



# The Effects of Calcineurin Inhibitor Levels on New Onset Diabetes Mellitus after Kidney Transplantation

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## Abstract

**Background:** The leading causes of death in patients who died with a functioning allograft are cardiovascular diseases, which account for almost 40 percent of all deaths in this population.

**Patients and Methods:** We studied prospectively basic data, immunosuppressive therapy, drug levels, serum electrolytes (Na, K, Mg), HbA1C, renal functions (serum creatinine, eGFR, and urea), and urinalysis. Then oral glucose tolerance test was performed as well, and HOMA index was calculated.

**Result:** The ratio of patients changed at Minute 120 of the test: there were 22 (37%) patients in the normal group, 26 (43%) patients in the IFG/IGT group, and 12 (20%) patients in the NODAT group. Regarding basic data, hemodialysis ( $p=0.662$ ) and body mass index ( $p=0.854$ ) did not influence the development of diabetes mellitus significantly. Development of NODAT was significantly different between the Tac and CsA groups ( $p=0.027$ ). Tac increased fasting drug level had a significant effect in the development of NODAT ( $p=0.036$ ). The results of laboratory tests showed no significant difference in serum electrolytes. HbA1C ( $p=0.009$ ) and HOMA index ( $p=0.09$ ) were significantly different. Renal function parameters, such as serum creatinine ( $p=0.001$ ) and eGFR ( $p=0.0001$ ), were also significantly different.

**Conclusion:** In our clinical study, the risk of NODAT related to Tacrolimus is dose dependent and high trough levels enhance this risk, in particular during the new onset diabetes mellitus period.

**Keywords:** Kidney transplantation; Calcineurin inhibitors; NODAT; Diabetes mellitus

## Introduction

New-Onset Diabetes After Transplantation (NODAT) is a serious and frequent metabolic complication after renal transplantation [1,2]. This entity has been well defined since the publication of the International Consensus Guidelines in 2003. The factors contributing to the risk of NODAT and the strategies related to modifiable factors, with emphasis on practical issues are reviewed in this paper. Many studies show that the Calcineurin Inhibitors (CNI), within them Tacrolimus (Tac) is the leading causes of the development of NODAT, and high Tac drug level contributes to the development of NODAT. Recognizing these factors may help clinicians to evaluate appropriate prevention strategies prospectively to minimize the risk of NODAT. Over the past 50 years, the concept of NODAT has evolved in terms of name and definition. Before 2003, *de novo* diabetes that developed after transplantation was described in various terms, most frequently as “new onset diabetes after transplantation” and suffered from a lack of consensus regarding its definition [3]. The most commonly used clinical definition was the requirement of insulin for a minimum period post-transplantation (often 30 days). This issue was addressed by the development of the 2003 Consensus Guidelines, developed by the American Diabetes Association (ADA) and the World Health Organization (WHO) [4]. A diagnosis of NODAT carries a threat to the renal allograft, as well as the same short-and long-term implications of type 2 diabetes seen in the general population. NODAT usually occurs early after transplantation and is usually diagnosed according to the general population guidelines. According to these guidelines, diabetes is present if the fasting blood

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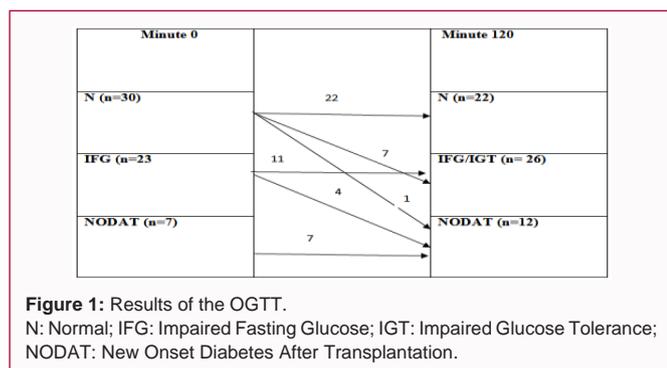
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glucose level is  $\geq 7$  mmol/L or if the blood glucose level measured 2-h following the oral administration of 75 g glucose, the Oral Glucose Tolerance Test (OGTT) is  $\geq 11.1$  mmol/L. Impaired Fasting Glucose (IFG) is defined as a fasting blood glucose level between 5.6 mmol/L and 6.9 mmol/L, whereas the Normal Value (N) for fasting blood glucose is  $<5.6$  mmol/L or Impaired Glucose Tolerance (IGT) (2-h values in the OGTT) is between 7.8 mmol/L and 11.0 mmol/L. OGTT was performed in each patient. Patients with blood glucose level  $\geq 11.0$  mmol/L were selected for the NODAT group. The general principle behind standardized NODAT incidence reporting is that the diagnostic criteria should reflect what is used in the general population. Hopefully, these developments will allow for more consistent reporting of NODAT in the future, leading in turn to more precise estimates of incidence rates.

