

Evaluation of HbA1c and fasting plasma glucose for the diagnosis of post-transplant diabetes mellitus and prediabetes in renal transplant recipients

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ABSTRACT

Background: Diabetes mellitus after renal transplantation (PTDM) is a frequent complication and if not timely diagnosed may result in life-threatening microvascular complications. Fasting plasma glucose (FPG) test is considered preliminary screening tool while oral glucose tolerance test (OGTT) is a 'benchmark test' for the screening of DM and prediabetes in PTDM. HbA1c test is also now being considered as a most convenient diagnostic tool for Type 2 diabetes mellitus and prediabetes. Therefore, current study was undertaken to evaluate HbA1c and FPG tests for the diagnosis of diabetes and prediabetes by taking OGTT as a gold standard.

Patients and methods: In this prospective study, total 40 renal transplant recipients were recruited from Jinnah and Mayo Hospitals Lahore from January to August 2012. The participants aged ≥ 18 years who underwent renal transplants more than 3 months ago with no prior history of diabetes mellitus were included. Blood samples were obtained for FPG, OGTT and HbA1c tests according to standard guidelines. Based on ADA thresholds of OGTT, patients were categorized into three groups: 1) DM; 2) prediabetes, and 3) normal plasma glucose levels.

Results: Hyperglycemia was seen in 22 (55%) patients including 6 (15%) with PTDM and 16 (40%) with prediabetes based on OGTT. High value of AUC of FPG (0.8469 $p < 0.001$) vs. AUC of HbA1c (0.7257 $p = 0.0012$) proved that it had relatively more diagnostic potential for early detection of prediabetes in RTR. Similarly, FPG had more AUC (0.8079, $p < 0.001$) value vs. HbA1c AUC (0.7272, $p = 0.0005$) value for screening of PTDM in RTR. Although, the specificity of both the tests were the same (25%). However, FPG was more sensitive (81.25%) as compared to HbA1c (51.52%).

Conclusions: FPG performs as a better screening tool for PTDM and prediabetes; and ADA proposed screening criteria of HbA1c is relatively less sensitive in RTR for local population. A combined use of both tests would be a more appropriate approach for the quick screening of PTDM and prediabetes in RTR.

Keywords:

PTDM, Prediabetes, transplantation, HbA1C, FPG

INTRODUCTION

Diabetes mellitus after renal transplantation (PTDM) is a frequent complication.¹ Incidence of diabetes among renal transplant recipients (RTR) is higher than in the general population.² If hyperglycemia is not timely diagnosed it may result in life-threatening microvascular complications.³ As per International Consensus Guidelines on PTDM, its diagnosis should be based on the criteria of type 2 DM set by American Diabetes Association (ADA) in 2003.⁴ Fasting plasma glucose (FPG) test is considered as preliminary screening tool for PTDM and prediabetes while oral glucose tolerance test (OGTT) is considered as a

'benchmark test' for the screening of DM and prediabetes. Various studies also advocate its diagnostic use in transplant settings.⁵⁻⁷

HbA1c test is now being considered as a most convenient diagnostic tool for Type 2 diabetes mellitus and prediabetes as it does not require any fasting state, and it presents mean blood glucose levels of previous 60-90 days. Moreover, elevated levels of HbA1c also associate with onset of micro vascular morbidities in diabetes and PTDM.³ As compared to plasma glucose testing, HbA1c profiling testing has more pre-analytical stability and rare biologic variability.⁸ According to ADA recommendations of 2010, 6.5% and 5.7–6.4% thresholds of HbA1c can be used for screening of Diabetes and prediabetes respectively.⁹ HbA1c monitoring along with afternoon capillary blood glucose testing can screen many undiagnosed cases without exploiting OGTT. A peculiar insulin resistance

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and hyperglycemia has been observed in transplant patients before taking lunch.¹⁰

A discrepancy still exists to diagnose diabetes in transplant settings, and only a little congruity can only be made for screening method of PTDM.^{11,12} HbA1c is an acceptable diagnostic test among the general population, yet its role to screen PTDM remains to be confirmed. No single approach other than OGTT can be deduced to accurately predict PTDM in RTR.¹³

Studies investigating the best screening marker for PTDM, are currently lacking in local population. The primary objective of this study was to compare screening potential of routinely used diagnostic tests (HbA1c and FPG) for early prediction PTDM in RTR and, to scrutinize applicability of ADA cut-off values of HbA1c and FPG in renal transplant settings.

