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Glucose intolerance in renal transplant recipients is associated with increased urinary albumin excretion

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ABSTRACT

Objective: New-onset diabetes mellitus after transplantation (NODAT) is a common and serious complication of renal transplantation, and its incidence is known to be increased by immunosuppressive therapy. It has been reported that urinary albumin excretion is a potent predictor of NODAT. This study was conducted to investigate the relationship between glucose intolerance and urinary albumin excretion in renal transplant recipients.
Methods: A cross-sectional study of 101 renal transplant recipients without prior evidence of diabetes was conducted. All patients underwent an oral glucose tolerance test with 75 g of glucose.
Results: The patients with glucose intolerance had a significantly greater urinary albumin excretion than those with normal glucose tolerance. Multivariate logistic regression analysis revealed that the increase of urinary albumin excretion correlated significantly with the homeostasis model assessment of insulin resistance and systolic pressure.
Conclusion: These results indicated that glucose intolerance is associated with increased albuminuria in renal transplant recipients. The rise in insulin resistance and systolic pressure may contribute to the increase of urinary albumin excretion in renal transplant recipients.

1. Introduction

New-onset diabetes mellitus after transplantation (NODAT) is a well-recognized and serious complication of renal transplantation, and immunosuppressive therapy is thought to induce the development of glucose intolerance [1,2]. Although elevated urinary excretion is more frequent in patients with metabolic syndrome and insulin resistance [3,4], it has been reported that urinary albumin excretion is a risk factor for diabetes mellitus (DM), independent of initial metabolic profile and development of insulin resistance [5]. The relationship between glucose tolerance and urinary albumin excretion has been studied in general populations [5,6], but there have been few reports regarding the relationship between glucose intolerance and urinary albumin excretion in renal transplant recipients. Microalbuminuria is a predictor of progressive renal damage and a marker of systemic inflammation and endothelial damage in general populations [7,8]. Urinary albumin excretion has been shown to be a potent predictor of NODAT in a large cohort study of renal transplant recipients [9]. Previous evidence has suggested that insulin resistance precedes and probably contributes to the development of microalbuminuria in type 2 diabetic patients [10] and in nondiabetic subjects [11]. We analyzed the relationship between glucose intolerance and urinary albumin excretion in renal transplant recipients. Additionally, the present study was conducted to test the hypothesis that microalbuminuria in renal transplant recipient with glucose intolerance is linked to insulin resistance, rather than the decrease in insulin secretion.

2. Patients and methods

2.1. Patients

This study is a cross-sectional study of 101 patients who received either living or deceased kidney transplantation at our institution. The inclusion criteria for candidates were as follows: (1) at least a year after transplantation, (2) no prior evidence of DM, (3) recipient of calcineurin-based immunosuppression, (4) stable calcineurin level for the last 6 months, (5) normal or slightly impaired renal function defined as serum creatinine below 2.0 mg/dl, and (6) stable

Abbreviations: NODAT, new-onset diabetes after transplantation; WHO, World Health Organization; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; BMI, body mass index; OGTT, oral glucose tolerance test; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; FPG, fasting plasma glucose; DM, diabetes mellitus; HOMA-R, the homeostasis model assessment of insulin resistance; HOMA-ß, the homeostasis model assessment of ß cell function; CAN, chronic allograft nephropathy; K/DOQI, Kidney Disease Outcome Quality Initiative.

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renal function for the last 6 months. The following patients were excluded from this study: (1) patients with liver dysfunction, abnormal thyroid tests, and history of gastrectomy and chronic pancreatitis and (2) patients who tested positive for hepatitis C virus antibody or hepatitis B virus surface antigen. Ninety-nine patients received triple drug immunosuppressive therapy (calcineurin inhibitors, antimetabolites, and steroids). Two patients received two-drug immunosuppressive therapy (calcineurin inhibitors and antimetabolites). All subjects gave informed consent for participation in the study, which was approved by the Human Ethics Committee of Osaka City University Hospital.

2.2. Measurements

Subjects were admitted at 8:00 AM to our institution without taking immunosuppressive medication after an 8–12 hour overnight fasting period. Fasting blood samples were obtained for biochemical studies including serum creatinine, total cholesterol, plasma glucose, triglyceride, and HbA1c, and for blood concentration of calcineurin inhibitors. The glomerular filtration rate was estimated by the modified Modification of Diet in Renal Disease equation using the new Japanese coefficient [12]. Urinary albumin excretion (urine albumin to creatinine ratio) was measured, and urine albumin and creatinine concentrations were determined on a morning spot-urine sample. This urine albumin to creatinine ratio measured in a spot-urine sample is highly correlated with 24-hour urine albumin excretion [13]. Blood pressure was reported as the average of five automated measurements taken at 3-min intervals. Hypertension was defined by the administration of antihypertensive agents, a systolic blood pressure greater than 140 mm Hg, or a diastolic blood pressure greater than 90 mm Hg. Pulse pressure was also calculated (systolic arterial pressure minus diastolic arterial pressure). Clinical parameters such as age at transplantation, gender, post-transplant duration, donor type, donor age, duration of dialysis before transplantation, and steroid doses were collected. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of body height in meters (kg/m^2). The administration of angiotensin converting enzyme inhibitor (ACEi) and/or angiotensin II receptor blocker (ARB), ß-blocker, and thiazide diuretic was also evaluated.

