Epiphyseal Osteonecrosis in Transplanted Patients: Effect of Surgical Treatment

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Renal transplantation has become an accepted treatment of terminal renal failure. Despite its increasing efficiency, however, it still entails a significant morbidity related largely to the use of immunosuppressive agents and corticosteroids.

Disabling bone necrosis in transplanted patients was first observed in 1964 (Starzl et al, 1964), but has been reported with an increasing frequency over the last years (Moens, 1966; Bravo et al, 1967; Cruess et al, 1968; Hall et al, 1969; Evrard & Phalen, 1971; Fisher & Bickel, 1971; Harrington et al, 1971). Although it appears clearly that steroid administration is mainly responsible for the development of this complication, the factors by which this relationship is mediated remain disputed. It has been suggested that steroid induced changes in fat metabolism result in fat embolism and, thus, ischaemic osteonecrosis (Bravo et al, 1967). Alternatively, the possibility that steroid induced osteoporosis produces microfractures with interruption of the bone vascular supply has been raised (Miles, 1968).

The present study was undertaken in order to evaluate the incidence of osteonecrosis in a large number of transplanted patients, to define the pathogenic factors involved in the development of this complication, and, finally, to analyse our experience of the surgical correction of hip osteonecrosis.

MATERIAL

Between June 3, 1963 and May 1, 1971, 152 renal allografts were performed on 138 patients at the St-Pierre University Hospital of Louvain. Of these patients, 10 had 2 transplants, and 2 others had 3. Twenty-two grafts came from living donors, 130 from cadavers. On May 1, 1972, 86 patients were alive, 71 of whom had a functioning graft, whereas 52 died between 1 day and $4\frac{1}{2}$ years after transplantation. The 1 year patient survival is 84% for the living donor series and 71% for the patients who received a cadaver transplant.

Immunosuppressive therapy remained basically unchanged throughout the
years: azathioprine was given from the first day (2-3 mg/kg/day). Most patients received Prednisolone only from the third day post-operatively (50 mg daily initially with a gradual reduction to reach 10-20 mg/day after one year) and Actinomycin C (200 μg weekly for the first six months). Antilymphocyte globulin has been given routinely during the first six months from 1968 through 1969. Acute rejection episodes were treated with massive, rapidly decreasing doses of Prednisolone (300 mg on day 1), occasionally by transplant irradiation and, since 1968, by antilymphocyte globulin in a few patients.

X-rays were reviewed for evidence of epiphyseal bone necrosis. Four stages of X-ray lesion were defined (Figure 1). Stage 0 refers to the possibility of necrosis as evidenced by areas of modified radiodensity of the epiphysis. Stage 1 is the first in which the diagnosis is unequivocal: there is a subchondral radiolucent crescent line (Norman & Bullough, 1963). The femoral head has a normal contour or presents a minimal loss of its spherical shape. In stage 2 the zone of necrosis assumes its familiar pattern: a wedge shaped

Figure 1. Evolution of femoral head necrosis. The description of the different stages of X-ray lesions is given in the text.
area of increased radiopacity with the base adjacent to the articular cartilage and with the apex pointing deep into the head. The collapse of the sequestrum is evident. Stage 3 is characterised by secondary osteoarthritic changes of the joint.

Other steroid-induced lesions such as spontaneous fractures of the ribs or of the pubic rami were not included. Only patients meeting the following criteria were included in the present study:

1. patients who were followed up at our institution after transplantation;
2. patients who had received steroid therapy for more than 3 months;
3. patients with appropriate X-ray data obtained more than 3 months after transplantation.

The total number of patients was 90, 54 males and 36 females, with a mean age of 35.2 years.

