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SKELETAL COMPLICATIONS FOLLOWING RENAL TRANSPLANTATION

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The occurrence of skeletal complications was examined in a series of 204 renal graft recipients who had maintained graft function for more than 12 months. Osteonecrosis was observed in 22 of the patients (11 per cent) from 5 to 46 months after the transplant operation. The lesions were often multifocal, with as many as 40 joints affected. The most common site was the femoral head, necrosis of which was recorded in 24 instances. The lesions here present a major clinical problem, and total hip replacement was deemed necessary in 4 cases, in all of which an excellent result was achieved.

Fractures had occurred after the transplantation in 53 patients (26 per cent), against only 6 before the operation. A total of 109 fractures had been sustained after periods ranging from 1 to 58 months, the most common site being the pelvic bones. The fractures were treated according to standard principles; no complications were encountered.

The skeletal complications were equally common among the males and females; they tended to occur at advanced ages.

They occurred to roughly the same extent whether the graft was from a related or a cadaveric donor and whether the patient had received one or more grafts.

Key words: corticosteroids; fractures; osteonecrosis; renal transplantation; total hip replacement

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In terminal renal failure, bone disorders – so-called renal osteodystrophy – are an almost constant finding (Nichols et al. 1972, Bonomini et al. 1973). The introduction of haemodialysis aggravated this situation by prolonging the life of the patient but rarely correcting the defect in bone metabolism (Bricker et al. 1969, Katz et al. 1969).

Renal transplantation seemed to offer better prospects through restoration of vitamin D metabolism (Haussler et al. 1976) and the calcium balance, and thus normalizing parathyroid function (Hampers et al. 1969, Zech et al. 1969, Pieper et al. 1977). Unfortunately, other skeletal complications arose, especially avascular bone necrosis (Bravo et al. 1967, Ibels et al. 1978, Pierides et al. 1975, Svahn et al. 1975) and fracturing (Nelson et al. 1971, Griffiths et al. 1974, Levine et al. 1977). These complications are often accompanied by incapacitating pain and dysfunction and they may well be the only factor standing in the way of rehabilitation of the patient.

The purpose of the present study was to analyse the occurrence of skeletal complications in a series of recipients of long-functioning renal grafts; special attention was given to the incidence of the complications, the clinical findings and the mode of treatment.

PATIENTS AND METHODS

In Stockholm between 1964 and 1976 a total of 392 renal transplantations were performed in 307 patients.

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Table 1. Age distribution for the 204 patients whose graft was still functioning after 12 months

Age, years	< 30	30 - 45	46 - 60	> 60	Total
No. of patients	53	72	68	11	204

Table 2. Occurrence of various primary renal diseases in the 204 patients with a functioning graft

	No. of patients
Renal disease	
Chronic glomerulonephritis	81
Chronic pyelonephritis	41
Polycystic kidney disease	25
Chronic nephritis	20
Diabetic nephropathy	9
Interstitial nephritis	7
Hydronephrosis	5
Nephrosclerosis	5
Nephrophthisis	4
Nephritis due to lupus erythematosus	3
Hamartoma	1
Arterial thrombosis	1
Cystinuria	1
Irreversible tubular necrosis	1

The 204 patients, whose graft was still functioning after 12 months constituted the series for this study.

The patients were followed up for between 12 and 165 months (median 46 months).

The patients – 117 males and 87 females – were aged from 6 to 66 years (Table 1). The most common underlying renal diseases were chronic glomerulonephritis, chronic pyelonephritis and polycystic kidney disease (Table 2). Parathyroidectomy was performed for hyperparathyroidism in 24 patients, in 18 of them before and in 6 after the transplantation. The indication for surgery in 22 cases was secondary, and in 2 cases, tertiary hyperparathyroidism. Two grafts had been received by 31 patients and three by 1 patient. Living related donors furnished 64 of the grafts, while 140 came from cadavers. A standard surgical technique was used: the graft artery was usually anastomised end-to-end to the hypogastric artery, except in a few instances when an end-to-side anastomosis to the external iliac artery was used. Venous drainage was effected by an end-to-side anastomosis to the external iliac vein. The ureter was implanted in the bladder and the kidney was placed extraperitoneally in the pelvis.

