TREATMENT OF DEEP CARTILAGE DEFECTS IN THE KNEE WITH AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

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Abstract *Background.* Full-thickness defects of articular cartilage in the knee have a poor capacity for repair. They may progress to osteoarthritis and require total knee replacement. We performed autologous chondrocyte transplantation in 23 people with deep cartilage defects in the knee.

Methods. The patients ranged in age from 14 to 48 years and had full-thickness cartilage defects that ranged in size from 1.6 to 6.5 cm^2. Healthy chondrocytes obtained from an uninvolved area of the injured knee during arthroscopy were isolated and cultured in the laboratory for 14 to 21 days. The cultured chondrocytes were then injected into the area of the defect. The defect was covered with a sutured periosteal flap taken from the proximal medial tibia. Evaluation included clinical examination according to explicit criteria and arthroscopic examination with a biopsy of the transplantation site.

Results. Patients were followed for 16 to 66 months (mean, 39). Initially, the transplants eliminated knee locking and reduced pain and swelling in all patients. After three months, arthroscopy showed that the transplants were level with the surrounding tissue and spongy when probed, with visible borders. A second arthroscopic examination showed that in many instances the transplants had the same macroscopic appearance as they had earlier but were firmer when probed and similar in appearance to the surrounding cartilage. Two years after transplantation, 14 of the 16 patients with femoral condylar transplants had good-to-excellent results. Two patients required a second operation because of severe central wear in the transplants, with locking and pain. A mean of 36 months after transplantation, the results were excellent or good in two of the seven patients with patellar transplants, fair in three, and poor in two; two patients required a second operation because of severe chondromalacia. Biopsies showed that 11 of the 15 femoral transplants and 1 of the 7 patellar transplants had the appearance of hyaline cartilage.

Conclusions. Cultured autologous chondrocytes can be used to repair deep cartilage defects in the femorotibial articular surface of the knee joint. (N Engl J Med 1994; 331:889-95.)

FULL-THICKNESS defects of articular cartilage in the knee may progress to osteoarthritis. In 1743 Hunter[1] stated, "From Hippocrates to the present age it is universally allowed that ulcerated cartilage is a troublesome thing and that, once destroyed, is not repaired." Articular cartilage defects are still a practical problem, especially in younger patients, and correlate with pain and joint dysfunction.[2]

Injuries of the knee cartilage leading to osteoarthritis include lesions disrupting both cartilage and subchondral bone (osteochondral lesions) and lesions limited to the cartilage tissue (chondral lesions). Chondral and osteochondral lesions are both common after trauma.[3-6] Repeated minor trauma, as well as overt injury of the knee, can cause osteoarthritis.[7-9]

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Presented at the first meeting of the Osteoarthritis Research Society, Paris, Dec. 10–12, 1992.

Supported by grants from the Lundberg Foundation, Swedish Medical Research Council, Trygg Hansa Research Foundation, King Gustaf V Eightieth Birthday Fund, and Assar Gabrielsson Research Foundation.

When osteoarthritis is severe, the usual treatment is replacement of the arthritic articular surface with an artificial prosthesis. Total knee replacement is most commonly performed in people over 60 years of age. Treatment of younger patients (under the age of 50 years) is more troublesome, because the prostheses have a limited lifetime.[10,11] Transplanted heterologous or autologous chondrocytes,[12-14] periosteum, perichondrium,[15,16] and osteochondral grafts are potential treatments for focal articular cartilage defects. These approaches have been studied in animals. A 1984 study in rabbits reported successful treatment of focal patellar defects with the use of transplanted cultured autologous chondrocytes.[17] The cultured chondrocytes were injected under a periosteal flap sutured over the defect. One year after transplantation, newly formed cartilage-like tissue typically covered about 70 percent of the defect.[18,19] Encouraged by these results, we used chondrocyte transplantation to treat 23 patients with deep cartilage defects in their knees.

