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NUTRITIONAL STATUS OF RENAL TRANSPLANT PATIENTS

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Objective. To assess the effect of renal transplantation on the nutritional status of patients.

Design. Prospective descriptive study.

Setting. Renal Transplant Clinic at Tygerberg Hospital, Western Cape.

Subjects. Fifty-eight renal transplant patients from Tygerberg Hospital were enrolled in the study. The sample was divided into two groups of 29 patients each: group 1, less than 28 months post-transplant; and group 2, more than 28 months post-transplant.

Outcome measures. Nutritional status assessment comprised biochemical evaluation, a dietary history, anthropometric measurements and a clinical examination.

Results. Serum vitamin B_6 levels were below normal in 56% of patients from group 1 and 59% from group 2. Vitamin B_6 intake, however, was insufficient in only 14% of patients from group 1 and 10% from group 2. Serum vitamin C levels were below normal in 7% of patients from group 1 and 24% from group 2, while vitamin C intake was insufficient in 21% and 14% of patients from groups 1 and 2 respectively. Serum magnesium levels were below normal in 55% of patients from group 1, and in 28% from group 2. Serum albumin and cholesterol levels increased significantly during the post-transplant period in the total sample ($P = 0.0001$). There was also a significant increase in body mass index ($P = 0.0001$) during the post-transplant period.

Conclusions. Several nutritional abnormalities were observed, which primarily reflect the side-effects of immunosuppressive therapy. The causes, consequences and treatment of the vitamin B_6 and vitamin C deficiencies in renal transplant recipients need further investigation.

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Chronic renal failure (CRF) is associated with several metabolic and nutritional abnormalities such as protein-energy malnutrition,[1-4] loss of muscle protein,[5-7] abnormal nitrogen balance,[8] vitamin deficiencies or surpluses,[9] as well as mineral[10] and lipid abnormalities.[11,12] Although renal transplantation improves these abnormalities, the lifelong immunosuppressive therapy associated with renal transplantation (usually consisting of corticosteroids, cyclosporin and azathioprine) adversely affects nutritional status by inducing micronutrient deficiencies or surpluses, hypertension, lipid abnormalities, obesity, protein catabolism and impaired glycaemic control.[13-16] This is a matter of concern since the pre-transplant nutritional status of most patients is already impaired as a result of CRF and the associated dialysis therapy.[2] The aim of this pilot study was to evaluate the nutritional status of renal transplant patients at Tygerberg Hospital by means of a dietary history, anthropometric measurements, biochemical measurements of blood, and a clinical examination. Since data on the vitamin status of renal transplant recipients are not readily available, special attention was given to this aspect in the nutritional assessment.

SUBJECTS AND METHODS

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Stellenbosch. All patients at the Renal Transplant Clinic, Tygerberg Hospital, were screened according to the following selection criteria: at least 6 months post-transplant in order to exclude unstable patients; serum creatinine < 200 µmol/l; on daily immunosuppressive therapy comprising cyclosporin, low-dose corticosteroids and azathioprine; absence of chronic diarrhoea and/or vomiting; and no complicating disease that could affect nutritional status. Informed consent was obtained from all patients. The median of the post-transplant follow-up period was 28 months, and this was used to divide the patients into two groups — group 1, 6 - 28 months post-transplant, and group 2, more than 28 months post-transplant. There were 29 patients in each group, and the groups were comparable with regard to sex, age and serum creatinine levels (Table I). The following investigations were performed once only on each subject.

Table I. Description of study groups

	Group 1 (6 - 28 months post-transplant)	Group 2 (> 28 months post-transplant)
Number of patients	29	29
Males *(N)*	15	14
Females *(N)*	14	15
Mean age (yrs) (SD)	35 (13)	41 (16)
Mean serum creatinine (µmol/l) (SD)	127 (42)	135 (50)

Biochemical evaluation

Fasting venous blood samples were obtained for determination of the following parameters (using standard laboratory techniques): serum levels of albumin (bromcresol green method), creatinine, urea, calcium (corrected for serum albumin),[17] magnesium, potassium, phosphate, and cholesterol; plasma pyridoxal-5-phosphate (tyrosine decarboxylase apoenzyme activation) and vitamin C (spectrophotometrically); and haemoglobin, mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV). Serum creatinine < 200 µmol/l was used as one of the selection criteria. For albumin and cholesterol, we also used retrospective measurements available for the period immediately before the transplant, in order to assess changes after the transplant. Serum cholesterol levels were compared with age-adjusted standards for males and females (South African Heart Foundation).

