Body Fat Area as a Predictive Marker of New-Onset Diabetes Mellitus After Kidney Transplantation

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ABSTRACT

Background. New-onset diabetes after kidney transplantation (NODAT) adversely affects patient survival. Excessive fat accumulation is generally considered a risk factor of NODAT. Body mass index (BMI) and abdominal circumference (AC) are frequently used to assess fat accumulation but cannot directly measure it. This study measured body fat area (BFA) via computed tomography and aimed to clarify whether preoperative BFA can predict the development of NODAT more accurately than BMI and AC.

Methods. This retrospective study included 62 patients without diabetes mellitus who received living-donor kidney transplantation at our institute between July 2005 and April 2016. We investigated the association between preoperative BMI, AC, and BFA and the development of NODAT.

Results. Eight patients (12.9%) developed NODAT during a mean follow-up period of 78.1 months. The preoperative BMI, AC, and BFA were markedly higher in NODAT patients than in patients without NODAT ($P = .05$, $P = .02$, $P < .01$, respectively). Correlation analyses revealed that BFA had a strong relationship with BMI ($r = 0.68$, $P < .01$) and AC ($r = 0.77$, $P < .01$). Receiver operating characteristic curve analyses demonstrated that BFA, compared to BMI and AC, had considerable predictive accuracy for the development of NODAT, with an area under the curve of 0.803 (sensitivity 75%, specificity 87%).

Conclusions. Preoperative BFA could be a predictive marker of NODAT in renal graft recipients. Our findings underline the importance of routine preoperative BFA measurements in clinical practice.

NEW-onset diabetes after kidney transplantation (NODAT), which is defined as de novo diabetes in nondiabetic kidney transplant recipients, is 1 of the most common complications after kidney transplantation. In a study, the cumulative incidence of NODAT ranged between 4% and 25% among renal graft recipients [1]. It has been reported that NODAT is associated with an increased risk of graft failure [2]. In addition, it can increase the incidence of infectious and cardiovascular events, which adversely affects patient survival [3,4]. Therefore, the reduction of risk and early treatment of NODAT are crucial for the prevention of its complications and adverse patient and graft outcomes.

As with type 2 diabetes mellitus (T2DM), NODAT may result from a combination of increased insulin resistance

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and decreased insulin production. Thus, the risk factors for NODAT include the conventional risk factors for T2DM and those specific to transplant patients, such as older age, obesity, hepatitis C virus infection, autosomal-dominant polycystic kidney disease, use of immunosuppressive drugs, and so on [5,6]. In particular, obesity is defined as the excessive accumulation of body fat and is widely identified as a risk factor for NODAT [7,8]. In clinical practice, body mass index (BMI) and abdominal circumference (AC) are frequently used to assess body fat accumulation [9] but cannot directly measure it.

Accurate quantitative assessment of body fat accumulation is important for evaluating the potential risk of NODAT. Recently, various clinical instruments have been proven useful for measuring body fat accumulation, including computed tomography (CT), magnetic resonance imaging, ultrasound, dual-energy X-ray absorptiometry, and bioelectrical impedance measurement [10]. This study measured body fat area (BFA) using CT in order to accurately estimate body fat accumulation and aimed to clarify whether preoperative BFA could predict the development of NODAT more accurately than BMI and AC in kidney transplant recipients.

MATERIALS AND METHODS

Study Design and Population

We retrospectively identified 111 consecutive patients who received living-donor kidney transplantation in our institution between July 2005 and April 2016. Forty-nine patients were excluded from this study for the following reasons: preoperative diabetes mellitus (n = 24), insufficient preoperative CT data (n = 24), and observation period of less than 2 years (n = 1). Finally, 62 patients were included in this study, written informed consent was obtained from all included patients, and this study was approved by the Ethics Committee of Kagawa University (Permission number: 30-193.

Immunosuppressive Regimens

Patients received immunosuppressive treatment consisting of methylprednisolone, tacrolimus or cyclosporine, mycophenolate mofetil, and basiliximab. In addition, patients who received ABO-incompatible kidney transplantation were administered a single dose of rituximab (200 mg) at 8 days preoperatively. Methylprednisolone was started at 250 mg or 500 mg with subsequent tapering to 4 mg by 2 months after kidney transplantation. Tacrolimus and cyclosporine were adjusted to maintain the initial trough levels of 8 to 10 ng/mL and 150 to 250 ng/mL, respectively, and the long-term target trough levels of 3 to 5 ng/mL and around 100 ng/mL, respectively.

