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Fatty acids profile in patients after heart or renal transplantation who developed metabolic complications

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ABSTRACT

Purpose: Diabetes mellitus and hyperlipidemia are frequently observed after organ transplantation. It is known that in these disorders the fatty acid metabolism is impaired. The aim of this study was to compare the fatty acid profile in the heart and renal transplant recipients who developed metabolic disorders since there is no such research available.

Materials and methods: The study included 55 patients treated with tacrolimus (Tac) after heart (n = 14; mean age: 60.4 ± 9.1) or renal (n = 41; mean age: 51 ± 13) transplantation. Diabetes and hyperlipidemia was present in 35.7% and 28.5% of heart transplant recipients, and 19.5% and 41% of renal transplant recipients. Concentrations of fatty acid in phospholipids fraction in serum were measured by gas chromatography.

Results: The concentration of C20:5 fatty acid was lower in heart transplant recipients, as compared to renal transplant recipients ($p = 0.001$), whereas the level of C20 + C18:3 fatty acid and the ratio of n-6/n-3 was higher ($p = 0.01$; $p = 0.03$, respectively). The observed differences were not related to metabolic disorders. Negative correlation between C16:1 and eGFR was seen in heart transplant recipients ($p = 001$). In renal transplant recipients with metabolic disorders, the concentration of C20:5 was correlated positively whereas the n-6/n-3 ratio was correlated negatively with eGFR ($p < 0.001$, $p = 0.01$, respectively). Hyperlipidemic renal transplant recipients had higher concentration of C20:2 ($p = 0.02$), C20:4 ($p = 0.05$), n-6 (0.04) and total fatty acid ($p = 0.01$) than patients without metabolic disorders.

Conclusion: The fatty acid profile differs depending on the transplanted organ, but the differences are not related to the metabolic disorders. The role of fatty acid in kidney function varies between heart transplant recipients and renal transplant recipients and depends on type of fatty acid.

1. Introduction

Fatty acids (FA) are critical to proper functioning of organism. They are not only a source of energy, but also an important structural component of cell membranes, affecting their fluidity, flexibility, and permeability. Recently, it has become more evident that the role of FA is even more significant, as membrane lipids influence the trafficking of cellular constituents, as well as the activity of membrane proteins and cell signal transduction. Studies showed that enhanced FA oxidation (FAO) was associated with enhanced cardiac function and survival, while impaired FAO was related to lipid accumulation and cardiomyopathy [1,2]. Lipid accumulation in nonadipose tissue is known as a lipotoxicity effect, described not only in pathogenesis of cardiomyopathy, but also in nephropathy [3,4]. It is believed that saturated fatty acids (SFA), mainly palmitic acid, are responsible for lipotoxicity, whereas monounsaturated fatty acids (MUFA), mainly oleic acid, have protective effect against apoptosis of cardiac and renal cells induced by SFA [1,5]. Interestingly, inhibition of FAO causes oleic acid to induce apoptotic cardiomyocytes death, while enhancing FAO attenuates cardiotoxic effect of palmitic acid [2]. It is the type of fatty acids and their metabolism that are crucial to normal cell and organs functioning.

So far, no biochemical studies have been carried out assessing the metabolism of FAs in organ transplant recipients. This subject deserves attention, as altered FA profile is augmented in patients suffering from

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obesity, insulin resistance (IR), hypertension and hyperlipidemia [6,7], the disorders often occurring after transplantation. What is more, a positive effect of n-3 FA rich diet or n-3 FA supplementation in non-transplant and transplant recipients with lipid or carbohydrate disorders is well documented [8,9]. Taking into account the FAs profile in relation to metabolic disorders and the kind of organ transplanted is very important from the post-transplantation dietary care point of view. Due to the significance of the FAs' role in human health, monitoring and adjusting their level by modifying diet and/or supplementation should result in improved well-being of patients after a solid organ transplant operation.

To the best of our knowledge, there is no research concerning the FAs profile in heart or kidney transplant recipients who developed metabolic disorders after transplantation. The aim of the study was to compare the FA profile in the heart and renal transplant recipients depending on the metabolic disorders.

2. Material and methods

The study was conducted in 55 patients who underwent organ transplantation: 14 patients were heart transplant recipients (HTR; group I) and 41 were renal transplant recipients (RTR; group II). None of the patients had diagnosed metabolic disorders before transplantation. The study was performed at the Department of Cardiovascular Surgery and Transplantation and at Department of Nephrology of the Jagiellonian University Medical College. Heart transplantations were performed between 1993 and 2011, and renal transplantations between 2009 and 2013. All the patients were on tacrolimus (Tac). In group I: 8 patients had no metabolic disorders and 6 patients developed metabolic disorders after transplantation (2 - diabetic, 1 - hyperlipidemic, 3 - diabetic and hyperlipidemic). In group II: 18 patients had no metabolic disorders, whereas 23 patients developed metabolic disorders after transplantation (5 - diabetic, 15 - hyperlipidemic, 3 - diabetic and hyperlipidemic). Baseline demographics and clinical characteristics of patients are presented in Table 1.