Dietary history

A quantified food frequency questionnaire (QFFQ), which was pre-tested for face validity, was used to determine usual dietary intake during the post-transplant period. A single observer (A du P) did all assessments. Portion sizes were determined by means of food models and the National Research Institute for Nutritional Diseases (NRIND) Food Quantities Manual,[18] and nutrient intake was determined using the software package FOODFINDER (South African Medical Research Council). Dietary analyses were compared with specific recommendations for kidney transplant patients where available or the recommended dietary allowances (RDA). Protein and energy intake were expressed per kilogram ideal body weight.

Anthropometric measurements

Body weight was assessed using an electronic platform scale which was standardised by means of zero calibration and a 5 kg weight. Height was determined using a measuring tape attached to a wall, as well as a head piece positioned on top of the patient's head. Elbow width was measured using a metal caliper, triceps skinfold thickness (done in triplicate) using a Harpenden skinfold caliper, and mid-arm circumference using a non-stretchable measuring tape. Standard measuring techniques were used for all anthropometric measurements,[19,20] and to avoid the problem of interobserver variation, all measurements were taken by a single observer (HR). These measurements were used to determine the body mass index (BMI) and bone-free arm muscle area. Retrospective measurements of body weight for the period immediately preceding the transplant were also recorded.

Clinical examination

Clinical signs of nutritional deficiencies and the presence of oedema were recorded by the same trained investigator (EE).

Biochemical analyses and anthropometric measurements were compared with standards for normal, healthy individuals. All the information was processed using descriptive statistics and unpaired two-sample *t*-tests where applicable.

RESULTS

Biochemical evaluation

Results of the biochemical determinations are shown in Table II. Although mean pre-transplant serum albumin was in the low-normal range in both groups, 52% and 62% of patients from groups 1 and 2 presented with hypoalbuminaemia. Serum albumin levels increased significantly during the post-transplant period in the group as a whole. The increase in serum cholesterol during the post-transplant period was also significant for the group as a whole, with no significant difference between the groups. Serum cholesterol levels were elevated in approximately 10% of patients before the transplant, and in 24% of patients during the post-transplant period, whereas approximately 30% of patients had low serum cholesterol levels before the transplant, compared with only 3% of patients from group 1 post-transplant. There was a significant correlation between serum cholesterol and BMI ($r = 0.35$, $P < 0.01$), and age ($r = 0.33$, $P < 0.01$).

Although mean serum calcium levels were within the normal range, hypercalcaemia was observed in 3% and 7% of patients from groups 1 and 2 respectively during the post-transplant period, with no patient suffering from hypocalcaemia (Table II). Mean serum magnesium levels fell in the low-normal range in both groups, with 55% and 28% of patients from groups 1 and 2 respectively presenting with hypomagnesaemia. Hypophosphataemia and hypokalaemia were present in a small number of patients only, although mean serum levels generally fell within the normal ranges.

Mean blood levels of pyridoxal-5-phosphate fell in the low-normal range. However, more than 55% of all patients had marginal vitamin B_6 status. Although vitamin C status was normal in the majority of patients, 7% of patients from group 1 and 24% from group 2 had marginal vitamin C status. There was no significant difference between the groups for these parameters.

Anaemia was present in 24% of patients from both groups. Although iron studies were not available for these patients, a hypochromic picture was present in 34% of patients from group 1 and 10% from group 2, with a significant difference in MCH between the groups ($P < 0.01$). There was no significant difference in MCV between the groups, but MCV was below normal in 17% and 3% of patients from groups 1 and 2, and increased in 10% and 14% of patients from groups 1 and 2 respectively.

Dietary history

An increase in appetite was reported in 76% of patients in group 1 and 48% in group 2 during the post-transplant period. With the exception of 1 patient from group 1, energy intake exceeded 130 kJ/kg in all patients, with mean intakes in the upper range of the recommendations (Table III). Protein intake exceeded the recommended 1 g/kg/day in 98% of patients. The intake of total fat and saturated fat exceeded the recommendations in 74% and 75% of patients respectively. Micronutrient intake of patients (Table IV) is given as a percentage of the RDA (corrected for age and sex), rather than actual intake. In contrast with macronutrients, the intake of a large number of patients was insufficient for pantothenic acid,

