ORIGINAL ARTICLE

LIPID DISORDERS IN KIDNEY TRANSPLANTATION: A PERSISTENT CONUNDRUM. IS THERE ANY CONNECTION WITH IMMUNOSUPPRESSIVE THERAPY?

IONUŢ-DORIN TARŢA[1], CARMEN DENISE CĂLDĂRARU[1]*, MARIA TITICA DOGARU[2], EMILIAN CARAŞCA[3], CRISTINA TARŢA[4], MIHAI CIPRIAN STOICA[1], GRIGORE ALOIZIU DOGARU[1]

University of Medicine and Pharmacy, Faculty of Pharmacy, 38 Gheorghe Marinescu Street, Târgu Mureş, 540139, Romania
[1]Department of Nephrology,
[2]Department of Pharmacology
[3]IV[th] Internal Medicine Department
[4]County Clinic Hospital Târgu-Mureş, Romania

**corresponding author: caldararuc@yahoo.com*

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Abstract

Abnormalities in lipid metabolism are frequent in renal transplant patients, and usually result in high cardiovascular risk. The aim of this study was to investigate the prevalence of lipid abnormalities in kidney transplant recipients and the influence of immunosuppressive drug regimens on the lipid profile. This is a retrospective study on 50 patients with kidney transplantations. Clinical and laboratory data were studied at 3, 12, 24 and 36 months after transplantation, for changes in lipid profile and the correlation with the immunosuppressive regimen. The prevalence of hypercholesterolemia was 69.69% at 3 months following transplantation. Total cholesterol values at 3 months after transplantation were significantly higher than after 12 months ($p = 0.0264$), 24 months ($p = 0.0009$) and 36 months ($p = 0.0037$). Hypertriglyceridemia was present in 54.54% of the patients at 3 months following the transplantation. Serum triglycerides were higher at 3 months and at 12 months after transplantation than they were at 36 months. Cyclosporine-based immunosuppressive regimen did not confer a more atherogenic lipid profile when compared with tacrolimus in our kidney transplant recipients. Hypercholesterolemia and hypertriglyceridemia are most common in the first 3 months after transplantation. Our study showed no statistically significant differences in serum lipids in relation to immunosuppression.

Rezumat

Anomaliile profilului lipidic sunt frecvente la pacienţii cu transplant renal, fiind implicate în creşterea riscului cardiovascular. Scopul acestui studiu este de a investiga prevalenţa anomaliilor lipidice şi influenţa terapiei imunosupresive asupra profilului lipidic la 3, 12, 24 şi 36 luni de la efectuarea transplantului renal. Studiul a fost efectuat retrospectiv pe 50 de pacienţi cu transplant renal. Au fost folosite în studiu datele clinice, paraclinice şi cele legate de terapia imunosupresivă la 3, 12, 24 şi 36 de luni de la realizarea transplantului renal. Prevalenţa hipercolesterolemiei a fost de 69,69% la 3 luni după transplant. Valorile colesterolului au fost semnificativ mai mari la 3 luni în comparaţie cu cele înregistrate la 12 luni ($p = 0,0264$), 24 luni ($p = 0,0009$) şi 36 luni ($p = 0,0037$) după transplant. Hipertrigliceridemia a fost prezentă la 54,54% din pacienţi la 3 luni după transplant. Trigliceridele serice au fost semnificativ mai mari la 3 luni şi la 12 luni comparativ cu valorile de la 36 luni după transplant. La pacienții studiați, regimul imunosupresiv bazat pe ciclosporina nu a conferit un profil lipidic cu caracter pro-aterogen mai pronunțat comparativ cu regimul cu tacrolimus. Hipercolesterolemia şi hipertrigliceridemia sunt mai frecvente la 3 luni post-transplant. Studiul nostru nu a arătat diferenţe statistic semnificative ale profilului lipidic în relaţie cu terapia imunosupresivă.

