Acta orthop. scand. 52, 397–404, 1981

OSTEONECROSIS AND SPONTANEOUS FRACTURES FOLLOWING RENAL TRANSPLANTATION

A Longitudinal Study of Radiological Bone Changes and Metacarpal Bone Mass

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Seventy-seven renal transplant (RT) recipients were studied radiologically with regard to bone lesions and metacarpal bone mass, at the time of and after renal transplantation. An increased incidence of rarefaction of the spine, a reduced metacarpal bone mass and an increased frequency of subperiosteal erosions were found at the time of transplantation in RT patients who subsequently developed osteonecrosis or spontaneous fractures as compared with RT patients who did not develop these bone complications. During the years after RT an increase in rarefaction of the spine, in subperiosteal erosions, in soft tissue calcifications and a decrease in metacarpal bone mass were found in all patient groups.

Key words: bone lesions; metacarpal bone mass; osteonecrosis; renal transplantation; spontaneous fractures

Accepted 21.xii.80

Osteonecrosis and spontaneous fractures are frequent and sometimes disabling complications of renal transplantation (RT) (Griffiths et al. 1974, Nielsen et al. 1977a, Nielsen et al. 1977b, Nielsen et al. 1979).

Various pathogenetic factors have been proposed. Steroid-induced osteoporosis (Editorial 1972, Solomon 1973), secondary hyperparathyroidism (Arfi et al. 1975, Chatterjee et al. 1976), ischemia of bone due to fat embolisms (Evarts & Phalen 1971) and vascular changes of other etiologies (Harrington et al. 1971) have been suggested.

The present investigation was performed in an attempt to elucidate the etiology of post-transplant aseptic necrosis and spontaneous fractures by analysis of the degree of osteoporosis, subperiosteal erosions, soft tissue calcifications, intracortical cyst formations, and acroosteolysis, and by measurement of the metacarpal bone mass on radiographs of the bones, at the time of transplantation and during the years after RT.

PATIENTS AND METHODS

Seventy-seven patients receiving a renal transplant in the years 1964–78 were investigated radiographically (skull, thoracic and lumbar spine, hands, feet, pelvis, including both hips, knees and both clavicles) at the time of transplantation and thereafter at intervals of 1 to 2 years. The RT patient group was made up of 20 patients who later developed osteonecrosis after RT, 15 patients who later developed spontaneous fractures, and an age- and sex-matched control group consisting of 42 patients who did not develop osteonecrosis or spontaneous fractures (Table 1).

The osteonecrosis developed in the hips in 14 patients, in the shoulders in 4 patients and in the knees in 3 patients (Figure 1). The most common site of the spontaneous fractures was the lumbar spine (11 cases).

Immunosuppressive therapy with prednisone and azathioprine was given to all patients. The initial daily dose of prednisone was 2 mg/kg body weight; 3 months

0001-6470/81/040397-08 $02.50/0

Table 1. Clinical data, radiological evaluation and metacarpal bone mass at the time of transplantation in 15 renal transplant (RT) recipients who developed spontaneous fractures after transplantation, in 20 RT recipients who developed osteonecrosis, and in a control group of 42 RT recipients who did not develop bone lesions after transplantation

	No. of patients	Age years		Duration of dialysis months		Rarefaction of the spine	Subperiosteal erosions	Soft tissue calcifications	Metacarpal bone mass $(D^2-d^2)/D^2$			
									absolute values		percentage	
		range	mean	range	mean				range	mean	range	mean
Osteonecrosis												
♂	11	23–58	35.1	0–28	10.3	7	4	8	0.61–0.87	0.75	78–107	93.3
♀	9	18–52	31.5	0–36	9.9	5	3	4	0.68–0.91	0.80	84–112	98.7
Spontaneous fract.												
♂	6	14–52	42.3	0–29	14.0	5	2	5	0.72–0.82	0.76	90–105	97.5
♀	9	17–55	37.6	0–34	11.3	5	5	2	0.64–0.92	0.74	78–112	90.3
Control group												
♂	19	19–57	33.2	0–26	6.8	5	4	8	0.69–0.92	0.79	88–114	99.1
♀	23	16–57	34.4	0–56	7.3	9	4	6	0.77–0.97	0.84	92–118	102.1

after the transplantation the dose was about 25 mg. During the first 2 years the steroid dose was reduced to 5–10 mg per day. The usual daily dose of azathioprine was 2 mg/kg body weight.

