Calcineurin inhibitor-associated new-onset diabetes mellitus in chronic kidney disease treatment: A four-year single-center cross-sectional study in China

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Abstract

Purpose To estimate the burden of CNI-associated NODM, determine its characteristics, and identify the risk factors of CNI-associated NODM in CKD treatment. Our findings can thereby provide a reference for the rational use of CNIs.

Methods

This was a single-center retrospective study performed at ZhongShan Hospital. We retrospectively screened patients treated with CNIs in our hospital from January 2015 to December 2018. T
The survey of patients with CNI-associated NODM was designed to include three steps (Figure 1). We initially screened patients treated with CNIs in our hospital. The inclusion criteria were as follows: (1) patients with a clear diagnosis of CKD and (2) those receiving CNI treatment. Patients were excluded if (1) they had undergone an organ transplant; (2) they received a diagnosis of DM or were using hypoglycemic agents prior to CNI treatment; (3) their initial immunosuppressive regimen included drugs other than CNIs combined with glucocorticoids; (4) the follow-up period was less than 6 months; or (5) medical history details were incomplete. Secondly, we recorded blood glucose levels in the included patients and separated these patients into two groups, namely, those with and without CNI-associated NODM. NODM was defined as newly diagnosed DM after CNI treatment according to the American Diabetes Association guidelines. Thirdly, for patients who developed NODM, we further analyzed the developments and outcomes.

Results Ninety-eight of the 336 assessed patients met the inclusion criteria, 15 [15.3% (15/98)] of whom developed CNI-associated NODM. The initial immunosuppressive regimens were CSA combined with glucocorticoids in 10 (66.7%) patients and TAC combined with glucocorticoids in five (33.3%) patients (including two patients who initially received TAC and later switched to CSA). Multiple logistic regression analysis revealed that baseline HbA1c (OR = 4.141; 95% Cl., 1.024–16.743; p = 0.046) and CNI trough concentration (1 year) (OR = 1.028; 95% Cl., 1.009–1.047; p = 0.004) were independent risk factors for NODM incidence. In contrast, glucocorticoid type (prednisone) (OR = 0.075; 95% Cl., 0.011–0.526; p = 0.009) was identified as an independent protective factor for NODM. Using a receiver operating characteristic curve, a cutoff cyclosporin A trough concentration of 102.1 ng/mL was identified as a predictive factor of NODM. The diagnosis time for NODM was 18.4 ± 4.8 months after CNI treatment. One NODM patient [6.7% (1/15)] recovered at 12.7 months after the onset of diabetes mellitus.

Conclusions We recommend that more attention be paid to patients with poorly controlled baseline glycosylated hemoglobin during CKD treatment with CNIs. High trough concentrations of cyclosporin A, particularly those >102.1 ng/mL, contribute to NODM. CNI-associated NODM may be reversible in the treatment of CKD.

Keywords: calcineurin inhibitor, new-onset diabetes mellitus, chronic kidney disease, risk factor, trough concentration of cyclosporin A

Introduction

Calcineurin inhibitors (CNIs), including tacrolimus (TAC) and cyclosporine (CSA), are immune-modulating agents used in the treatment of autoimmune disorders and glomerulonephritis, and also after transplantation[1]. However, although CNIs are implicated as diabetogenic drugs, the underlying mechanisms have yet to be clearly elucidated[1]. Studies on CNIs conducted to date have tended to focus primarily on transplant recipients. The reported incidence of diabetes mellitus (DM) after liver transplantation (LT) ranges from 9% to 63.3%, and similar incidence rates of DM have been reported in renal transplantation[2]. New-onset diabetes mellitus (NODM) is associated with undesirable outcomes such as an increased incidence of graft failure, increased mortality rate, frequent occurrence of diabetic complications, and increased costs[1]. The risk factors for post-transplantation diabetes mellitus (PTDM) in patients receiving CNIs include male gender, old age, obesity, a high body mass index (BMI), large waist circumference, African–American ethnic background, genetic predisposition, a family history of diabetes, impaired fasting glucose levels, pre-transplantation high plasma glucose levels, TAC use, hepatitis C virus (HCV) infection, post-transplantation high blood pressure, dyslipidemia, and low pre-transplantation magnesium levels[2-7]. Most of the relevant studies to date have reported that TAC has a higher risk of inducing PTDM than CSA[8], with a high mean concentration of TAC being associated with an increased risk of PTDM[9]. This diabetogenic effect can, however, be minimized by targeting for low trough levels of TAC[10, 11].

