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Prevalence and risk factors of new-onset diabetes after transplantation: A single-center experience

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Abstract. *New-onset diabetes after transplantation (NODAT) is a serious complication following solid organ transplantation. NODAT occurs in 2.5% to 40% of all solid organ transplant recipients. The identification of high-risk patients and the implementation of measures to limit the development of NODAT can improve the long-term prognosis of patients. The present study aimed to assess NODAT frequency and risk factors in kidney transplant recipients.*

Methods. A cohort of 103 kidney transplant patients was included in this retrospective single-center study, excluding 31 with pre-existing diabetes. The remaining 72 were divided into NODAT (n=17) and non-NODAT (n=55) groups. The logistic regression analysis was used to assess the risk factors for NODAT.

Results. NODAT occurred in 17 (23.6%) out of 72 patients without diagnosed diabetes before kidney transplantation. Age was significantly associated with increased NODAT risk ($p<0.0001$). Pre-transplant impaired fasting plasma glucose (FPG) and impaired glucose tolerance were significant predictors of NODAT. A statistically significant correlation was found between fasting plasma glucose (FPG) and postprandial blood glucose levels at various time points during the first month post-transplantation, and the development of NODAT. Similarly, patients requiring temporary insulin during hospitalization after transplantation had a significantly increased risk of NODAT. Multivariate analysis identified age ≥45 years ($p=0.01$), pre-transplant impaired FPG ($p=0.001$), post-transplant insulin requirement ($p=0.01$), and first-month tacrolimus levels ($p=0.04$) as statistically significant independent risk factors for NODAT development.

Conclusion. Age over 45 years, pre-transplant impaired FPG, perioperative insulin requirement, and first-month tacrolimus blood concentration were identified as independent factors associated with the development of NODAT.

Keywords: *diabetes, kidney transplantation, risk factors, new-onset diabetes after transplantation.*

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Поширеність та фактори ризику посттрансплантаційного діабету: досвід одного центру

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Резюме. *Постерансплантаційний цукровий діабет (ПТЦД) є серйозним ускладненням, яке діагностується у 2,5% - 40% усіх реципієнтів солідних органів. Виявлення пацієнтів групи високого ризику та впровадження заходів щодо обмеження розвитку ПТЦД може покращити віддалений прогноз пацієнтів. Це дослідження мало на меті оцінити частоту ПТЦД та визначити його фактори ризику у реципієнтів трансплантованої нирки.*

Методи. У цьому ретроспективному одноцентровому дослідженні проаналізовано когорту з 103 пацієнтів після трансплантації нирки, за винятком 31 пацієнта з вже існуючим діабетом. Решта 72 були розділені на групи з ПТЦД (n = 17) і без ПТЦД (n = 55). Логістичний регресійний аналіз використовувався для оцінки факторів ризику ПТЦД.

Результати. ПТЦД дігностовано у 17 (23,6%) із 72 пацієнтів, які не мали цукрового діабету до трансплантації нирки. Ризик розвитку ПТЦД зростав з віком (p<0,0001). Підвищення рівня глюкози крові перед трансплантацією та порушення толерантності до глюкози були значущими прогностичними факторами ПТЦД. Крім того, встановлено статистично значущу асоціацію між рівнем глюкози натще і постпрандіальним рівнем глюкози крові в різні періоди протягом першого місяця після трансплантації та розвитком ПТЦД. Подібним чином, пацієнти, які потребували тимчасового лікування інсуліном під час госпіталізації після трансплантації, мали значно підвищений ризик ПТЦД. Багатофакторний логістичний аналіз визначив вік ≥45 років (p=0,01), підвищення рівня глюкози крові до трансплантації (p=0,001), потребу в інсуліні після трансплантації (p=0,01) та концентрацію такролімусу в перший посттрансплантаційний місяць (p=0,04) як незалежні фактори ризику розвитку ПТЦД.

Висновок. Враховуючи зв'язок діабету з серцево-судинними ускладненнями, відторгненням трансплантата, смертністю та зниженням якості життя, раннє виявлення пацієнтів групи високого ризику ПТЦД та профілактичні заходи мають вирішальне значення для покращення віддалених результатів лікування.