METHODS

The transplantation procedure is outlined in Figure 1. The study was approved by the ethics committee of the Medical Faculty, University of Göteborg. In accordance with Swedish law, patients

Reprinted from the *New England Journal of Medicine*
331:889-895 (October 6), 1994

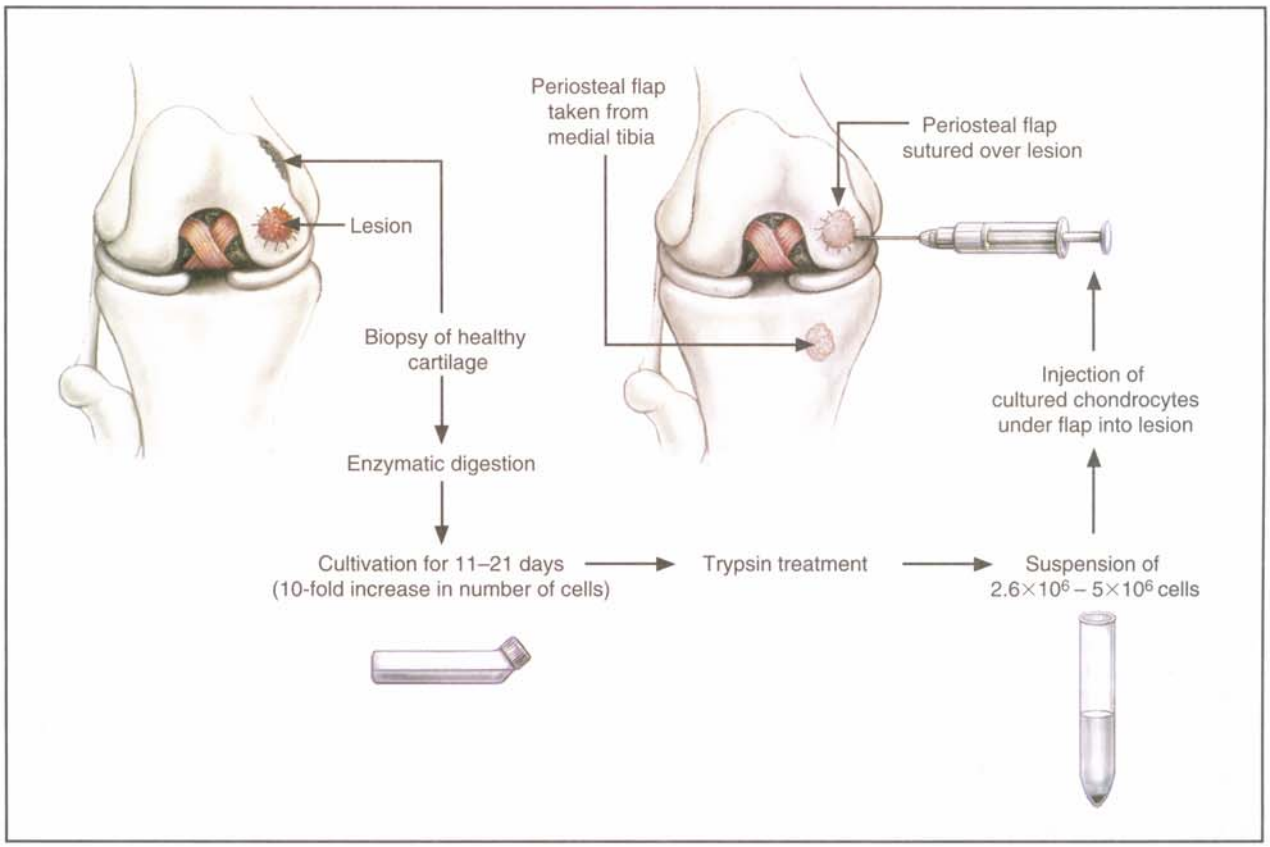


Figure 1. Diagram of Chondrocyte Transplantation in the Right Femoral Condyle.
The distal part of the femur and proximal part of the tibia are shown.

were informed of the nature of the study and gave their oral consent. All patients had cartilage defects down to, but not through, the subchondral bone, on a load-bearing surface of the femoral condyle or the patellar facet (Fig. 2A), with disabling symptoms of the knee, including locking, localized pain, swelling, and retropatellar crepitus.