In addition to transplantation, CNIs are used as an initial therapy for idiopathic membranous nephropathy, and are recommended as a therapy for frequently relapsing/steroid-dependent minimal-change disease, steroid-resistant focal segmental glomerulosclerosis, and lupus nephritis[12-15]. A lower CNI dosage, lower target drug serum concentration, more rapid drug volume reduction, and shorter length of therapy have been reported in the treatment of kidney disease than after transplantation[15, 16]. However, CNI-associated NODM in the treatment of kidney disease has yet to be evaluated. In addition, it is unclear whether TAC has a higher risk of inducing NODM than CSA in CKD treatment. To the best of our knowledge, this is the first study to estimate the burden of CNI-associated NODM, determine its characteristics, and identify the risk factors of CNI-associated NODM in CKD treatment. Our findings can thereby provide a reference for the rational use of CNIs.

Methods

Study design and population

This was a single-center retrospective study performed at ZhongShan Hospital, which is a 2005-bed comprehensive teaching hospital affiliated to FuDan University, Shanghai, China. We recruited all inpatients treated with CNIs at our hospital from January 2015 to December 2018.

The survey of patients with CNI-associated NODM was designed to include three steps (Figure 1). We initially screened patients treated with CNIs in our hospital. The inclusion criteria were as follows: (1) patients with a clear diagnosis of CKD and (2) those receiving CNI treatment. Patients were excluded if (1) they had undergone an organ transplant; (2) they received a diagnosis of DM or were using hypoglycemic agents prior to CNI treatment; (3) their initial immunosuppressive regimen included drugs other than CNIs combined with glucocorticoids; (4) the follow-up period was less than 6 months; or (5) medical history details were incomplete. Secondly, we recorded blood glucose levels in the included patients and separated these patients into two groups, namely, those with and without CNI-associated NODM. NODM was defined as newly diagnosed DM after CNI treatment

according to the American Diabetes Association guidelines[17]. Thirdly, for patients who developed NODM, we further analyzed the developments and outcomes.

Data collection

We retrieved the following information for the included patients: demographic information (gender, age, and BMI); basic disease status [basic CKD stage, renal puncture pathology type, baseline serum magnesium, baseline glycosylated hemoglobin (HbA1c), baseline proteinuria, and family history of diabetes]; concomitant diseases [anemia, coronary heart disease, hypertension, hyperlipidemia, hyperuricemia, cancer, hepatitis b virus (HBV) infection, and osteoporosis]; medication [CNI types (TAC vs. CSA), CNI trough concentrations (1 month, 3 months, and 1 year), CNI daily total dose, CNI course (month), glucocorticoid type (prednisone vs. methylprednisolone), glucocorticoid course (months), and switch CNI type]; prognosis and follow-up [last follow-up proteinuria, last follow-up stage of CKD, length of follow-up (months), and initial diagnosis of DM].

Data analysis

Normally distributed continuous variables were expressed as the means ± standard deviation (SD), and groups were compared using an independent *t*-test. Non-normally distributed continuous variables were presented as the medians [interquartile range (IQR)], and groups were compared using a rank-sum test. In addition, categorical variables were expressed as numbers (percentages) and analyzed using a chi-square test or Fisher's exact test. Logistic regression models were used to assess independent risk factors for NODM incidence. Multiple logistic regression models were used to identify variables with a p value of less than 0.3 in descriptive analysis. These variables were further examined in multivariate analysis to identify the independent risk factors. The covariates included in multiple logistic regression analysis of CNI-associated NODM included gender (male vs. female), age (years), BMI (kg/m^2), basic CKD stage (stages 1, 2, 3, 4, and 5), baseline HbA1c (%), baseline 24-h proteinuria quantification (g), renal puncture pathology type (membranous nephropathy vs. other type), hypertension (yes or no), total daily dose of CNIs (mg), CNI trough concentration (1 month; ng/mL), CNI trough concentration (1 year; ng/mL), glucocorticoid type (prednisone vs. methylprednisolone), glucocorticoid dose (mg), and glucocorticoid course (months). A forward logistic model was used for the selection of variables. The best cut-off of CNI trough concentration (1 year) after CNI treatment was determined using a receiver operating characteristic (ROC) curve. All p values were two-sided, and a p value of less than 0.05 was deemed significant. Statistical analyses were conducted using the Statistical Package for Social Sciences version 23.0 (IBM, 187 Chicago, Ill, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Zhongshan Hospital, FuDan University (Approval No.: B2019-236). Data obtained for the purposes of the study were based on medical records of discharged patients. Patient data were anonymized prior to analysis by an independent researcher who did not participate in this study. Consequently, the ethics committee waived the requirement of written informed consent for participation.

