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ORIGINAL ARTICLE

Validity of glycated haemoglobin to diagnose new onset diabetes after transplantation

Shazia Shabir, Seema Jham, Lorraine Harper, Simon Ball, Richard Borrows and Adnan Sharif

Renal Institute of Birmingham, Queen Elizabeth Hospital, Birmingham, UK

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Correspondence
Dr Adnan Sharif, Renal Institute of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2WB, UK.
Tel.: 0121 371 5861;
fax: 0121 472 4942;
e-mail: sharif_adnan@hotmail.com

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Summary

Diagnosing new onset diabetes after transplantation (NODAT) by glycated haemoglobin (HbA1c) has not been validated against the gold-standard oral glucose tolerance test (OGTT). We analysed the predictive and optimum value of HbA1c to diagnose NODAT amongst nondiabetic renal transplant recipients. Assessment of glucose metabolism (OGTT and HbA1c) was prospectively undertaken at 3 and 12 months post-transplantation in 71 nondiabetic renal transplant recipients. Receiver operator characteristic (ROC) curve analyses were performed to determine accuracy, sensitivity, specificity and area under curve (*c*-statistic). Incidence of NODAT at 3 and 12 months post-transplantation was 14.3% and 9.5% respectively. At 3 months, optimum HbA1c cut-off value for predicting NODAT based on fasting glucose was 7.35 [AUC 1.00 (sensitivity 100.0%, specificity 100.0%, $P = 0.004$)] and for postprandial glucose-defined NODAT was 6.20 [AUC 0.98 (sensitivity 100.0%, specificity 88.9%, $P < 0.001$)]. At 12 months, optimum HbA1c cut-off value for both fasting- and postprandial glucose-defined NODAT was 6.45 [AUC 0.92 (sensitivity 100.0%, specificity 87.5%, $P = 0.048$) and AUC 0.84 (sensitivity 75.0%, specificity 89.5%, $P = 0.026$) respectively]. Concordance between diagnosis of NODAT (OGTT+, HbA1c+) and nondiagnosis of NODAT (OGTT−, HbA1c−) was 88.9% and 98.7% respectively. To conclude, HbA1c ($\geq 6.5\%$) can be utilized to diagnose NODAT beyond 3 months post-transplantation but the OGTT remains the gold-standard tool.

Introduction

The incidence and prevalence of new onset diabetes after transplantation (NODAT), and its contribution to adverse outcomes post solid organ transplantation [1], has focussed attention on timely and accurate diagnosis to facilitate targeted intervention. Although historically the diagnosis of NODAT was heterogeneous amongst transplantation centres, consensus guidelines in 2003 [2] established uniform diagnostic criteria for NODAT modelled on contemporaneous guidelines issued by the American Diabetes Association (ADA) for diagnosis of diabetes mellitus. Specifically, it established a triad of diagnostic criteria for the diagnosis of NODAT based upon fasting glucose, postprandial glucose and symptomatic hyperglycaemia. This introduced consistency in diagnosis of NODAT and allowed comparative analysis for clinical and research perspectives.

However, NODAT consensus guidelines are now outdated and differ from contemporaneous ADA diabetes guidelines in one important aspect with regards to diagnosis; the utility of glycated haemoglobin (HbA1c). Although HbA1c-based diagnosis is now established with the latest diagnostic classifications of diabetes mellitus in the general population [3], there has been no official adoption of HbA1c to diagnose NODAT. This reflects a lack of validation for HbA1c use for this specific purpose in the context of transplantation. There are numerous limitations to ubiquitous use of HbA1c post kidney transplantation [4] and in the absence of any clinical evidence for efficacy it is difficult to make clear recommendations. However, use of HbA1c to diagnose NODAT is beginning to occur within the kidney transplant community on the assumption of validity [5,6]. It is therefore critical to substantiate its validity amongst kidney transplant recipients and the aim of this

study was to correlate HbA1c with fasting and postprandial glucose metabolism, assessed by an oral glucose tolerance test (OGTT), and to determine the optimum cut-off HbA1c value to diagnose NODAT.

Patients and methods

Patient cohort

This was a prospective analysis of incident nondiabetic renal transplant recipients who received serial assessment of glucose metabolism by concomitant OGTT and HbA1c. Pretransplantation diabetes mellitus was excluded from the patient cohort with the use of fasting glucose criteria. Recipients with overt clinical NODAT post kidney transplantation (with subsequent omission of OGTT and/or HbA1c) were excluded from analysis. Although performing these tests in recipients with overt NODAT could have influenced the outcome of these results, excluding such recipients is consistent with actual clinical practice and therefore the methodology is relevant to current practice. In total 71 patients without evidence of diabetes prior to transplantation were recruited into this prospective study between February 2009 and October 2010. Ethical approval for this study was obtained from the North Staffordshire Research and Ethics Committee and written informed consent was obtained from all patients.