Ключові слова: *цукровий діабет, трансплантація нирки, фактори ризику, посттрансплантаційний діабет.*

Introduction. New-onset diabetes after transplantation (NODAT) is a serious complication in patients receiving kidney and other solid organ transplants that significantly increases morbidity and mortality and decreases quality of life. In the literature, the incidence of NODAT ranges from 2.5% to 40% [1-3].

The diagnosis of NODAT is currently made using unmodified criteria for diagnosing diabetes in the general population. These criteria are based on the World Health Organization criteria proposed by the American Diabetes Association [4].

Many risk factors that cause diabetes mellitus in patients in the normal population are similar to the risk factors for diabetes mellitus that may develop after transplantation. These include age, obesity, African American and Hispanic race, family history, and impaired glucose tolerance (IGT). In addition, some risk factors are specific to the transplant population. Immunosuppressive agents, Human Leukocyte Antigens (HLA) incompatibility, donor gender, and underlying renal disease can be given as examples [5]. IGT before transplantation and the development of hyperglycemia in the perioperative period are increased risk factors for NODAT [6-8]. The risk of developing NODAT is increased by specific drugs administered following organ transplantation, particularly immunosuppressants such as glucocorticosteroids, calcineurin inhibitors like cyclosporine and tacrolimus and mTOR kinase inhibitors like sirolimus and everolimus. Cytomegalovirus (CMV) infection, hepatitis C, male sex of the recipient and donor, and immunological reactions such as acute rejection are other risk factors for the development of NODAT [2, 9, 10].

NODAT increases the risk of major cardiovascular events, graft loss and death after transplantation [11, 12]. Identification of high-risk patients and implementation of measures to reduce the development of NODAT may improve the long-term survival of patients.

The present study aimed to assess NODAT frequency and risk factors in kidney transplant recipients.

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Material and methods. Patients who underwent kidney transplantation at Istanbul Bilim University Faculty of Medicine Hospital between November 2010 and October 2012, were over 18 years of age, had no previous diagnosis of diabetes mellitus, had at least one year of follow-up, and had adequate data in the outpatient follow-up file were included in the study. The patients files were retrospectively reviewed; including information on age, gender, time to NODAT diagnosis, height, weight, body mass index (BMI) values before transplantation, BMI values at post-transplant follow-up, primary disease, history of dialysis, blood group, HLA tissue group, HLA tissue compatibility, age, gender of kidney donor, history of hepatitis B or C in the recipient, pre-transplant thyroid hormones, lipid profiles and post-transplant follow-up, pre and post-transplant magnesium values, pre and post-transplant systolic blood pressures, preoperative fasting, postprandial blood glucose (PBG) and HbA1c values, postoperative 1st week fasting and PBG values, postoperative insulin requirement, postoperative 2nd week, 3rd week, 1st month, 3rd month, 6th month, 12th month and 24th month FPG values, 3rd month and 1st year HbA1c values, 1st month, 3rd month, 6th month, 12th month and 24th month creatinine values, 1st month, 3rd month, 6th month, 12th month and 24th month immunosuppressive drug types and blood levels, pulse steroid history, history of cellular or humoral rejection, history of CMV infection, history of pyelonephritis, antihypertensive use and treatment regimens given to patients for NODAT were recorded.

The data obtained from patient files and hospital computer system records were evaluated using SPSS.20 statistical software. Descriptive statistics were conducted for the available variables, with the study endpoint defined as the development of NODAT. The normality of variable distribution was assessed using the Shapiro-Wilk W-test. Univariate analyses utilized Chi-square, independent samples T-test, and Mann-Whitney U-test. Odds ratios were calculated for these comparisons using multivariate logistic regression. Age, pre-transplant BMI, pre-transplant fasting plasma glucose (FPG), post-transplant FPG, FPG levels during post-transplant weeks 1 through 4, post-transplant 1-month BMI were variables with significant p-values in univariate analysis, which were then converted into dichotomous data (FPG ≥100 mg/dL, <100 mg/dL; postprandial blood glucose (PBG) ≥140 mg/dL, <140 mg/dL; BMI ≥30 kg/m^2, <30 kg/m^2). Because of insufficient sample size and the risk of type II error, only the data with $p<0.05$ (age≥45 years, pre-transplant and 1st month BMI≥30 kg/m^2, pre-transplant impaired FPG, IGT, post-transplant 2nd, 3rd, 4th week impaired FPG, postoperative insulin requirement, 1st-month tacrolimus level) were included in the regression analysis with the backward stepwise elimination LR model. Among the variables with $p>0.1$ at each step, those with the largest p value were excluded from the model. When at least 9 evaluations per variable were considered sufficient for the 12 variables included in the model, it was considered that there was sufficient sample size for multiple regression analysis. Since the standard error values obtained at the end of the analysis were <2.0, it was accepted that there was no collinearity between the variables. Multiple regression analysis results were reported as odds ratio (OR), 95% confidence interval (95% CI), p-value, B coefficient and standard error.

