

# Unstable Stifles without Clinical or Radiographic Osteoarthritis in Young Goats: An Experimental Study

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**Rørvik, A.M. and J. Teige: Unstable stifles without clinical and radiographic osteoarthritis in young goats. An experimental study. Acta vet. scand. 1996, 37, 265-272.** – Thirteen young, castrated male goats had instability of one stifle (knee joint) created by surgical transection of the cranial cruciate ligament, but did not develop any signs of osteoarthritis (OA) in treated joints when confined in limited space for 8 months. At the end of the experiment, the instability in the stifles had not improved, the joints were normal at radiographic examination, there were no signs of inflammation in the synovial membrane or joint capsule, and fibrosis in these tissues was not evident. The articular cartilage was normal both visually and histologically. This may indicate that the young age of the goats and the restricted physical activity on soft floor had prevented the expected development of OA in the experimentally operated joints. Synovial fluid volumes and proteoglycan concentration were measured in the treated and control joints in 6 of the goats. There seemed to be increased quantity of the proteoglycan aggrecan in the synovial fluid from the treated joints compared to the contralateral joints throughout the course of this study. It was concluded that the turnover of aggrecan in the articular cartilage of the treated joints may have been increased.

*Synovial fluid; proteoglycan; cruciate ligament; animal model.*

## Introduction

Surgical transection of the cranial (anterior) cruciate ligament in the stifle is a frequently used model for the study of chronic pathological changes in joints (Brandt 1991). The cartilage changes that usually occur are similar to those of a slowly developing osteoarthritis (OA) and are considered to be a consequence of the instability of the joint and not a result of inflammation (Brandt 1991). Ho *et al.* (1992) reported that OA had developed 4-6 weeks after cruciate ligament transection in 4 goats. Ghosh *et al.* (1991) reported that OA had developed slowly during 6 months following unilateral medial meniscectomy in the stifles of 26 sheep.

OA may develop when chondrocytes are exposed to abnormal physiologic stress, either as a result of normal stress on abnormal cartilage or abnormal stress on normal cartilage (Mitchell & Cruess 1977).

No single compound or combination of compounds have gained acceptance as a suitable biochemical marker to be used in the diagnosis of osteoarthritis (OA). However, increased amounts of proteoglycan (PG) and fractions of these compounds are liberated into the synovial fluid (SF) when articular cartilage matrix is degraded (Heinegård *et al.* 1985, Ratcliffe *et al.* 1988, Lohmander 1988, Dahlberg *et al.* 1992, Poole *et al.* 1994). PG is found in SF of normal

joints in small concentrations as a result of normal turnover of cartilage matrix (Lohmander 1988). The total turnover of PG in diseased cartilage matrix is increased (McDevitt & Muir 1977, Carney *et al.* 1984, Sandy *et al.* 1984) due to both increased anabolic and catabolic activity, and elevated levels of PG in SF may thus indicate early osteoarthritis in the joint (Heinegård *et al.* 1985, Lohmander 1988, Lohmander *et al.* 1992).

The purpose of this study was to create stifle (knee) instability in young goats and expose the animals to restricted physical stress while following the development of OA. The quantity of the large aggregating type of PG (aggrecan) originating from the articular cartilage liberated into the SF was estimated in SF from the unstable stifles and the contralaterals in some of the goats to detect possible changes in matrix turnover of the operated stifles.

### Materials and methods

The 13 goats used in this experiment were males that were castrated and dehorned at 2 months of age. They were dewormed on arrival (<sup>a</sup>) and kept in the same stalls from the time they

were castrated until the end of the experiment. The floor was concrete, covered with a thick layer of dry sawdust. The goats were fed high quality grass hay, some barley and had a continuous supply of fresh water.