Assessment of glucose metabolism

An OGTT was performed according to the World Health Organization (WHO) criteria at two time points post-transplantation: 3 and 12 months respectively. With regards to OGTT methodology, fasting blood samples were taken for glucose and lipids in addition to routine clinic bloods after an overnight 12 h fast. Patients were then administered 75 g of glucose 113 ml of Polycal® (Nutricia Clinical, Trowbridge, UK) with postprandial samples taken 2 h after administration of glucose. Pre- and post-OGTT samples were hand delivered to the laboratory for urgent analysis. Patients refrained from physical exercise during the 2 h of the OGTT. The results of the test were classified by WHO guidelines [7].

Concomitant HbA1c at 3 and 12 months post-transplantation was measured by ion exchange, high-performance liquid chromatography using the Tosoh G8 A1C Variant Mode analyser with PIANO Data Management System (TOSOH Europe, Tessenderlo, Belgium; imprecision CV <3.0%). Conversion of HbA1c from DCCT (Diabetes Control and Complications Trial) to IFCC (International Federation of Clinical Chemistry) units is by the formula: IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) − 2.15] × 10.929. In this article, we have utilized DCCT-HbA1c units throughout.

Established NODAT consensus guidelines [2] were utilized to diagnose patients with new-onset diabetes after kidney transplantation (either by random, fasting or postprandial hyperglycaemia). For the purpose of this study, we did not utilize HbA1c for diagnostic purpose but simply to correlate with diagnosis of NODAT. Other biochemical and clinical parameters were concomitantly checked. We specifically checked both haemoglobin and estimated glomerular filtration rate (eGFR) by modification of diet in renal disease (MDRD) formula to allow accurate interpretation of the HbA1c assay in the context of these potential confounders.

Immunosuppression

All patients received standardized immunosuppression consisting of basiliximab induction (20 mg intravenously day 0 and 4) and methylprednisolone (500 mg intravenously day 0). Maintenance immunosuppression for all kidney transplant recipients was with tacrolimus (target trough level 5–8 ng/ml measured by high-performance liquid chromatography with tandem mass spectrometry), mycophenolate mofetil (2 g daily in split doses) and corticosteroids (starting dose 20 mg daily and titrated down to long-term maintenance dose of 5 mg daily by 3 months post-transplantation). Episodes of acute rejection were biopsy-proven in all cases, and treated with corticosteroid boluses. 100 days of valganciclovir (renal dose adjusted) was given as CMV prophylaxis to seronegative recipients of kidneys from seropositive donors. Tuberculosis prophylaxis was given to high-risk patients (South Asian ethnicity, previous exposure). Nystatin oral solution and co-trimoxazole was administered to all patients for 3 and 6 months respectively.

Statistics

Statistical analysis was performed using standard software (SPSS Version 20, Chicago, IL, USA). Receiver operator characteristic (ROC) curve analyses were performed as graphical plots based upon a binary classifier system (NODAT or not) to determine accuracy, sensitivity, specificity and area under curve (*c*-statistic). A *P*-value <0.05 was considered significant in the statistical analysis.

Results

Seventy-one nondiabetic renal transplant recipients were recruited into this study and had their glucose metabolism prospectively analysed by means of an OGTT and concomitant HbA1c. The baseline demographics of these recipients are displayed in Table 1.

Table 1. Demographics of renal transplant recipients participating in prospective analysis of glucose metabolism.

Demographic	Number (total = 71)	Percentage (%)
Gender		
Male		58.8
Female		41.2
Recipient age		
Median (range)	43 (17–70)	
Ethnicity		
White		74.1
South-Asian		16.5
Black		8.2
Mixed race		1.2
Cause of end stage renal failure		
Glomerular		43.5
Hereditary structural/cystic		14.1
Vascular		8.2
Interstitial		13
Other		7.1
Unknown		14.1
Type of transplant		
Living donor		52.9
Deceased donor		47.1
Recipient's CMV status		
Seropositive		54.1
Seronegative		45.9

Diagnosis of new-onset diabetes after kidney transplantation

At 3 months post-transplantation, 14.3% of the cohort was diagnosed with NODAT by OGTT. AT 12 months post-transplantation, 9.5% were diagnosed with NODAT in a similar fashion.

