Pretransplant Homeostasis Model Assessment of Insulin Resistance and Fasting Plasma Glucose Predict New-Onset Diabetes After Renal Transplant in Chinese Patients

R. Cai[a], M. Wu[b], M. Lin[a], X. Guo[a], and Y. Xing[c,*]

[a]Department of Organ Transplantation, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; [b]Department of Nephrology, Longyan First Hospital, Longyan, Fujian, China; and [c]Department of Nephrology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China

ABSTRACT

Background and Aim. The present study aims to determine if homeostasis model assessment of insulin resistance (HOMA-IR) index, fasting plasma glucose (FPG), and plasma insulin (Ins) are able to predict development of new onset diabetes after transplant (NODAT) for kidney recipients.

Methods. We performed a single-center retrospective study of 123 nondiabetic patients receiving a first renal transplant. The NODAT was diagnosed between 1 month and 1 year post transplant. Both univariate and multivariable analyses, including logistic regression analysis and Cox proportional hazards model, were applied to dissect potential pretransplant risk factors of NODAT.

Results. A total of 26.8% (33/123) of recipients developed NODAT in the first year post transplant. The NODAT patients showed higher HOMA-IR index and increased levels of FPG and Ins than non-NODAT. Interestingly, we consistently revealed that both FPG (logistic: odds ratio [OR], 3.17 [1.41–6.45]; $P = .01$; Cox: OR, 2.75 [1.26–4.56]; $P = .02$) and HOMA-IR index (logistic: OR, 1.73 [1.21–2.87]; $P = .02$; Cox: OR, 1.72 [1.21–2.46]; $P = .002$) robustly predicted the development of NODAT. However, these analyses showed that neither plasma Ins nor hemoglobin A_{1c} was associated with NODAT.

Conclusion. Our findings suggest that pretransplant HOMA-IR and FPG are independent predictors for the development of NODAT in Chinese nondiabetic patients receiving a first renal transplant.

NEW-ONSET diabetes after transplant (NODAT) remains one of the most common complications following kidney transplant [1,2]. A majority (15%–30%) of nondiabetic recipients develop NODAT in the first year after renal transplant [3,4]. It has been documented that NODAT is frequently associated with subsequent graft failure, increased mortality rate, and huge economic burden on recipients [3–5].

There are compelling reasons to develop clinical strategies for prevention of NODAT. Because NODAT mainly develops in the first year after transplant, pretransplant risk factors are considered to contribute to its development [6–8]. Currently, the established pretransplant risk factors of NODAT include older age [3,7,9,10]; minority race [3,11]; higher body mass index (BMI) [3,7–9]; family history of diabetes mellitus (DM) [7,9,12]; elevated fasting plasma glucose (FPG), triglycerides, and cholesterols [3,6,7,9,10]; and increased fasting insulin (Ins) [13]. Apparently, these risk factors are primarily components of metabolic

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*Address correspondence to Yanfang Xing, No. 63 Duobao Rd, Liwan District, Guangzhou 510150, Guangdong, China. Tel: 86-020-81292889. E-mail: 2574410512@qq.com

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syndrome that underlie type 2 diabetes mellitus (T2DM). Identification of the pretransplant modifiable risk factors may allow timely intervention for prevention of NODAT. For example, it is suggested that lifestyle modification (eg, restrained calories intake and moderate-intense physical activity) before transplant aiming to reduce BMI may lower the incidence of NODAT [1].

Homeostasis model assessment of insulin resistance (HOMA-IR) is strongly correlated with insulin resistance and is a reliable predictor of T2DM [14–17]. An elevated FPG as well as increased Ins are risk factors of NODAT as aforementioned; it is expected that HOMA-IR should be able to predict NODAT. However, previous studies have provided different results. Nagaraja et al demonstrated that HOMA-IR calculated before transplant and at 3 months post transplant did not predict NODAT [18], while positive results were also obtained that HOMA-IR was an independent risk factor of NODAT [8,19]. Therefore, the predictive power of HOMA-IR for NODAT remains to be explored.