Twenty-three patients (11 men and 12 women) with a mean age of 27 years (range, 14 to 48) were treated for a mean period of 44 months (range, 12 to 120) after the initial arthroscopic detection of the injury (Fig. 3A). Thirteen patients had defects of the femoral condyle primarily due to trauma, and three had localized osteochondral lesions due to abnormalities of the underlying bone (osteochondritis dissecans). The other seven patients had painful defects of the patellar facet: six had chondromalacia patellae (grade IV, according to the Outerbridge classification[20]), and one had a defect of traumatic origin. The defects ranged in size from 1.6 to 6.5 cm^2 (mean, 3.1). Ten of the patients had previously undergone shaving and débridement of fibrillated cartilage and unstable chondral flaps, with a transient improvement in symptoms.

Isolation and Culture of Chondrocytes

With the patients under general anesthesia, surgery was performed in a tourniquet-controlled, bloodless field. Cartilage slices (weight, 300 to 500 mg) were obtained through an arthroscope from a minor load-bearing area on the upper medial femoral condyle of the damaged knee.

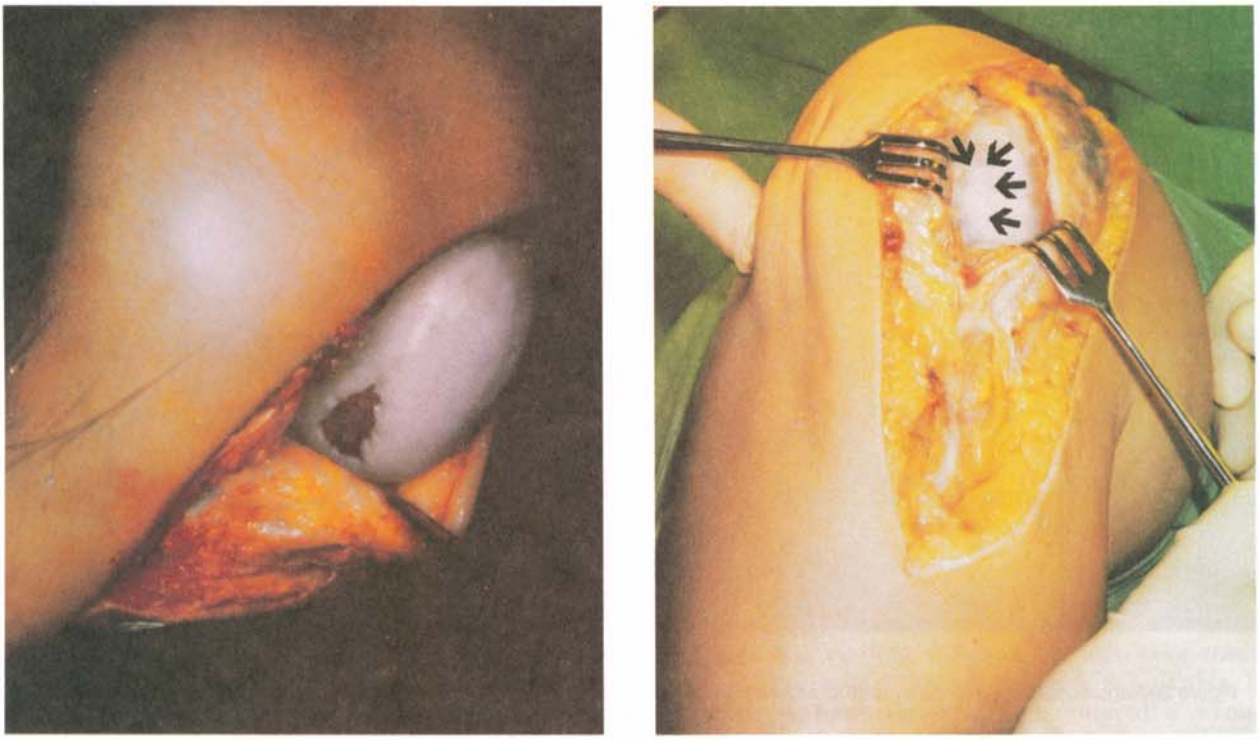
The cartilage was placed in chilled sterile 0.9 percent (weight per volume) sodium chloride. Cells were isolated within two to five hours. Cartilage specimens were minced and washed three times in culture medium containing Ham's F12 medium supplemented with HEPES buffer (10 mmol per liter), gentamicin sulfate (50 μg per milliliter [approximately 70 μmol per liter]), amphotericin B (2 μg per milliliter [2.2 μmol per liter]), and L-ascorbic acid (50 μg per milliliter [300 μmol per liter]). The minced cartilage was digested for 16 hours in a spinner bottle in 10 ml of culture medium containing clostridial collagenase (1 mg per milliliter [150 U per liter]) and deoxyribonuclease I (0.1 mg per milliliter [25,000 U per liter]). The cells were then filtered through nylon mesh with a pore diameter of 25 μm, washed three times, counted (range, 180,000 to 455,000 cells), resuspended in culture medium supplemented with 15 percent of the patient's serum (autologous serum), and seeded at a cell density of 5000 to 10,000 cells per square centimeter in 25-cm^2 or 75-cm^2 culture flasks (Costar, Cambridge, Mass.).

