Proteoglycan epitope in synovial fluid in gonarthrosis

28 cases of tibial osteotomy studied prospectively for 2 years

Sten Odenbring[1], Niels Egund[2], Anders Lindstrand[1] and L. Stefan Lohmander[1]

High tibial osteotomy was performed for medial gonarthrosis in 28 patients. Preoperatively, and at 3, 12, and 24 months after surgery, clinical and radiographic examinations were made, and joint-fluid samples were aspirated. Arthroscopy was performed preoperatively and at 24 months. Immunoassay of proteoglycan epitope in joint fluid showed an increase in concentration at all times as compared with a reference population with normal knee joints. An increase in both the concentration and the total amount of proteoglycan epitope in joint fluid was noted at 3 months postoperatively with a return to preoperative values at later times. Regrowth of fibrocartilage did not correlate with proteoglycan epitope data.

Lund University Hospital Departments of [1]Orthopedics and [2]Diagnostic Radiology, S-221 85 Lund, Sweden
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During normal and pathologic turnover of joint cartilage matrix, degradation products are released into the synovial fluid (Lohmander 1988). Newly developed immunoassays of cartilage proteoglycan fragments allow sensitive and specific detection of these fragments (Heinegård et al. 1985). Recent investigations have suggested that determinations of cartilage-specific molecular markers in joint fluid, serum, or urine may facilitate the diagnosis, prognostication, and treatment of joint disease (Lohmander 1988, 1990a, b).

Analysis of proteoglycan epitope in joint fluid from patients with rheumatoid or reactive arthritis has shown elevated concentrations of proteoglycan fragments that correlate with the disease activity (Saxne et al. 1985, 1987a, 1987b, Lohmander 1988). However, the joint-fluid levels of this marker are also inversely related to the radiographic stage of the disorder, which suggests that the synovial fluid levels are influenced by the remaining mass of cartilage in the joint (Saxne et al. 1985). Subsequent investigations of patients with ligamentous or meniscal lesions of the knee joint have demonstrated high levels of proteoglycan epitope in joint fluid shortly after injury, but also persisting raised levels in many patients several years after the trauma (Lohmander et al. 1989). In analogy with rheumatoid joints, it was further shown that the average levels of cartilage proteoglycan epitope in knee-joint fluid gradually decreased with progressive arthrosis (Lohmander et al. 1990).

We report a longitudinal study of the levels of cartilage proteoglycan epitope in knee-joint fluid of patients with medial gonarthrosis treated with tibial osteotomy.

Patients and methods

From 1985 to 1987, high tibial osteotomy was performed on 28 patients—median age 58 (40–68) years (Table 1)—for medial gonarthrosis stages I–III (Ahlbäck 1968, Egund et al. 1988). Preoperatively, and at 3, 12, and 24 months after surgery, the patients reported the painless walking distance and pain at rest as continuous or present after exercise. A knee-function score (Lysholm et al. 1982) was obtained, as well as the active range of motion and the stability during walking. A satisfactory knee has a painless walking distance of more then 500 meters, a range of motion of at least 5°–90°, and is stable during walking (Jónsson 1981).

At surgery and at the clinical examinations, the joint fluid was aspirated and the volume was recorded. Next, 20 mL of physiologic saline was injected into the joint, and five passive knee bendings were performed. The saline was then aspirated and the volume was recorded. The samples were stored at –20 °C. The content of cartilage proteoglycan antigen in the joint-fluid samples was analyzed with an enzyme-linked immunosorbent assay (ELISA) using antibodies produced in goat against

