Endokrynologia Polska
Tom/Volume 64; Numer/Number 1/2013
ISSN 0423–104X

# Factors associated with glucose metabolism disorders after kidney transplantation

## Czynniki ryzyka wystąpienia zaburzeń gospodarki węglowodanowej po przeszczepieniu nerki

***Barbara Brzezińska[1], Roman Junik[1], Anna Kamińska[1], Zbigniew Włodarczyk[2], Andrzej Adamowicz[2]***

*[1]Department of Endocrinology and Diabetology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*
*[2]Department of Transplantology and Surgery, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*

**Abstract**

**Introduction:** Post-transplant diabetes mellitus (PTDM), pre-diabetes-impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are frequent complications after organ transplantation. The aim of this study was to assess the frequency of PTDM, IFG and IGT in a group of renal transplant recipients, to compare the frequency of glucose metabolism disorders in subjects treated with tacrolimus and with cyclosporine, and to establish the influence of different risk factors on the development of glucose metabolism disorders.

**Material and methods:** We examined 206 non-diabetic kidney allograft recipients (age 46.4 ± 12.3 years, time since transplantation 45.5 ± ± 33.6 months, BMI 26.3 ± 4.5 kg/m$^2$). Glucose metabolism disorders were diagnosed using an oral glucose tolerance test. Logistic regression was used to assess the influence of each risk factor (age, BMI, waist circumference, physical activity, the presence of cardiovascular disease, positive family history of diabetes, cholesterol and triglycerides concentration) on the development of glucose metabolism disorders.

**Results:** In 103 patients (50%), we diagnosed glucose metabolism disorders. 19% of patients had PTDM, 14% IFG, and 17% IGT. We did not find any differences in the frequency of glucose metabolism disorders between patients treated with tacrolimus and with cyclosporine. Multivariate analysis identified BMI and a family history of diabetes as independent risk factors of glucose metabolism disorders.

**Conclusions:** We found a high prevalence of glucose metabolism disorders in the examined group. This suggests that kidney transplant recipients should be screened for these disturbances. Patients with higher BMI and with first-degree relatives with diabetes had an increased risk of glucose metabolism disorders after kidney transplantation**. (Endokrynol Pol 2013; 64 (1): 21–25)**

***Key words:*** *post-transplant diabetes mellitus, risk factors, kidney transplantation*

**Streszczenie**

**Wstęp:** Cukrzyca potransplantacyjna (PTDM) jak również stan przedcukrzycowy — nieprawidłowa glikemia na czczo (IFG) i nieprawidłowa tolerancja glukozy (IGT) są jednymi z częstszych powikłań po przeszczepieniu narządu. Celem pracy była ocena częstości występowania PTDM, IFG i IGT u osób po przeszczepieniu nerki, porównanie częstości występowania zaburzeń gospodarki węglowodanowej u osób leczonych takrolimusem i cyklosporyną oraz ocena wpływu różnych czynników ryzyka na rozwój tych zaburzeń.

**Materiał i metody:** W badaniu wzięło udział 206 osób po przeszczepieniu nerki bez rozpoznanych dotychczas zaburzeń gospodarki węglowodanowej (wiek 46,4 ± 12,3 lat, czas od przeszczepienia 45,5 ± 33,6 miesięcy, BMI 26,3 ± 4,5 kg/m$^2$). U wszystkich badanych wykonano test doustnego obciążenia glukozą. W celu oceny wpływu poszczególnych czynników ryzyka (wiek, BMI, obwód talii, aktywność fizyczna, obecność choroby sercowo-naczyniowej, dodatni wywiad rodzinny w kierunku cukrzycy, stężenie cholesterolu i triglicerydów) na rozwój zaburzeń gospodarki węglowodanowej wykorzystano model regresji logistycznej.

