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EXHIBIT SELECTION

Bipolar Fresh Total Osteochondral Allograft: Why, Where, When

AAOS Exhibit Selection

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Severe posttraumatic arthritis poses a reconstructive challenge in young, active patients. Surgical treatment typically relies on arthroplasty or arthrodesis. Nevertheless, the inevitable loosening of joint arthroplasty components over time, the nonapplicability of arthrodesis to some anatomical regions, and the possible nonacceptance of these treatments by the patient have led to a search for a biological method of articular cartilage repair.

Complete substitution of a damaged joint represents a possible solution. Frozen allografts have been widely used in limb salvage surgery following major trauma or resection of malignant bone tumors, alone or in association with a prosthesis[1,2]. Disadvantages of these allografts include absence of chondrocyte survival, reduced healing potential, and fractures. Bipolar fresh total osteochondral allograft is intended to provide viable articular cartilage that can survive the transplantation and possesses a thin osseous component that is progressively integrated by the host[3]. Although there is general agreement on the validity of the use of partial allografts, such allografting has been proposed primarily in the ankle joint, with controversial results; to our knowledge, only single case reports have described its applicability to the knee and shoulder[4-9].

The primary aim of the present study was to describe the application of fresh total osteochondral allograft to the shoulder, knee, ankle, and first metatarsophalangeal joints, including clinical and imaging results at a mean follow-up of four years. An overview of factors influencing the outcome is also provided. The secondary aim was to investigate the integration process of the graft and the capability of the host to recolonize the newly implanted joint up to the cartilage layer, using both genotyping and gene expression analysis.

Materials and Methods

The study was approved by the ethical committee of our institution, and informed consent was obtained from all patients. Seventy-one patients (mean age [and standard deviation], 37.3 ± 10.2 years) underwent bipolar allografting for end-stage arthritis of the shoulder (three patients), knee (seven patients), ankle (fifty-seven patients), or first metatarsophalangeal joint (four patients, two treated bilaterally) (Table I).

The most common indication for bipolar allografting was end-stage arthritis of posttraumatic origin in patients younger than fifty years of age. However, the allografts in one knee and one ankle were used for conversion of a prior arthrodesis, and the allografts in three patients who had hallux rigidus and were older (51.0 ± 18.6 years) than the series as a whole were used to treat primary arthritis. A rheumatologic disease, osteoporosis, osteonecrosis, untreated limb malalignments, and infection of the affected joint were contraindications to surgery. For the shoulder, rotator cuff disease was an exclusion criterion.

Patient evaluation included clinical and radiographic assessment preoperatively; at one, two, four, six, and twelve months postoperatively; and annually thereafter. Clinical follow-up was performed with use of outcome instruments specific for each anatomical site: the Constant score for the shoulder, IKDC (International Knee Documentation Committee) form for the knee[10], and AOFAS (American Orthopaedic Foot & Ankle Society) score for the ankle and the first metatarsophalangeal joint[11]. Range of motion was measured at

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TABLE I Demographics

Joint	No. of Patients	Age* *(yr)*	Sex	Time from Harvest to Implantation* *(d)*	Follow-up* *(mo)*
Shoulder	3	44.0 ± 3.6	2 M, 1 F	14.0 ± 1.0	34.6 ± 4.0
Knee	7	38.3 ± 8.9	5 M, 2 F	14.0 ± 1.8	48
Ankle	57	35.5 ± 7.9	41 M, 16 F	13.2 ± 2.8	47.3 ± 16.7
1st MTP†	4 (2 bilateral)	51.0 ± 20.2	4 F	13.8 ± 1.5	57.0 ± 3.5

*The values are given as the mean and the standard deviation. †First metatarsophalangeal joint.

the final follow-up visit and was expressed as a percentage of the normal value for the joint. Preoperative computed tomography (CT) scans of the patient and the graft were made in all but one case (a metatarsophalangeal joint) to identify the matching allograft size. A CT scan was also made four months after surgery to verify the allograft integration process. Magnetic resonance imaging (MRI) was performed six months after surgery to verify the general status of the newly implanted joint.

Donors were identified through the bone bank program for tissue donation. Harvesting of the joint from the donor involved excision of the entire joint. The allograft was then placed in a sterile container with L-glutamine, $NaHCO_3$, and antibiotic solution and stored at 4°C until transplantation, which was performed within sixteen days.

Surgical Techniques

General or spinal anesthesia was used. The patient was positioned in the beach chair position if the procedure involved the shoulder or positioned supine, with a tourniquet applied to the ipsilateral thigh, if the procedures involved the lower limb. The surgical procedure involved two steps, graft preparation and graft implantation.