PATIENTS AND METHODS

This research study is part of a research project, which was ethically sanctioned by the Human Research Ethical Committees of King Edward Medical University/Mayo Hospital, Lahore (No. PSW52A/MH; Dated 21.4.2011), and Allama Iqbal Medical College/Jinnah Hospital, Lahore (No. 77A; Dated 19.4.2011).

In this prospective study, a total of 108 follow up RTR of either sex, registered at the Kidneys centers of Jinnah Hospital, Lahore and Mayo Hospital Lahore, were considered for the study. Duration of study was from January 2012 to August 2012. However, only 40 (35.19%) volunteers (aged 18 years or above, having renal transplantation at least 3 months before enrolment, with no prior history of any type of diabetes or prediabetes, cancer, polycythemia or anemia) were recruited in this study.

Each participant was physically examined for height, weight, blood pressure, and circumferences of hip and waist. The blood samples of each participant, having overnight fasting of as a minimum of eight hours, were drawn in plain test tubes for FPG; and for HbA1c, tubes containing EDTA were used for sample collection.¹³ Then each participant was given a drink of 75g anhydrous glucose in 250mL water; and after two hours second blood sample was taken for OGTT. The blood glucose was estimated by enzymatic colorimetric method using commercial kit (REF 1129005, Linear Chemicals, Spain); and HbA1c was analyzed by fast ion-exchange resin separation method (Cat. No.10657 Human Diagnostic, Germany).

The diagnostic performance of HbA1c test in comparison with FPG test, and the diagnostic potential

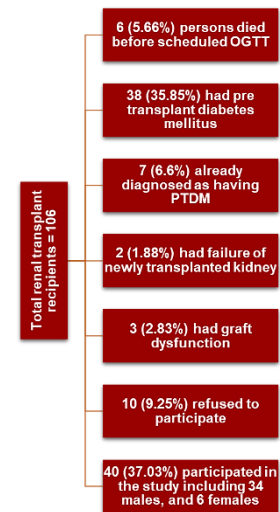


Figure 1. Patient disposition chart

of ADA recommended thresholds of HbA1c for DM and prediabetes were assessed by considering OGTT as a gold standard test. On ADA thresholds, patients were categorized into three groups of PTDM based on OGTT: (a) having normal blood glucose levels (i.e. FPG <6.1mmol/L and after 2 hours <7.8mmol/L); (b) prediabetics were classified into two subcategories including patients with impaired glucose tolerance (i.e. FPG <7.0 mmol/L and after 2 hours sugar level between 7.8-11.1 mmol/L), and impaired fasting glucose (FPG between 6.1-7.0 mmol/L with a normal 2 hours value); and (c) diabetes mellitus type 2 (i.e. FPG >7.0 mmol/L and/or after 2 hours >11.1 mmol/L). For HbA1c, a value of <5.7% was taken as normal while for prediabetes 5.7-6.4%, and for diabetes mellitus $\geq 6.5\%$.¹⁴ Both PTDM and prediabetes groups were collectively termed as hyperglycemic.¹⁵

All the data was statistically analyzed by SPSS version 20 (IBM Statistics, USA). The demographic, anthropometric and clinical characteristics of patients were presented as mean \pm standard deviation (SD) and frequencies as percentages. ROC curve analysis including specificity, sensitivity, PPV and NPV, were used to examine comparative diagnostic performance of HbA1c and FPG tests to predict PTDM and prediabetes defined by OGTT. 0.5 AUC represents the uncritical reference line, whereas perfect accuracy is shown by 1.0 AUC.^{9,13} A p-value <0.05 was defined as statistically significant.