RESULTS

Incidence Out of the 90 patients, 13 (15%) showed evidence of epiphyseal bone necrosis. Femoral head necrosis was observed in 12 patients. It was bilateral in 10 and unilateral in 2. In 1 patient the only lesion consisted of bilateral femoral condyle necrosis. Additional epiphyseal necroses were found in 3 patients (humeral capitellum necrosis in 1 patient, humeral head necrosis in 3 patients). In addition, 4 patients showed patchy metaphyseal lesions of the tibia and/or of the inferior femoral metaphysis, similar to those observed in pancreatitis (Immelman et al, 1964).

The incidence of bone necrosis was the same throughout the years: it appeared in 4 patients out of 27 transplanted from 1963 to 1967, in 5 out of 33 transplanted from 1968 through 1969 and in 4 out of 30 transplanted from 1970 to May 1, 1971.

Table I. Effect of age on the incidence of epiphyseal bone necrosis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>10-20</th>
<th>20-30</th>
<th>30-40</th>
<th>40-50</th>
<th>50-60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>8</td>
<td>13</td>
<td>39</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients with EBN</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Age of the affected patients averaged 32 years at the time of transplantation (range 17-44). The incidence of epiphyseal bone necrosis was similar in all age groups as shown in Table I. Sex did not appear to predispose to bone lesions as 6 out of 36 females versus 7 out of 54 males had epiphyseal necrosis.

Evolution of epiphyseal bone necrosis X-ray diagnosis of the first epiphyseal bone necrosis was made on average 17.2 months (range 5-49 months) after
transplantation. In the 3 patients with multiple epiphyseal lesions the first involved joint was always the hip. Pain in the hip or in the knees preceded bone lesions in the lower limbs, by an average of 1.8 months (range 0-9). In some instances, repeated X-ray examination failed to detect significant lesions up to 2 months after the beginning of the complaints, a finding which has already been reported (Hall et al, 1969; Harrington et al, 1971).

Out of 12 patients with necrosis of the femoral head, 3 had bilateral lesions at the time of the first diagnosis. In 9 patients, only one hip was initially involved but in 7 of them the disease became bilateral within an average of 5.9 months (range 0.5 to 12 months).

The evolution of the hip lesion has been evaluated. Transition from stage 0 to 1 was observed in 10 hips within 8 months (range 1 to 20 months), from stage 1 to stage 2 in 11 hips within 8.4 months (range 1.5 to 21 months) and from stage 2 to stage 3 in 6 hips within 5.9 months (range 2 to 14.5 months). It should be pointed out that in 2 patients femoral head involvement has remained unilateral, the other hip showing signs compatible with stage 0 for a period of follow-up of 22 and 2 months respectively.

Surgical treatment A total of 14 cup arthroplasties following the technique of Merle d'Aubigné et al (1965) were performed up to May 1, 1972 in 9 patients (Figure 2). At the time of operation, femoral head necrosis had reached stage

Figure 2. Successful bilateral cup arthroplasty. Note that more than two years after operation the cups are well located and that there is no tendency to protrusion through the acetabulum
Figure 3. Failure of cup arthroplasty. Stage 3 bone necrosis was reached before operation (left). Despite a cup arthroplasty, the head protruded through the acetabulum (centre) so that, 31 months later, a total hip prosthesis (right) was performed.

1 and 2 in 7 patients (11 hips) and stage 3 in 2 patients (3 hips). In one of these latter cases, cup arthroplasty resulted in a progressive acetabular protrusion and a total replacement prosthesis was made 31 months later (Figure 3). Interval between diagnosis and surgical repair averaged 10.1 months (range 0-31 months). Surgical complications were minimal, except in one patient who developed paraarticular calcification.

The results of the cup arthroplasties (12) and of the total hip replacement performed prior to February 1, 1972 and still in use on May 1, 1972 were rated according to Merle d'Aubigné and Postel (1954) for pain, mobility and gait. Follow-up ranged from 3 months to 4 years. Results for pain were rated as excellent (score 6 or 5) in 10 hips, average in 2 (score 4) and poor (score 3) in 1 hip. Results for mobility were excellent in the 13 hips. Results for gait were excellent for 6 patients and average in 2.