Graft preparation was performed on a separate surgical table. The allograft articular surfaces were cut with specifically designed jigs (for knee procedures and for ankle procedures performed with a lateral approach) or with a freehand technique with a pneumatic saw, maintaining the whole articular surface and approximately 10 to 12 mm of subchondral bone intact. The prepared articular surfaces were then placed temporarily in a container with saline solution.

Shoulder (Three Patients)

A standard deltopectoral incision was used. The capsule was opened and the humeral head was dislocated anteriorly. Four parallel Kirschner wires (two in the humeral neck, perpendicular to the neck axis; two in the base of the glenoid, parallel to the articular surface) were placed under fluoroscopic control to define the plane for the osseous cut, which was made using a pneumatic saw (Fig. 1). The articular surfaces were removed and were replaced with the allograft components. The newly implanted glenoid was fixed with two small-fragment screws, and the humeral head was fixed with twist-off screws (Fig. 2).

Postoperative care during weeks zero through four involved use of a sling with an abduction pillow. During weeks five through twelve, the sling was removed temporarily for passive and active mobilization exercises, avoiding the extremes of the range of motion. During week thirteen, use of the sling was gradually discontinued and a full rehabilitation program was begun.

Knee (Seven Patients)

An anterior longitudinal skin incision was made starting 5 cm proximal to the apex of the patella and extending to the tibial tubercle, and this was followed by an anteromedial arthrotomy. The patella was everted and the knee was flexed 90°. The medial and lateral femoral jigs (previously used for preparing the graft) were positioned congruently in the host condyles. Three 2-mm Kirschner wires were used to stabilize the jigs and to create multiple perforations to guide the cutting of the femoral surface. The cut was completed with use of a specific curved chisel. Precise linear cuts of the tibial plateau and the patella were made

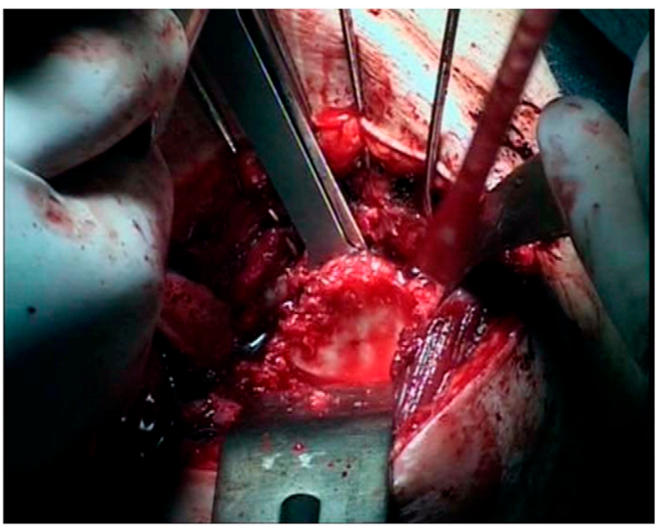

Fig. 1

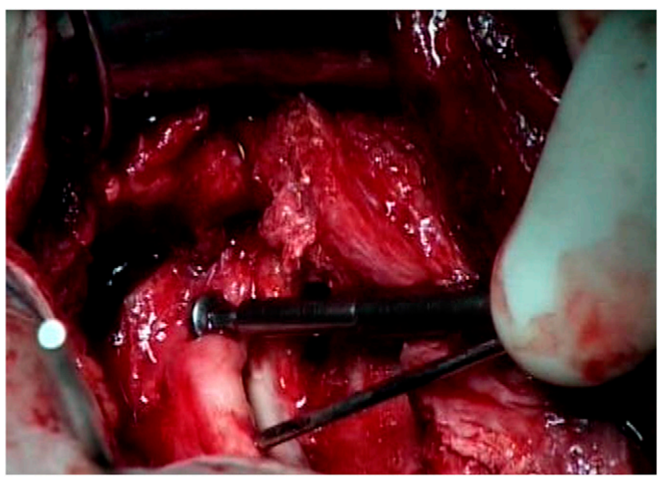

Fig. 2

Fig. 1 Surgical field showing the proper glenoid cut. **Fig. 2** Surgical field showing the newly implanted graft.