Table II. Blood values for albumin, cholesterol, selected minerals and vitamins

		Means (SD)			Percentage above normal		Percentage below normal	
Measurement	Normal range	Total sample	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Albumin								
Pre-transplant (g/l)	35 - 50	34 (7)	36 (8)	33 (7)	0	0	52	62
Post-transplant (g/l)	35 - 50	39 (4)*	40 (5)†	38 (4)†	0	0	7	10
Cholesterol								
Pre-transplant (mmol/l)	3.8 - 5.7	4.8 (1.3)	4.8 (1.7)	4.8 (1.5)	7	13	29	31
Post-transplant (mmol/l)	3.8 - 5.7	5.9 (1.4)*	5.7 (1.4)	6.1 (1.4)	24	24	3	0
Calcium (mmol/l)	2.1 - 2.6	2.4 (0.2)	2.4 (0.1)	2.5 (0.3)	3	7	0	0
Phosphorus (mmol/l)	0.8 - 1.4	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0	3	7	14
Magnesium (mmol/l)	0.75 - 1.0	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	0	3	55	28
Potassium (mmol/l)	3.5 - 5.3	3.9 (0.5)	3.9 (0.5)	3.8 (0.4)	0	0	14	10
Pyridoxal-5-P (ng/ml)	6 - 20	6.8 (5.9)	6.2 (4.0)	7.3 (7.0)	0	3	56	59
Vitamin C (ng/100 ml)	0.25 - 1.2	0.5 (0.2)	0.5 (0.2)	0.5 (0.3)	0	3	7	24

*$P = 0.0001$ (significant increase post-transplant).
†$P = 0.0492$ (significant difference between groups 1 and 2).

Table III. Daily macronutrient intake of patients (mean (SD)), compared with recommendations for renal transplant recipients[16]

Nutrient	Recommendation	Total sample	Group 1	Group 2
Protein (g/kg)	1.0	1.3 (0.4)	1.4 (0.4)	1.3 (0.4)
Energy (kJ/kg)	130 - 150	153.7 (40.8)	160.2 (40.5)	147 (40.8)
Carbohydrates (% of total energy)	50	50 (9)	51 (9)	50 (9)
Fat (% of total energy)	30	33 (6)	34 (5)	33 (7)
Saturated fat (% of total energy)	< 10	10 (2)	11 (1)	10 (2)
Polyunsaturated fat (% of total energy)	< 10	8 (3)	9 (3)	7 (3)
Cholesterol (mg/d)	< 300	284 (141)	300 (109)	268 (167)

Table IV. Daily micronutrient intake of patients (mean (SD)), expressed as a percentage of the Recommended Dietary Allowance (RDA)

	Percentage of RDA		Percentage of patients < 67% of RDA	
Nutrient	Group 1	Group 2	Group 1	Group 2
Riboflavin (mg/d)	93 (23)	100 (30)	7	14
Niacin (mg/d)	120 (32)	92 (20)	3	7
Pyridoxine (mg/d)	134 (56)	178 (32)	14	10
Ascorbic acid (mg/d)	189 (167)	161 (195)	21	14
Folate (mg/d)	134 (44)	111 (34)	7	3
Pantothenic acid (mg/d)	87 (27)	82 (26)	24	31
Magnesium (mg/d)	95 (28)	93 (23)	7	10
Calcium (mg/d)*	55 (32)	57 (34)	28	45
Phosphorus (mg/d)*	85 (58)	98 (66)	0	0
Potassium (mg/d)	162 (46)	144 (38)	0	0
Iron (mg/d)	95 (39)	86 (31)	28	31

*Intake of calcium and phosphorus expressed as % of recommendations for renal transplant patients (1 200 mg/d each).[16]

calcium and iron. Vitamin B_6 intake exceeded the recommendations in 62% of patients from group 1 and 55% from group 2, and was insufficient in only 14% from group 1 and 10% from group 2. Similarly, the intake of vitamin C exceeded the recommendations in 48% and 31% of patients from groups 1 and 2 respectively, whereas 21% and 14% had insufficient intakes. There were no clinical manifestations of vitamin deficiencies.

Anthropometric measurements

There was a significant increase in mean BMI from 23 to 25 kg/m^2 during the post-transplant period ($P = 0.0001$) in the combined groups, with a large number of patients being classified as overweight or obese (Table V). With pre-transplant muscle mass data not available, the relative contribution of muscle tissue or adiposity to weight gain is unfortunately not known. Pitting oedema of the feet and ankles was observed in 43% of patients from group 1 and 48% from group 2. Because of uncertainties regarding the fluid status of patients at the time of renal transplantation, we analysed the results of patients without oedema at the time of this investigation separately. Twenty-six per cent and 43% of patients from groups 1 and 2 respectively were still classified as overweight or obese. Bone-free arm muscle area was unexpectedly high, with 53% of patients from groups 1 and 2 falling above the 90th percentile, and none showing signs of depletion (Table VI).

