

PREVALENCE OF NEW ONSET DIABETES IN PATIENTS AFTER KIDNEY TRANSPLANTATION – THE PROSPECTIVE STUDY

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Objective While kidney transplantation is the best treatment of renal insufficiency and is recommended for patients with a glomerular filtration rate below 30 mL/min, new onset diabetes after transplantation (NODAT) reduces the benefits of this treatment, and present a significant, independent predictor of patient mortality and loss of graft function. The aim of the study was to determine the incidence of NODAT, as well as the risk factors for new onset diabetes mellitus (DM).

The study included 84 patients older than 18 years, who underwent kidney transplantation in the Clinical Center Niš in the period from 2007 to 2016. Impaired glucose tolerance was found in all of these patients in the first three post-transplantation months. In addition to physical examination and basic laboratory analyses, in all of kidney transplant patients the levels of tacrolimus and glycosylated hemoglobin HbA1c were determined.

NODAT was registered in 7 (8.3%) patients after average 17.2±10.8 days of kidney transplantation. The patients with NODAT had significantly higher levels of serum creatinine 210.72±120.29 µmol/L and decreased creatinine clearance 43.31±17.57 ml/min/1.73m² compared with a group of patients with diabetes prior to kidney trans-plantation 180.16±82.78 µmol/L and 52.12±18.45 ml/min/1.73m², respectively (p <0.01), and a statistically significantly shorter follow-up period after kidney transplantation (p <0.05). The results showed a significantly higher level of body mass index (BMI) 30.6 ± 6.4% compared to patients with already present diabetes before transplantation 28.5±6.8%, as well as the level of triglycerides 2.87±0.79 mmol/L vs. 1.73±0.82 mmol/L (p <0.05). The level of tacrolimus was adequate for the given post-transplantation period.

NODAT is a significant complication of kidney transplantation and is associated with risk factors, primarily with older recipient age and hereditary burden, but also with variable factors such as obesity and hypertriglyceridemia. We believe that the prevalence of NODAT can be changed if oral glucose tolerance test (OGTT) is done prior to transplantation in the potential kidney graft recipients

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Key words: kidney transplantation, new onset diabetes, risk factors

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Introduction

Kidney transplantation is the best treatment for end-stage renal diseases, but the new onset of diabetes after kidney transplantation reverse many of the benefits by reducing the survival of transplant allograft and patient survival too. New onset diabetes after kidney transplantation is a significant and common complication that follows the transplantation of solid organs. Earlier studies have shown that approximately 15-30% of trans-

planted individuals without diabetes develop de novo diabetes in the first years after the transplant. Many others develop glucose intolerance which does not satisfy the criteria for diabetes diagnosis (1-3). Evidence suggest that immunosuppressive drugs account for 74% of the risk for NODAT development. These patients often use corticosteroids, calcineurin inhibitors, including tacrolimus, cyclosporine, as well as mammalian target of rapamycin inhibitors (sirolimus and everolimus). Steroids reduce the expression of GLUT2 and glucokinase, significantly increasing the glucose-stimulated secretion of insulin. Although cyclosporine (CYC) therapy allows a reduction in steroid dosages with subsequent reduction of NODAT incidence, calcineurin inhibitors (CNI) have also been associated with glucose metabolism impairment. Clinical studies indicate that tacrolimus (TAC) is associated with a higher risk for IGT and

NODAT than is cyclosporine. It is not defined whether the effect of CNI on glucose metabolism is dosage-dependent (4). A large retrospective registry showed that new onset diabetes after kidney transplantation is a significant, independent predictor of total mortality and loss of graft function.(5)

The international expert commission composed of experts in the field of transplantation and diabetes, has put forward their consensus guideline for the diagnosis and treatment of de novo diabetes. It is recommended that the definition and diagnosis of new onset diabetes after transplantation should be based on the definition of diabetes and impaired glucose tolerance as given by the World Health Organization (WHO) and 2003 updated American Diabetes Association (ADA) criteria for the diagnosis of diabetes mellitus: symptoms of DM plus plasma glucose concentration 11.1 mmol/l; fasting plasma glucose concentration of 7.0 mmol/l; 2-hour plasma glucose concentration of 11.1 mmol/l during the oral glucose tolerance test (6).

