Failure of a bovine xenograft for reconstruction of the anterior cruciate ligament

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Fourteen patients with gross anterior instability had the anterior cruciate ligament reconstructed with a bovine xenograft. Major problems with swelling, pain, and synovitis were encountered in 13 patients, of whom 3 developed a synovial fistula. Histologic evidence for allergic reactions was found in 3 patients. Revisional surgery had to be performed in 10 patients because of substantial problems or rupture of the graft. At 3 years, there was only one possibly functioning graft. The 3 nonrevised patients were unstable at clinical examination. This type of reconstruction cannot be recommended for clinical use.

In 1982, clinical trials began in the United States with the objective to examine the potential of a bovine xenograft as a substitute for the anterior cruciate ligament. In Holland a short-term follow-up of 17 months seemed promising (Abbink and Kramer 1982). Berg et al. (1983) have shown glutaraldehyde-fixed bovine xenografts to possess greater tensile strength and larger modulus of elasticity than human ligaments of comparable size. The biocompatibility of the glutaraldehyde-fixed bovine material has been evaluated in rabbits and chickens by McMaster et al. (1976). No host cellular rejection was found.

Encouraged by these reports, we designed a prospective study on replacement of the cruciate ligament in patients who had previously been subjected to unsuccessful reconstructions (Cases 1–9). In our presentation, we have added retrospective experience from Gothenburg (Cases 10–14).

Patients and methods

From May 1982 to May 1984, 14 patients (9 men and 5 women, mean age 28 [16–55] years) underwent a ligament reconstruction with a bovine xenograft (Xenotech Lab. Inc., Irvine, CA). The mean time elapsed from the first injury to the xenograft reconstruction was 3 (1–8) years. One patient (Case 1) had either a very early injury that could not be dated or a congenital deficiency of the anterior cruciate ligament (Table 1). The other patients were injured during sports or traffic accidents.

Thirteen patients had undergone a total of 20 operations for ligament deficiency before the xenograft operation. Five of these were acute repairs, 9 were patellar tendon reconstructions, 2 were Ellison procedures, 3 were pes anserinus transfers, and 1 was a carbon-fiber reconstruction.

Ten patients had a total of 13 meniscal lesions. Of the medial tears, five menisci had been removed earlier and three were sutured during the reconstruction. Of the lateral tears, three menisci were previously partially removed, one was sutured, and one was left without specific treatment.

The medial collateral ligament had previously been reconstructed in 5 patients, and 6 patients had abduction instability that required surgical reefing during the reconstruction. Three patients had had acute repair of the lateral collateral ligament, and 4 patients had adduction instability that required surgical reefing during the reconstruction. Two patients had had acute repair of the posterior cruciate ligaments; 1 of them had a reconstruction along with the xenograft for the anterior ligament.

A clinical examination under general anesthesia and preoperative arthroscopy were performed on all the patients. Further, the thigh-muscle torque was measured isokinetically at 30° per second with a Cybex II dynamometer (Lumex MC, Bayshore, NY) and recorded as a percentage of the maximal torque produced by the uninjured leg. A knee function score (Lysholm

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Table 1. Reconstruction of the anterior cruciate ligament with a bovine xenograft in 14 patients

A	B	C	D	E	F	G	H	I	K	L	M	N
1	F	21	?	36	2	2	45	37	a	r	x	c
2	F	21	33	24	1	4	58	99	ab	i		
3	M	22	16	30	2	4	–	85	b	i		
4	M	29	52	27	2	5	54	73	ab	i		
5	F	16	8	27	5	2	85	90	c	l	x	a
6	F	19	48	22	3	1	–	55	ab	r	x	a
7	M	24	31	10	0	0	57	42	ab	r	x	c
8	M	27	96	23	5	0	44	–	a	r	x	b
9	M	28	28	22	2	1	41	23	ac	r	x	a
10	M	37	22	20			39	11	ab	r	x	
11	M	55	33	10			16	11	ac	r	x	
12	F	41	53	34			36	26	ab	r	x	
13	M	27	60	18			36	24	a	r	x	
14	M	27	66	12			36	83		–		