The utility of HbA1c in predicting NODAT was assessed against a diagnosis of NODAT based upon: (i) fasting blood glucose, (ii) postprandial blood glucose and (iii) either fasting or postprandial blood glucose. At both the 3- and 12-month time points, all patients with NODAT on the basis of fasting blood glucose also displayed NODAT based on postprandial blood glucose (although the reverse was not true). Therefore, two analyses were conducted for fasting (and postprandial) blood glucose, and for postprandial blood glucose alone.

Correlation of HbA1c with OGTT at 3 months post-transplantation

At 3 months post-transplantation, the optimum HbA1c cut-off value for predicting NODAT based on fasting glucose was 7.35 (AUC 1.00, sensitivity 100.0%, specificity 100.0%, $P = 0.004$) and for postprandial glucose-defined NODAT was 6.20 (AUC 0.98, sensitivity 100.0%, specificity 88.9%, $P < 0.001$). ROC curve analyses are shown in Fig. 1a. Table 2 displays the sensitivities and specificities of different values of HbA1c in predicting NODAT. Based upon binary logistic regression models, the rates of positive OGTT results at different levels of HbA1c were subsequently plotted (see Fig. 1b).

Correlation of HbA1c with OGTT at 12 months post-transplantation

Similarly, to choose the optimum cut-off value at 12 months, the sensitivity and specificity for each observed HbA1c measurement was calculated (see Table 3). The optimum HbA1c cut-off value for both fasting glucose and postprandial glucose-derived NODAT was 6.45 (fasting glucose: AUC 0.92, sensitivity 100.0%, specificity 87.5%, $P = 0.048$ and postprandial glucose: AUC 0.84, sensitivity 75.0%, specificity 89.5%, $P = 0.026$). ROC curves are shown in Fig. 2a. Based upon binary logistic regression models, the rates of positive OGTT results at different levels of HbA1c were subsequently plotted (see Fig. 2b).

Concordance between HbA1c and OGTT-diagnosed NODAT

Pooling all results together, 3 and 12 months glycaemic assessments, we observed 88.9% concordance for a positive OGTT-derived NODAT diagnosis independently by either HbA1c ($\geq$ 6.5%) or by OGTT (fasting glucose $\geq$7.0 mmol/l and/or postprandial glucose $\geq$11.1 mmol/l). In patients not diagnosed with NODAT by OGTT, there was 98.7% concordance for a negative HbA1c (< 6.5%) or OGTT (fasting glucose <7.0 mmol/l and/or postprandial glucose <11.1 mmol/l) respectively.

Comparing those renal transplant recipients with HbA1c $\geq$ 6.5% vs. <6.5%, respectively, there was no statistically significant difference in haemoglobin (12.4 vs. 12.8 g/l), eGFR (47.7 vs. 58.1 ml/min), isotopic GFR (49.2 vs. 59.4 ml/min)) or urine albumin–creatinine ratio (6.2 vs. 6.5 mg/mmol) respectively.

Discussion

In this study, we have determined the optimum HbA1c level for diagnostic classification of NODAT that is broadly similar to that recommended in the general population; i.e. 6.5% (or 48 mmol/mol by IFCC criteria). There was also high concordance between OGTTs and HbA1c for both positive and negative results respectively. Finally no difference in allograft function, haemoglobin or proteinuria was observed between patients with glycated haemoglobin above or below 6.5%. It is our opinion that HbA1c can be utilized to diagnose NODAT in clinical/research settings, and diagnostic criteria should mirror those amongst the