### *Surgical procedure on 13 goats*

Surgical transection of the cranial cruciate ligament in the left stifle was performed when the goats were 6 months old. The right stifles had no treatment. The goats were sedated (<sup>b</sup>); epidural anaesthesia was administered at the lumbosacral junction (<sup>c</sup>) and stifle arthrotomy was performed through a lateral incision. The patella was luxated medially, and the joint was placed in maximum flexion providing clear visualization of the joint and the cruciate ligaments. The cranial cruciate ligament was transected using a scalpel. Cranial and caudal displacement of the femur relative to the tibia was visualized by manipulating the limb before the joint incision was closed, to be certain that the ligament had been completely transected. Joint lavage was performed with 0.9% saline. The joint capsule, muscular fascia (<sup>d</sup>) and the cutis (<sup>e</sup>) were sutured with absorbable and nonabsorbable sutures respectively using an interrupted pattern. Obvious cranial instability was demonstrated in all the operated joints following completion of the surgical procedure. Antibiotics (<sup>f</sup>) were administered intramuscularly on the day of surgery and repeated on the second postoperative day.

### *Sampling of synovial fluid on 6 goats*

Synovial fluid sampling was performed on both stifles prior to, and again at 4, 8 and 18 weeks following surgery. Ten ml of saline, containing RISA(<sup>g</sup>) (I<sup>125</sup>labelled goat serum albumin), added to enable volume measurements, were injected slowly intraarticularly, between the patella and the lateral patellar ridge. A glass-syringe was used and gentle, "one-finger" pres-

<sup>a</sup> Fenbendazol 5mg/kg per os (Panacur<sup>®</sup> vet boli). Hoechst AG, Norske Hoechst A/S, Oslo, Norway.

<sup>b</sup> Medetomidine chloride 20 mg/kg i.v.; Domitor<sup>®</sup>, Orion -Farmos Corporation, Turku, Finland

<sup>c</sup> Xylocain adrenalin<sup>®</sup>, (2%), Astra Läkemedel, Södertälje, Sweden.

<sup>d</sup> Vicryl<sup>®</sup> 2-0. Ethicon, Johnson & Johnson, Sollentuna, Sweden.

<sup>e</sup> Prolene<sup>®</sup> 2-0. Ethicon, Johnson & Johnson, Nordestedt, Holland

<sup>f</sup> Benzylpenicillinprocaine 50 mg/kg/day, Penovet<sup>®</sup> Vet, Boehringer Ingelheim Agrovot A/S, Hellerup, Denmark.

<sup>g</sup> RISA containing 48 mCi/mg of I<sup>125</sup>-marked goat serum albumin was produced and provided by The Hormone Laboratory, Aker Hospital, Oslo.

sure was applied to the plunger to perform the injection. The needle was removed and the joint was passively manipulated by extension and flexion 20 times in 20 seconds before arthrocentesis was performed. Aspirated fluid was collected in glasses containing EDTA solution and was centrifuged at 2200 G for 30 min to remove cartilage fragments and cells. The supernatant was used to calculate SF volume and was kept frozen at temperature maximum 18°C until PG analysis was performed.

#### *Volume measurements on 6 goats*

SF volumes were calculated each time samples were collected for PG analysis, by measuring how much the SF in the joint diluted the saline/RISA solution following injection. Dilution was calculated from the decrease in radioactivity as measured using automated well scintigraphy (<sup>h</sup>). The following formula was used:

$$V_{SF} = \frac{V_{INJ}(C_{INJ} - C_{DIL})}{C_{DIL}}$$

$C_{INJ}$  was the radioactivity per ml of injected RISA solution,  $C_{DIL}$  was the radioactivity per ml of evacuated sample and  $V_{INJ}$  was injected volume.

#### *PG measurements on 6 goats*

The concentration of PG in SF samples was determined, at a collaborating laboratory (<sup>i</sup>), using an ELISA produced for goats. The procedures, described by *Heinegård et al.* (1985) for ELISA of PG in dog SF and later described in more de-

tail by *Saxne et al.* (1986) for PG analysis in human SF, were followed in every aspect, except that antibodies were produced in calves using PG extracts from goat articular cartilage as antigen. The concentration of the protein core fragments from the large, aggregating PG (aggrecan), found only in articular cartilage, was measured.