A Case.
B Sex.
C Age years.
D Time injury to op, months.
E Follow-up, months.
F Tegner activity level preop.
G Tegner activity level postop.
H Lysholm score preop.
I Lysholm score postop.
K *Complications; a pain, b swelling, c synovial fistula.*
L Graft integrity; r rupture, l loose graft, i instability, – unknown.
M Revised.
N Histology; a allergic foreign body reaction, b foreign body reaction, c chronic inflammation.

and Gillquist 1982) was obtained on each patient. Activity level rating (Tegner and Lysholm 1985) was obtained in Cases 1–9. The Lysholm score maximum is 100 points: > 84 is good/excellent and < 84 is fair/poor. The activity level is graded from 0–10, where 10 corresponds to playing soccer on an international level and 0 corresponds to disability pension due to a knee injury.

The patients were examined before surgery and on several occasions during the follow-up period. Preoperatively, all the patients had significant instability, with a positive pivot shift and Lachman sign. The mean thigh-muscle torque was 81 (69–91) percent. The mean Lysholm score was 45 (16–85), and the median of the activity level (n 1–9) was 2 (0–5). Prior to the first injury, the median activity level was 6 (2–9).

In 3 patients the follow-up was < 20 months because of early failure and revision. In one instance the patient was lost to further follow-up after 2 months. In the other 10 patients, the follow-up was > 20 months (Table 1).

Control arthroscopy was performed between 7 and 12 months in 8 patients. In 2 patients an additional arthroscopy was done after 20 months, and in 1 patient after 36 months because of increasing instability and pain. The meniscal lesions, repaired or left without treatment, were all healed at follow-up arthroscopy.

A routine light microscopic examination of removed samples from the grafts (hematoxylin van Gieson stain) was performed by Dr. B. Risberg at the Department of Pathology in Linköping.

Surgical technique

Using knowledge from dissections of cadaver knees, the aim was to establish an isometric positioning of the graft (Odensten and Gillquist 1985). The drilling of the bone channels was preceded by a notch plasty, which ensured an intercondylar notch width of 21 mm. A test ligament of cotton and four steel sutures was pulled through the drill channels, clamped to the femur, and then held tight by hand at the external opening of the tibial channel while the joint was taken through a full range of motion. If the telescopic movement of the test ligament exceeded 2 mm, adjustments of the drill channels were made. Six- or, in a few instances, 8-mm drills were used to ensure close contact between the prosthesis and the bone. The xenograft was thoroughly rinsed in several washes of physiologic saline solution according to the manufacturer's instructions. After insertion and proper tightening, the graft was fixed with Richard barbed ligament staples.

Rehabilitation

A plaster cast was applied for 5–6 weeks, followed by a rehabilitation program supervised by a physiotherapist. Extension of the knee joint was limited to –20° for 6 months, and no running or jumping was allowed for at least 9 months and until 90 percent of the thigh-muscle strength was regained.

Results

One patient had an infectious joint reaction 4 days after the reconstruction. Joint-fluid cultures showed moderate growth of *Staphylococcus epidermidis*. The reaction disappeared after a few days of treatment with lavage and antibiotics. One control arthroscopy was followed by synovitis, but repeated aerobic and anaerobic cultures were negative, and the symptoms vanished rapidly after joint lavage.

Pain and swelling were major symptoms during rehabilitation. Eleven patients had experienced pain, usually at the fixation sites of the femur and the tibia. Seven patients had synovitis. In 3 patients, it was transitional and caused no subjective problems. Two patients had progressive synovitis, which eventually led to removal of the graft. Three patients developed synovial fistulae; the grafts were removed and the channels were plugged with bone.

At follow-up arthroscopy, 8 patients had synovitis. Most, commonly, the reactions started 8–9 months after surgery, but two reactions began already after 4 months.

Graft failure

At follow-up arthroscopy of eight knees within 12 months, we found one graft rupture and two partial ruptures. Three grafts were tight and one showed poor tension, although discontinuity could not be demonstrated. One graft could not be visualized owing to severe synovitis and adhesions.

