Can Autologous Matrix-Induced Chondrogenesis (AMIC) provide positive outcomes in the treatment of retropatellar chondral lesions?

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Abstract

**Background:** The patellofemoral joint is a challenging environment for treating chondral defects. Among the surgical options for the treatment of chondral defects, the single-stage AMIC procedure uses a collagen I/III membrane to enhance bone-marrow stimulation. However, longer term outcomes data are rare for this specific indication. In order to provide real-world information, an ongoing registry has been established in order to record patient data and outcomes when AMIC is used to treat chondral and osteochondral lesions, which for this study were those of the patella.

**Methods:** Patient data were retrieved from an ongoing, prospective, multisite registry of patients who had undergone surgical repair of chondral defects via AMIC. We identified 65 patients, all of whom had been treated by one of the authors and for whom pre-operative and at least 1 post-operative score was available. Outcomes were assessed via the KOOS and the Lysholm scores. Outcomes at the post-operative time-points were analysed using a factorial ANOVA with post-hoc testing while linear regression was used to assess associations between the change in the Lysholm score and lesion size.

**Results:** The mean lesion size was 3.1 ±1.4 cm². The most common surgical approach was mini-open, the most common fixation was via fibrin glue and the mean length of follow-up of 5.8 years (range 1 – 10 years). There was a significant improvement in the KOOS scores from pre-operative to the 1st year post-operative (p<0.001), which was maintained during the follow-up. Likewise, a significant improvement in the sports-recreation score (p>0.001) as well as in ADL and QOL (p>0.001 for both) were maintained throughout the follow-up.

**Conclusions:** The forces exerted on the patellofemoral joint make this a challenging scenario for chondral repair. Our data demonstrates that the AMIC procedure is an effective treatment for retropatellar cartilage lesions, and provides reliable results, with decreased pain and improved function. Importantly, these improvements were maintained through the follow-up period.

**Keywords:** cartilage, patella, AMIC, autologous matrix-induced chondrogenesis, chondral
**Background**

Articular cartilage is essential to the proper functioning of synovial joints, as it transmits loads and provides an articulating surface with a low coefficient of friction. (1, 2) In the patellofemoral joint (PFJ), this low friction environment is essential as the patella glides in the trochlear groove, enhancing the moment arm of the quadriceps (3) as well as contributing to the optimization of control strategies in locomotion. (4) While patellofemoral compressive forces have been calculated to be somewhat more than 4 times body weight (5) there is also data that shows these can be as high as 11 times body weight. (6) Thus, the gliding movement and the high compressive forces create an environment that could be challenging, and it well-known that articular cartilage has minimal regenerative capacity due to its avascular and hypocellular character. (7)

In considering the biomechanical complexity of and the forces exerted on the articular surfaces, it is not surprising that the PFJ is a common site of pathology, whether chronic or acute. A systematic review had noted that patellofemoral defects were the most common, comprising 37% of the lesion sites. (8) This is consistent with the conditions that had been recorded for over 5 000 arthroscopic surgeries, in which it was reported that patellofemoral defects accounted for 37.5% of the lesions. (9) Whether the underlying factors are the result of pathological loading that contributes to a deterioration of the articular surface (10) or an acute event leading to a focal chondral lesion (11) it is essential to restore the integrity of the articular surface in order to prevent further breakdown of the cartilage and thus a progression to osteoarthritis. (12)

While first-line treatment will often be conservative management, (10) persistent symptoms may indicate a need for surgical treatments. While there are a number of options, (13) it is essential to evaluate the clinical evidence that is available for the various techniques currently performed. Among surgical options, a single-stage procedure known as autologous matrix induced chondrogenesis (AMIC) uses bone marrow stimulation techniques, often via microfracturing, and then covers the treated site with a bilayer collagen I/III membrane (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland) in order to contain the subchondral bleeding and provide a matrix for repair tissue to mature. (14) However, the data that has focused specifically on patellar lesions has been limited, with relatively short follow-up (15) or small cohorts. (16, 17) Therefore, the purpose of this project was to evaluate the post-operative outcomes over longer follow-ups using data from a multi-centre registry, which we believe reflects real-world clinical experience.