Discussion

Malnutrition is an important cause of morbidity and mortality among patients on long-term haemodialysis.[21-23] Hypo-albuminaemia has further been shown to be a strong and independent risk factor for all-cause mortality after renal transplantation.[24]

In this study, visceral protein status before the transplant was inadequate, as indicated by the fact that more than 50% of patients had pre-transplant serum albumin levels below 35 g/l. The significant increase in serum albumin levels post-transplant may indicate improved nutritional status as a result of the increase in appetite as well as improved renal function. However, it should also be noted that serum albumin is

Table V. Anthropometric measurements, expressed as the percentage of patients in each category

	BMI (kg/m²)						
	< 16	16 - 16.9	17 - 18.4	18.5 - 24.9	25 - 29.9	30 - 40	> 40
Pre-transplant							
Group 1 (*N* = 28)	0	0	7	61	29	4	0
Group 2 (*N* = 28)	4	4	4	64	14	4	4
Post-transplant							
Group 1 (*N* = 28)	0	0	0	54	25	21	0
Group 2 (*N* = 29)	0	0	7	41	38	0	0
Post-transplant (Patients with oedema excluded)							
Group 1 (*N* = 16)	0	0	0	75	13	13	0
Group 2 (*N* = 15)	0	0	13	40	30	13	0

Table VI. Bone-free arm muscle area percentiles, expressed as the percentage of patients in each category during the post-transplant period

	Bone-free arm muscle area percentiles			
	< 15	15 - 85	85 - 95	> 95
Group 1 (*N* = 28)	0	36	25	39
Group 2 (*N* = 29)	0	39	18	43
Total sample	0	38	22	40

affected to a large extent by intravascular fluid status. Improved renal function post-transplant may therefore lead to a reduction in intravascular fluid and hence an increase in serum albumin levels, and may falsely suggest improved nutritional status.[25] The increase in serum albumin may also represent a corticosteroid-induced shift of albumin from the extravascular to the intravascular space.[26] All these factors restrict the value of serum albumin as an indicator of nutritional status in renal transplant recipients.

The significant increase in serum cholesterol levels post-transplant is in agreement with the findings of Kasiske and Umen,[27] Bumgardner *et al.*,[28] and Vathsala *et al.*,[29] and may partly indicate an improvement in nutritional status. However, corticosteroids have been shown to induce elevated hepatic cholesterol synthesis, which may be related to hyperinsulinaemia caused by peripheral insulin resistance,[11] as well as depressed activity of adipose tissue lipoprotein lipase.[30] Cyclosporin has also been reported to raise serum cholesterol levels, although the mechanism is less certain.[31,32] Others have suggested that hyperlipidaemia is not correlated with cyclosporin or prednisone dosage but to the degree of obesity,[28] and that patients who do not gain weight post-transplant do not have a worsening in lipid profiles.[15] In this study we also found a significant correlation between BMI and serum cholesterol levels. Dietary intake in this study did not comply with the step 1 diet and was higher in total and saturated fat during the post-transplant period, which may have contributed, together with obesity, to the increased serum cholesterol levels. The hyperlipidaemia observed in these patients may predispose them to cardiovascular disease, a major cause of death in many renal transplant recipients.[16]

Although calcium, phosphorus and potassium levels were normal in the majority of patients, a small percentage of patients presented with hypercalcaemia. This is not an unexpected finding and may have been caused by improved action of parathyroid hormone and hence bone resorption, improved 1-hydroxylation of vitamin D,[33] as well as steroid-induced over-secretion of the parathyroid gland.[16] Since bone stores may contribute significantly to maintain serum levels in cases of magnesium depletion, serum levels of magnesium may be normal even in the presence of intracellular magnesium depletion. Occurrence of low serum magnesium therefore usually indicates significant magnesium deficiency.[34] Low muscle magnesium content has also previously been reported in renal transplant recipients.[35] Impaired magnesium status as reflected by the serum component, is probably due to the use of cyclosporin, which has been shown to be nephrotoxic, resulting in urinary magnesium loss.[36] The majority of patients in this study had magnesium intakes exceeding the RDA, indicating that the latter might not be sufficient for patients on cyclosporin. Since hypomagnesaemia is known to produce cardiac arrhythmias and neuromuscular irritability, correction of hypomagnesaemia should be considered. The hypophosphataemia which occurred in some patients may have been caused by a parathyroid hormone excess due to previous renal failure, or a derangement in renal phosphate transport.[10,14] Hypophosphataemia may cause haemolysis, rhabdomyolysis or central nervous system dysfunction at levels below 0.32 mmol/l (1 mg/dl).[14]

