The Surgical Management of Symptomatic Articular Cartilage Defects of the Knee: Consensus Statements from UK Knee Surgeons

Abstract
Symptomatic articular cartilage and osteochondral lesions in the knee are an important source of pain and disability, and may lead to osteoarthritis. There are several surgical treatments for the condition, with emerging data evaluating their clinical effectiveness and longer-term clinical outcome. Health care providers have challenged the indications for the use of expensive techniques and have been reluctant to authorize funding or reimbursement.

The UK Cartilage Consensus Meeting was convened, involving clinicians in the UK with experience in the treatment options, decision-making and evaluation of the literature on the subject. This paper reports the consensus of attendees regarding appropriate surgical options for managing articular cartilage defects in the knee, validated by a cohort of surgeons in the UK who are active in the field of articular cartilage surgery.
Introduction

Articular cartilage injuries in the knee are common. Approximately 60% of patients undergoing arthroscopy for any indication have an articular cartilage lesion\textsuperscript{1,2} with a preponderance for location on the femoral condyles. Cartilage lesions can be the result of trauma, or other conditions such as osteochondritis dissecans, previous sepsis or inflammation. Articular cartilage lesions are not symptomatic in all patients, but those that are can give rise to symptoms that are equivalent in magnitude and disability to end stage osteoarthritis of the knee\textsuperscript{3}. Symptoms can include pain, swelling, catching, locking and instability symptoms. History and physical examination alone are not diagnostic, and patients usually undergo plain radiography of the knee to evaluate alignment of the joint, to detect the presence of any radio-opaque loose bodies and determine radiographic signs of arthritis. MRI scanning (with or without gadolinium enhancement) can identify and partly quantify articular cartilage defects. Arthroscopy is the gold standard for assessment of the size of the lesion and functional integrity of the surrounding cartilage. Articular cartilage has very limited capacity of self-repair in adults and the natural history of articular cartilage lesions is that those over 9mm diameter are biomechanically unstable and will progress to degeneration of the joint surfaces\textsuperscript{4,5}.

Context of the UK Cartilage Consensus Meeting.

There is accruing evidence to the most effective treatments for symptomatic articular cartilage lesions. Some treatments are more expensive than others, and there is a wide disparity and geographical variation between health boards,
hospitals, health insurance companies and other healthcare providers as to which treatments can be offered. Clinicians are restricted on economic grounds in treating their patient with what they would deem to be the best evidence-based surgical management for that individual patient.

Licensing by the European Medicines Agency of cell therapy products is rigorous, and companies providing this treatment commercially are obligated to invest in multicentre RCTs to establish product effectiveness. Industry therefore attempts to recoup these investments by raising the price of the treatment they have proven to be effective. Government Human Tissue Authority licensing of individual hospitals is necessary to undertake cell therapy for articular cartilage repair, at a significant additional cost to the treatment. Reluctant health care providers have termed some cartilage repair techniques “experimental” and therefore not suitable for funding. Knee surgeons do not accept this, as they recognize that some of these so called “experimental” techniques have been in safe clinical practice for over 25 years, with published long-term patient reported outcomes. Cartilage repair treatments are on the front line of innovation and tissue engineering, with new techniques and products constantly emerging that need rigorous trial evaluation. Surgeons who treat patients with symptomatic articular cartilage lesions in the UK are cognisant of the financial restraints within the system within which they work. However, they have recognized the need for a UK Consensus Paper to summarize the evidence-based best treatment for their patients and make this paper available to health care providers.
This paper reports the conclusions of the UK Cartilage Consensus Meeting regarding appropriate surgical options for managing articular cartilage defects in the knee, when conservative measures have failed.

Methods
The UK Cartilage Consensus Meeting was held on 23\textsuperscript{rd} March 2014 at The Royal College of Surgeons of Edinburgh. It was an open meeting, free to attend for any interested clinician. The meeting was held in the absence of Industry sponsorship and was funded by an unrestricted grant from the Scottish Orthopaedic Research Trust into Trauma (SORTiT) whose remit is to promote research and education for improved care of the injured. An experienced non-medical facilitator chairman ensured all participants had an equal opportunity to participate, amend and veto suggestions. During the meeting, participants had access to all peer-reviewed literature (paper or electronic) on the subject of articular cartilage injury and repair to consult as necessary.