The radiographs were evaluated blindly at the time of this investigation with regard to the presence or absence of rarefaction of the spine, subperiosteal erosions, soft tissue calcifications (periarticular and intravascular), intracortical cyst formations and acroosteolysis.

The cortical area of the second left metacarpal bone $(D^2-d^2)/D^2$ was measured as an index of bone mass, measuring the outer diameter of periosteal width (D) and the inner diameter of the medullary space (d) of the cortex at the midpoint of the shaft at right angles to the long axis, using the same technique as Dequeker (Dequeker 1976, Garn et al. 1971). The results were expressed in absolute values and as a percentage of the age- and sex-matched normal controls (Andresen et al., unpublished). The intra-observer variation coefficient of $(D^2-d^2)/D^2$ was 1.6 per cent and the inter-observer variation coefficient 2.4 per cent.

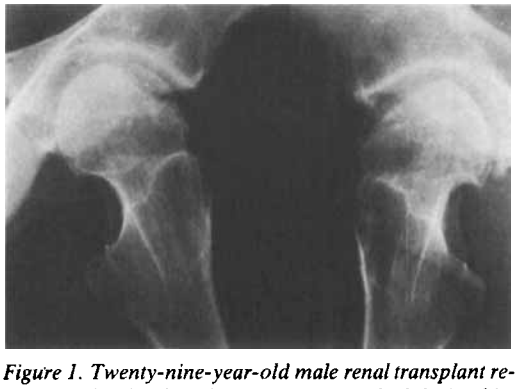

Figure 1. Twenty-nine-year-old male renal transplant recipient, who developed osteonecrosis in the left shoulder (a) and in both hips (b) 3 years after renal transplantation.

Statistical evaluation

Statistical differences between group means were determined by the Mann-Whitney U-test and the significance of changes during the observation period was tested with the Wilcoxon rank sign test for paired comparisons.

χ^2 test was used for comparison of frequencies in groups.

RESULTS

Radiological evaluation at the time of transplantation (Table 1)

In the RT control group, those who later on did not develop osteonecrosis or spontaneous fractures, 14 out of 42 patients had rarefaction of the spine (33 per cent) as compared with an incidence of 63 per cent in patients who developed osteonecrosis or spontaneous fractures (22 out of 35 patients) ($P < 0.01$).

There was a significantly higher frequency of patients with subperiosteal erosions in the groups with osteonecrosis or spontaneous fractures (35 and 47 per cent, respectively) as compared to the control group (19 per cent) ($P < 0.05$). The erosions were most commonly localized to the hands and feet (middle phalanges and terminal tufts), medial end of the clavicle, the sternoclavicular and acromioclavicular joints and the sacroiliac joint (Figure 2).

No significant difference was found in the inci-

Figure 2. Fifty-two-year-old male renal transplant recipient with resorptive bone changes, acroosteolysis and soft tissue calcifications 5 years after renal transplantation. The subperiosteal erosions are most pronounced in the head of the right and left 5th metacarpal bone (where the calcifications are seen) and in the proximal and middle phalanges radially of the right 5th finger. Acroosteolysis is demonstrated in the second left finger.

Figure 3. Thirty-year-old male renal transplant recipient with subperiosteal erosions in the head of the right 2nd–4th metatarsal bones laterally. Intracortical cyst formation is seen in the head of the right 2nd, 4th and 5th metatarsal bones medially.

dence of soft tissue calcifications in the three groups, being 33 per cent in the control group, 60 per cent in the group of patients with osteonecrosis and 47 per cent in the group of patients with spontaneous fractures. Vascular calcifications occurred most often in the abdominal aorta and periarticular calcifications were most frequently localized to the humero-scapular joint.

