Obesity and Hyperhomocysteinemia after Kidney Transplantation

Vladimír Teplan[1], Otto Schück[1], Milena Štollová[1], Štefan Vítko[2]
[1]Department of Nephrology, Transplant Center, Institute for Clinical and Experimental Medicine and Chair of Nephrology, Institute for Postgraduate Medical Education, Prague, Czech Republic
[2]Transplant Center, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Introduction

Obesity associated with secondary hyperlipoproteinemia is one of the most common long-term metabolic complications in renal transplant recipients. After renal transplantation, total homocystein level (tHcy) decreases as renal function improves, but remains higher than mean levels in the general population (1). Obesity and hyperhomocysteinemia are independent risk factors for atherosclerosis (2). The last decade has seen a marked increase in the survival times of functioning renal grafts. Improved pre- and post-transplant care has resulted in a growing number of recipients in the older age groups, many of whom suffer from associated diseases (hypertension and diabetes in particular) and had long been on dialysis treatment (3, 4, 5). Besides hyperlipidemia, development of atherosclerotic and/or nephrosclerotic lesions is enhanced by a variety of other factors, particularly arterial hypertension (in more than 80% of patients), primary vessel wall lesions (vasculitis, calcification), primary or secondary diabetes (insulin- or non-insulin-dependent diabetes mellitus), significant decrease in renal function, and proteinuria. A most important role is played by long-term administration of immunosuppressive therapy, in particular cyclosporin A and corticoids (5).

Our previous studies have demonstrated that transplant recipients do not differ, genetically, from the general Czech population. However, the body weight of the former is increased significantly (6).

The aim of our study was to evaluate the effect of a new regimen for the treatment of obese transplant patients with BMI ≥ 30 kg/m^2 and hyperhomocysteinemia in a long-term study.

Patients and methods

In a prospective metabolic study, we evaluated, for a period of 24 months, a total of 118 (55 M/63F) patients after their first cadaveric renal transplantation at 22-78 years of age. The patients had their transplantation at the Transplant Center of the Institute for Clinical and Experimental Medicine and collection of patient data was completed by 30 September 2002. We compared the findings of 118 pts with BMI ≥ 30 (kg/m^2 on a new regimen at one year (start of the study) and two years after renal transplantation.

Based on a Subjective Global Assessment Scoring Sheet an experienced dietetic nurse performed individualized dietetic intervention for DIETA computer software preparing individualized hypoenergic-hypolipidemic diet (IHHD) with energy intake < 30 kcal/kg BW. Subsequently, after corticoid withdrawal, IHHD was supplemented with orlistat at a dose of up to 3x 120 mg/day, statins (pravastatin 10-40 mg), folic acid 5 mg/day, and vit B6 50 mg/day and followed for up to 2 years.

The patients were on follow-up at the Department of Nephrology, Transplant Center of the Institute for Clinical and Experimental Medicine where their laboratory, anthropometric, and dietetic profiles and therapeutic interventions were regularly evaluated at a three-month interval.

Long-term immunosuppressive therapy included cyclosporin A with effective levels of 150-250 ng/ml. In addition, the patients received mycophenolate mofetil 1-2 g/day not shown to affect lipid metabolism.

Results

During the study period, there was a significant decrease of BMI ($p < 0.025$) and tHcy level ($p < 0.001$). Decrease of BMI on long-term therapy was associated with significant decrease of serum leptin ($p < 0.001$) and lipid metabolism parameters ($p < 0.01$).

The mean values of serum folate and vit. B6 increased significantly ($p < 0.01$), creatinine clearance, mean blood pressure, proteinuria, Lp(a) and apoE isoforms did not differ significantly (Table1).

Discussion

Obesity represents a risk factor in patients after renal transplantation. It is characterized by the abdominal (visceral) type of obesity in men and women alike. The prevalence is high, ranging between 25 % and 35 % in the first post-transplant year. Obesity is associated with other risk factor, primarily hyperlipidemia (5,6).

Hyperhomocysteinemia is an independent risk factor for development of cardiovascular disease. Stable renal-transplant recipients have disproportionately high rates of arteriosclerotic processes and recent reports provide controlled evidence that clinically stable transplant patients have a high prevalence of hyperhomocysteinemia (7,8,9).

Correspondence to: Vladimir Teplan, Videnska 1958/9, Prague 4, 140 21, Czech Republic, tel: 420-26136-4110
Fax: 420-26136-3168, e-mail: vladimir.teplan@medicon.cz

Table 1: Basic metabolic parameters in obese patients first and second year after renal transplantation (x ± SD)