**Methods**

**Study Design**

This study was an analysis of the data of patients who had been treated with AMIC and prospectively enrolled in a registry. The registry is an ongoing, multicenter database designed to longitudinally track changes in function and symptoms in patients who have undergone repair of chondral lesions via this procedure.(18, 19) Documentation was made on electronic case report forms, with surgeons having
access to the registry via a web interface. Surgeons had access to their own patients’ data, whereas the summary and overall performance data were anonymized. All patients were educated in detail about the surgical technique as well as all alternative procedures, including the attendant advantages and disadvantages of each. Thereafter, the patients who chose to undergo AMIC were enrolled in the registry. All patients signed an informed consent to participate in the registry, and all treatment and follow-up examinations followed the standard of care, with no additional visits imposed on the patients. The study was performed in compliance with regulations of the ethical review board of all institutions. Because the registry has no provision for radiographic follow-up, data were not available regarding the development of radiographically verified osteoarthritis.

Patients

Patients were included in this analysis if their retropatellar chondral lesion had been treated via AMIC and they had completed pre- and post-operative measures of knee function and pain. The indication for chondral repair was a symptomatic, circumscribed cartilage lesion on the retropatellar surface, with an Outerbridge classification of grade III or IV. Data were collected at baseline and at each subsequent year, with the longest follow-up currently being 14 years postoperatively. The main exclusion criteria were concomitant surgery at the time of the index procedure (e.g. ACL reconstruction), advanced osteoarthritis, significant narrowing of the joint lines, underlying rheumatic disease, total meniscectomy, or deviation of the mechanical axis of the affected compartment. Baseline data collection included surgical history, lesion size, concurrent procedures, age, BMI, and sex.

Treatment

The operative procedure was performed through either a mini-open approach or arthroscopically, at the discretion of the surgeon. After debridement, bone marrow stimulation was performed using a 1.2mm drill to perforate the subchondral bone plate, typically to a depth of 1 cm, thereby mobilizing bone marrow stem cells into the defect. Care was taken to leave areas of intact subchondral bone plate between the drill holes. The membrane (Chondro-Gide®) was then placed and fixed by either sutures or a fibrin sealant, as previous research has shown these 2 fixation methods to provide equivalent outcomes. (20, 21)

Outcomes Assessment

Therapeutic outcomes were assessed based on KOOS subscales, VAS and Lysholm. Preoperatively and at each subsequent follow-up, patients rated their pain using the VAS, with 0 indicating no pain and 10 indicating the worst pain the patient has known. Functional outcomes were assessed using the Lysholm score and the KOOS, both of which are validated, functional scores. (22, 23) Because the data from this study were based on a registry, which followed standard of care, there were no additional, predefined, clinical follow-up visits. Each clinic had maintained contact with their patients, and actively motivated them to adhere to the follow-up protocol as well as sending follow-up questionnaires to patients. Patients were not financially compensated for their time in completing the data-collection forms.
Statistical Analysis

The outcome variables, KOOS subscales and Lysholm, were evaluated via a factorial analysis of variance (ANOVA) across all time points. Exploratory analyses were conducted to test for relationships between the change in scores from baseline and the patients’ BMI, age and defect size. The *a priori* alpha level was set at $p = 0.05$. Statistical analyses were performed using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium).
Results

The current registry was queried in order to find all patients who had been treated for a patellar, chondral lesion by one of the 5 co-authors. Of the 86 patients that were identified, only those who had pre-operative and at least 1 post-operative outcome measure were included in the statistical analysis. Therefore, we have included 65 patients in this report. The number of patients at each time point is shown in Table 1. As there was only 1 patient at years 11 and 14, these were not included in the statistical analysis.

<table>
<thead>
<tr>
<th>Visit</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td>65</td>
</tr>
<tr>
<td>Year 1</td>
<td>40</td>
</tr>
<tr>
<td>Year 2</td>
<td>24</td>
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<td>Year 6</td>
<td>11</td>
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<td>Year 7</td>
<td>4</td>
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<td>Year 8</td>
<td>6</td>
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<td>Year 10</td>
<td>10</td>
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<td>Year 11</td>
<td>1</td>
</tr>
<tr>
<td>Year 14</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. The number of patients with available data at each time point.

Patient demographics

The mean length of follow-up was $5.8 \pm 3.2$ years. Of the 65 patients that we have included in this analysis, 56 patients have a follow-up of 2 or more years. The patient demographics are presented in Table 2. There were no significant differences when the lesion size, age or BMI were compared relative to the sex of the patient. Of these patients, sport was the most commonly listed cause of the injury, followed by activities of daily living (ADL).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Lesion size (cm²)</th>
<th>Age (years)</th>
<th>BMI</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>32</td>
<td>2.9 ± 1.4</td>
<td>36.1 ± 15.4</td>
<td>24.9 ± 3.2</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
<td>3.1 ± 1.4</td>
<td>33.7 ± 11.6</td>
<td>23.9 ± 5.2</td>
</tr>
</tbody>
</table>

Table 2. The characteristics of the patients that were included in this study.

