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SELECTED INDICATORS OF BONE METABOLISM IN PATIENTS AFTER KIDNEY TRANSPLANT

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Bone metabolism defects and skeleton diseases, so called renal osteopathy (RO), represent very serious clinical problems in the care of patients with kidney dysfunction. Renal osteopathy is a complicated skeletal disorder with a very complicated pathogenesis and we can encounter its individual forms in kidney transplant patients.

INTRODUCTION

Kidney transplant is indicated method for chronic kidney failure in some patients. After successful kidney transplant, bone metabolism may improve owing to normalization of serum levels of calcium, phosphorus and the restoration of calcitriol production. However a successful transplantation is no guarantee of complete adjustment to pre-existing RO. In addition in kidney transplant patients bone complications related to long-term immunosuppressive therapy are often manifest.

OBJECTIVE

The prime objective of the presented prospective study was an evaluation of the development of selected bone metabolism indicators and bone density within a two-year time period following a kidney transplant. A partial objective was assessment of the effectiveness of prophylactic administration of D-vitamin and calcium preparations for the prevention of osteopathy progression following kidney transplant.

POPULATION AND METHODOLOGY

The patient population consisted of 40 patients who received a cadaverous kidney. There were 22 males and 18 females average age of 51.5 ± 13.2 years. After transplantation all patients were treated with a combination of cyclosporin-A, mycophenolate mophetil or azathioprin and after the transplantation, they were prophylactically given AD-vitamin and calcium effervescens in doses of 1,000 mg Ca effervescent tablets and 800 IU AD-vitamin. During the whole two-year period of monitoring, the serum creatinine concentration in all individuals was lower than 200 µmol/l. During the transplantation (up to 2 weeks) and two years after the kidney transplant, the concentration of serum parathormon (PTH), serum level of bone fraction of alkaline phosphatase (ALP), serum phosphorus (P) and calcium (Ca) concentration and P and Ca loss in urine/24 hours were examined in all the monitored patients. In the same time period, radiographic pictures of thoracic and lumbar spine and hip joints were taken and by means of Dual-Energy-X-Ray, the bone density (BMD) in the L spine area and femur cervix was determined.

RESULTS

The results are presented in the form of tables 1–3 and are shown individually for the subgroup of patients with creatinine content lower than 120 µmol/l and for the subgroup of patients with creatinine concentration in the range of 120–200 µmol/l.

In individuals with creatinine concentration <120 µmol/l, two years after the kidney transplant, the average PTH concentration was 82.92 ± 66.01 pg/ml while in patients with creatinine concentration >120 µmol/l, the average PTH concentration was 140.34 ± 150.41 pg/ml (Table 1).

Two years after the transplantation, in 20 individuals with creatinine concentration <120 µmol/l, there was a decrease of BMD in 7 patients (35 %) in the L spine area and in 9 patients (45 %) in the femur cervix area. An increase in BMD occurred in 2 patients (10 %) in the L spine are and only in one patient in the femur cervix area. A stabilized bone density finding in the L spine area was detected in 11 patients (55 %) and in 10 patients in the femur cervix area (Table 2).

In 20 other patients with creatinine concentrations over 120 µmol/l, there was a BMD decrease in 9 patients

(45 %) in the L spine area and in 10 patients (50 %) in the femur cervix area. A BMD increase occurred in 2 patients (10 %) in the L spine area and in 3 patients in the femur cervix area. Stabilized BMD was found in 9 individuals (45 %) in the L spine area and in 7 patients (35 %) in the femur cervix area (Table 3).