In all cases azathioprine and prednisone were given orally as a prophylactic immunosuppressive measure, the former in doses of 2–3 mg/kg/d, but less if leucopenia had developed. Prednisone treatment was usually introduced with 200 mg/d the amount being smaller for children and also adults of very small stature; the dose was gradually lowered to 20–40 mg/d at 1 month after the transplantation and then at a slower rate down to a maintenance dose of 10–20 mg/d at 1 year. In a few patients who were among the earliest to be treated the initial dose was as high as 400 mg/d and at 1 month 40–70 mg/d. From 1970 onwards 1 g of alpha-methylprednisolone was given intravenously on each of the first 3 days after transplantation. Most of the patients also received anti-lymphocyte globulin as prophylactic immunosuppressive treatment. Between 1966 and 1971 various preparations and dose schedules were used, but from September 1971 onwards the drug was given as a commercially available standardized product (Behring). The dose was 15–30 mg/kg of body weight, given intravenously for the first 21 days after the transplantation. Drainage of lymph through a duct fistula was performed as an adjunctive immunosuppressive measure in 52 of the patients. Where possible the fistulas were kept open for 1–2 months.

In the case of an acute rejection episode the daily oral dose of prednisone was increased to 200 mg; and then gradually reduced again to maintenance levels. During the period 1964–71 this treatment was combined with Actinomycin C given intravenously – 100 mg daily on 3 consecutive days. During the period 1964–71 the treatment for most of the rejection episodes included local irradiation of the graft kidney – 150 R on 3 consecutive days. From 1970 the treatment schedule was supplemented by the administration of alpha-methylprednisolone by intravenous injection – 1 g on 3 consecutive days. On diagnosis of chronic rejection the oral maintenance dose of steroids was in some cases increased to 5–20 mg.

The diagnosis of skeletal complications was based on hospital records, patient interviews and clinical and radiological findings. In the event of symptoms in any one site – the shoulders, hips, or knees – radiographic and scintigraphic examinations were made of all these joints (5 mCi $^{99}Tc^{m}$-pyrophosphate).

The chi-square method of analysis was applied.

RESULTS

Avascular necrosis

Incidence. In none of the patients was avascular bone necrosis present prior to the transplantation. This disease developed in 22 of the 204 recipients (11 per cent). The age of the afflicted patients ranged from 21 to 61 years, but the complication was most common among the patients over 45 years of age ($P < 0.01$) (Table 3). The incidence of avascular necrosis did not differ significantly in the recipients of related and cadaveric grafts (5/64 – 8 per cent; and 17/140 – 12 per cent, respectively). The incidence for the 32 patients receiving two or three renal grafts was

Table 3. Age distribution for the 22 patients with avascular necrosis of bone

Age, years	<30	30-45	46-60	>60	Total
Total number	53	72	68	11	204
Avascular necrosis					
No.	4	4	11	3	22
Per cent	8	6	16	27	11

not significantly different from that for the 172 given a single graft (3/32 – 9 per cent and 19/172 – 11 per cent, respectively). The complication was equally common among the female and the male patients (8/87 – 9 per cent and 14/117 – 11 per cent, respectively). Although diabetes mellitus and lupus erythematosus are diseases associated with spontaneous avascular necrosis of bone (Park 1976) none of the 11 patients with this complication suffered from either of these diseases. Avascular necrosis developed in 4 of the 18 patients who had had parathyroidectomy prior to the transplant operation (22 per cent) and in 18 of the 186 per cent who had not (10 per cent); the difference is not statistically significant.