In order to focus the scope of the Consensus Meeting and paper, it was assumed that surgery would be considered when the articular cartilage lesion of the knee was no longer responsive to effective pro-active conservative treatment, including specialized lower limb physiotherapy and rehabilitation, activity modification and weight management.\textsuperscript{11}

This consensus was established based upon an isolated defect of the knee joint which was stable or surgically stabilized by ligament reconstruction, where alignment was normal or surgically corrected by osteotomy, and free of inflammatory joint disease and with some functional meniscal tissue remaining.
Following the meeting, the paper was circulated in draft form to all meeting participants, other interested clinicians who were unable to attend the meeting and to all members of The British Association for Surgery of the Knee (BASK) to engage more widely. Participating clinicians were asked to declare any conflict of interest and the signatories to this consensus paper agree with the majority of its content.

The consensus meeting and consensus statements cover isolated articular cartilage defects in the adult knee. There are many patients who are outside this description who benefit from chondral surgery as part of their management. They should not be excluded from appropriate treatment methods on the basis that their specific indications are not discussed in this document.
Overview of Surgical Treatment Strategies

Surgical strategies used to repair articular cartilage lesions of the adult knee fall into four broad categories detailed below. Many patients may have had prior arthroscopic surgery to diagnose chondral or osteochondral lesions combined with mechanical or radio-frequency debridement procedures designed to remove unstable tissue and reshape defect edges.

1. Bone marrow stimulation techniques (microfracture, augmented microfracture). The bone in the base of a defect is multiply pierced and allowed to bleed. Cells within the resultant blood clot form a fibrous scar tissue composed predominantly of type I collagen. The fibrocartilagenous scar tissue has poorer biomechanical properties compared to the surrounding hyaline articular cartilage and is thought to degenerate by around 24 months. However, there may be a short-term improvement in symptoms. Clinical outcome is poor in the medium-term for young active patients or patients with larger defects. Techniques are described for performing a microfracture with the addition of a membrane or matrix overlying the clot to retain the clot in the defect. The longer-term outcome data of this technique is awaited, and there are currently no sufficiently powered randomised studies in the literature to prove any superiority over unaugmented microfracture.

2. Osteochondral grafting. Usually autologous, a core of intact articular cartilage and its underlying bone is harvested from an area of the knee less involved in weight-bearing and implanted into the symptomatic
articular cartilage defect of the same knee\textsuperscript{20,21}. In this technique, autologous donor tissue is limited\textsuperscript{22}. The bony element of the graft usually heals well, and patients can have a good short-term outcome. There is concern regarding the poor integration of the transferred cartilage tissue with the host hyaline cartilage, and there is evidence to confirm that significant portions of the chondrocytes in the periphery of the graft are rendered non-viable by the harvesting process itself \textsuperscript{23}. Longer-term cohort studies and a randomized trial have shown poorer outcomes at medium- and long-term\textsuperscript{24-26}. Patients with larger defects requiring multiple plugs and patients with lesions of the patella fare particularly badly with this technique. Allograft osteochondral grafting has been used successfully in some centres\textsuperscript{27-29}. Suitable allograft is often difficult to obtain in the UK. The optimum balance between microbiological safety and graft cell viability, and the effect of storage is not yet established.

3. Osteochondral Scaffolds. These are a group of treatments where matrices are implanted into defects\textsuperscript{30}. The principle is that cells migrate into the scaffold, which provides a structural framework upon which they can proliferate. Long-term cohort results and randomized studies of these techniques are awaited.