RESULTS

Out of 40 participants, 34 (84.21%) were male and 6 (15.79%) were females. The disposition of the patients

is shown in Figure 1. A high BMI (25.76kg/m²) was recorded for PTDM patients as compared to normal population (20.89 kg/m²). Based on OGTT, hyperglycemia was recorded in 22 (55%) patients, including 6 (15%) with post transplantation diabetes mellitus and 16 (40%) with prediabetes. In renal transplant recipients, mean duration of post transplantation diabetes mellitus was 60 (range 34-87.85) months; whereas it was 29.65 (range 15.25-69.25) months for pre-diabetic patients at the time of study. Table 1 summarizes clinical and anthropometric characteristics of the study participants.

When the patients were tested for PTDM and prediabetes, differences were noted in the frequency of the patients with the diagnostic test used. Out of total 40 patients, 16 (40%) were identified as having PTDM and 7 (17.5%) as prediabetes with HbA1c (Table 2). However, FPG detected 6 (15%) PTDM patients and patients 8 (20%) prediabetes patients (Table 2).

As compared to OGTT, ADA thresholds of HbA1c (5.7%-6.4%) could only screen 17.5% of prediabetes patients. Moreover, 70.83% (95% CL 52.648- 89.018) sensitivity, 47.06 (95% CL 30.281-63.837), 48.57% (95% CL 32.013- 65.130) PPV and 69.57% (95% CL 50.760- 88.370) NPV were noted for HbA1c to predict prediabetes. HbA1c predicted more cases (40%) of PTDM at ADA threshold (6.5%) in comparison with OGTT. Yet, HbA1c had 51.52% (95% CL 34.463- 68.567) sensitivity, 25.00% (95% CL 7.676-42.324) specificity, 48.57% (95% CL 32.013-65.130) PPV and 27.27% (95% CL 8.662-45.883) NPV for screening of PTDM. OGTT diagnosed 40% of the patients as prediabetic, of whom FPG at ADA thresholds (6.1 moml/L-7.0 moml/L) could only diagnose 20% of the patients. The specificity, sensitivity, PPV, and NPV of FPG to predict prediabetes in RTR was 47.06 % (95% CI 30.281-63.837), 76.47% (95% CI 62.212-90.729), 59.09% (95% CI 44.563-73.619) and 66.67% (95% CI 47.807-85.527), respectively. FPG test at ADA threshold (FPG \geq 7.1moml/L) detected all patients of PTDM diagnosed by OGTT with high sensitivity (81.25% (95% CI 67.726- 94.774) but low specificity (25% (95% CI 17.676-42.324). Its PPV and NPV were 59.09% (95% CI 44.563-73.619) and 50.00% (95% CI 21.710-78.290), respectively.

High value of AUC of FPG (0.8469 p<0.001) vs. AUC of HbA1c (0.7257 p=0.0012) proved that it had relatively more diagnostic potential for early detection of prediabetes in RTR. Similarly, FPG had more AUC (0.8079, p<0.001) value vs. HbA1c AUC (0.7272,

Table 1. Anthropometric and clinical characteristics of the study participants

Characteristics	Mean±SD
Age (years)	32.3± 11.54
Body mass index	23.83±6.58
Male waist circumference (inches)	32.25±5.55
Female waist circumference (inches)	30.33±4.76
Males waist hip ratio	0.82±0.06
Females waist hip ratio	0.80±0.06
Systolic blood pressure (mmHg)	126±15.49
Diastolic blood pressure (mmHg)	90.35±23.48
Renal transplant duration (months)	50.58±40.89
Fasting Plasma Glucose (moml/L)	5.35±1.25
2-hour OGTT (moml/L)	8.02±2.92
HbA1c (%)	5.8825±1.35
<i>Drug treatment</i>	<i>n (%)</i>
Azathioprine	8 (20)
Cyclosporine	35 (87.5)
Myclophenolate mofetil	19 (47.5)
Prednisone	30 (75)
<i>Family history</i>	
Diabetes	19 (47.5)
Hypertension	29 (72.5)
Obesity	25 (62.5)

p=0.0005) value for screening of PTDM in RTR. Therefore, FPG had comparatively more diagnostic potential for the screening of prediabetes after transplantation (Figure 2).

