Avascular necrosis of bone following renal transplantation

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Abstract **This study was undertaken to determine the incidence and clinical features of avascular necrosis of bone in 69 transplant recipients all of whom had a functioning allograft for a least 12 months. An attempt was also made to identify any potential predisposing factors. The patients were assessed by an orthopaedic surgeon. The diagnosis of avascular necrosis was made on the basis of radiographs and isotope bone scans. Fourteen patients (20,2%) developed avascular necrosis with a mean onset of 19 months post-transplantation.**

The hip joint was most commonly affected. The isotope bone scan was the most sensitive diagnostic tool; abnormalities were detected before the onset of symptoms in 4 patients.

Avascular necrosis was more common in Indian transplant recipients and was also associated with: (*i*) cadaver transplants; (*ii*) more frequent bouts of acute rejection ($P < 0,05$); and (*iii*) a greater incidence of other steroid-associated side-effects ($P < 0,05$).

Alcohol consumption and radiological evidence of osteoporosis were more prevalent in the avascular necrosis group (42,8% v. 29,0% and 28,5% v. 7,2% respectively). Avascular necrosis did not correlate with age, sex, renal function at 1 year or severe secondary hyperparathyroidism.

This study suggests that corticosteroid therapy plays an important role in the pathogenesis of avascular necrosis. Excessive alcohol consumption and osteoporosis also appear to be risk factors.

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Avascular necrosis of bone is most often associated with conditions in which there is interruption of the blood supply. It is most commonly encountered after traumatic disruption of the blood supply associated with a fractured neck of the femur, slipped femoral capital epiphysis or traumatic dislocation.[1]

Various disease states associated with arterial occlusion such as atheromatous and embolic arterial disease, neoplastic infiltration, inflammation associated with osteomyelitis and sickle cell anaemia may also give rise to the disorder.[1]

The first association between corticosteroid therapy and avascular necrosis was reported in 1957 in a patient with pemphigus vulgaris who had received cortisone for 4 years.[2]

In 1964 Starzl *et al.*[3] first described the development of avascular necrosis of the femoral head in 2 renal transplant recipients. Since then avascular necrosis of bone has become a well-recognised complication of renal transplantation.

The pathogenesis of avascular necrosis in this setting remains controversial, however, with numerous conflict-

ing reports concerning the importance of several possible predisposing factors. The absolute dosage of corticosteroids,[4] steroid-induced metabolic disturbances such as hyperlipidaemia,[5] osteoporosis,[4] abnormal blood viscosity and coagulability have all been implicated. Some authors have suggested that secondary hyperparathyroidism plays an important role in the pathogenesis.[7] The incidence of avascular necrosis following renal transplantation is unpredictable; reported incidences range from 3% to 41%.[8]

The study was undertaken to determine the incidence and clinical features of avascular necrosis in our renal transplant population. An attempt was made to identify any potential predisposing factors.

Patients and methods

We selected only those patients who had had a functioning allograft for a minimum period of 12 months. Patients who had returned to dialysis, having lost their allograft after 12 months, were excluded, as were patients whose underlying renal disease required therapy with corticosteroids, e.g. collagen vascular disease.

Sixty-nine patients (49 men, 20 women) were selected, all of whom were interviewed and examined by an orthopaedic surgeon. Radiographs of the pelvis and isotope (methylene diphosphonate technetium-99) bone scans were performed on all patients with the exception of those in whom avascular necrosis had been diagnosed before initiation of the study. Radiographs of other joints were taken where indicated.

The diagnosis of avascular necrosis was based on radiological and/or radionuclide demonstration of bone necrosis. The control group comprised patients who did not have evidence of avascular necrosis. The diagnostic sensitivity of symptoms and positive findings on clinical examination were determined by review of the orthopaedic assessment. All necessary clinical and biochemical data were obtained from patient records.

Age at the time of transplantation, sex, race and organ source were listed for all patients. The possibility of a correlation between the occurrence of avascular necrosis and the following factors was examined: (*i*) number of bouts of acute rejection; (*ii*) mean dose of methylprednisolone (consumed by the patient at 12 months post-transplantation); (*iii*) incidence of other steroid-associated side-effects (cataracts, peptic ulcers and corticosteroid-induced diabetes); (*iv*) severe secondary hyperparathyroidism; (*v*) obesity; (*vi*) significant alcohol intake; and (*vii*) radiological evidence of osteoporosis.

