Ivana Dedinská[1], Juraj Miklušica[1], Blažej Palkoci[1], Peter Galajda[2], Marián Mokáň[2]
[1]Surgery Clinic and Transplant Center, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Slovak Republic
[2]Clinic of Internal Medicine I, University Hospital Martin and Jessenius Faculty of Medicine, Comenius University, Slovak Republic

Body mass index before kidney transplantation — principal risk factor for NODAT

ABSTRACT

Purpose. Pretransplant obesity is a well-known risk factor for post-transplant outcomes such as patient and graft survival, delayed graft function, rejection, and wound complications. According to the recommendations of the European Renal Best Practice, patients who have body mass index (BMI) value of more than 30 kg/m^2 before kidney transplantation should reduce their weight.

Materials and methods. In the group of 297 patients who had undergone primary kidney transplantation from post-mortem donors, we found that assessed the impact of BMI on the development of new onset diabetes after transplantation (NODAT). Additionally, relationships between immunosuppression, weight gain and BMI in patients after kidney transplantation were also analysed. We measured the value of the patients' BMI and weight before kidney transplantation, 12 months after kidney transplantation, and 5 years after kidney transplantation. The group contained only those patients who, at the time of the kidney transplantation, did not suffer from diabetes mellitus. According to the development of NODAT in the monitored period, the group of patients was divided into the control group and NODAT group. We detected analysed the data on the type of immunosuppression (tacrolimus, cyclosporine A, mTOR inhibitor) and the average levels in the monitored period and identified whether BMI or increased weight 12 months and 5 years after kidney transplantation is related to the level (or dose) of the used immunosuppression.

Results. In our group, the patients who developed NODAT in the post-transplant period were significantly older in the 12-month analysis ($p < 0.0001$) and also in the 5-year analysis ($p = 0.0001$); had higher BMI at the time of transplantation ($p = 0.0003$) and higher BMI 12 months after kidney transplantation ($p = 0.0004$) and a significantly higher weight gain 12 months after kidney transplantation ($p = 0.0469$). We discovered that neither the level of immunosuppression nor the dose of prednisone had any effect on the increase in BMI or weight gain during the monitored period.

Conclusion. The patients in the waiting list, who have any risk factors for the development of diabetes mellitus, should be informed how to eliminate these risk factors (weight control, diet, physical exercises, etc.). In addition to the above, all candidates for kidney transplantation are recommended to stop smoking, to control blood pressure, and perform a lipidogram. (Clin Diabet 2016; 5, 1: 1–6)

Key words: body mass index, immunosuppression, NODAT, kidney transplantation

Address for correspondence:
MU Dr. Juraj Miklušica, PhD.
Surgery Clinic and Transplant Center
University Hospital Martin
Kollárova 2, 036 01 Martin
Slovak Republic
e-mail: juraj.miklusica@gmail.com
Phone: +421 43 4203 246
Clinical Diabetology 2016, 5, 1, 1–6
DOI: 10.5603/DK.2016.0001
Received: 10.12.2015 Accepted: 09.02.2016

Introduction

The risk factors of cardiovascular diseases are eliminated after kidney transplantation by the recovery of renal function. However, new risks factors occur at the same time, such as impaired glucose tolerance, diabetes

Table 1. Risk factors for NODAT development [5]

Non-modifiable risk factors for NODAT	Modifiable risk factors for NODAT
Age at the time of transplantation	Immunosuppression (corticosteroids, CNIs, mTOR inhibitors)
Population (Afro-Americans, Hispanics)	Obesity
Positive family history of DM2	Hypertriacylglycerolaemia
Male gender	Artery hypertension
HLA A30, B27, B42	Hypomagnesemia
Higher number of HLA mismatches	Prediabetes before transplantation
Polycystic kidney disease	Viral hepatitis C
	Cytomegalovirus infection
	Basiliximab in induction
	Proteinuria

DM2 — diabetes mellitus type 2; CNI — calcineurin inhibitor; mTOR — mammalian target of rapamycin

mellitus, arterial hypertension, lipid metabolism disorders, and other issues. The newly diagnosed diabetes mellitus after transplantation (NODAT) represents a serious and frequent complication in the transplantation of solid organs. The incidence varies from 4% to 25%, depending on the transplanted organ, the duration of monitoring of the patient, and the used immunosuppression protocol [1–4]. Risk factors for NODAT are shown in Table 1.

