DOI: 10.4149/BLL_2022_092

Bratisl Med J 2022; 123 (8)
573–578

CLINICAL STUDY

Hyperleptinemia as a risk factor for post-transplant diabetes mellitus development after kidney transplantation

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ABSTRACT

INTRODUCTION: Adipose tissue is involved in the synthesis of hormones that have an impact on food intake regulation, control of insulin sensitivity or regulation of inflammatory processes. The aim of this study was to determine the importance of adipocytokines and interleukins levels for the development of post-transplant diabetes mellitus (PTDM) after kidney transplantation (KT).

MATERIAL AND METHODS: In the prospective analysis, the studied sample (n = 104) was divided into the control group, prediabetes group and PTDM group. Prior to transplantation, and subsequently, at 3, 6 and 12 months after KT, we recorded the basic characteristics of the donor and recipient, including parameters reflecting graft function, metabolic and anthropometric parameters. At the same time, we monitored the levels of adiponectin, leptin and interleukins during the monitored period.

RESULTS: Using multivariate logistic regression, we identified hyperleptinemia 12 months after KT as an independent risk factor for PTDM development 1 year after KT [OR 1.0320; 95% CI 0.9785–1.0884 (p=0.0038)]. At the same time, we confirmed that age at the time of KT is also an independent risk factor for PTDM [OR 1.0903; 95% CI 1.0149–1.1714 (p=0.0180)].

CONCLUSION: We confirmed that elevated leptin level 12 months after KT is associated with the development of PTDM *(Tab. 3, Fig. 4, Ref. 22)*. Text in PDF *www.elis.sk*

KEY WORDS: adipocytokines, interleukins, post-transplant diabetes mellitus, kidney transplantation, leptin.

Abbreviations: ADA – American Diabetes Association, BMI – body mass index, CKD – chronic kidney disease, CKD-EPI – chronic kidney disease epidemiology collaboration index, DM – diabetes mellitus, ELISA – enzyme-linked immunosorbent assay, FCXM – flow cytometry crossmatch, HDL – high-density lipoprotein, HLA – human leukocyte antigen, IL – interleukin, KT – kidney transplantation, LDL – low-density lipoprotein, oGTT – oral glucose tolerance test, PTDM – post-transplant diabetes mellitus, SOCS-3 – suppressor of cytokine signaling 3, TNF – tumor necrosis factor

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Acknowledgements: This study was supported by grant VEGA-1/0238/21: Continual glucose monitoring and glycemic variability in early post-transplantation period as a predictor of complications after kidney transplantation.

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Introduction

Post-transplant diabetes mellitus (PTDM) is now a well-known and common complication after kidney transplantation (KT). It is associated with increased morbidity and mortality, especially associated with higher incidences of cardiovascular and infectious complications, which are the leading causes of death in this group of patients. According to available studies that have used current criteria to diagnose PTDM, more than a third of recipients after KT have developed pre-diabetic conditions or PTDM (1). In addition to the risk factors already described (immunosuppressive treatment, infections, hypomagnesaemia, obesity, age, race, genetic factors, etc.), attention has been focused on hormonal influences for the last years.

Visceral adipose tissue, as the endocrine and paracrine organ, is involved in the synthesis of hormones that have an impact on several processes, including regulation of food intake, control of insulin sensitivity, or as mediators of inflammatory processes. Some of the adipocytokines are pro-inflammatory and atherogenic, such as leptin, tumor necrosis factor a, resistin, interleukin (IL)-6, while others have anti-inflammatory effects (adiponectin). In patients with metabolic syndrome, adipocytokine secretion by excessive visceral fat is responsible for the ongoing chronic inflammatory process. These patients show decreased serum adiponec-

tin levels and, conversely, proinflammatory cytokine levels were elevated. This imbalance leads to endothelial dysfunction, which contributes to the loss of their vasodilatory, antiatherogenic and antithrombotic properties (2).