Fasting blood samples for serum FA of phospholipids (PL) fraction determination were obtained from each patient. The blood serum was separated and kept frozen at −70 °C until measurements. We performed the following analytical steps: lipids extraction from serum with the use of Folsch method [21], separation of lipid fractions, and methylation of FA of PL fraction. Separation of the FA methyl esters was performed using gas chromatography equipped with flame ionization detector (Agilent Technologies 6890 Network GC Systems, Wilmington, De., USA).

After the gas chromatography separation, the following FAs were quantified using ChemStation software: myristic acid (C14), palmitic acid (C16), stearic acid (C18), palmitoleic acid (C16:1cis [n-7]), oleic acid (C18:1cis [n-9]), linoleic acid (LA; C18-2cis [n-6]), α-linolenic acid (ALA; C18:3cis [n-3]), 11,14-eicosadienoic acid (20:2cis [n-6]), arachidonic acid (AA; C20:4cis [n-6]), eicosapentaenoic acid (EPA; C20:5cis [n-3]), docosahexaenoic acid (DHA; C22:6cis [n-3]), lignoceric acid (C24).

Table 1
Baseline demographics and clinical characteristics of heart transplant recipients and renal transplant recipients.

Renal Transplant Recipients (N = 41)	Heart Transplant Recipients (N = 14)	Characteristic
27 - 70	43 - 77	Age range (y)
51 ± 13*	60.4 ± 9.1	Mean age (y)
26/15	13/1	Male/ Female
75.41 (31.78 – 126.47)*	61.4 (38.5 – 90)	eGFR (mean; range) mL/min
5 (12%)	2 (14%)	Onset of Diabetes (after transplantation)
15 (37%)	1 (7%)	Onset of Lipid disorders (after transplantation)
3 (7%)	3 (21%)	Onset of Diabetes and Lipid disorders (after transplantation)
6.05 (3.9 - 11.5)**	9.23 (5.4 - 14)	Tacrolimus level (mean; range) ng/mL

* $p < 0.02$.
** $p < 0.0001$.

2.1. Statistical analysis

We calculated the total FA content in PL, the sum of: SFA, MUFA, PUFA n-6, and PUFA n-3 concentrations (μmol/L), as well as, the ratio of PUFA n-6 to PUFA n-3. Descriptive statistics including mean values and standard deviation (SD) were performed separately for all HTR and all RTR as well as for HTR and RTR with and without metabolic disorders. Additionally, in the RTR group separate analysis was performed in patients who developed diabetes and in patients with hyperlipidemia. Differences between the groups concerning FA and estimated GFR (eGFR; calculated according to Cockcroft-Gault formula) were evaluated using Student's t-Test. The Mann-Whitney *U* test was performed to compare the differences in age and Tac level between the study groups. Pearson's correlation coefficients were used to assess the relationship between each of the FA concentrations and the eGFR. All analyses were performed using Statistica 12 (StatSoft Polska Sp. z o. o.). Statistical significance was set at $p < 0.05$.

2.2. Ethical issues

The study protocols were approved by the Bioethics Committee of the Jagiellonian University (Approval numbers: KBET/323/B/2012, dated: 29.11.2012 and 122.6120.9.2015, dated: 29.01.2015). Written informed consent was obtained from all the patients.

3. Results

A large inter-individual variation of each individual fatty acid concentration was observed in all the patients. The mean concentration of C20:5 FA was significantly lower in the HTR, as compared to the RTR (group II, $p = 0.001$), whereas the mean level of C20 + C18:3 (n-6) FA and mean ratio of n-6/n-3 ratio was higher ($p = 0.01$; $p = 0.03$, respectively) (Fig. 1). The mean values of SFAs (C14, C16 and C24) were also higher in the HTR as compared to the RTR, but the differences were not statistically significant (Fig. 1). For other FAs (C18:2, C20:2, C20:4, C18:3, and C22:6) no difference was observed (data not shown).

Analysis of individual FA in the HTR and RTR in respect to the presence or absence of metabolic disorder showed similar results: significantly higher mean value of C20 + C18:3 (n-6) FA and significantly lower mean value of C20:5 in the HTR. Also, lower value of the n-6/n-3 ratio was observed in the RTR, regardless of the presence or absence of the metabolic disorders, as compared to HTR. However, this difference was statistically significant only in case of patients with metabolic disorders (Fig. 2).

In the RTR with the metabolic disorders FAs profile was analyzed separately for patients with hyperlipidemia and patients with diabetes. In the hyperlipidemic RTR, the concentration of C24 ($p = 0.06$), C16 ($p = 0.04$) and the sum of SFA ($p = 0.06$) was higher as compared to the RTR without the metabolic disorders, but the statistically significant difference was noted only for C16. Among the PUFAs n-6, the higher levels of C20:2 ($p = 0.02$), C20:4 ($p = 0.05$), as well as the total concentration of all n-6 FA measured were observed in the hyperlipidemic RTR (Fig. 3). Additionally, in the hyperlipidemic RTR, the total FA concentration was also higher ($p = 0.01$) than in the RTR without the metabolic disorders. The FAs profile was similar in the RTR with diabetes mellitus and in the RTR without diabetes or hyperlipidemia. The levels of C16, C24 and n-6 in patients with diabetes were lower than in patients with hyperlipidemia ($p = 0.01$; $p = 0.001$; $p = 0.02$).