Clinical findings. The period elapsing between the transplant operation and the onset of signs and symptoms ranged from 5 to 46 months (mean 15); in 11 of the 22 patients it was less than 12 months. A single bone was involved in 14 patients, while in the rest of the patients there were between two and six sites. Altogether 40 bones were affected, 35 of them weight-bearing (Table 4). The most common sites were the femoral heads, both of which were affected in 6 patients (Figure 1). Involvement of the femoral condyles was less frequent (Figure 2). Other sites were the humeral head, proximal tibia, talus, scaphoid and navicular bones (Table 5). In 6 of the 12 recipients with unilateral necrosis of the femoral head the renal graft was on the same side. Fractures occurred in 8 of the patients with avascular necrosis.

Table 4. Occurrence of various numbers of sites of avascular necrosis in the 22 patients with this complication

Number of necrotic sites	1	2	3	4	6	Total
Number of patients	14	3	2	2	1	22

Figure 1. Typical appearance of a hip joint with advanced osteonecrosis, with fragmentation and compression of the femoral head.

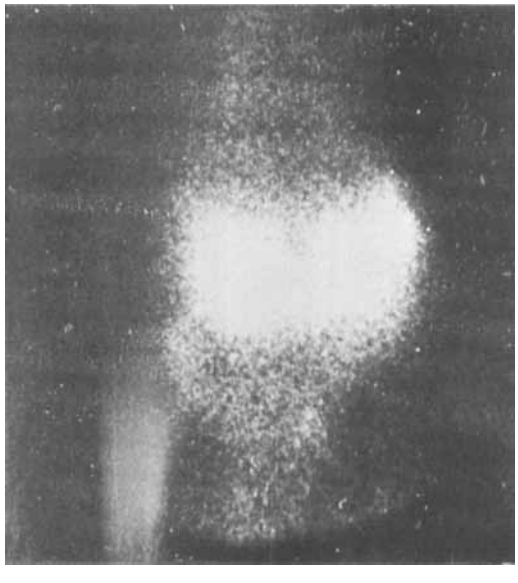

Figure 2. Increased uptake of the isotope, reflected in an intensification of osteoblastic activity due to extensive osteonecrosis in both femoral condyles.

Table 5. Location of avascular necrosis of bone

Site	No. of sites	No. of patients
Humerus, head	4	2
Scaphoid bone	1	1
Femur, head	24	18
" lateral condyle	3	2
" medial "	4	2
Tibia, medial "	2	1
Talar bone	1	1
Navicular bone	1	1

Treatment. Occasional or self-limiting pain was a feature of avascular necrosis at sites other than the hips; conservative measures taken during periods of aggravation were adequate. Necrosis of a femoral head could give rise to severe and incapacitating pain.

Non-weight-bearing was tried initially. Where this regimen was unsuccessful in alleviating the pain and where the osteonecrosis had progressed for at least 6 months total hip replacement was recommended (Figure 3). Charnley-Müller prostheses were used in four hip joints in 3 patients. The operations were performed under conditions of laminar air flow (Allander ceiling), with total body exhaust (Charnley); 2 g of cloxacillin was given intravenously every 6 hours, beginning 2 hours prior to surgery and continuing for 3 days. In all cases there was massive avulsion of osteocartilaginous fragments as described by Hall & Hume (1970) (Figure 4). The recovery was uneventful, and there was no evidence of a change in renal function. For all four hips the end result was excellent, with good strength and mobility, and no pain. The follow-up time ranged from 10 to 26 months.