Leptin plays an important role in the regulation of body weight, insulin resistance, glucose and fat metabolism (3). Previous data indicate that it is an independent risk factor for cardiovascular disease (5). In obese patients, high serum levels have been detected, suggesting the resistance of target tissues to its effect on its excessive production (6). In patients with diabetes mellitus (DM) type II, a correlation between high leptin levels, body mass index (BMI) and insulin resistance was confirmed (20). It is insulin resistance, as well as hyperinsulinemia, in most cases accompanied with obesity, that contributes to hyperleptinemia and increased expression of obesitogenic genes. Therefore, the association of leptin and insulin may reflect the size of fat stores. Chronically elevated leptin levels lead to a decrease in the sensitivity of pancreatic b cell receptors, which results in higher insulin production. Hyperinsulinemia subsequently exacerbates obesity and further increases the leptin levels, which closes this diabetogenic positive feedback (5, 20).

Adiponectin is characterized by its anti-atherogenic, anti-inflammatory and anti-diabetic properties. Previous clinical studies implemented low levels of adiponectin in the pathogenesis of DM type II, cardiovascular disease, or arterial hypertension. The accumulation of adipose tissue negatively regulates the level of adiponectin in plasma which is therefore low in obese patients (21). By activating its receptors, leptin exerts its anti-inflammatory effect. In terms of cardiovascular disease, it can be considered a prognostic factor. In previous work, the association between its high levels and reduced cardiovascular risk in diabetics and patients with end-stage renal disease has been confirmed (22). The role of interleukins in the pathogenesis of PTDM in patients after KT is unclear, but elevated levels of pro-inflammatory types (IL-6), the regulation of which is directly affected by leptin, can be expected.

The aim of our study was to determine the effect of serum levels of adipocytokines (leptin, adiponectin) and interleukins on the development of pre-diabetic conditions and PTDM in a 12-month follow-up of patients who underwent primary KT.

Material and methods

In our prospective study, patients active on the primary KT waiting list at the Martin Transplant Center, who underwent KT during the study period, were followed. Patients whose diagnosis of DM type I or II had already been confirmed were not included in the follow-up. In KT recipients, the baseline serum levels of leptin, adiponectin, IL-6 and IL-10 were measured at the time of flow cytometry crossmatch (FCXM), approximately 4 to 5 hours before the surgery, and followed at 3, 6 and 12 months after KT. Adipocytokine and interleukin levels were assessed by ELISA (Biomedica kits). All participants were set up for the same immunosuppressive protocol. Antithymocyte immunoglobulin was used in the induction at a cumulative dose of 3.5 mg/kg body weight as well as tacrolimus and mycophenolic acid in standard prophylactic regimen dosage. As to corticosteroids, methylprednisolone was administered at a dose of 500 mg intravenously prior to transplantation and on the first day after KT, which was then changed into oral prednisone. In all subjects we observed basic characteristics at the time of KT, i.e., those of the donor (donor with extended criteria, time of cold ischemia) and those of the recipient (age, sex, length of dialysis treatment, main cause of renal failure, delayed graft function, panel of reactive autoantibodies, number of mismatches in human leukocyte antigens (HLA) class A, B, DR and DQ). After KT, we monitored risk factors for PTDM at specified intervals (from 3 months) such as waist circumference, BMI, c-peptide and immunoreactive insulin levels, lipid profile [total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides], vitamin D, tacrolimus levels and parameters reflecting graft function such as glomerular filtration rate as determined by the Chronic Kidney Disease - Epidemiology Collaboration Index (CKD-EPI) formula and quantitative proteinuria from 24-hour urine collection. Protocol graft biopsy was performed 10 - 12 weeks after KT. At 10-12 weeks and then at 12 months after KT, we examined the presence of donor-specific antibodies in the serum of the recipients using the Luminex method and every patient underwent an oral glucose tolerance test (oGTT) at this time. We used the valid criteria of the American Diabetes Association (ADA) for the diagnosis of PTDM and pre-diabetic conditions (fasting hyperglycemia, impaired glucose tolerance). The total follow-up lasted one year.

We used a certified statistical program, MedCalc version 13.1.2. (MedCalc Software VAT registration number BE 0809 344,640, Member of International Association of Statistical Computing, Ostend, Belgium). Comparisons of continuous variables between groups were carried out using parametric (t-test) or non-parametric (Mann-Whitney) tests; associations between categorical variables were analyzed using the c^2 test and Fisher's exact test, as appropriate. Logistic regression was used for multivariate analysis for independent predictors of PTDM. We identified independent risk factors by means of the Cox proportional Hazard model. A P-value <0.05 was considered statistically significant.

Ethical approval

All procedures involving human participants have been approved according to the ethical standards of the institutional and/or national research committee, including the 1964 Helsinki Declaration and its later amendments of comparable ethical standards.