**Wyniki:** U 103 pacjentów (50%) zostały rozpoznane zaburzenia gospodarki węglowodanowej. U 19% badanych zdiagnozowano PTDM, u 14% IFG, u 17% IGT. Nie stwierdzono różnic w częstości występowania zaburzeń gospodarki węglowodanowej u leczonych takrolimusem w porównaniu z leczonymi cyklosporyną. W analizie wieloczynnikowej tylko BMI i dodatni wywiad rodzinny w kierunku cukrzycy okazały się niezależnymi czynnikami ryzyka zaburzeń gospodarki węglowodanowej.

**Wnioski:** W badanej przez nas grupie chorych stwierdziliśmy wysoką częstość występowania zaburzeń gospodarki węglowodanowej. Wskazuje to na potrzebę prowadzenia badań przesiewowych w tym kierunku u osób po przeszczepieniu nerki. Osoby z wyższym BMI i z rodzinnym obciążeniem cukrzycą mają podwyższone ryzyko rozwoju zaburzeń gospodarki węglowodanowej po przeszczepieniu nerki. **(Endokrynol Pol 2013; 64 (1): 21–25)**

***Słowa kluczowe:*** *cukrzyca potransplantacyjna, czynniki ryzyka, przeszczepienie nerki*

## Introduction

Post-transplant diabetes mellitus (PTDM), pre-diabetes-impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are the most frequent complications after renal transplantation. PTDM is associated with higher costs of post-transplant care and increased risk of graft rejection, infection, cardiovascular disease and

Anna Kamińska M.D., Department of Endocrinology and Diabetology Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel.: +48 52 585 40 20, fax: +48 52 585 40 41, e-mail: amikam@wp.pl

**Table I.** *Characteristics of the examined patients*
**Tabela I.** *Charakterystyka badanej grupy*

| Parameter | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| Age (years) | 46.4 | 12.3 | 19 | 72 |
| Time since transplantation (months) | 45.5 | 33.6 | 1 | 182 |
| Weight [kg] | 74.9 | 13.0 | 45 | 111 |
| Height [m] | 1.7 | 0.09 | 1.5 | 2.0 |
| BMI [kg/m$^2$] | 26.3 | 4.5 | 16.3 | 39.1 |
| Waist circumference — women [cm] | 85.2 | 13.6 | 45 | 114 |
| Waist circumference — men [cm] | 93.5 | 11.0 | 67 | 130 |
| Systolic blood pressure [mm Hg] | 132 | 14.3 | 90 | 180 |
| Diastolic blood pressure [mm Hg] | 82 | 8.0 | 60 | 110 |
| Total cholesterol [mg/dL] | 213 | 44.2 | 124 | 460 |
| Triglycerides [mg/dL] | 163 | 85.3 | 53 | 577 |
| Cyclosporine dose [mg] | 226 | 72.2 | 100 | 600 |
| Tacrolimus dose [mg] | 5.5 | 2.9 | 2.0 | 13.0 |
| Prednisone dose [mg] | 8.3 | 3.0 | 2.5 | 20.0 |



death. In PTDM, as in type 2 diabetes, two defects coexist — insulin resistance and impaired -cell function. The pathogenesis of PTDM is multifactorial and constitutes a combination of traditional risk factors typical for diabetes type 2 plus specific factors such as pre-existing chronic kidney disease, exposure to immunosuppressive drugs such as corticosteroids and calcineurin inhibitors — tacrolimus and cyclosporine [1–3]. The importance of different risk factors on the development of glucose metabolism disorders after renal transplantation is not well established.

The aim of this study was to assess the frequency of PTDM, IFG and IGT in a group of renal transplant recipients, to compare the frequency of glucose metabolism disorders in subjects treated with tacrolimus and treated with cyclosporine, and to establish the influence of different risk factors on the development of glucose metabolism disorders.

## Material and methods

During routine visits in the hospital outpatient transplantology clinic we examined 206 patients (80 women and 126 men), with no history of earlier glucose metabolism disorders (normal concentration of fasting and postprandial plasma glucose), who had had renal transplantation between 2000 and 2006. Age and the time since renal transplantation were recorded.