HbA1c assay is not used for the diagnosis of NODAT, because end stage renal disease (ESRD) patients and newly transplanted kidney patients frequently have anemia (due to surgical blood loss, iron deficiency, immunosuppressive drugs, graft dysfunction, and abrupt discontinuation of erythropoietin administration), leading to false A1c results (5, 6).

Risk factors for the development of NODAT are classified as nonmodifiable, modifiable and potentially modifiable. Nonmodifiable factors are age, race, heritage; modifiable are corticosteroids, calcineurin inhibitors, sirolimus metabolites of azathioprine and mycophenolate mofetil, tacrolimus interaction and present HCV infection, obesity, hypertriglyceridemia and hypertension, proteinuria, hypomagnesemia; potentially modifiable are impaired glucose tolerance prior to transplantation, HCV and CMV infections. This classification makes it easier to identify people at risk for NODAT, as well as their monitoring and treatment (6-8).

The aim of the present study was to determine the incidence of new onset diabetes in patients after kidney transplantation, as well as the risk factors for new onset diabetes in these subjects.

Methods

Subjects

The present study was carried out at the Clinic of Nephrology, Faculty of Medicine, University of Niš, Serbia. The study included 84 patients, mean age 43.86±10.68 years, who had underwent kidney transplantation at the Clinical Center Niš in the period from 2007 to 2016. Impaired glucose tolerance was estimated for all of these patients within the first three months post-transplantation.

Methods

Basic biochemical analyses (total protein and albumin in serum and urine, creatinine in serum and urine, glucose, total cholesterol and triglycerides in the serum fibrinogen) were done in biosystems SA (Costa Brava, Barcelona, Spain) using the standardized protocols. Blood samples and urine were taken after an overnight fasting of 12 hours.

In addition to the physical examination and routine laboratory analysis, the following parameters were determined in all individuals:

- LDH, AST, ALT, alkaline phosphatase,
- urinary protein and albumin excretion,
- level of tacrolimus,
- level of glycosylated hemoglobin HbA1c.

Statistical analysis

The data were analyzed using the statistical software Jandel SigmaStar for Windows Version 2.0. All the results were expressed as mean plus standard deviation (SD) or median with the range in parentheses. In order to determine the statistical significance of differences in the mean values of individual groups, the Student t-test was used, and in the analysis of enzyme activity Mann-Whitney U-test was used. The assessment of the proportion of parameters monitored during the study was performed using the statistical method of linear regression correlation test, and p value of less than 0.05 was taken as statistically significant.

Results

Baseline anthropometric and biochemical characteristics of all investigated patients with kidney transplantation are given in Table 1.

Table 1. Baseline anthropometric and biochemical characteristics of patients with kidney transplantation

	All patients with Tx kidney
<i>N (M:F)</i>	84 (52:32)
Age (years)	43.86±10.68
The average time from kidney Tx	50.88±23.98
Hemoglobin (g/dl)	11.22 ± 1.76
WBC (x10 ⁹ /ml)	7.57 ± 2.13
Creatinine (µmol/l)	203.04±170.12
CCr (ml/min)	46.17 ± 17.92
T Proteins (g/l)	69.43 ± 7.32
Albumins (g/l)	38.66 ± 6.05
TCholesterol (mmol/l)	5.68 ± 1.54
Triglycerides (mmol/l)	1.18 ± 1.49
Glucose (mmol/l)	6.08 ± 3.04
HbA1c (%)	5.3 ± 1.67
Tac (ng/ml)	7.01±3.78
BMI (%)	24.5±4.33
hsCRP (mg/dl)	1.19 ± 0.72

Results are given as means ± SD.