The current study aims to determine whether the pretransplant variable, HOMA-IR, as well as its related parameters (FPG and Ins), are able to predict NODAT in a retrospective cohort of Chinese nondiabetic patients receiving a first kidney transplant.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the clinical records of 297 patients undergoing a renal transplant at the Department of Organ Transplantation, The Third Affiliated Hospital of Guangzhou Medical University between 2010 and 2016. Clinical information for each recipient was retrieved and assembled from the local electronic database, which was approved by the local Ethics Committee. All recipients provided written informed consent before organ transplant. Exclusion criteria included recipients 1. with a history of DM or with DM before the renal transplant, 2. with allograft functioning no more than 1 year, 3. with a history of renal transplant, 4. with other solid organ transplant(s), 5. with no more than 1 year of follow-up post transplant, and 6. with incomplete data of FPG or Ins. Finally, data from 123 nondiabetic recipients receiving a first renal transplant were assembled and analyzed. Characteristics of the study cohort are shown in Table 1.

Immunosuppression

All included recipients were on a tacrolimus-based regimen as their initial immunosuppressant treatment. Generally, doses of tacrolimus were titrated to plasma levels of 8 to 15 ng/mL during the first 6 months and titrated to 5 to 7 ng/mL by the first year. At the time of transplant, recipients also received mycophenolate mofetil as well as a 5-day tapering course of glucocorticoids (intravenous methylprednisolone 500 mg, 250 mg, and 125 mg on day 1, day 2, and day 3, respectively; oral prednisone 60 mg on day 4 and 30 mg on day 5). For those requiring ongoing steroid therapy, a maintenance dose of 5 mg prednisone daily was applied by 3 months post transplant.

Definition of NODAT

The NODAT was diagnosed according to the American Diabetes Association criteria: 1. hemoglobin A_{1c} (HbA_{1c}) $\geq$ 6.5%, 2. FPG $\geq$7.0 mmol/L, 3. two-hour plasma glucose $\geq$11.1 mmol/L during an oral glucose tolerance test, or 4. classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose $\geq$11.1 mmol/L [20]. The diagnosis of NODAT was performed between 1 month and 1 year post transplant. We chose the time window (1 month to 1 year post transplant) because 1. this period rules out recipients who develop transient hyperglycemia immediately after transplant as a result of high-dose glucocorticoids and/or surgery stress, 2. the immunosuppressive regimen is relatively stable at this time window, and 3. a majority of NODAT occurs within the first year post transplant [3,4]. It is noteworthy that time to the presence of NODAT post transplant was also recorded for survival analyses.

Homeostasis Model Assessment of Insulin Resistance

The HOMA-IR is calculated as (FPG [mmol/L] $\times$ Ins [mU/L])/22.5. To calculate HOMA-IR, data of FPG and Ins were collected

Table 1. Clinical Characteristics of NODAT and Non-NODAT Patients

	NODAT (n = 33)	Non-NODAT (n = 90)	*P* Value
Age, mean (SD), y	51 (8)	47 (9)	.007
Female sex, %	54.5	52.2	.82
BMI, mean (SD)	24.9 (2.4)	23.6 (2.3)	.004
Family history of DM, %	39.4	21.1	.04
Smoking, %	24.2	21.1	.71
Hemodialysis, %	81.8	84.4	.07
Time to NODAT, mean (SD), mo	5.6 (2.0)	-	-
HBV positive, %	15.2	12.2	.67
HCV positive, %	9.1	8.9	.97
Antihypertensive medication, %	84.8	81.1	.63
Statin medication, %	21.2	18.9	.77
FPG, mean (SD), mmol/L	5.4 (0.4)	5.1 (0.5)	.001
Insulin, mean (SD), mU/L	14.0 (2.7)	12.4 (2.6)	.003
HOMA-IR	3.4 (0.9)	2.8 (0.9)	.002
HbA_{1c}, mean (SD), %	5.3 (0.5)	5.1 (0.4)	.12

The *t* test and χ^2 test were used to compare continuous and categorical variables between groups, respectively.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HBV, hepatitis B virus; HCV, hepatitis C virus; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NODAT, new-onset diabetes after transplant; non-NODAT, without new-onset diabetes after transplant; SD, standard deviation.

from each recipient. Because HbA_{1c} is able to identify the 3-month average plasma glucose level, we also collected data of HbA_{1c} for analysis. Note that all the data represented the latest data that were obtained 2 to 3 days before transplant.