Weight, height and waist circumference were measured. Body mass index (BMI) was calculated. Information about coexisting cardiovascular diseases (hypertension, ischaemic heart disease, heart failure, cerebrovascular disease, atherosclerosis of lower extremities' arteries), family history of diabetes (the presence of type 2 diabetes in parents or siblings) and the level of physical activity (low — a sedentary lifestyle, high — physical exercise lasting more than one hour three times a week, and moderate — between 'low' and 'high') was also obtained. The scheme of immunosuppressive regimen was analysed. Plasma cyclosporine and tacrolimus concentrations were determined 12 hours after administration of the drug. Serum triglycerides and cholesterol concentrations were estimated.

Glucose metabolism disorders were diagnosed on the basis of an oral glucose tolerance test (OGTT) according to the ADA/WHO criteria [4]. IFG was diagnosed when fasting plasma glucose level was ≥ 100 mg/dL and ≤ 125 mg/dL. IGT was diagnosed if plasma glucose two hours after administration of 75 g of glucose was ≥ 140 and ≤ 199 mg/dL. Diabetes was diagnosed if fasting plasma glucose was ≥ 126 mg/dL (confirmed twice) or glucose in the second hour of OGTT was ≥ 200 mg/dL [2].

The characteristics of the examined group are set out in Table I.

A total of 57 (28%) subjects suffered from at least one cardiovascular disease. In 32 patients (16%), we found a positive family history of type 2 diabetes. Low, moderate and high levels of physical activity were declared by 44 (25%), 97 (54%) and 37 (21%) subjects, respectively.

All patients had been receiving immunosuppressive therapy according to the scheme: prednisone (n = 206),

**Table II.** *Characteristics of the group of patients treated with tacrolimus compared to the group treated with cyclosporine*
**Tabela II.** *Charakterystyka pacjentów leczonych takrolimusem w porównaniu z pacjentami leczonymi cyklosporyną*

| Parameter | Group treated with tacrolimus (n = 65) | Group treated with cyclosporine (n = 141) | p |
|---|---|---|---|
| Number/percentage of women [n /%] | 23/45 | 57/40 | p = 0.69 |
| Number/percentage of men [n/%] | 42/65 | 84/60 | |
| Age (years) | 42.1 ± 11.7 | 48.6 ± 11.9 | p < 0.001 |
| BMI [kg/m$^2$] | 25.64 ± 3.58 | 26.39 ± 4.67 | p = 0.27 |

calcineurin inhibitor (tacrolimus (n = 65) or cyclosporine (n = 141)) and antiproliferative drug (azathioprine or mycophenolate mofetil). The characteristics of the group of patients treated with tacrolimus compared to the group treated with cyclosporine are set out in Table II.

Data is expressed as means ± SD. The comparisons between the two groups (one treated with tacrolimus and the other treated with cyclosporine) were performed by z-test or Student's t-test, or by non-parametric U Mann Whitney test if the data was not normally distributed. Multiple logistic regression was used to assess the influence of each risk factor (age, BMI, waist circumference, physical activity, the presence of cardiovascular disease, positive family history of diabetes, cholesterol and triglycerides concentration) on the development of glucose metabolism disorders. Results were considered statistically significant where p < 0.05. Data analysis was made using Statistica® 2000 for Windows.

The study was approved by the Ethics Committee for Medical Research, Collegium Medicum in Bydgoszcz, and is in accordance with the Helsinki Declaration. Informed consent was given by all patients participating in the study.