2.3. Glucose intolerance, insulin resistance, and ß cell function

All patients underwent an oral glucose tolerance test (OGTT) with 75 g of glucose according to the recommendations of the National Diabetes Data Group of the National Institute of Health. After overnight fasting, blood samples were drawn for determining plasma glucose and insulin before glucose loading and at 30 and 120 min after glucose loading. Categories of glucose tolerance were defined according to the World Health Organization (WHO) criteria [14]. Normal glucose tolerance (NGT) was defined as fasting plasma glucose (FPG) and 2-h plasma glucose of <110 mg/dl and <140 mg/dl, isolated impaired fasting glucose (IFG) as 110–126 mg/dl and <140 mg/dl, isolated impaired glucose tolerance (IGT) as <110 mg/dl and 140–200 mg/dl, IFG/IGT as 110–126 mg/dl and 140–200 mg/dl, and DM as ≥126 mg/dl and ≥200 mg/dl, respectively. Glucose intolerance included IFG, IGT, IFG/IGT, and DM. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-R) according to the formula HOMA-R = fasting insulin (mU/l) × FPG (mg/dl)/405 [15]. For the assessment of pancreatic ß cell function, we used the homeostasis model assessment of ß cell function (HOMA-ß) according to the formula HOMA-ß = 360 × fasting insulin (mU/l)/(FPG (mg/dl)-63) [15], and the insulinogenic index was calculated according to the formula insulinogenic index = [insulin 30 min-fasting insulin (mU/l)]/[plasma glucose 30min-FPG (mg/dl)][16]. Insulin secretion and insulin resistance were evaluated after OGTT.

2.4. Statistical analysis

All analyses and calculations were performed using the Stat View V Statistical System. The results were presented as mean ± standard deviation for continuous variables and as the proportion for categorical variables. Differences between the groups were examined with Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were compared using chi-squared analysis. Univariate associations between variables were assessed using linear regression and logistic regression. Multivariate liner regression analysis as continuous variable and multiple logistic regression analysis using microalbuminuria as categorical variable were performed to determine the factors related to urinary albumin excretion. A p-value of less than 0.05 was considered significant.

3. Results

3.1. Urinary albumin excretion and insulin resistance and secretion in patients with NGT and glucose intolerance

Urinary albumin excretion was significantly higher in the patients with glucose intolerance than in the patients with NGT. HOMA-R was higher in the patients with glucose intolerance than in those with NGT. There was no significant difference in total insulin secretion evaluated by HOMA-ß between the two groups, whereas the early phase insulin response evaluated by the insulinogenic index was significantly lower in the patients with glucose intolerance than in those with NGT (Fig. 1). NGT was detected in 73 patients (72.3%), while 28 patients (27.7%) had glucose intolerance: 5 had IFG, 14 had IGT, 7 had IFG and IGT, and 2 had DM. The mean age of the patients with glucose intolerance at transplant was significantly older than that of the patients with NGT. The BMI and HbA1c of the patients with glucose intolerance were significantly greater than those of the patients with NGT. Post-transplant duration of the patients with glucose intolerance was significantly longer than that of the patients with NGT. Other clinical variables did not differ significantly.

3.2. Comparison of patient characteristics between those with microalbuminuria and normoalbuminuria

Table 1 shows the comparison of clinical parameters between the recipients with microalbuminuria and those with normoalbuminuria. HOMA-R was significantly higher in the patients with microalbuminuria than in the patients with normoalbuminuria. Pancreas ß-cell function (insulinogenic index and HOMA-ß) did not differ significantly between the patients with and without microalbuminuria. Systolic and diastolic pressures were higher in the patients with microalbuminuria than in those with normoalbuminuria. There was no significant difference in pulse pressure between the two groups. Post-transplant duration of the patients with microalbuminuria was significantly longer than that of the patients with normoalbuminuria. Other clinical variables also did not differ significantly between the two groups. There was no significant difference in frequency of ACEi/ARB, ß-blocker and thiazide diuretic administrations between the two groups. There was no significant difference in steroid doses between the two groups.

3.3. Relationship between urinary albumin excretion and clinical parameters

Univariate liner regression analysis revealed that urinary albumin excretion correlated positively with HOMA-R ($R = 0.28$ and $p = 0.0065$, Fig. 2), arterial pressure [systolic ($R = 0.23$ and $p = 0.0232$) and diastolic ($R = 0.26$ and $p = 0.0101$)] and post-transplant duration ($R = 0.33$ and $p = 0.0062$). Urinary albumin excretion did not correlate with pancreas ß–cell function (Fig. 3). As shown in Table 2, multivariate liner regression analysis indicated that post-transplant duration and HOMA-R were independently associated with urinary albumin excretion. Univariate logistic analysis identified that HOMA-R, post-transplant duration and arterial pressure (systolic and diastolic) were independently associated with microalbuminuria. HOMA-R, systolic pressure, and post-transplant duration were independent risk factors for microalbuminuria by multiple logistic regression analysis (Table 3).

3.4. Relationship between arterial pressure and pancreas ß-cell function

Arterial pressure (systolic and diastolic) and pulse pressure did not correlate with pancreas ß-cell function (insulinogenic index and HOMA-ß).