Keywords: lipid profile, renal transplantation, tacrolimus, cyclosporine

Introduction

Cardiovascular disease is the main cause of death in renal transplant recipients. Among the great number of cardiovascular risk factors, dyslipidaemia is particularly frequent in renal transplantation, and is caused by various factors, but also by immuno-suppression [15, 19].

Dyslipidaemia may be one of the causes for kidney rejection, which represents a major factor of morbidity in these patients [6, 8, 26].

A good knowledge of risk factors, as well as the limitation of their occurrence is needed to prevent cardiovascular damage.

In this context, the present study aimed to analyse the prevalence of lipid abnormalities in kidney transplant recipients, and to investigate the relationship between these abnormalities and immunosuppression.

Materials and Methods

We retrospectively evaluated the records of 50 patients with stable renal function that had underwent kidney transplantation (KT) between 1st of July 1997 and 1st of July 2012 and who were under continuous and rigurous monitoring in the Nephrology Unit of the County Clinic Hospital in Targu-Mures. The study has been accepted by the ethics committee of the University of Medicine and Pharmacy, Targu-Mures, Romania.

Demographical data (sex, weight, height, age at transplantation, smoker/non-smoker), transplant related data (donor type, immunosuppression type, cause of end-stage renal disease (ESRD), chronic graft failure and clinical and laboratory data (blood pressure, serum creatinine, lipid profile) were documented at 3, 12, 24 and 36 months after renal transplantation.

Hypercholesterolemia was defined as total cholesterol serum concentration higher than 200 mg/dL and hypertriglyceridemia as triglycerides higher than 200 mg/dL. LDL cholesterol was considered above normal at levels exceeding 160 mg/dL and HDL cholesterol was considered below normal at levels under 40 mg/dL.

Glomerular filtration rate was estimated using the four-variable Modified Diet in Renal Disease formula.

We included in our study only the patients with stable immunosuppression therapy during the 36 months of observation. Patients were treated with one of the following immunosuppressive regimen: cyclosporine A, mycophenolate mofetil and prednisone or tacrolimus, mycophenolate mofetil and prednisone.

Body mass index (BMI) was calculated using the Quatelet index (kg/m^2)

Statistical analysis was performed using T-student test with Graph Pad Prism 5 and p was considered statistically significant if < 0.05.

Results and Discussion

50 kidney transplanted patients were included in our study (Table I) of these, 58% were males. The average age of the patients in our study was 41.31 ± 11.38 years. Eleven patients were active smokers but we had documented 5 patients with smoking cessation after renal transplant.

Kidney transplantation was performed from living donors in 60% of our patients and from brain dead donors in 40% of cases.

The most common cause for end-stage renal disease was glomerular impairment (62%, Table I).

Body mass index was higher than 25 kg/m^2 in 48% of patients.

The prevalence of hypercholesterolemia was 69.69% at 3 months following transplantation, 45.61% at 12 months, 39.39% at 24 months and 26.66% at 36 months after transplantation.

Table I

Demographic, clinical and laboratory features of the study group

Demographic, clinical and laboratory features	Number of patients
SEX	
Male	29 (58%)
Female	21 (42%)
AGE AT TRANSPLANTATION (years)	41.31 ± 11.38
BODY MASS INDEX (kg/m²)	24.51 ± 4.888
ESTIMATED GLOMERULAR FILTRATION RATE	
MDRD (mL/min/1.73 m²)	55.92 ± 24.89
COCKROFT-GAULT (mL/min)	66.64 ± 25.94
SMOKING STATUS	
Smoker	11 (22%)
Non-smoker	39 (78%)
DONOR TYPE	
Living unrelated	29 (58%)
Brain dead	20 (40%)
Living related	1 (2%)
CAUSE OF THE ESRD	
Glomerular nephropathies	31 (62%)
Tubular-interstitial nephropathies	10 (20%)
Cystic diseases of the kidney	6 (12%)
Lupus nephropathy	2 (4%)
Diabetic nephropathy	1 (2%)

Values of total cholesterol in the first 3 months after transplantation were significantly higher than at 12 months, 24 months and 36 months (Table II).