Intracortical cyst formation and acroosteolysis were found in only two and four patients, respectively (Figures 2 and 3). The metacarpal bone mass $(D^2-d^2)/D^2$ was significantly reduced at the time of transplantation in RT recipients who developed osteonecrosis or spontaneous fractures as compared with RT controls ($P < 0.05$) and normal controls ($P < 0.02$) whereas normal

Table 2. Radiological bone changes after renal transplantation in renal transplant (RT) recipients who developed fractures and osteonecrosis and in RT controls. Only patients with pathologic bone changes at the time of transplantation or later are included in the table

		Rarefaction of the spine			Subperiosteal erosions			Soft tissue calcifications			Intracortical cyst formations			Acroosteolysis		
		↑	↓	→	↑	↓	→	↑	↓	→	↑	↓	→	↑	↓	→
RT control group	♂	9	0	2	6	0	1	7	0	1	0	0	1	0	0	0
(n = 20)	♀	6	0	3	2	0	1	5	0	3	0	1	0	0	0	0
RT spontaneous fractures	♂	6	0	0	6	0	0	5	1	0	0	0	0	3	0	0
(n = 14)	♀	8	0	0	7	0	1	6	0	0	2	0	0	0	0	1
RT osteonecrosis	♂	8	0	3	8	0	1	6	1	2	0	0	1	0	0	0
(n = 19)	♀	6	0	2	6	0	1	4	2	1	2	0	0	0	0	1

metacarpal bone mass was present in patients who did not develop bone lesions after RT.

Radiological bone changes after RT

After RT an increase in the incidence of rarefaction of the spine, of subperiosteal erosions and of soft tissue calcifications could be observed in all patient groups (Table 2), the changes being most pronounced in patients who developed osteonecrosis or spontaneous fractures. No changes in the incidence of intracortical cyst formation or acroosteolysis were seen during the observation period after RT. A significant decrease in metacarpal bone mass occurred in the patient group with spontaneous fractures ($P < 0.01$), in the patients with osteonecrosis ($P < 0.01$ and in the control group ($P < 0.01$) (Figures 4–6).

No significant difference was found between the three groups with regard to the annual decrease in metacarpal bone mass.

DISCUSSION

Osteonecrosis and spontaneous fractures are frequent and sometimes severe bone complications after renal transplantation. The frequency of osteonecrosis has been reported to be 5–37 per cent (Aird & Pierides 1977, Briggs et al. 1972, Cruess et al. 1968, Gottlieb et al. 1978). At our centre 11 per cent of the patients with a kidney transplant functioning for more than 6 months developed osteonecrosis and 9 per cent spontaneous fractures after transplantation (Nielsen et al. 1977a, Nielsen et al. 1979).

The localization of bone lesions was most commonly the weight-bearing areas consisting of cancellous bone, i.e. the femoral head, the knee or the spine.

The present investigation is a longitudinal study of radiographs obtained at the time of transplantation and thereafter at intervals of 1–2 years. At the time of transplantation, a higher incidence of rarefaction of the spine and a lower