Results

Included and excluded patients

Ninety-eight of the initially assessed 336 patients met the inclusion criteria. Among the 238 patients who were excluded, the most common reason was that the initial immunosuppressive regimen included drugs other than CNIs combined with glucocorticoids (35.7%, 85/238) (Supplement Figure 1). Of the 98 patients included, 82.1% (78/95) received a diagnosis of membranous nephropathy based on a renal biopsy (Supplement Figure 2). The initial immunosuppressive regimens were CSA combined with glucocorticoids in 76.5% (75/98) of patients and TAC combined with glucocorticoids in 23.5% (23/98). Thirteen (13.3%) patients switched CNI type during hospitalization (one patient initially received CSA and later switched to TAC; 12 patients who initially received TAC switched to CSA).

Clinical characteristics of CNI-associated NODM

A total of 15 patients [15.3% (15/98)] developed CNI-associated NODM. The initial immunosuppressive regimens were CSA combined with glucocorticoids in 10 (66.7%) patients and TAC combined with glucocorticoids in five (33.3%) patients (including two patients who initially received TAC and later switched to CSA). There were no significant differences in CNI types between patients with and without NODM. Similarly, we detected no significant differences with respect to gender, age, BMI, baseline serum magnesium, baseline HbA1c, baseline proteinuria, basic CKD stage, renal puncture pathology type, last follow-up proteinuria, last follow-up stage of CKD, or length of follow-up between the two groups (Table 1). Moreover, there were no significant differences in CNI daily total dose, drug strength grading, CNI trough concentration (1 month), cCNIs (3 months), CNI course, glucocorticoid type, prednisone equivalent dose, glucocorticoid course, or switch CNI type. Patients with NODM were, however, more likely to have concomitant hypertension (60 vs. 32.5%, $p = 0.042$) (Table 1.) and high CNI trough concentrations (1 year) (121.4 vs. 80.6 ng/mL, $p = 0.008$) (Table 2).

Risk factors for NODM

Multiple logistic regression analysis revealed that baseline HbA1c (OR = 4.141; 95% Cl., 1.024–16.743; $p = 0.046$) and CNI trough concentration (1 year) (OR = 1.028; 95% Cl., 1.009–1.047; $p = 0.004$) were independent risk factors for NODM incidence. In contrast, glucocorticoid type (prednisone) (OR = 0.075; 95% Cl., 0.011–0.526; $p = 0.009$) was identified as an independent protective factor for NODM (Table 3).

Cutoff mean concentration of CNIs after 12 months

In our hospital, although concentrations of CNIs were measured, measurement were not taken at each visit. The findings of this study indicate that the CNI trough concentrations were higher in patients with NODM (121.4 ng/mL) than in patients without NODM (80.6 ng/mL, $p < 0.05$) (Table 2). A cutoff CSA trough concentration of 102.1 ng/mL was identified as being predictive of NODM based on ROC curve analysis (Figure 2). The diagnostic value of the cutoff value indicated that the area under the curve (AUC) was 0.786 (95%CI: 0.657–0.915, $p = 0.003$), with a sensitivity of 0.909 and specificity of 0.608. Similarly, a cutoff TAC trough concentration of 5.05 ng/mL was identified as being predictive of NODM based on ROC curve analysis (Figure 3). The diagnostic value indicated that the AUC was 0.833 (95%CI: 0.616–1.000, $p = 0.136$), with a sensitivity of 1.0 and specificity of 0.733.

Situation and outcome of NODM

The diagnosis time for NODM was 18.4 ± 4.8 months after CNI treatment. The most rapid diagnosis of DM was made at 2.1 months after administration, whereas the slowest was made at 69.5 months.

NODM occurred in 40.0% (6/15) of the patients within 6 months (Table 4). In total, 6.7% (1/15) of patients with NODM had recovered at 12.7 months after the onset of DM.