In order to evaluate the predictive risk factors for the diagnosis of NODAT, which was the endpoint of the study, patients were divided into two groups those who developed NODAT during follow-up and those who did not.

Results. Our study cohort consisted of 103 patients undergoing a kidney transplant at the Istanbul Bilim University Faculty of Medicine Hospital between November 2010 and October 2012. There were 31 patients who were diagnosed with diabetes prior to surgery and these were excluded from analysis. The remaining 72 patients were divided into two groups: 17 with NODAT and 55 without NODAT.

Of the 72 patients included in the study, 33 were male (46%) and 39 were female (54%). The mean age of the patients was 40.65±12.6 years. 64 (89%) of the patients had a history of dialysis before transplantation. 8 patients (11%) had preemptive kidney transplantation. 13 patients (18%) had cadaveric transplantation and 59 patients (82%) had kidney transplantation from living donors. Of the kidney donors, 29 were male (40%) and 43 were female (60%). The mean age of the donors was 46.2±13.6 years. 4 patients had a history of hepatitis B (5.6%) and 3 patients had a history of hepatitis C (4.2%).

During at least one year follow-up of the 72 study participants, NODAT developed in 17 patients (23.6%). Among these cases, NODAT was diagnosed in 11 patients (65%) within the first month, 4 patients (24%) within the first 6 months, and 2 patients (11%) within the first year.

No significant differences were observed between NODAT and non-NODAT groups in terms of gender, history of dialysis, history of hepatitis B or C infection, cadaveric or living kidney transplantation, donor age, and donor gender. The risk of NODAT development increased with age ($p<0.0001$) (Table 1).

Table 1

Clinical and demographic characteristics of the patients

Variable	All patients	NODAT (+)	NODAT (-)	P	OR (95% CI)
Number of patients (n, %)	72 (100%)	17 (23.6%)	55 (76.4%)	-	-
Age (years)	40.65 ± 12.6	51.4 ± 12.4	37 ± 10.8	<0.0001	-
≥45 Age (n, %) vs ≤45 Age (n, %)	30(42%) 42(58%)	15 2	15 40	<0.0001	20 (4.0-98.1)
Male (n, %)	33(46%)	8 (47.1%)	25 (45.5%)	0.9	1.06 (0.35-3.17)
Female (n, %)	39(54%)	9 (52.9%)	30 (54.5%)		
Cadaveric transplant (n, %)	13 (18%)	3(17.6%)	10 (18%)	0.9	1.03 (0.25-4.30)
Living transplant (n, %)	59 (82%)	14(82.4%)	45 (82%)		
History of dialysis (n, %)	64 (88.9%)	16 (94.1%)	48 (87.3%)	0.4	2.3 (0.26-20.44)
Age of donor (years)	46.2 ± 13.6	44.7 ± 13.8	46.7 ± 13.7	0.5	-
Donor gender					
Male (n, %)	29 (40%)	8 (47.1%)	21 (38%)	0.5	1.4 (0.48-4.31)
Female (n, %)	43 (60%)	9 (52.9%)	34 (62%)		
History of hepatitis B (n, %)	4 (5.6%)	1 (5.9%)	3 (5.5%)	0.9	1.08 (0.10-11.15)
History of hepatitis C (n, %)	3 (4.2%)	1 (5.9%)	2 (3.6%)	0.6	1.65 (0.14-19.47)

Abbreviations: NODAT: New-onset diabetes after transplantation.

