Recurring synovitis as a possible reason for aseptic loosening of knee endoprostheses in patients with rheumatoid arthritis

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We evaluated histologically samples of synovial tissue from the knees of 50 patients with rheumatoid arthritis (RA). The samples were taken during revision for aseptic loosening. The findings were compared with those in 64 knees with osteoarthritis (OA) and aseptic loosening and in 18 knees with RA without loosening. The last group had been revised because of failure of the inlay or the coupling system of a constrained prosthesis. All the patients had had a total ventral synovectomy before implantation of the primary prosthesis.

In all three groups a foreign-body reaction and lymphocellular infiltration were seen in more than 80% of the tissue samples. Deposits of fibrin were observed in about one-third to one-half of the knees in all groups. Typical signs of the reactivation of RA such as rheumatoid necrosis and/or proliferation of synovial stromal cells were found in 26% of knees with RA and loosening, but not in those with OA and loosening and in those with RA without loosening.

Our findings show that reactivation of rheumatoid synovitis occurs after total knee replacement and may be a cofactor in aseptic loosening in patients with RA.

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There are many causes of aseptic loosening of joint replacements. The technique of fixation and the quality of the bone determine the initial result, but the long-term outcome depends on the extent of the biomechanical stress on the components due to the activities of daily living and the exact axial positioning of the prosthesis. Malalignment has been found to be the main reason for aseptic loosening of the tibial component which is the most common site of loosening in total knee replacement.1-3

In a study of aseptic loosening of ten endoprostheses in nine patients with rheumatoid arthritis (RA) Inoue et al4 found rheumatoid noduli at the cement-bone interface in two and lymphoplasmatic cellular infiltrations at the cement-bone interface or in the regenerated synovium in three. They concluded that a recurrence of RA can be a cofactor in aseptic loosening. The series, however, was small, four hip and six knee replacements, and did not include a control group of patients with RA without aseptic loosening. Thus, their conclusions that these histomorphological findings cause aseptic loosening could only be drawn with some reservations. In another study, Cooke5,6 suggested that rheumatoid synovitis does not recur after total joint replacement with complete removal of the antigen-containing cartilage.

We have therefore carried out a prospective study in patients with RA and aseptic loosening of total knee replacement and compared the histological findings in the synovium with those of a group of patients with osteoarthritis (OA) and aseptic loosening and with a group of patients with RA without any loosening of the component.

**Patients and Methods**

We studied 50 patients (42 men, 8 women) with RA and aseptic loosening of a cemented knee prosthesis. During revision we performed a total ventral synovectomy and examined the synovial tissue histologically. The results were compared with those of 64 patients (48 women, 16 men) with OA who had undergone the same procedure, and with those of 18 (13 women, 5 men) with RA with fixed components. In the last group synovial tissue was removed during the course of changing the inlay or coupling system of a cemented hinged knee prosthesis because of failure.
We included in the study only those patients who had had a total ventral synovectomy during the primary implantation of the prosthesis. Implants with malaligned components were excluded because the malalignment was most probably the main reason for aseptic loosening. In addition, joints with histological or microbiological findings of infection were excluded. For patients in whom both knees were affected, the joints were randomised.

All the patients with RA were taking disease-modifying drugs. In those with loosening of the component 27 received methotrexate, eight gold, eight chloroquine or hydroxychloroquine, four sulphasalazine and three azathioprine. Of the 18 patients without loosening ten received methotrexate, three gold, three chloroquine or hydroxychloroquine, one sulphasalazine and one azathioprine. In the patients with RA and loosening 42 were taking nonsteroidal anti-inflammatory drugs (NSAIDs) and 26 steroids. In the other group, 17 patients received NSAIDs and four steroids.

Histological examination. The synovial tissue removed during revision surgery was fixed in 4% formalin, cut and embedded in paraffin. The histological samples were processed in the conventional manner. Slices 3 to 4 μm in thickness were stained with haematoxylin and eosin, van Gieson, Goldner and PAS. Immunohistochemical staining was performed using the avidin-biotin-streptavidin peroxidase technique with monoclonal antibodies against T lymphocytes (CD3, CD4, CD8), B lymphocytes (CD 19) and macrophages (CD 68).