Discussion

In this study, we aimed to identify the risk factors of CNI-associated NODM in CKD treatment and accordingly found that poorly controlled baseline HbA1c and a high trough concentration of CSA, particularly >102.1 ng/mL, contributed to NODM. Our findings revealed that the incidence of CNI-associated NODM was 15.3%, which is considerably lower than the incidence of NODM after organ transplantation[2]. This finding is consistent with our expectations and may have been attributed to differences in the exposure to diseases and drug treatment plans. Although the unique post-transplantation milieu in susceptible patients may be one of the main mechanisms underlying the development of PTDM[1], this risk factor is not applicable in the case of CKD treatment.

Treatment with glucocorticoids can contribute to the development of steroid diabetes, and studies have shown that glucocorticoid-free immunosuppressive regimens, or even low doses of glucocorticoids, can reduce the incidence of NODM[18, 19]. Nevertheless, glucocorticoids are the basis of CKD treatment, and the 15.3% incidence of CNI-associated NODM may be over-estimated by concomitant therapy with glucocorticoids. To avoid the effects of other immunosuppressive drugs that may cause diabetes, we excluded patients in whom the initial treatment regimen included drugs other than CNIs combined with glucocorticoids. We showed that the type of glucocorticoids may have an important influence on the development of NODM. Logistic regression analysis revealed that prednisone is an independent protective factor for NODM, indicating that the use of methylprednisolone is associated with a higher risk of developing NODM than using prednisone. On the basis of the findings of our literature search, we believe that the present study is the first to report this observation. Methylprednisolone is a synthetic intermediate-acting glucocorticoid characterized by methylation at the 6th position of prednisolone, and has a stronger anti-inflammatory effect, which could be one of the reasons why it is more likely to induce NODM[20]. A further possibility is that among those patients who received methylprednisolone, a high proportion received high-dose shock treatment during the early stages of treatment, which can cause insulin secretion disorders, insulin resistance, and the release of counter-regulatory hormones, as well as changes in the secretion and action of incretins, thereby increasing the risk of diabetes[21].

No significant differences were observed with respect gender, age, BMI, baseline HbA1c, basic CKD stage, or CNI daily total dose between patients with and without CNI-associated NODM, thus indicating that there may be good comparability between the two groups. A previous study showed that TAC is an independent risk factor for PTDM when compared with CSA[1], and it has also been established that glucose-stimulated insulin sensitivity and overall glucose tolerance are significantly improved after conversion from TAC to CSA in HCV-positive renal transplant recipients[8]. However, Yu et al. reported that the use of TAC is not associated with the development of PTDM[5]. In the present study, we detected no significant differences in the types of CNIs between the two patient groups, which we believe may be related to the characteristics of the drug treatment plan. This is the first study that has examined the use of CNIs for the treatment of CKD, and compared with their use post-transplantation, the target concentration of CNIs in the treatment of CKD is lower, the drug volume is reduced more rapidly, and the course of treatment is relatively shorter[15, 16].

The findings of the present study indicate that baseline HbA1c is an independent risk factor for NODM. HbA1c can reflect the blood glucose status of patients in the previous 3 months. In this regard, Li et al., who conducted a meta-analysis involving 4580 liver transplant patients, reported that impaired fasting glucose prior to transplantation is an independent risk factor for NODM[2]. Similarly, Yu et al. showed that a high pre-transplantation plasma glucose level is an independent risk factor for NODM in a Korean population[5]. Basic glycemic control is important in controlling

the development of NODM, and consequently, in clinical practice, patients with poorly controlled HbA1c who are treated with CNIs need to be carefully monitor for the side effects of NODM.