Table 1. Biochemical findings in patients a 2 years after kidney transplant.
(a_n = 20)

Indicator	Creatinine <120 µmol/l n = 20	Creatinine 120–200 µmol/l n = 20
Parathormon (pg/ml)	82.99 ± 66.01	140.34 ± 150.41
ALP (µkat/l)	1.26 ± 0.53	1.39 ± 0.50
Serum Ca (mmol/l)	2.46 ± 0.14	2.40 ± 0.15
Urine Ca (mmol/24 hours)	1.56 ± 1.02	1.47 ± 1.06
Serum P (mmol/l)	1.13 ± 0.26	1.18 ± 0.25
Urine P (mmol/24 hours)	7.42 ± 4.57	7.90 ± 4.48

Table 2. Development of densitometric findings in individuals a with creatinine <120 µmol/l.
(a_n = 20)

Finding	L-spine		Femur cervix	
Stabilized	11	55 %	10	50 %
Improved	2	10 %	1	5 %
Aggravated	7	35 %	9	45 %

Table 3. Development of densitometric findings in patients a with level of serum creatinine between 120–200 µmol/l.
(a_n = 20)

Finding	L-spine		Femur cervix	
Stabilized	9	45 %	7	35 %
Improved	2	10 %	3	15 %
Aggravated	9	45 %	10	50 %

DISCUSSION

Renal osteopathy, developing as a progression of kidney disease, is characterized by a phospho-calcium metabolism defect which develops due to lower phosphorus excretion (kidney excretion dysfunction), lack of 1.25 cholecalciferol (kidney endocrine dysfunction) and PTH overproduction[1]. Generally known RO forms include osteopathy with a high bone turnover of the secondary hyperparathyreosis (fibrosis osteodystrophy) and osteopathy with a low bone turnover of the osteomalacia type or aplastic (adynamic) bone diseases. Mixed forms of osteopathy with participation of all the above mentioned mechanisms occurr most frequently[1].

A successfully performed kidney transplant will, for the most part, solve ethiopathogenetic mechanisms of RO development and the phospho-calcium metabolism defect will improve in a majority of the patients, but some RO forms may, however, continue after transplantation.

A relatively frequent complication after kidney transplant is persistent PTH overproduction leading to a further bone loss. Persistent hyperparathyroidism was found in 43 % of patients after kidney transplant with a serum creatinine concentration of 150 µmol/l (ref.[2]).

Another clinical study of a population of 129 patients showed hypercalcaemia in 52 % of the individuals in the first three months after kidney transplant[11]. The basis for this finding is permanent autonomic stimulation of the synthesis and secretion of PTH in parathyroid adenoma as a consequence of reduced expression of receptors for D-vitamin – calcitriol and calcium ions[3,4]. In such cases, suppression of the secondary hyperfunction does not occur even in a very well functioning transplanted kidney and the disease progresses to tertiary hyperparathyreosis[5–6].The persistent hypercalcaemia can lead to nephrocalcinosis, deteriording function of the transplanted kidney and further progression of the bone disease[12].

Current assessment on optimal concentration of the intact PTH in circulation in patients with inadequate graft function is not completely understood and the majority of authors are convinced that they are three or four times the quantity of the upper limit of a levels in a healthy population, approximately 200–250 pg/ml. It appears that PTH levels above 500 pg/ml indicate an increased bone turnover and hyperparathyreosis while values below 100 pg/ml indicate a low turnover bone disease[6]. Prospective monitoring of densitometric findings in patients with different post-transplantation PTH levels could help determine so called "safe" upper limit of PTH concentration and decide on the further therapeutic procedures.

Another defect of phospho-calcium metabolism after kidney transplant is hypophosphataemia due to reduced reabsorption of phosphates in the proximal kidney tubule[8]. In its pathogenesis, both PTH surplus and calcitriol insufficiency are present. Hypophosphataemia may contribute to development of osteoporosis[10]. The post-transplantation hypophosphateamia may adjust spontaneously or within the calcitriol therapy[9].