The clinical and research activities reported herein are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Results

A total of 170 patients after primary deceased-donor KT were enrolled in the study. A total of 28 patients were excluded because of known DM type I or II, followed by another 38 patients (4 deaths, 14 with infectious complications, 20 did not undergo protocol graft biopsy due to high risk). Thus, 104 patients were selected for the prospective follow-up.

Tab. 1. Group characteristics.

n = 104	Control group n = 40	Prediabetes n = 42	PTDM n = 22	p*	p**	p***
Men (%)	60	61.9	72.7	0.8609	0.3213	0.3914
Age in time of KT (years)	40.1±13.8	50.1±11.7	51.6±10.5	**0.0007**	**0.0012**	0.6160
time in dialysis (months)	16.8±13	29.5±15	43.1±27.5	**0.0001**	**<0.0001**	**0.0127**
ECD (%)	35	14.3	18.2	**0.0301**	0.1667	0.6857
CIT (min)	796±384	930±402	740±336	0.1270	0.5685	0.0627
DGF (%)	5	19	0	0.0541	0.2903	**0.0301**
PRA (%)	2.2±1	3.8±1	3.8±1	**<0.0001**	**<0.0001**	1.0000
Mismatch A	1.3±0.6	1.2±0.8	1.4±0.7	0.5254	0.5563	0.3260
Mismatch B	1.5±0.6	1.3±0.6	1.5±0.5	0.1353	1.0000	0.1859
Mismatch DR	1.4±0.6	1±0.7	1.6±0.5	**0.0069**	0.1889	**0.0007**
Mismatch DQ	1.2±0.8	1±0.6	1.5±0.7	0.2026	0.1456	**0.0040**
BMI base line (kg/m^2)	25±4.5	25.6±3.8	28.2±4.7	0.5153	**0.0106**	**0.0197**
BMI 3M (kg/m^2)	25.4±4.3	25.3±3.8	27.4±4.6	0.9113	0.0925	0.0555
BMI 6M (kg/m^2)	25.5±5	26.9±3.6	27.4±3.5	0.1418	0.1195	0.5961
BMI 1Y (kg/m^2)	25.5±5.7	27.3±3.5	27.9±3.3	0.0870	0.0752	0.5092
Waist circumference 3M (cm)	89.8±13.8	99.9±11.2	95.1±8.2	**0.0005**	0.1052	0.0810
Waist circumference 6M (cm)	93±16	105.2±24.5	97.1±9.6	**0.0096**	0.2775	0.1420
Waist circumference 1Y (cm)	93.2±15.4	100.3±13	96.8±7.9	**0.0265**	0.3107	0.2531
C-peptide 3M (µg/l)	4.2±1.9	4.2±2.3	4.3±1.9	1.0000	0.8435	0.8617
C-peptide 1Y (µg/l)	3.5±1.6	4.1±2.9	3.1±1.6	0.2528	0.3500	0.1390
IRI 3M (mU/l)	7.8±3.1	7.8±3.5	8.9±4.7	1.0000	0.2721	0.2938
IRI 1Y (mU/l)	8±3.7	9.2±4.2	8±3.8	0.1745	1.0000	0.2668
Cholesterol 3M (mmol/l)	5.2±1.2	5.3±1.6	5.7±1.3	0.7506	0.1327	0.3165
cholesterol 6M (mmol/l)	5.1±1.3	5.6±1.4	5.2±1.2	0.0981	0.7670	0.2595
Cholesterol 1Y (mmol/l)	4.8±0.8	5.2±1.2	4.8±1	0.0811	1.0000	0.1859
LDL 3M (mmol/l)	2.8±0.8	3.2±1.4	3.3±1	0.1185	**0.0354**	0.7673
LDL 6M (mmol/l)	2.8±0.9	3.4±1.2	2.9±0.8	**0.0126**	0.6652	0.0838
