ORIGINAL ARTICLE

Title

Effect of Calcineurin Inhibitor on Blood Glucose Level in Non-Diabetic Kidney Transplant Patients

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Abstract

Background Calcineurin inhibitor (CNI) is a class of immunosuppressant agent used in kidney transplant management, known to pose risk for new-onset diabetes after transplant (NODAT). Tacrolimus and cyclosporine cause NODAT through multiple mechanisms, such as decreasing insulin secretion, increasing insulin resistance, and a direct effect on the pancreatic beta cell. **Method** This is a retrospective study on patients receiving immunosuppressant agents for kidney transplant patients in Surabaya. The immunosuppressant agents studied were CNI (tacrolimus and cyclosporine) in combination with mycophenolate mofetil (MMF) or azathioprine (Aza) and steroid. The blood glucose measured were fasting blood glucose (FBD) and 2-hour postprandial blood glucose (2PPBG). **Objective** Aim of this study is to determine the effect of calcineurin inhibitor (CNI) on glucose regulation in the nondiabetic renal transplant patient. **Result** Fifty-six subjects were included in the study, divided into two groups. One group of 28 patients (50%) received tacrolimus-MMF-MP and the other group received cyclosporine-MMF-MP. A significant increase in fasting blood glucose (pre-intervention level 86 ± 6 mg/dl vs post-intervention level 109 ± 34 mg/dl with p = 0.01) and 2-hour postprandial blood glucose (pre-intervention level 117 ± 20 mg/dl vs post-intervention level 150 ± 43 mg/dl with p < 0.001) was found in the tacrolimus group. A significant increase was also found in the cyclosporine group, both in fasting blood glucose (pre-intervention value 85 ± 7 mg/dl vs post-intervention value 97 ± 22 mg/dl with p = 0.002) and 2-hour postprandial blood glucose (pre-intervention value 119 ± 18 mg/dl vs post-intervention value 148 ± 55 mg/dl with p = 0.001). Tacrolimus was found to have a relative risk of NODAT up to 1.2 fold compared to cyclosporine. **Conclusion** Tacrolimus poses 1.29 relative risk of NODAT compared to cyclosporine. However, both drugs significantly increase fasting blood glucose and 2-hour postprandial blood glucose in non-diabetic patients receiving kidney transplantation.

Keyword: new-onset diabetes after transplant, calcineurin inhibitor, kidney transplant

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BACKGROUND

For patients with end-stage renal disease (ESRD), a kidney transplant is the most optimal modality of renal replacement therapy (RRT). The procedure is associated with a higher survival rate, better quality of life, reduced hospitalization rate, and better cost-efficiency compared to dialysis.[1] The management of kidney transplant patients includes the administration of immunosuppressant drugs such as calcineurin inhibitor (CNI) combined with mycophenolate mofetil (MMF) or azathioprine (Aza) and methylprednisolone (MP). The immunosuppressant agents are administered in the induction phase and maintenance phase. The CNI drugs used in kidney transplant management are tacrolimus and cyclosporine, known to increase the risk of

post-transplantation diabetes.[2,3]

New onset diabetes after transplantation (NODAT), formerly known as post-transplantation diabetes mellitus (PTDM), was found to be a complication after kidney transplant around 40 years ago by Starz et al. The incidence of NODAT was found to be 4-25% in kidney transplant patients, 2.5-25% in liver transplant patient, and 2-53% in patients of other solid organ transplantation.[4,5,6] NODAT is associated with higher risk for cardiovascular diseases (CVD) and post-procedural infection, leading to poor survival rate and graft failure.[7]

The incidence of NODAT varies between 20-50% in over 1-year post-transplantation. Tacrolimus and cyclosporine cause NODAT through multiple mechanisms: decreasing insulin secretion, increasing insulin resistance, and a direct effect on pancreatic beta-cells. A study by Pramudya et al (2016) with 56 subjects receiving kidney donor in Surabaya found 18 of the subjects developing diabetes in one year after transplant, with the mean age of 53 years old and 80% of them are male. Of the subjects developing diabetes, 53% received tacrolimus and 46.6% received cyclosporine.[8] Glucocorticoid, another drug routinely administered in transplant patients, can also induce insulin resistance, increase lipolysis, and increase liver glycogenolysis and gluconeogenesis, leading to increased plasma glucose levels.