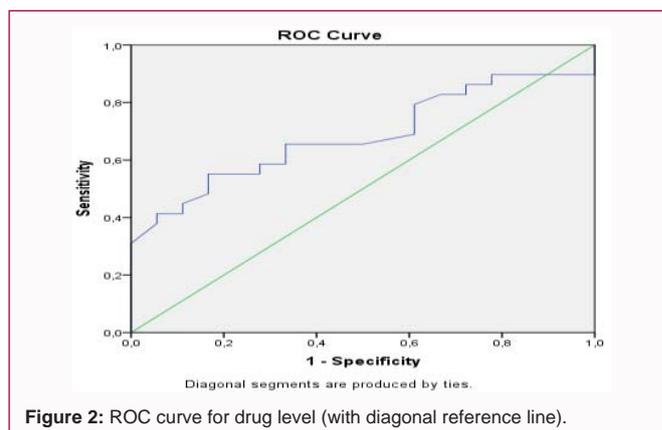
The aim of our study was to compare the risk factors and incidence of NODAT. We aimed to compare the effects of the Calcineurin inhibitors such as Tacrolimus (Tac) and Cyclosporin-A (CsA) on NODAT. The further aim of the study was to decide whether the Tac drug level was suppressed by the development of NODAT, and what effects it had on the allograft function.

## Material and Methods

Our prospective study was performed in the Department of Surgery, University of Szeged, Hungary. Patients who had cadaver kidney transplantation within at least one year, were above the age of 18, had no diabetes mellitus in the past medical history, have not received steroid burst therapy, and had no cardiac disease in the past medical history were enrolled in the study. A total of 60 patients were involved in our study.

Basic data (age, gender, and BMI), time spent in hemodialysis, and the applied Immunosuppressive (IS) therapy-CNI such as Tac and Cyclosporine-A (CsA) were analyzed. Laboratory tests were performed including serum electrolytes (Na, K, Mg), drug level, HbA1C, renal functions (serum creatinine, estimated glomerular filtration rate (eGFR), and urea) and urinalysis (total protein and glucose secretion). Then OGTT was performed as well, during which glucose and insulin levels were measured 0 and 120 mins after the administration of 75 g oral glucose, and then insulin resistance was calculated by using the Homeostatic Model Assessment (HOMA) index (fasting glucose\* fasting glucose/22.5). Based on the value, the risk of Insulin Resistance (IR) can be determined, if the value is above 2, the patient is susceptible to have diabetes mellitus, and in case of a value above 4, the patient has IR.

Our study was approved by the Regional Human Biomedical Research Ethics Committee of the Albert Szent-Györgyi Clinical



Center, University of Szeged (Reg No: 18/2017-SZTE). Each patient was provided comprehensive information regarding the study.

## Statistical Methods

Continuous data were expressed as mean  $\pm$  standard deviation; categorical data were expressed as number of cases and percentages. Univariate comparisons were performed by Welch's ANOVA or Chi-square test for continuous or categorical variables, respectively. The relationship between drug level and the development of diabetes mellitus was evaluated with ROC analysis; AUC ROC and 95% confidence interval for AUC were calculated. A p-value  $p < 0.05$  was regarded statistically significant. Statistical software IBM SPSS statistics version 24 (64bit) was used.

## Results

In our study, there were 30 patients in the normal group, 23 patients in the IFG group, and 7 patients in the NODAT at Minute 0 of OGTT. The ratio of patients changed at Minute 120 of the test: there were 22 (37%) patients in the normal group, 26 (43%) patients in the IFG/IGT group, and 12 (20%) patients in the NODAT group (Figure 1). After the transplantation, every patient was administered steroid therapy. In 50 cases, basic IS therapy included Tac, 9 patients received CsA based therapy, and 1 patient received CNI-free IS therapy. 10 (16%) patients from the NODAT group received Tac based therapy, and 2 (3%) patients received CsA based IS, significant difference was found between these two groups ( $p=0.027$ ). ROC analysis of patients receiving Tac showed that increased fasting drug level had a significant effect in the development of diabetes mellitus (AUC=0.684,  $p=0.036$ , 95% CI: 0.534, 0.834) (Figure 2, Table 1).