Statistical Analyses

Data are expressed as means (standard deviation [SD]) unless otherwise indicated. The *t* test and χ^2 test were used to compare continuous and categorical variables, respectively, between patients with and without NODAT. To determine if HOMA-IR, as well as other pretransplant variables including FPG, Ins, HbA_{1c}, and demographic characteristics could predict NODAT, we first performed univariate analysis to assess the association of individual variable with development of NODAT. Variables with a P value $< .15$, as well as those of previous known associations with NODAT, were selected for subsequent analyses using multivariate logistic regression and Cox proportional hazards model. IBM SPSS Statistics v.19 (IBM, Armonk, NY, United States) was applied for the statistical analyses. A P value less than .05 was considered statistically significant.

RESULTS

Clinical Characteristics of Patients

The demographic characteristics and pretransplant laboratory measurements between NODAT and non-NODAT patients are displayed in Table 1. We observed that 26.8% (33/123) of the included nondiabetic renal recipients developed NODAT in the first year post transplant, and the average time to NODAT was 5.6 (SD, 2.0) months. A majority of the NODAT patients (72.7%) were diagnosed within 6 months post transplant. We did not detect any difference between the 2 study groups regarding sex, smoking, hemodialysis rate, hepatitis B virus or hepatitis C virus (HCV) infection, antihypertensive medication, or statin usage. However, the NODAT recipients were older ($P = .007$), had increased BMI ($P = .004$), and had increased family history of DM ($P = .04$) compared with non-NODAT. More interestingly, the NODAT patients obviously presented higher levels of FPG (5.4 [SD, 0.4] vs 5.1 [SD, 0.5] mmol/L; $P = .001$) and Ins (14.0 [SD, 2.7] vs 12.4 [SD, 2.6] mU/L; $P = .003$) as well as elevated HOMA-IR (3.4 [SD, 0.9] vs 2.8 [SD, 0.9]; $P = .002$) when compared with non-NODAT patients. Surprisingly, the 2 study groups showed comparable level of plasma HbA_{1c} (5.3 [SD, 0.5] vs 5.1 [SD, 0.4]%; $P = .12$). To exclude the potential disturbance of the usage of prednisone (post-transplant factor) on the prediction power of the current study, we also took this factor into consideration. After careful comparison, we did not observe any difference regarding the usage of prednisone between NODAT and non-NODAT (data not included).

Logistic Regression Analyses

To dissect potential pretransplant risk factors of NODAT, we first performed univariate analysis (with odds ratio [OR] unadjusted) for each collected variable (Table 2). The analyses indicated that the following variables were probably related with higher risk of NODAT (all $P < .15$): age, BMI, family history of DM, FPG, Ins, HOMA-IR, and HbA_{1c}. Next, we performed multivariable logistic regression analysis adjusted for age, sex, BMI, and family history of DM. Our analyses revealed that FPG level (adjusted OR, 3.17 [1.41–6.45]; $P = .01$) and HOMA-IR (adjusted OR, 1.73 [1.21–2.87]; $P = .02$) were independent risk factors for the development of NODAT (Table 2), while plasma Ins or HbA_{1c} did not predict NODAT ($P > .05$).