LDL 1Y (mmol/l)	2.7±0.8	3.2±0.9	3.1±1	**0.0096**	0.0903	0.6859
HDL 3M (mmol/l)	1.4±0.6	1.3±0.4	1.5±0.4	0.3751	0.4869	0.0621
HDL 6M (mmol/l)	1.4±0.6	1.4±0.3	1.5±0.6	1.0000	0.5324	0.3758
HDL 1Y (mmol/l)	1.4±0.4	1.4±0.3	1.5±0.6	1.0000	0.4352	0.3758
Triglycerides 3M (mmol/l)	2.3±1.3	2.9±1.8	2.7±1.3	0.0887	0.2510	0.6463
Triglycerides 6M (mmol/l)	2.1±1.1	2.1±0.6	1.9±0.9	1.0000	0.4692	0.2925
Triglycerides 1Y (mmol/l)	1.8±0.9	1.9±1	2±1	0.6360	0.4241	0.7053
Leptin base line (µg/ml)	32.8±30	45.6±23	53.4±37.3	**0.0326**	**0.0210**	0.3050
Leptin 3m (µg/ml)	27.5±9.5	37.9±17	36.5±23	**0.0011**	**0.0339**	0.7831
Leptin 6m (µg/ml)	24.4±16	22.3±17.5	39.4±32	0.5728	**0.0165**	**0.0073**
Leptin 1y (µg/ml)	19±11	35.9±18	51.7±38	**<0.0001**	**<0.0001**	**0.0271**
Adiponectin base line (µg/ml)	19.1±9.8	18.7±10.6	20.1±7.3	0.8598	0.6771	0.5819
Adiponectin 3m (µg/ml)	19.6±8.3	13.6±6.4	15.8±7.8	**0.0004**	0.0833	0.2307
Adiponectin 6m (µg/ml)	16.2±9.9	14.3±9.5	15.8±6.7	0.3778	0.8663	0.5126
Adiponectin 1y (µg/ml)	19.6±9.1	11±9.8	9.6±7	**0.0001**	**<0.0001**	0.5544
IL6 base line (pg/ml)	12.8±9.8	21.4±14.3	40.7±23	**0.0022**	**<0.0001**	**0.0001**
IL6 3M (pg/ml)	29.1±22.1	29.7±16.1	29.9±16.2	0.8882	0.8821	0.9626
IL6 6M (pg/ml)	22.7±14.3	22.3±6.5	27±11	0.8699	0.2259	**0.0354**
IL6 1Y (pg/ml)	19.3±8.6	14.3±7.9	27±22	**0.0075**	0.0538	**0.0013**
IL10 base line (pg/ml)	5.4±2.5	4.7±2.2	4.3±3.1	0.1816	0.1336	0.5519
IL10 3M (pg/ml)	11±5.5	4.7±3.6	5.5±4.3	**<0.0001**	**0.0001**	0.4330
IL10 6M (pg/ml)	6.6±5.5	4±2.3	3.6±2.4	**0.0061**	**0.0182**	0.5174
IL10 1Y (pg/ml)	8.1±7.9	3.9±2.6	4.6±2.5	**0.0016**	**0.0482**	0.3041
Vitamin D 6M (µg/l)	22±8.6	24±8.4	24.7±6.8	0.2900	0.2094	0.7373
Vitamin D 1Y (µg/l)	28.9±17.9	29.3±13.8	25.4±10.7	0.9098	0.4061	0.2527
TAC serum level 3M (ng/ml)	9.1±3	8±2.9	8±1.2	0.0953	0.1054	1.0000
TAC serum level 6M (ng/ml)	7.2±2.6	6.5±1	6.4±3.9	0.1084	03375	0.8753
TAC serum level 1Y (ng/ml)	6.5±2.5	5.7±1.7	6.5±1.5	0.0927	1.0000	0.0678
eGFR 3M (ml/min)	52.2±22.9	54.6±23.8	60.8±21.1	0.6432	0.1512	0.3080
eGFR 6M (ml/min)	49.7±15.9	56.5±21.6	53.2±21.1	0.1098	0.4640	0.5606
eGFR 1Y (ml/min)	53±21.2	58.7±23.3	61.7±19.7	0.2508	0.1184	0.6086
Proteinuria 3M (g/day)	0.31±0.25	0.35±0.23	0.4±0.32	0.4528	0.2249	0.4744
Proteinuria 6M (g/day)	0.37±0.26	0.34±0.14	0.37±0.2	0.6197	1.0000	0.5332
Proteinuria 1Y (g/day)	0.4±0.18	0.38±0.29	0.37±0.15	0.7386	0.5090	0.5478

