ORTHO SUPERSITE
The Journal of Knee Surgery

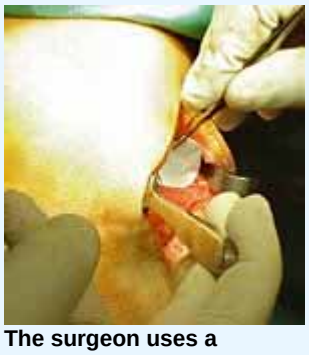
Microfracture meets MACI in hybrid cartilage repair technique

Animal and histology studies paved the way for a multicenter trial on autologous matrix-induced chondrogenesis now underway.

By Susan M. Rapp
ORTHOPAEDICS TODAY INTERNATIONAL 2005; 8:7

May 2005

As clinicians and researchers grapple with innovative ways to regenerate articular cartilage, early work done with a new hybrid cartilage repair technique showed its potential for consistently repairing knee cartilage, according to an investigator. The open procedure combines microfracture with matrix-induced autologous chondrocyte implantation.



The surgeon uses a template to create a properly sized piece of Chondro-Gide collagen matrix and places it in the defect, rough side down.

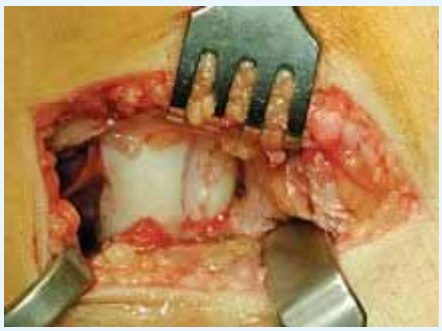
Courtesy of Peter Behrens

Peter Behrens, MD, of the orthopaedic department at Lübeck University Hospital in Lübeck, Germany, developed the autologous matrix-induced chondrogenesis technique (AMIC) a few years ago after German insurance companies stopped reimbursing physicians there for the two-surgery cartilage repair techniques they performed, like autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI).

AMIC's advantage over those procedures, according to Behrens, is it can be completed in a single surgery and, except for involving implantation of an off-the-shelf collagen matrix, it is completely autologous, he told *Orthopaedics Today*.

Microfracture under cover

AMIC is indicated for patients aged 18 to 50 years for treating knee cartilage defects up to 15 cm^2 located anywhere in the knee — on the medial/lateral condyle, trochlea or patella.



The collagen matrix is glued in place with fibrin glue mixed with the patient's serum or anchored with a few stitches prior to closing the incision.

After confirming the lesion location and size with an arthroscope, the surgeon performs an arthrotomy of a size corresponding to the lesion size. He or she then trims away any loose cartilage and, with a sharp awl or pick, performs microfracture to penetrate the subchondral bone and stimulate production of mesenchymal stem cells (MSC) at the site.
The surgeon next applies an acellular collagen type I/III matrix (Chondro-Gide, Geistlich Biomaterials) cut to the contours of the defect, which protects the newly activated cells and stabilizes the area. He or she fixes it with fibrin glue mixed with 10 mL of the patient's blood serum, a mixture Behrens calls partial autologous fibrin glue or PAF. Behrens said he occasionally sutures the matrix to anchor it.
To finish, the surgeon closes the arthrotomy incision in layers using a standard technique. Following surgery, patients keep their knees immobilized in extension for seven days and then begin performing continuous passive motion exercises for six weeks. They are nonweight-bearing for six weeks.

Let the healing begin

According to Behrens, two aspects of the AMIC procedure make it particularly reparative. The MSCs bind to the matrix, which keeps them near the defect site throughout healing and during matrix resorption. It is theorized that with ACI, for example, cell loss or apoptosis occurs and using AMIC helps avoid this, he said. In addition, the PAF may foster improved repair since it is packed with transforming growth factors-beta (TGF-ß).
"TGF-ß is one of the factors which can modulate the MSCs in the direction to become more chondrocytes. And, now you have a cover on top of all of this. It's like a hamburger, like a sandwich, and the cells that are coming out get in contact with the matrix," he said.