Cox Proportional Hazards Model

In addition to logistic regression analysis, we introduced Cox proportional hazards model for survival analysis. By univariate analyses, we detected identical variables that probably associated the following with higher risk of NODAT (all $P < .15$): age, BMI, family history of DM, FPG, Ins, HOMA-IR, and HbA_{1c} (Table 3). Next, we conducted the survival analyses adjusted for age, sex, BMI, and family history of DM. Similar with the multivariable logistic regression analyses, the survival analyses revealed

Table 2. Logistic Regression Analyses of the Pretransplant Risk Factors of NODAT

	Unadjusted OR (CI 95%)	*P* Value	Adjusted OR (CI 95%)	*P* Value
Age by year	1.07 (1.02–1.12)	.01		
Female sex	1.12 (0.51–2.50)	.78		
BMI	1.27 (1.07–1.50)	.006		
Family history of DM	1.51 (0.68–3.16)	.03		
Smoking	1.16 (0.52–2.59)	.71		
Hemodialysis	1.21 (0.91–2.12)	.57		
HBV-positive	1.43 (0.62–3.32)	.41		
HCV-positive	0.98 (0.32–2.98)	.98		
Antihypertensive medication	1.57 (0.53–4.88)	.50		
Statin medication	1.13 (0.44–2.89)	.49		
FPG, mmol/L	3.13 (1.40–6.09)	.009	3.17 (1.41–6.45)	.01
Insulin, mU/L	1.18 (1.02–1.33)	.02		
HOMA-IR	1.88 (1.27–3.01)	.01	1.73 (1.21–2.87)	.02
HbA_{1c}, %	2.04 (0.83–5.05)	.12		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HBV, hepatitis B virus; HCV, hepatitis C virus; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NODAT, new-onset diabetes after transplant; OR, odds ratio.

Table 3. Cox Proportional Hazards Model for Prediction of Pretransplant Risk Factors of NODAT

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age by year	1.05 (1.01–1.09)	.007		
Female sex	1.11 (0.56–2.19)	.78		
BMI	1.19 (1.05–1.34)	.005		
Family history of DM	1.34 (0.68–2.65)	.04		
Smoking	1.10 (0.55–2.18)	.79		
Hemodialysis	1.31 (0.60–2.29)	.52		
HBV-positive	1.45 (0.71–2.94)	.31		
HCV-positive	1.01 (0.39–2.62)	.98		
Antihypertensive medication	1.38 (0.61–3.28)	.42		
Statin medication	1.17 (0.53–2.66)	.77		
FPG, mmol/L	2.93 (1.43–5.00)	.01	2.75 (1.26–4.56)	.02
Insulin, mU/L	1.18 (1.01–1.31)	.02		
HOMA-IR	1.78 (1.27–2.51)	.001	1.72 (1.21–2.46)	.002
HbA_{1c}, %	2.04 (0.94–4.44)	.07		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HBV, hepatitis B virus; HCV, hepatitis C virus; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; NODAT, new-onset diabetes after transplant; OR, odds ratio.

that FPG level (adjusted OR, 2.75 [1.26–4.56]; $P = .02$) and HOMA-IR (adjusted OR, 1.72 [1.21–2.46]; $P = .002$) were robustly associated with the development of NODAT, and plasma Ins or HbA_{1c} might not be able to predict NODAT ($P > .05$) (Table 3).

DISCUSSION

The present study mainly tested if HOMA-IR and its related parameters (FPG and Ins) are able to predict development of NODAT in Chinese nondiabetic patients receiving a first renal transplant. Our analyses revealed that pretransplant HOMA-IR and FPG were independent risk factors of NODAT in our cohort; plasma Ins or HbA_{1c}, a widely used measurement reflecting 3-month average plasma glucose level, were not associated with NODAT as indicated by the multivariable analyses. Because HOMA-IR and FPG are manageable before transplant, identification of the risk factors may allow timely intervention to prevent development of NODAT for kidney recipients.