At repeat arthroscopy of three knees, between 12 and 36 months, one of the partially ruptured grafts and one of those with good tension were completely ruptured. The third patient with an early partial rupture still had a partial rupture at 36 months. This graft was eventually revised because of increasing instability. The nonvisible graft was entirely loose in its bony channels, a fact revealed at a later surgical revision.

At the final follow-up at 36 months, 13 grafts had failed. Ten knees had revisional surgery. Of the 4 remaining patients, 3 had clinical instability at follow-up not shorter than 24 months, and 1 patient was lost to follow-up after 12 months, leaving only that one graft with possible function.

Function

At follow-up, the mean thigh-muscle torque was 74 (46–92) percent. The average Lysholm score was 51 (11–99).

No rise in activity level could be seen after rehabilitation; the median level was 2 (0–5). In fact, several patients decreased or did not change activity after the operation.

All the patients had unstable knees, with a positive pivot-shift and Lachman sign at follow-up, except the patient with only 12 months' follow-up.

Histology

The histologic analysis of six removed grafts and the samples previously taken from subcutaneous fixation sites showed a similar picture. Of specimens from 6 patients, three showed a severe allergic foreign-body reaction, characterized by a tuberculoid pattern consisting of many epithelioid cells and a few giant cells. Also caseation necrosis was present (Figure 1). One specimen showed a foreign-body reaction with mostly giant cells and relatively few epithelioid cells, which could not be distinguished from a nonallergic type of reaction. In 2 patients the reaction was more of a chronic inflammatory type. In another patient, development from a nonallergic to an allergic type of reaction could be followed over a 1-year period (Figure 2).

None of the specimens showed evidence of ingrowth of collagenous tissue into the graft.

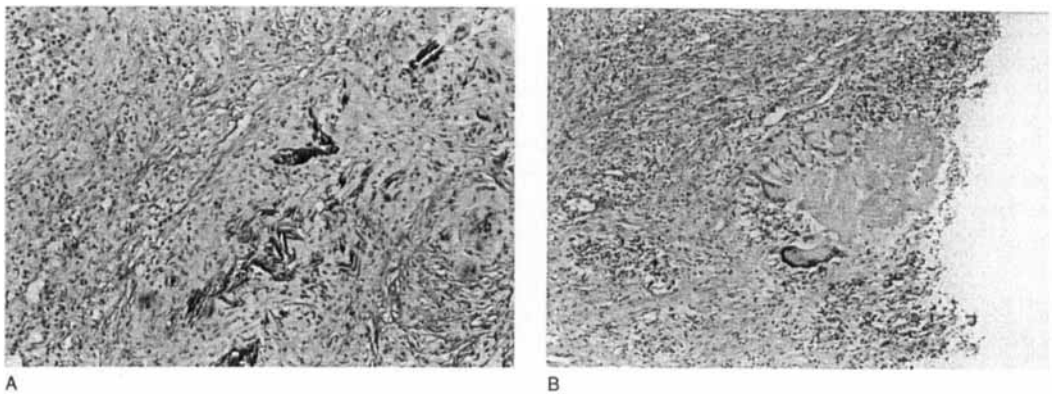
Discussion

Originally the Linköping study was planned to include 50 patients, but it was stopped when the extent of the adverse reactions became evident.

At xenograft implantation in mongrel dogs (McMaster 1985) and rabbits (Gambardella et al. 1984), there were no adverse histologic reactions, but tissue ingrowth was reported. However, our results in humans resemble those of Teitge and Rojas (1984), who reported 70 percent graft failure and persistent large effusions of the knee joint in 83 percent of their cases, and those of van Steensel et al. (1987), who reported 70 percent synovitis or graft ruptures.