The target trough concentration of CNIs is lower in CKD therapy than in organ transplantation. For example, in the treatment of membranous nephropathy, the target trough concentration of CSA is 120–200 ng/mL, whereas that of TAC is 3–5 ng/mL[15]. Comparatively, for kidney transplant patients, the target trough concentration of CSA is 200–300 ng/mL for 1–3 months after transplantation and that of TAC is 7–10 ng/mL for the first month[22]. For liver transplant patients, the target trough concentration of CSA in the first 3 months is typically 200–250 ng/mL and that of TAC is 7–10 ng/mL[23], whereas for heart transplant patients, the target trough concentration of CSA in the first year after transplantation is maintained at 200–350 ng/mL and that of TAC for the first 6 months is generally 10–15 ng/mL[24]. The findings of the present study indicate that the concentration of CNIs is an independent risk factor for the development of NODM. Which is consistent with the findings of numerous studies that have shown that a high concentration of CNIs is a risk factor for NODM[10,11]. In this regard, Song et al. found that minimizing the trough concentration of TAC reduced the risk of NODM development after liver transplantation[11], whereas Jouve et al. showed that minimizing the trough concentration of TAC improved its safety profile and reduced the risk of NODM in kidney transplant recipients[10]. In the present study, our ROC results indicated that the cutoff value of CSA trough concentration was 102.1 ng/mL, with a significant difference ($p = 0.003$). This indicates that a CSA trough concentration >102.1 ng/mL may increase the risk of NODM. Although the mechanism of action of CSA on glucose metabolism has yet to be fully elucidated, it is believed to be primarily associated with a reduction in insulin secretion. In this respect, a previous *in vitro* study has revealed that CNIs have a direct dose-dependent effect on pancreatic β-cells, resulting in morphological changes and reduced insulin and C-peptide release [25]. Thus, in clinical practice, close attention should be paid to the risk of NODM in patients with a CSA trough concentration >102.1 ng/mL. On the basis of further evaluations of the occurrence of CNI-associated NODM, we found that 40% of NODM occurred within 6 months, which is higher than the occurrence of PTDM[9, 11]. This may be related to the higher initial dose and more rapid dose reduction of CNIs in CKD treatment than in PTDM treatment. In previous studies, the prognostic indicators of CNIs for organ transplantation have mainly been shown to be mortality rate and graft failure, whereas in contrast, the recovery of DM is rarely evaluated[1]. Given that CKD is a chronic disease, we evaluated the recovery of DM, and accordingly found that 6.7% of patients recovered during low-dose maintenance therapy, thereby indicating that the NODM that develops during the treatment of CKD may be reversible. Thus, during treatment, it may be beneficial to reduce the dose of CNIs as soon as possible, whilst continuing to ensure efficacy. In addition, blood sugar should be actively controlled during the treatment of CKD .

The strengths of this study are as follows. First, on the basis of the findings of a literature search, we assume this study to be the first that has examined CNI-associated NODM during CKD treatment. We believe that our findings on CNI-associated NODM, including incidence and risk factors, will have good reference value for clinical practice. Second, we quantified the trough baseline HbA1c levels and CSA trough concentrations, which are conducive to determining the precise treatment of CKD in clinical practice. Third, the median follow-up period for the NODM group was 39.7 months, which is notably longer than that of most studies.

The study does, nevertheless, have certain limitations, namely the fact that this was a single-center retrospective study. Moreover, values were missing for some data, which may have influenced statistical performance. In addition, although we analyzed data for 4 years, the final sample size was not particularly large owing to the strict inclusion and exclusion criteria. Accordingly, in future, studies including larger sample sizes should be performed.

Conclusions

On the basis of the findings of this study, we recommend that during CKD treatment using CNIs, more attention should be paid to patients with poorly controlled baseline HbA1c. High trough concentrations of cyclosporin A, particularly those >102.1 ng/mL, contribute to NODM. However, CNI-associated NODM that develops during the treatment of CKD may be reversible.

Author Contributions PKM, LQZ, and LXY contributed to the conception and design of the study. PKM, XQ, and WW ontributed to data acquisition and collection. PKM and CC contributed to the statistical analyses. PKM wrote the first draft of the manuscript. All authors contributed to manuscript revision, and have read and approved the submitted version.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Zhongshan Hospital, FuDan University (Approval No.: B2019-236).

Informed consent Patient data were anonymized prior to analysis by an independent researcher who did not participate in this study. Consequently, the ethics committee waived the requirement of written informed consent for participation.

Data haring statements The data used and/or analyzed in this study are available from the corresponding author on reasonable request.

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Table 1. Comparison of clinical characteristics between patients with and without CNIs associated NODM