The culture medium was changed twice weekly and tested for bacterial growth on blood-agar plates after one week. During the 24 hours before culturing, antibiotics were omitted from the culture medium so that bacterial contamination, if present, would be more likely to be detected.

Transplantation took place 14 to 21 days after the initial surgery. Chondrocytes were suspended by means of treatment with trypsin, pelleted in a centrifuge, and washed three times in culture medium supplemented with 20 percent autologous serum. After the last centrifugation, the cell suspension was aspirated into a 1-ml tuberculin syringe (Terumo, Leuven, Belgium) with a 1.2-mm needle. The final volume of the cell suspension was 50 to 100 μl, with a total of 2.6 million to 5 million cells. The chondrogenic phenotype (determined by microscopical evaluation of clonal growth and metachromatic staining) was studied in a minor fraction of the isolated cells, which were placed in a suspension culture stabilized with agarose for three weeks.

Transplantation of Chondrocytes

Prophylactic antibiotics were given intravenously in three doses over a 24-hour period during and after the surgery. Most of the patients received cloxacillin (1 g given three times). Patients who were allergic to penicillin received clindamycin (600 mg given three



A B

Figure 2. Results of Autologous Chondrocyte Transplantation in a 22-Year-Old Woman (Patient 9).
Panel A shows the cartilage defect in the medial femoral condyle before cell transplantation. Panel B shows the defect (1.1 by 4.0 cm) 46 months after transplantation. The borders of the transplant are indicated by the arrows. Knee surgery was performed at 46 months because of patellar trauma that was unrelated to the transplantation.

times) instead. With the patients under general anesthesia, a medial or lateral parapatellar arthrotomy was performed in a tourniquet-controlled, bloodless field. The chondral lesion was excised as far as the normal surrounding cartilage but not as far as the subchondral bone plate. The cartilage defect was covered with a periosteal flap taken from the proximal medial tibia. The flap was sutured to the surrounding rim of the normal cartilage with interrupted 5-0 Dexon sutures. The cultured chondrocytes were injected beneath the periosteal flap. The joint capsule, retinaculum layer, and skin were sutured in separate layers. The knee was covered with a small elastic bandage. Active movement of the knee without weight bearing was initiated two to three days after surgery. Weight bearing was gradually introduced and increased to the full extent, with isometric quadriceps training, during the first eight weeks after surgery.

Evaluation

Patients were evaluated every 8 to 12 weeks, and the condition of the knee was graded as excellent (no pain, swelling, or locking with strenuous activity), good (mild aching with strenuous activity but no swelling or locking), fair (moderate pain with strenuous activity and occasional swelling but no locking), or poor (pain at rest, swelling, and locking).