Hypertriglyceridemia was present in 54.54% of the patients at 3 months, 37.50% at 12 months, 30.30%

at 24 months and in 13.33% at 36 months following kidney transplantation.

Both hypertriglyceridemia and hypercholesterolemia were present in 45.45% of patients at 3 months, in 28.12% at 12 months, in 15.15% after 24 months and in 6.66% after 36 months.

After one year, the proportion of patients with normal plasma lipids was 45.45%, at two years was 45.45% and three years was 66.66%.

Table II

The lipid parameters profile in the kidney transplant patients

Lipid profile (mg/dL)	At 3 months	At 12 months	At 24 months	At 36 months
Total cholesterol	234.4 ± 10.92	200.5 ± 10.07 *p = 0.0264	186.9 ± 8.072 **p = 0.0009	187.9 ± 9.190 ***p = 0.0037
Triglycerides	268.7 ± 37.63	210.8 ± 19.55 *p = 0.1808	185.5 ± 21.59 **p = 0.0597	146.6 ± 12.31 ***p = 0.0043 ****p = 0.0082

*values at 3 months *versus* values at 12 months; **values at 3 months *versus* values at 24 months; ***values at 3 months *versus* values at 36 months; ****values at 12 months *versus* values at 36 months

In the group of renal graft recipients that were under immunosuppression therapy with tacrolimus, values of total cholesterol were significantly higher at 3 months follow up, than at 24 months (p = 0.0066) and 36 months (p = 0.0056, Table III). Triglycerides were significantly higher at 3 months follow up, than at 12 months (p = 0.0390), 24 months (p = 0.0272) and 36 months (p = 0.0064). Triglycerides were significantly higher at 12 months than at 36 months after (p = 0.0178) kidney transplantation.

Table III

Lipid profile changes and the relationship with immunosuppression therapy

Lipid profile	Immunosuppression therapy	3 months	12 months	24 months	36 months
Total cholesterol (mg/dL)	tacrolimus	231.8 ± 12.65	202.90 ± 12.92 NS	185.60 ± 9.67 **p = 0.0066	183.40 ± 10.13 ***p = 0.0056
	cyclosporine	255.5 ± 22.86	185.70 ± 7.22 *p = 0.0099	186.4 ± 19.38 **p = 0.0405	206.60 ± 19.60 NS
Triglycerides (mg/dL)	tacrolimus	283.8 ± 47.28	202.00 ± 24.25 *p = 0.0390	187.7 ± 28.74 **p = 0.0272	134.50 ± 9.75 ***p = 0.0064 ****p = 0.0178
	cyclosporine	220.8 ± 19.30	214.6 ± 33.87 NS	165.0 ± 23.18 NS	164.6 ± 38.57 NS

*values at 3 months *versus* values at 12 months; **values at 3 months *versus* values at 24 months; ***values at 3 months *versus* values at 36 months; ****values at 12 months *versus* values at 36 months; NS = statistically non-significant

In patients treated with cyclosporine as immunosuppressive agent, total cholesterol values were significantly higher at 3 months than at 12 months (p = 0.0099) and 24 months (p = 0.0405) after transplantation.

The comparative study of the lipid profile in patients with cyclosporine-based immunosuppression *versus* tacrolimus-based immunosuppression therapy, showed no significant differences at 3, 12, 24 and 36 months after transplantation.

Dyslipidaemia is one of the main risk factors for cardiovascular disease in the general population.

In kidney transplant recipients, the direct relationship between lipid unbalances and death is not established, but there is evidence that cardiovascular disease is the main cause of death.

Thus, we consider that dyslipidaemia control becomes an important target in kidney transplantation patient.

Recent studies demonstrate that treatment goals for lipid control in transplanted patients are usually not achieved, especially in the first year post-transplantation [18].

Risk factors for dyslipidaemia in kidney graft recipients are characterized differently by various authors: immunosuppression type and dosage [2, 20, 24], dyslipidaemia before transplantation, associated with diet, diabetes, obesity etc. [3, 21, 25].

