analysis

Clearly the cost of ACI greatly exceeds other therapies. On the basis of the trials there have been efforts to justify the cost of the ACI procedure. However, these economic analyses make some significant assumptions. It is generally assumed that chondral lesions will progress to osteoarthritis and knee joint replacement, and there will be a significant requirement for revision knee replacement. As noted above the natural history of chondral lesions is uncertain, but the majority do not progress to osteoarthritis significant enough to necessitate knee replacement surgery. The incidence of total knee replacement in the UK population is 0.1% and chondral defects in the knee are a good deal more common than this. It has to be assumed therefore that the majority of chondral lesions do not progress to osteoarthritis severe enough to warrant knee replacement surgery. Another assumption is that a knee joint replacement will inevitably require revision surgery. The actual requirement for revision knee replacement is modest and only 15% of all primary knee arthroplasties are subsequently revised.

Current position

All 3 modalities seem to be clinically effective but the exact role for each is still not clear. A trial with a nonoperative arm or a sham surgery arm with longer term follow-up would be useful in defining the natural history of chondral defects and whether any of the treatments is superior to doing nothing. Mosaicplasty is cheap and relatively effective for small defects. ACI may be superior to the other treatment methods but larger trials with modern techniques are required to validate this conclusion. It is of course considerably more expensive and any further trials should incorporate a health economic analysis to demonstrate whether ACI is a cost-effective treatment.