The major aethiopathogenetic factor leading to bone loss during post-transplantation period is long-term immunosuppressive therapy. The most significant drug with negative effect on bone is generally considered corticosteroids. The negative impact of costicosteroids on bone metabolism results from acceleration of bone resorption and inhibition of new bone production[13]. The costicosteroids inhibit posphate transport on the luminous side of the basal side of the membrane of the proximal tubule and suppress calcium resorption from the digestive tract. Their negative effect on bone is generally dependent on the cumulative dosage[12]. According to the literature, the greatest BMD loss occurs in the first year after kidney transplant when the BMD drop represents up to 10 % of the initial value (Fig. 1–3). During the next period, the drop continues at an average of 1.7 % annually[12, 15-7, 22]. Furthermore, during rejection episodes and their therapy, cytokines begin to loosen. The cytokines support differentiation of osteoclasts and incite apoptosis of the osteoblasts and osteocytes. Another very serious clinical problem, which represents one of the gravest complications of corticosteroid therapy after the kidney transplant, is avascular bone necrosis. This most frequent is an affliction of the femur cervix.

Bone loss caused by the calcineurin inhibitors (cyclosporin-A and tacrolimus) progresses with increased bone turnover, conditional on stimulated IL-1and IL-2 recrement, originated in activated lymphocytes, particularly in later stages after the transplantation[18-20]. Progression of bone disease can theoretically also occur as a result of nephrotoxic effect of cyclosporin, which may aggravate the functional deterioration of the transplanted kidney and lead to activation of parathyroid function. Calcineurin inhibitors may stimulate also so called algic bone syndrome, which is caused by intrabony hypertension and vasoconstriction and is manifest mostly in early post-transplantation stages[12].

The remaining immunosuppressive substances, azathioprin, mycophenolate mophetil and TOR inhibitors have no known any unfavorable effects[21-22].

Based on the results, we can draw the following conclusions:

1. PTH concentration in the serum is higher than in patients with the creatine concentration exceeding 120 μmol/l.
2. Development of densitometric findings evaluated 2 years after the transplantation is affected by graft function.
3. The densitometric findings in individuals with the creatinine concentration lower than 120 μmol/l are more frequently stabilized and less frequently aggravated.
4. A large number of patients with the decline in bone density in the post-transplantation period indicates the seriousness of the problem and is a challenge for optimal procedures to be found.

At present, administration of calcium and D-vitamin is recommended for all individuals after kidney transplant. For patients with inadequate graft function, this is recommended in a form of active metabolites (1.25 dihydroxy -cholecalciferol). The significance and indication of bisfosfonates in the therapy and prevention of osteopenia in transplant patients needs to be specified in greater detail in further prospective, on-going long-term studies.