It has been documented that insulin resistance is significantly affected by renal transplant [21–24]; however, controversial results have been obtained. Nam et al reported an improvement in insulin sensitivity post transplant both in patients who sustained normal plasma glucose and in those who developed NODAT [22], Hornum et al found a deterioration in insulin sensitivity post transplant [25], and Sato et al detected no alteration in patients treated with either tacrolimus or cyclosporine [26]. These inconsistent results have raised a concern whether pretransplant insulin resistance is able to predict development of NODAT. The HOMA-IR, a method used to quantify insulin resistance, was first described by Matthews et al in 1985 [27]. Since then, HOMA-IR has been intensively and reliably applied to predict T2DM in different populations with varying ethnic composition [14–17,28–30]. Chakkera et al suggest that NODAT and T2DM share highly overlapped pretransplant risk factors, for example, obesity [1]. The FPG and Ins are associated with development of NODAT [3,6,7,9,10,13]. Thus, HOMA-IR is likely to predict NODAT. Consistently, we found that pretransplant HOMA-IR was a robust predictor for NODAT in the present study, which is supported by previous reports [8,19]. Nagaraja et al demonstrated an opposing conclusion that pretransplant HOMA-IR was not associated with NODAT [18]. The possible explanations might be that 1. the diagnosis of NODAT in that study was only based on FPG (while our study and most previous studies were based on the criteria for T2DM) and 2. pharmacologic therapy for lowering plasma glucose was allowed, which together likely disrupted the identification of NODAT patients and thereby masked the predictive power of HOMA-IR.

The FPG, a most direct parameter reflecting glucose metabolism, robustly predicts T2DM in the general population [31–33]. In kidney recipients, FPG is frequently associated with development of NODAT [6,10]. An FPG >5.6 mmol/L, defined as impaired fasting glycemia, is a major component of metabolic syndrome and also independently predicts NODAT [7,9]. Consistently, we observed that FPG was an independent predictor of NODAT when calculated as a continuous variable. Besides, NODAT patients showed apparently higher level of FPG than non-NODAT before transplant. Thus, we argue that intervention lowering pretransplant FPG may reduce the incidence of NODAT for kidney recipients.

Insulin, a direct parameter strongly reflecting insulin resistance and secretion, is closely related with glucose metabolism. Shehab-Eldin et al showed that pretransplant Ins level was a significant risk factor for NODAT, and a baseline Ins of 54.54 mU/L predicted NODAT with a specificity of more than 95% [13]. However, this was not a universal finding. For example, Bayes et al demonstrated that pretransplant Ins level did not predict NODAT as revealed by multivariable logistic regression analysis ($P = .42$) [8]. Similarly, we did not detect a significant association between pretransplant Ins and development of

NODAT either by multivariable logistic regression analysis or Cox proportional hazards model, although we observed that NODAT patients had higher Ins level than non-NODAT patients before transplant.

By multivariable analyses, we detected that older age, family history of DM, and higher BMI were independent predictors for NODAT (data not shown), which is consistent with previous findings [3,7,9,10,12]. However, sex composition or hepatitis B virus infection was not significantly associated with NODAT in the current analyses, which is also supported by previous studies [3,6,8,34]. Hepatitis C virus infection, a previous identified independent predictor for NODAT [3,10,35], was not able to predict NODAT in our cohort. It has been revealed that HCV promotes insulin resistance [36] and that the diabetogenic effect is prompted by viral hindering of hepatic glucose and insulin metabolism [37–39]. Although the HCV infection rate was similar between NODAT and non-NODAT patients in our study, we still argue the possibility that the HCV disease was probably more active in the NODAT group, which might contribute to the impaired glucose profile of this cohort. Therefore, to better address the relationship between HCV infection (as well as other infectious diseases) and NODAT, it is recommended to take the disease activity and/or severity into consideration.

There are 2 apparent limitations of this study. First, our data were collected from a single center with a retrospective cohort of 123 patients that might be regarded as a relatively small sample size. Second, it is widely recognized that tacrolimus is more diabetogenic than other immunosuppressants, for example, cyclosporine [40–42]. Although the immunosuppressive regimen was to the most extent defined as tacrolimus-based in our cohort, the dose and/or duration of tacrolimus were likely to vary between NODAT and non-NODAT, which might interfere with our analyses. Therefore, future studies with larger sample size and with more strict definition of immunosuppressive regimen are warranted to validate the current findings.

Collectively, we have demonstrated that pretransplant HOMA-IR and FPG are significant predictors for development of NODAT in Chinese nondiabetic patients receiving a first renal transplant. Interventions aimed at improving insulin resistance and/or glucose metabolism before transplant may likely protect kidney recipients from development of NODAT.

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