MATTERS ARISING

Cartilage metabolism—a response

On the basis of measurements of the concentration of aggrecan fragments, cartilage oligomeric matrix protein (COMP), stromelysin, and TIMP in samples of synovial fluid obtained from injured and uninjured knees of subjects with unilateral knee trauma, Dahlberg and colleagues¹ concluded that an abnormality of cartilage metabolism existed in the contralateral knee and suggested that mechanical compensation for the injury, or cytokines or other products released from the injured joint initiated a pathological process in the uninjured knee.

The authors provided reference values for concentrations of the above molecules in a control group of '... 10 healthy athletes without knee symptoms and with no previous knee injury.' However, the median volume of synovial fluid aspirated from the reference group (2.5 ml) was some 3.5 times greater than that from the uninjured knee of subjects with unilateral knee injury, strongly suggesting that the reference group was not 'normal'; unfortunately, results of routine synovial fluid analyses (total leucocyte count and differential) were not provided.

If concentrations of the various markers are normalised for dilution, using the median synovial fluid volume in the uninjured knee of the subjects with unilateral injury (0.7-1.0 ml), the median quantity of aggrecan, for example, present in synovial fluid samples from the reference group was nearly 150% greater than that in samples from the contralateral knee of the subjects with knee injury, raising doubt about the authors' interpretation of the findings for the contralateral knee.

Other factors may also have confounded the results. Did subjects limit usage of the injured joint as a result of pain? This would have decreased the rate of clearance of protein from the joint space. In contrast, synovial inflammation resulting from the injury would have increased clearance of the 'marker' from the joint space; even low grade synovitis, with a synovial fluid leucocyte count no greater than 1000-2000 cells/mm³, may increase clearance of protein from the joint space three- to fourfold.² If the rate of clearance is not controlled for, the authors' conclusion that abnormalities in synovial fluid concentrations of the molecules measured reflect quantitative changes in articular cartilage metabolism may be misleading.²⁻⁴ The possibility that joint structures other than articular cartilage (inflamed synovium, damaged cruciate ligament or meniscus) contributed significantly to the synovial fluid concentrations of the molecules measured also should not be overlooked.

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- 1 Dahlberg L, Roos H, Saxne T, *et al.* Cartilage metabolism in the injured and uninjured knee of the same patient. *Ann Rheum Dis* 1994; 53: 823-7.
- 2 Myers S L, Brandt K D, Eilam O. Even low-grade synovitis significantly accelerates clearance of protein from the canine knee. Implications for measurement of synovial fluid "markers" of osteoarthritis. *Arthritis Rheum* 1995. In press.
- 3 Wallis W J, Simkin P A, Nelp W B, Foster D M. Intraarticular volume and clearance in human synovial effusions. *Arthritis Rheum* 1985; 28: 441-9.
- 4 Levick J R. Synovial fluid: determinants of volume turnover and material concentration. In: Kuettner K, Schleyerbach R, Peyron J G, Hascall V C, eds. *Articular cartilage and osteoarthritis*. New York: Raven Press, 1992; 529-41.

AUTHORS' REPLY:

The intra-articular volume and rate of removal of fluid from the joint have to be considered when interpreting the results of studies of matrix products in synovial fluid.^{1,2} We have discussed this previously;³⁻⁵ it is one reason why we suggested changes in cartilage metabolism in both knees after unilateral knee injury rather than concluded that a difference in cartilage metabolism existed in both knees after unilateral knee injury, as wrongly quoted by Myers and Brandt.

As all the fluid in a joint cannot be aspirated, the total intra-articular fluid volume is not easily established. A possible method for such calculations is to use the concentration difference of a particular molecule between the fluid initially aspirated and in the aspirate obtained after saline lavage. Because of the discomfort for the patients, it is difficult to use this method routinely. However, Geborek *et al.*⁶ have shown that when aspirated volumes are less than 10 ml there is a considerable discrepancy between aspirated volume and total intra-articular volume. In our healthy athletes, as in the uninjured and injured knees in the chronic phase (more than six months after the injury), the aspirated joint fluid volumes were generally small.⁷ Accordingly, the difference in aspirated volume between the reference knees and the injured and uninjured knees may not be significant. Furthermore, the group of athletes had been extensively examined and we considered them healthy.^{8,9} We disagree with the approach that Myers and Brandt suggest to normalise for dilution between groups. The proportion of the total synovial fluid that is aspirated in a given subject is much too variable to allow such an approach. Furthermore, the efficiency of aspiration in the contralateral knee joint may be quite different from that of a normal knee. From the experience of the authors, there seems to be a positive correlation between the synovial fluid marker concentration and total amount of the marker in the joint, rather than a 'volume dilution effect'.^{3,10}

Unfortunately, we do not have access to the first study referred to by Myers and Brandt, which is still in press; thus it is impossible for us to comment upon these results. In the study they cite by Wallis *et al.*,¹ a relationship was demonstrated between the degree of inflammation and the clearance rate in patients with osteoarthritis and rheumatoid arthritis with obvious joint effusion. In our study,⁷ the patients did not have rheumatoid arthritis or osteoarthritis, and they did not show any clinical or arthroscopic signs of inflammation. It therefore seems unlikely that a difference

in clearance would have contributed significantly to the results. However, if such a difference existed between the injured and uninjured joint, this would only reinforce our suggestion that the contralateral uninjured joint cannot be recommended as the only control joint in synovial fluid studies.

We agree with Myers and Brandt that a change in gait pattern may be the reason for the difference in synovial fluid marker concentration between the injured and uninjured joint.⁷ However, the relative importance of changes in joint loading or clearance for the difference in synovial fluid marker concentration between the injured and uninjured joint is not known.

The findings in our study are further supported by a study by Bensen *et al.*¹¹ in which the authors showed evidence for degenerative changes in the articular cartilage of the contralateral, unoperated knee joint in the Pond-Nuki model of osteoarthritis.

We appreciate the interest and comments of Drs Myers and Brandt; however, we feel that their main concern regarding the presence of an abnormality of cartilage metabolism in the uninjured knee is not warranted on the basis of statements in our paper. We suggest, rather than conclude, that cartilage metabolism is altered also in the uninjured knee joint. The underlying mechanism for the observed alterations is not known, which was also stated. However, we believe that the findings support the conclusion that the contralateral knee cannot be recommended as the only control joint in synovial fluid studies of patients with unilateral knee injury.

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