ORIGINAL RESEARCH

Risk Factors of New-onset Diabetes After Renal Transplantation and Prognostic Analysis

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ABSTRACT

Context • New-onset diabetes after transplantation (NODAT) is one of the most common complications after renal transplantation and in kidney-transplant recipients is closely related to long-term adverse outcomes for recipients and transplants. The risk factors for NODAT still require exploration.

Objectives • The study intended to explore the risk factors for new-onset diabetes after transplantation (NODAT) for patients receiving a renal transplantation, to provide a theoretical basis for reducing the incidence rate of NODAT and promoting a better outcome for patients.

Design • The research team designed a retrospective study using clinical data of patients receiving renal transplantation at a hospital.

Setting • The study took place in the Department of Urology at Xuanwu Hospital at Capital Medical University in Beijing, China.

Participants • Participants were 396 patients who had undergone renal transplantation at the hospital, of whom 28 had NODAT syndrome, the NODAT group, and 368 didn't meet the diagnostic criteria for NODAT, the N-NODAT group.

Outcome Measures • The research team calculated the incidence rate of NODAT and determined the causes of the disease, evaluated participants' preoperative risk factors—gender, preoperative systolic blood pressure (SBP), preoperative diastolic blood pressure (DBP), height, family history of diabetes, weight, smoking habits, age, drinking habits, pretransplant body mass index (BMI), preoperative fasting blood glucose, triglycerides (TG), total cholesterol (TC)—and their postoperative risk factors—acute rejection, use of immunosuppressive agents, blood CsA concentration, blood FK506 concentration, and renal function. Additionally, the team subjected the data in the two groups to univariate, logistic regression analysis and to multivariate, unconditional, logistic regression analysis to discover risk factors for NODAT.

Results • Among the 396 participants, 28 had NODAT (7.1%), and 368 didn't suffer NODAT (92.9%). Statistically significant differences existed between the groups in participants' ages (0.013), weights (P=.032), smoking habits (P = .034), drinking habits (P = .034), BMIs (P = .023), preoperative fasting blood glucose (P < .05), preoperative TG (P<.05), and preoperative TC (P<.01). In the univariate logistic regression analysis, significant associations existed between age (P = .016), weight (P = .033), BMI (P = .025), smoking habits (P = .035), drinking habits (P = .043), preoperative fasting blood glucose (P = .048), preoperative TG (P = .049), preoperative TC (P = .009), acute rejection (P = .009), and immunosuppressive agents (P = .012) and the occurrence of NODAT (P < .05). In the multivariate unconditional logistic stepwise regression analysis, acute rejection (P = .011) and use of FK506 in immunotherapy (P = .013) were independent risk factors for NODAT.

Conclusions • The risk factors of NODAT include age, weight, BMI, smoking habits, drinking habits, preoperative fasting blood glucose, preoperative TG, preoperative TC, acute rejection and exposure to immunosuppressive agents. Among them, only acute rejection and immunosuppressive agents are modifiable factors. The application of CsA as an immunosuppressive agent after surgery may decrease the incidence rate of NODAT and prolong the longevity of patients receiving renal transplantation. (*Altern Ther Health Med.* 2023;29(2):230-235)

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Renal transplantation is the best renal-replacement therapy for patients with end-stage renal diseases and can have a positive impact on the survival of the patients and the quality of life of patients and their families.[1]

However, renal transplantation also can result in complications that have associations with surgical and medical factors and that can occur in an early or late stage

after transplantation. New-onset diabetes after transplantation (NODAT) is one of the most common complications after renal transplantation. It refers to sustained hyperglycemia after surgery in patients without a history of diabetes in organ-transplant recipients.

