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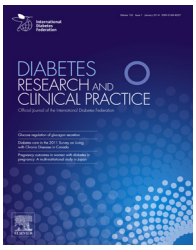

The 5-time point oral glucose tolerance test as a predictor of new-onset diabetes after kidney transplantation

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ABSTRACT

Aims: To evaluate the predictive power of the 5-time point oral glucose tolerance test (OGTT) for new-onset diabetes after kidney transplantation (NODAT).

Methods: We performed a retrospective study of 145 patients without diabetes who received kidney transplantations at our hospital. The 5-time point OGTT was performed before transplantation. The area under a receiver-operating characteristic curve (aROC) was used for evaluating the predictive power of 5-time point OGTT values.

Results: Seventeen patients developed NODAT within 1 year after transplantation. All postload plasma glucose (PPG) levels were higher in patients who developed NODAT than in those who did not; fasting plasma glucose levels were not different. The aROC for the area under the glucose concentration-time curve was significantly greater than that for fasting plasma glucose. Univariate and multivariate analyses showed that each PPG level was an independent risk factor for NODAT. Furthermore, patients with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) could be stratified with a 1-h plasma glucose (1h-PG) cut-off point of 8.4 mmol/L. The incidences of NODAT were 23.5%, 16.7%, 9.1%, and 0% for patients with IGT + 1h-PG $\geq$8.4 mmol/L,IGT + 1h-PG $<$8.4 mmol/L, NGT + 1h-PG $\geq$ 8.4 mmol/L, and NGT + 1h-PG $<$ 8.4 mmol/L, respectively.

Conclusions: The area under the glucose concentration-time curve and each PPG concentration during the 5-time point OGTT are strong predictors of NODAT. A 1h-PG cut-off point of 8.4 mmol/L plus NGT/IGT can be used to identify patients at intermediate and high risk of developing NODAT.

1. Introduction

New-onset diabetes after transplantation (NODAT) is a serious and frequent complication after kidney transplantation. The development of NODAT is associated with the increased cardiovascular morbidity and mortality observed in transplant patients [1,2] and is also associated with graft failure [2–5]. Pretransplant identification of patients at high risk of developing NODAT would be a major advantage because NODAT can be modified through use of less diabetogenic immunosuppressive drugs or implementation of lifestyle-change

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interventions. The efficacy of lifestyle-change interventions has been well reported for type 2 diabetes mellitus (T2DM) and appears to be applicable to NODAT. We have reported that the post-transplant increase in body mass index and body fat percentage are associated with the development of NODAT [6,7], suggesting that lifestyle-change interventions are useful for preventing NODAT.

Unwin et al. reported that the 2-h plasma glucose (2h-PG) level during an oral glucose tolerance test (OGTT) is a strong predictor of future T2DM [8]. However, several models based on fasting plasma glucose (FPG) or 1-h plasma glucose (1h-PG) level during the OGTT can also predict the development of T2DM. Only 30–40% of subjects diagnosed with impaired glucose tolerance (IGT), which was defined as $7.8 \leq$ 2h-PG < 11.1 mmol/L, developed T2DM [8,9]. Furthermore, Abdul-Ghani et al. reported that the 1h-PG levels had a stronger correlation with insulin secretion and insulin resistance than with the 2h-PG level [10,11]. Joshipura et al. showed the stronger associations of 1h-PG with major established predictors of diabetes compared to 2h-PG [12]. The interpretation of OGTT has not been fully established, although the 2h-PG level has been deemed sufficiently important to be used as a diagnostic criterion. In the transplant setting, pretransplant 2h-PG levels have been shown to predict NODAT [13,14]. However, plasma glucose concentrations at the other time points and the area under the glucose concentration-time curve derived from a 5-time OGTT have rarely been evaluated.

Performing an OGTT is time consuming, and models based on FPG levels, in addition to plasma lipid profile and anthropometric measurements, have been developed to predict the risk of T2DM [15–19]. However, successful kidney transplant recipients have a predisposition to develop diabetes because of increase in body mass index [6,20], use of corticosteroids [21–23], and use of a calcineurin inhibitor [24–29]. Therefore, transplant recipients constitute a special population that requires precise evaluations of glucose tolerance.