4. Cell Therapy (Autologous Chondrocyte Implantation). In this technique\textsuperscript{31}, a small biopsy of autologous articular cartilage is harvested from an area of minimal weight-bearing of the knee or from the damaged tissue of cartilage defect itself. The cartilage is enzymatically digested in the
laboratory to release the chondrocytes. These are cultured, and returned to the surgeon for implantation into the defect at a second surgery. First generation surgery at introduction of the technique in 1984 included using autologous periosteum as a patch under which cells were injected\(^3\). The periosteum was prone to hypertrophy\(^3\), and the techniques currently licensed by the European Medicines Agency use a collagen patch, either as a cover for injected cells, or as a structure to be preloaded with cells. Key papers have emerged on the results of ACI. Long-term cohort studies of ACI\(^9\), and two series independent of the surgeon-inventors of the technique have recently been published from the UK and USA\(^6,9\). These demonstrate good long-term outcomes for ACI of the femoral condyles and patella, with over 70\% still successful at minimum of 10 years. Two high quality multi-centre randomized controlled trials (RCT) of ACI vs microfracture have been published\(^6,7\) demonstrating the clinical and histological superiority of cell therapy at two and at five years. A long-term RCT of ACI vs Mosaicplasty at minimum ten years\(^26\) demonstrated superiority of ACI in large lesions. Results of ACI have been shown to be worse if performed following bone marrow stimulation techniques with a six fold increase in the failure rate of ACI after previous microfracture\(^34,35\). One RCT of ACI vs microfracture\(^36\) has results that differ with all other reported RCTs. This study reports no clinical difference between ACI and microfracture at 5 years, although better histology for ACI. At 5 years, 40\% of this cohort had osteoarthritis, so a possible explanation for the result is a different indication for surgery at the outset. Long-term results of these patients is awaited.
5. Stem cell therapy may be the next innovation in cartilage regeneration. Further pre-clinical work is in progress to establish the optimal cell to utilise, the safety and efficacy of the techniques. Clinical trials for certain stem cell techniques are in progress. Good quality clinical trial data of stem cell regeneration of articular cartilage is not yet available.

Results
The consensus group reached conclusions on the inter-related aspects of decision-making and treatment options for symptomatic articular cartilage defects in the knee. The findings are summarized as consensus statements.

1. Consensus statements on the Indications for Treatment:
Not all articular cartilage lesions are symptomatic, and surgical treatment of the defect should be reserved for symptomatic lesions of ICRS grade 3 or 4\textsuperscript{37}. Prior to embarking on any articular cartilage surgery, the knee must be normally aligned or surgically normalized by osteotomy. The knee should be stable, or surgically stabilized by ligament reconstruction. There should be sufficient meniscal tissue remaining. This may need to be judged by the surgeon, as it can vary with the size of the knee and functional demand of the patient. The patient should have an absence of inflammatory arthropathy, and no significant medical co-morbidity. Patients should be counselled of the evidence of poorer outcomes of any cartilage repair surgery in smokers, patients with a body mass index $>30$ and a long duration of pre-operative symptoms. Patients should be willing to
comply with the long rehabilitation phase, which is important to gaining a successful outcome for any technique used to treat articular cartilage injury.

2. Consensus statements on quantifying the size of lesion

The size of the lesion post debridement should be measured as length x width and expressed as an area in square centimetres. Consideration should be given to the relative size of a defect in context of the size of the knee. A relatively small lesion may be the majority of a condyle in a small knee.

3. Consensus statements on treatment options using the size of the lesion as the primary determinant

3.1 The size of the lesion following debridement of non-functional damaged cartilage tissue is the primary determining factor in decision making for the most appropriate surgical treatment. Secondary factors include patient physical demand, expectations and compliance with rehabilitation.

3.2 In symptomatic contained defects less than 2cm² in an average sized knee, bone marrow stimulation techniques and osteochondral grafting are appropriate treatment options. In the absence of comparative trials in small lesions showing superiority of cell therapy, the cost of cell therapy would need special circumstances to justify use.

3.3 For lesions 2-4cm² in the average sized knee, cell therapy is the most effective treatment option based on published literature. The available evidence reports a poor intermediate term result following marrow
stimulation techniques and high donor site morbidity following osteochondral grafting procedures. Augmented microfracture techniques and other novel microfracture techniques may be indicated in this situation, but the current evidence base is not conclusive, and should be carefully evaluated if performed.