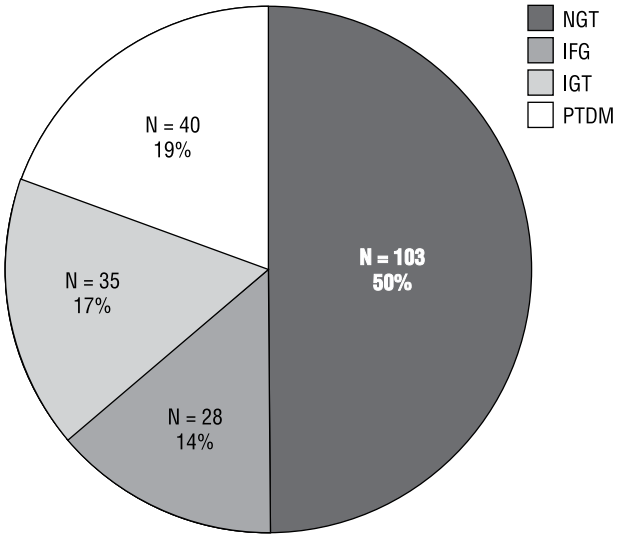


**Figure 1.** *Distribution of normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and post-transplant diabetes mellitus (PTDM) in the examined group*

**Rycina 1.** *Częstość występowania prawidłowej tolerancji glukozy (NGT), nieprawidłowej tolerancji glukozy (IGT), nieprawidłowej glikemii na czczo (IFG) i cukrzycy potransplantacyjnej (PTDM) w badanej grupie chorych*

## Results

In 50% of examined patients after kidney transplantation, we found glucose metabolism disorders. The distributions of normal glucose tolerance, IGT, IFG and PTDM in the examined group are shown in Figure 1.

In the group treated with tacrolimus, 23 patients (15%) had PTDM, 11 (17%) had IFG, and seven (11%) had IGT. In the group treated with cyclosporine, we found PTDM in 18 (25%) patients, IFG in 17 (12%), and IGT in 28 (20%). The differences in the frequency of these disorders between the two groups were not statistically significant.

Tacrolimus concentration was significantly higher in patients with glucose metabolism disorders than in patients with normoglycaemia (10.32 v. 8.63 ng/mL; p < 0.01). Cyclosporine level did not differ between patients with and without glucose metabolism impairment (163.1 v. 149.9 ng/mL; p = 0.09).

In logistic regression, six risk factors of diabetes, i.e. the presence of cardiovascular disease (p = 0.7), cholesterol concentration (p = 0.41), triglycerides concentration (p = 0.29), waist circumference (p = 0.24), age (p = 0.16) and physical activity (p = 0.1) did not influence significantly the occurrence of glucose metabolism disorders. Only positive family history of diabetes (regression factor = 1.023; p = 0.028951) and BMI (regression factor = 0.142; p = 0.0016) were independent risk factors.

## Discussion

The prevalence of PTDM has been previously widely studied, but the frequency of prediabetes in kidney transplant recipients has not been sufficiently examined. In this study, we used OGTT as the most reliable method in the screening of diabetes and as the sole method of

diagnosing IFG and IGT. We found a high prevalence (50%) of glucose metabolism disorders in the examined group of patients. The incidence rates of PTDM vary by organ transplanted and by post-transplant interval. In the first year after transplantation, 20-50% of kidney transplant recipients develop PTDM [3]. In our study, the incidence of PTDM was 19%, which is similar to that reported by other authors [1, 5, 6]. The frequency of IFG and IGT was also high — 14% and 17%, respectively. Mathew found IGT in 24.1% according to OGTT results performed six months after transplantation [1]. In a French study, IFG was found in 7.9% of patients after kidney transplantation, but this condition was diagnosed only on the basis of fasting blood glucose concentration according to a previous ADA/WHO definition (fasting glucose between 110 and 125 mg/dL) [7]. Patients with prediabetes are at increased risk of cardiovascular events. About 7% of them progress to diabetes every year. They require therapeutic interventions to prevent the progression to overt diabetes [8]. Therefore, in our study further analyses were made in the whole group of patients with glucose metabolism disorders — with PTDM, as well as IFG and IGT.