NODAT's cumulative incidence rate is 7.9-50%.[2-4] The occurrence of NODAT in kidney-transplant recipients is closely related to long-term adverse outcomes for recipients and transplants.[3-5] As a major complication, NODAT affects both the life of the transplanted kidney and the survival of patients and elevates the risk of cardiovascular diseases. In addition, renal transplantation increases the risk of diabetes in patients with normal pretransplant blood glucose, which has an association with immunosuppressive agents used after transplantation.[6]

Diabetes is a risk factor for postoperative cardiovascular diseases.[7] Cohen et al found that diabetes can result in reduced function or dysfunction of the transplanted kidney, lowering the postoperative survival rate of patients.[8] In addition, Duan et al found that patients with NODAT are more likely to have diabetes complications than other patients.[9] In addition, incidental NODAT directly brings additional financial burdens to patients.[10]

NODAT's Risk Factors

Up to now, researchers have identified several risk factors for NODAT, including the age of recipients, a family history of diabetes, obesity, high preoperative fasting blood glucose, and long-term exposure to immunosuppressive agents.[11,12]

Age. Ouni et al found that the incidence of NODAT increased by 29% with every increase of 10 years in age.[13] In addition, the risk of diabetes is higher in young patients than that in adult patients.[13]

Family history. A positive family history of diabetes in first- or second-degree relatives is an unmodifiable risk factor and is related to a high risk of NODAT in adults and children.[13] African-American and Caucasian patients have a higher risk of NODAT than Hispanic patients.[5]

Obesity. Ouni et al also found that a relationship exists between obesity and NODAT; a body mass index (BMI) ≥30 kg/m2 can be connected to the occurrence of NODAT.[13,14]

High preoperative fasting blood glucose. Ouni et al also found that impaired preoperative fasting blood glucose is an independent risk factor for NODAT.[13] Gierczak et al found that preoperative triglycerides (TG) and preoperative total cholesterol (TC) are risk factors for NODAT because the increase in blood lipids can suppress the synthesis and secretion of insulin and promote the apoptosis of insulin β cells.[15]

Long-term exposure to immunosuppressive agents. Gierczak et al found that the incidence rate of NODAT is 30% and 18% of adult patients who receive cyclosporine A (CsA) and tacrolimus (FK506), respectively, in the first year after transplantation.[15] Zolota et al also found tacrolimus to a risk factor.[16] Two other studies also found immunosuppressive agents to be a risk factor, including glucocorticoids[17] and sirolimus.[18]

Other risk factors. Other risk factors include patients having hepatitis C[10] and cytomegalovirus infection.[19] Moreover, some other diseases also contribute to a high incidence of NODAT, including cystinosis, hemolytic uremic syndrome, and autosomal, recessive, polycystic kidney disease.[20,21]

Marin found that NODAT has a close relationship with acute rejection after transplantation.[22] Chanchlani et al found that organ rejection can result in impaired function of the transplanted kidney, weakening the ability of the kidney to degrade insulin and glucagon and giving rise to an abnormal glucose metabolism.[23]

Current Study

NODAT has attracted a great amount of attention of doctors and aroused the interest of many scholars. Age, weight, BMI, smoking habits, drinking habits, preoperative fasting blood glucose, preoperative TG, and preoperative TC are unmodifiable factors in the short term before surgery, while acute rejection and immunosuppressive agents are modifiable factors.

The current study intended explore the risk factors for new-onset diabetes after transplantation (NODAT) for patients receiving a renal transplantation, to provide a theoretical basis for reducing the incidence rate of NODAT and promoting a better outcome for patients.

METHODS

Participants

The research team designed a retrospective study using clinical data of patients receiving renal transplantation at a hospital. The study took place in the Department of Urology at Xuanwu Hospital at Capital Medical University in Beijing, China. Potential participants were patients who had undergone renal transplantation at the hospital.

Potential participants were included in the study if they: (1) had undergone renal transplantation for the first time, (2) had been available for follow-up for 6 months after the surgery.

Potential participants were excluded from the study if they: (1) were aged ≤18 years old, (2) had incomplete clinical data available, (3) were not born and residing in China, (4) had a history of diabetes before the operation, (5) had taken glucocorticoids before surgery or diuretics after surgery, (6) had undergone multiple transplantations, or (7) had dysfunction of the transplants within half a year after surgery, had interrupted follow-up midway, or had died.