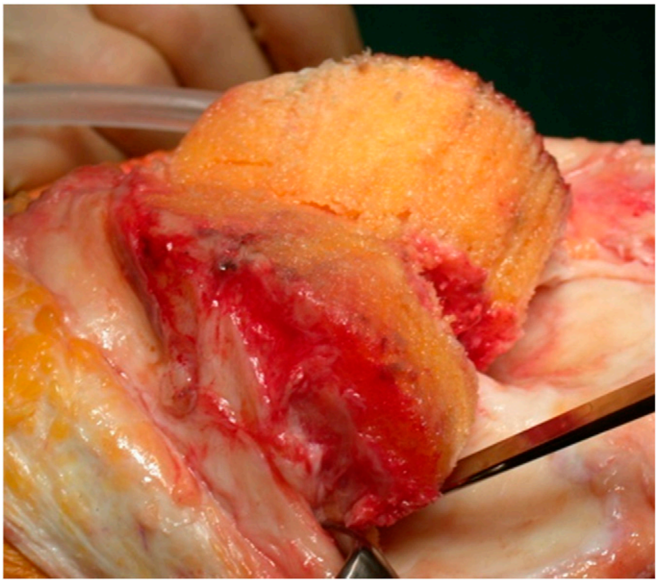

Fig. 3
Surgical field showing preparation of the femur for the graft implantation.

with use of an extramedullary tibial alignment guide and patellar clamp. Once the host site preparation was complete (Fig. 3), all of the allograft surfaces were positioned (Fig. 4). The grafts were fixed with twist-off screws, and the newly implanted menisci were stabilized with nonabsorbable suture.

Postoperative care during the first four months involved continual passive motion for eight hours a day, with a gradual increase in range of motion, and no weight-bearing. During the fifth and sixth months, partial weight-bearing was permitted, it was recommended that continuous passive motion be continued until the end of this time period, and swimming was added. A gradual increase to complete weight-bearing was permitted during the seventh and eighth months.

Ankle (Fifty-Seven Patients)

Ankle allografting was performed through a lateral approach in thirty-two cases and through an anterior approach in twenty-five.

The lateral technique involved combined mini-open anteromedial and lateral approaches. The fibula was reflected and the donor surfaces were prepared with the aid of specific jigs. The articular surfaces were removed, and the allograft was positioned and fixed with twist-off screws (Figs. 5 and 6).

The anterior technique involved an anterior longitudinal approach running between the extensor hallucis longus and tibialis anterior tendons. Two parallel Kirschner wires were positioned through the tibia and the talus, under fluoroscopic control, to define the direction of the cut. Care was taken during the cutting to preserve the external wall of the medial malleolus. The damaged

Fig. 4
Postoperative radiographs showing correct positioning of the grafts.

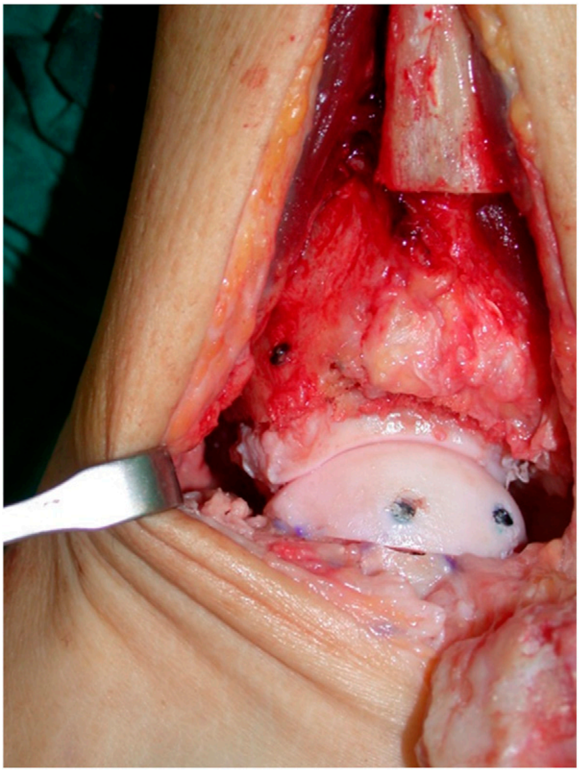

Fig. 5
Surgical field showing the graft implanted and fixed with twist-off screws.

articular surfaces were removed, and the graft was positioned and fixed with twist-off screws (Fig. 7).

Postoperative care during the first four months involved continual passive motion for eight hours a day, with a gradual increase in range of motion, and no weight-bearing. During the fifth and sixth months, partial weight-bearing was permitted, with slow progression to full weight-bearing, continuous passive motion was continued, and swimming was added.

First Metatarsophalangeal Joint (Four Patients, Six Joints)

A medial incision was made over the first metatarsophalangeal joint. The portion of the joint to be resected and the direction of the cut were marked from medial to lateral, under fluoroscopic guidance, with two Kirschner wires. The cut was made parallel to the Kirschner wires with use of a saw, and the articular surfaces were removed. The allograft surfaces were then inserted and were fixed in place with twist-off screws (Fig. 8).

Postoperative care during the first month involved heel weight-bearing with a talus shoe. During the second month, active and passive mobilization of the first metatarsophalangeal joint were performed, with progression to full weight-bearing.