During the pre-transplant period, 15 (21%) patients exhibited impaired fasting plasma glucose (FPG), and 11 (15%) had impaired glucose tolerance (IGT). Among the 17 patients who developed NODAT, 7 (41%) had impaired FPG and 6 (35%) had IGT pre-transplantation. Impaired FPG and IGT prior to transplantation were significantly associated with NODAT development (p<0.0001, p=0.009, respectively) (Table 2).

Table 2

The relationship between NODAT and height, weight, BMI, fasting and postprandial blood glucose and HbA1c levels of the patients before transplantation

Variable	All patients	NODAT (+) (n=17)	NODAT (-) (n=55)	P	OR (%95 CI)
Pre-transplant weight (kg)	64.3 ±13.6	68.9 ±13.7	62.8 ± 13.4	0.1	-
Height (cm)	165.4 ± 9.2	164.4 ± 9.9	165.7 ± 9.1	0.5	-
Pre-transplant BMI kg/m^2	23.5 ± 4.7	25.7 ± 6.1	22.8 ± 3.97	0.02	-
Pre-transplant BMI ≥30kg/m^2	6 (8.3%)	4 (23.5%)	2(3.5%)	0.009	8.1 (1.34-49.45)
Pre-transplant FPG (mg/dL)	89.2 ± 14.9	96.4 ± 24.1	87 ± 9.9	0.02	-
Pre-transplant PBG (mg/dL)	118.4 ± 20.9	132.1 ± 21.3	114 ± 19.1	0.002	-
Pre-transplant HbA1c (%)	5.2 ± 0.49	5.4 ± 0.5	5.2 ± 0.4	0.14	-

Abbreviations: NODAT: New-onset diabetes after transplantation, BMI: Body mass index, FPG: Fasting plasma glucose, PBG: Postprandial blood glucose

While height, weight, and HbA1c levels measured before kidney transplantation did not correlate significantly with NODAT development, body mass index (BMI), FPG, and postprandial blood glucose (PBG) levels were significant risk factors for NODAT. The likelihood of NODAT development was significantly higher in patients with a BMI above 30 compared to those with a BMI below 30 (OR=8.1, p=0.009) (see Table 2). Triglyceride levels, LDL levels, and hypertension, diagnostic criteria for metabolic syndrome, were not statistically significant for NODAT development. Similarly, no significant association was found between low blood magnesium and TSH levels and NODAT development.

A significant correlation was observed between FPG levels during the first, second, and third weeks and PBG levels during the first week of the first month post-transplantation and NODAT development. Likewise, patients requiring temporary insulin during hospitalization after transplantation had a significantly increased risk of developing NODAT (p<0.0001) (Table 3).

Table 3

Postoperative insulin requirements and weekly blood glucose levels during the first month after transplantation and their relationship with NODAT

Variable	All patients	NODAT (+) (n=17)	NODAT (-) (n=55)	P	OR (%95 CI)
1st week FPG (mg/dL)	102.1 ± 21.6	114.2 ± 28.2	98.3 ± 17.8	0.007	-
1st week PBG (mg/dL)	144.2 ± 44.1	175.8 ± 58.8	135.1 ± 34.4	0.001	-
2nd week FPG (mg/dL)	102.6 ± 25.8	119.9 ± 36.1	97.2 ± 19.2	0.001	-
3rd week FPG (mg/dL)	100.2 ± 21.0	120.8 ± 27.8	93.8 ± 13.3	0.0001	-
4th week FPG (mg/dL)	102.7 ± 27.3	120.2 ± 30.9	97.3 ± 23.8	0.002	-
Postoperative insulin requirements (n, %)	11 (15.3%)	8 (47.1%)	3 (5.5%)	<0.0001	15.4 (3.42-69.31)

Abbreviations: NODAT: New-onset diabetes after transplantation, FPG: Fasting plasma glucose, PBG: Postprandial blood glucose

Although there was no correlation between weight and BMI and NODAT development in the first month post-transplantation, the incidence of NODAT was significantly higher in patients with a BMI above 30 (p=0.002) (Table 4).