KT – kidney transplant; BMI – body mass index; ECD – expanded criteria donor; CIT – cold ischemia time; DGF – delayed graft function; PRA – panel-reactive antibodies; IL – interleukin; PTDM – post-transplant diabetes mellitus; IFG – impaired fasting glucose; IGT – impaired glucose tolerance; IRI – immunoreactive insulin; LDL - low-density lipoprotein; HDL – high-density lipoprotein; TAC – tacrolimus; DSA – donor-specific antibodies; eGFR CKD EPI – estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration

*control group versus prediabetes **control group versus PTDM ***prediabetes versus PTDM

Tacrolimus levels were maintained in the range of 3.0 to 6.0 ng/L, and we did not observe any differences in tacrolimus levels between the study groups during the study period. There was also no significant difference in the daily dose of prednisone.

During the follow-up, PTDM was confirmed in 23.1 % of patients, prediabetic condition in 38.5 %, fasting hyperglycemia in 7.7 % and impaired glucose tolerance in 30.8 %. The characteristics of the study group are shown in Table 1. We found that the leptin level was significantly higher throughout the study period in the groups that developed PTDM and prediabetes as compared to the control group. In fact, its level was significantly higher at 6 and 12 months in the group with PTDM compared to the group of patients with prediabetes. In contrast, adiponectin levels decreased significantly in both groups (prediabetes, PTDM) at 12 months of follow-up as compared to the control group. Serum concentrations of interleukins showed a declining trend in the prediabetes and PTDM groups. We observed a significant difference in IL-6 levels at the 12-month follow-up in patients with prediabetes as compared to the control as well as PTDM groups. IL-10 levels were significantly lower in both groups at 3, 6 and 12 months as compared to the control group. The development of leptin, adiponectin and interleukin levels during the whole observed period in individual groups is shown in Figures 1–4. Patients who developed prediabetes or PTDM were older at the time of KT, spent a longer time in the hemodialysis program, and had a higher titer of panel-reactive antibodies (PRA). In the group of patients with pre-diabetic conditions, we recorded a significantly higher waist circumference at 3, 6 and 12 months of follow-up as compared to the control group (Tab. 1).

After adjusting for differences in the baseline donor and recipient characteristics, we found risk factors for PTDM 12 months after KT in a univariate analysis: hyperleptinemia levels at baseline (p = 0.0458) and 12 months (p = 0.0464), low adiponectin concentration at 12 months (p = 0.0108), low IL-6 at baseline (p = 0.0180), low IL-10 levels at 6 months (p = 0.0271) and 12 months (p = 0.0397), LDL level (p = 0.0252), values of BMI (p = 0.0393) and waist circumference at 12 months (p = 0.0173) (Tab. 2).

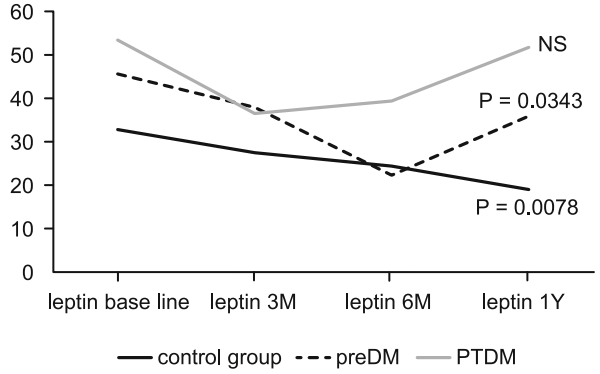

Fig. 1. Development of leptin levels in all groups during the monitored period.

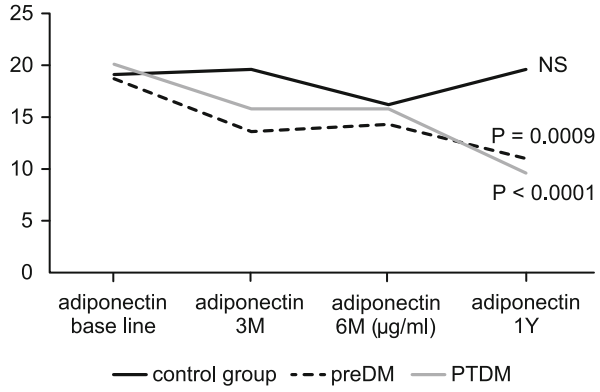

Fig. 2. Development of adiponectin levels in all groups during the monitored period.