The prevalence of obesity was determined by reference to Fogarty's table and alcohol consumption was assessed by means of a specially designed questionnaire. Significant alcohol consumption was defined as the regular intake of a minimum of 10 drinks per week. A drink was defined as: 1 can of beer (340 ml), 1 glass of wine (100 ml) or 1 measure of spirits (37,5 ml). The following biochemical levels were recorded: serum creatinine, cholesterol, triglycerides, calcium, phosphate and alkaline phosphatase. Liver function tests (albumin, globulin, bilirubin, gamma transpeptidase, alanine aminotransferase and aspartate aminotransferase) were done and parathyroid hormone levels assessed (where indicated).

Mean values were calculated for each patient based on post-transplantation measurements which were done at 3, 6 and 12 months, and thereafter annually until the time of the study. The following were regarded as markers of severe secondary hyperparathyroidism: (*i*) persistent hypercalcaemia; (*ii*) significantly elevated alkaline phosphatase levels (> 2 x upper limit of normal); (*iii*) elevated parathyroid hormone levels; and (*iv*) classic radiological features of osteitis fibrosa. Standard immunosuppression consisted of 0,5 g intravenous methylprednisolone sodium succinate (Solu-Medrol) intra-operatively. This was followed by oral methylprednisolone 32 mg/d for cadaver transplant recipients and 20 mg/d for living related transplant recipients. These doses were gradually tapered to a maintenance dose by 12 months. Cyclosporin A was employed in a dose of 10 mg/kg/d in two divided doses and doses were adjusted according to whole blood radio-immunoassay trough levels. All patients barring those with an HLA-identical match also received azathioprine 1 mg/kg/d.

Acute rejection was treated with intravenous methylprednisolone sodium succinate 500 mg daily for a maximum of 5 days. Patients received either aluminium hydroxide or calcium carbonate as phosphate binders. Oral calcium preparations and vitamin D supplements were utilised when necessary.

The statistical analysis of the data was performed by means of Student's *t*-test. The probability attached to differences between percentages was calculated by division of the latter by their respective standard errors. A probability ratio greater than 1,0 was regarded as significant.

Results

Incidence and clinical features

Avascular necrosis was diagnosed in 14 of the 69 patients (20,2%). Onset of pain ranged from 2 months to 36 months post-transplantation with the mean onset at 19,1 months. A positive history was obtained in 10 patients, whereas clinical examination was abnormal in only 4 patients (Table I). Radiographs demonstrated avascular necrosis in 11 patients (78,5%); the isotope bone scan was the most sensitive diagnostic tool, and was positive in all of the patients in which it was done (Table II). Two patients who underwent total hip replacements several years before this study did not have isotope bone scans; their diagnoses were made on clinical and radiological grounds.

TABLE I.
Diagnosis of avascular necrosis

	Diagnostic sensitivity	
	No.	%
History	10/14	71,5
Clinical examination	4/14	28,5
Radiographs	11/14	78,5
Isotope bone scans	12/12	100

TABLE II.
Clinical data correlations with avascular necrosis

Variables	Present	Absent	
Age (yrs)	39,1	35,1	NS
Men/women	11/3 (78,5%)	38/17 (69%)	NS
Organ source (cadavers/LRD)	10/4 (71,4%)	28/27 (51%)	$r = 1,47$
Bouts of acute rejection/patient	1,08	0,58	$P < 0,05$
Dose methylprednisolone, 12 mo.	8,56 mg	7,24 mg	NS
Serum creatinine (μmol/l), 12 mo.	117 ± 29,2	110 ± 35,2	NS
Steroid side-effects	0,85	0,34	$P < 0,05$

NS = not significant; LRD = living related donor.