Table 4

First-month weight and BMI values of patients and their relationship with NODAT

Variable	All patients	NODAT (+) (n=17)	NODAT (-) (n=55)	P	OR (%95 CI)
1st month weight (kg)	64.6 ± 13.2	69.0 ± 12.5	63.2 ± 13.2	p=0.1	-
1st month BMI kg/m2	23.6 ± 4.6	25.8 ± 5.9	22.9 ± 3.9	p=0.09	-
1st month BMI ≥30kg/m^2	7 (9.7%)	5(29%)	2(3.6%)	p=0.002	11.04 (1.90-63.88)

Abbreviations: NODAT: New-onset diabetes after transplantation, BMI: Body mass index

In addition to corticosteroids, all patients received calcineurin inhibitors and antimetabolites for immunosuppression. 66 patients (92%) were treated with tacrolimus and 6 patients (8%) were treated with cyclosporine. Of the patients diagnosed with NODAT, 15 (88%) were receiving tacrolimus and 2 (12%) were receiving cyclosporine. In patients without NODAT, 51 (93%) were on tacrolimus and 4 (7%) were on cyclosporine. No significant difference was found between tacrolimus and cyclosporine use in terms of NODAT development (p=0.5). The mean tacrolimus blood level in the first month was 9.7±3.1 ng/ml, 11.1±3.1 ng/ml in patients who developed NODAT and 9.3±3 ng/ml in patients who did not develop NODAT. A statistically significant correlation was found between the tacrolimus blood level in the first month and the development of NODAT (p=0.04) (Table 5).

Table 5

Association of immunosuppressive therapies and blood levels with NODAT

Variable	All patients	NODAT (+) (n=17)	NODAT (-) (n=55)	P	OR (%95 CI)
Tacrolimus (n, %) Cyclosporine (n, %)	66 (92%) 6 (8%)	15 (88%) 2 (12%)	51 (93%) 4 (7%)	0.5	0.58 (0.09-3.53)
Tacrolimus 1st month level (ng/ml)	9.7±3.1	11.1±3.17	9.3±3.0	0.04	-
Tacrolimus 3rd month level (ng/ml)	8.8±2.7	9.8±3.2	8.5±2.5	0.1	-
Tacrolimus 6th month level (ng/ml)	7.5±2.4	8.8±2.2	7.2±2.4	0.03	-
Tacrolimus 12th month level (ng/ml)	5.7±1.7	6.0±1.7	5.6±1.7	0.4	-
Tacrolimus 24th month level (ng/ml)	5.3±1.5	4.9±1.1	5.4±1.6	0.3	-
Cyclosporine C0 1st month level (ng/ml)	323±185)	318±61	326±236	0.3	-
Cyclosporine C0 3rd month level (ng/ml)	245±49	231±41	252±56.9	0.6	-
Cyclosporine C0 6th month level (ng/ml)	249±105	217±45	266±129	0.8	-
Cyclosporine C0 12th month level (ng/ml)	188±55	189±14	188±70.5	0.8	-
Cyclosporine C0 24th month level (ng/ml)	173±39	201±1.4	155±43.5	0.2	-
Mycophenolate mofetil (n, %) Mycophenolic acid (n, %)	54 18	13 (77%) 4 (23%)	41 (75%) 14 (25%)	0.8	0.90(0.25-3.22)
Steroid pulse (n, %)	23 (31%)	5 (29%)	18 (32%)	0.7	0.85 (0.26-2.80)

Abbreviations: NODAT: New-onset diabetes after transplantation

In the follow-up of patients who developed NODAT, a significant difference in tacrolimus levels was found at month 6 compared to patients without NODAT (p=0.03), but this difference was not observed at months 3, 12 and 24. While 29% of patients with NODAT received pulse steroid treatment, there was no significant difference compared to patients without NODAT (p=0.7) (Table 5). Similarly, no association was found between acute cellular and humoral rejection and the development of NODAT (p=0.2, p=0.3 respectively).

While the frequency of NODAT was increased in patients with CMV infection (12%) compared to those who did not develop NODAT (2%), it was not statistically significant (p=0.07).

In univariate analysis, age≥45 years (p<0.0001), pre-transplant and 1st month BMI≥30kg/m2 (p=0.009, p=0.002), postoperative insulin requirement (p<0.0001), pre-transplant and 2nd, 3rd, 4th week Impaired FPG (p<0.0001, p=0.001, p=0.004, p<0. 0001), pre-transplant IGT (p=0.0001, p=0.001, p=0.004, p<0.0001), pre-transplant IGT (p=0.009) and tacrolimus blood level≥10ng/dl (p=0.006) were statistically significant in relation to the risk of developing NODAT.