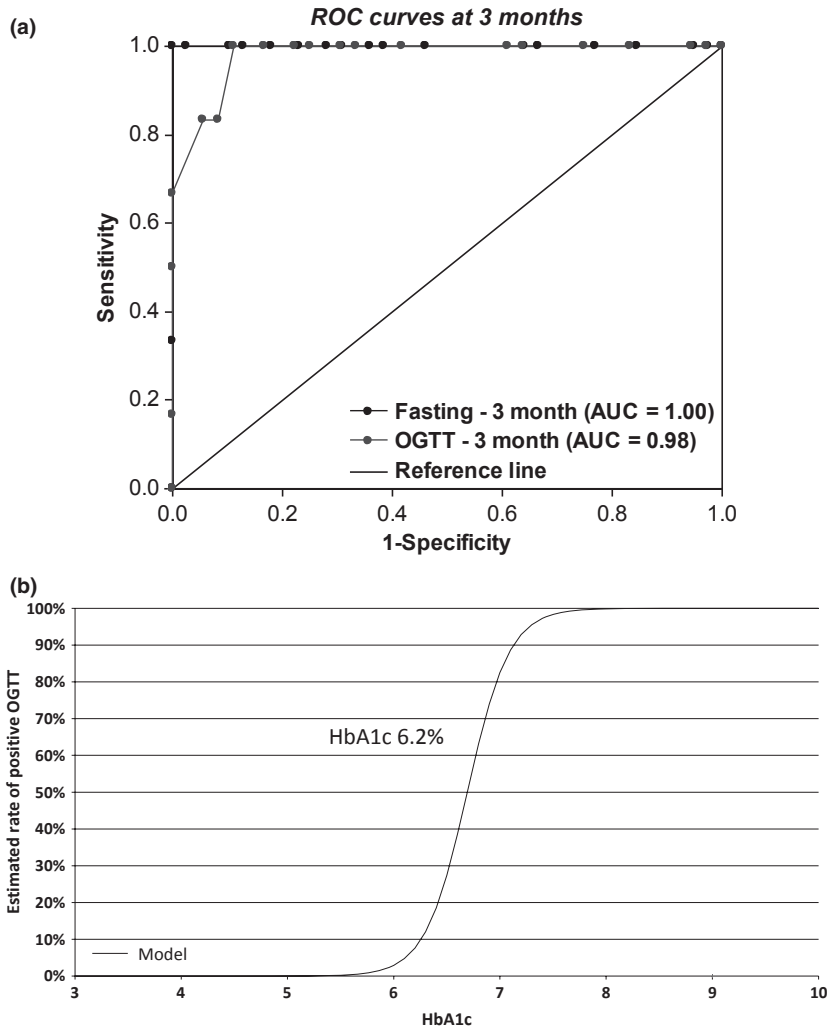

Figure 1 (a) demonstrates receiver operator curves of HbA1c with fasting/postprandial glucose [from oral glucose tolerance test (OGTT)] at 3 months post-transplantation. Based upon binary logistic regression models, the rates of positive OGTT results at different levels of HbA1c were subsequently plotted and demonstrated in (b).

general population. This should simplify the diagnosis of NODAT and is therefore of clinical importance. Nevertheless, although the advantage of HbA1c lies in its convenience and logistic simplicity for glycaemic assessment, at the present moment the OGTT should remain the gold standard investigation of glucose metabolism post-transplantation, particularly at earlier stages following transplantation.

Our data are consistent with diabetes mellitus literature indicating shifts in the relative contribution from postprandial glucose at good to fair HbA1c levels (<7.3% to <9.2%) to fasting plasma glucose at high HbA1c (>9.3%) respectively [8]. HbA1c, fasting glucose and postprandial glucose are considered to be distinct components of monitoring glycaemic control [9,10]. Therefore, although it is often assumed that changes in HbA1c, fasting glucose and postprandial glucose values mirror each other, the reality of the situation is more complex because of their dissimilar profiles. However, there are numerous cautions in relation with interpretation of the HbA1c assay in the context of kidney transplantation that must be acknowledged including post-transplantation anaemia and degree of renal (or renal allograft) function [11–18]. The optimum cut-off value for HbA1c to diagnose NODAT at 12 months post-transplant in our study mirrored that in the general population, while at 3 months post-transplantation there was some variability. This would support the argument that the HbA1c assay earlier post kidney transplantation is fraught with technical and logistical issues. The use of the 3-month time point in our study was arbitrary and clearly more work is required to validate accuracy, efficacy and optimum timing for use of the HbA1c assay.

Table 2. Determination of the optimum cut-off value for HbA1c against 3-month oral glucose tolerance test (%).

3 months				
	Fasting glucose		Postprandial glucose	
Hba1c	Sensitivity	Specificity	Sensitivity	Specificity
3.20	100.0	0.0	100.0	0.0
4.50	100.0	2.6	100.0	2.8
4.90	100.0	5.1	100.0	5.6
5.10	100.0	15.4	100.0	16.7
5.25	100.0	23.1	100.0	25.0
5.35	100.0	33.3	100.0	36.1
5.45	100.0	35.9	100.0	38.9
5.55	100.0	53.8	100.0	58.3
5.65	100.0	61.5	100.0	66.7
5.75	100.0	64.1	100.0	69.4
5.85	100.0	69.2	100.0	75.0
5.95	100.0	71.8	100.0	77.8
6.05	100.0	76.9	100.0	83.3
6.20	100.0	82.1	100.0	88.9
6.35	100.0	87.2	83.3	91.7
6.55	100.0	89.7	83.3	94.4
6.85	100.0	97.4	66.7	100.0
7.35	100.0	100.0	50.0	100.0
7.85	33.3	100.0	16.7	100.0
9.00	0.0	100.0	0.0	100.0
AUC	1.00 ($P = 0.004$)		0.98 ($P < 0.001$)	

Table 3. Determination of the optimum cut-off value for HbA1c against 12-month oral glucose tolerance test (%).

