Abstract

Introduction

Cartilage damage of the lower limb is a frequent problem and represents a predisposition for osteoarthritis which in consequence leads to a manifest loss of quality of life. The low intrinsic healing capacity of human articular cartilage is a well-known problem in orthopaedic surgery and so a variety of surgical techniques have been developed to treat cartilage defects. The autologous matrix induced chondrogenesis technique combines microfractures with a collagen I/III scaffold (Chondro-Gide®, Geistlich Pharma AG, Switzerland) and represents an established treatment for full-thickness cartilage defects.

This article reviews clinical outcome studies of the autologous matrix induced chondrogenesis technique and gives an outlook on the upcoming modification of this technique.

Discussion

Current studies regarding the autologous matrix induced chondrogenesis technique for treating cartilage defects in the knee, ankle, hip and first metatarsophalangeal joint are presented. All clinical follow-up studies showed a significant increase of functional outcome scores and decline of pain scores.

Conclusion

The autologous matrix induced chondrogenesis technique represents an effective and safe method of treating full-thickness chondral defects of the knee, ankle, hip and first metatarsophalangeal joint in selected cases. Further studies with long-term follow-up are needed whether the grafted area will maintain functional improvement and structural integrity over time.

Pre-clinical rationale

Dickhut et al. 1 demonstrated that a collagen type I/III carrier and fibrin glue (FG) combined to a biphasic collagen type I/III carrier and fibrin glue (FG) combined to a biphasic collagen type I/III/IV carrier and fibrin glue allows MSCs into the adipogenic, chondrogenic and osteogenic lineage and can lead to a manifest loss of quality of life. The low intrinsic healing capacity of human articular cartilage is a well-known problem in orthopaedic surgery and thus a variety of surgical techniques have been developed to treat articular cartilage defects.

Penetration of the subchondral bone by drilling or microfracturing focuses on the recruitment of mesenchymal stem cells (MSCs); these techniques actually represent the most commonly used surgical techniques in cartilage defects. Cartilage regenerative surgery aims at diminishing joint pain, restoring joint function and delaying the onset of osteoarthritis. Bone marrow stimulation methods as the microfracture as well as the edaphic, chondrogenic and osteogenic lineage could be demonstrated by cultivation of MSCs as a monolayer, as micromass bodies or mesenchymal microspheres. This study demonstrates that MSCs

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can be attracted to a cartilage defect by guidance of a collagenous matrix after perforating subchondral bone. Indeed, Kramer et al. were reproducibly able to detect the rapid appearance of human MSCs in the collagenous matrix.

In an ovine model with a follow-up period of 12 months, the average thickness of the repair tissue was significantly greater when a scaffold was used, especially a collagen I/III membrane. No differences were detected when comparing cell-free and cell-laden collagen membrane biomechanically and histologically. Preclinical studies suggest that the AMIC technique leads to the accessibility of the intrinsic cartilage repair resources represented by MS cells in the bone marrow. Animal studies showed an enhanced defect filling and repair tissue of higher quality when a collagen matrix was used.

**Surgical technique**
The AMIC technique is a one-step-procedure based on perforations of the subchondral bone and is an enhanced technique for bone marrow stimulation. The treatment approach is based on a stimulation of MSCs in the bone marrow. After performing a diagnostic arthroscopy the joint is either opened by a miniarthrotomy or surgery is done arthroscopically. The cartilage defect is prepared to the subchondral bone and a stable chondral shoulder is created. Figure 1A–D shows step-by-step an open AMIC procedure. Then the subchondral bone is perforated by an awl or K-wire in gap of 3–5 mm. After that an adjusted collagen I/III membrane (Chondro-Gide®, Geistlich Pharma AG, Switzerland) is fixed in the defect using commercial FG (Baxter-Immuno, Heidelberg, Germany). The joint is held in extended position for 5 minutes before it is flexed 10 times to test the stability and position of the matrix.

AMIC procedures are performed with a miniopen approach, but an all-arthroscopic AMIC procedure has been described for the knee joint. In arthroscopic assisted AMIC, the implantation of the matrix is performed under dry, arthroscopic conditions, as published before. Circular patches of Chondro-Gide are placed in the prepared defect area with Pean clamps. The patches overlap and are fixed with commercial FG.

**Clinical studies**
AMIC has been established and performed in the knee since 2003. There is an increasing interest and experience also for the hip, ankle joint and first metatarsophalangeal joint in the latest years.

**Knee joint**
AMIC is indicated in focal and traumatic chondral and osteochondral lesion grade III–IV (Outerbridge classification). Exclusion criteria are two or more corresponding cartilage defects (‘kissing lesions’), infections of the knee joint, rheumatoid arthritis, total meniskektomie, varus-/valgus malalignment, haemophilia A/B and a known allergy against collagen.

Gille et al. treated 27 patients with overall 32 chondral lesions with the AMIC technique and evaluated these patients in a prospective investigation for up to 5 years after surgery with a mean of 37 months. The mean age was 39 years and defect size was 4.2 cm². Eighty-seven percent of the patients were subjectively highly satisfied and a significant improvement of all used functional outcome scores was found at 2 years after surgery. Magnetic resonance imaging (MRI) analysis showed moderate-to-complete filling in most cases.