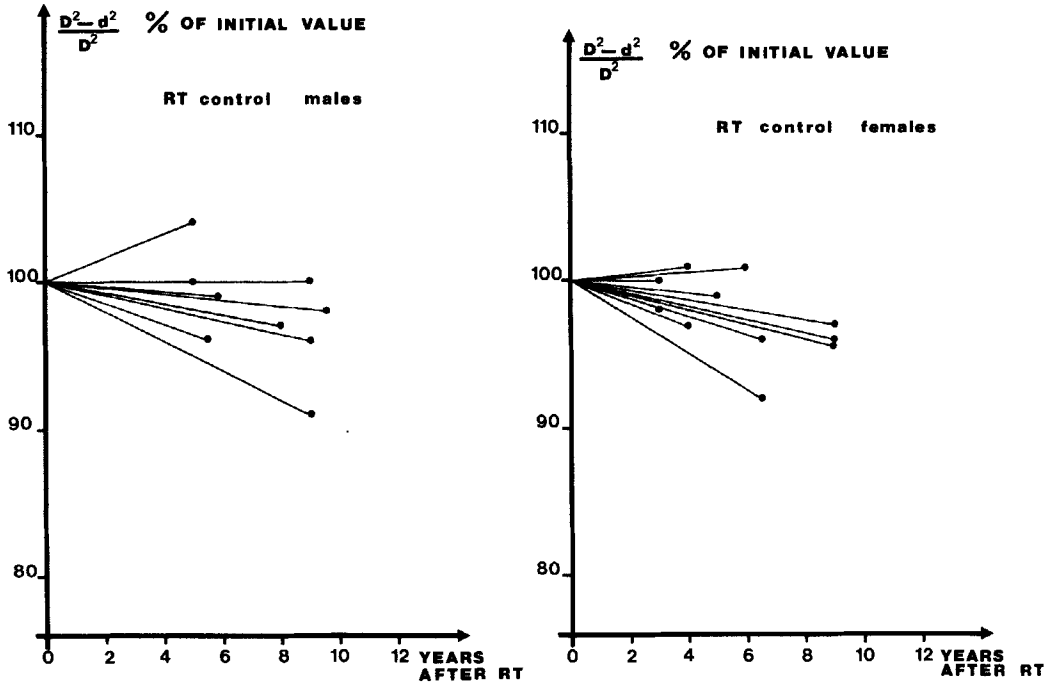

Figure 4. Metacarpal bone mass $(D^2–d^2)/D^2$, corrected for normal age variation, in 9 RT controls males (left) and in 11 RT control females (right) before and after renal transplantation.

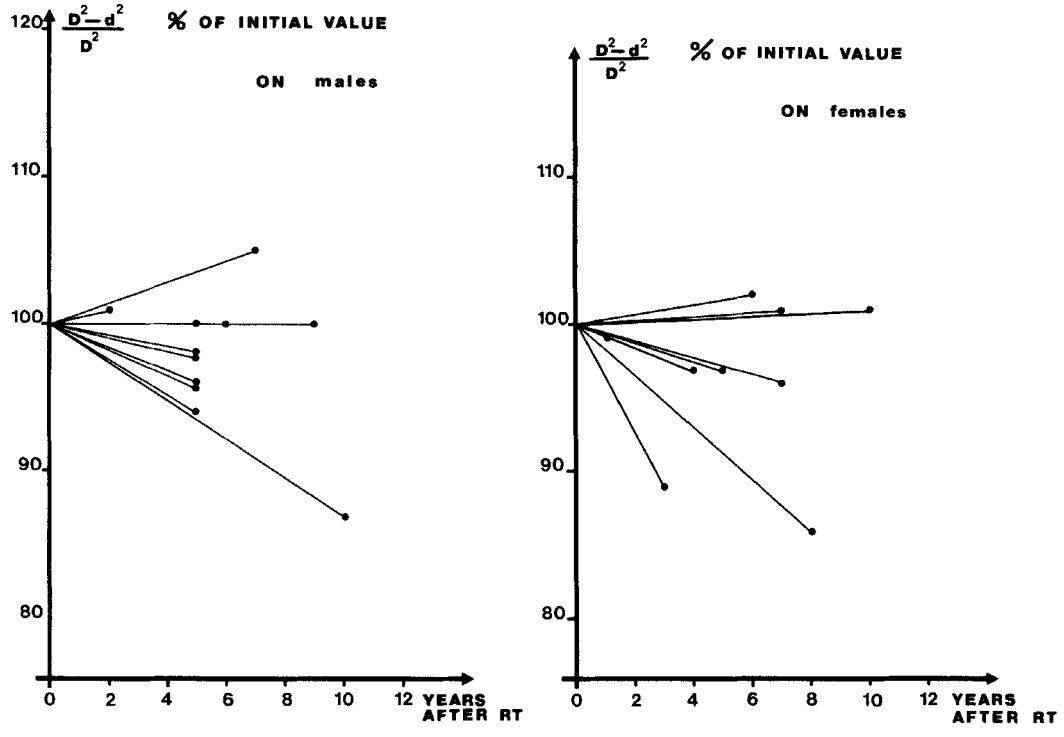

Figure 5. Metacarpal bone mass $(D^2-d^2)/D^2$, corrected for normal age variation, in 11 RT males (left) and in 8 RT females (right) with osteonecrosis, before and after renal transplantation.