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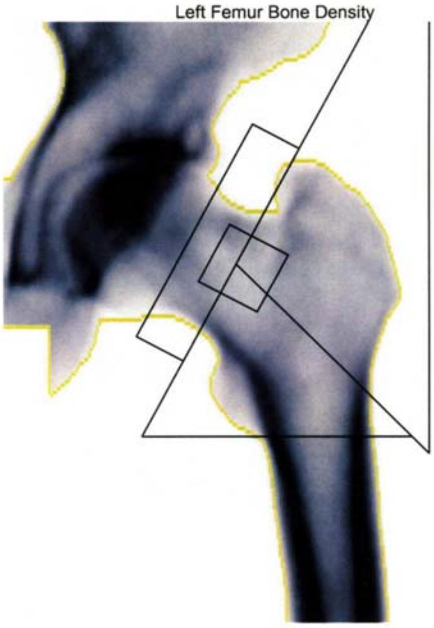
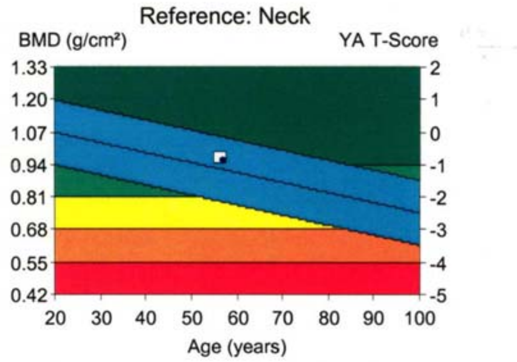
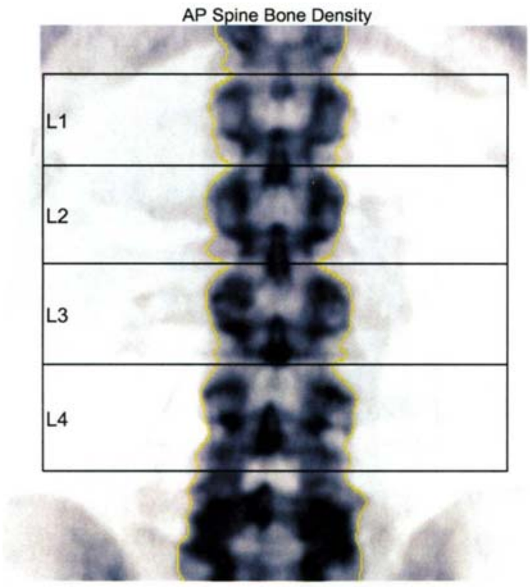
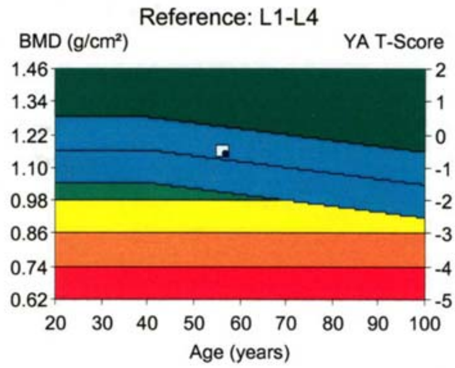




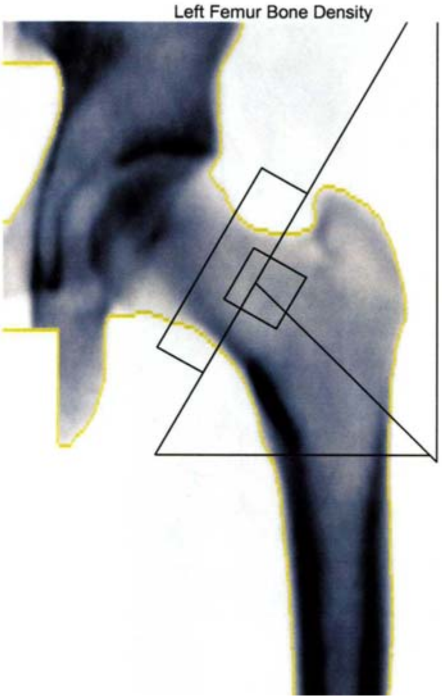
Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
Neck	0.966	90	-0.8	105	0.3
Wards	0.857	89	-0.8	113	0.7
Troch	0.930	100	0.0	110	0.7
Shaft	1.281	-	-	-	-
Total	1.070	98	-0.2	110	0.7