Table 1. Arthroscopic, radiographic, and clinical findings of 28 patients

A	B	C	D	E	F	G	H	I	J	K	L	M
1	62	2	M	1	68	86	4/3	1/1	15	10	1	1
2	61	2	M	1	57	99	3/2	1/1	11	9	1	1
3	53	2	M	1	65	100	4/4		16	–	1	2
4	50	1	F	1	55	73	4/4		–	–	3	1
5	55	2	F	1	57	100	4/4		16	–	2	1
6	66	1	M	2	57	69	3/3	1/1	11	11	2	1
7	59	1	M	1	49	90	3/3	1/1	12	12	1	0
8	63	1	M	1	55	96	4/4	1/1	16	16	2	2
9	64	2	M	1	65	95	4/4		16	–	2	2
10	64	1	M	1	69	95	3/3	1/1	10	14	2	1
11	56	2	M	1	74	90	2/3	1/1	13	11	1	1
12	60	1	F	1	60	99	4/4	2/2	16	10	1	1
13	58	2	M	1	73	89	3/3		13	–	1	1
14	58	2	M	1	77	96	4/4		16	–	2	2
15	54	1	F	1	74	89	4/4		14	–	1	2
16	58	2	M	1	77	96	3/3	2/1	13	15	1	1
17	54	1	M	1	67	100	4/4	1/1	14	14	3	3
18	60	1	M	1	59	81	4/4		14	–	3	2
19	55	1	M	1	68	80	3/3	1/2	14	13	1	2
20	40	1	F	1	60	85	4/4		12	–	1	0
21	68	2	M	2	61	95	3/3	1/1	12	6	1	1
22	63	2	M	1	72	100	3/4	1/1	13	8	2	1
23	58	2	F	1	52	94	3/3		12	–	1	1
24	56	1	M	1	65	92	4/4	2/2	14	13	2	2
25	57	1	M	1	69	100	4/4		14	–	2	1
26	53	1	F	2	64	75	4/4	1/1	14	10	1	1
27	57	1	F	2	56	70	4/4	1/1	17	11	2	1
28	60	1	M	1	79	100	4/4		16	–	3	1

In Case 4, the patellofemoral joint could not be visualized at arthroscopy.
In Case 9, the follow-up arthroscopy was done 9 months after surgery.

A Case
B Age at surgery
C Mobilization
  1 plaster cast
  2 cast brace
D Sex
E 1 Satisfactory knee according to Jónsson
  0 Not satisfactory
F Lysholm's score preoperatively
G Lysholm's score 2 years after surgery
H Joint cartilage destruction on the medial femoral/tibial condyle at surgery
I Joint cartilage destruction on the medial femoral/tibial condyle at follow-up arthroscopy
J Total joint cartilage score at surgery
K Total joint cartilage score at follow-up arthroscopy
L Stage of arthrosis preoperatively (Ahlbäck's)
M Stage of arthrosis 2 years after surgery (Ahlbäck's)

intact human articular cartilage proteoglycans. Samples were digested with testicular hyaluronidase before analysis. Polyvinyl-chloride microtiter plates were coated with human articular cartilage proteoglycan digested with chondroitinase ABC (Heinegård et al. 1985, Saxne 1987).

Three patients declined aspiration of joint fluid at the clinical examinations; another 2 patients declined at the 12- and 24-month follow-ups.

At the time of osteotomy, all the patients were examined by arthroscopy to monitor the condition of the joint cartilage, and a punch biopsy was obtained from the medial femoral condyle either in the center at 90° of knee flexion or, if naked bone was present in this area, from the immediately adjacent cartilage. Twenty-four months after surgery, 16 patients accepted a control arthroscopy for evaluation of the status of the cartilage and for obtaining a new punch biopsy. In 1 patient the follow-up examination was performed 9 months after surgery.

The examinations with arthroscopy, cartilage-bone biopsy, and joint-fluid aspiration were approved by the ethics committee of Lund University.

Joint cartilage degenerative changes were recorded at the time of arthroscopy in accordance with a modified Outerbridge (1961) classification (Lindberg et al. 1986):

1. Normal cartilage.
2. Superficial fibrillation and/or softening.
3. Fragmentation and deep fissuring.
4. Erosion down to subchondral bone.

A total cartilage score was calculated from the sum of the recorded cartilage degenerative changes on the lateral and the medial tibial and femoral condyles and on the joint surfaces of the femur and patella in the patellar articulation.

Surgical procedures

Arthroscopy was carried out as described by Gillquist and Hagberg (1976) using the central approach. The knee was irrigated with saline through an infusion pump and drained with a separate outflow catheter. The thigh was stabilized with a leg holder. The cartilage surfaces were inspected and examined with a probe. A cartilage-bone punch biopsy was obtained. The same procedure was used at osteotomy and at follow-up arthroscopy.

Tibial osteotomy was performed using the Tjörnstrand guide (Odenbring et al. 1989a). The intended wedge was calculated from the frontal whole lower limb radiograph with an angle corresponding to the varus alignment including the desired overcorrection of 4°. Postoperatively, 16 patients received a cylinder plaster cast, whereas 12 patients had a hinged cast brace for 6 weeks (Odenbring et al. 1989b).

Results were tested using the Students *t*-test and chi-square test. A value of $P < 0.05$ was considered significant.

Results

The concentration of joint-fluid proteoglycan epitope varied widely among the individual patients and at different times, but the mean concentration was at all times higher than that found in a reference group of patients with normal knee-joint cartilage (Lohmander et al. 1989).

