

Obesity and hyperhomocysteinaemia after kidney transplantation

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Abstract

Obesity and hyperhomocysteinaemia are found very frequently after kidney transplantation (Tx). They may independently represent risk factors for development of atherosclerosis and chronic allograft nephropathy. In a prospective metabolic study, we monitored, over a period of 24 months, a total of 118 obese transplant patients [body mass index (BMI) ≥ 30 kg/m²] with hyperhomocysteinaemia. We compared the findings of a new therapeutic regimen at 1 year (start of the study) and 2 years after renal transplantation. Based on a Subjective Global Assessment Scoring Sheet, we started at the end of the first year with an individualized hypoenergetic–hypolipidaemic diet (IHHD). Subsequently, after corticoid withdrawal, IHHD was supplemented regularly with orlistat at a dose of up to 3×120 mg/day, statins (pravastatin 10–40 mg), folic acid 5 mg/day and vitamin B6 50 mg/day, and followed-up for up to 2 years. All patients were on a regimen of cyclosporin A and mycophenolate mofetil. During the study period, there was a significant decrease in BMI ($P < 0.025$) and total homocysteine level ($P < 0.001$). Long-term therapy was associated with a significant decrease in serum leptin ($P < 0.001$) and lipid metabolism parameters ($P < 0.01$). The mean values of serum folate and vitamin B6 also increased significantly ($P < 0.01$); creatinine clearance, mean blood pressure, proteinuria, lipoprotein(a) and apolipoprotein E isoforms did not differ significantly. Based on our results, we assume that obesity and hyperhomocysteinaemia after renal transplantation can be treated effectively by modified immunosuppression (corticosteroid withdrawal), long-term diet (IHHD), folic acid and vitamin B6 supplementation, and drugs suppressing digestion or absorption to

reduce atherosclerotic and chronic allograft nephropathy processes.

Keywords: atherosclerosis; hyperhomocysteinaemia; hyperlipidaemia; kidney transplantation; leptin; obesity

Introduction

Obesity associated with secondary hyperlipoproteinaemia is one of the most common long-term metabolic complications in renal transplant recipients. After renal transplantation, total homocysteine (tHcy) levels decrease as renal function improves, but remain higher than the mean levels in the general population [1]. Obesity and hyperhomocysteinaemia 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 have been on long-term dialysis treatment [3–5]. Besides hyperlipidaemia, development of atherosclerotic and/or nephrosclerotic lesions is enhanced by a variety of other factors, particularly arterial hypertension (in $> 80\%$ 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 the 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

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patients with a body mass index (BMI) ≥ 30 kg/m² and hyperhomocysteinaemia in a long-term study.

Patients and method

The study protocol was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine.

In a prospective metabolic study, we evaluated, during a period of 24 months, a total of 118 (55M/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 patients with BMI ≥ 30 kg/m² on a new regimen at 1 year (start of the study) and 2 years after renal transplantation.

Based on a Subjective Global Assessment Scoring Sheet, an experienced dietetic nurse performed individualized dietetic interventions for DIETA computer software, preparing an individualized hypoenergetic–hypolipidaemic diet (IHHD) with an energy intake < 30 kcal/kg bw. Subsequently, after corticoid withdrawal, IHHD was supplemented with orlistat at a dose of up to 3×120 mg/day, statins (pravastatin 10–40 mg), folic acid 5 mg/day, and vitamin B6 50 mg/day, and followed-up 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 evaluated regularly at 3-monthly intervals.

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

The following biochemical investigations were determined using standard biochemical procedures:

- Total homocysteine (tHcy), i.e. the sum of all homocysteine derivatives present in plasma in free or protein-bound form after reduction, was estimated by the enzymatic FIA method on Abbott AxSYM under ERDNIM quality control. Fasting blood samples for tHcy were obtained within 20 min after blood taking, and centrifuged plasma was kept at below -20°C till analysis.
- Folate was determined by chemiluminescence EIA on Immulite, and vitamin B6 on HPLC Gold Beckman by Chromsystems.
- Leptin and Ob-Re were determined by BVELISA kit BioVendor.
- Cyclosporin A levels were determined by Cyclo-Trac SP Diasorin radioimmunoassay.
- Apolipoprotein E (apoE) isoforms were determined by PCR and restricted isotyping.
- For the dietary profile ASTRIS, DIETA software was used.
- BMI was calculated by body weight and height (kg/m²)
- Routine biochemical, haematological and immunochemical analyses were performed on Synchron CLX20, Advia 120 and Beckman Array analysers.