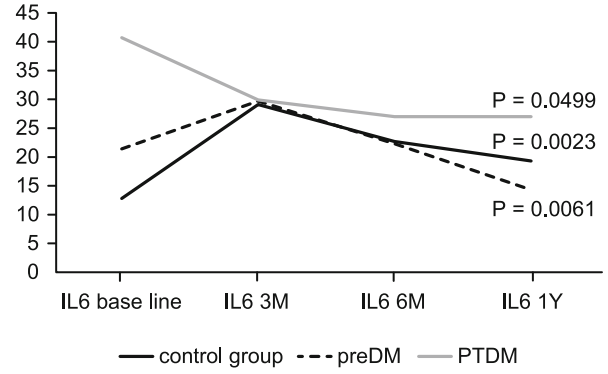

Fig. 3. Development of interleukin 6 levels in all groups during the monitored period.

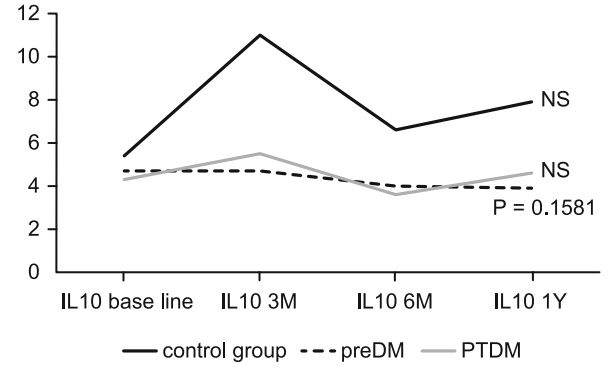

Fig. 4. Development of interleukin 10 levels in all groups during the monitored period.

Using multivariate logistic regression, we identified hyperleptinemia 12 months after KT as an independent risk factor for PTDM development 1 year after KT [OR 1.0320; 95% Cl 0.9785–1.0884 (p = 0.0038)]. At the same time, we confirmed that age at the time of KT is also an independent risk factor for PTDM [OR 1.0903; 95% Cl 1.0149–1.1714 (p = 0.0180)] (Tab. 3).

Discussion

In our analysis, we confirmed that hyperleptinemia 12 months after KT is an independent risk factor for the development of PTDM. At the same time, leptin levels before KT and at 3 months after KT significantly correlated with the recipient's BMI. As we expected, its level in the post-transplant period showed an increasing trend in the group of patients who developed PTDM or pre-diabetic condition, in patients with normal glucose tolerance it had a decreasing trend. We found that serum adiponectin levels decreased significantly in recipients with prediabetes and PTDM, while they increased in the control group after KT. However, in a multivariate analysis, we did not confirm that low adiponectin levels represent an independent risk factor for the development of PTDM.

Although adipocytokines, as white adipose tissue products, are associated with a higher risk of metabolic syndrome, obesity, insulin resistance, or DM type II in the general population for a longer period of time, a minimum of relevant studies have been performed in the transplant patient population. In 2018, the first study was published in which Dedinska et al. identified leptin as an independent risk factor for PTDM in patients after KT. Specifically, serum levels in excess of 55 ng/mL in men and 110 ng/mL in women were evaluated as indicators of patients at risk. In this analysis, low adiponectin levels were associated with insulin resistance and obesity. This pilot study evaluated the significance of adipokines in a smaller sample of patients (n = 70) with a total follow-up of 6 months after KT (4). In 2015, Romanowski et al. investigated a possible predisposition for PTDM development in relation to the polymorphism of the genes for adiponectin (rs266729 and rs1501299) and leptin (rs2167270). Three Cox regression analysis models were used in a study that confirmed a significant association of leptin gene polymorphism (rs2167270) with PTDM in tacrolimus-treated patients. This association was also confirmed in a multivariate regression analysis. It was the first study to analyze leptin gene polymorphisms in relation to PTDM (3). Previously, adiponectin and leptin gene polymorphisms had

Tab. 2. Univariate analysis.