Predisposing factors In order to evaluate factors predisposing to epiphyseal necrosis, the 13 patients with epiphyseal bone necrosis (patient group) were paired with 13 others chosen on the basis of having their operation about the same time, having similar ages and the same sex (control group). Several parameters obtained prior to transplantation and/or around the time at which the diagnosis was made in the patients with bone lesions were compared.
1. Total amount of prednisolone:
   An average of 13,452 mg of prednisolone had been given in the patient
group up to the diagnosis of bone lesion, versus 12,739 mg of prednisolone
in the control group over the same interval. There was no significant
difference between the two series.

2. Number of acute rejection episodes:
   Over the time interval considered, the patient group had an average of
1.8 rejection episodes (range 0-5) as compared with a mean of 1.1
(range 0-4) in the control group. It is especially noteworthy that epi-
physyeal bone necrosis developed in 3 patients who had never undergone
rejection. At the time of the diagnosis there was no significant difference
in mean plasma creatinine value, measured in 12 pairs, between
the patient (mean 1.28 mg/100 ml) and the control group (mean 1.42 mg/
100 ml).

3. Serum albumin level:
   Corticosteroid toxicity has been related to the serum albumin level
(Lewis et al., 1971). No significant difference was found between the
patient and the control groups, serum albumin averaging 2.98 g/100 ml
versus 3.36 g/100 ml respectively prior to transplantation and 3.25 g/
100 ml versus 3.47 g/100 ml respectively at the time of diagnosis.

4. Cholesterol:
   Serum cholesterol values were not different in the two groups. It aver-
aged 227 mg/100 ml versus 212 mg/100 ml prior to transplantation in
the patient and in the control group respectively and 265 mg/100 ml
versus 249 mg/100 ml at the time of diagnosis.

5. Osteoporosis
   The degree of osteoporosis was evaluated by means of the femoral score
as determined by Barnett and Nordin (1960). At the time of diagnosis, it
was virtually identical in both groups: 54.2% in the patients versus 54.8%
in the control series.
   The possible role of pre-existing hyperparathyroid bone disease was
excluded as no patients with bone necrosis showed any X-ray signs of
parathyroid overactivity prior to transplantation versus 3 in the control

6. Weight gain
   In view of the possible effect of weight on weight bearing joints, the gain
in weight observed after transplantation was compared in both groups.
It was not different, averaging 15 kg in the patients versus 14 kg in the
control subjects.

DISCUSSION

The present results underline the frequency of bone necrosis as a complica-
tion of renal transplantation. Indeed, 15% of the patients receiving immuno-
suppressive therapy for more than 3 months develop severe disabling joint
disease. Several groups have reported their experience of epiphyseal bone
necrosis in transplanted subjects. The incidence ranges from 5 to 13% (Bravo
Harrington et al, 1971). These figures are probably too low as they are calculat-
ed on the total number of transplanted patients without distinction between
early failures in which necrosis is unlikely to have had sufficient time to de-
velop and longer survivals. Cruess et al (1968) have reported an incidence
of 37% in their series of 27 patients treated with steroids for more than six
months, a value strikingly higher than that observed in the present study.

The success of surgical repair of the hip obtained in our patients deserves
emphasis. Until recently, a conservative attitude has been advocated in the
management of femoral head necrosis in transplanted patients (Hall et al, 1969).
Poor results were reported by Cruess et al (1968) after an Austin Moore pros-
thesis insertion in one patient. More recently, however, Harrington et al
(1971) and Evrarts and Phalen (1971) have published results showing improve-
ment in a total of 12 patients treated with cephalic prostheses. Just as in our
patients, morbidity of surgery was low.

The present technique of arthroplasty with a cup fitted to the femoral head
without any removal of acetabular cartilage was described by Merle d'Aubigné
et al (1965). It offers several advantages over other types of prostheses. It
respects the elastic properties of the femoral neck and thus is likely to de-
crease the incidence of secondary lesions of the acetabulum and to provide
better long term results than the Austin Moore prosthesis. Furthermore,
failure of cup arthroplasty leaves the possibility open to several other recon-
structive procedures. Finally, risk of sepsis is lower than with the other
larger prostheses.