In a more recent study, Gille et al. evaluated the data of 57 patients from the AMIC Registry, which is an internet-based tool to longitudinally monitor the final manuscript. All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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**Figure 1:** Intraoperative findings of an open AMIC procedure at the medial femoral condyle. (A) Perforations into the subchondral bone are performed. (B) A template can be cut back to defect size to adjust the scaffold. (C) Application of fibrin glue (Baxter-Immuno, Heidelberg, Germany). (D) The collagen I/III matrix (Geistlich Pharma AG, Switzerland) is applied.
track changes in function and symptoms by the Lysholm score and visual analog scale (VAS)\textsuperscript{9}. The follow-up period was 2 years. A significant decrease of pain in the VAS from a mean of 7.0 preoperatively to 2.7 at 1 year postoperatively and 2.0 at 2 years postoperatively was observed. Improvement of the Lysholm score also showed significant results with a mean score of 50.1 preoperatively, 79.9 at 1 year postoperatively and 85.2 at 2 years postoperatively. Younger patients with no ligamen-tous instability, meniscal deficiency or patellofemoral malalignment exhibited the best outcome\textsuperscript{6-10}.

A current randomised, controlled trial by Anders et al. compared the AMIC technique with microfracture during 1- and 2-year follow-up\textsuperscript{11}. The authors included 38 patients with a mean defect size of 3.4 cm\textsuperscript{2} and mean age of 37 years and randomised them in three groups. One group was treated with microfracture, the others with sutured or glued AMIC. They could assess 30 patients at 1 year and 27 patients at 2 years postoperatively by the modified Cincinnati and the ICRS scores. Furthermore, the authors assessed 29 patients after one and 25 patients after 2 years by MRI to evaluate the defect filling. No significant statistical differences could be found between the three groups but improvements in both scores were seen at 1 and 2 years postoperatively. MRI findings revealed a homogenous defect filling in the majority of patients. It can be concluded that a significant difference was not to be expected within the first 2 years of follow-up. It will be interesting to see, if the AMIC technique will show superiority in the mid- and long-term follow-up, since it is known that results after microfracture can deteriorate with time and particularly if defect sizes are over 2 cm\textsuperscript{2} in area\textsuperscript{2}.

Oheim et al. presented summarised data of the two cohort showing the mid-term results of AMIC in cartilage knee surgery\textsuperscript{12}. Eighty-four patients were evaluated preoperatively by established knee scores (e.g. Lysholm, IKDC) and followed-up to 5 years after initial surgery and in selected cases by MRI. The mean age was 37 years and the mean defect size was 3.4 cm\textsuperscript{2}. The majority of patients were satisfied reporting a significant decrease of pain level. Likewise, the authors could find significant improvements of the mean Lysholm and VAS score after 1 year and further increased values up to 5 years postoperatively (Figure 2).

Kusano et al. presented clinical and radiographic results in a retrospective study with a mean follow-up of 29 months of patients treated with AMIC for full-thickness cartilage defects of the knee\textsuperscript{13}. They found significant improvements in the IKDC, Lysholm, Tegner and VAS pain score. Moreover, the patients were satisfied while the MRI findings showed generally incomplete or inhomogeneous tissue filling.

In comparison to microfractures, drilling does not seem to have such a deleterious effect on the subchondral bone matrix but instead leads to better access to the bone-marrow stroma in the rabbit model\textsuperscript{14}. Following these new findings, the AMIC technique in the knee was modified and drilling instead of microfractures used to penetrate the subchondral layer\textsuperscript{15,16}. An arthroscopic approach of the AMIC technique was published by Piontek et al.\textsuperscript{7}. Compared to open surgery, the described arthroscopic technique may offer advantages including minimal soft tissue trauma and minimal blood loss.

AMIC in the knee has been reported to be an effective and safe method of treating symptomatic full-thickness chondral defects of the knee in appropriately selected cases.

**Ankle joint**
The AMIC technique of the talus was first described in 2008 with good clinical results after an open procedure\textsuperscript{17}. Three years later Simon et al. published the results of an arthroscopic AMIC technique with no need for a medial malleolar osteotomy\textsuperscript{18}. Walther et al. treated 72 patients with osteochondral lesions at the talus (Outerbridge III–IV). In 47 patients additional bone defect filling with autologous bone from the calcaneus was performed. They could show an increase of the American Orthopaedic Foot and Ankle Society (AOFAS) score from 47.3 to 88.3 with a follow-up of 12 months and more. The follow-up MRI also demonstrated good cartilage regeneration\textsuperscript{19}. Valderrabano et al. treated 26 patients with osteochondral lesions of the talus with an AMIC repair consisting of...
debridement, autologous grafting, and covering of the defect with a collagen scaffold. They found a significant improvement in the Score of the AOFAS and the VAS from a mean of 60 points preoperatively to 89 points postoperatively. The MOCART score for cartilage repair tissue on postoperative MRI averaged 62 points. So the authors concluded that the above described modified AMIC procedure is safe for the treatment of osteochondral lesions (OCLs) in the ankle with overall good clinical and MRI results (Figure 3).