Multivariate analysis revealed that age ≥45 years (p=0.01), pre-transplant impaired FPG (p=0.001), post-transplant insulin requirement (p=0.01) and tacrolimus level in the first month (p=0.04) were statistically significant independent risk factors for the development of NODAT (Table 6).

Table 6

Multivariate analysis results

Variable	Coefficient value	Standard mistake	HR	95% CI Lower limit	95% CI Upper limit	p
Age≥45	2.772	1.161	15.99	1.64	155.55	0.01
Pre-transplant Imparied FPG	3.709	1.158	40.82	4.21	395.23	0.001
Perioperative insulin requirement	3.354	1.336	28.6	2.087	392.08	0.01
1st month Tacrolimus level	0.337	0.164	1.4	1.016	1.93	0.04

Abbreviations: FPG: Fasting plasma glucose

Discussion. In previous studies, the incidence of NODAT was reported between 4% and 25% in renal transplant recipients, 2.5% and 25% in liver transplant recipients, 4% and 40% in heart transplant recipients, and 30% and 35% in lung transplant recipients [1, 2, 3, 13]. In our study, the prevalence of NODAT was 23.6%, which is similar to other studies.

Studies from the Organ Procurement and Transplantation Network / United Network for Organ Sharing database found that the relative risk increased by 90% in kidney recipients aged 45-49 years and by 160% in those aged over 60 years compared with kidney recipients aged 18-44 years [11]. Another study showed that the risk of NODAT increased 1.5-fold every 10 years with increasing age [14]. Similarly, the incidence of NODAT increased with age in our study. While 42% of our patients were aged 45 years or older, 50% of these patients were diagnosed with NODAT. As a result of univariate and multivariate analyses of our study, it was found that the development of NODAT increased 16-fold at the age of 45 years and older. This finding was similar to studies in the literature.

In the retrospective study conducted by Tokodai and colleagues on 158 kidney transplant patients, a significant relationship was found between the increase in BMI and the development of NODAT [15]. In our study, univariate analyses revealed that the pre-transplant BMI value was statistically higher in patients who developed NODAT compared to those who did not. No statistically significant difference was found between the BMI in the 1st month and the development of NODAT.

In a single-center retrospective study involving 254 kidney transplant patients conducted by Van Laecke and colleagues, it was demonstrated that hypomagnesemia in the first month after transplantation is associated with the development of NODAT, independent of the immunosuppressive regimen [16]. In a subsequent study by the same authors, pre-transplant hypomagnesemia and hypomagnesemia in the first month after liver transplantation were identified as independent risk factors for NODAT [17]. Post-transplant hypomagnesemia is often associated with the use of calcineurin inhibitors. In our study, hypomagnesemia was not found to be a significant risk factor for the development of NODAT. There was no difference in magnesium levels between patients who developed NODAT and others during their follow-up.

The diabetogenic effects of CMV infection on pancreatic beta cells are known [18]. In previous studies, asymptomatic CMV infection has been found to increase the risk of NODAT by 4 times [19]. In our study, no association was found between NODAT and symptomatic or asymptomatic CMV infection. This may be due to our limited sample size or the fact that a significant portion of patients received valganciclovir prophylaxis in the first three months after transplantation.

It is believed that Hepatitis C infection has a diabetogenic effect, especially when used in conjunction with tacrolimus [20]. In our study, no significant relationship was found between Hepatitis C infection and NODAT. This may be attributed to our limited number of Hepatitis C patients and our use of cyclosporine instead of tacrolimus in patients with known Hepatitis C, which could have led to no observed increase in the frequency of NODAT development.