Postoperative arthroscopy was performed 3 months after the surgery and was repeated 12 to 46 months after the surgery. The hardness of the transplant was tested with the tip of a probing hook, and the extent of repair of the tissue was documented macroscopically on videotape. The gross appearance was considered biologically acceptable if the cartilage defect was filled with cartilaginous tissue that was in contact with, as well as level with, the surrounding articular cartilage.[21]

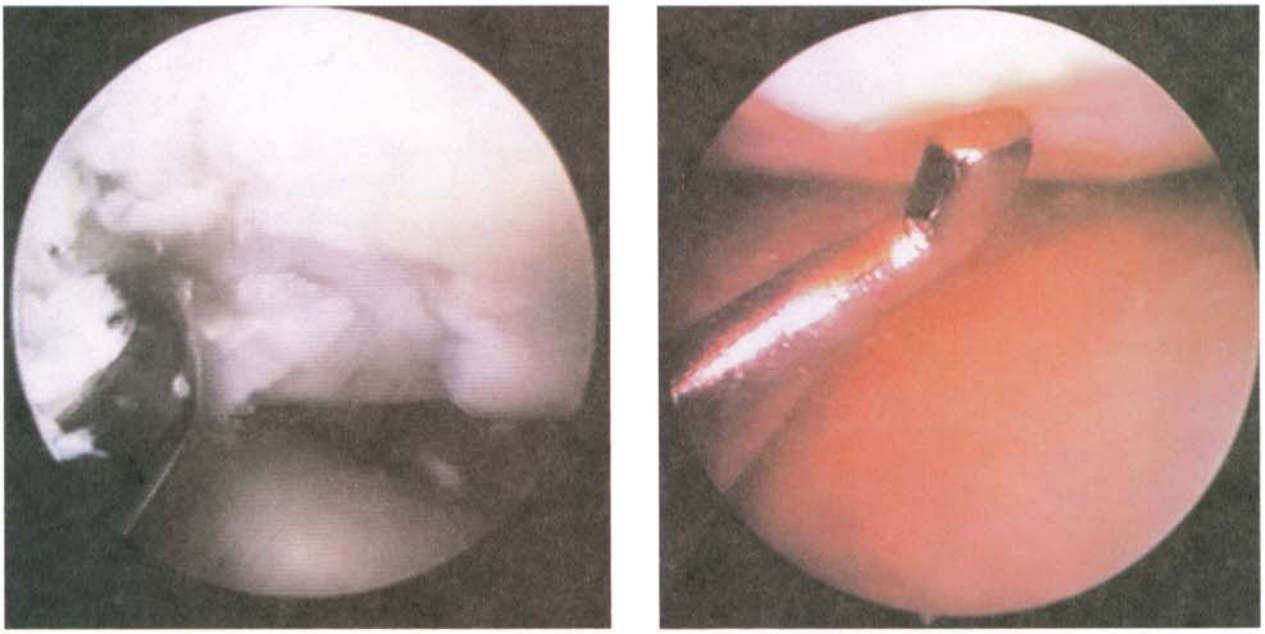
During the second arthroscopic procedure, biopsy specimens extending to the subchondral bone were taken from the central part of the transplant. The specimens were fixed in 5 percent formaldehyde, embedded in paraffin, sectioned, and stained with Weigert's iron hematoxylin, van Gieson's solution, and Alcian blue. The articular cartilage appeared red with this staining. Histologic sections were coded and examined by a pathologist who was unaware of the study.

Immunohistochemical staining for type II collagen was performed in biopsy specimens from five patients (Patients 11, 13, 14, 15, and 16) (Table 1). Normal articular cartilage was used as a positive control, and periosteum as a negative control. The first antibody was omitted to control for nonspecific binding of the second antibody. Three monoclonal antibodies were tested (CIIB1, CIIC1, and CIIC2; courtesy of Professor L. Klareskog, University of Uppsala, Uppsala, Sweden). These antibodies recognize three different epitopes on native type II collagen[22] (data not shown).

Results

The results of chondrocyte transplantation in the 16 patients with femoral defects are summarized in Table 1, and the results of transplantation in the 7 patients with patellar transplants are summarized in Table 2. The cells placed in agarose cultures demonstrated clonal growth with metachromatic staining of the surrounding matrix (data not shown). None of the cell cultures contained bacteria or fungi, and none of the patients had knee infections after the transplantation.

