Effects of Immunosuppressive Drugs on Serum Fatty Acids of Phospholipids Fraction in Renal Transplant Recipients

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ABSTRACT

Background. Immunosuppressive medications often cause posttransplant hyperlipidemia. The effects of cyclosporine (CsA) and tacrolimus (Tac) on lipid profile is well-known; however, there are very few studies related to the effect of these immunosuppressants on fatty acids (FA) of phosholipids fraction (PL) in renal transplant recipients (RTR). We sought to analyze the FA profile in PL fraction of RTR treated with Tac or CsA.

Methods. The study included 65 renal transplant patients on CsA (n = 24, group I) or Tac (n = 41, group II), and 14 healthy controls. Individual serum FA concentrations were measured by gas chromatography. Chemstation software was used to analyze the data.

Results. No differences between studied groups and controls were noted for monounsaturated FA, polyunsaturated n-3 FA (PUFA n-3), PUFA n-6, or the ratio of PUFA n-6 to PUFA n-3. The following mean values of FA were significantly higher in the CsA-RTR and Tac-RTR as compared with controls: total FA ($P < .01$ in both cases), saturated FA (SFA; $P < .02$ in both cases), C12 ($P < .003$ in both cases), C18 ($P < .003$ in both cases), and C18:2 ($P < .01$ for CsA RTR; $P < .02$ for Tac RTR). No differences between the measurements in patients on CsA and in patients on Tac were noticed. Significant correlation between SFA and eGFR was observed only in the CsA RTR group ($P < .05$). A negative relationship between PUFA n-6 and the estimated glomerular filtration rate was seen, but the correlation was not significant.

Conclusions. Immunosuppressive drugs may affect FA metabolism, but the FA profile does not depend on the type of immunosuppressive drug administered.

PROGRESS in immunosuppressive management of patients after organ transplantation has significantly increased their overall survival. Tacrolimus (Tac) and cyclosporine (CsA) are among the most commonly used immunosuppressive drugs. These medications may, however, cause different side effects, among which lipid metabolic disorders are most frequently observed [1–4]. It has been shown that in patients receiving Tac the triglyceride (TG) levels are lower as compared with patients prescribed with CsA [3,5]. In contrast, treatment of the organ transplant patients with CsA causes significant increase of total cholesterol and low-density lipoprotein cholesterol levels [2,3,6]. Disturbances in lipid metabolism may also contribute to glomerular and interstitial injury that in turn can promote renal disease progression. Posttransplant hyperlipidemia has been linked to cardiovascular disease, leading to a high morbidity and mortality rate [7,8]. Hyperlipidemia not only leads to development of atherosclerosis of coronary arteries, but also of renal artery, which can affect graft function [9,10].

Accumulation of lipids in nonadipose tissues may lead to cellular dysfunction and cell death, the phenomenon called lipotoxicity [11]. It has been confirmed that saturated fatty

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acids (SFA), mainly palmitic acid, can be responsible for lipotoxicity of most cells, including renal cells (podocytes) [12]. Unlike SFA, it has been shown that monounsaturated fatty acids (MUFA) have protective effect on renal lipotoxicity, but the mechanism has not been fully understood yet. It is believed that the presence of oleic acid in podocytes can facilitate incorporation of palmitic acid into TG. Because of that lower level of intracellular concentration of palmitic acid is seen. On the other hand, increased rate of the β-oxidation of palmitic acid prevent accumulation of SFA in the cell [13,14]. Another class of fatty acids (FAs)—the n-3 FA—may protect kidney function by modulating the inflammatory response through downregulation of proinflammatory cytokines production, cyclooxygenase-2 activity, and an expression of endothelial leukocyte adhesion molecules [15–17]. In contrast, progressive deterioration of kidney function after dietary supplementation with n-6 FA has been shown [17]. Eicosanoids, which are the products of arachidonic acids (AAs) metabolism, have a wide range of biological action in inflammatory processes and immunity [18,19]. According to Brown et al. [20], the production of vasoactive eicosanoids may contribute to glomerular hyperfunction and consequently to glomerular damage. Dyslipidemia may also affect kidney function indirectly through vascular injury and oxidative stress. Cristol at al. [21] suggested that oxidation of polyunsaturated FAs (PUFA) may play a significant role in the vascular lesions.