Lysholm

The Lysholm scores exhibited similar statistical results as were seen for the other tests. There was significant difference in the scores ($P < 0.001$) while the post-hoc tests revealed that the pre-operative Lysholm score was significantly different from all post-operative scores, but there were no significant differences noted between any of the post-operative scores.
KOOS Scores

According to recommendations for use of the KOOS score, (24) we did not take into account the total KOOS in our results but separately evaluated the 5 domains (symptoms, pain, quality of life, sport and leisure and activities of daily life). We noted a significant improvement in all the domains of the KOOS, as depicted in Figure 1. The KOOS score for symptoms improved from a mean of 48.7±23 to a mean of 87.5±12.5 (p < 0.001). The pain subscale improved from a mean of 52.4 ±16.3 to 89.8±13.2 (p<0.001), while quality of life (QoL) more than doubled, going from 26.8±178 pre-op to 83.3±14.6 post-operatively (p<0.001) and sports and leisure activities showed a similarly large improvement, rising from 21.7±14.4 pre-operatively to 85±12.6 post-operatively (p<0.001) while the KOOS domain for activities of daily living (ADL) improved from 55.2±21.2 pre-operatively to 92.6±8.8 post-operatively (p<0.001). The changes in QoL is shown in Figure 2 while the scale for symptoms s depicted in Figure 3.
Pain

Similar to the previous outcomes that have been listed, the VAS score for pain showed a significant difference between the pre-operative mean of 5.7±1.8 and all post-operative scores (p < 0.001). It should be noted that there were no significant differences between any of the post-operative scores.

Regression of delta KOOS vs. defect size

As an exploratory analysis, we plotted the change in Lysholm score relative to the defect size. There was a trend (p = 0.073) towards a relation between the defect size and the improvement in the Lysholm score, as shown in Figure 5. The regression plot that shows the change in Lysholm score relative to the patient's defect size. The data suggested that patients with larger defects exhibited greater changes in Lysholm score at their latest visit.
Responder rate and MCID

In evaluating clinical data, we also considered the minimal clinically important difference in the outcomes. This has been reported to 10.1 points for Lysholm (25). Therefore, among the patients who exceeded the MCID for Lysholm at their last follow-up visit, we noted a responder rate of 0.83 for the Lysholm tests. For the sport and recreation subscale of the KOOS, the responder rate was 0.84.
Discussion

The results of this study, showing a sustained improvement in patient outcomes for several years after surgery, supports the use of the AMIC surgical technique in the treatment of chondral lesions of the patella. We observed a significant improvement, between pre-operative and the post-operative scores related to function (Lysholm and KOOS) as well as a significant reduction in pain (VAS). Among our patients, the improvements in all KOOS subscales, well above the MCID and with a correspondingly high responder rate, indicates that the treatment is an effective means of treating patellar chondral lesions. Importantly, there were no significant differences noted between any of the post-operative time points. It seems apparent that the improvements in the patients’ outcomes are maintained for several years after treatment.

The results that we observed are consistent with our own experience in the knee, in which we noted positive outcomes up to 7 years postoperatively. (19) In that dataset, we had recorded outcomes after treatment of lesions on all articulating surfaces of the knee. While derived from the same registry, the current dataset focuses strictly on the retropatellar surface while also including more surgeons and more patients in the 2+ years since we extracted the previous data from the registry.

In addition to our results, there have been several publications that have detailed positive patient outcomes following AMIC in the knee. Mid-term follow-ups have consistently shown improvements in patient outcomes. (26) A randomized controlled trial (RCT) that compared microfracture to AMIC reported that while AMIC showed a sustained benefit, the outcomes for microfracture patients started to worsen between the 2-year and 5-year follow-ups. (20) Similarly, it was seen in a case-control study with 4-year follow-up that the AMIC procedure for the treatment of patellar chondral defects results in better IKDC and Lysholm scores along with a significant reduction of the VAS score. (27) Additionally, the Tegner scale demonstrated that patients exhibited a higher level of activity after AMIC, relative to microfracture, while the AMIC group evidenced a lower rate of failure. (27) Over a notably longer timespan, an RCT with a follow-up of 9 years reported significant improvements in function and pain when compared to pre-operative levels. (28)