n = 104	Outcome PTDM 1Y OR (95% CI)	p
Gender – men	1.944 (0.6179–6.1184)	0.2537
Age in time of KT	1.0677 (1.0143–1.1240)	**0.0058**
Hemodialysis duration	1.0250 (0.9957–1.0552)	**0.0322**
BMI base line	1.0918 (0.9552–1.2479)	0.1858
BMI 3M	0.0861 (0.0252–1.2606)	0.5618
BMI 6M	1.0731 (0.9331–1.2339)	0.3150
BMI 1Y	1.1108 (0.9732–1.2679)	**0.0393**
Waist circumference 3M	1.0353 (0.9885–1.0842)	0.1290
Waist circumference 6M	1.0383 (0.9924–1.0863)	0.0606
Waist circumference 1Y	1.0614 (1.0063–1.1196)	**0.0173**
C-peptide 3M	1.0109 (0.7623–1.3408)	0.9397
C-peptide 1Y	1.0570 (0.8667–1.3851)	0.6826
IRI 3M	1.0361 (0.8852–1.2128)	0.6561
IRI 1Y	1.0505 (0.9027–1.2224)	0.5196
Cholesterol 3M	1.1726 (0.7616–1.8054)	0.4620
Cholesterol 6M	1.2273 (0.7892–1.9085)	0.3548
Cholesterol 1Y	1.3366 (0.7155–2.4971)	0.3485
LDL 3M	1.4040 (0.7830–2.5176)	0.2299
LDL 6M	1.6282 (0.8628–3.0728)	0.1091
LDL 1Y	2.3209 (1.0136–5.3142)	**0.0252**
HDL 3M	0.8418 (0.2651–2.6728)	0.7702
HDL 6M	1.0553)0.3428–3.2486)	0.9252
HDL 1Y	1.0020 (0.2812–3.5701)	0.9976
Triglycerides 3M	1.2246 (0.8016–1.8708)	0.3239
Triglycerides 6M	0.9577 (0.5126–1.7892)	0.8923
Triglycerides 1Y	1.1499 (0.6272–2.1082)	0.6494
Leptin base line	1.0160 (0.9994–1.0329)	**0.0458**
Leptin 3M	0.9984 (0.9793–1.0178)	0.8690
Leptin 6M	0.9942 (0.9785–1.0101)	0.1474
Leptin 1Y	1.0994 (0.9363–1.6001)	**0.0464**
Adiponectin base line	1.0018 (0.9437–1.0635)	0.9523
Adiponectin 3M	0.9282 (0.8535–1.0099)	0.0715
Adiponectin 6M	1.0006 (0.9942–1.0070)	0.2327
Adiponectin 1Y	0.9182 (0.8567–0.9841)	**0.0108**
IL-6 base line	1.0865 (0.9963–1.1848)	**0.0180**
IL-6 3M	1.0002 (0.9635–1.0384)	0.9900
IL-6 6M	1.0070 (0.9471–1.0705)	0.8222
IL-6 1Y	1.0016 (0.9306–1.0780)	0.9658
IL-10 base line	0.9668 (0.8623–1.0840)	0.5622
IL-10 3M	0.8457 (0.6533–1.0947)	0.1501
IL-10 6M	0.8900 (0.7854–1.0085)	**0.0271**
IL-10 1Y	0.8970 (0.8020–1.0032)	**0.0397**
Vitamin D 6M	1.0368 (0.9638–1.1154)	0.3262
Vitamin D 1Y	0.9949 (0.9566–1.0348)	0.7995
Serum levels of TAC 3M	0.8930 (0.7325–1.0886)	0.2515
Serum levels of TAC 6M	0.8201 (0.5917–1.1368)	0.2094
Serum levels of TAC 1Y	0.7899 (0.5581–1.1179)	0.1422

KT – kidney transplantation, BMI – body mass index, IRI – immunoreactive insulin, LDL – low-density lipoprotein, HDL – high-density lipoprotein, IL – interleukin, TAC – tacrolimus, M – month, Y – year, PTDM – post-transplant diabetes mellitus

Tab. 3. Multivariate analysis (logistic regression).

n = 104	Outcome PTDM 1Y OR (95% CI)	p
Age at the time of KT	1.0903 (1.0149–1.1714)	0.0180
Time in dialysis	1.0323 (0.9876–1.0789)	0.1589
Bmi 1y	0.9414 (0.7338–1.2079)	0.6351
Waist circumference 1Y	1.0124 (0.9402–1.0901)	0.7435
Ldl 1y	4.0591 (0.1837–13.9201)	0.0259
Leptin baseline	1.0181 (0.9950–1.0417)	0.1248
Leptin 1Y	1.0320 (0.9785–1.0884)	**0.0038**
Adiponectin 1Y	1.0272 (0.8692–1.2139)	0.7529
IL-6 baseline	1.0776 (0.9812–1.1834)	0.1179
IL-10 6m	0.8123 (0.5806–1.1365)	0.2251
IL-10 1y	0.9415 (0.7836–1.1311)	0.5195