The patients were followed for 16 to 66 months (mean, 39). In all the patients, knee pain, swelling, and crepitation were considerably reduced, and knee locking completely disappeared. The initial arthroscopy, performed three months after the transplantation,



A B

Figure 3. Arthroscopic View of a Femoral Condylar Defect before Transplantation (Panel A) and 22 Months after Transplantation (Panel B) in a 40-Year-Old Man (Patient 7).

showed regenerated areas of cartilage with visible borders that were level with the surrounding articular surface. The color and texture of the transplanted area were similar to those of the surrounding, undamaged cartilage. In the central area of the transplant, a soft indentation, without subchondral bone contact, was felt with probing. In most cases, there were wavelike movements of the transplant area when it was probed, suggesting that the transplant was loosely attached to the underlying bone. In Patient 1, the condylar transplant, which had loosened, was sutured to the surrounding articular cartilage six months after the initial surgery. Ten months later, one third of the transplant was removed, because it was still loose and causing locking of the knee.

Table 1. Femoral Condylar Defects in 16 Patients Treated with Transplanted Chondrocytes.*

Patient No.	Age (yr)/ Sex	Duration of Symptoms (yr)	Size of Defect (cm^2)	Macroscopic Appearance	Histologic Appearance	Biopsy (mo)†	Duration of Follow-up (mo)	Clinical Grade
1	27/M	3	1.6	Not BA	FH	16	16	Poor (2nd operation)
2	24/M	3	2.0	BA, CW	FH	14	48	Good
3	22/M	2	3.0	Not BA, CW	FH	12, 36	36	Poor (2nd operation)
4	48/F	3	3.0	BA, CW	FH	12, 24	48	Good
5	14/F	2	2.0	BA	HL	12, 46	46	Good
6	25/F	1	1.6	BA	HL	12	55	Excellent
7	40/M	3	2.2	BA	HL	22	59	Excellent
8	46/M	2	2.0	BA	HL	16	48	Good
9	22/F	3	4.0	BA	HL	12, 46	46	Excellent
10	26/M	3	2.4	BA	HL	12	36	Excellent
11	27/M	4	2.5	BA	HL	12	54	Good
12	27/F	2	2.0	BA	No biopsy	—	36	Good
13	23/M	6	5.0	BA	HL	17	24	Good
14	18/F	6	4.4	BA	HL	12, 32	32	Good
15	32/F	3	4.5	BA	HL	12	27	Excellent
16	19/M	2	4.0	BA	HL	12, 36	36	Excellent

*Patients 3 and 11 had injuries of the lateral femoral condyle, and all other patients had injuries of the medial femoral condyle. The follow-up period for Patients 1 and 3 ended at the time of the second operation. BA denotes biologically acceptable, FH fibrous hyaline cartilage, CW central wear, and HL hyaline-like cartilage.

†Mo refers to the number of months after transplantation.

Femoral Condylar Transplants

Two years after transplantation, 14 of the 16 patients had results that were graded either excellent (in 6 patients) or good (in 8). The two patients followed for the longest period had excellent results 55 and 59 months after transplantation. The second arthroscopy, performed 12 to 46 months (mean, 24) after transplantation, showed that in the 14 patients with excellent or good results, the transplants had a biologically acceptable gross appearance with visible borders and were level with the surrounding articular cartilage (Fig. 3B). The transplants and the surrounding cartilage felt similarly firm when probed, and wavelike movements of the transplants were no longer observed.

In Patients 1 and 3 (Table 1) severe central wear developed in the transplants, with locking of the knee and pain, 14 and 11 months, respectively, after transplantation. Both patients required a second operation. Degenerative tissue was débrided and resurfaced with subchondral drill holes filled with carbon-fiber implants.[23] Six months

Table 2. Patellar Defects in Seven Patients Treated with Transplanted Chondrocytes.*

Patient No.	Age (yr)/ Sex	Duration of Symptoms (yr)	Size of Defect (cm^2)	Macroscopic Appearance	Histologic Appearance	Biopsy (mo)†	Duration of Follow-up (mo)	Clinical Grade
17	27/F	10	1.6	BA	HL	17	66	Excellent
18	17/M	4	3.0	BA	FH	26	26	Poor (2nd operation)
19	22/F	4	2.5	BA, CW	FH	12	37	Fair
20	24/F	3	3.8	BA, CW	FH	29	54	Fair
21	32/F	4	3.1	Not BA	FH	24	24	Poor (2nd operation)
22	28/M	6	4.0	BA	FH	15	24	Fair
23	31/F	6	6.5	BA, CW	FH	12	24	Good

*Patients 17 through 22 had chondromalacia patellae, and Patient 23 had a cartilage defect due to trauma. The follow-up period for Patients 18 and 21 ended at the time of the second operation. Abbreviations are explained in the footnote to Table 1.