Variable	1st year	2nd year	Statistical significance
Number of pts	118	118	
Gender (M/F)	55/63	55/63	NS
BMI (kg/m^2)	35.5 ± 3.2	27.4 ± 28	p < 0.025
tHcy (umol/L)	35.2 ± 12.4	12.7 ± 2.9	p < 0.001
Folate (mmol/L)	17.8 ± 8.5	32.9 ± 9.0	p < 0.01
Vit B6 (μg/L)	5.4 ± 1.5	9.3 ± 2.2	p < 0.01
Cholesterol (mmol/L)	7.2 ± 2.4	6.1 ± 2.0	p p< 0.01
LDL-cholesterol (mmol/L)	4.1 ± 1.2	3.0 ± 0.7	p < 0.01
HDL-cholesterol (mmol/L)	1.1 ± 0.2	1.0 ± 0.2	NS
Triglycerides (mmol/L)	3.8 ± 1.6	2.6 ± 0.6	p < 0.01
HDL-c/TG	0.28 ± 0.07	0.38 ± 0.06	p <0.01
Lp(a) (mg/dL)	23.6 ± 20.9	20.4 ± 18.6	NS
apo E isoform ε 2:ε 3: ε 4 (%)	8:80:12	9:82:9	NS
Leptin (ng/L)	48.3 ± 20.7	16.8 ± 8	p < 0.001
Ob Re (U/mL)	16.2 ± 7.4	26.1 ± 13.1	p < 0.01
Proteinuria (g/24 hrs)	0.5 ± 0.2	0.3 ± 0.2	NS
Creatinine clearance (ml/s)	1.0 ± 0.5	0.9 ± 4	NS
Cyclosporine level (ng/ml)	190 ± 30	205 ± 35	NS
Mean BP (torr)	135/85	130/85	NS

Major determinants of plasma tHcy are renal function, folate level and a lesser extent vitamin B6 concentration. Treatment for hyperhomocysteinemia with supraphysiological doses of folic acid and B vitamin could be effective because renal transplant patients have less impairment in renal function relative to dialysis patients. It is possible that tHcy-lowering treatment may reduce the risk for and severity of atherosclerotic vascular disease in renal transplant patients, who would likely achieve normal or near normal tHcy levels with high-dose folic acid and vitamin B-based treatment.

Hyperlipidemia after kidney transplantation is of mixed etiology (9,10). After chronic renal disease with subsequent renal insufficiency and long-term dialysis therapy, patients presenting for transplantation often show various degrees of lipid metabolic disorders.

The mechanism of hyperlipidemia of recent onset or exacerbating after renal transplantation differs significantly in at least two aspects. If the function of the kidney transplant is good, resumption of the metabolic function of the kidney has a beneficial effect. An adverse effect is exerted by long-term use of immunosuppressive therapy (cyclosporin A, prednisone), previous hyperlipidemia associated with genetic predisposition, reduced kidney transplant function, repeat rejection episodes controlled by high doses of corticoids, major proteinuria, secondary diabetes mellitus, age, gender and obesity.

Very marked, in this respect, is also the increase in body weight, often associated with the development of secondary diabetes (6,8,10). In patients on immunosuppressive therapy who are, moreover, relatively often unwilling to cooperate, a more marked reduction of weight is difficult to achieve and requires long-term determined dietetic intervention. The most remarkable our finding not given adequate attention to date is that obese female transplant recipients over 60 years of age could be the most significant risk group in terms of development of atherosclerotic lesions. Their levels of total cholesterol, LDL-cholesterol, but, also, triglycerides appreciably exceeded those levels in men over 60. No doubt a role was played in this by their body weight (BMI). The parameters monitored through the diet-related questionnaire revealed a significant increase in energy intake (145 ± 12 kJ/kg b.w., $p < 0.01$) and reduced intake of fiber (0.7 g/kg; $p < 0.05$).

In conclusion, obesity with BMI ≥ 30 kg/m^2 associated with significant hyperlipidemia and hyporhomocysteinemia should be treated effectively as a high-risk factors after renal transplantation.

The study was supported by grant No. 6586-3 awarded by the Internal Grant Agency of the Czech Republic.

References

1. Bostom AG, Gohh RY, Morrissey P. Hyperhomocysteinemia in chronic renal transplant recipients. Graft 2000; 3:197-204
2. Wiecek A, Kokot F, Chudek J, Adamczak M. The adipose tissue-a novel endocrine organ of interest to

the nephrologist. Nephrol Dial Transplant 2002; 17:191-193
3. Kokot F, Adamczak M, Wiecek A. Plasma leptin concentration in kidney transplant patients during the early post-transplant period. Nephrol Dial Transplantation 1998; 13:2276-2280
4. Shemin D, Bostom AG, Selhub J. Treatment of hyperhomocysteinemia in end-stage renal disease. Am J. Kidney Dis 2001; 38:S91-S94, Suppl 1
5. Kasiske BL, Vasques MA, Harmon WE et al. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol 2000; 15:S1-S86, Suppl 11
6. Teplan V, Poledne R, Scück O, Ritz E, Vitko Š. Hyperlipidemia and obesity after renal transplantation. Annals Transplant 2001; 6:21-23
7. Perna AF, Ingrasso D, De Santo NG. Metabolic consequences of folate induced reduction of hyperhomocysteinemia in uremia. J Am Soc Nephrol 1997; 8:1899-1905
8. Kasiske BL, Guijarro C, Massy ZA et al. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7: 158
9. Massy ZA, Kasiske BL: Post-transplant hyperlipidemia: Mechanism and management. J Am Soc Nephrol 1996; 7: 971
10. Praga M. Obesity – a neglected culprit in renal disease. Nephrol Dial Transplant 2002; 17:1157-1159