DISCUSSION

HbA1c is a recommended test for the screening of hyperglycemia in general population¹⁶ and its diagnostic use in RTR have also been advocated in some studies, but in this study it was not a well performing screening marker in comparison with FPG test. Moreover, the proposed ADA criteria of HbA1c test for the screening of PTDM and prediabetes¹⁶ were also found to be less sensitive in local population.

In this study, ROC analysis showed that FPG had comparatively more screening potential; both for the screening PTDM and prediabetes. For the first time Hoban and colleagues¹⁶ assessed screening potential of HbA1c to diagnose PTDM in 199 RTR and concluded that HbA1c levels had more screening potential as compared to FPG; but, in this study neither ROC analysis was reported nor OGTT was used as diagnostic verification test. In transplant settings, Valderhaug and colleagues⁹ were first to use ROC analysis to determine diagnostic potential of FPG (n = 1467) and

Table 2. Distribution of Patients in different categories of glycemic control by oral glucose tolerance test (OGTT), HbA1c and fasting plasma glucose (FPG)

Diagnosis	OGTT <i>n (%)</i>	HbA1c <i>n (%)</i>	FPG <i>n (%)</i>
Normal	18 (45)	17 (42.5)	26 (65)
Prediabetes	16 (40)	7 (17.5)	8 (20)
Diabetes mellitus	6 (15)	16 (40)	6 (15)

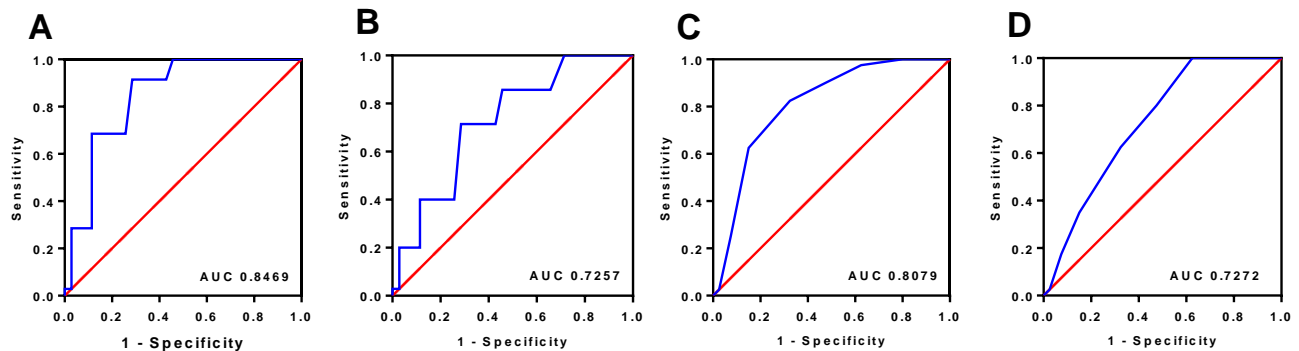


Figure 2. Receiver operating curves for (A and B) prediabetes FPG and HbA1c respectively; (C and D) FPG diabetes mellitus and HbA1c respectively.