N (M: F), the number of (male: female); Hb, hemoglobin; WBC, leukocytes; CCR creatinine clearance; TChol, total cholesterol; Trigl, triglycerides; BMI, body mass index; HbA1c, level of glycosylated hemoglobin; Tac, level of tacrolimus; hsCRP, high-sensitive C-reactive protein.

NODAT was registered in 7 (8.3%) patients. Diabetes patients before renal transplantation were significantly younger than patients with new onset of diabetes ($p < 0.01$). Patients with NODAT had significantly higher levels of serum creatinine and decreased creatinine clearance compared to the group of patients who had diabetes prior to kidney transplantation. NODAT developed 17.2 ± 10.8 days after kidney transplantation. The patients

with new onset diabetes had statistically significantly shorter follow-up period after kidney transplantation. Blood glucose concentration was not controlled adequately, particularly in the patients with diabetes after renal transplantation. This study showed that the patients who developed new onset diabetes had significantly higher levels of body mass index (BMI) compared to those with diabetes present already before transplantation, as well as the triglyceride level ($p < 0.05$). The level of tacrolimus was appropriate for the given post-transplantation period.

The results for the patients with DM (previous and with new onset) are given in Table 2.

Table 2. Baseline anthropometric and biochemical characteristics of patients with kidney transplantation and Diabetes Mellitus

	DM before Tx kidney (n=13)	NODAT (n=7)
N (M:F)	9 : 4	5: 2
Time from kidney Tx	45.14±25.05 ^B	38.17±22.28
Age (years)	42.2± 14.9 ^A	56,8 ± 11,2
Hemoglobin (g/dl)	13.62 ± 1.84 ^c	14.58 ± 1.18
WBC (x10 ⁹ /ml)	5.87 ± 1.33	6.68 ± 1.46
Creatinine (µmol/l)	180.16 ± 82.78 ^c	210.72 ± 120.29
CCr (ml/min)	52.12 ± 18.45 ^c	43.31 ± 17.57
T Proteins (g/l)	72.54 ± 11.88	74.43 ± 5.02
Albumins (g/l)	38.80 ± 7.93	40.84 ± 3.02
TChol (mmol/l)	4.78 ± 1.62 ^B	5.92 ± 0.86
Trigl (mmol/l)	1.73 ± 0.82 ^c	2.87 ± 0.79
Glucose (mmol/l)	14.24 ± 6.62 ^A	12,72 ± 2,63
HbA1c (%)	8.89±1.82 ^B	7.75±1.66
Tac (ng/ml)	7.23±4.16	6.98±3.55
hsCRP (mg/dl)	2.72 ± 1.07	2.56 ± 1.69
BMI (%)	28.5 ± 6.8 ^A	30.6 ± 6.4

Results are given as means ± SD.

NODAT, new onset diabetes after transplantation; N (M: F), the number of (male: female); Hb, hemoglobin; WBC, leukocytes; CCR creatinine clearance; TChol, total cholesterol; Trigl, triglycerides; BMI, body mass index; HbA1c, The level of glycosylated hemoglobin; Tac, level of tacrolimus; hsCRP, high-sensitive C-reactive protein.

^A $P < 0.01$ compared to de novo DM

^B $P < 0.05$ compared to de novo DM

^C $P < 0.001$ compared to de novo DM

Discussion

In the Research US Renal Data System, out of 11,659 patients transplanted between 1996-2000, new onset diabetes was associated with increase in the incidence of graft failure in more than 60% patients, and over 90% increase in mortality (6). With an increasing number of patients with end-stage renal diseases and kidney transplantations, the number of patients with de novo diabetes is also growing. One study suggested that the incidence of new onset diabetes was really growing, offering two possible explanations: 1) the bioavailability of calcineurin inhibitors was significantly increased, leading to an increase of concentration in the blood and thus to their increased

diabetogenic effect, and 2) significant changes in body weight, primarily occurring in the recipient. The literature describes numerous modifiable and nonmodifiable risk factors. Nonmodifiable factors include age, race, heredity, family history and previous glucose intolerance. Modifiable risk factors include obesity, hepatitis C infection, cytomegalovirus, and immunosuppression. A large number of immunosuppressants that are frequently used in transplantation have diabetogenic side effects (10-13).