3.4. Lesions >4 cm² should not be treated with bone marrow stimulating techniques or autologous osteochondral grafting. Cell therapy is the best evidence-based treatment in this situation. Allograft osteochondral grafting has sufficient evidence to consider use in large defects where it is available. Viral and bacterial infection risks need to be taken into consideration, as does the effect of storage on chondrocyte viability.

4. Consensus statements on Location of the Lesion within the Knee in Relation to Treatment

The multicentre randomized controlled trials of cell therapy vs microfracture have been conducted in patients with femoral condyle lesions. Data from other series and RCTs demonstrates that osteochondral cylinder transfer is suboptimal in the patellofemoral joint and should not be used for lesions of the patella that require more than one plug. The articular cartilage of the patella is the thickest within the knee, and there is also low volume of bone marrow in the patella. Microfracture of the patella has poorer outcomes compared to elsewhere in the knee. Long-term series indicates that for a normally tracking patella, cell therapy is an effective option for treatment of symptomatic lesions of this location.
5. Consensus statements on Data Collection

5.1 Responsible innovation, and continued evaluation of new or established treatments is acknowledged. Ideally, UK cartilage repair patients should submit pre-operative and post-operative validated patient reported outcome measures and should have recorded objective functional measures.

5.2 Long-term pooled data of standardized patient measures is important in the evaluation of different treatments. The consensus meeting supports the establishment of a registry.

5.3 Treatment failures should be recorded. A secondary pathology within the joint must be excluded before diagnosing failure of the cartilage repair surgery. The definition of treatment failure should include a poor patient-reported outcome score combined with objective evidence of failure of the repair on imaging or arthroscopic assessment. New articular cartilage lesions occurring in other sites within the knee are not a failure of the primary repair.

5.4 Reporting of serious adverse events in ATMPs (Advanced Therapy Medicinal Products) is mandatory. Cell therapy products licensed by the European Medicines Agency are ATMPs. Surgeons report implant-related failures to the ATMP company who are obligated to report it to the
competent authority in each country (The MHRA in the UK). Surgeons have the option of reporting directly to the MHRA.

5.5 Clinicians acknowledge the necessity of responsible innovation and evaluation of emerging technologies, and continued evaluation of established techniques.

6. Consensus statements on Physical Therapy and Cartilage Repair

An effective physical therapy programme delivered by specialist physiotherapists may be effective in controlling the symptoms in some patients. Therefore, this should occur before surgery is considered. The UK Cartilage Consensus group acknowledges that effective rehabilitation has an integral role in optimizing patient outcome following reparative cartilage surgery. Further randomized controlled trials are essential in the field of rehabilitation and pre-habilitation for cartilage surgery patients for long-term goals to be optimised.

7. Consensus statements on First Line and Second Line Treatments.

When cell-based treatments are considered appropriate, such treatment should be performed as a first line therapy, and should not be considered only as a second line treatment after failed alternative treatment. On current evidence, patient outcome for articular cartilage surgery is optimized when surgeons are enabled to provide the best evidence-based treatment for the primary defect surgery for that patient. Historically, expensive cell therapy was reserved for patients who failed other inferior and cheaper techniques. The evidence is now available that clearly demonstrates that, although cell therapy is the best option
in the second line situation in lesions >2cm², patients who have cell therapy as the first line treatment for these lesions have outcomes that are far superior to patients undergoing this treatment for failure of other treatment options\textsuperscript{34,35}.

Conclusion.

This paper has outlined the current understanding of best treatment options for the surgical management of symptomatic chondral defects of the knee by a group of expert clinicians. The information has been summarized into 7 consensus statements. This consensus will need to be updated in light of new evidence as it arises.
References:


37. ICRS Scoring System (last accessed 26th October 2014) 
www.cartilage.org/_files/contentmanagement/ICRS_evaluation.pdf
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