12 months				
	Fasting glucose		Postprandial glucose	
Hba1c	Sensitivity	Specificity	Sensitivity	Specificity
3.30	100.0	0.0	100.0	0.0
4.55	100.0	2.5	100.0	2.6
4.95	100.0	5.0	100.0	5.3
5.15	100.0	7.5	100.0	7.9
5.25	100.0	10.0	100.0	10.5
5.35	100.0	17.5	100.0	18.4
5.45	100.0	35.0	100.0	36.8
5.55	100.0	42.5	100.0	44.7
5.65	100.0	47.5	100.0	50.0
5.75	100.0	57.5	75.0	57.9
5.90	100.0	65.0	75.0	65.8
6.10	100.0	77.5	75.0	78.9
6.25	100.0	82.5	75.0	84.2
6.35	100.0	85.0	75.0	86.8
6.45	100.0	87.5	75.0	89.5
6.55	50.0	90.0	50.0	92.1
6.65	50.0	92.5	50.0	94.7
6.90	0.0	97.5	0.0	97.4
8.10	0.0	100.0	0.0	100.0
AUC	0.92 ($P = 0.048$)		0.84 ($P = 0.026$)	

Determining the optimum threshold is important as HbA1c is an important marker of surreptitious deteriorating glucose metabolism in nondiabetic renal transplant recipients [19]. Valderhaug *et al.* [20] showed the advantage of the HbA1c assay, both independently and in combination with fasting blood glucose, for risk stratification of renal transplant recipients who would benefit from an OGTT for diagnostic verification of NODAT. The benefit of the HbA1c assay has also been demonstrated as a screening tool for identifying subclinical NODAT by Hoban *et al.* [21]. Although previously there was concern at adoption of HbA1c post kidney transplantation [22], in the contemporaneous setting many of these concerns can be safely disregarded [4].

The value of a postprandial glucose, by OGTT, rather than fasting glucose for diagnosis of abnormal glucose metabolism is now well-documented in the transplantation literature [23,24]. Although we have outlined the potential usage of HbA1c for diagnosis of NODAT, the OGTT should remain the investigation of choice for diagnosis of abnormal glucose metabolism post-transplantation where logistically possible. Although increasing levels of fasting glycaemia has been associated with increasing risk of cardiovascular events post-transplantation [25], only abnormal postprandial hyperglycaemia has been associated with long-term risk of mortality in a robust analysis. Valderhaug *et al.* [26] assessed 1410 nondiabetic renal transplant recipients with an OGTT at 10 weeks post-transplantation and longitudinally observed these patients for a median of 6.7 years (range 0.3–13.8 years). Compared with recipients with normal glucose tolerance, patients with NODAT had higher all-cause [hazard ratio 1.54 (95% CI 1.09–2.17)] and cardiovascular mortality [hazard ratio 1.80 (95% CI 1.10–2.96)], patients with impaired glucose tolerance had higher all-cause mortality alone [hazard ratio 1.39 (1.01–1.91)] and recipients with impaired fasting glucose had no increased risk of either all-cause or cardiovascular mortality. No similar analysis has been done looking at HbA1c and future risk of death in a transplantation model.

There are limitations to this work that should be appreciated in the interpretation of these results. First, there are the generic limitations associated with the use of the HbA1c assay in the context of transplantation [4] that have already been discussed. Second, the analysis was performed on a small patient cohort, although we contend the benefit of performing ROC curve analyses statistically overcomes the shortcomings of a small population sample. Finally, the utility of HbA1c as a diagnostic tool may be validated in this analysis, however, its prognostic ability has not been ascertained. Although the evidence for postprandial transplant-associated hyperglycaemia as a risk factor for cardiovascular events [26] post-transplantation has been established, similar