In this study, we aim to evaluate the effect of CNI on fasting blood glucose and 2-hour postprandial blood glucose in kidney transplant patients.

METHODS

Subjects

The subjects of the study were patients diagnosed with CKD who have undergone kidney transplant surgery and received immunosuppressant regiments in Surabaya from 1998-2015 in private clinic. The data were collected from medical records. The diagnosis of NODAT was established using criteria provided by the American Diabetes Association (ADA) (Table 1).

The exclusion criteria for the study subjects are 1) diabetic patients receiving oral antidiabetic drugs or insulin, 2) patients with infection, 3) patients who were severely ill (Karnoffsky score < 50). Fifty-two patients were found to be eligible for the study.

Table 1. NODAT criteria by ADA

Diagnostic criteria for Diabetes Mellitus (American Diabetes Association)
1. HbA1c ≥ 6.5 with the result obtained from certified laboratories **OR**
2. Fasting blood glucose ≥ 126 mg/dl, fasting is defined as no caloric intake for 8 consecutive hours, **OR**
3. 2-hour postprandial blood glucose ≥ 200 mg/dl using 75 g glucose load dissolved in water **OR**
4. Random blood glucose ≥ 200 mg/dl in patients with hyperglycemia symptoms

Data Collection

The data collected were the patients' characteristics (age, gender, history of previous non-diabetic illness), and patients' blood glucose levels. The pre-intervention blood glucose levels were defined as the fasting blood glucose and 2-hour post-prandial blood glucose levels 1 month prior to transplantation. During treatment, patients receive immunosuppressant regiments and after three years, immunosuppressant dosage was relatively stable. This period is when the post-intervention data were obtained; fasting and post-prandial blood glucose level, body mass index, blood pressure, and triglyceride.

Statistical Analysis

The data obtained from the study were analyzed using the SPSS 20th version. Descriptive data comprised of comparison of blood glucose levels, BMI, blood pressure, and lipid profile between tacrolimus and cyclosporine groups. The comparison between pre and post intervention blood glucose levels in the tacrolimus and cyclosporine group was statistically tested with the threshold value of $p < 0.005$ for significant difference and relative risk comparison between each group.

RESULT

Of the 56 patients included as study subjects, 45 of them were male (80.4%) and 11 female (19.6%). The data characteristics can be seen in Table 1.

An increase of blood glucose levels from pre to post-intervention were observed both in the tacrolimus group and cyclosporine group. (Table 2).

According to the ADA criteria, 11 out of 28 (39.28%) subjects from the tacrolimus group and 7 out of 28 (25%) subjects from the cyclosporine group develop NODAT. There was no significant difference in the prevalence of NODAT between two groups, but the

Table 1. Subjects' characteristics

Variable	Tacrolimus	Cyclosporine	
Age (yrs)	44.39 ± 10.39	42.92 ± 14.032	p = 0.48
BMI (kg/m^2)	23.52 ± 2.36	23.18 ± 2	p = 0.55
Total cholesterol (mg/dl)	217.25 ± 2.36	196 ± 34.96	p = 0.37
Triglyceride (mg/dl)	182.52 ± 56.43	149.42 ± 92.15	p = 0.82
Serum creatinine (mg/dl)	1.96 ± 2.35	1.57 ± 1.17	p = 0.45

Table 2. Pre and Post Intervention Blood Glucose Levels

	Blood Glucose Level (mg/dl)		
	Pre	**Post**	
Tacrolimus			
FBG	86.2 ± 6.8	109.6 ± 34.4	p = 0.01
2PPBG	117.5 ± 20.2	150.4 ± 43.7	p < 0.01
Cyclosporine			
FBG	85.1 ± 7.1	97.0 ± 22.8	p < 0.01
2PPBG	119.8 ± 18.6	148.3 ± 22.1	p < 0.01

FBG: fasting blood glucose, 2PPBG: 2-hour post prandial blood glucose

tacrolimus group had 1.12 relative risk of NODAT compared to cyclosporine group.