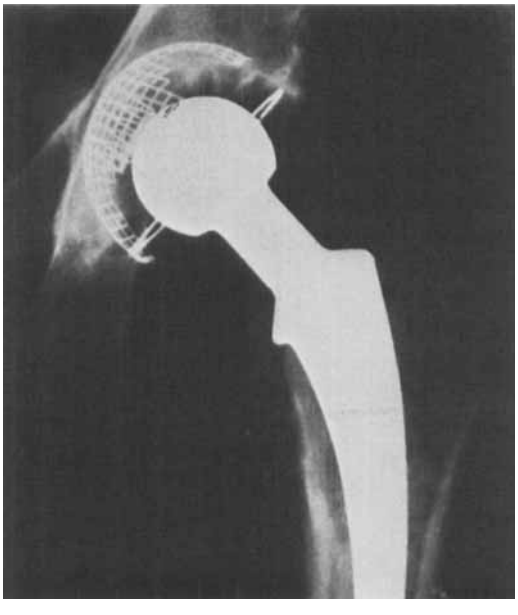

Figure 3. The hip joint in Figure 1 after its replacement with a Charnley-Müller prosthesis.

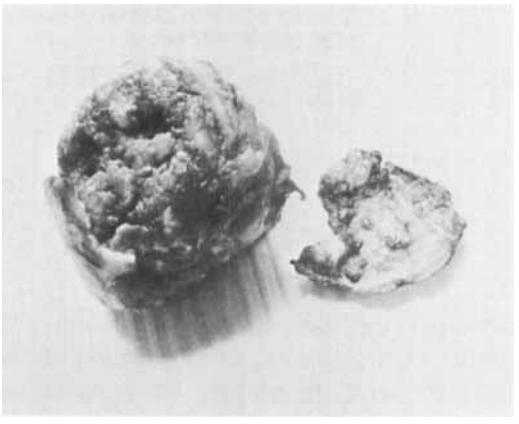

Figure 4. The femoral head in Figure 1 with a separated osteocartilaginous fragment removed at operation.

Fractures

Incidence. Fractures were sustained by 6 of the 204 patients prior to transplantation and by 53 after the operation (3 and 26 per cent, respectively); 2 of the latter also had fractures before the operation. The patients ranged in age from 10 to 63 years; this complication was most common above 45 years of age ($P < 0.05$) (Table 6).

Table 6. Age distribution of patients sustaining fractures

Age	< 30	30-45	46-60	> 60	Total
Total patients	53	72	68	11	
Patients with fracture					
No.	7	20	23	3	
Per cent	13	28	34	22	26

Of the 64 recipients of related donor kidneys 13 sustained fractures, against 40 of the 140 recipients of cadaveric grafts (20 and 29 per cent, respectively). Of the 32 patients receiving more than one kidney 11 had fractures, compared with 42 of the 172 receiving only one transplant (32 and 24 per cent, respectively). The sexes were equally represented (23/87 women – 26 per cent – and 30/117 males – 26 per cent). Of the 18 patients undergoing parathyroid surgery before the transplant operation 7 sustained fractures, against 46 of the 186 not so treated (39 and 25 per cent respectively). The corresponding figures for the patients having parathyroid surgery after the transplantation were 33 and 24 per cent. None of these differences is statistically significant.

Clinical findings. The interval between the transplantation and the first fracture ranged from 1 to 58 months (median 15). The 53 patients sustained a total of 109 fractures (Figure 5). A single fracture was recorded in 29 patients, while one recipient had as many as seven (right femoral neck, all four ischiopubic rami, right calcaneus and fibula) (Table 7). The axial skeleton and trunk were the site of 69 per cent of the fractures and the bones most commonly affected were the pubic bones (36/109 – 33 per cent). Seven per cent involved non-weight-bearing structures (upper extremity), one half of them the radii (Table 8).