All participants signed written informed consent forms before the study. The ethics committee of Xuanwu Hospital at Capital Medical University (XW-EC-01) approved the study's protocols.

Procedures

Data collection. The research team collected the clinical data of patients receiving renal transplantation in the hospital through follow-up.

Diagnostic criteria for NODAT and grouping. The World Health Organization (WHO) considers NODAT to be secondary diabetes meeting the diagnostic criteria for diabetes after surgery, excluding acute dysglycemia.[3]

Groups. The research team grouped the participants in accordance with the diagnostic criteria for NODAT. The NODAT group included patients with NODAT syndrome, whereas patients who didn't meet the diagnostic criteria for NODAT became the N-NODAT group.

Basic epidemiological data of participants. The research team collected participants' basic demographic and clinical data, including age, gender, height, weight, smoking habits, drinking habits, pretransplant BMI, causes of kidney disease before surgery, preoperative systolic blood pressure (SBP), preoperative diastolic blood pressure (DBP), family history of diabetes, preoperative fasting blood glucose, preoperative triglycerides (TG), and preoperative total cholesterol (TC).

Clinical biochemical examination of blood. During organ transplantation, medical staff must follow the principles of blood transfusion.

The medical staff collected participants' blood to measure preoperative fasting blood glucose, preoperative TG, preoperative TC, postoperative renal function, and postoperative blood cyclosporine A (CsA) concentration and blood FK506 concentration.

Immunotherapy plans. After renal transplantation, the medical staff conducted the immunotherapy as follows: (1) intravenously injected 1000 mg of methylprednisolone on the day of and 500 mg/d on the next two days after the renal transplantation; (2) administered 30 mg/d of prednisone orally on day 4 after transplantation; the dosage of prednisone decreased to 20 mg/d after one month and 5-10 mg/d after one year; (3) on the third day after transplantation, orally administered FK506 at 0.1 mg/(kg·d-1) or CsA at 5 mg/(kg·d-1) + mycophenolate mofetil (MMF) at 1.5-2.0 g/d, with the oral dose being adjusted according to patients' blood concentrations. For the hormone treatment plan, patients received 15-20 mg/d of methylprednisolone until clinical symptoms or biological indicators changed.

Outcome measures. The research team calculated the incidence rate of NODAT and determined the disease's causes, evaluated participants' preoperative risk factors—gender, preoperative systolic blood pressure (SBP), preoperative diastolic blood pressure (DBP), height, family history of diabetes, weight, smoking habits, age, drinking habits, pretransplant body mass index (BMI), preoperative fasting blood glucose, preoperative TG, preoperative TC—and their postoperative risk factors—acute rejection, use of immunosuppressive agents, blood CsA concentration, blood FK506 concentration, and renal function.

Statistical Analysis

The research team processed and analyzed all experimental data scientifically using Statistical Product and Service Solutions (SPSS) 26.0 software (SPSS, Chicago, IL, USA). The team: (1) expressed the data as means ± standard deviations (SDs) or numbers and percentages (%), (2) used the *t* test and chi-square test to analyze the two independent samples, and (3) subjected the groups' data to univariate logistic regression analysis and multivariate, unconditional, logistic regression analysis to discover the risk factors related to NODAT. $P < .05$ indicated that the difference was statistically significant.

Table 1. Comparisons of Demographic and Clinical Characteristics Between the NODAT and N-NODAT Groups as Pre-operative Risk Factors for NODAT (N = 396)

Characteristics	NODAT Group n = 28 Mean ± SD n (%)	N-NODAT Group n = 368 Mean ± SD n (%)	*P* value	χ^2/t
Age, y	50.3 ± 6.2	38.5 ± 8.5	.013[a]	-2.182
Gender				
Male	15 (53.6)	218 (59.2)	.231	5.423
Female	13 (46.4)	150 (40.8)	.134	-0.456
Weight, kg	63.2 ± 7.5	51.3 ± 8.4	.032[a]	-2.576
Height, cm	172.3 ± 6.3	173.1 ± 7.9	.897	-1.106
Smoking			.034[a]	-2.892
Yes	10 (35.7)	60 (16.3)		
No	18 (64.3)	308 (83.7)		
Drinking			.042[a]	-2.564
Yes	9 (32.1)	69 (18.8)		
No	19 (67.9)	299 (81.2)		
BMI, kg/m2	30.5 ± 5.3	23.4±4.3	.023[a]	-3.569
Preoperative SBP, mmHg[b]	102.2 ± 11.3	103.7 ± 9.9	.637	0.164
Preoperative DBP, mmHg[b]	73.3 ± 8.3	65.3 ± 7.4	.458	0.358
Family history of DM			.834	0.274
Yes	2 (7.1)	25 (6.8)		
No	26 (92.9)	343 (93.2)		