#### *Radiographic examination of 13 goats*

Radiography of the stifles using orthogonal projections was performed prior to and at 2 and 8 months following surgery.

#### *Necropsy on 13 goats*

The goats were killed and exsanguinated 8 months following surgery. Necropsy was performed immediately and the stifles were opened and inspected. Tissue samples were taken from the synovium and capsule of test and control stifles at a consistent location on the distal medial side. A section of cartilage and subchondral bone, transverse to the patellar ridges and transverse to the lateral and medial condyle of the femur, was sampled for histological examination. Tissue samples were fixed in 10% formalin. Cartilage/bone samples were demineralized in 12% HCl following fixation. Tissue samples were embedded in paraffin and sectioned. Sections of all tissues were stained with haematoxylin-eosin and with Van Gieson.

#### *Exclusion of samples*

Samples were excluded if only a small sample was obtained.

#### *Statistical evaluation*

The amount of PG was analysed using t-test for paired comparisons (*Sokal & Rohlf* 1981) and univariate procedure (*SAS* 1989). Additional analyses were made using Wilcoxon Sign Test (*Kirkwood* 1988).

<sup>h</sup> Packard Auto-Gamma® 5650, Packard Instrument Company Inc, Downers Grove, IL 60515.

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## Results

### *Clinical signs and pathologic findings on 13 goats*

The goats did not bear weight on the operated limb for several days following surgery. No persistent, obvious lameness was observed beyond 2-3 weeks following surgery. However, the goats seemed not to bear full weight on the operated limb, and episodes of slight lameness recurred. Instability in the operated stifles was obvious throughout the experimental period, although there may have been some improvement by the 8 month.

There were no visible pathologic changes in any of the 26 stifles at necropsy except for a grey mass of granulation tissue located in the transection site of the cruciate ligament. The cartilage appeared normal with no sign of rim formation, and there was no evidence of bony proliferation at joint margins.

Cartilage from operated and control stifles was compared histologically on the 13 goats. The cartilage surface was smooth with cells that appeared normal, and the cartilage seemed to have the same thickness in both joint categories.

The synovium and joint capsule showed no obvious difference in thickness, and no cellular infiltrates or fibrosis were observed at histological examination.

### *Radiographic findings on 13 goats*

There were no radiographic signs of pathologic change in any of the stifles of the 13 goats.

### *Synovial fluid analysis on 6 goats*

The results of quantitative measurements of PG in SF from the stifles prior to operation and at 4, 8 and 18 weeks following surgery are given in Table 1. Using two-sided t-test for paired comparison, the difference was not significant at 8 weeks following operation, but significant at 4 and 18 weeks. Using the the Wilcoxon Sign

Test, however, there was a significantly increased amount of PG in the operated stifles also at 8 weeks after surgery ( $p = 0.0312$ ).

## Discussion

Although marked and persisting stifle instability was induced in the present study, no signs of OA were recognised clinically or by autopsy and histology in the stifles of the 13 goats 8 months following transection of the cranial cruciate ligament. *Palmoski & Brandt* (1982) found that immobilisation of the knee prevented OA after cranial cruciate ligament transection in dogs. Young goats were used in the study, which may have contributed to a delayed development of OA changes, although OA may develop in young animals (*Grøndalen & Grøndalen* 1981). Other similar experimental protocols have used adult animals (*Palmoski & Brandt* 1982, *Sandy et al.* 1984, *Carney et al.* 1984, *Heinegård et al.* 1985, *Brandt* 1991, *Brandt et al.* 1991, *Gosh et al.* 1991, *Ho et al.* 1992). It was concluded that limited activity, due to stall confinement and sedentary behaviour resulting from castration of the goats combined with the soft ground, may have reduced stress on the cartilage enough to delay or even prevent development of OA, and the young age may also have influenced this development. *Brandt et al.* (1991) found increased thickness of cartilage matrix during the first years following cranial cruciate ligament transection in stifles of mature dogs. The thickness of the articular cartilage seemed unchanged in the operated goat stifles compared to the controls. Reduced concentration of PG in the cartilage is described in the first stages of OA measured by safranin O staining in the matrix (*Mankin* 1971). Unfortunately, because histochemical staining of the articular cartilage of the stifles using safranin O and toluidine blue (*Rosenberg* 1971, *Getzy et al.* 1982) was not success-