Table 7. Frequency of various numbers of fractures in the 53 patients with this complication

Number of fractures	1	2	3	4	5	7
Number of patients	29	7	8	5	3	1

Table 8. Site of fractures

	No. of fractures	No. of patients
Site		
Humerus, neck	2	2
Ulna, shaft	1	1
olecranon	1	1
Radius	4	4
Vertebra, thoracic	13	6
lumbar	3	3
Rib	22	14
Ischiopubic ramus, superior	13	9
inferior	23	14
Innominate bone	1	1
Femur, neck	7	7
trochanter	1	1
supracondylar	1	1
Tibia, shaft	2	2
Fibula (isolated)	3	3
Ankle	1	1
Calcaneus	3	2
Metatarsal bones	8	5
Total	109	

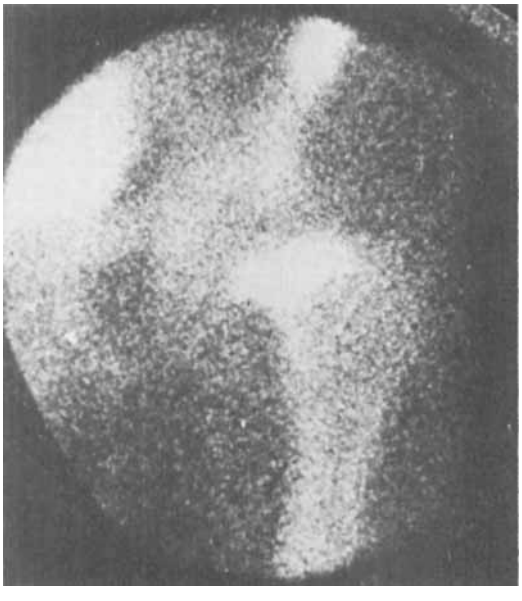

Figure 5. Increased activity of $^{99}Tc^{m}$ pyrophosphate, 3 weeks after spontaneous fracturing of the femoral neck, with the isotope outlining the fracture. The fracture was not visualized at the initial radiographic examination.

Treatment. The treatment followed standard principles. For the seven femoral neck fractures screw techniques were used and for the trochanteric fracture Ender nails. The olecranon fracture was stabilized with Rush pins and the malleolar fracture with pins, wire and a staple. Prophylactic antibiotics were given and in the same doses as for the patients undergoing hip replacement.

No case of pseudarthrosis or delayed union was recorded in any of the patients, whether given surgical or conservative treatment. Nor was femoral neck fracture followed by avascular necrosis of the head.

DISCUSSION

The reported incidence of avascular necrosis in renal transplant recipients varies widely – from 3 to 41 per cent (Bewick et al. 1976 Hawking 1976). This wide range is due at least in part to differences between the patient materials: in some cases the figures are based on all the patients receiving renal grafts, but in others the patients must have carried their grafts for a certain minimum time. Moreover, the follow-up times differ. If all the patients are taken into the series, including those that lost their graft at an early stage and thus received immunosuppressive therapy for only a short period, the incidence of osteonecrosis will be underestimated. The same applies if the follow-up time is short. We chose a minimum graft survival of 12 months as a criterion for inclusion of the patient in the study.

In the only two other studies where the follow-up time was of this length the series were small; the incidences of avascular necrosis were 18 and 14 per cent (Arfi et al. 1975, Pierides et al. 1975), against 11 per cent for our larger series. The interval elapsing between the transplant operation and the onset of osteonecrosis in the present study was consistent with the figures for other series, as were the characteristics of the lesion, such as a multifocal nature and a tendency for weight-bearing joints to be affected more than others. There is also agreement as regards the absence of any correlation between the occurrence of avascular necrosis and sex or graft origin (Bewick et al. 1976, Ibels et al. 1978, Levine et al. 1977, Pierides et al. 1975, Troch et al. 1972).

While the pathogenesis of avascular necrosis is not known, there is convincing evidence that the use of corticosteroids in high doses is an important factor. In 1971 Harrington and associates found a lower incidence of avascular necrosis in patients that had received smaller amounts of corticosteroids during the first 3 weeks after the transplant operation than had been found in an earlier series where larger amounts of corticosteroids had been given. Similar experience has been reported from other centres (Harris et al. 1974, Nelson et al. 1971). In another study, however, no change in the incidence of avascular necrosis was found when the dose of corticosteroids was increased (Susan et al. 1978). The correlation between avascular necrosis and the number of transplantations found by some authors has been taken as indirect evidence of the role of corticosteroids, since with each transplantation the steroid regimen is renewed (Murray 1973). This finding is not supported by the results of this study.