Assessments of Preoperative BMI, AC, and BFA

BMI was calculated as weight in kilograms divided by square of height in meters using data at hospitalization for kidney transplantation. In addition, to determine AC and BFA, we used single-slice CT images at the umbilical level, which were scanned before kidney transplantation. Using the slice, AC and BFA, including subcutaneous fat area (SFA) and visceral fat area (VFA), were automatically calculated by the image analysis software Ziostation2 (Ziosoft Inc., Tokyo, Japan) [11].

Definition of NODAT

International consensus guidelines on NODAT published in 2003 [12] indicated that a diagnosis should be based on the American Diabetes Association criteria for T2DM. Thus, in this study, NODAT was diagnosed according to the American Diabetes Association criteria [13] as diabetes symptoms plus random plasma glucose concentration $\geq$ 200 mg/dL, fasting plasma glucose concentration $\geq$ 126 mg/dL, or hemoglobin A1C $\geq$ 6.5%.

Statistical Analyses

Comparisons of clinical characteristics and BMI, AC, and BFA were made between patients with and without NODAT using the Mann-Whitney U test. Correlations between BMI, AC, and BFA were examined via Spearman's rank correlation analysis. To evaluate the predictive performance of BMI, AC, and BFA, we plotted receiver operating characteristic (ROC) curves. Predictive accuracy in the validation set for the entire model was summarized using sensitivity and specificity, as well as area under the ROC curve (AUC), with associated 95% confidence intervals. The maximum sensitivity and specificity that reflected the intention to maximize the correct classification rate were used as optimal standards to find the best cutoff values. All statistical analyses were performed using SPSS version 12 for Windows (SPSS Inc., Chicago, IL). *P* values less than .05 were considered to indicate statistical significance.

RESULTS

Baseline Characteristics

Table 1 shows the baseline clinical characteristics of patients who did and did not develop NODAT. Of the 62 patients included in this study, 8 (12.9%) developed NODAT during a mean follow-up period of 78.1 months. Of these 8 patients, 5 (62.5%) were diagnosed with NODAT within 1 year of kidney transplantation. In addition, all patients who developed NODAT were administered tacrolimus.

Table 1. Baseline Characteristics

Variable		NODAT	Non-DM	*P* Value
Case	n (%)	8 (12.9)	54 (87.1)	
Diagnosis of NODAT within 1 year	n (%)	5 (62.5)		
Follow-up duration (months)	mean ± SD	78.1 ± 37.9	75.7 ± 37.1	$P = .96^{*}$
Age (years)	mean ± SD	53.3 ± 8.1	45.5 ± 13.2	$P = .22^{*}$
Sex				$P = 1.00^{\dagger}$
Male	n (%)	5 (56.8)	31 (57.4)	
Female	n (%)	3 (43.2)	23 (42.6)	
Blood type				$P = .71^{\dagger}$
Compatible	n (%)	4 (50.0)	34 (62.9)	
Incompatible	n (%)	4 (50.0)	20 (37.1)	
Type of CNI				$P = 1.00^{\dagger}$
Tacrolimus	n (%)	8 (100)	48 (88.7)	
Cyclosporine	n (%)	0 (0)	6 (11.3)	

CNI, calcineurin inhibitor; DM, diabetes mellitus; NODAT, new-onset diabetes after transplant; SD, standard deviation.
*Mann-Whitney U test.
†Chi-square for independence.

Table 2. Body Composition and Regional Fat Mass

Variables		NODAT	Non-DM	*P* value*
Abdominal circumference (cm)	mean ± SD	87.2 ± 11.5	76.9 ± 10.7	$P = .05$
Body mass index (kg/m^2)	mean ± SD	24.7 ± 4.5	21.5 ± 3.7	$P = .02$
Body fat area (cm^2)	mean ± SD	267.7 ± 120.4	132.7 ± 10.5	$P = .01$
Subcutaneous fat area (cm^2)	mean ± SD	170.2 ± 89.7	81.3 ± 68.8	$P < .01$
Visceral fat area (cm^2)	mean ± SD	97.5 ± 48.6	51.4 ± 51.3	$P = .01$

DM, diabetes mellitus; NODAT, new-onset diabetes after transplant; SD, standard deviation.
*Mann-Whitney U test.

However, there was no significant difference concerning the rate of incompatible transplantation, type of calcineurin inhibitor, age at time of kidney transplantation, and sex between those with and without NODAT.