Outcome Assessment

Sixteen patients treated with ankle surgery and three treated with shoulder surgery underwent a light immunosuppressive protocol (3 mg/kg/day cyclosporin for six months and 10 mg/day Deltacortene (prednisone) for the first month followed by 5 mg/day for two additional months) in an attempt to reduce the immunological reaction to the transplanted surfaces during the integration phase and reduce the postoperative arthritic progression of the graft[4].

Nine to fifteen months after surgery, the patients underwent implant removal and biopsy of the implanted allograft. Biopsy evaluations included histological and immunohistochemical analyses and genetic typing by analysis of microsatellite DNA.

Genotyping of allografts from three knees and fifteen ankles was performed by microsatellite analysis at five simple repeat sequences. Graft cartilage DNA was compared with DNA profiles of the recipient, obtained from patient peripheral blood, and of the donor, obtained from osteocartilaginous tissue[12]. Six ankle allograft cartilage samples were used for total RNA extraction and gene expression analysis of specific cartilage markers by semiquantitative real-time polymerase chain reaction (RT-PCR), normalized with respect to the housekeeping GAPDH (glyceraldehyde 3-phosphate dehydrogenase) gene.

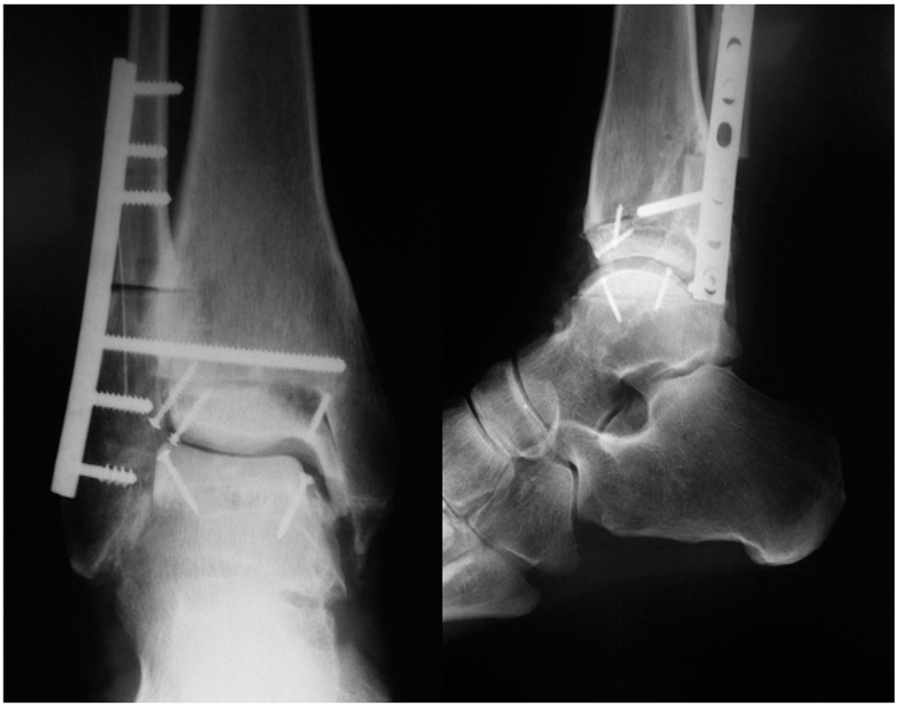

Fig. 6
Postoperative radiographs showing correct positioning of the graft.

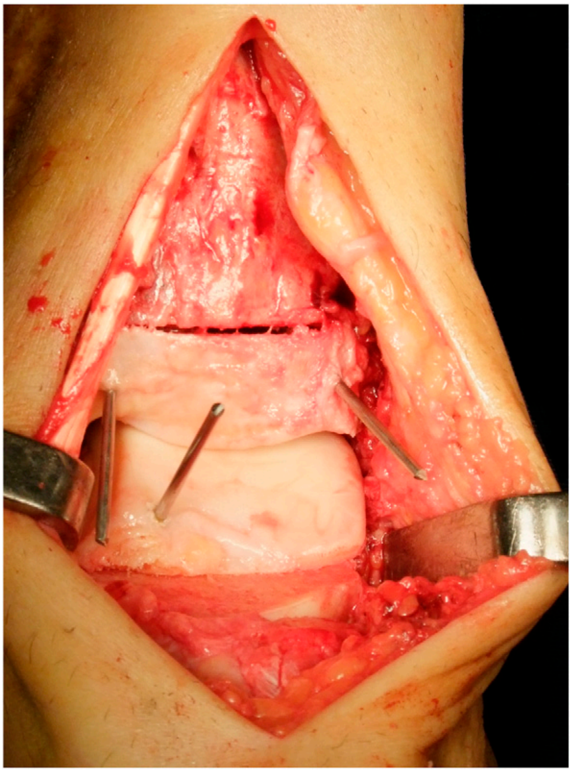

Fig. 7
Surgical field showing the position of the graft in a different patient through an anterior approach to the ankle joint.