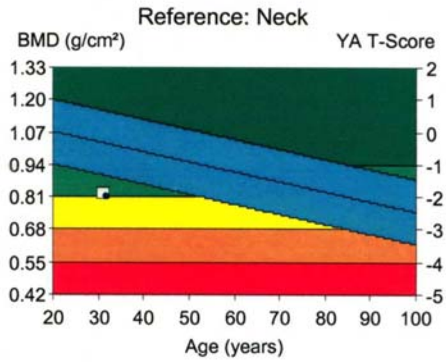




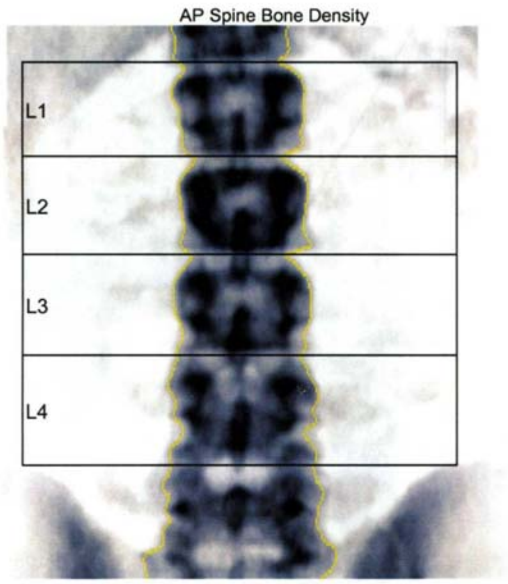
Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
L1	1.053	91	-0.9	98	-0.1
L2	1.177	95	-0.5	102	0.2
L3	1.233	99	-0.1	107	0.7
L4	1.175	95	-0.5	102	0.2
L1-L3	1.158	96	-0.4	103	0.3
L1-L4	1.163	95	-0.5	103	0.3
L2-L3	1.206	97	-0.3	105	0.5
L2-L4	1.194	96	-0.4	104	0.4
L3-L4	1.202	97	-0.3	105	0.4

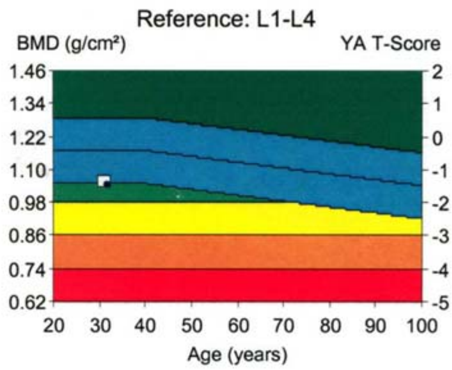
Fig. 1. Normal densitometric finding in the L-spine and femur cervix areas.
(Patient: B. V., 1947, 2 months after cadaverous kidney transplant, serum creatinine 100 μmol/l).





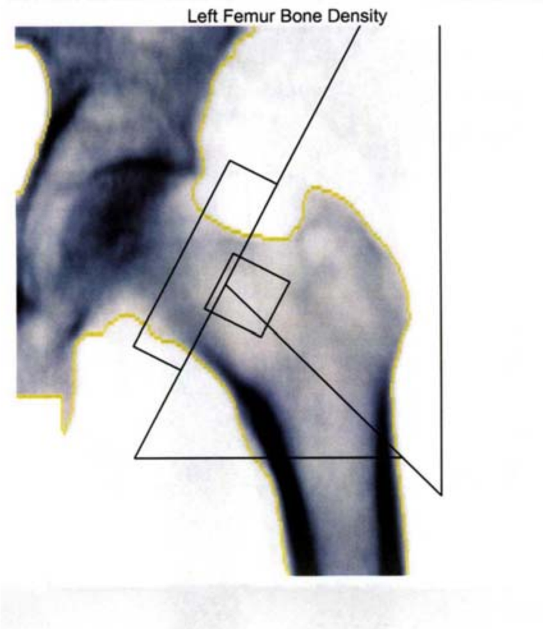
Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
Neck	0.829	77	-1.9	81	-1.5
Wards	0.724	75	-1.8	79	-1.5
Troch	0.726	78	-1.9	82	-1.5
Shaft	1.103	-	-	-	-
Total	0.890	82	-1.5	85	-1.2