A number of investigators consider the presence of hyperparathyroidism to be an important factor in the pathogenesis of post-transplant osteonecrosis. In one series of 23 dialysis patients with avascular necrosis none of whom had recently been on corticosteroid therapy nearly all presented evidence of hyperparathyroidism (Bailey et al. 1972). Among 16 patients with persistent hypercalcaemia after renal transplantation Chatterjee et al. (1976) found avascular necrosis in 7 compared with 3 out of 44 patients without hypercalcaemia. The absence of avascular necrosis in those patients of a series who had required parathyroid surgery prior to transplantation is at variance with our experience – 22 per cent of such patients developed the complication (Briggs et al. 1972).

In two series unilateral avascular necrosis of the femoral head usually occurred on the side of the graft (Hall et al. 1969, Olgaard & Heerfordt 1975). By way of explanation it was suggested that ligation of the hypogastric artery could compromise the blood supply to the femoral head. However, no support for this view is furnished by the present series, where unilateral necrosis occurred just as often on the contralateral side.

Concerning the mechanism of bone destruction Lindsay et al. (1976) found that patients subsequently developing avascular necrosis exhibited a lower bone density, as measured by radiological densitometry, 6 weeks after transplantation. This tendency was confirmed by Nielsen et al. (1977 a, b), who proposed that avascular necrosis of bone may be due to the occurrence of microfracturing of osteopenic bone. Some indirect support for this possibility is provided by the present study, where 8 of the patients with osteonecrosis also sustained fractures (36 per cent) and also by the observation that the complication was more common at higher ages.

Surgical treatment was required only in cases where the femoral head was involved. Because a satisfactory status is often maintained despite advanced radiographic changes of the femoral head we postponed any decision on hip replacement for 6 months, during which time conservative management with crutches was continued. In the event, surgery was needed in only four hips in 3 patients; in all these cases the outcome was highly satisfactory, and we agree with Gustafsson (1976) that total hip replacement should be recommended to the post-transplant patient who is much troubled by pain and where a radiographic examination has visualized avascular necrosis of the femoral head. Less radical measures such as grafting, osteotomy and forage have yielded discouraging results (Lecestre et al. 1977, Springfield & Enneking 1978) as did the former use of femoral head prostheses, with rapid migration of the prosthesis in the osteopenic bone (Cruess et al. 1968, Elmore 1972). With the low-friction arthroplasties available today the risk of loosening is small and the risk of infection can be minimized by using special ventilation systems in the operating theatre (Schreiber & Zollinger 1977) and prophylactic antibiotics (Gustafsson et al. 1976).

The incidence of fracture in various series of renal graft patients ranges from 4 to 13 per cent (Nelson 1971, Griffiths 1974). In these studies the follow-up time was less than 6 months. In the present large series of recipients whose grafts had functioned for more than 12 months as many as 26 per cent developed this complication. The observation that most of the fractures occurred early on but were not uncommon as late as 5 years after the transplant operation is consistent with findings related to bone mineral content: Dalén & Alvestrand (1973) found significantly lower bone mineral content 2–4 months after renal transplantation. Aird & Pierides (1977) found reduced levels in 57 per cent of their patients 6 months after transplantation but in only 17 per cent at 30 months, while Madsen and associates (1979) still found subnormal values after 6 years.

As union occurred after a normal time in all our patients and no complications were encountered during the period covered by the treatment we see no reason to recommend any departure from the conventional management of fractures for this type of patient.

In view of the high incidence of avascular necrosis and fracture and their often crippling nature, it is important to find means of avoiding them. As several causal factors are probably involved we should perhaps reconsider our approach to, for example, the steroid regimen and parathyroid policy.

In an investigation along these lines we are carrying out a comprehensive analysis of such possible risk factors.

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