The patients who had undergone a kidney transplant in the Clinical Center Niš were treated with standard protocols for inducing immunosuppression, which includes pulse doses of corticosteroids, which over the next month were reduced

to the maintenance dose of 10 mg daily. For the purpose of kidney graft survival, therapy with calcineurin inhibitors (with determination of the drug concentration in the blood), and anti-proliferative drugs are applied. Some large studies have shown that glucocorticoids decrease glucose transporter GLUT2 and glucokinase expression, significantly increasing glucose-stimulated secretion of insulin (10, 11). It has been shown that glucocorticoids stimulate transcription deometazon serum and glucocorticoid-induced kinase 1, upregulate activity of voltage-dependent K⁺ channels, and to lead to reduction of Ca²⁺ through voltage-dependent channels, which leads to a drop in insulin secretion (11, 12). Calcineurin inhibitors are also commonly prescribed medications after transplantation. Both CYC and TAC strongly correlated with the development of new onset diabetes, but it seems that TAC had an increased diabetogenic effect, as shown in prospective-retrospective studies. It turns out that calcineurin inhibitors have two mechanisms: reduction of insulin secretion and toxic effects on pancreatic beta cells (13). mTOR inhibitors have been linked to a significant increase of the risk of developing de novo diabetes, especially in combination with TAC, with a tendency of sirolimus to have a significantly higher frequency of occurrence of de novo diabetes than TAC. We observed that our patients did not show a statistically significant correlation between the high level of calcineurine inhibitors and new onset diabetes.

The two most important causes for the loss of transplanted kidneys is chronic allograft nephropathy, but also the development of graft failure in patients with new onset diabetes, which is significantly associated with reduced patient survival, as well as with increased cardiovascular mortality (6, 12-14).

Age increased the risk for diabetes 1.5-fold for every 10-year increase in age. Older age is the strongest and most consistent risk factor for NODAT in kidney transplantation and is reported in the majority of studies (15). In addition, the rate of increase in NODAT cases after the first 6 months is significantly faster in older than in younger individuals. The immutable risk factor in a group of patients with de novo diabetes was older age of the total population of patients with kidney transplant in the Clinical Center Niš. There is conflicting evidence regarding the importance of family history of diabetes and impaired glucose tolerance before transplantation. Individuals with a history of diabetes among first-degree relatives

should be identified in order to prevent the development of NODAT. Some reports suggested that a family history of diabetes increases up to seven times the risk for NODAT (11, 16). In our study, a positive family history was found in 5 out of 7 patients. Further, we noted statistically significantly higher levels of triglycerides and BMI values in patients with NODAT. However, in our study there were no statistically significant differences in the levels of tacrolimus among all estimated patients with kidney transplants. Sharif et al (17) demonstrated that in a prospective study designed to evaluate the use of oral glucose tolerance test (OGTT) for risk-stratification of patients for NODAT, among 122 renal transplant recipients without diabetes who had two fasting plasma glucose (FPG) level measurements within the range of 100–125 mg/dL (5.6–6.9 mmol/L) for more than 6 months after transplantation, OGTTs revealed that 10% had overt diabetes mellitus, 9% had impaired glucose tolerance (IGT) alone, 18% had impaired fasting glucose (IFG) alone (all defined by the WHO criteria), and 14% had combined IFG and IGT. Unfortunately, in our patients, OGTT was not done prior to transplantation.

A progressive reduction in CNI target levels has led to a lower incidence of NODAT. Tacrolimus concentrations of ≤ 10 ng/ml are associated with both a maximum benefit on graft survival and a minimal risk for NODAT (18).

Conclusion

New onset diabetes after transplantation is a significant complication of kidney transplantation and is associated with risk factors, primarily older age of recipients and hereditary load, or variable factors, such as obesity and hypertriglyceridemia. We found that the incidence of NODAT was lower similar to that in larger studies. A possible reason for the low frequency is the relatively small number of patients with kidney transplant compared with large multicenter studies, but also good control and maintaining the level of calcineurin inhibitors within normal values for the period after transplantation, as well as reducing the dose corticosteroids induction, and protocol maintenance to the level of safe applications.