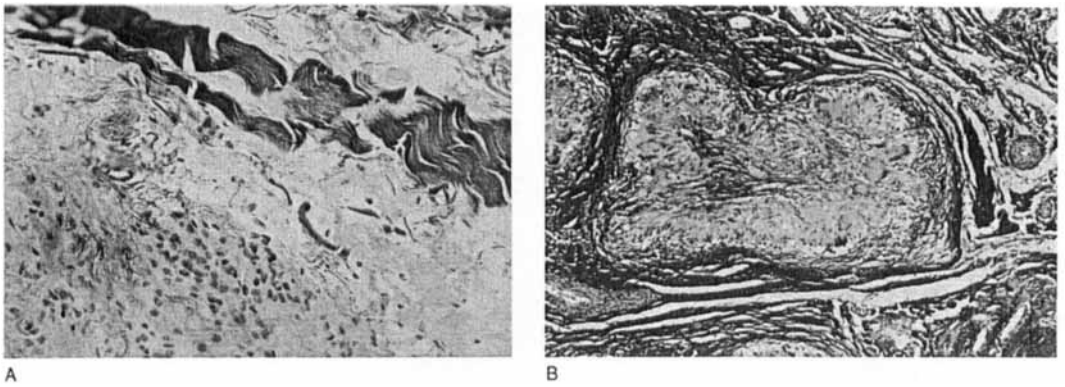
Only 3 patients in our study increased their functional score and their activity level, and had a slight improvement of muscle strength, which must be compared with 10 complete failures. The improvement was gained in spite of clinically unstable knees and cannot be explained by a successful graft, but instead by the employment of systematic exercises as described by Tegner et al. (1984, 1986).

The problems encountered may be explained by the following factors alone or in combination: 1) surgical



A B

Figure 1. A. Case 9. Strong allergic foreign-body reaction with many epithelioid cells and a few giant cells surrounding the darkly stained xenograft.
B. Case 5. Caseation necrosis, epithelioid and occasional giant cells in specimen from excised tissue surrounding subcutaneous graft end.



A B

Figure 2. Case 6. A. Subcutaneous tissue showing darkly stained xenograft end excised at 11 months; numerous giant cells are seen indicating a foreign-body reaction without allergic evidence in the form of small epithelioid cells.
B. At graft removal at 22 months, a striking pattern of allergic foreign-body reaction is observed with front lines of epithelioid cells' palisades facing the darkly stained xenograft. Occasional giant cells are also seen.

technique, 1) patient selection, 3) reactions to the graft or its fixation medium.

In the surgical manual supplied by the manufacturer, an "over-the-top" procedure or a "double-tunnel" technique is recommended. Bulletins from the manufacturer (1984, 1985) emphasize the importance of isometric positioning, notch plasty, and tightly fitted bony channels to avoid pistoning motions, which could lead to breakage and synovial fistulae. Isometry is not accomplished with the "over-the-top" technique (Odensten and Gillquist 1985, Hoogland and Hillen 1984); therefore, we chose the double-tunnel technique. The operations were also performed with concomitant notch plasty and adequately sized bony channels. The possibility that the xenograft is especially sensitive to mechanical errors cannot be overlooked.

The fact that all but one knee were previously operated on and that most of the operations were salvage procedures might predispose to failure, as Franke (1984) has described a lower success rate in reoperated on patients. Nevertheless, all 3 of the relatively satisfied patients had previous reconstructions, and the one virgin knee required graft removal because of a severe allergic reaction already at 8 months. Further, Lukianov et al. (1988) have shown a rather high success rate in similar patients using a dacron prosthesis.

The graft material is probably the major reason for failure itself; during degradation of the ruptured graft, small molecules that can act as antigens are being released. The development of a nonallergic granulomatous reaction into an allergic one is probably the result of later sensitization, which has previously been described in cases with sea-urchin spines and silica (Lever and Schamburg-Lever 1983). Further, the fixation

medium, glutaraldehyde, is known to have allergenic properties, causing occupational dermatitis (Hansen 1983, Jordan et al. 1972). Glutaraldehyde-tanned collagen sponge has cytotoxic effects both in vivo and in vitro; also foreign-body cells are described following glutaraldehyde sponge implantation in the knee joints of rabbits (Speer et al. 1980). van Steensel et al. (1987) showed leakage of glutaraldehyde from the graft even after rinsing according to the manufacturer's manual; they strongly suggest this to be the cause of the synovitis. However, this does not explain the high rupture rate and short survival time of our grafts.