The three knee and fifteen ankle allograft samples also underwent histological and immunohistochemical analyses. Histological samples were fixed in 10% buffered formalin and embedded in paraffin. Serial sections, 5 μm thick, were then stained with hematoxylin and eosin and with 0.1% safranin-O/0.02% fast green. Immunohistochemical samples were analyzed for the expression of tartrate-resistant acid phosphatase (TRAP) and CD90 markers, utilizing monoclonal primary antibodies after antigen-specific unmasking with biotinylated secondary antibodies and alkaline phosphatase-labeled streptavidin. Reactions were developed with use of fast red substrate and slides were counterstained with hematoxylin.

Statistical Analysis

All continuous and interval variables are reported with use of the mean and standard deviation. The paired t test was used to identify significant differences between the preoperative and postoperative scores. One-way analysis of variance (ANOVA) was used to test hypotheses regarding the means of different subgroups. When the Levene test for homogeneity of variances was significant ($p < 0.05$), the Mann-Whitney test (for two independent groups) or the Kruskal-Wallis test (for three or more independent groups) was used. The Sceffé test was used for post hoc pairwise analysis of ANOVA results, and the Mann-Whitney test with Bonferroni correction was used for post hoc pairwise analysis of Kruskal-Wallis test results. Spearman rank correlation analysis was used to investigate relationships between two quantitative measurements. The Kendall tau-b correlation test was used to investigate relationships between continuous or interval variables and the condition of the chondral layer (expressed as an ordinal variable). Life-table survival analysis with the Wilcoxon-Gehan test was used to assess the influence of categorical variables on the survival, and Cox regression survival analysis was used to assess the influence of continuous and interval variables on survival. A p value of <0.05 was considered significant for all tests. Statistical analyses were performed with use of SPSS software (version 14.0; SPSS Inc., Chicago, Illinois). The percentage of full clinical recovery (to a score of 100 on the appropriate outcome instrument) was calculated as follows: (postoperative – preoperative)/(100 – preoperative) × 100.

Results

Clinical

The clinical improvement obtained in the entire group and at each anatomical site is reported in Table II. No relationship between age, sex, or time elapsed from allograft harvesting to implantation and the clinical score or survivorship rate was found. Use of immunosuppressive therapy was associated with a positive effect on the clinical score at the twelve-month follow-up ($p = 0.041$).

For the shoulder procedures, the mean improvement at the time of final follow-up was 32.3% ± 39.8% of full recovery.

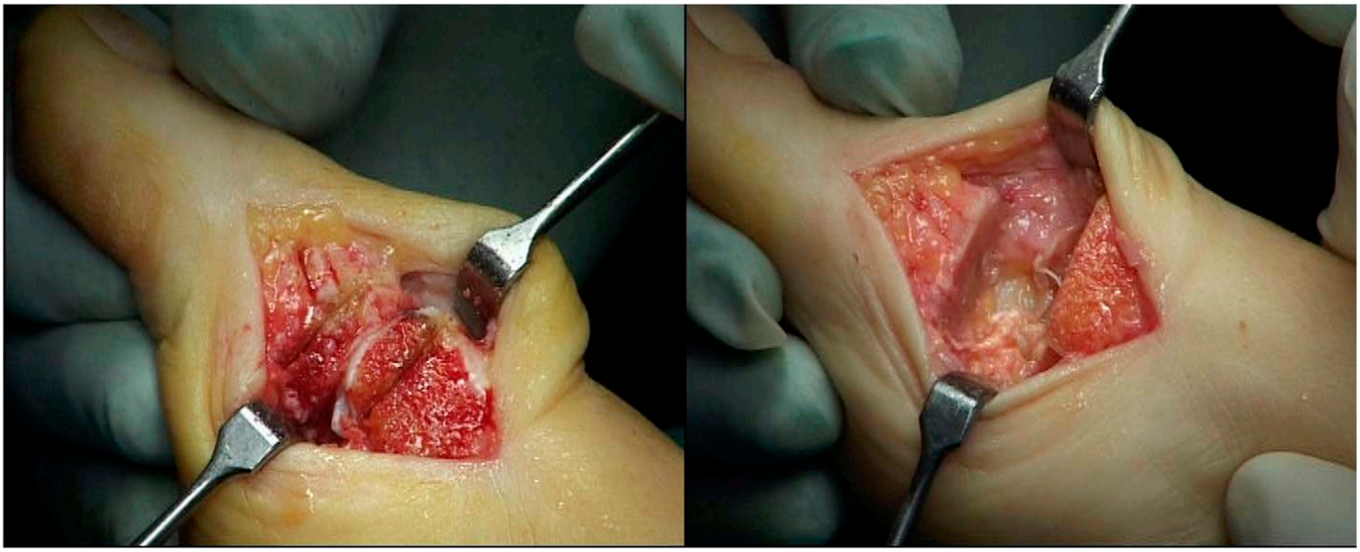

Fig. 8
Surgical field showing accurate cutting of the graft surfaces in a different patient to preserve 10 to 12 mm of subchondral bone.