There are few studies related to the effect of different immunosuppressants on FA patterns in renal transplant recipients. Such findings would be significant, because FA play an important role in renal homeostasis and renal function. Furthermore, it may be speculated that changes in dietary habits towards higher intake of unsaturated FA could prevent or delay the progression of dyslipidemia-related renal disease.

MATERIALS AND METHODS

The study included 65 renal transplant recipients on immunosuppressive therapy: 24 patients treated with CsA (9 females, 15 males; mean age, 54 ± 12 years [range, 25–65]) and 41 patients treated with Tac (15 females, 26 males; mean age, 51 ± 13 years [range, 27–70]). All patients underwent renal transplantation, and were treated at the Department of Nephrology, Jagiellonian University Medical College, Cracow, Poland. The average time since transplantation was 42 months (range, 15–120). Therapeutic regimens were established individually for each patient, taking into account immunologic risk, comorbidity, ischemia time, and clinical experience. Safety and efficacy assessments were performed at scheduled study visits and therapy adjustments were introduced if necessary. Only patients who maintained their originally assigned calcineurin inhibitor were included in the study. The majority of patients received triple drug immunosuppressive therapy with a calcineurin inhibitor (CsA or Tac), mycophenolic acid, and glucocorticoids. Renal transplant recipients were treated with prednisone (in CsA group: 20 patients; in Tac group: 29 patients), methylprednisolone (in CsA group: 3 patients; in Tac group: 6 patients), and prednisolone (2 patients in Tac group). Five patients did not receive steroid therapy during the survey (1 in CsA group and 4 in Tac group). Each patient was ≥1 year posttransplant. Regardless of the calcineurin inhibitor used, all patients received low doses of steroids (average dose of glucocorticoids based on prednisone in CsA group, 6.66 mg; in Tac group, 5.19 mg). Furthermore, in patients of both groups glucocorticoids were used at comparable doses; thus, the effect of steroids was not taken into account in the statistical analysis.

Patients with diabetes mellitus before renal transplantation, and the patients with a glomerular filtration rate (GFR) of <30 mL/min were excluded. The control group consisted of 14 healthy volunteers (3 males and 11 females; mean age, 48 ± 12 years [range, 26–69]). The study protocol was approved by the Bioethics Committee of the Jagiellonian University and written informed consent was obtained from all patients. Baseline demographics and clinical characteristics of patients are presented in Table 1.

Fasting blood samples for serum FA of PL determination were obtained from each patient. The blood serum was separated and

Table 1. Baseline Demographics and Clinical Characteristics of Patients

Characteristic	Cyclosporine Group (n = 24)	Tacrolimus Group (n = 41)
Age range (y)	25–65	27–70
Mean age (y)	54 ± 12	51 ± 13
Male	15	26
Female	9	15
eGFR, mean (range), mL/min	65.3 (35.3–119.9)	75.4 (31.8–126.5)
BMI, mean (range), kg/m^2	26.7 (17.8–33.2)	26.8 (19.7–38.1)
Acute graft rejection	2	3
Diabetes type II (after transplantation)	8	8
Hypertension	8	15
Lipid profile, mean (range), mmol/L		
TC	4.97 (3.4–7.0) | 41.7%*	4.80 (3.0–6.9) | 43.9%*
TG	1.93 (0.53–3.3) | 33.3%*	1.89 (0.6–3.6) | 39.0%*
LDL-C	2.95 (1.2–5.0) | 20.8%*	2.66 (1.5–4.1) | 21.9%*
HDL-C	1.45 (0.7–2.1) | 12.5%*	1.32 (0.9–2.5) | 12.2%*
Drug levels at the time of measurement, mean (range), ng/mL	452.00 (60.7–1167.5)	6.05 (3.9–11.5)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

*Percent of results above (TC ≥5 mmol/L; TG ≥1.7 mmol/L; LDL ≥3 mmol/L) or below (HDL <1 mmol/L for men, <1.2 mmol/L for women) recommended values.