As expected the hip joint (femoral head) was most frequently involved (13 patients); 1 patient had avascular necrosis of the knee and 1 patient had both hip and ankle (talus) involvement. Avascular necrosis has been reported in the shoulder and elbow joints, i.e. humeral head, distal humerus, proximal radius and ulna,[1] as well as the vertebrae, ribs, calcanea and metatarsal heads.[4]

Predisposing factors

Clinical variables between the avascular necrosis and control groups were compared and the findings are listed in Table II. Mean age was similar in the two groups as was the sex ratio. The apparent increased incidence in men reflects the overall preponderance of men in our transplant population. Avascular necrosis was associated with cadaver transplants (71,4% v. 51%), more frequent bouts of acute rejection (1,08 per patient v. 0,58) and a greater incidence of other steroid-associated side-effects (0,85 per patient v. 0,34). The mean dose of methylprednisolone and mean serum creatinine levels at 12 months post-transplantation did not differ significantly between the two groups (8,56 v. 7,2 mg and 117 v. 110 μmol/l respectively).

The influence of alcohol consumption, pre-existing osteoporosis and obesity is indicated in Table III. Significant alcohol consumption and radiological evidence of osteoporosis were more prevalent in the avascular necrosis group and the differences were statistically significant.

TABLE III.
Avascular necrosis

	Present	Absent	
Alcohol	6/14 (42,8%)	16/55 (29,0%)	$r = 1,0$
Osteoporosis	4/14 (28,5%)	4/55 (7,3%)	$r = 1,69$
Obesity	2/14 (14,28%)	13/55 (23,6%)	$r = 0,85$

Obesity was more prevalent in the control group; this difference, however, did not attain statistical significance. Both triglyceride (2,13 v. 1,9 μmol/l) and cholesterol levels (6,70 v. 6,15 μmol) were higher in the avascular necrosis group, but this difference was not statistically significant.

Severe secondary hyperparathyroidism occurred in a minority of patients: 1/14 (7,1%) in the avascular necrosis group and 5/55 (9,0%) of the controls. Mean calcium, phosphate, alkaline phosphatase and liver function tests were within the normal range in both groups of patients.

Subdivision of patients according to race (Table IV) demonstrates that the incidence of avascular necrosis was significantly greater in Indians (25,6%) compared with whites (5,9%). Avascular necrosis was present in 2 of the 3 coloured patients and did not occur in the 6 black patients. Statistical analysis of these two race groups is not possible because of the small numbers involved.

TABLE IV.
Correlation of race with avascular necrosis

	Present	Absent		
		No.	%	
Indian	11	32	25,6	$r = 2,24$
White	1	16	5,9	
Coloured	2	1	66,6	
Black	0	6	0	

Discussion

While it is apparent that avascular necrosis is an important complication of renal transplantation, there is considerable variability in the reported incidence and the pathogenesis remains controversial. The marked variability in the incidence of avascular necrosis following renal transplantation has been attributed to differences in the methods of evaluation, follow-up time before analysis, and the relatively small number of patients in some series.[9]

Immunosuppressive regimens have also altered dramatically since the introduction of cyclosporin A. This agent has made it possible for nephrologists to utilise lower doses of corticosteroids as maintenance treatment; some centres advocate cyclosporin monotherapy as a viable alternative.[10] Furthermore the use of cyclosporin A has also brought about a reduction in the cumulative dose of steroids as a result of fewer rejection episodes in the first 12 months following transplantation.[10]

These cyclosporin A low-dose steroid regimens have been associated with a reduction in the incidence of avascular necrosis of bone following renal transplantation.[9,11,12] Corticosteroid therapy appears to occupy a central role in the pathogenesis of avascular necrosis although the exact mechanism remains controversial. One hypothesis is that corticosteroids, by enhancing peripheral resistance to the action of insulin, elevate insulin levels and stimulate the synthesis of very-low-density lipoproteins. This accounts for the hypertriglyceridaemia which develops post-transplantation but does not explain the hypercholesterolaemia which also occurs and which is rarely present while the patients are on dialysis. Thus corticosteroid-induced hyperlipidaemia is thought to predispose to fatty infiltration of the liver[1] and subsequent ischaemic necrosis of bone secondary to subchondral arteriolar fat embolisation.[1]

Exogenous steroid therapy has also been linked to the development of osteoporosis[4] consequent upon inhibition of osteoblastic activity. Elmstedt[13] supports the hypothesis that avascular necrosis is due to microfractures in osteoporotic bone giving rise to local disturbance of the blood supply.