The risk of cardiovascular (CVS) diseases in patients with NODAT is increased also by hyperlipoproteinaemia, arterial hypertension, or smoking. NODAT is connected also with other complications, namely: rejection of the graft, recurring infections, and worse long-term function of the graft [5, 6].

Pretransplant obesity is a well-known risk factor for post-transplant outcomes such as patient and graft survival, delayed graft function, rejection, and wound complications [7–11]. Several recent studies have shown that significant post-transplant weight gain is also a risk factor for the patient and for graft survival. Identifying patients at high risk of significant post-transplant weight gain and using various methods to help control their body weight may improve the patient and the graft survival [12–14].

According to the recommendations of the European Renal Best Practice (ERBP), patients with a body mass index (BMI) value of more than 30 kg/m^2 before kidney transplantation should reduce their weight.

There is uncertainty regarding the relationship between obesity and outcomes after kidney transplantation. Obese kidney transplant recipients may have poorer outcomes compared with non-obese recipients; however, the outcomes may be better compared with patients who remain on dialysis. There is no consensus on whether obesity should be an exclusion criterion for kidney transplantation, and the policies differ among transplant centres [15, 16].

Materials and methods

In the group of 297 patients (of Central European origin) who had undergone primary kidney transplantation from post-mortem donors (in the years 2003–2014) at the Transplantation Center in Martin, we measured their body mass index value and weight before kidney transplantation, 12 months and 5 years after kidney transplantation. The aim of the study was to determine the impact of BMI on the development of NODAT and relationships between immunosuppression level and weight gain and BMI in patients after kidney transplantation. The group included only those patients who, at the time of kidney transplantation, did not suffer from diabetes mellitus. According to development of NODAT in the monitored period, the group of patients was divided into the control group and the NODAT group. NODAT was diagnosed according to the American Diabetes Association's (ADA) criteria. The individually monitored parameters were compared in both groups. Furthermore, we noted the type of immunosuppression (tacrolimus, cyclosporine A, mTOR inhibitor), the average levels of immunosuppressive drugs, and the average dose of prednisone in the monitored period. By the correlation coefficient, we identified whether BMI or weight gain 12 months and 5 years after kidney transplantation is related to the level (or dose) of the used immunosuppression. In the statistical evaluation, we used the certified statistics program MedCalc version 13.1.2 and the following statistical analyses: student's t-test, chi-quadrate test, and correlation coefficient. We found the value of $p < 0.05$ to be statistically significant.

Results

The group was composed of 297 patients who had undergone primary kidney transplantation from post-mortem donors and who were included in the

12-month analysis, and 182 patients who had received a kidney transplant 5 years ago (5-year analysis). The data were collected on the presence of polycystic kidney disease as a cause of kidney failure, as well as the presence of hypertension and a family history of type 2 diabetes (parents, siblings, and grandparents). The mean levels of tacrolimus in the control group was 4.7 ± 0.9 ng/mL; in the NODAT group it was 4.8 ± ± 1.2 ng/mL (p = 0.5592). The mean cyclosporin A levels in the control group was 86.9 ± 44.6 ng/mL; in the NODAT group it was 96 ± 10.7 ng/mL (p = 0.7946). Mean sirolimus levels in the control group was 6.8 ± ± 0.7 ng/mL; in the NODAT group it was 6.7 ± 0.5 ng/mL (p = 0.7210). Average daily dose of prednisone in the control group, was 8.2 ± 2.3 mg/day and in the NODAT group it was 8.8 ± 2.0 mg/day (p = 0.1734).

12-month analysis

The average age of the patients at the time of kidney transplantation (n = 297) was 47.4 ± 13.2 years. The group comprised 187 males (63%) and 110 females (37%). There were 178 patients (59.9%) with the average age of 43.7 ± 12.8 years in the control group. NODAT in the monitored period developed in 119 patients (40.1%) with the average age of 51.1 ± 13.6 years (p < 0.0001). The value of BMI at the time of transplantation in the entire group was 24.9 ± 4.9 kg/m^2. The value of BMI 12 months after kidney transplantation was 27.8 ± 4.9 kg/m^2. The average value of BMI before kidney transplantation in the control group was 23.8 ± 4.7 kg/m^2, and in the NODAT group it was 25.9 ± ± 5.1 kg/m^2 (p = 0.0003). The value of BMI 12 months after kidney transplantation in the control group was 26.7 ± 5 kg/m^2, and in the NODAT group it was 28.8 ± 4.9 kg/m^2 (p = 0.0004). The average weight gain 12 months after kidney transplantation in the entire group was 5.5 ± 5.2 kg, in the control group it was 4.9 ± 4.7 kg, and in the NODAT group it was 6.1 ± 5.6 kg (p =0.0469). Polycystic kidney disease as a cause of renal failure was present in 10.4% of the control group and in 17.2% of the NODAT group (p = 0.2839). Arterial hypertension was diagnosed in 99.4% of the control group and 100% of the NODAT group (p = 0.8866). Positive family history for NODAT in the control group was present in 33.7% and in the NODAT group it was present in 50.4% (0.0059).