Fig. 9

Radiograph at twelve months showing the onset of arthritis in the implanted graft.

At the time of writing, one patient was not satisfied because of instability and reduced strength but declined revision surgery involving a prosthetic joint replacement.

For the knee procedures, only one patient (the youngest in the series, who received the allograft for converting a knee arthrodesis) achieved a satisfactory result, with a score of 65 points at twenty-four months that was maintained up to the final follow-up at forty-eight months. This patient was one of the most subjectively satisfied in the entire series. In the other six patients, the graft was judged to have failed at a mean of 19.5 ± 3.9 months because of severe laxity and effusion of the newly implanted knee. An anterior cruciate ligament reconstruction was attempted unsuccessfully in all six of these patients, who subsequently underwent total knee arthroplasty.

For the ankle procedures, the mean percentage of improvement at the time of final follow-up was 59.3% ± 24.2%. In nine patients, the graft was judged to have failed at a mean of 22.7 ± 20.6 months because of unauthorized early weight-bearing (two patients), infection (one), malpositioning (two), an unknown cause leading to severe chondral damage and graft resorption (three), or inability to meet high functional expectations (one). All nine of these patients underwent arthrodesis and achieved a satisfactory outcome. When the ankle subgroup was analyzed separately, use of immunosuppressive therapy was associated with a faster recovery, with a better outcome at twelve months ($p = 0.041$) but no significant difference at later follow-up times. In the patients not in the ankle subgroup, immunosuppression therapy was associated with a significantly better rate of allograft survivorship at the time of final follow-up ($p = 0.05$).

For the first metatarsophalangeal joint procedures, the mean percentage of improvement at the time of final follow-up was 81.9% ± 4.6%. In one patient (treated bilaterally), graft failure occurred at one month because of soft-tissue complications; both first metatarsals had been short following a previous failed bilateral hallux valgus procedure, and the allografts had been used to elongate the first rays.

When the anatomical sites were compared at twelve and at twenty-four months of follow-up, the clinical result for the first metatarsophalangeal joint was more satisfactory than that for the shoulder ($p = 0.05$ and $p = 0.003$, respectively), the knee ($p = 0.0001$ at twelve months), and the ankle ($p = 0.01$ and $p = 0.03$, respectively). Both shoulder and ankle procedures resulted in a significantly better outcome than knee procedures ($p = 0.0001$). The survivorship of the graft over time was clearly the poorest for the knee ($p < 0.0005$), whereas the shoulder had the best survivorship rate.

Radiographic

All allografts showed signs of integration on the four-month CT scan. On the basis of the radiographs, all sites were considered healed at six months (two months for the first metatarsophalangeal joints). The six-month MRI scans showed

Fig. 10

Radiograph at nineteen months showing arthritis and resorption of the implanted graft.

TABLE II Outcomes*

	Preop.	Time Point		
		12 Months	24 Months	Final
Constant score in shoulder	38.3 ± 2.9	78.7 ± 16.2	72.3 ± 15.3	59.3 ± 22.0
IKDC score in knee	33.7 ± 4.0	40.4 ± 13.0	48	48
AOFAS score in ankle	29.5 ± 10.9	76.5 ± 12.0	74.1 ± 13.3	72.5 ± 13.3
AOFAS score in 1st MTP†	28.7 ± 4.1	91.0 ± 1.2	92.0 ± 2.3	87.3 ± 2.6
All	30.3 ± 10.0	73.7 ± 16.7	75.1 ± 13.5	72.7 ± 14.0

*The values are given as the mean and the standard deviation. †First metatarsophalangeal joint.

well-maintained articular cartilage layers in all of the joints evaluated. (No first metatarsophalangeal joint underwent MRI.) Intra-articular effusion was evident in the knees; no effusion was evident in the ankles and shoulders, but subchondral bone edema was noted.

In the series as a whole, radiographically evident arthritis recurred in all of the implanted allografts, with a significant increase at each follow-up time point (Kendall W coefficient = 0.705, $p < 0.0005$) (Figs. 9 through 13). The grade of arthritis was not associated with the clinical score or use of immunosuppressive therapy at any follow-up time point. A higher grade of arthritis was associated with poorer range of motion at twelve months ($p = 0.003$), at twenty-four months ($p = 0.001$), and at the time of final follow-up ($p < 0.0005$).