Table 1. Total quantity (mg) and concentration (mg/ml) of proteoglycan in diluted synovial fluid from operated(#) and control(\*) stifles before operation and at 4, 8 and 18 weeks after operation. The total quantity of PG was calculated as the product of concentration of PG (given in parentheses) and estimated synovial fluid volume. The mean difference and SEM was calculated on paired comparisons.

| Goat            | Before operation |             | 4 weeks postop.     |             | 8 weeks postop.     |            | 18 weeks postop.    |            |
|-----------------|------------------|-------------|---------------------|-------------|---------------------|------------|---------------------|------------|
|                 | Left             | Right       | Operated            | Control     | Operated            | Control    | Operated            | Control    |
| 1               | 22.7 (2.1)       | 12.2 (4.7)  | 65.3 (8.9)          | 14.0 (3.9)  | 19.4 (4.9)          | 6.9 (2.1)  | 15.7 (2.7)          | 7.1 (2.1)  |
| 2               | 17.6 (5.9)       | 7.2 (4.2)   | 21.6 (4.0)          | ---- (----) | 6.3 (1.6)           | 3.6 (1.5)  | 43.4 (12.8)         | 3.4 (2.9)  |
| 3               | 13.2 (2.4)       | ---- (----) | 76.7 (8.3)          | 49.1 (7.8)  | 24.5 (4.0)          | 23.1 (6.1) | 32.7 (4.4)          | 14.3 (3.1) |
| 4               | ---- (4.1)       | ---- (5.8)  | 52.7 (7.2)          | 15.7 (3.4)  | 30.6 (5.4)          | 10.2 (2.8) | 42.9 (8.6)          | 23.6 (6.7) |
| 5               | 12.9 (1.6)       | 14.7 (3.2)  | 43.7 (5.8)          | 41.2 (4.9)  | 77.1 (10.3)         | 24.0 (5.0) | 75.4 (16.4)         | 21.5 (5.7) |
| 6               | 16.7 (3.0)       | 16.6 (2.9)  | 50.6 (5.6)          | 6.9 (2.0)   | 50.6 (16.4)         | 6.9 (5.7)  | 32.8 (5.7)          | 7.9 (2.9)  |
| Mean            | 16.6 (3.2)       | 12.7 (4.2)  | 51.8 (6.7)          | 25.4 (4.4)  | 34.6 (7.1)          | 12.3 (3.9) | 40.5 (8.4)          | 12.9 (3.9) |
| SD              | 4.0 (1.6)        | 4.1 (1.2)   | 18.9 (1.9)          | 18.6 (2.2)  | 25.3 (5.4)          | 9.0 (2.0)  | 19.8 (5.3)          | 8.2 (1.9)  |
| Mean difference | 4.8 (-0.85)      |             | 32.4 (2.76)         |             | 22.6 (3.09)         |            | 27.5 (4.56)         |            |
| SEM             | 3.3 (0.76)       |             | 8.43 (0.88)         |             | 8.85 (1.86)         |            | 6.25 (1.85)         |            |
|                 |                  |             | p = 0.0192 (0.0346) |             | p = 0.0524 (0.1350) |            | p = 0.0096 (0.0579) |            |

(#): transected cranial cruciate ligament

(\*): contralateral stifle

ful in the present study, it cannot be evaluated whether a net loss of PG from the cartilage had occurred. According to *Mankin's* grading system (1971), however, this reduced staining occurs when surface irregularities are present in the cartilage. No such irregularity was detected in any of the operated goat stifles.