Body Composition and Regional Fat Mass in Renal Graft Recipients

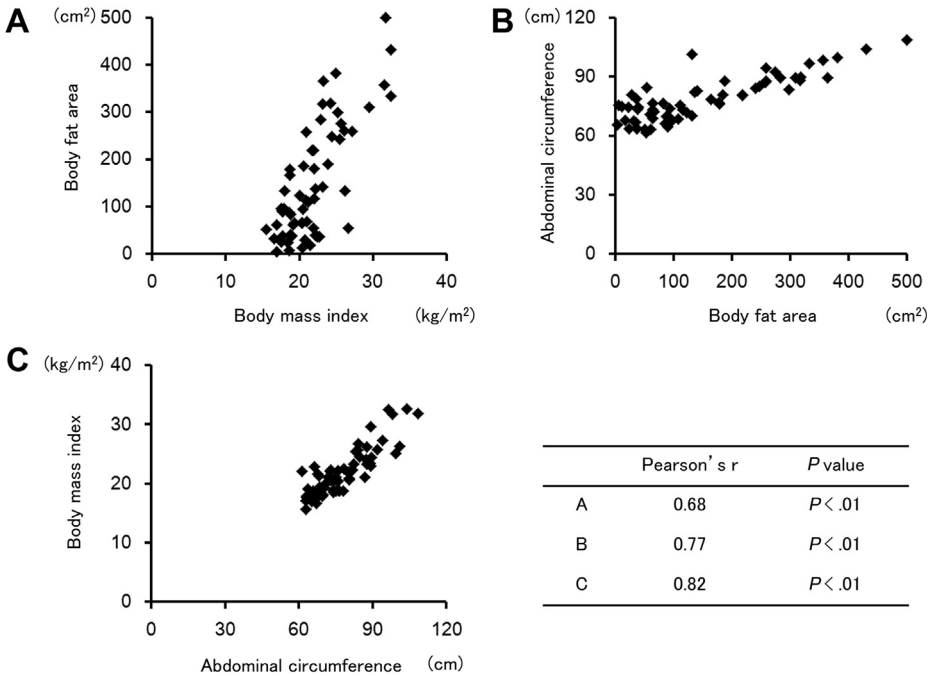
Table 2 shows the preoperative body composition and regional fat mass in patients with or without NODAT. The mean preoperative values of BMI and AC in patients with NODAT were 24.7 kg/m^2 and 87.2 cm, respectively, and were notably higher than in those without NODAT ($P = .02$, $P = .05$, respectively). In addition, BFA was significantly larger in patients with NODAT than in those without NODAT ($P < .01$). Furthermore, the mean values of preoperative SFA and VFA in patients with NODAT were 170.2 cm^2 and 97.5 cm^2 and were significantly larger than in patients without NODAT ($P = .01$ both).

Relationships Between BFA, BMI, and AC in Renal Graft Recipients

The relationships between BFA, BMI, and AC in renal graft recipients are shown in Fig 1. The correlation analyses revealed relationships between BFA and BMI ($r = 0.68$, $P < .01$). BFA was also correlated with AC ($r = 0.77$, $P < .01$). In addition, AC was positively correlated with BMI ($r = 0.82$, $P < .01$).

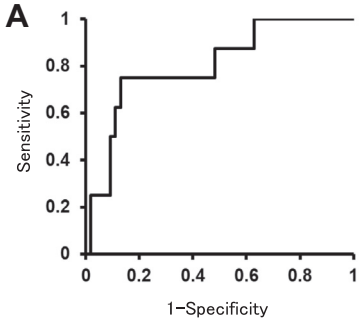
Predictors of NODAT in Renal Graft Recipients

To determine the most accurate predictor of NODAT in renal graft recipients between BMI, AC, and BFA, including SFA and VFA, we compared the area under the curve (AUC) of those indicators (Fig 2). ROC curve analyses demonstrated that preoperative BFA had a considerable predictive accuracy for the development of NODAT with an AUC of 0.803 (sensitivity 75%, specificity 87%) among all the indicators, and its cutoff value was 259.2 cm^2.



	Pearson's r	*P* value
A	0.68	$P < .01$
B	0.77	$P < .01$
C	0.82	$P < .01$

Fig 1. The correlation analyses revealed relationships between **(A)** BFA and BMI, **(B)** BFA and AC, and **(C)** AC and BMI. AC, abdominal circumference; BFA, body fat area; BMI, body mass index.