	Without NODM (N = 83)	With NODM (N = 15)	P value
Male	49 (59.0)	10 (66.7)	0.578
Age (year)	48 ± 2	52 ± 3	0.383
BMI (kg m-2), n=93	23.9 ± 0.4	24.6 ± 0.7	0.416
Family history of diabetes	0 (0)	1 (6.7)	0.153**
Baseline serum magnesium (m mol L-1), n=80	0.82 ± 0.01	0.80 ± 0.02	0.474
Baseline glycosylated hemoglobin (%), n=83	5.5 (0.4)	5.7(1.4)	0.085
Baseline proteinuria (g), n=95	5.97 (4.47)	4.50 (5.98)	0.264
Basic CKD stage, n=96			
0	1 (1.2)	0 (0)	0.232
1	39 (48.1)	12 (80.0)	
2	32(39.5)	3 (20.0)	
3	8 (9.9)	0 (0)	
4	0 (0)	0 (0)	
5	5 (1.2)	0 (0)	
Renal puncture pathology type, n=95			0.109*
Membranous nephropathy	63 (78.7)	15 (100)	
Other types	17 (21.3)	0 (0)	
Anemia	4 (4.5)	1 (6.7)	0.572**
Coronary heart disease n (%)	3 (3.6)	1 (6.7)	0.491**
Hypertension	27 (32.5)	9 (60.0)	0.042
Hyperlipidemia	7 (8.4)	2 (13.3)	0.905*
Hyperuricemia	4 (4.8)	1 (6.7)	0.572**
Cancer	2 (2.4)	0 (0)	1.0**
HBV infection	1 (4.8)	0 (0)	1.0**
Osteoporosis	0 (0)	2 (13.3)	0.022**
Last follow-up proteinuria, n=77	0.72 (1.85)	0.53 (1.76)	0.867
Last follow-up stage of CKD, n=78			0.757
0	7 (10.8)	0 (0)	
1	21 (32.2)	6 (46.2)	
2	22 (33.8)	4 (30.8)	
3	10 (15.4)	2 (15.4)	
4	3 (4.6)	1 (7.7)	

5	2 (3.1)	0 (0)	
Length of follow-up (months)	28 (30)	39.7 (57)	0.314

NODM = new-onset diabetes mellitus, BMI = Body Mass Index, CKD = Chronic kidney disease, HBV= Hepatitis B Virus, CNIs = Calcineurin inhibitors, CSA = Cyclosporin a, TAC = Tacrolimus.
* = Continuity correctionb , ** = Fisher Exact Test

Table 2. Comparison of medication characteristics between patients with and without CNI-associated NODM

	Without NODM (N = 83)	With NODM (N = 15)	P value
CNIs variety			0.517
CSA	65 (78.3)	10 (66.7)	
TAC	18 (21.7)	5 (33.3)	
CNIs daily total dose (mg/g)	200 (50)	150 (196)	0.289
Drug strength grading			0.906
1	24 (28.9)	4 (26.7)	
2	45 (54.2)	9 (60.0)	
3	14 (16.9)	2 (13.3)	
CNIs trough concentration (1 month) (ng ml^{-1}), n = 42	112.3 ± 10.8	109.8 ± 15.6	0.917
CNIs trough concentration (3 months) (ng ml^{-1}), n = 47	117.9 ± 8.2	86.2 ± 16.2	0.095
CNIs trough concentration (1 year) (ng ml^{-1}), n = 79	80.6 (79.5)	121.4 (50.0)	0.008
CNIs course (month)	26.9 (33)	27.8 (59)	0.76
Glucocorticoid variety (prednisone)	64 (88.9%)	8 (11.1)	0.091*
Glucocorticoid dose (mg)	30 (10)	28 (6)	0.071
Glucocorticoid course (month)	20.1 (21)	27.8 (59)	0.284
Adjust CNIs variety	13 (86.7)	2 (13.3)	1.000*

NODM = new-onset diabetes mellitus, CKD = Chronic kidney disease, CNIs = Calcineurin inhibitors, CSA= Cyclosporin A, TAC = Tacrolimus.
* =Continuity correctionb, **=Fisher Exact Test

Table 3. Risk factors for CNI-associated NODM.

Factors	Sig.	Exp. (B)	95% Cl.
Baseline glycosylated hemoglobin (%)	0.046	4.141	1.024 - 16.743
CNIs trough concentration (1 year)(ng ml^{-1})	0.004	1.028	1.009 - 1.047
Glucocorticoid variety (prednisone) n (%)	0.009	0.075	0.011 - 0.526

NODM= new-onset diabetes mellitus, CNIs = Calcineurin inhibitors

Table 4. The time of diabetes diagnosed

Time	N	%
In six months	6	40.0%
In one year	1	6.7%
In two years	4	26.7%

In three years	4	26.7%

Figure captions

Figure 1. The three steps - survey of CNI-associated NODM

Figure 2 Receiver operating characteristic curve for mean trough concentration of CSA after 12 months to predict NODM after CNIs treatment.

Figure 3 Receiver operating characteristic curve for mean trough concentration TAC after 12 months to predict NODM after CNIs treatment.

Figure S1. Patients excluded.

Figure S2 Patients' pathological type by renal biopsy.