All the histological sections were examined independently and blindly by two pathologists specialised in RA (JB, CM-S). We excluded bacterial synovitis according to the following morphological criteria: absence of granulocyte infiltration in synovial and scar tissue and synovial surface fibrin, and absence of lamellar fibrin. The following parameters were determined: mechanically-degenerative changes, foreign-body reactions, deposits of fibrin, lymphocellular infiltration, proliferation of synovial stromal cells and rheumatoid necroses. Mechanically-degenerative changes included synovial or scar tissue with mucoid degeneration of fibrous tissue, loosening of collagen fibres and hyalinoses according to the description of Fassbender.7 Rheumatoid necroses belong to the specific morphological feature of seropositive rheumatoid arthritis as described by Fassbender.8 The centre is formed by necrotic type-I collagenous fibres, and is surrounded by a dense palisade of connective-tissue cells. Proliferation of synovial stromal cells has been described by Fassbender9 and is a characteristic feature of RA. Because rheumatoid necrosis and proliferation of synovial stromal cells are specific for RA both were combined to form a histological parameter named rheumatoid synovitis. The frequency of these changes was compared in all three groups of patients and between the different compartmental replacement techniques in each group.

Statistical analysis. Values for the continuous variables (age, years between primary replacement and revision and Larsen grading of rheumatic joint destruction) were quoted as the mean and standard deviation for each group. For binary variables absolute and relative frequencies were tabulated. We used the Mann-Whitney U test to determine differences concerning age and years of revision between the patients with RA and loosening of the component and the two control groups. The odds ratios (OR) and the exact 95% confidence limits (CI) were calculated using StatXact version 4.01 (Cytel Software Corporation, Cambridge, Massachusetts) and adjusted odds ratios by the logistic regression model. Because there were no real differences between the adjusted and unadjusted odds ratios for simplicity only exact unadjusted odds ratios are presented. To compare frequencies we used Fisher’s test in two-by-two tables; otherwise we used the generalised Fisher test. The level of significance was determined at p < 0.05.

Results

The mean age of the RA patients with loosening at the time of revision was 60.7 years (sd 9.8), of the OA patients with loosening 71.7 years (sd 10.1) (p < 0.001) and of the RA patients without loosening 64.2 years (sd 7.7) (p < 0.001 and p = 0.189) (Table I). In the RA patients with loosening the mean time for revision was 8.3 years (sd 4.0), in the OA patients 9.2 years (sd 3.8) and in the RA patients without loosening 7.1 years (sd 2.6) after primary implantation (p = 0.026 and p = 0.188) (Table I). At the time of primary joint replacement the radiological grading of rheumatic destruction of the joint according to Larsen, Dale and Eek10 was 3.9 (sd 0.7) for RA with loosening and 4.0 (sd 0.4) for RA without loosening (p = 0.705) (Table I).

In the RA patients with loosening 29 had tricompartmental replacements (21 hinged total endoprostheses and eight surface replacements), 11 had bicondylar sledge prostheses and ten had unicompartmental replacements (four medial and six lateral sledge prostheses). In the patients with OA 34 had tricompartmental replacements (19 hinged total endoprostheses and 15 surface replacements), eight bicondylar sledge prostheses and 22 unicompartmental sledge prostheses (15 medial and seven lateral). In the patients with RA and no loosening a constrained prosthesis with a sliding hinged system (Interplanta; Link, Norderstedt, Germany) had been used. We used this implant frequently in the late 1980s and early 1990s. After some years the coupling mechanism frequently fails and has to be changed. In this group of 18 patients 11 had a patellar replacement and seven did not. The distribution of frequencies was significantly different between the three groups (generalised Fisher’s test p = 0.007).

Histological examination. The intraobserver reproducibility of the two pathologists and the test and retest reliability for the histological findings were 99%.

Mechanically-degenerative changes were found in 21 (42%) of the knees with RA and loosening, in 54 (84%) of those with OA (p < 0.001, OR = 0.13, CI = 0.05 to 0.32)
and in 11 (61%) of those with RA without loosening (p = 0.182, OR = 0.46, CI = 0.15 to 1.38) (Table I). With the exception of three knees with RA and loosening and one with RA without loosening all the knees (94% RA with loosening, 100% OA (p = 0.082, OR = 0.0, CI = 0.0 to 1.86)) and 94% of RA without loosening (p = 1.0, OR = 0.92, CI = 0.02 to 12.47) had a macrophage foreign-body reaction (Fig. 1, Table I). Lymphocellular infiltration was seen in 43 (86%) of the knees with RA with loosening, in 56 (88%) of those with OA (p = 1.0, OR = 0.88, CI 0.29 to 2.6) and in 15 (83%) of those with RA and no loosening (p = 0.717, OR = 1.23, CI = 0.28 to 5.36) (Fig. 1; Table I). There was no lymphocellular infiltration without an accompanying foreign-body reaction. Fibrin was detected in 17 (34%) of the knees with RA and loosening, in 27 (42%) of those with OA (p = 0.44, OR = 0.71, CI = 0.32 to 1.52) and in 9 (50%) of those with RA and no loosening (p = 0.267, OR = 0.52, CI = 0.17 to 1.53) (Table I). The fibrin was older with cartilage, bone fragments, and signs of organisation.