Moreover, we believed that the prevalence of NODAT can be changed if oral glucose tolerance test (OGTT) is done prior to transplantation in potential kidney graft recipients.

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PREVALENCIJA NOVOOTKRIVENOG DIJABETESA KOD BOLESNIKA NAKON TRANSPLANTACIJE BUBREGA

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Iako je transplantacija bubrega najbolja terapija terminalne bubrežne insuficijencije i preporučuje se bolesnicima sa jačinom glomerulske filtracije ispod 30 ml/min, novootkriveni dijabetes posle transplantacije u mnogome smanjuje povoljnosti ovog načina lečenja i predstavlja značajan, nezavisan prediktor ukupne smrtnosti i gubitka funkcije grafta. Cilj studije bio je da se utvrdi učestalost novootkrivenog dijabetesa kod bolesnika nakon transplantacije bubrega, kao i faktori rizika za pojavu dijabetesa nakon transplantacije.

Studijom su obuhvaćeni bolesnici stariji od 18 godina kod kojih je urađena transplantacija bubrega u Kliničkom centru Niš u periodu od 2007. do 2016. godine. Procena poremećaja tolerancije na glukozu vršena je kod svih bolesnika u prva tri meseca posle transplantacije. Pored fizikalnog pregleda i osnovnih laboratorijskih analiza, kod svih ispitivanih osoba određeni su i nivoi takrolimusa i glikoziliranog hemoglobina HbA1c.

Novootkriveni dijabetes je dijagnostikovao kod 7 (8,3%) bolesnika posle 17,2+10,8 dana od transplantacije bubrega. Bolesnici sa novootkrivenim dijabetesom su imali značajno viši nivo serumskog kreatinina $210,72 \pm 120,29 \mu\text{mol/L}$ i snižen klirens kreatinina $43,31 \pm 17,57 \text{ ml/min/1,73 m}^2$ u poređenju sa grupom bolesnika koja je imala dijabetes pre transplantacije bubrega $180,16 \pm 82,78 \mu\text{mol/L}$ i $52,12 \pm 18,45 \text{ ml/min/1,73 m}^2$ ($p < 0,01$), i statistički signifikantno kraći period praćenja nakon transplantacije bubrega ($p < 0,05$). Rezultati pokazuju statistički značajno viši nivo BMI $30,6 \pm 6,4\%$ u odnosu na bolesnike sa već prisutnim dijabetesom pre transplantacije $28,5 \pm 6,8\%$, kao i nivo triglicerida $2,87 \pm 0,79 \text{ mmol/L}$ vs. $1,73 \pm 0,82 \text{ mmol/L}$ ($p < 0,05$). Nivo takrolimusa je bio adekvatan za posmatrani posttransplantacioni period.

Novootkriveni dijabetes posle transplantacije je značajna komplikacija bubrega i udružena je sa faktorima rizika, pre svega, starijim životnim dobom recipijenata i naslednim opterećenjem, ali i promenljivim faktorima kao što su gojaznost i hipertrigliceridemija. Mogući razlog za nisku učestalost NODAT je relativno mali broj bolesnika sa transplantacijom bubrega u poređenju sa velikim multicentričnim studijama, ali isto tako i dobra kontrola i održavanje nivoa kalcineurinskih inhibitora u okviru normalnih vrednosti za period nakon transplantacije, kao i smanjenje indukciono doze kortikosteroida i primena terapijskih protokola na nivo sigurnih aplikacija. Smatramo da bi se prevalencija novootkrivenog dijabetesa posle transplantacije promenila ukoliko bi se oralni test tolerancije na glukozu (OGTT) radio pre transplantacije kod potencijalnih primalaca grafta bubrega.

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Ključne reči: transplantacija bubrega, novootkriveni dijabetes, faktori rizika