[a]$P < .05$, indicating that the NODAT group's demographic and clinical characteristics were significantly different from those of the N-NODAT group

[b]One mmHg = 0.133 KPa

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; NODAT, new-onset diabetes after transplantation; N-NODAT, no new-onset diabetes after transplantation; SBP, systolic blood pressure.

RESULTS

Demographic and Clinical Characteristics

Among the 396 participants, 28 had NODAT (7.1%), and 368 didn't suffer NODAT (92.9%). The fasting blood glucose of some cases was higher than a normal level during the 6 months after transplantation, but it had returned to a normal level by 6 months after transplantation, after a reduction in the dose of hormones; these patients weren't included in NODAT group.

As Table 1 shows, no statistically significant differences existed between the NODAT and N-NODAT groups in gender, height, preoperative SBP, preoperative DBP, or family

Table 2. Comparisons of Other Preoperative Risk Factors Between NODAT and N-NODAT Groups (N=396)

Group	n (%)	Preoperative Fasting Blood Glucose		Preoperative TG		Preoperative TC	
		Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
NODAT	28 (7.1)	10 (35.7)	18 (64.3)	8 (28.6)	20 (71.4)	5 (17.9)	23 (82.1)
N-NODAT	368 (92.9)	258 (70.1)	110 (29.9)	248 (67.4)	120 (32.6)	191 (51.9)	177 (48.1)
P value		<.05[a]		<.05[a]		<.01[a]	

[a]$P < .05$, indicating that the NODAT group's preoperative fasting blood glucose, preoperative TG, and preoperative TC were significantly higher than those of the N-NODAT group

Abbreviations: NODAT, new-onset diabetes after transplantation; N-NODAT, no new-onset diabetes after transplantation; TG, triglycerides.

Figure 1. Incidence Rate of NODAT After Renal Transplantation

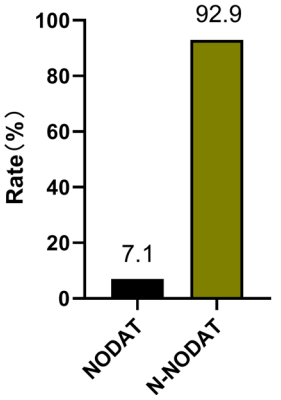


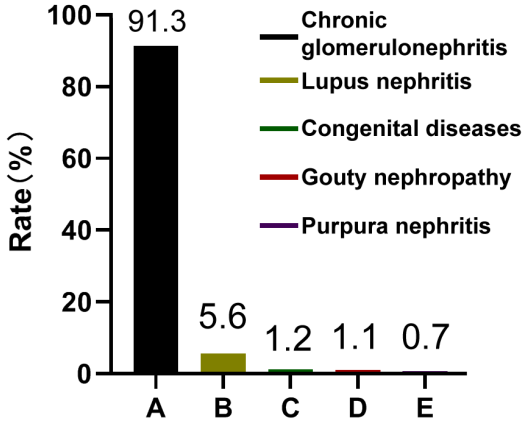
Table 3. Comparisons of Postoperative Risk Factors Between NODAT and N-NODAT Groups (N = 396)