The use of immunosuppressive drugs such as corticosteroids and calcineurin inhibitors after renal transplantation affects the carbohydrate metabolism. Tacrolimus-based regimens are associated with more profound beta-cell morphological changes and inhibition of insulin secretion to a greater extent than cyclosporine-based regimens [9]. Clinical studies have confirmed that tacrolimus exerts a stronger diabetogenic effect than cyclosporine [5, 10]. This effect of tacrolimus is dose-dependent [11]. We also found a higher tacrolimus concentration in patients with glucose metabolism disorders than in patients with normoglycaemia. We did not reveal any significant differences in the frequency of glucose metabolism disorders between the group receiving tacrolimus and the group receiving cyclosporine. However, patients treated with cyclosporine were older than subjects treated with tacrolimus. The incidence of glucose metabolism disorders increases with age and this may explain the similar frequency of PTDM, IFG and IGT in both groups: younger, treated with potentially stronger diabetogenic drug (tacrolimus) and older, treated with cyclosporine. The different characteristics of both groups do not allow us to draw conclusions about the influence of the type of calcineurin inhibitor on glucose metabolism.

In our study, logistic regression revealed two independent risk factors of glucose metabolism disorders after renal transplantation: BMI and positive family history of type 2 diabetes mellitus.

Obesity is one of the strongest risk factors for diabetes type 2. The results of several studies have confirmed that obesity at transplantation is an independent risk factor also for PTDM [5, 10, 12–18]. Gonzales-Posada in a group of 3,365 renal transplant recipients showed that the risk of PTDM increases in patients with overweight (BMI > 25 kg/m$^2$), and becomes apparent in obese subjects (BMI > 30 kg/m$^2$) [19]. Maximum lifetime body mass index > 25 kg/m$^2$ was found to be a risk factor for PTDM in the study by Kamar [7].

The strong familial clustering of diabetes emphasises the important role of genetic factors in the pathogenesis of type 2 diabetes: 15–25% of first-degree relatives of patients with type 2 diabetes develop impaired glucose tolerance or diabetes [20]. In most papers assessing different risk factors of PTDM, data regarding family history of diabetes has not been collected [1, 5, 10, 12–14]. In the study by Kamar, 27% of patients had at least one family member with diabetes, and a first-degree relation was found in 66% of them. In this study, a family history of diabetes did not correlate with the development of PTDM [7]. Similarly in the group of cyclosporine-treated renal transplant recipients, a family history of diabetes was not associated with PTDM [21]. Also, Sulanc did not find any relationship between a family history of diabetes and the risk of development of new-onset diabetes after kidney transplantation [22]. In our study, the presence of diabetes in first-degree relatives was an independent risk factor of glucose metabolism disorders after kidney transplantation. Marin et al. also found a significant correlation between a family history of diabetes and the onset of PTDM, diagnosed on the basis of fasting glucose concentrations [15]. Similarly, a positive family history of diabetes was an independent predictor of new-onset post-transplant diabetes mellitus in the study by Madziarska [23].

Our study has some limitations. Its cross-sectional, not prospective, design is one of them. Other limitations are the large differences in the time since transplantation (high SD value), and the different, non-comparable, characteristics of patients treated with tacrolimus and cyclosporine.

On the other hand, we assessed different traditional risk factors, including family history of diabetes, the presence of cardiovascular disease, and the level of physical activity. These factors are often ignored in studies evaluating the risk of PTDM in kidney transplant recipients. In contrast to most previous studies, we diagnosed PTDM and prediabetes using OGTT and according to current ADA/WHO criteria.

## Conclusions

We found a high prevalence of glucose metabolism disorders in the examined group of kidney transplant recipients. Our results showed that patients with higher

BMI and with first-degree relatives with diabetes had an increased risk of developing glucose metabolism disorders after kidney transplantation. They should be screened for these disturbances. A positive family history of diabetes is not a modifiable risk factor. Overweight and obesity, potentially modifiable risk factors, are difficult to modify in clinical practice. Lifestyle modification should be applied to decrease weight and to reduce the risk of PTDM and prediabetes. Another preventative strategy is the selection of a potentially less diabetogenic immunosuppressive regimen in patients at high risk of glucose metabolism disorders.