The risk factors of diabetes were examined to determine which factors influence the development of diabetes mellitus significantly. Regarding basic data, gender and age did not influence the development of diabetes mellitus significantly, although patients with NODAT spent more time in HD; the difference was not statistically significant ( $p=0.662$ ). In our study, BMI ( $26.55 \pm 3.84$  vs.  $28.58 \pm 5.26$ ;  $p=0.854$ ) did not play a significant role in the development of NODAT (Table 2).

The results of laboratory tests showed no significant difference in serum electrolytes, such as Na ( $p=0.761$ ), K ( $p=0.648$ ), and Mg ( $p=0.306$ ). Renal function parameters, such as serum creatinine ( $p=0.001$ ) and eGFR ( $p=0.0001$ ) were significantly different, while urea ( $p=0.176$ ) level did not differ significantly between groups with different carbohydrate metabolism. The urine total protein level was

**Table 1:** Calcineurin inhibitors fasting drugs levels.

	N	IFG/IGT	NODAT	p value
<b>Tac</b> (number of patients)	18	22	10	
drug level	6.29 ± 1.27	8.46 ± 5.13	8.48 ± 2.24	0.016
<b>CsA</b> (number of patients)	3	4	2	
drug level	76.00 ± 36.7	34.82 ± 58.11	26.65 ± 33.02	0.511

Tac: Tacrolimus; CsA: Cyclosporine A; N: Normal; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; NODAT: New Onset Diabetes After Transplantation

**Table 2:** Basic data of the different glucose metabolism groups.

	N (n=22) Mean ± SD	IFG/IGT (n=26) Mean ± SD	NODAT (n=12) Mean ± SD	p value
age (years)	48.86 ± 5.83	48.38 ± 6.85	48.83 ± 7.16	0.616
gender (women/men)	7/15	10/16	5/7	0.824
BMI (kg/m <sup>2</sup> )	26.55 ± 3.84	26.43 ± 3.41	28.58 ± 5.26	0.854
hemodialysis (months)	22.91 ± 20.30	29.38 ± 36.16	20.58 ± 25.26	0.662

N: Normal; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; NODAT: New Onset Diabetes After Transplantation; BMI: Body Mass Index; SD: Standard Deviation

**Table 3:** Results of the blood and urine tests.

	N (n=22) mean ± SD	IFG/IGT (n=26) mean ± SD	NODAT (n=12) mean ± SD	p value
sodium	142.59 ± 2.64	142.26 ± 3.05	142.91 ± 91	0.761
potassium	4.51 ± 0.67	4.68 ± 0.65	4.56 ± 0.69	0.648
magnesium	0.76 ± 0.09	0.72 ± 0.10	0.77 ± 0.08	0.306
se. creatinine (µmol/L)	131.45 ± 18.25	120.88 ± 32.69	247.33 ± 91.35	<b>0.001</b>
urea (µmol/L)	10.31 ± 4.46	9.69 ± 6.71	14.02 ± 9.65	0.176
eGFR(mL/min/1.73m <sup>2</sup> )	50.90 ± 11.27	58.46 ± 17.94	27.25 ± 15.83	<b>1.00E:04</b>
C: peptide	3.14 ± 2.19	2.49 ± 1.29	5.05 ± 2.86	<b>0.2</b>
urine total protein	14.10 ± 15.21	26.53 ± 22.48	207.18 ± 154.30	<b>1.00E:04</b>
HbA1C	5.59 ± 0.51	5.57 ± 0.43	6.62 ± 0.91	<b>0.003</b>
HOMA 1 index (IR)	1.96 ± 1.24	2.36 ± 3.20	6.68 ± 7.02	<b>0.09</b>

N: Normal; IFG: Impaired Fasting Glucose; IGT: Impaired Glucose Tolerance; NODAT: New Onset Diabetes After Transplantation; eGFR: Estimated Glomerular Filtration Rate; IR: Insulin Resistance; HOMA: Homeostatic Model Assessment

significantly different in the groups ( $p=0.0001$ ). HbA1C ( $p=0.009$ ) and HOMA index were considered to be the indicator of insulin resistance ( $p=0.09$ ), and C-peptide levels ( $p=0.20$ ) were significantly different as well. Significant difference was found in the total urine protein level between the different glucose metabolic groups (Table 3). The analysis of the glucose content of the urine showed that there was no glucose in the urine except for 4 cases of patients having NODAT, and 3 (+) glucose was found in the urine in 2 cases. Patients having normal carbohydrate metabolism had no glucose in the urine ( $p=0.0001$ ).

