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Should Pre-Transplant Hemoglobin A_{1c} Be Used to Predict Post-Transplant Compliance in End-Stage Renal Disease Patients Undergoing Kidney Transplantation?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF **Samantha L. Terranella**
ACDE **Jennifer Poirier**
ADE **Edie Y. Chan**
ADE **Martin Hertl**
ABCDEF **Oyedolamu K. Olaitan**

Department of Surgery, Rush University Medical Center, Chicago, IL, U.S.A.

Corresponding Author: Oyedolamu K. Olaitan, e-mail: Oyedolamu_Olaitan@rush.edu
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Background: Patient compliance with immunosuppressive therapy after transplant has impacts on both graft and patient outcomes. For diabetic end-stage renal disease (ESRD) patients who are undergoing evaluation for kidney transplantation in our program, hemoglobin A_{1c} (HbA_{1c}) level of >10% is used as a flag that the patient may be at risk for noncompliance and that more comprehensive psychosocial screening is needed prior to transplant. We evaluated the association between pre-transplant HbA_{1c} level and post-transplant compliance, as no study to date has looked at this in the transplant population.

Material/Methods: The charts of 392 patients who received a kidney transplant at a single institution between July 2008 and June 2012 were retrospectively reviewed. One hundred and sixty-five diabetic patients who received a kidney transplant alone were included in the final analysis. Our predictive variable was HbA_{1c} level greater than 7.7% based on previous reports in the diabetic population. Outcome measures were graft survival, rejection episodes, unexplained low immunosuppressant levels, and documented noncompliance.

Results: There were no statistically significant differences between the HbA_{1c} groups of ≤7.7% and >7.7% in outcomes of failed grafts (22.0% and 17.8%, p=0.2), rejection episodes (15.0% and 6.7%, p=0.3), unexplained low immunosuppressant level (46.6% and 37.9%, p=0.3), and documented noncompliance (25.0% and 16.7%, p=0.4).

Conclusions: In diabetic ESRD patients selected for renal transplantation, elevated pre-transplant HbA_{1c} levels, defined as HbA_{1c} >7.7%, are not predictive of post-transplant medication compliance. We advocate that this group of patients should not be denied transplant solely on their elevated pre-transplant HbA_{1c}.

MeSH Keywords: Diabetes Mellitus • Kidney Failure, Chronic • Kidney Transplantation • Patient Compliance

Abbreviations: **ESRD** – End-Stage Renal Disease; **HbA_{1c}** – hemoglobin A_{1c}; **OPTN** – Organ Procurement and Transplantation Network; **SRTR** – Scientific Registry of Transplant Recipients; **PRA** – Panel Reactive Antibody; **USRDS** – United States Renal Data System

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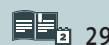
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Background

According to the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) 2017 Annual Data Report, there were 92,685 patients on the waitlist for a kidney transplant, with an increasing number of patients waiting 5 years or longer to be transplanted [1]. As such, it is important to identify those patients who are at higher risk of graft loss prior to listing in order to reduce wait times for those more likely to have long-term graft survival. Identifying patients at risk for post-transplant noncompliance could theoretically increase patient years gained by kidney transplantation, as well as lead to huge savings in health-care costs [2–9].

Previous studies have found significant correlation between post-transplant noncompliance and graft rejection when using pre-transplant measures such as compliance with dialysis visits, drug screening, and documented history of medical noncompliance [10]. Since about 40% of ESRD patients are diabetic, HbA_{1c} could be a useful and objective tool for predicting post-transplant compliance in this group. Previous studies have examined the correlation between HbA_{1c} and graft outcomes, finding that post-transplant glycemic control is more important than pre-transplant glycemic control for long-term graft outcomes, but that acute rejection was not associated with either [11]. Several studies [12–14] have also looked at the relationship between HbA_{1c} level and compliance with anti-diabetic medication in diabetic patients, but none has assessed whether this data translates to using pre-transplant HbA_{1c} to predict compliance in the post-transplant period. Given that many institutions, including our own, still rely on pre-transplant HbA_{1c} to determine patient appropriateness for listing, despite the paucity of relevant literature, we sought to further examine if, beyond graft outcomes, HbA_{1c} is correlated with patient compliance following kidney transplant.

Compliance is the extent to which patient behavior coincides with health advice given [10,15,16]. The opposite – noncompliance – is an important cause of graft dysfunction in transplant patients secondary to rejection episodes. The prevalence of noncompliance is widely variable. Reviewed cohort and cross-sectional studies found that 15–22% of post-transplant patients are noncompliant [17]. In a large meta-analysis that included over 29,000 transplant patients, a non-adherence rate of about 33% per-patient-year was noted in North America [18]. Noncompliance is significant in that it leads to recurrent hospitalization, decreased graft function, and eventually to graft loss necessitating return to dialysis; therefore, identifying potential non-compliers is important [2–9].

The pre-transplant evaluation process is widely variable across United States transplant centers. In our program, several

measures are used pre-transplant to predict a patient's post-transplant compliance, including compliance with dialysis visits, compliance with office visits, and HbA_{1c} level in diabetic patients. A HbA_{1c} level of >10% is used at our center, based mainly on historical institutional practice, as a flag that the patient may be at high risk for post-transplant noncompliance and that more comprehensive psychosocial screening and teaching is needed prior to listing for transplant.