Fig. 11

Radiographs at eighteen months showing arthritic changes of the implanted graft despite reconstruction of the anterior, medial, and lateral collateral ligaments.

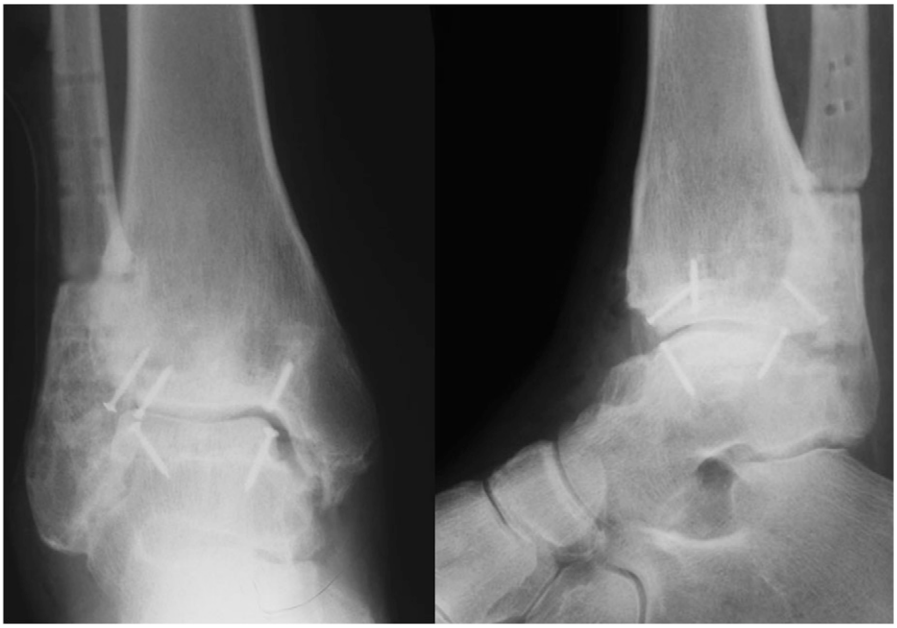

Fig. 12
Radiographs at thirty-two months showing arthritic degeneration of the implanted graft in a different patient.

In the ankle group, no influence of graft dimensions or sagittal alignment on the survivorship of the allograft over time was found. However, correct alignment of the graft in the coronal plane (<3° of either varus or valgus) was associated with better survivorship (p = 0.041; odds ratio = 1.14, 95% confidence interval = 1.005 to 1.294). Furthermore, malalignment in the coronal plane was associated with worse arthritis at the twenty-four-month follow-up (tau = 0.287, p = 0.013).

Histological

The articular cartilage tissue in the three analyzed knee allografts (all failures) exhibited many degenerative features. Safranin-O staining showed a structure compatible with fibrocartilage and little proteoglycan content, which was confined to the subchondral bone.

Cartilage tissue from the fifteen ankle allograft samples (both failed and successful) exhibited structures with various degrees of tissue remodeling. All of the components of the extracellular matrix were evident with safranin-O staining, and proteoglycans were particularly expressed near the subchondral bone.

Genotyping of allograft cartilage samples showed the presence of cells from the recipient in the transplanted cartilage. In some cases there was a complete match between the DNA of the recipient and that of the allograft, indicating the exclusive presence of host cells; in other cases a partial match between

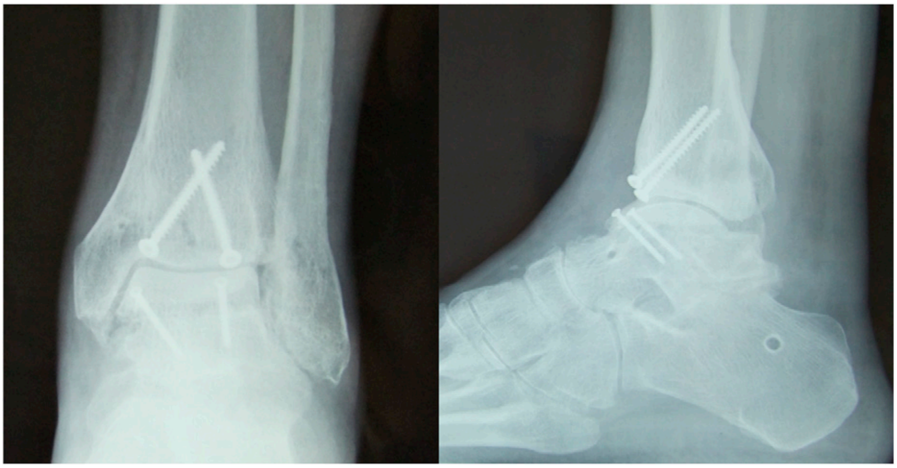

Fig. 13
Radiographs at twenty-two months showing recurrence of arthritic changes in the implanted graft, although the changes may not clinically related to the procedure.