Graft dysfunction, age, sex, donor type, genetic and environmental factors may increase the risk for altered lipid profile in renal transplantation [1, 16].

The objective of the study was to determine the spectrum of lipid changes 1, 2 and 3 years from renal transplantation and the role of immuno-suppression in generating dyslipidaemia.

The main finding of our study is that dyslipidaemia is common after renal transplantation even after a long follow up period.

Previous research studies show that the most frequent lipid changes are recorded in the first month after transplantation, with a possible relation-ship with high corticosteroids doses [17].

Six months after transplantation plasma lipids begin to decline, and at 1 year the percentage of patients with dyslipidaemia is significantly lower [9, 29].

Our study did not assess lipid changes and the effect of immunosuppression in early post-transplant period.

Hypercholesterolemia was the most common lipid disturbance in all periods studied here, with the highest prevalence in the first 3 months.

This observation is in accordance with other results who found hypercholesterolemia as the most frequent form of dyslipidaemia [10].

After 3 months, lipid parameters control improved across follow-up periods.

Serum cholesterol values were significantly higher at 3 months *versus* 12, 24 and 36 months, but no significant differences were found at 12 *versus* 24 and 36, or at 24 *versus* 36 months after transplantation.

The prevalence of hypertriglyceridemia was smaller than of hypercholesterolemia at all checkpoints. The peak of prevalence of hypertriglyceridemia was registered at three months after transplantation, in contrast to the study of Baliga KV *et al.*, who found a greater incidence at one year after transplantation [4].

A significant reduction in triglyceride level was documented at 12 months, 24 months and 36 months *versus* the 3 months follow-up and also at 36 months *versus* 12 months after transplantation.

Our results correspond to those in similar research studies in terms of higher prevalence of dyslipidaemia, although this study was conducted on a relatively young population (age 41.31 ± 11.38 years), with a small percentage of diabetics, and with a 48% rate of patients with body mass index (BMI) over 24 kg/m^2 [27].

The long downward trend in plasma lipid values was also mentioned by other authors.

Some studies show low values for plasma lipids at 3 months or at 6 months after transplantation and most authors agree that the mechanism rely on the reduction of immunosuppression [28].

In our study, patients receiving tacrolimus had lower total cholesterol and triglycerides serum levels for months 3 *versus* 24 and 3 *versus* 36, respectively and lower triglycerides for months 3 *versus* 12. No differences were found between months 12 *versus* 24, months 12 *versus* 36 or months 24 *versus* 36. The results can be interpreted as a stabilization of the lipid profile at 12 months after transplantation.

The same kinetics of lipid changes were demonstrated after administration of tacrolimus in liver transplant recipients [22].

Regarding the spectrum of dyslipidaemia related to immunosuppression, there is evidence that cyclosporine determines a more atherogenic lipid profile compared to tacrolimus [7, 11, 14, 29].

Some authors showed that the administration of cyclosporine results in significant increases of total cholesterol, triglycerides and of cholesterol contents in very-low-density lipoprotein (VLDL) which enhance the atherosclerotic risk [5, 13, 23, 24].

In a retrospective study on 1391 kidney transplant patients, Hosseini *et al.* showed that even if there is evidence that cyclosporine predisposes patients to lipid disturbances, there is no correlation between serum lipids and cyclosporine level [12].

We did not find any statistically significant differences for serum cholesterol and triglycerides in patients treated with tacrolimus compared with cyclosporine for any of the checkpoints of the study.

The small number of patients with stable triple immunosuppression regimen may explain our findings.

Conclusions

Lipid disorders have a long-term persistence after kidney transplantation, although the most atherogenic lipid profile is characteristic for the first 6 months after transplantation.

Tacrolimus based immunosuppressive regimen did not confer a more atherogenic lipid profile when compared with Cyclosporine in the studied kidney transplant recipients.

Our study has some limitations, like the retrospective analysis of the data, the small sample size, the lack of data to configure the full lipid profile, lack of data about treatment with statins and fibrates, which tend to modify the real prevalence of the disease.

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