†Mo refers to the number of months after transplantation.

after this additional surgery, the results in both patients were graded fair. The knee joint in Patient 9 (Table 1) was opened 46 months after transplantation because of a patellar injury, unrelated to the treated defect, which caused recurrent instability. The transplant was slightly whiter than the surrounding articular cartilage and when probed had a resistance to pressure similar to that of the surrounding cartilage (Fig. 2B). This patient underwent surgical realignment of the patella, and six months later the results were graded excellent.

Biopsy specimens were obtained from 15 of the 16 patients with femoral transplants. The specimens from 11 of the patients had an intact articular surface and a hyaline appearance, with chondrocytes in lacunae and metachromatic staining comparable with that of the surrounding cartilage (Fig. 4). These findings indicate that the transplanted cells and the periosteum were able to regenerate normal hyaline cartilage in the area of the defect. In most of the biopsy specimens, remnants of the periosteal tissue were seen close to the articular surface. Specimens from four patients contained areas of irregular fibrous tissue surrounded by more hyaline-like tissue. The results of immunohistochemical testing for type II collagen in biopsy specimens from five patients were positive, and the results in the control specimens were negative (data not shown).

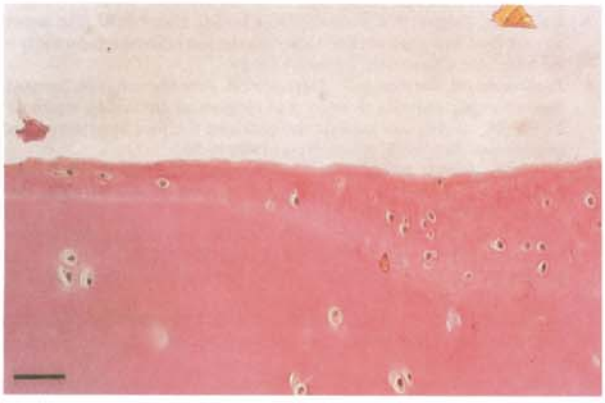


Figure 4. Histologic Section from a Biopsy Specimen Obtained 36 Months after Surgery in a 19-Year-Old Man with a Femoral Condylar Defect (Patient 16).

The articular surface is at the top of the section, with newly formed cartilage in the lower part of the section and a thin layer of remaining periosteal tissue in between. The cartilage defect was approximately 4 mm deep before transplantation (Weigert's iron hematoxylin, van Gieson, and Alcian blue). The scale bar represents 100 μm.

Patellar Transplants

The results of transplantation in the seven patients with patellar defects were graded excellent or good in two, fair in three, and poor in two at a mean follow-up of 36 months (range, 24 to 66) after transplantation. Five patients had improved knee function after the transplantation, largely because they had no locking. The second arthroscopic procedure (performed a mean of 19 months after surgery) revealed an acceptable gross appearance of the transplants in three of these five patients and central wear in two. The two patients with poor transplantation results (Patients 18 and 21) (Table 2) had severe chondromalacia and required a second operation with débridement and surgical resection of the failed graft and subchondral bone combined with the implantation of carbon-fiber pads[23] 16 and 24 months, respectively, after transplantation. The results in these two patients were fair six months after surgery.

Only one of the seven patients with patellar transplants had a biopsy specimen with an intact articular surface and a hyaline appearance with metachromatic staining comparable with that of the surrounding cartilage. The biopsy specimens from the other six patients had central areas of irregular fibrous tissue surrounded by more hyaline-like tissue.

Discussion

More than 500,000 arthroplastic procedures and total joint replacements are performed each year in the United States, including about 95,000 total knee replacements and 41,000 other procedures to repair defects of the knee.[24] If the treatment of cartilage injuries of the knee at an early stage could prevent the development of osteochondritis, the need for a total joint replacement might be postponed or eliminated.