B

Variable	AUC	Sensitivity	Specificity	Cutoff value
Abdominal circumference	0.745	0.63	0.85	87.7 cm
Body mass index	0.711	0.75	0.74	22.9 kg/m^2
Body fat area	0.803	0.75	0.87	259.2 cm^2
Subcutaneous fat area	0.780	0.75	0.82	139.6 cm^2
Visceral fat area	0.759	0.75	0.78	83.3 cm^2

Fig 2. ROC curve analyses demonstrated that preoperative BFA had the greatest predictive accuracy for the development of NODAT, with an AUC of 0.803 (sensitivity 75%, specificity 87%) among all indicators (**A** and **B**). AUC, area under the curve; BFA, body fat area; NODAT, new-onset diabetes after kidney transplantation; ROC, receiver operating characteristic.

DISCUSSION

With improvements in patient and graft survival, increasing attention has been placed on complications that contribute to long-term patient morbidity and mortality. NODAT was first described as a complication of kidney transplantation 50 years ago by Starzl et al [14]. Currently, it is widely identified as 1 of the common complications of kidney transplantation and is a strong predictor of graft failure and cardiovascular mortality in renal graft recipients [2–4,6]. However, the cumulative incidence of NODAT ranges between 13% and 16% at 1-year post-transplantation and increases with time [2,15]. This study also showed that 12.9% of recipients developed NODAT, and 62.5% of NODAT recipients were diagnosed with NODAT within 1 year of kidney transplantation. The incidence of NODAT in renal graft recipients is still high, particularly in the first year.

Risk factors for NODAT are categorized as nonmodifiable, modifiable, or potentially modifiable [1]. Excessive accumulation of body fat is a modifiable risk factor and is generally considered a risk factor for NODAT in the early phase after kidney transplantation [1,7,8]. Recently, adiponectin, which is mainly secreted by the adipocytes in fat tissues, has been reported to improve insulin sensitivity and exert antidiabetic effects [16]. Serum adiponectin was shown to have a negative correlation with BFA [17]. Moreover, it has been reported that a reduction of adiponectin was correlated with the development of diabetes in renal graft recipients [18]. This study demonstrated that preoperative BFA was notably larger in patients with NODAT than in patients without NODAT. Identifying the excessive accumulation of body fat, particularly within 1 year after kidney transplantation, may help to reduce the risk and facilitate the early treatment of NODAT, leading to the prevention of its complications and adverse patient and graft outcomes.

A recent meta-analysis showed that BMI was an independent risk factor of NODAT in renal graft recipients [9]. In addition, Tokodai et al demonstrated that an increase in BMI is associated with the development of NODAT [7]. In clinical practice, BMI is the most common diagnostic index of obesity; however, BMI cannot directly measure body fat accumulation. This study measured BFA using CT in order to estimate body fat accumulation accurately. Although our correlation analyses revealed a relationship between BFA and BMI, preoperative BFA could be a more accurate predictive marker of NODAT in renal graft recipients compared to preoperative BMI. These findings underline the importance of routine preoperative BFA measurements in clinical practice.

CT is the gold standard for the quantitative assessment of body fat accumulation [19]. Currently, the volume of body fat can be generated using multiple single-slice CT images. In addition, three-dimensional volumetric analysis is more accurate than two-dimensional assessment for body fat accumulation [10]. However, single-slice images are usually employed in clinical practice to reduce costs and radiation exposure. Kobayashi et al showed that single-slice BFA at the umbilicus level was strongly correlated with the value of three-dimensional volumetric analysis [20]. This study used BFA, which was calculated using the single slice at the umbilical level of CT images. Further investigation is needed to clarify whether preoperative body fat volume can predict the development of NODAT more accurately compared with BFA in kidney transplant recipients.

The limitations of this study include its small sample size and retrospective design. In addition, the incidence of NODAT was probably underestimated because the oral glucose tolerance test was not available for the diagnosis of NODAT. Furthermore, although post-transplantation risk factors such as delayed graft function, acute rejection, and infection are also important regarding the occurrence of NODAT, their presence was not ascertained before kidney transplantation. Therefore, this study did not investigate their effects on the development of NODAT.

CONCLUSIONS

To our knowledge, this is the first study showing that preoperative BFA calculated using CT could be used a predictive marker of NODAT in renal graft recipients. This finding underlines the importance of routine preoperative BFA measurements in clinical practice.

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