In our experience, no other ligament reconstruction technique has shown the very striking reaction pattern seen with the xenografts. The results stress the importance of extensive controlled testing before introducing new implant materials for human use.

References

Abbink E P, Kramer F J K. Preliminary report on the use of xenografts in knee instability problems. Read at the 13th annual meeting of Eastern Orthopaedic Association. Orthopaedic Transactions 1982;7:84.

Berg W S, Stahurski T M, Moran J M, Greenwald A S. Mechanical properties of bovine xenografts. Orthopaedic Transactions 1983;7:279–80.

Franke K. One thousand operations due to ligamentous lesion of the knee joint 1971–1983 (Abstract). ESKA, Berlin 1984.

Gambardella R, Jurgutis J, Nimni M, Marshall G J, Gendler E, Sarmiento A, Sweeney J. The replacement of anterior cruciate ligaments with xenograft implants. Read at the 30th Annual ORS meeting 1984.

Hansen K S. Glutaraldehyde occupational dermatitis. Contact Dermatitis 1983;9(1):81–2.

Hoogland T, Hillen B. Intra-articular reconstruction of the anterior cruciate ligament. An experimental study of length changes in different ligament reconstructions. Clin Orthop 1984;(185):197–202.

Jordan W P, Dahl M V, Albert H L. Contact dermatitis from glutaraldehyde. Arch Dermatol 1972;105:94–5.

Lever W F, Schamburg-Lever G. Histopathology of the Skin. 6th ed. J.B. Lippincott Co, Philadelphia 1983.

Lukianov V A, Richmond J, Barrett G, Gillquist J. A multicenter study on the results of anterior cruciate ligament (ACL) reconstruction using a dacron ligament prosthesis. Read at the AAOS meeting 1988.

Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med 1982;10(3):150–4.

McMaster W C. A histologic assessment of canine anterior cruciate substitution with bovine xenograft. Clin Orthop 1985;(196):196–201.

McMaster W C, Kouzelos J, Liddle S, Waugh T R. Tendon grafting with glutaraldehyde fixed material. J Biomed Mater Res 1976;10(2):259–71.

Odensten M, Gillquist J. Functional anatomy of the anterior cruciate ligament and a rationale for reconstruction. J Bone Joint Surg (Am) 1985;67(2):257–62.

Orthopaedic Bioprosthesis. Anterior Cruciate Reconstruction, Clinical Experience. Xenotech Laboratories Incorporated, Clinical Report, Jan 1984, No 3.

Precautions and directions for use of Tendon Xenograft Bioprosthesis Model CLR. Xenotech Laboratories Incorporated, Product Information.

Speer D P, Chvapil M, Eskelson C D, Ulreich J. Biological effects of residual glutaraldehyde in glutaraldehyde tanned collagen biomaterials. J Biomed Mater Res 1980;14(6):753–64.

Summary of clinical experience with the Xenotech Laboratories tendon and ligament bioprosthesis in the United States. Xenotech Laboratories Incorporated, Clinical Report, Jan 1985, No 5.

Tegner Y, Lysholm J, Gillquist J, Öberg B. Two-year follow-up of conservative treatment of knee ligament injuries. Acta Orthop Scand 1984;55(2):176–80.

Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop 1985;(198):43–9.

Tegner Y, Lysholm J, Lysholm M, Gillquist J. Strengthening exercises for old cruciate ligament tears. Acta Orthop Scand 1986;57(2):130–4.

Teitge R A, Rojas F. Anterior cruciate ligament reconstruction using a bovine xenograft prosthesis. Read at the Annual Meeting of the American Orthopaedic Society for Sports Medicine 1984.

van Steensel C J, Schreuder O, van den Bosch B F, van Paassen H C, Menke H E, Voorhorst G, Gratama S. Failure of anterior cruciate ligament reconstruction using tendon xenograft. J Bone Joint Surg (Am) 1987;69(6):860–4