In a study involving 490 kidney transplant patients conducted by Cosio and colleagues, it was demonstrated that elevated pre-transplant glucose levels are a risk factor for the development of NODAT in the first year. When pre-transplant plasma FPG levels between 90mg/dl and 100mg/dl were considered as a reference, individuals with plasma glucose <90mg/dl were found to have a low risk for NODAT development (OR=0.46, p=0.01). As plasma glucose levels increased, an increase in the risk of NODAT was observed (FPG=101-109, OR=1.5, and FPG=110-125, OR=7.6, p<0.0001) [21]. In our study, similarly, both univariate and multivariate analyses revealed an increased risk of NODAT in individuals with impaired FPG (100-125mg/dl) pre-transplant (p<0.0001, OR=14). For those with IGT (PBG 140-199mg/dl), univariate analyses also showed a similar increase in the risk of NODAT (p=0.009, OR=5).

Post-transplant early glucose measurements may serve as predictors for the development of NODAT [22]. In a study by Rodrigo and colleagues, monitoring 208 kidney transplant patients without diabetes prior to transplantation, an FPG>126 on the 5th day was found to be associated with a 4-fold increase in the risk of NODAT [23]. In the study by Kuypers and colleagues, the normal finding of oral glucose tolerance tests on the 5th day was determined to reduce the risk of NODAT [10]. In our study, univariate analyses revealed a statistically significant relationship between post-transplant fasting blood glucose elevation in the 1st, 2nd, 3rd, and 4th weeks and PBG elevation in the 1st week with the development of NODAT.

The risk of NODAT is increased in patients with postoperative hyperglycemia requiring insulin use [8]. In one study, among 23 patients with perioperative transient hyperglycemia, 11 developed persistent hyperglycemia after maintaining normoglycemia for 6-12 months [7].

In our study, both univariate and multivariate analyses revealed an increased frequency of NODAT development in patients requiring insulin during the early postoperative period, specifically during the hospitalization period (p=0.01, HR=28). Although perioperative hyperglycemia may develop due to immunosuppressive protocols, it can assist in identifying patients at an increased risk for NODAT.

In a retrospective study conducted with patients from the OPTN/SRTR database, a significant decrease in the risk of NODAT was observed when patients receiving a steroid-free immunosuppressive regimen were compared to those receiving a steroid-based regimen [24].

In our patient group, as there was no steroid-free regimen, the impact of steroid treatment on NODAT could not be evaluated.

The use of calcineurin inhibitors, cyclosporine, and tacrolimus, is a known risk factor for the development of NODAT [14]. Compared to cyclosporine, tacrolimus generally has a more diabetogenic effect [25-28]. In our study, the number of patients using cyclosporine was very small compared to those using tacrolimus (1:11), so a statistically significant relationship between the two drugs and NODAT development could not be found. Similar to other studies, a statistically significant relationship between the 1-month level of tacrolimus and the development of NODAT was found in both univariate and multivariate analyses (p=0.04, HR=1.4). There is a strong association between increasing levels of tacrolimus and IGT and NODAT. In one study, it was demonstrated that a blood tacrolimus level above 15 ng/ml is significant for the risk of glucose intolerance (15%) and NODAT (32%) in the first year [29]. In our study, in univariate analyses, an increase in NODAT development was found in those with a 1-month tacrolimus level of 10 ng/ml and above (p=0.006, OR=5.5).

Our study has several limitations. These include the small number of patients included, as well as the study being designed as a single-center, retrospective analysis. While our findings generally align with existing literature on NODAT, some discrepancies were noted due to the constraints of our study design.

Conclusions. NODAT presents a significant complication post-solid organ transplantation. Our study revealed that 23.6% of kidney transplant recipients develop this complication, with age over 45 years identified as an unmodifiable independent risk factor for diabetes development. Pre-transplant impaired FPG, perioperative insulin requirement, and first-month tacrolimus blood concentration were identified as independent factors associated with the development of NODAT. Given the association of diabetes with increased risk of cardiovascular complications, graft rejection, mortality, and reduced quality of life, it is crucial to identify high-risk patients and implement measures to mitigate NODAT development, ultimately enhancing long-term patient prognosis.

Conflict of interest statement. The authors declare that there are no competing interests associated with the manuscript.

Data availability statement. The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

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The authors' contributions.

Fatih Gokhan AKBAY: The study design, samples collection and data curation, writing the manuscript, data interpretation, and drafting of the work;

Zeki Toprak: Writing the manuscript, data interpretation, drafting, and revising. All authors read and approved the final manuscript.

Pinar Seymen: The study design, manuscript reviewing.

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