Statistical analysis was performed using two-way analysis of variance (ANOVA) complemented by multiple comparison and ANOVA with repeated measures and grouping factor.

Table 1. Basic metabolic parameters in obese patients in the first and second year after renal transplantation (\pm SD)

Variable	Year 1	Year 2	Significance
No. of patients	118	118	
Gender (M/F)	55/63	55/63	NS
BMI (kg/m ²)	35.5 \pm 3.2	27.4 \pm 2.8	$P < 0.025$
tHcy ($\mu\text{mol/l}$)	35.2 \pm 12.4	12.7 \pm 2.9	$P < 0.001$
Folate (nmol/l)	17.8 \pm 8.5	32.9 \pm 9.0	$P < 0.01$
Vitamin B6 ($\mu\text{g/l}$)	5.4 \pm 1.5	9.3 \pm 2.2	$P < 0.01$
Cholesterol (mmol/l)	7.2 \pm 2.4	6.1 \pm 2.0	$P < 0.01$
LDL-cholesterol (mmol/l)	4.1 \pm 1.2	3.0 \pm 0.7	$P < 0.01$
HDL-cholesterol (mmol/l)	1.1 \pm 0.2	1.0 \pm 0.2	NS
Triglycerides (mmol/l)	3.8 \pm 1.6	2.6 \pm 0.6	$P < 0.01$
HDL-c/TG	0.28 \pm 0.07	0.38 \pm 0.06	$P < 0.01$
Lp(a) (mg/dl)	23.6 \pm 20.9	20.4 \pm 18.6	NS
Apo E isoforms	8:80:12	9:82:9	NS
$\epsilon 2:\epsilon 3:\epsilon 4$ (%)			
Leptin (ng/l)	48.3 \pm 20.7	16.8 \pm 8	$P < 0.001$
Ob Re (U/ml)	16.2 \pm 7.4	26.1 \pm 13.1	$P < 0.01$
Proteinuria (g/24 h)	0.5 \pm 0.2	0.3 \pm 0.2	NS
Creatinine clearance (ml/s)	1.0 \pm 0.5	0.9 \pm 0.4	NS
Cyclosporin level (ng/ml)	190 \pm 30	205 \pm 35	NS
Mean BP (torr)	135/85	130/85	NS

Results (Table 1)

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

The mean values of serum folate and vitamin B6 increased significantly ($P < 0.01$); creatinine clearance, mean blood pressure, proteinuria, lipoprotein(a) and apoE isoforms did not differ significantly (Table 1).

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 factors, primarily hyperlipidaemia [5,6].

Hyperhomocysteinaemia 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 evidence that clinically stable transplant patients have a high prevalence of hyperhomocysteinaemia [7–9]. The major determinants of plasma tHcy are renal function, folate levels and, to a lesser extent, vitamin B6 concentrations. Treatment for hyperhomocysteinaemia with supra-physiological doses of folic acid and B vitamin could be effective because renal transplant patients, relative to dialysis patients, have less impairment in renal

function. It is possible that tHcy-lowering treatment may reduce the risk for and severity of atherosclerotic vascular disease in renal transplant patients, who would be able to achieve normal or near normal tHcy levels with high-dose folic acid and vitamin B-based treatment.

Hyperlipidaemia after kidney transplantation is of mixed aetiology [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 hyperlipidaemia 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 hyperlipidaemia 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]. Moreover, in patients on immunosuppressive therapy who often are relatively unwilling to cooperate, a more marked reduction of weight is difficult to achieve and requires long-term strict dietetic intervention. Our most remarkable finding which has not received 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, low-density lipoprotein cholesterol and triglycerides appreciably exceeded those observed 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 bw, $P < 0.01$) and reduced intake of fibre (0.7 g/kg; $P < 0.05$).

In conclusion, obesity with BMI ≥ 30 kg/m² associated with significant hyperlipidaemia and hyperhomocysteinaemia should be treated effectively as a high-risk factor after renal transplantation.

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