In four knees with RA with loosening the synovial tissue contained rheumatoid necroses (8%) (Fig. 2), but none was seen in knees with OA (p = 0.035, OR = +∞, CI = 0.87 to +∞) and in knees with RA without loosening (p = 0.567, OR = +∞, CI = 0.24 to +∞) (Table I). Ten knees (20%) with RA and loosening showed a proliferation of synovial stromal cells (Figs 3 and 4) which was not observed in knees with OA (p < 0.001, CI = 3.32 to +∞) or in knees with RA without loosening (p = 0.052, OR +∞, CI = 0.88 to +∞) (Table I). The stromal cell proliferation was never observed in close proximity to a foreign-body reaction. In one patient of the first group (RA with loosening) we saw both rheumatoid necrosis and synovial stromal cell proliferation. Thirteen knees (26%) showed histomorphological findings of a recurrence of rheumatoid synovitis. Thus these histological characteristics were significantly more common in knees with RA and loosening compared with the other two groups for all the replacement groups (p < 0.001, OR = +∞, CI = 4.84 to +∞), p = 0.015, OR = +∞, CI = 1.28 to +∞) (Table I). In a comparison of the different replacements within the group of patients with RA and loosening, synovial stromal cell proliferation was more common in tricompartmental than in uni- or bicompartamental replacements (Table I). These differences in frequency did not, however, reach statistical significance. The other histological parameters showed similar changes in the different replacements (Table I).
Our findings show a high percentage of foreign-body reactions and lymphocellular infiltrations in all three groups of patients. A lymphocellular infiltration without an accompanying foreign-body reaction was never seen. Kaufman, Tong and Beardmore\textsuperscript{11} made the same observation in 12 patients with RA and eight with OA on synovial samples taken during revision. Five of their patients had no loosening of the component. Thus, lymphocellular infiltration and a macrophage foreign-body reaction are found in prosthetic synovitis with debris synovitis due to wear as has also been pointed out by Boynton et al\textsuperscript{12} and Sandhu et al.\textsuperscript{13} This limits the specificity of a lymphoplasmacellular infiltration of synovial tissue as an indicator for the reactivation of RA as was suggested by Inoue et al.,\textsuperscript{4} even if it is one of the characteristics of rheumatoid synovitis.\textsuperscript{14-17}

We saw clear histomorphological evidence of rheumatoid synovitis (rheumatoid necroses and/or synovial stromal cell proliferations) in 13 (26%) of the knees with RA and loosening. Low et al\textsuperscript{18} observed a recurrence of RA in about 15% (five of 34 joints) after a mean of 28.6 months after knee replacement. Even after a primary synovectomy reactivation of RA is theoretically possible since the histomorphological quality of the subsequently regenerating new synovial tissue is similar to that of primary synovial tissue, and has only a distinctly lower inflammatory activity at first.\textsuperscript{19}

Reactivation of rheumatoid synovitis does not appear to be controllable solely by total removal of all cartilage during implantation of a tricompartmental prosthesis as was postulated by Cooke.\textsuperscript{5,6} In our study 9 of 13 knees (70%) with reactivation of rheumatoid synovitis had received a tricompartmental prosthesis as the primary implant. Moreover, Low et al\textsuperscript{18} did not find a statistically significant difference in the degree of synovialitic reactivation between prostheses with and without patellar replacement.

We found that histological signs of recurring synovitis were seen only in patients with RA with loosening but not in those without loosening. We did not examine the tissues of the interface membrane of the femur and tibia because of insufficient tissue for comparison with the group with RA and no loosening. Nevertheless, our findings may still indicate that recurring synovitis has a role in aseptic loosening as suggested by Inoue et al.\textsuperscript{4}

It is also possible that chronically inflamed synovitis tissue which was not removed during the primary procedure, may have a similar effect and thus lead to loosening. Since such a synovitis cannot be controlled solely by the replacement of all joint surfaces, primary implantation in RA should include radical synovectomy to lessen the risk of aseptic loosening. This is supported by the findings of Low et al\textsuperscript{18} who observed a postoperative reactivation of RA in four of 12 patients in whom synovectomy had not been carried out during the primary implantation. Of 22 patients who had received primary synovectomy, however, only one had reactivation of RA.
The deposits of fibrin observed in all three groups may be related to an inflammatory process secondary to wear debris. They could represent a reaction to the primary arthroplasty procedure, but this is unlikely since there is usually a long interval between the primary implantation and revision. In the patients with OA with loosening it is likely that the higher frequency of mechanical degenerative changes in comparison with the RA group with loosening is due to mechanical destruction of the joint in OA.

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References