5-year analysis

The average age of the patients at the time of kidney transplantation (n = 182) was 48 ± 13 years. There were 106 patients (58.2%) with the average age of 44.1 ± 12.2 years in the control group. NODAT in the monitored period developed in 76 patients (41.8%) with the average age 51.9 ± 13.8 years (p = 0.0001). The value of BMI 5 years after kidney transplantation in the control group was 27.9 ± 5.1 kg/m^2. In the NODAT group it was 29.5 ± 6.4 kg/m^2 (p = 0.0624). The average weight gain5 years after kidney transplantation in the entire group was 9.4 ± 8.7 kg, in the control group it was 8.6 ± 7.7 kg, and in the NODAT group it was 10.2 ± 9.7 kg (p = 0.2169) (see Tab. 1). By the correlation coefficient, we discovered that the average level of immunosuppression (tacrolimus, cyclosporine A, mTOR inhibitor, or the dose of prednisone) was not related to the BMI value and the increased weight (see Tab. 3–7).

Discussion

In our group, the patients who developed NODAT in the post-transplantation period were significantly older (both in the 12-month and the 5-year analysis), had higher BMI at the time of transplantation, higher

Table 2. Characteristics of the group

12-month analysis	Control group (n = 178)	NODAT (n = 119)	P value
Age at the time of transplantation (years)	43.7 ± 12.8	51.1 ± 13.6	**< 0.0001**
ADPKD (%)	10,4	17.2	0.839
Arterial hypertension (%)	99.4	100	0.8866
Positive family history of DM2 (%)	33.7	50.4	**0.0059**
BMI at the time of transplantation [kg/m^2]	23.8 ± 4.7	25.9 ± 5.1	**0.0003**
BMI 12 months after transplantation [kg/m^2]	26.7 ± 5	28.8 ± 4.9	**0.0004**
Weight gain 12 months from transplantation	4.9 ± 4.7	6.1 ± 5.6	**0.0469**
5-year analysis	**Control group (n = 106)**	**NODAT (n = 76)**	**P value**
Age at the time of transplantation (years)	44.1 ± 12.2	51.9 ± 13.8	**0.0001**
BMI 5 years after transplantation [kg/m^2]	27.9 ± 5.1	29.5 ± 6.4	0.0624
Weight gain 5 years after transplantation [kg]	8.6 ± 7.7	10.2 ± 9.7	0.2169

ADPKD — polycystic kidney disease; DM2 — diabetes mellitus type 2

Table 3. Correlation between BMI 12 months after transplantation and average level of immunosuppression

BMI 12 months after transplantation	Correlation coefficient r	95% confidence interval for r	P value
Level of tacrolimus	0.06254	–0.2816 to 0.3924	0.7253
Level of cyclosporine A	0.1087	–0.7709 to 0.8457	0.8375
Level of mTOR inhibitor	0.09117	–0.8603 to 0.9010	0.8841
Dose of prednisone	0.07241	–0.08271 to 0.2241	0.3598

Table 4. Correlation between BMI 5 years after transplantation and average level of immunosuppression

BMI 5 years after transplantation	Correlation coefficient r	95% confidence interval for r	P value
Level of tacrolimus	–0.1283	–0.4471 to 0.2194	0.4697
Level of cyclosporine A	–0.4138	–0.9494 to 0.7379	0.4886
Level of mTOR inhibitor	0.3909	–0.7500 to 0.9467	0.5152
Dose of prednisone	–0.04342	–0.1968 to 0.1120	0.5844

Table 5. Correlation between weight gain 12 months after transplantation and average level of immunosuppression

Weight gain 12 months after transplantation	Correlation coefficient r	95% confidence interval for r	P value
Level of tacrolimus	0.09826	–0.1241 to 0.3113	0.3859
Level of cyclosporine A	0.1160	–0.7678 to 0.8478	0.8267
Level of mTOR inhibitor	0.3849	–0.7531 to 0.9459	0.5223
Dose of prednisone	–0.09038	–0.2412 to 0.06472	0.2527

BMI 12 months after kidney transplantation, and significantly higher weight gain 12 months after kidney transplantation.