DISCUSSION

Despite its adverse effects, CNI is still considered drug of choice for immunosuppressant regimen for over 20 years due to the strong evidence of its benefit in increasing up to 95% survival rate in 1-2 years after kidney transplantation.[12,13]

The combination of CNI, MMF, and MP was found to prevent acute reaction and long-term graft function failure and was not found to be nephrotoxic, cause hyperlipidemia, hypertension, and diabetes.[14]

In this study, the subjects are divided into two groups, one group receiving a combination of tacrolimus, MMF, and MP and the other group receiving a combination of cyclosporine, MMF, and MP. No significant difference of age, BMI, and lipid profile was found between the two groups, although both groups' subjects exhibit dyslipidemia.

Many studies have compared the diabetogenic effects of tacrolimus and cyclosporine with varying results. However, evidence suggests that tacrolimus have a higher diabetogenic effect. A recent study from the US shows that the incidence of NODAT was higher in patients receiving tacrolimus compared to cyclosporine 2 years after transplant (30% vs 18%).[14]

The DIRECT study (Diabetes Incidence after Renal Transplantation: Neoral C2 monitoring versus Tacrolimus), the first multicenter study examining the diabetogenic effect of tacrolimus showed higher risk of diabetes posed by tacrolimus compared to cyclosporine (33.06% vs 26% with p = .046). In a meta-analysis by Heisel et al, NODAT occurred in 9.8% of patients receiving tacrolimus and 2.7% in patients receiving cyclosporine (p = .00001). A study by Maes et al showed over 15 ng/ml of tacrolimus in the blood for the first month after transplant was a significant risk factor for impaired fasting glucose or NODAT after 1 year since transplantation.[7,15]

Tacrolimus induces the suppression of insulin secretion in mRNA transcription level, mediated by the binding of the drug to FK506 binding protein-12 and tacrolimus effect on B cells.[7] Disruption of insulin secretion contributes to the diabetogenic effect of CNI. Experimental studies also showed the effect of CNI in the inhibition of gene expression of insulin. Pancreas biopsy showed a positive correlation between beta-cell damage and the concentration of tacrolimus or cyclosporine in the blood.[16]

Diabetes in patients receiving CNI such as cyclosporine might be due to the effect of calcineurin signal/NFAT towards the adaptive properties of pancreatic

islet cells, however, this is not yet clearly proven in vivo. A study by Heit et al in mice with deletion of specific subunit beta cell calcineurin phosphatase, calcineurinb1 (Cnb1), developed diabetes marked with decreased proliferation of B cells, decreased the production of insulin from the pancreas, and hypoinsulinemia. Therefore it can be concluded that the decrease of Cnb1 will reduce the expression of beta cell proliferation.

Active NFATc1 in beta-cell with low Cnb1 can prevent the occurrence of diabetes. The expression of NFATc1 in healthy adult pancreatic beta-cell increase the proliferation of beta-cell mass, leading to hyperinsulinemia. Activation of NFATc1 also induces the expression of important genes with endocrine properties including 6 genetic mutations in the form of monogenic hereditary type 2 diabetes. Hence calcineurin/NFAT regulate multiple factors of the growth and function of the pancreatic beta-cell, a potential site for diabetic therapy field of research.[17,18,19]

Calcineurin deficiency leads to decreased insulin secretion. CNI inhibits glucose uptake by decreasing the number glucose transporter type 4 (GLUT-4) in adipocyte membrane. The decrease of GLUT-4 also results in hyperglycemia.[20]

However, the result of this study does not directly illustrate the condition of the general population, on the grounds that it is done only in one health center with a limited number of samples.

CONCLUSION

This study found tacrolimus to have a higher risk of causing NODAT compared to cyclosporine, with the relative risk of 1.219. However, both drugs significantly cause the increase of fasting blood glucose and 2-hour postprandial blood glucose levels.

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