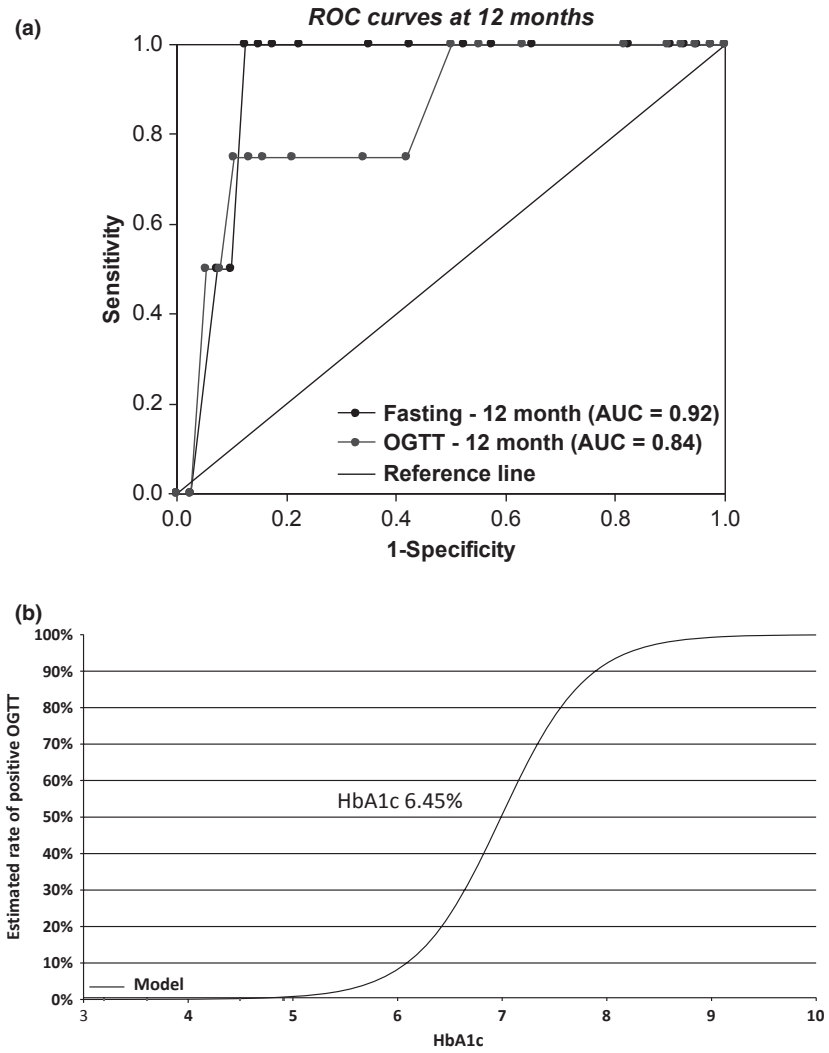

Figure 2 (a) demonstrates receiver operator curves of HbA1c with fasting/postprandial glucose [from oral glucose tolerance test (OGTT)] at 12 months post-transplantation. Based upon binary logistic regression models, the rates of positive OGTT results at different levels of HbA1c were subsequently plotted and demonstrated in (b).

evidence for HbA1c is lacking. It should be appreciated that the association of HbA1c and microvascular diabetes-related complication is well-established in the general population, but dichotomous reports exist regarding correlation with macrovascular diabetes-related complications. In the post-transplantation setting, microvascular diabetes-related complications have been rarely reported [27] and this may reflect low prevalence or under-reporting. As ADA-derived diagnostic thresholds are primarily based upon correlation with emergence of microvascular disease, it remains to be seen whether ADA diagnostic thresholds should be simply translated from the general to the transplant population. However, the ability to maintain consistency in diagnostic capabilities and to maintain consensus would argue retention of the ADA-derived diagnostic thresholds but further research is required to ensure translatability in a post-transplant setting.

To conclude, this study is the only validation of the use of HbA1c for the purpose of diagnosing NODAT. It would be prudent to translate the cut-off level of 6.5% from the general population to the transplant population, although this is likely to be more accurate at the 12-month point compared with 3 months. Further work is required to look at the utility of HbA1c in the context of transplantation but our results suggest it should be acknowledged as a diagnostic tool for NODAT screening beyond the early period post-transplantation, with caveats in mind. However, where logistically possible, we believe the OGTT should remain the gold-standard test for diagnosis of NODAT.

Authorship

SS, RB and AS: conception/design. SS, RB and AS: analysis and interpretation of data. SS, SJ, LH and RB: contribution to conduct of research. SS, SJ, LH, SB, RB and AS: drafting the article or revising it.

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