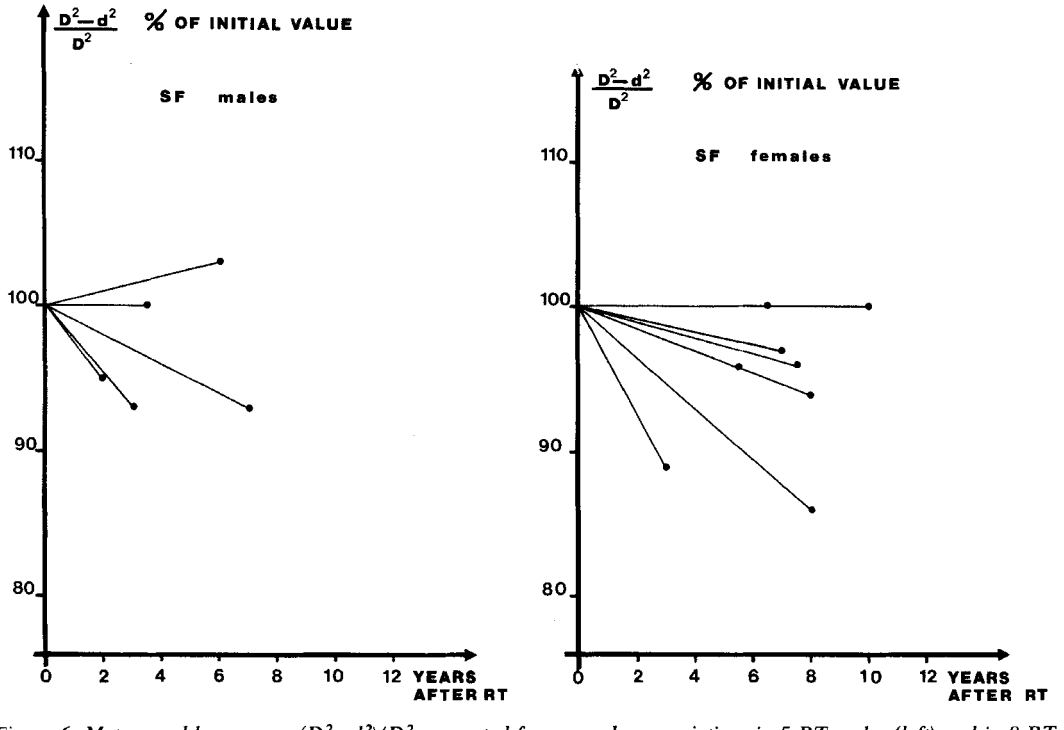

Figure 6. Metacarpal bone mass $(D^2-d^2)/D^2$, corrected for normal age variation, in 5 RT males (left) and in 8 RT females (right) with spontaneous fractures, before and after renal transplantation.

metacarpal bone mass were found in patients who developed osteonecrosis or spontaneous fractures as compared with RT patients who did not develop these bone lesions. Furthermore, a significantly higher frequency of subperiosteal erosions was seen in osteonecrosis and spontaneous fracture patients.

Previous investigations (Cohen et al. 1970, Nielsen et al. 1977a, Nielsen et al. 1979) have shown a longer duration of dialysis before transplantation in patients who developed osteonecrosis or spontaneous fractures compared with dialysis patients who did not. The present study and previous investigations indicate that bone status at the time of transplantation is a major factor in the development of bone complications after RT. Furthermore, previous studies seem to indicate that osteopenia is an important pathogenetic factor (Nielsen et al. 1977a, Melsen & Nielsen 1977).

After RT a progressive increase in the incidence of rarefaction of the spine, in subperiosteal erosions and in vascular calcifications, were observed in all three RT patient groups, in spite of normalization of kidney function after transplantation. Furthermore, a significant fall in metacarpal bone mass was seen both in patients who developed osteonecrosis and spontaneous fractures and in RT controls. The change in metacarpal bone mass did not differ between the patient groups. Previous reports (Bortolotti et al. 1977, Huffer et al. 1975) described an increasing osteopenia in spongious bone after transplantation. However, the study of Nielsen (1978) showed no consistent time related change, after transplantation, in bone mineral content in the forearm (consisting mainly of compact bone) measured by photon absorptiometry, and in the study of Aird & Pierides of bone mineral content in the femur, the number of patients losing bone gradually decreased with time (Aird & Pierides 1977).

The present study indicates, in agreement with previous investigations, that a major factor in the pathogenesis of osteonecrosis and spontaneous fractures after RT is the bone status at the time of transplantation. After transplantation similar changes in bone mass, in subperiosteal erosions and in soft tissue calcifications occur both in patients who develop bone lesions and in those who do not.

ACKNOWLEDGEMENT

The authors wish to thank Hanne Lindgreen for secretarial assistance.

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