According to other studies, which agree with our study, the age at the time of kidney transplantation is considered to be an independent risk factor for the development of NODAT. Cosio et al. found a 2.2 times higher risk of the development of NODAT in recipients older than 45 years of age, compared to younger recipients [17]. The USRDS data show a strong relationship between the recipient's age and the development of NODAT. The recipients at the age of 45–59 years had a 1.9 times higher risk of the development of NODAT compared with recipients in the age of 18–33 years. In the recipients older than 60 years, the risk of the development of NODAT was 2 times higher than in the younger recipients [18].

Obesity before transplantation (defined as BMI > 30 kg/m^2) increases the risk of losing the graft. After transplantation, it increases the risk of cardiovascular diseases [19, 20]. Weight gain is almost a rule in the patients after transplantation [21, 22]. According to the IDF criteria for metabolic syndrome, the waist circumference is the basic parameter. Obesity of potential recipients before transplantation is a frequent finding. A BMI value of more than 35 kg/m^2 represents a contraindication for kidney transplantation, and a BMI the value of 33–35 kg/m^2 represents a relative contraindication for transplantation, with necessary pretransplantation examination by a surgeon. Higher BMI values before transplantation are connected with insulin resistance after transplantation, and education of the patients on reduction of their weight before transplantation gives the opportunity for reduced risk of the development of NODAT and cardiovascular diseases [23–25].

In our group, we did not record any effect of the level of the used immunosuppression or the dose of prednisone on the BMI values after transplantation.

An interesting finding in our analysis is the fact that the levels of the used immunosuppression have no effect on increased BMI neither 12 months nor 5 years after kidney transplantation. Tacrolimus inhibits the reversible suppression of the secretion of insulin in the level of transcription of mRNA insulin by binding to the FK506 binding protein-12, which leads to subsequent inhibition of calcineurin in pancreas B-cells. A high concentration of FK506 binding protein-12 in pancreas may explain why tacrolimus inhibits secretion of insulin in higher rates than cyclosporine A.

Table 6. Correlation between weight gain 5 years after transplantation and average level of immunosuppression

Weight gain 5 years after transplantation	Correlation coefficient r	95% confidence interval for r	P value
Level of tacrolimus	0.1482	–0.07394 to 0.3563	0.1896
Level of cyclosporine A	0.3949	–0.7480 to 0.9472	0.5106
Level of mTOR inhibitor	–0.9552	–0.9971 to –0.4642	0.1013
Dose of prednisone	0.04812	–0.1064 to 0.2004	0.5418

Table 7. Comparison of graft function (creatinine and eGFR) 12 months after transplantation and 5 years after transplantation

12-month analysis	Control group (n = 178)	NODAT (n = 119)	P value
Creatinine 12 months after transplantation [μmol/L]	139.4 ± 38.1	140.1 ± 43.6	0.9144
eGFR 12 months after transplantation [mL/min]	51 ± 14.4	46.8 ± 13.2	0.0635
5-year analysis	**Control group (n = 106)**	**NODAT group (n = 76)**	**P value**
Creatinine 5 years after transplantation [μmol/L]	136.8 ± 34.6	137.3 ± 40.3	0.9423
eGFR 5 years after transplantation [mL/min]	49.8 ± 12	46.8 ± 12	0.1794

Our finding is supported also by the study by Rodriguez-Rodriguez et al. who confirm that the inhibitors of calcineurin have no effect on the patient's weight; however, the pro-diabetogenic effect related to this is visible particularly in patients who had insulin resistance already before transplantation [26]. Similarly, in regard to the level of immunosuppression, the dose of prednisone has no effect on increased BMI or weight gain. Based on the above findings, we may say that the patient's diet had a clear effect on weight after kidney transplantation.

Conclusion

In our group, we identified BMI and weight gain as the risk factors for NODAT both in the 12-month and the 5-year analysis. Screening of the risk factors for development of diabetes mellitus should be performed before inserting the patient in the waiting list. It is also recommended to perform oral glucose tolerance test (OGTT) in patients with normal fasting glycaemia. Therefore, patients on the waiting list who have risk factors for the development of diabetes mellitus should be informed about the elimination of these risk factors (weight control, diet, physical exercises, etc.). In addition to the above, standard recommendations to all candidates for kidney transplant include the following: to stop smoking, to control blood pressure, and to perform a lipidogram.

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