In order to be effective, cup arthroplasty should be performed at an early
stage, preferably at the beginning of stage 2 femoral head necrosis. The only
failure of this series was encountered in a patient with severe osteoarthritic
changes (stage 3). As a consequence, acetabular protrusion progressed,
necessitating total hip replacement.

Further support for early surgical treatment is gained from our experi-
ence of the natural history of femoral head necrosis. The evolution appears
to be relentless in the majority of patients, progression from stage 1 to stage
3 averaging approximately 14 months. This evolution appears to be more
rapid than that observed in idiopathic femoral head necrosis (Merle d'Aubigné
et al, 1965).

Several discussions of the aetiology of epiphyseal bone necrosis after renal
transplantation have been published. It appears quite clearly that the main
culprit is corticosteroid therapy (Fisher & Bickel, 1971; British Medical
Journal, 1972). We have attempted to define further the factors predisposing to bone lesions in our affected patients by matching each of them with another unaffected subject. This analysis has been disappointing. As previously reported by others (Cruess et al, 1968) age and sex played no role. Neither total dosage of corticosteroids, nor the number of rejection episodes differed in the two groups, a finding which is at variance with those of Harrington et al (1971), but similar to those of Hall et al (1969) and Cruess et al (1968).

The fact that bone necrosis developed in three patients who had never undergone rejection further emphasises that the amount of corticosteroids given is not necessarily a crucial factor in the development of bone disease. However, it should be noticed that the range of prednisolone dosage used in our patients is much smaller than that reported by Harrington et al (1971).

Among the other factors reported to influence the toxic effects of steroids (Lewis et al, 1971), serum albumin levels were not found different in affected and unaffected patients. Unfortunately, no detailed analyses of lipid metabolism were done. Nevertheless, cholesterol levels were similar in both groups of patients, a finding which stands in contrast with the observation of Fisher and Bickel (1971) who found elevated levels in 12 out of 19 patients with corticosteroid induced osteonecrosis. Finally, no effect of previous osteoporotic or hyperparathyroid bone disease could be documented, a finding which is in agreement with Cruess et al (1971). Therefore, our data do not cast any light on the mechanism by which corticosteroid administration predisposes to osteonecrosis.

**SUMMARY**

The incidence of epiphyseal bone necrosis was assessed in a series of 90 transplanted patients who had received immunosuppressive therapy for more than three months.

Lesions were found in 13 patients (15%) within 5 to 49 months after transplantation. The femoral condyle was involved in 1 case, the femoral head in 12 cases, the humeral head in 3 cases and the humeral capitellum in 1 case. Hip necrosis progressed from stage 0 (probable diagnosis) to stage 3 (femoral head collapse associated with osteoarthritic changes) within an average of 22 months.

Fourteen cup arthroplasties of the hip were performed in 9 patients. In one patient, cup arthroplasty was followed within 31 months by a total hip prosthesis. Results of 13 prostheses performed in 8 patients followed for more than 3 months (range 4 years - 3 months) were excellent for 10, average in 2 and poor in one hip for pain, excellent in the 12 hips for mobility, whereas gait was excellent in 6 patients and average in 2.

Factors predisposing to steroid induced osteonecrosis were evaluated. The 13 affected patients were matched for sex, age and time of operation
with 13 transplanted subjects unaffected by bone necrosis. No difference was found between the two groups as to the total dosage of prednisolone, the number of rejection episodes, serum albumin and cholesterol levels, degree of osteoporosis, incidence of hyperparathyroidism or weight gain after transplantation.

ACKNOWLEDGMENT

This work was supported by a grant from the Fonds de la Recherche Scientifique Médicale.