HbA1c ($n = 929$) for early screening of PTDM defined by OGTT. They recommended that both tests had considerable screening potential for PTDM, yet HbA1c had higher diagnostic accuracy with (0.817 AUC) at optimal threshold of 5.8% as compared to FPG (0.761 AUC) at optimal threshold of 5.3 mmol/L. Although, findings of this study are somewhat inconsistent with two aforesaid initial studies^{9,16}; however, are consistent with recent study conducted by Bergrem and colleagues who examined the diagnostic accuracy HbA1c and FPG for screening of diabetes based on OGTT cutoffs in the candidates of kidney transplantation.¹⁷ They also used ROC analysis and recommended that contrary to FPG (AUC: 0.734 (95% CI, 0.674-0.795%) with its somewhat low sensitivity, HbA1c (AUC: 0.578 (95% CI, 0.482-0.673%) has not been proved as a well performing test to screen diabetic 2hr-PG in pre-transplant settings. Although, the screening accuracy of HbA1c (AUC: 0.689 (95% CI; 0.586-0.791%) was improved in pre-dialysis patients; but it was still less than that of the FPG (AUC: 0.710 (95% CI, 0.624-0.795%).

In a cohort study¹⁸, FPG test found as a good predictor of onset diabetes (AUC: 0.811 (95% CI, 0.745-0.877%) as compared to HbA1c test (AUC: 0.634 (95% CI, 0.549-0.718%). Furthermore, another study¹⁹ has assessed the diagnostic potential of HbA1c for prediabetes; and in which it was concluded that HbA1c testing was not a good screening tool for prediabetes in RTR. Likewise, our findings also support the findings of the sub-analysis of New Hoorn Study, FPG was recommended as a better screening tool (AUC: 0.937 (95% CI, 0.905-0.969%) for newly diagnosed diabetes vs. HbA1c (AUC: 0.895 (95% CI, 0.861-0.930%).²⁰ In a comparative cross sectional study of HbA1c and FPG in general population, FPG test was recommended as relatively more suitable test to screen diabetic patients.²¹

Zhou and colleagues in their study found that HbA1c had somewhat low predictive ability for both diabetes and prediabetes as compared to FPG test.²²

In our study, the proposed ADA screening criteria of HbA1c for diabetes (HbA1c $\geq 6.5\%$) was very less specific (25% (95% CL 7.676-42.324) and less sensitive (51.52% (95% CL 34.463- 68.567) for PTDM. Moreover, the PPV (48.57% (95% CL 32.013- 65.130) NPV (27.27% (95% CL 8.662-45.883) of ADA criteria were also very low.

Tillman and colleagues¹⁸ also assessed the screening potential of HbA1c for prediabetes (defined by OGTT at ADA thresholds) in RTR, yet no definite cut-off level of HbA1c could be concluded in their cohort. Particularly, the recommended range of HbA1c (5.7%-6.5%) was very less sensitive 26% with 73% NPV.

Comparatively high BMI (25.76kg/m²) in patients of PTDM vs. BMI (20.89 kg/m²) of norm-glycemic individuals was observed local population. These findings were congruent with a study conducted in Caucasians' ethnicity.²³ Studies have also reported necessary risk factors of PTDM in addition demographic, anthropometric, and clinical findings of RTRs.^{24, 25}

More than 84.21% PTDM were males in this study. Gender differences have been found to be linked with onset of PTDM in RTR. Dysfunction in beta cells is more common in women; while men suffer from metabolic syndrome and insulin resistance.²⁶

The predictive potential of the ADA prediabetes criteria of HbA1c was also examined extensively in three different ethnicities i.e. non-Hispanic whites, African Americans, and Hispanics) by Lorenzo and colleagues.²⁷ However, the proposed criteria was again proved less sensitive and could only detect 23.6% of prediabetes patients. Furthermore, only identified one

third diabetic cases could only be detected at HbA1c $\geq 6.5\%$. Another study also assessed the HbA1c $\geq 6.5\%$ as a new definition of diabetes and found this criterion as having low diabetic predictive ability.²² One of the limitations of this study include, small sample size due to high cost of renal transplantation and follow up expenses.

CONCLUSION

In this study, FPG measurements performed better than HbA1c for diagnose PTDM and prediabetes in RTR; yet combined use of both would cover almost all cases of PTDM and prediabetes. More multicenter prospective and long-term clinical trials are needed to authenticate our findings.

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