In this study, we sought to evaluate the predictive power of the 5-time point OGTT for the development of NODAT. To elucidate the utility of pretransplant OGTT, we assessed the predictive models based on 1h-PG concentrations in addition to normal glucose tolerance (NGT)/IGT classifications defined by the 2h-PG level.

2. Patients and Methods

2.1. Selection of the population

We retrospectively identified 185 consecutive patients who received living donor kidney transplants in Sendai Shakaiho-ken Hospital (Sendai, Japan) between March 2000 and June 2011. Forty patients were excluded from this study for the following reasons: Pretransplant diabetes mellitus (DM) (n = 21), recipient age < 18 years (n = 8), insufficient evaluation of glucose tolerance (n = 3), and early graft or patient loss (n = 8). Finally, 145 patients were included in this study (Figure 1). Written informed consent was obtained from all of the included patients, and the local institutional internal review board approved the study.

2.2. Immunosuppressive regimens

Patients received immunosuppressive treatment consisting of prednisolone, tacrolimus or cyclosporine, mycophenolate mofetil or mizoribine (Asahi Kasei Pharma, Tokyo, Japan), and anti-IL-2 receptor antibodies (Basiliximab, Novartis, Basel, Switzerland). Prednisolone was started at 1 mg/kg with subsequent tapering to 0.2 mg/kg 1 month after transplantation. Tacrolimus or cyclosporine was started 2 days before transplantation and adjusted to maintain the initial trough level of 10 to 12 ng/mL or 100 to 150 ng/mL and the long-term target trough level of 6 to 8 ng/mL or 70 to 100 ng/mL, respectively. Mycophenolate mofetil or mizoribine was started on the day after transplantation. Basiliximab 20 mg was administered intravenously on day 0 and day 4.

2.3. Definition of NODAT

NODAT was defined according to the American Diabetes Association [30]: as the presence of diabetes symptoms plus casual plasma glucose concentrations ≥ 11.1 mmol/L (200 mg/dL) or FPG concentrations ≥ 7 mmol/L (126 mg/dL); fasting was defined as the absence of caloric intake for at least 8 h. Impaired fasting glucose was defined as $5.6 \leq$ FPG < 7 mmol/L. In this study, patients with transient elevations of FPG concentrations were not diagnosed with NODAT. Subjects receiving insulin or oral anti-hyperglycemic medications were also considered to have diabetes.

2.4. Five-time point OGTT

A 75-g OGTT was performed after an overnight fast of at least 10 h as a screening test mostly within 6 months prior to transplantation. Blood samples were obtained before and at 30, 60, 90, and 120 min after ingesting a 75-g glucose solution. Blood collected during the studies was separated into serum.

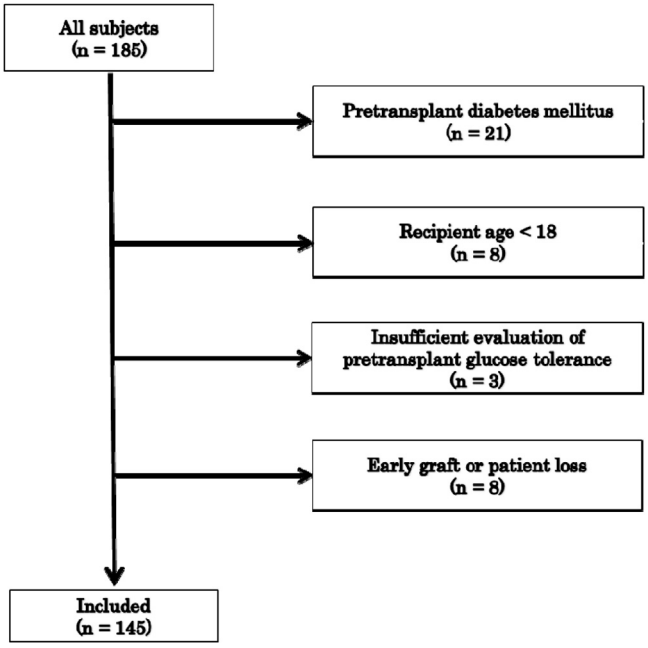

Fig. 1 – Patient disposition.