A single surgery

Biologically what happens with the hybrid AMIC procedure in vivo is similar to what occurs with MACI treatment, the cartilage-repair technique Behrens developed. With MACI, however, the cell source differs, with replacement cells being harvested from the patient's intact knee cartilage and cultured off-site rather than being produced through microfracture.
With AMIC "you do this directly in the knee. It's only one operation and you can do it whenever you want," he said. The matrix might be stocked at the surgical center and used as needed, like any other piece of surgical equipment. "If you see there's a defect, you take it out and you go forward with it," said Behrens, who started performing AMIC in 2002.
Gunnar Knutsen, MD, who has studied microfracture and ACI extensively, told *Orthopaedics Today*, "Some investigators have combined microfracture with a covering membrane. This is also very interesting; microfracture may release stem cells and the membrane gives them protection." Knutsen, a consultant orthopaedic surgeon at University Hospital North Norway in Tromso, Norway, said he used ACI, but not the MACI or AMIC techniques.

During autologous matrix-induced chondrogenesis (AMIC), the surgeon performs microfracture to perforate the subchondral bone plate beneath a femoral lesion.

Courtesy of Peter Behrens

Used internationally

To date, surgeons worldwide have done about 100 AMIC procedures. Most use the Chondro-Gide collagen product as their matrix, which Behrens has used and studied for years. Surgeons and patients in Germany, Italy, Switzerland and South Africa are participating in a randomized multicenter clinical trial into the AMIC technique.

In Germany, AMIC costs approximately 800 Euros compared to about 4000 Euros for ACI or MACI procedures, he said. “This new … autologous regenerative technique is much cheaper; no special cell transplantation is necessary and only one operation.”

Research that Behrens conducted helped confirm his theory that AMIC might improve on techniques that use periosteal flaps as the defect-covering step, such with the highly popular ACI procedure. Following a sheep study, he and his co-authors, including Myron Spector, PhD, concluded that the periosteum did not affect the cartilage repair process.

Instead, they found it appeared to stimulate an unexplained but statistically significant bone density increase beneath the sheep’s cartilage when used during an ACI-like procedure (P<.0001; power=1). In those defects covered by periosteal flaps, they found the subchondral bone was 45% to 70% denser than normal; remodeling they attributed to being caused by the periosteum. Because these bone changes increase the stress in the cartilage, researchers think this process could have a degenerative effect on any newly repaired cartilage.

Chondro-Gide is an acellular porcine collagen matrix used as a defect/cell covering for some autologous chondrocyte implantation procedures and autologous matrix-induced chondrogenesis. It is manufactured by Geistlich Biomaterials, Wolhusen, Switzerland.

Periosteum performance

Spector, in the department of orthopaedic surgery at Brigham and Women’s Hospital and Harvard Medical School in Boston, commented on the findings: “What has come out of that work would suggest that there is no benefit of the periosteum as some people had speculated. The fact that one gets the same cartilage repair using an off-the-shelf acellular collagen membrane would suggest the cells of the periosteum are not contributing to the chondrogenic process.”

Spector described the researchers' highly unexpected finding concerning bone changes as "dramatic densification of subchondral bone. The clinical sequelae, the potential problems, are that when you have dense bone under cartilage it places that cartilage at risk for breakdown because of the increased mechanical stress in the cartilage," he said.

Why this occurs is unknown, but Spector theorized the bone-specific periosteal cells "may be releasing factors to stimulate this subchondral bone densification." Whatever the cause, anything that might reduce the cushioning effect on cartilage should be avoided, since it might contribute to the onset of osteoarthritis, he said.

Instead of using the periosteum, "it's probably better to look for an alternative."

Drs. Behrens and Spector have a financial interest in the product mentioned in this article and are paid consultants to its manufacturer.

For more information:

- Russlies M, Behrens P, Ehlers E-M, et al. Periosteum stimulates subchondral bone densifications in autologous chondrocyte transplantation in a sheep model. *Cell Tissue Res.* 2005; 319:133-142.