REFERENCES

Editorial (1972) British Medical Journal, 1, 1581
Immelman, E. J., Bank, S., Krige, H. and Marks, I. N. (1964) American Journal of Medicine, 36, 96
OPEN DISCUSSION

C M KJELLSTRAND (Minneapolis): A very excellent presentation of a most distressing problem in the transplanted patient. There was in The Lancet a few years ago an article suggesting a connection between urologic chronic renal disease with urinary tract abnormalities and osteoarthritis. Have you tried to correlate the patient’s original kidney disease with the occurrence of this complication?

TROCH: No.

G THIEL (Basle): I wonder if you have some experience on just doing nothing in these patients? We saw a couple of patients in Switzerland with femoral head necrosis not treated and it looked to us as if, after two or three years, their symptoms just seemed to level off and disappear without doing anything. I was wondering if you treat them early you might treat patients who don’t really need treatment, even if the X-ray looks terrible.

TROCH: And the patients — are they now symptom free?

THIEL: Generally we have observed a progressive evolution with symptoms.

A D BARNES (Birmingham): We would like to agree with Dr Thiel that if you wait these patients lose their symptoms very markedly. The other comment I would like to make is the time it took your patients to develop this complication. Certainly one of ours developed changes within two months of transplantation and the condition radiologically was much more rapidly progressive than yours. Was there a great variation between your patients?

TROCH: Yes, very great variation.

V PARSONS (London): You must have got a lot of bone from these patients since you operated on them. What did the femoral heads look like when you sectioned the bone, under the microscope?

TROCH: The technique is a cup arthroplasty — it is not a head replacement.

PARSONS: You have no bone from these patients to look at?

TROCH: One.

PARSONS: What did the bone show?
TROCH: I have no information on this.

K F KOPP (Salt Lake City): You stated that you found no correlation with the dosage of prednisone. Would you maintain that the necrosis had nothing to do with medication of steroids at all?

TROCH: No. There was a control group that showed about the same mean and range.

KOPP: What are your feelings about corticosteroids as such?

TROCH: There is a relation, naturally, between corticoid therapy and bone necrosis.

KOPP: There are no controlled studies without steroids.

J H THAYSEN (Copenhagen): Did you ever see this complication in dialysed patients before transplantation?

TROCH: No, we have no patients with this sort of complication.

THIEL: I wonder if you or somebody else in the audience has experience with $^{85}$Sr scintigraphy in these patients. It looked to us as if a change in the Strontium scintigram was the earliest way to detect the beginning of femoral head necrosis.

Ch van YPERSELE (Louvain): In view of the comment there has been about the relationship between steroids and necrosis, I think it is quite obvious from the literature that steroids play a role of paramount importance in the development of bone necrosis. What we have tried to do within the population which was on the same basic schedule of steroids, was to see whether we could predict who was going to have bone necrosis in relation to how many rejections we had, and how much steroids he had received. Well, within a very narrow range, of prednisolone dosage, there is no detectable difference between the controls. This does not bring any point against the very well founded evidence that steroids are mainly responsible for bone necrosis. The second question was about the histology of the femoral head. We had only one femoral head removed to do a total hip replacement, and in this head we found very severe osteoporotic change.

F PARSONS (Leeds): We have been following the calcium content of the lower end of the femur in patients who have been treated by regular dialysis and
those following transplantation. The loss of calcium after transplantation is higher than any of our cases that have been treated by regular dialysis only. I think in assessing this particular problem post-transplantation, it is of vital importance to have the level of calcium in the bone monitored pre-transplant whilst the patient is on dialysis, because I am sure this increases post-transplantation and this may be one of the major factors involved in this situation.

M McGEOWN (Belfast): I have had a patient develop bilateral necrosis of the lower end of the femur at the knee joint. This was originally very painful but after about two years became pain free. Two years after that, the right knee joint suddenly locked due to a loose body, and loose bodies have subsequently been removed from both knees. Has anyone else had this experience? (No response, Editors).