Excessive alcohol intake is another factor implicated in the pathogenesis of avascular necrosis of bone and the observations for the aforementioned two factors could apply equally in this area. Subchondral arteriolar fat emboli have been demonstrated in bones of alcoholics presenting with avascular necrosis.[14] Furthermore, alcohol is regarded as an important dietary risk factor for the development of osteoporosis.[15] The mechanisms include a direct toxic effect on bone, alcohol-induced calcium diuresis, poor nutritional status, hypogonadism and reduced physical activity.

Pre-existing or persistent hyperparathyroidism after transplantation is regarded by some authors[7] as playing an important role in the pathogenesis of avascular necrosis. It is speculated that increased bone resorption combined with osteoporosis could lead to trabecular collapse consequent upon weight bearing,[1] particularly in the obese patient. The incidence of avascular necrosis in our renal transplant patients was 20,2% which is well within the reported range of 3 - 41%. It has been reported that most patients develop symptoms within 2 years of transplantation.[1] Although the time of onset of pain in our patients ranged from 2 months to 36 months post-transplant, the mean onset was 19,1 ± 9,8 months. Joint pain was present in 71,5% of our patients with avascular necrosis whereas clinical examination was abnormal in only 28,5%. This is not surprising as joint pain is the presenting symptom in most cases and may precede the appearance of radiological abnormalities by several months.[4]

Four patients, however, were asymptomatic; the diagnosis was made on the basis of an isotope bone scan. Furthermore only 1 of these patients had an abnormal radiograph; this underlines the high diagnostic sensitivity of the isotope bone scan.

With regard to predisposing factors, we found that avascular necrosis was more frequently observed in association with cadaver transplants and consequently with more bouts of acute rejection. These differences were statistically significant. This association suggests a pathogenetic role for corticosteroids as cadaver transplant recipients receive larger doses of oral corticosteroids and would also receive larger cumulative doses of corticosteroids consequent upon the increased incidence of acute rejection. Interestingly we also noted an increased incidence of other steroid-associated side-effects in the avascular necrosis group, which suggests that these patients may have been unduly sensitive to steroids. It is known that considerable individual variability exists in the propensity of renal transplant patients to develop avascular necrosis. Avascular necrosis has been seen to develop in patients who experienced no rejection episodes and who received relatively small doses of corticosteroids, and yet did not develop in patients who had many rejection episodes and who received large doses of corticosteroids.[1]

Although our patients in the avascular necrosis group experienced more bouts of acute rejection, the difference between the two groups as regards the mean corticosteroid dosage and mean serum creatinine levels at 1 year post-transplant did not attain statistical significance.

We found an association between significant alcohol consumption, radiological evidence of osteoporosis and the development of avascular necrosis. Severe secondary hyperparathyroidism and hyperlipidaemia did not correlate with the development of avascular necrosis in this study. Nevertheless the hypothesis that corticosteroid-induced hyperlipidaemia gives rise to fatty infiltration of the liver and subsequent arteriolar fat embolisation cannot be entirely discounted by this study; lipid levels were noted to be higher in the avascular necrosis group, although this difference did not attain statistical significance. Furthermore the normal liver function test results observed in both groups of patients do not preclude the possibility of hepatic fatty infiltration.

This study supports the hypothesis that corticosteroid-induced osteoporosis leads to avascular necrosis secondary to the development of microfractures. Although only 28,5% of the patients with avascular necrosis had radiological evidence of osteoporosis, the prevalence could well have been higher had bone been examined histologically.

It was interesting to note the increased incidence of avascular necrosis in our Indian transplant recipients. The number of patients in our avascular necrosis group, however, was too small to permit a meaningful interracial comparison of potential risk factors so the reason for this phenomenon remains obscure. A racial predisposition has previously been reported by Patton *et al.*[4] who found an increased incidence of avascular necrosis in their black transplant recipients.

This study has demonstrated that most patients who develop avascular necrosis following renal transplantation present with symptoms within 2 years. The isotope bone scan was the most sensitive diagnostic tool and was capable of detecting avascular necrosis even before the development of symptoms. Regular isotope bone scanning, however, is not recommended as definitive surgical therapy would be inappropriate at such an early stage in the development of avascular necrosis. This study suggests that corticosteroid therapy plays an important role in the pathogenesis of avascular necrosis following renal transplantation. Excessive alcohol consumption and radiological evidence of osteoporosis also appear to be risk factors.

The trend towards triple-drug immunosuppressive regimens or cyclosporin monotherapy should result in a decline in the incidence of this complication.

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