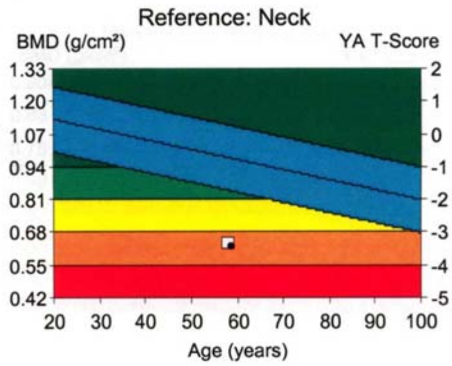




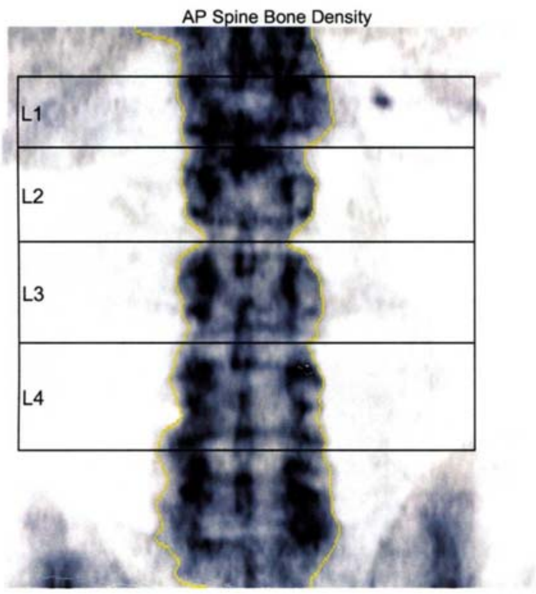
Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
L1	0.990	85	-1.4	89	-1.0
L2	1.149	93	-0.8	97	-0.3
L3	1.080	87	-1.3	91	-0.9
L4	1.026	83	-1.8	86	-1.4
L1-L3	1.074	89	-1.1	93	-0.7
L1-L4	1.060	87	-1.3	91	-0.9
L2-L3	1.113	90	-1.1	94	-0.6
L2-L4	1.080	87	-1.3	91	-0.9
L3-L4	1.051	85	-1.6	88	-1.1

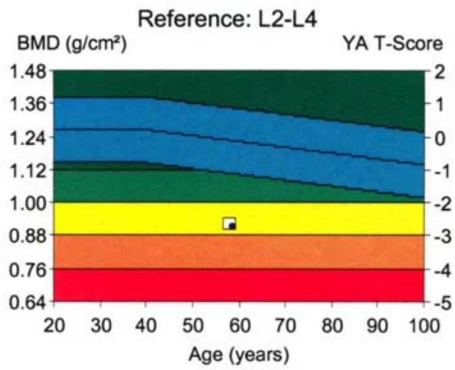
Fig. 2. Osteopenia finding in the L-spine (T-score – 1.3 SD) and femur cervix (T-score – 1.5 SD) areas. (Patient: S. J., 1972, 6.5 months after cadaverous kidney transplant, serum creatinine 116 μmol/l).





Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
Neck	0.639	60	-3.3	65	-2.6
Wards	0.375	39	-4.5	46	-3.3
Troch	0.640	69	-2.6	71	-2.4
Shaft	0.920	-	-	-	-
Total	0.736	67	-2.7	71	-2.3





Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	T-Score	Age-Matched[3] (%)	Z-Score
L1	0.966	83	-1.6	84	-1.5
L2	0.948	76	-2.4	77	-2.3
L3	0.962	78	-2.3	78	-2.2
L4	0.883	71	-3.0	72	-2.9
L1-L3	0.959	79	-2.1	80	-2.0
L1-L4	0.935	77	-2.4	78	-2.3
L2-L3	0.956	77	-2.4	78	-2.3
L2-L4	0.927	75	-2.6	76	-2.5
L3-L4	0.919	74	-2.7	75	-2.6

Fig. 3. Osteoporosis finding in the L-spine (T-score – 2.6 SD) and femur cervix (T-score – 2.7 SD) areas. (Patient: K. L., 1945, 9.5 months after cadaverous kidney transplant, serum creatinine 146 µmol/l).

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