The marginal levels of vitamin B_6 and vitamin C in a large proportion of the study group might be the result of low dietary intakes in some patients, as well as the use of corticosteroids.[37] A previous study also reported a deficiency of vitamin B_6 in 65% of non-uraemic kidney transplant patients.[38] However, supplementation of vitamin B_6 received no attention in the general guidelines for nutritional support of kidney transplant patients. The mechanism for deficiency of vitamin B_6 is not known. Vitamin B_6 deficiency may be associated with the hyperhomocysteinaemia previously described in transplant patients,[39] and may also lead to impaired neurological function and hypochromic microcytic anaemia.[40] Although vitamin B_6 supplementation failed to improve plasma total homocysteine concentrations, it has been reported to cause a 22% decrease in post-methionine-loading increases in plasma homocysteine.[41,42] Low plasma levels of vitamin B_6 have recently been shown to be an independent risk factor for cardiovascular disease, more so than increased plasma homocysteine concentrations.[43]

It has previously been shown that corticosteroids may induce urinary loss of vitamin C.[37] An increased demand for antioxidant nutrients post-transplant may have contributed to low blood levels of vitamin C as well.[44] Vitamin C deficiency may be associated with anaemia, atherosclerotic plaques and pinpoint bleedings.[45] Although the mean dietary intake of vitamins B_6 and C in our patients was well above the recommended limits, quite a number of individual patients had suboptimal intake, especially in the case of vitamin C.

The origin of the anaemia observed in our patients was unfortunately not investigated in this study, but iron deficiency may have played a role in causing hypochromic microcytic anaemia, especially in the light of the low intake of dietary iron observed in almost all of our patients, and the rapid expansion of the red cell mass following restoration of renal function. The possible contributory role of vitamin B_6 and vitamin C deficiency as a cause of anaemia in some patients should also be investigated.[40,45]

An increase in appetite induced by corticosteroids[40] could be associated with the relatively high energy intake of the study group. However, it has been reported by others that post-transplant weight gain is related mainly to demographic factors and not to steroid dosage.[15] An improved sense of wellbeing as a result of improved anaemia and renal function may also have caused the patients' improvement in appetite. The high energy intake of the study group may account for the increase in BMI of patients during the post-transplant period. Corticosteroids *per se* may also cause an increase, and a change in the distribution of body fat.[46] Because of this corticosteroid-induced alteration in body fat distribution, body fat percentages were not determined in this study. This, together with the unavailable data on pre-transplant muscle mass, complicated the quantification of fat or muscle tissue as a contribution to weight gain. A BMI above 26 has previously been shown to reduce graft survival significantly, with the effect especially important in those with a BMI exceeding 36.[47,48] Larger people also had a greater need for dialysis in the post-transplant period. Others have reported that wound infections and delayed graft function occurred more commonly in moderately and morbidly obese recipients, but there was no significant correlation between obesity and graft survival.[49] Modlin *et al.*[50] further reported that obesity *per se* has little effect on long-term graft function, and that outcome differences in obese transplant patients were primarily as a result of higher mortality from cardiac events. For this reason it is recommended that obese patients should not be transplanted until weight reduction has been achieved.[48,50]

The relatively high bone-free arm muscle area in the majority of our patients is unexpected in the light of the catabolic effect of corticosteroids, even at low dosages as in this study.[14,16] Miller *et al.*[51] reported that 25 - 50% of their non-diabetic and diabetic patients respectively presented with mid-arm muscle circumferences below the 5th percentile 2 years post-transplant. Protein and energy intake in their patients amounted to 1 g/kg and 105 - 147 kJ/kg respectively, which is considerably lower than the intakes of our patients. Horber *et al.*[52] also showed that their patients had 20% less mid-thigh muscle area as measured by computed tomography. Unfortunately they did not report the dietary intake for protein and energy, and their results can therefore not be compared directly with ours. It seems possible that the relatively high protein and energy intakes of our patients may have been sufficient to preserve muscle mass.

CONCLUSION AND RECOMMENDATIONS

With the exception of some micronutrients, the majority of our patients received adequate nutrition during the post-transplant period. However, several nutritional abnormalities were observed, namely overweight and obesity; increased serum cholesterol; and low serum levels of magnesium, vitamin B_6 and vitamin C. Although these abnormalities may partly reflect typical side-effects of immunosuppressive therapy, further research should explore the mechanisms behind the development of the reported nutrient deficiencies. Subsequent findings should be used to develop strategies to prevent malnutrition and the consequences thereof.

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