## References


1. Mathew JT, Rao M, Job V et al. Post — transplant hyperglycaemia: a study of risk factors. Nephrol Dial Transplant 2003; 18: 164–171.
2. Gosmanov AR, Dagogo-Jack S. Predicting, managing and preventing new-onset diabetes after transplantation. Minerva Endorinol 2012; 37: 233–246.
3. Lane JT, Dagogo-Jack S. Approach to the patent with New-onset diabetes after transplantation (NODAT). J Clin Endocrinol Metab 2011; 96: 3289–3297.
4. The Expert Committee on the diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160–3167.
5. Kasiske BL, Snyder JJ, Gilbertson D et al. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003; 10: 178–185.
6. Davidson JA, Wilkinson A. New-onset diabetes after transplantation 2003. International consensus guidelines. Diabetes Care 2004; 3: 805–812.
7. Kamar N, Mariat C, Delahousse M et al. Diabetes mellitus after kidney transplantation: a French multicenter observational study. Nephrol Dial Transplant 2007; 22: 1986–1993.
8. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393–403.
9. Vincenti F., Friman S., Scheuermann E. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007; 7: 1506–1514.
10. Gonzalez-Posada JM, Hernandez D, Genis BB et al. Increased cardiovascular risk profile and mortality in kidney allograft recipients with post-transplant diabetes mellitus in Spain. Clin Transplant 2006; 20: 650–658.
11. Rodrigo E, de Cos MA, Fernandez-Fresnedo G et al. Higher initial tacrolimus blood levels and concentration-dose ratios in kidney transplant recipients who develop diabetes mellitus. Transplant Proc 2005; 37: 3819–3820.
12. Marcen R, Morales J, Castillo D et al. Posttransplant diabetes mellitus in renal allograft recipients: a prospective multicenter study at 2 years. Transplant Proc 2006; 38: 3530–3532.
13. Silva SM, Guerra JO, Santana A et al. Risk factors for posttransplant diabetes mellitus. Port J Hypert. 2008; 22: 319–324.
14. Shah T, Kasravi A, Huang E. Risk factors for development of new-onset diabetes mellitus After kidney transplantation. Transplantation 2006; 82:1673–1676.
15. Marin M, Renoult E, Bondor CI et al. Factors influencing the onset of diabetes mellitus after kidney transplantation: a single French center experience. Transplant Proc. 2005; 37: 1851–1856.
16. Seifi S, Rahbar M, Lessan-Pezeshki M et al. Posttransplant diabetes mellitus: incidence and risk factors. Transplant Proc 2009; 41: 2811–2813.
17. Madhav D, Ram R, Dakshinamurty KV. Posttransplant diabetes mellitus: analysis of risk factors, effects on biochemical parameters and graft function 5 years after renal transplantation. Transplant Proc 2010; 42: 4069–4071.
18. Ali IH, Adberrahim E, Ben Abdelghani K et al. Incidence and risk factors for post-renal transplant diabetes mellitus. Transplant Proc 2011; 43: 568–571.
19. Gonzales-Posada J, Hernandez D, Bayes Genis B et al. Impact of diabetes mellitus on kidney transplant recipients in Spain. Nephrol Dial Transplant 2004; 19: 57–61.
20. Pierce M, Keen H, Bradley C. Risk of diabetes in offspring of parents with non-insulin-dependent diabetes. Diabet Med 1995; 12: 6–13.
21. Copstein LA, Zelmanowitz T, Goncalvez LF et al. Posttransplant diabetes mellitus in cyclosporine-treated renal allograft patients: a case-control study. Transplant Proc 2004; 36: 882–883.
22. Sulanc E, Lane JT, Puumala SE i wsp. New-onset diabetes after kidney transplantation: an application of 2003 International Guidelines. Transplantation 2005; 80: 945–952.
23. Madziarska K, Klinger M i wsp. New-onset posttransplant diabetes mellitus begins in the dialysis period. J Ren Nutr 2012; 22: 162–165.