We performed autologous chondrocyte transplantation in 23 patients with isolated defects of knee cartilage due to trauma or osteochondritis dissecans. After three years of follow-up, the transplants restored considerable knee function in 14 of the 16 patients with femoral defects. The treatment resulted in the formation of new cartilage that was similar to normal cartilage in that it had an abundance of type II collagen and metachromatically stained matrix. The detection of immunoreactivity to type II collagen in biopsy specimens from the regenerated tissue is an important finding; type II collagen fibers, unlike type I fibers, are critical for the macromolecular frame-

work of the extracellular matrix that gives articular (i.e., hyaline) cartilage its unique biomechanical properties.

The results in the seven patients with patellar transplants were disappointing. Five patients had improved joint function, but only two had a good or excellent outcome.

To minimize the potential side effects of the treatment, we used autologous chondrocytes cultured in autologous serum. Studies of transplantation in animals with the use of allogeneic chondrocytes have had conflicting results; immunologic rejection of the transplant is possible.[25-28] The use of autologous chondrocytes also minimized the likelihood of transmitting infectious diseases.

The chondrogenic cells in the transplant may be able to repair cartilage more efficiently than the chondrocytes at the margin of the injured cartilage. The culturing procedure increased the number of chondrocytes initially isolated by 10 to 20 times. A fraction of the cultured cells were able to reexpress their chondrogenic phenotype, after the use of culturing procedures known to facilitate the production of cartilage matrix. These results are similar to those obtained with the use of rabbit articular chondrocytes in a similar culture protocol.[29]

Articular resurfacing techniques that have been used to help repair cartilage include subchondral drilling, abrasion, and the procedure termed "spongialization" (excision of diseased patellar cartilage and subchondral bone, leaving well-vascularized cancellous bone exposed).[30-32] The tissue that results from these reparative techniques is disorganized fibrocartilaginous tissue with type I collagen fibers[33,34] that is unable to restore the biomechanical properties of normal articular cartilage.[35]

The use of periosteal or perichondrial grafts as a treatment for localized cartilage defects in animals has resulted in the formation of chondroid tissue with metachromatic staining of the extracellular matrix.[36,37] However, the results of transplantation with both periosteum and perichondrium are inconsistent.[16,38,39]

In our study the treatment of chondromalacia patellae (in which the defect of the cartilage is confined to the patella) was less successful than the treatment of femoral condylar defects caused by trauma. One possible explanation is that the patellar defects we treated had different causes — that is, malalignment of the patellae with a lateral hyperpressure syndrome, patellar lateral subluxation, osteochondral injury, osteoarthritis,[40] or greater contact stress in the patellofemoral joint than in the tibiofemoral articulation. The correction of underlying joint abnormalities concomitantly with the transplantation of chondrocytes may improve the success rate for patients with patellar defects. Similar considerations apply to cartilage injuries with ligament instability in the femorotibial compartment.

The mechanism of the repair process is unknown. The biopsies indicate that new cartilage is formed close to the underlying calcified cartilage and bone and is clearly distinguishable from remnants of the periosteum. There are at least three theoretical explanations for the repair process. One explanation is that the transplanted cells consist of chondrocytes that are able to repopulate the area of the defect and produce new cartilage matrix; the function of the periosteum is only to seal off the defect. A second explanation is that the periosteum stimulates the replication of the transplanted cultured chondrocytes. A third explanation is that the periosteum and transplanted cells stimulate chondrocytes in the surrounding cartilage or cells in the deep noncalcified and calcified layers of the articular cartilage or in the periosteum itself to enter the area of the defect, divide, and repair the defect. The importance of the transplanted cells to the repair process is supported by previous studies in rabbits, which showed that periosteum alone could not repair defective cartilage.[17-19]

Our results indicate that cultured autologous chondrocytes can be used to repair articular cartilage defects in the femorotibial joint and that this treatment restores the function of the joint by forming predominantly hyaline-like cartilage containing type II collagen.

We are indebted to Drs. Howard Green, Ben Bronstein, and Jim Rheinwald for their critical comments and helpful suggestions.

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