When the postoperative values of each patient were normalized against the preoperative value of the same patient, there was an increase in both the average concentration ($P < 0.01$) and the total amount ($P < 0.01$) of proteoglycan epitope in the synovial fluid from the preoperative condition to the 3-month follow-up. One or 2 years after surgery, the values tended to return to the preoperative levels (Figure 1). The volume of aspirated synovial fluid was also increased at 3 months as compared with the preoperative volumes.

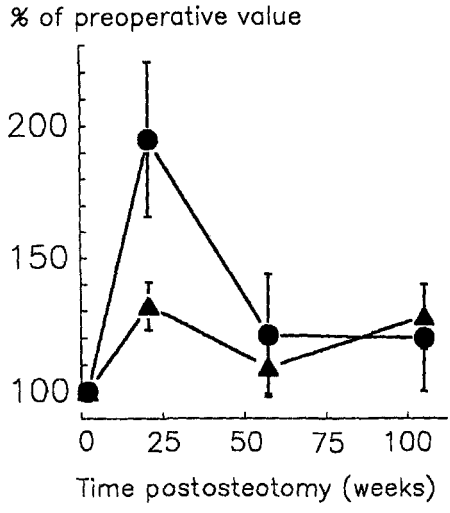

Figure 1. The average proteoglycan epitope concentration (●) and the total proteoglycan epitope mass (▲) in knee-joint fluid after a tibial osteotomy. Values are expressed as the mean of the normalized values. Values for each patient were normalized to the preoperative value (0 weeks) for the same patient, and the mean normalized value was calculated for the whole group at each time interval. Bars represent the standard error of the mean.

There was no difference in the average concentration or the total amount of proteoglycan epitope in the knees treated postoperatively with a plaster cast or a brace. Neither did we observe any relationship between the epitope concentration or total mass and that of postoperative regrowth of fibrocartilage tissue in the joint.

Discussion

The early clinical results of high tibial valgus osteotomy in arthrosis are favorable (Tjörnstrand et al. 1981, Aglietti et al. 1983), and indicate at least a temporary arrest in the progress of the disease. With proper indication and precise surgery, good long-lasting results can be expected (Odenbring et al. 1990).

In this prospective, longitudinal series of patients, we observed regrowth of fibrocartilage in the medial joint compartment in about three fourths of the patients after the osteotomy—in half of them on the medial tibial condyle and in half on the medial femoral condyle, which was a lower proportion than was observed in a previous study (Fujisawa et al. 1979).

The mean preoperative synovial-fluid concentrations of proteoglycan epitope agreed with those found in a previous study of patients with a comparable degree of gonarthrosis (Lohmander et al. 1990). Although the arthrosis was only moderately advanced from a clinical or radiographic point of view, arthroscopy revealed extensive cartilage damage (Table 1). The synovial fluid levels of proteoglycan epitope in arthrosis are higher at earlier stages of the disease development, and then slowly decrease with advancement of the cartilage damage (Lohmander et al. 1990). A similar relationship between arthrosis staging and proteoglycan epitope concentration was observed in the present study. As previously noted, this may suggest that the joint-fluid concentration of this marker is related to the mass of cartilage remaining in the joint and that the rate of cartilage-matrix turnover decreases at the later stages of the disease (Lohmander et al. 1990). The latter suggestion is also supported by in vitro studies of the metabolism of cartilage biopsies from arthrotic joints, which indicate increased levels of synthesis of matrix components in the earlier stages of the disease and a progressive decrease in the late stages (Mankin et al. 1971, Thompson and Oegema, 1979, Bulstra et al. 1989). The increase in the total amount of proteoglycan epitope in knees with more advanced gonarthrosis was directly related to a larger volume of aspirated synovial fluid.

Our assays of proteoglycan epitope in joint fluid after tibial osteotomy suggested an increase in both the concentration and the total amount of fluid aspirated from the joint in the early postoperative phase, and a return toward the preoperative levels after 1–2 years (Figure 1). The trend was present when total values were expressed both as the mean of absolute values and as the mean of normalized values. This increase in the early postoperative phase may be due to a change in the mechanical loading of the joint after the osteotomy, to the punch-biopsy procedure, or to the postoperative relative physical inactivity. The fact that the levels of proteoglycan epitope in synovial fluid are largely unchanged after 2 years as compared with the preoperative levels suggests that the average mass of remaining cartilage within the joint and the turnover rates of the tissue and synovial fluid do not change during the observation time.

In this study, we were unable to find a relationship between the presence of fibrocartilage regrowth on the joint surface and the levels of proteoglycan epitope in the synovial fluid. This may be due to a relative lack of hyaline cartilage proteoglycan epitope in the regrowing fibrocartilage.

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