KT – kidney transplant; BMI – body mass index; LDL – low-density lipoprotein; IL – interleukin; PTDM – post-transplant diabetes mellitus

been studied in DM patients in different populations, but among transplant patients it was only adiponectin whose gene polymorphisms were repeatedly identified as indicators of patients at risk for PTDM development (7, 8, 9).

In recent years, several IL have attracted attention as potential factors influencing the physiology of DM type II and obesity-associated insulin resistance (10). IL-6 is one of the major pro-inflammatory cytokines. A proportion of 10-35% is produced in adipose tissue, while the increase in its concentration depends on the amount of fat. IL-6 leads to insulin resistance by disrupting the phosphorylation of insulin receptor, as well as insulin receptor substrate-1 by inducing the expression of suppressor of cytokine signaling 3 (SOCS-3) which is an inhibitor of insulin signaling. Elevated IL-6 levels have been associated with the development of DM type II. These findings support the fact that IL-6 is highly involved in the activity of subclinical tissue-specific or systemic inflammation and thus in the development of insulin resistance and DM type II (11). Patients with chronic kidney disease (CKD) are characterized by elevated levels of pro-inflammatory markers of multifactorial etiology and their contribution to morbidity and mortality should be considered. A 2005 prospective study found that patients who underwent KT experienced a significant reduction in pro-inflammatory markers, including IL-6, and those of oxidative stress (12). Some works in the past showed that proinflammatory cytokine levels are higher in patients with pre-existing and newly diagnosed DM after KT, suggesting a possible role in the etiopathogenesis of PTDM (13, 14). The most recent study from 2016 which dealt with the prognostic significance of pro-inflammatory markers for the development of metabolic complications in patients with KT evaluated a total of 82 individuals. The authors found that baseline levels of IL-6 and tumor necrosis factor (TNF) -RII were significantly higher in those who developed PTDM. However, in the later post-transplant period, the levels of inflammatory factors did not show differences between those who did not suffer from DM and those who did (15). IL-10 is a pleiotropic cytokine, produced by helper type 2 T cells, B cells, monocytes and macrophages, that inhibits many immune parameters. IL-10 is likely to exert its anti-inflammatory effects mostly by inhibiting leukocyte interactions with endothelial cells and inhibiting the production of pro-inflammatory cytokines and chemokines (16). The circulating levels of IL-10 have been found to be lower in patients with DM type II (17). Several studies have dealt with the genetic analysis of polymorphisms in IL-10 genes. The authors of Naz et al confirmed that the polymorphism in the IL-10 gene (rs1800896) was associated with DM type II (18). Recently, a cross-sectional study of the Ethiopian population comparing patients with DM type II with healthy controls was published. Genetic polymorphism of the IL-6 GG genotype has been

identified as a risk factor for DM type II and at the same time the genotype of IL-10 AA was negatively associated with its origin (19). However, no studies have been performed in the population of KT recipients that investigated the association of IL-10 with the risk of developing PTDM. In our analysis, we observed a significantly higher baseline IL-6 concentration in the group of patients who developed prediabetes or PTDM one year after KT. During the next monitoring periods (3rd, 6th, and 12th month) there was a significant decrease in its concentration in all groups. We assume that the reason lies in the restoration of renal function after successful KT with regression of chronic inflammation and oxidative stress, as we stated earlier. IL-10 concentrations at baseline did not show differences between groups, but at 3, 6, and 12 months, we observed significantly lower concentrations in the prediabetes and PTDM groups as compared to the control group. However, there were no significant shifts in its concentration in individual groups during the entire monitored period. We did not confirm that IL concentrations are an independent risk factors for PTDM development in a multivariate model.

Conclusion

In our study, we confirmed that elevated leptin level 12 months after KT is associated with PTDM development in patients after primary KT. The levels of inflammatory process mediators (IL-6 and IL-10) did not clearly correlate with the higher incidence of metabolic complications, but this relationship requires further investigation.

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Received February 14, 2022.
Accepted March 14, 2022.