In a recent study Wiewiorski et al. assessed cartilage quality using delayed gadolinium-enhanced MRI after repair of osteochondral lesions of the talus using AMIC. The results of 23 patients suggest that repair cartilage resulting from AMIC-aided repair has a significantly lower glycosaminoglycan content than normal hyaline cartilage, but can be regarded as having hyaline-like properties.

**Hip joint**

Leuning et al. described the AMIC technique for chondropathies of the acetabulum or the femoral head as an open procedure by surgical hip dislocation. Recently Fontana published a surgical technique for a fully arthroscopic approach for AMIC at the hip. The same author showed in a retrospective case series of two groups, one treated with AMIC (62 patients) and the other only with microfracture (50 patients), a significant increase of the Harris Hip Score (HHS) at 1 year after surgery. Noticeable was that the AMIC group could maintain the improvements over time while the HHS results in the microfractured group were declining. Fontana also compared 182 patients treated with arthroscopic ACT (120 patients, mean defect size 2.6 cm²) and with AMIC (62 patients, mean defect size 2.8 cm²) with a follow-up of 24 months. In both groups the HHS improved significantly without seeing a difference between the two treatment groups. The authors concluded that the AMIC is as effective as ACT with the advantages of a one-step procedure for the AMIC. In conclusion, the AMIC technique is technically feasible for the hip joint in an open or all-arthroscopic procedure. Preliminary findings after AMIC for femoroacetabular cartilage lesions are promising, but further studies are necessary to elucidate this fact.

**Metatarsophalangeal joint**

Kriegelstein et al. presented a case report describing the treatment of an osteochondral lesion on the head of the first metatarsal bone by use of the AMIC-technique. They found an increased range of motion and pain cessation could be achieved by the procedure. To date, no further studies have been published on this topic.

**Summary**

The limited intrinsic healing potential of human articular cartilage is a well-known problem in orthopaedic surgery. Thus, a variety of surgical techniques have been developed to reduce joint pain, improve joint function and delay the onset of osteoarthritis. The microfracture as a bone marrow stimulation technique is the most common applied articular cartilage repair procedure today. But the deficiencies of fibrocartilaginous repair tissue inevitably lead to...
breakdown under normal joint loading and clinical results deteriorate with time. To overcome the shortcomings of microfracture, Behrens et al. developed an enhanced microfracture technique with a collagen I/III membrane in 2003. The first area of application was the knee joint but meanwhile it is a standard procedure at the hip and ankle joint and has been described for the first metatarsophalangeal joint, too.

First in vitro and animal studies showed an enhanced defect filling and higher quality of the repair tissue when a collagen I/III matrix was used and so the authors concluded that repair tissue formation is encouraged when a collagen I/III matrix is used.

Regarding the AMIC technique in the knee joint several studies could show that this method is an effective and safe method of treating full-thickness chondral defects. In the treatment of the ankle joint with the AMIC technique good early and mid-term results are reported; however, the literature today is limited to case series and reports.

The AMIC technique is technically feasible for the hip joint in an open or all-arthroscopic procedure (Figure 4). Preliminary findings after AMIC for femoroacetabular cartilage lesions are promising, but further studies are necessary to elucidate this fact.

The application of AMIC in the first metatarsophalangeal joint was presented in a case report and showed a very good clinical outcome regarding pain and function and further data are on their way for publication.

AMIC presents an effective and safe method of treating full-thickness chondral defects of the knee, ankle, hip and first metatarsophalangeal joint either by mini open or all-arthroscopic approach.

Definite conclusions about long-term effectiveness of AMIC are not possible. Further studies with long-term follow-up need to prove that the grafted area will maintain functional and structural integrity over time. Recent developments in the surgical technique are subject of actually research. Dohlender et al., e.g. performed a modified so called AMIC plus technique (AMIC plus platelet-rich plasma gel) and were able to show clinical improvements.

Emerging techniques, e.g. the addition of concentrated bone marrow from the iliac crest or platelet rich plasma gel will continue to possibly enhance the AMIC technique.

**Conclusion**

AMIC is an innovative treatment that made its way from ‘bench to bedside’ and is today a well-established surgical procedure for articular cartilage defect therapy in the knee, hip, ankle and first metatarsophalangeal joint. Clinical studies prove a significant decrease of pain and increase of the functional outcome scores after AMIC.

**References**


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**Figure 4:** Intraoperative findings of an all-arthroscopic AMIC technique at the hip. (A) Debridement of the cartilage defect. (B) The matrix, which was trimmed to defect size, is placed in the cartilage defect.

Review


25. Fontana A. Chondrocyte transplantation: ACT or AMIC. Extended Abstract, 8th World Congress of the International Cartilage Repair Society (ICRS), Miami, USA 2009.