### Calcineurin inhibitors

The initial daily dose of Tac (0.20 mg/kg in 2 portions) was adjusted to target blood trough levels of 10-15 ng/mL at Week 6, and 5-10 ng/mL thereafter. The initial CsA dose was 8-10 mg/kg daily in 2 portions with target blood levels at two hours post-dose of 1,300-1,600 ng/mL at Month 1; 900-1300 ng/mL at Months 2 and 3; 750-950 ng/mL at Months 4-6; and 700 ng/mL thereafter.

The reported rates of NODAT in patients treated with Calcineurin inhibitors vary widely [1,3,5-9] for many of the same reasons that were stated earlier. However, some patient populations appear to be at increased risk for NODAT, depending on the type of CNI used. Although African Americans and Hispanics are more likely to develop

new-onset DM regardless of the immunosuppressant used, they are particularly susceptible to DM after treatment with Tac [10,11].

### Mechanism of calcineurin inhibitor-induced NODAT

The exact mechanism of NODAT induced by Tac and CsA is not known. *In vitro* and *in vivo* studies suggest that CsA affects the synthesis and secretion of insulin through reversible toxicity to  $\beta$ -cells [12,13]. In addition, insulin release may be independently affected by CsA, because CsA also inhibits the release of insulin in response to a glucose challenge *in vitro* and in the perfused pancreas [9,14]. CsA also affects peripheral glucose tolerance, presumably through a mechanism of insulin resistance. In the rat model, glucose intolerance precedes a drop in insulin secretion, suggesting peripheral mechanisms that reduce insulin secretion by  $\beta$ -cells [15]. Tac appears to have a similar mechanism of action to CsA, affecting  $\beta$ -cells and peripheral insulin sensitivity [3,11]. However, in human pancreatic  $\beta$ -cells, Tac has been shown to produce a greater alteration in the normal insulin secretion pattern than CsA [16]. There is also evidence that both Tac and CsA may act directly on the transcriptional regulation of insulin gene expression in  $\beta$ -cells [17-19].

### Discussion

After kidney transplantation, the incidence of NODAT was

20%. In our clinical study, it was found that the recipients basic data (recipients age, gender, and the time of the hemodialysis) were not significantly different concerning the onset of NODAT, and the difference in the BMI was also not significant, although the average BMI of patients having NODAT was higher compared to patients with normal carbohydrate metabolism [7,20]. The low BMI in our recipients should reflect the fact that we keep our patients fit. According to the WHO, the number of patients worldwide with diabetes mellitus has doubled from 170 million to 340 million over the past ten years. In addition, the WHO predicts that diabetes mellitus will be the seventh leading cause of death by 2030. The insulin resistance of HbA1C was significantly different between the normal and diabetes groups. The study proved that the time of the hemodialysis did not affect the development of NODAT. The diabetogenic effect of glucocorticoids, mainly due to insulin resistance, is mediated by both impaired insulin-dependent glucose uptake in the peripheral tissues and enhanced gluconeogenesis in the kidney. We did not investigate the effect of steroids on NODAT because all patients received steroids after kidney transplantation. Several clinical studies indicate that Tac is associated with a higher risk for IGT and NODAT than CsA [21]. Our study showed that in patients taking Tac IS therapy, the incidence of the NODAT was 16%; however, the incidence of NODAT in CsA immunosuppression therapy was 3% ( $p=0.027$ ). We found that the drug level of Tac had significant influence on NODAT ( $p=0.016$ ). In our clinical study, it was shown that the risk of NODAT related to Tac was dose dependent, and high trough levels enhanced the risk, in particular during the NODAT period. Calcineurin inhibitors are diabetogenic by inducing a defect in insulin secretion by interfering with the nuclear factor of activated T-cell signaling in pancreatic  $\beta$ -cells. This pathway triggers the expression of genes critical for  $\beta$ -cell function, including at least six genes mutated in hereditary forms of monogenic diabetes [17]. Tac induces a reversible suppression of insulin secretion at the level of insulin mRNA transcription, mediated by the binding of the drug to FK506 binding protein-12 and a subsequent Tac in the  $\beta$ -cells [19]. The high level of Tac binding protein-12 present in pancreatic  $\beta$ -cells might explain why Tac more profoundly inhibits insulin secretion than CsA. Registry analyses, meta-analyses, and the prospective study of Vincenti et al. [22] have shown that the risk of NODAT was significantly higher in patients on Tac versus CsA [5,23-25]. Our study found that the incidence of NODAT was higher among patients who were treated with Tac compared with CsA Maes et al. [25] who have reported that the number of Tac trough levels  $>15$  ng/mL during the first month determined the development of NODAT.