recipient and allograft DNA indicated the presence of a mixed population of recipient and donor cells. The three knee allografts all showed a mixed DNA profile. Samples from twelve of the fifteen ankle allografts showed a DNA profile matching that of the host, one showed a mixed DNA profile, and two matched the donor DNA profile. These results suggest colonization of the donor cartilage tissue by host cells. Recipient cells colonizing the allograft showed characteristics of a chondrocyte-like phenotype, as suggested by mRNA (messenger RNA) expression analysis of specific cartilage markers in selected ankle allograft samples. Allograft cartilage tissue tested positive for mesenchymal stem cell markers. TRAP staining of retrieved allograft samples showed a marked positivity (98% ± 2%) only in multinucleated cells invading the cartilage matrix near the tidemark; cellular positivity for CD90 was detected in all specimens.

Discussion

Use of Bipolar Allograft—Why

This allografting procedure has a potential role in the treatment paradigm for advanced osteoarthritis because traditional solutions (arthroplasty and arthrodesis) may be inadequate for a young and active patient. There is a great need for research aimed at providing a biological joint replacement and thus delaying the use of a traditional prosthetic replacement. To our knowledge, the molecular analyses in the present study are the first to demonstrate the capability of cells from the host to recolonize both the osseous and the cartilage layer, with the possibility of eventually obtaining full integration of the newly implanted joint.

Where

In the shoulder, the clinical results were satisfactory in terms of pain, function, and survivorship, although the very small number of patients in this group and the short follow-up limit this analysis. Shoulder arthrodesis or total shoulder arthroplasty is rarely indicated in young patients, so a possible alternative solution may be extremely appealing. However, indications for bipolar allografting in the shoulder are limited by the need for an intact rotator cuff.

In the knee, bipolar allografting resulted in failure in almost every case, even if every care was taken in sizing, surgery, and postoperative care. All of the allografts were nicely integrated at the six-month follow-up, with no cases of nonunion or allograft fracture. However, a major inflammatory reaction occurred, with consequent joint instability and failure, possibly as a result of the large size of the graft and the need to transplant soft tissue.

In the ankle, bipolar allograft offers a viable alternative for the treatment of end-stage arthritis, even if arthrodesis remains the gold standard[6,13,14]. The clinical outcome in the present series was satisfactory and substantially stable up to the time of final follow-up. The survivorship rate was satisfactory, and the importance of proper alignment of the graft was evident in the series. Range of motion was significantly lower than normal at the time of final follow-up but was sufficient for patient satisfaction. A limited number of complications occurred, often resulting from patient failure to observe the postoperative protocol or from technical error.

The metatarsophalangeal joint provided a more satisfactory clinical result compared with the other anatomical sites, and the mean percentage of improvement at the time of final follow-up was also highest for this site, although the small number of patients in this subgroup limited the analysis. However, as in the ankle, the recurrence of arthritis gradually limited range of motion over time, and it is necessary to take into consideration that this is a very expensive surgery for an anatomical site at which arthrodesis yields good results.

When

A surgeon should consider this allografting procedure when the patient is young and has a strong motivation to have a biological substitution of the damaged joint because he or she does not wish to accept arthrodesis and total joint arthroplasty is not indicated. The surgeon must be experienced in this technically difficult procedure, being aware of the pearls and pitfalls: (1) Be careful regarding the alignment of the allograft, as this factor is a main cause of failure. Allograft cannot be used to correct limb malalignment or a limb-length deficit, as this leads to failure or major complications. (2) Fill the gaps between the allograft and host tissue with morselized bone. (Even though no cases of nonunion and failure of integration occurred in the present series, these have been described in the literature.) (3) Give the allograft time to fully integrate and maintain non-weight-bearing status for four to six months, particularly in the ankle. (4) Look for the optimal size matching between donor and recipient. (5) Use rehabilitation activities to improve the range of motion, particularly in the ankle and metatarsophalangeal joint. (6) Use a light immunosuppressive therapy for at least six months.

Implications

The road to complete success, involving predictable and entirely satisfactory use of bipolar allograft, still requires further research on transplanted cartilage. Bipolar allografts are applicable, and provide satisfactory pain relief, in the shoulder, ankle, and first metatarsophalangeal joint; however, arthritis recurrence in the transplanted joint and consequent reduction in the range of motion are major drawbacks of this method. Multidisciplinary investigations are needed on the various factors influencing this outcome, such as immunology, biomechanics, the local environment, and graft integration. ■

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