During the early stages of osteoarthritis, chondrocytes may produce as much as 8 times the normal amount of PG (*Lohmander* 1988), and increased degradation of cartilage matrix occurs as a result of chondrocyte production and activation of matrix metalloproteases (*Nojima et al.* 1986, *Murphy et al.* 1990). The quantity of PG liberated into the SF during OA is correlated to the mass of cartilage matrix remaining in the joint and the degree of inflammation (*Dahlberg et al.* 1992). It is likely that it is also correlated to the rate of chondrocytic activity or the number of chondrocytes that are affected or both. *Lohmander et al.* (1992) and *Dahlberg et*

*al.* (1992) found persistent increased concentration of PG in SF from human knee joints following trauma, before any signs of OA were visible in the cartilage at arthroscopy. The amount of the PG aggrecan was measured in the synovial fluid of the operated and the contralateral stifles, and the results were compared by paired comparison. The contralateral joint, although bearing more weight than normal, functioned as a control. In spite of the obvious errors in SF volume measurements (*Rørvik* 1995) the authors chose to calculate and use the total amount of PG rather than the concentration. The half-life of PG in SF was found to be 12 hours in rabbit knees, regardless of joint disease and inflammation with increased SF volume (*Page-Thomas et al.* 1987). Protein and macromolecules like PG in synovial fluid are eliminated through the lymphatics by a "bulk flow" (*Wallis et al.* 1987). If the volume of SF is increased, the amount of fluid running through

the joint per time unit is increased, although the "half-life" is not (Levick 1990), and measuring the concentration of a marker in SF will strongly underestimate the total liberation of marker to the SF from the cartilage (Heinegård *et al.* 1985, Levick 1990, Myers 1995).

The number of goats and samples were few, and the amount of PG found in the SF was variable. The value of statistical evaluation on such a set of data is limited. Every amount of PG found in the operated stifles given in Table 1 was larger than that found in the control contralateral stifle, and all but one concentration of PG. The differences were strongly significant 4 and 18 weeks postoperatively, and significant or very near significant (depending on method) at 8 weeks postoperative, and the probability of no difference is after all very small. It was concluded that there at least were periods of increased liberation of PG into the SF of the unstable stifles compared to the controls. This may indicate a change in articular cartilage chondrocyte biochemical activity in the operated stifles, fitting into the concept of "pre-OA", a term introduced by Lohmander *et al.* (1992). This experiment could, from practical reasons, not be prolonged, but it would be interesting to repeat the experiment and expand the follow up time several years (Brandt *et al.* 1991) and increase the number of SF samples. Several markers of OA have been introduced since this experiment was planned, some of them perhaps more interesting than PG (Rørvik & Grøndahl 1995). Future diagnostics of OA may develop in few years if dedicated scientific efforts are made.

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**Sammendrag**

*Ustabile kneledd uten utvikling av arthrose på unge geiter. Et eksperimentelt studium*

Det kraniale crusiata-ligamentet i venstre kneledd ble knuttet ved kirurgisk inngrep på 13 unge, kastrerte geitebukker, men geitebukkene utviklet ikke artrose i de opererte kneleddene i løpet av en postoperativ periode på 8 måneder. Geitebukkene ble oppstallet med begrenset bevegelsesfrihet og mykt underlag. Ved slutten av forsøket var ikke stabiliteten i de opererte kneleddene forbedret, men bortsett fra dette ble det ikke registrert unormale funn klinisk eller røntgenologisk. Histologisk var det ingen tydelige tegn til inflammasjon eller unormal bindevevsinnvekst i leddhin-

ner eller leddkapsel. Brusken var normal makroskopisk og histologisk. Man antok at den rolige tilværelsen på grunn av god foring, kastrasjon og begrenset bevegelsesfrihet, det bløte underlaget og geitebukkens unge alder hadde bidratt til å forsinke eller forhindre utvikling av artrose i de opererte kneleddene.

Leddvæske-volum og proteoglykan-konsentrasjon ble målt i de opererte ledd og de kollaterale kontrollledd på 6 af geitene. Det ble funnet en økning av mengden proteoglykan i de opererte ledd sammenlignet med kontrollene. Forskjellene var små, men syntes å være tilstede gjennom hele studiet. Det ble konkludert med at omsetningen av proteoglykaner i bruskmatrix på de opererte ledd kunne være forøket.

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