Although CsA therapy allows a reduction in steroid dosages with the subsequent reduction of NODAT incidence, Calcineurin inhibitors also have been associated with glucose metabolism impairment [1,7,19,22]. Several clinical studies indicate that Tac is associated with a higher risk for IGT and NODAT than CsA. The United States Renal Data System (USRDS) shows that the risk for NODAT is 53% higher in patients who receive Tac, and the rate of NODAT diagnosis during the second year is also higher [23,26]. Retrospective studies and randomized, controlled trials have found that the incidence of NODAT is higher among patients who are treated with Tac compared with CsA [3-6,19,22]. The appearance of a first Tac level  $>20$  ng/mL was associated with a NODAT RR of 9.33 (95% CI 2.28 to 38.03;  $p=0.001$ ) after adjusting for age. Nearly 81% of patients with NODAT showed a first level  $>20$  ng/mL, whereas only 22% of patients without NODAT had such a high first level. After this point, we did not find any difference in the levels between patients

with and without NODAT. By contrast, patients with NODAT maintained higher concentration-dosage ratios for 6 months, which can be explained by the differences in the drug metabolism [27].

The progressive reduction in Calcineurin inhibitor target levels has led to a lower incidence of NODAT [6,19,22,27]. Tac concentrations of  $\leq 10$  ng/mL are associated with both a maximal benefit on graft survival and a minimal risk for NODAT [20]. This finding is in accordance with several studies that have analyzed the glucose metabolism by glucose tolerance tests. After the initiation of Tac therapy, there was a 39% reduction in the insulin sensitivity index. This index was inversely correlated with the Tac trough level. No patients with Tac trough levels  $<15$  ng/mL showed an abnormal index. A 33% Tac level reduction resulted in a 36% improvement in pancreatic  $\beta$  cell secretion capacity [20]. Because glucose metabolism depends more on Tac area under the curve and trough level than on peak level, it seems that the change to the new modified release formulation of Tac (MR4) will not alter the current knowledge about the NODAT-Tac relationship [21].

Tac is associated with a higher rate of NODAT but not with a reduced risk for graft failure [2,6,19]. According to Webster et al. [25], treating 100 recipients with Tac instead of CsA for the first year after transplantation has prevented 12 patients from having acute rejection and two from losing their graft but has made an extra five patients develop insulin-dependent diabetes. In regard to the function of the allograft, we found that there was significant difference in the serum creatinine ( $p=0.001$ ) and eGFR levels ( $p=0.0001$ ). NODAT leads to the deterioration of renal function and urinary proteinuria ( $p=0.0001$ ). In the NODAT group, it seems more reasonable to convert to a Calcineurin inhibitor-free regimen to improve glucose metabolism, although there is some risk to have an acute rejection episode or to reduce Tac dosages [16]. A reduction in blood levels of Calcineurin inhibitor may help diminish the risk for NODAT. If it is clear that lifestyle modification alone will be insufficient to control hyperglycemia, pharmacotherapy targeting glucose metabolism should be initiated. In the very early post-transplant phase, when corticosteroids are being rapidly tapered, additional pharmacotherapy may not be required if the hyperglycemia is mild. The choice between insulin and oral hypoglycemic agents depends on the severity, timing, and expected duration of hyperglycemia [28]. Insulin therapy is safe, particularly when the graft function is not yet established or is unstable. Since corticosteroids and Tac are typically administered in the morning in patients with kidney transplantation, a combination of intermediate and short-acting insulin administered several times during the day and corresponding to mealtimes may be required [29]. In less urgent instances, oral hypoglycemic agents can be commenced without resorting to insulin first-hand.

Our study was limited by the fact that patients came from various counties; therefore, we did not set up and change any antidiabetic therapies. We would like to look at these patient groups further and evaluate the severity of the effects of diabetes on the eyes and peripheral nervous system.

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