Postoperative Risk Factor		NODAT Group n = 28 n (%)	N-NODAT Group n = 368 n (%)	*P* value	χ^2/t
Acute Rejection	No	15 (53.6)	263 (71.5)	.008[a]	-8.367
	Yes	13 (46.4)	105 (28.5)		
Immunosuppressive Agents	CsA	12 (42.9)	228 (62.0)	.01[a]	-7.384
	FK506	16 (57.1)	140 (38.0)		
Blood CsA concentration	Normal	15 (53.6)	183 (49.7)	.563	2.156
	Abnormal	13 (46.4)	185 (50.3)		
Blood FK506 Concentration	Normal	13 (46.4)	195 (53.0)	.423	1.897
	Abnormal	15 (53.6)	173 (47.0)		
Renal Function	Normal	16 (57.1)	175 (47.6)	.489	2.039
	Abnormal	12 (42.9)	193 (52.4)		

[a]$P < .05$, indicating that the NODAT group's postoperative acute rejections of the transplants and use of FK506 as the immunosuppressive agent compared to use of CsA were significantly higher than those of the N-NODAT group

Abbreviations: CsA, cyclosporine A; FK506, tacrolimus; NODAT, new-onset diabetes after transplantation; N-NODAT, no new-onset diabetes after transplantation.

Figure 2. Causes of NODAT After Renal Transplantation



history of diabetes ($P > .05$). However, statistically significant differences existed between the groups in participants' ages (0.013), weights ($P = .032$), smoking habits ($P = .034$), ages ($P = .13$), drinking habits ($P = .042$), and BMIs ($P = .023$).

Other Preoperative Risk Factors

As Table 2 shows, the NODAT group's preoperative fasting blood glucose ($P < .05$), preoperative TGs ($P < .05$), and preoperative TCs ($P < .01$) were significantly higher than those of the N-NODAT group

Incidence of NODAT

As Figure 1 shows, 28 patients had NODAT after renal transplantation (7.1%), and the N-NODAT group included 368 participants (92.9%). The participants in the NODAT group all needed to take insulin to control blood glucose at a normal level after treatment.

Causes of NODAT

As Figure 2 shows, the causes of NODAT included chronic glomerulonephritis (91.3%), lupus nephritis (5.6%), congenital diseases (1.2%), gouty nephropathy (1.1%), and purpura nephritis (0.7%).

Postoperative Risk Factors

For the analysis on postoperative risk factors, Table 3 shows that the NODAT group's postoperative acute rejection of the transplant ($P = .08$) and use of FK506 as the immunosuppressive agent compared to use of CsA were significantly higher than those of the N-NODAT group. However, no statistically significant differences existed between the two groups in blood CsA concentration, blood FK506 concentration, and renal function ($P > .05$).

Univariate Analysis

Table 4 shows that no significant correlations existed between gender, height, preoperative SBP, preoperative DBP, or family history of diabetes and the occurrence of NODAT ($P > .05$). However, significant associations existed between age ($P = .016$), weight ($P = .033$), BMI ($P = .025$), smoking habits ($P = .035$), drinking habits ($P = .043$), preoperative fasting blood glucose ($P = .048$), preoperative TG ($P = .049$), preoperative TC ($P = .009$), acute rejection ($P = .009$), and immunosuppressive agents ($P = .012$) and the occurrence of NODAT ($P < .05$).

Additionally, the risk of NODAT was 2.421 times higher in patients with FK506 as the immunosuppressive agent than that in patients with CsA as the immunosuppressive agent (data not shown). In addition, compared with participants without acute rejection after surgery, the risk of NODAT was 3.632 times higher in participants with acute rejection after surgery (data not shown).

Multivariate Analysis

The multivariate unconditional logistic stepwise regression analysis showed that acute rejection ($P = .011$) and use of FK506 in immunotherapy ($P = .013$) were independent risk factors for NODAT (Table 5).