There is no shortage of data concerning cartilage repair in the knee, with numerous peer-reviewed publications concerning the various techniques, whether microfracture (MFx) (29), autologous chondrocyte implantation (ACI) (30), osteochondral allograft transplantation (OAT) (31), matrix autologous chondrocyte implantation (MACI) (32) and mosaicplasty. (33) While a thorough review of these myriad surgical approaches is beyond the scope of this paper, it needs to be stated that there are several choices, each with its own advantages and disadvantages, thus necessitating an objective overview by the clinician with respect to available data concerning clinical outcomes and patient preferences.

Additionally, we took into consideration the minimal clinically important difference (MCID) in the assessment of outcomes. The MCID for Lysholm and VAS has been reported to be 10.1 and 2.7, respectively (25) and among this cohort, we had a responder rate of 0.83, which is somewhat better than the responder rate of 0.7 that was recently reported for ACI. (34) Considering that more patients presented with
injuries resulting from sports activities, we also felt it would be worthwhile to examine the responder rate with regard to the KOOS sport and recreation subscale, with an MCID calculated as 12.5 – 18.6 points. (35) Our patients cohort showed a responder rate of 0.84 for this subscale.

Recent data has noted that concomitant corrective surgery for patellar instability results in low failure rate with satisfactory clinical outcomes at mid-term follow-up. (15) Among the cohort in our study, corrective tibial osteotomies for some patients had been recorded, but the numbers do not allow for a meaningful comparison of outcomes data with regard to this aspect of the procedure. The necessity of physiological knee function, as a component of chondral repair, was clearly emphasized with regard to proper alignment being a critical factor in long-term success of cartilage repair. (36) Indeed, it has recently been stated that cartilage repair without respecting alignment is fruitless. (37)

Certainly, our study is not without limitations. While a registry collects real-world data based on all patients, the follow-up can be problematic. In contrast to an RCT with dedicated time points, the follow-up in a registry simply follows standard of care. As an example, if a patient is unsatisfied with their treatment and they seek treatment elsewhere, then they will be lost to follow-up, thus revisions or even conversions to TKA will not be captured. In the recent study the number of patients who had data at each post-operative time point decreased as time progressed from the baseline evaluation, which is a limitation of the registry and one that would have certainly decreased the power of the statistical analysis. Furthermore, we did not collect radiographs outside of the normal standard of care. Whole an assessment of such images can provide research utility, all of the surgeons would have used imaging as part of the normal treatment, and would have detected any anomalies in the course of treatment.

Conclusion

The complexity and mechanical demands of the patellofemoral joints create a challenging environment for the repair of patellar chondral lesions. The results of our ongoing registry study, in which patients reported significant, sustained improvements in KOOS, Lysholm and VAS, support the use of this surgical technique for the repair of chondral lesions on the retropatellar surface.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACI</td>
<td>autologous chondrocyte implantation</td>
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<tr>
<td>ADL</td>
<td>activities of daily living</td>
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<td>AMIC</td>
<td>autologous matrix-induced chondrogenesis</td>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>KOOS</td>
<td>knee osteoarthritis outcome score</td>
</tr>
<tr>
<td>MACI</td>
<td>matrix-induced autologous chondrocyte implantation</td>
</tr>
<tr>
<td>MCID</td>
<td>minimal clinically important difference</td>
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<tr>
<td>MFx</td>
<td>microfracture</td>
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<tr>
<td>PFJ</td>
<td>patellofemoral joint</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>TKA</td>
<td>total knee arthroplasty</td>
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<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
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References


Declarations

Availability of data and materials
Datasets generated and analysed during current study are not publicly available due to controlled personal data agreement and data security.

Acknowledgements
None.

Authors’ contributions
JG, ER, PB, RJ, TP performed the surgical procedures on the patients in this study. JG wrote the original draft of the manuscript. ER, PB, RJ, and TP reviewed and edited the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable

Ethics approval and consent to participate
The study was performed in compliance with the regulations of the ethical review boards of all participating institutions. All participants provided informed consent prior to their participation in the registry. The conduct of the study, the acquisition, provision and analyses of data in this study are in agreement with the European General Data Protection Regulations and in accordance with the Declaration of Helsinki.

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