Table 4. Risk Factors in NODAT and N-NODAT Groups Analyzed Using Univariate Logistic Regression Analysis

Variable	β	Wald	*P* value	OR (95% CI)
Age	0.958	5.849	.016[a]	2.764 (1.064-5.067)
Gender	0.589	2.576	.127	1.853 (0.735-3.876)
Weight	0.879	5.312	.033[a]	2.427 (0.892-4.753)
Height	0.743	4.125	.728	3.427 (1.222-6.352)
BMI	0.954	6.728	.025[a]	2.409 (1.154-4.838)
Smoking	1.038	7.051	.035[a]	2.473 (1.078-5.024)
Drinking	1.046	7.232	.043[a]	2.532 (1.329-5.623)
Preoperative fasting blood glucose	0.986	6.875	.048[a]	2.496 (1.086-6.032)
Preoperative TG	1.085	7.352	.049[a]	2.543 (1.312-5.725)
Preoperative TC	0.786	4.682	.009[a]	1.572 (0.325-2.735)
Preoperative SBP	0.023	0.634	.532	0.856 (0.838-1.085)
Preoperative DBP	-0.143	1.213	.476	0.893 (0.952-1.428)
Family history of DM	0.894	4.536	.848	2.351 (1.043-5.847)
Acute rejection (FK506)	1.345	0.493	.009[a]	3.632 (1.218-8.432)
Immunosuppressive agents	0.951	5.347	.012[a]	2.421 (1.134-4.837)

[a]$P < .05$, indicating using univariate logistic regression analysis that the NODAT group's pre-operative and postoperative risk factors were significantly associated with the occurrence of NODAT

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FK506, tacrolimus; NODAT, new-onset diabetes after transplantation; N-NODAT, no new-onset diabetes after transplantation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 5. Risk Factors in NODAT and N-NODAT Groups Analyzed Using Multivariate, Unconditional, Logistic Stepwise Regression Analysis

Variable	β	Wald	*P* value	OR (95% CI)
Acute rejection	1.325	6.432	.011[a]	3.611 (1.202-8.632)
Immunotherapy (FK506)	0.735	4.865	.013[a]	2.123 (1.142-4.731)

[a]$P < .05$, indicating using multivariate, unconditional, logistic stepwise regression analysis that the NODAT group's postoperative risk factors were significantly associated with the occurrence of NODAT

Abbreviations: FK506, tacrolimus; NODAT, new-onset diabetes after transplantation; N-NODAT, no new-onset diabetes after transplantation.

DISCUSSION

In the present study, the incidence rate of NODAT was 7.1%; 28 of 396 patients suffered NODAT after renal transplantation. The low incidence rate of NODAT in the current study may have been due to the fact that some patients weren't included in the NODAT group because their higher-than-normal glucose level after transplantation had returned to a normal level by 6 months after transplantation after a reduction in the dose of hormones.

In concurrence with Ouni et al's finding,[13] the present study found that older patients were more prone to NODAT, which confirms that the repair of postoperative B cell function impairment can depend on the age.

The current study found that weight, smoking habits, drinking habits, BMI, preoperative fasting blood glucose, preoperative TG, and preoperative TC were closely related to the occurrence of NODAT, and they might be risk factors for NODAT. Therefore, medical practitioners should encourage patients to change these factors before surgery, which may reduce the incidence rate of NODAT.

The current study found that acute rejection and FK506 used in immunotherapy were independent risk factors for NODAT. This implies that medical practitioners should pay attention to the application of immunosuppressive agents and the prevention of acute rejection in patients after transplantation.

There are still limitations existed in this study. The sample size of the enrolled participants of NODAT group was only 38, additionally, the length of the follow-up was not long. What's more, this was not a multi-center study, which weakened the evidence level of our findings. In the future, we plan to conduct a multi-center study and make further analyzes based on a larger sample size.

CONCLUSIONS

The risk factors for NODAT include age, weight, BMI, smoking habits, drinking habits, preoperative fasting blood glucose, preoperative TG, preoperative TC, the occurrence of acute rejection, and the type of immunosuppressive agents. Among them, age, weight, BMI, smoking, drinking, preoperative fasting blood glucose, preoperative TG and preoperative TC are unmodifiable factors, while acute rejection and immunosuppressive agents are modifiable factors. The application of CsA as an immunosuppressive agent after surgery may decrease the incidence rate of NODAT and prolong the longevity of patients receiving renal transplantation.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest related to the study.

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