This study aimed to evaluate the association between pre-transplant HbA_{1c} level and post-transplant compliance. We hypothesized that assessment of pre-transplant diabetic control, using HbA_{1c} level, will lead to identifying those patients with high risk of post-transplant noncompliance.

Material and Methods

After obtaining Institutional Review Board approval, data of diabetic kidney transplant recipients between July 2008 and June 2012 at our institution were retrieved from a prospectively maintained database. Additional information such as patient demographics, type of diabetes, pre-transplant HbA_{1c}, graft outcomes, immunosuppressant levels, and documented noncompliance were obtained by retrospective electronic chart review. Factors that may affect graft and patient outcomes, such as cold ischemia time, warm ischemia time, donor age, graft type, and panel reactive antibody (PRA), were also reviewed. Diabetic patients that received a kidney transplant alone were included in the statistical analysis. The follow-up period ranged from 1 to 5 years post-transplant, with a mean follow-up of 3.5 years.

The HbA_{1c} cutoff used in this study was chosen based upon previously published literature in the non-transplant diabetic population which examined the correlation between HbA_{1c} and compliance and found that HbA_{1c} level higher than 7.7% is associated with poor compliance with medications [12]. Based on this literature, a value of 7.7% was used as the cutoff to define preoperative compliance, with values of less than or equal to 7.7% defined as compliant and values of greater than 7.7% defined as noncompliant.

The primary outcome of interest was post-transplant compliance. Surrogate outcome measures for compliance included graft failure, graft rejection episodes, medical noncompliance, and unexplained low immunosuppressant blood levels (less than 4 ng/ml for Tacrolimus or Rapamycin after 1 month from the date of transplant procedure). At the institution where the study was conducted, the transplant team aims to achieve target immunosuppression levels by 4 weeks post-transplant; therefore, if immunosuppression levels are sub-therapeutic at that time without a clear explanation, a patient was suspected

Table 1. Baseline recipient characteristics.

	N	Percent (%)	Mean
Total	165		
Gender			
Male	107	65.0	
Female	58	35.0	
Age (17–81 years)			57.6
Race			
White	41	24.8	
Black	63	38.2	
Hispanic	49	29.7	
Other	12	7.3	
BMI (kg/m ²)			29.5
HbA _{1c} (%)			6.5
Time on hemodialysis (months)			45.0

to be noncompliant with medication. Rejection episodes were confirmed by histopathology reports of kidney biopsy samples.

A summary of the baseline recipient, donor, and operative characteristics is presented in terms of mean and standard deviation for continuous variables and frequencies and percentages for dichotomous variables. Group differences in continuous variables were tested with *t* tests in data expected to be normally distributed and with Mann-Whitney-Wilcoxon test for data expected to be non-normally distributed. The relationships among categorical variables were examined with the chi-square test. Regression analyses were used to assess the predictive value of HbA_{1c} on outcome measures. The analysis was conducted using SPSS® (version 18).

Results

The total number of patients who were diabetic and had a kidney transplant alone in the study period was 165. Baseline patient demographics are found in Table 1. Additional measures included were average cold ischemia time of 21.6 h and the average anastomotic time of 48.8 min. The overall number of patients who had graft failure was 30 (18.0%) and the number of patients who had at least 1 rejection episode was 22 (13.0%). Baseline characteristics, with HbA_{1c} level of 7.7% as a cutoff point, are shown in Table 2. There were no significant differences in the donor, recipient, and operative characteristics between the 2 groups.

There was no statistically significant difference in the outcomes of interest, including failed graft (22.2% and 13.3%, *p*=0.2), rejection episodes (14.8% and 6.7%, *p*=0.3), low

immunosuppressant level (46.7% and 60.0%, *p*=0.3), and documented noncompliance (25.9% and 16.7%, *p*=0.4) when comparing recipients with HbA_{1c} less than or equal to and greater than 7.7%, respectively (see Table 3). This was true whether chi-square tests or logistic regression analyses were used.

Additionally, we examined the mean HbA_{1c} levels for patients who had graft failure, rejection, or documented noncompliance to determine if there was a more sensitive HbA_{1c} cutoff which could be used. In doing this, we found there were no significant differences between mean HbA_{1c} levels for patients who had graft failure compared to those with functioning grafts (6.6% and 6.5%, respectively, *p*=0.4) and for patients who had rejection episodes and those who did not (6.6% and 6.5%, respectively, *p*=0.8). There was also no significant difference between HbA_{1c} level of patients who were documented to be noncompliant with their medications compared with those who had no documentation of noncompliance (6.6% and 6.4%, respectively, *p*=0.7); see Table 4.

Discussion

ESRD is a major health issue, costing the United States Medicare program an estimated \$35 billion in 2016 [19]. In the United States, the incidence and prevalence of ESRD continues to rise. According to United States Renal Data System (USRDS), on December 31, 2016, there were 726,331 prevalent cases of ESRD in the United States, with the number of prevalent ESRD cases rising by approximately 20,000 per year [19]. The main treatment option for ESRD is kidney transplant. However, with 92,685 patients on the waitlist for kidney transplant, there is a strong need to determine which patients will benefit from

Table 2. Baseline recipient, donor, and operative characteristics by HbA_{1c} level.

	HbA _{1c} ≤7.7% (135 patients)	HbA _{1c} >7.7% (30 patients)	p-Value
Recipient age (years)	57.9 (10.2)	56.1 (9.6)	0.40
BMI (kg/m ²)	29 (5.2)	30.5 (5.2)	0.13
Time on dialysis (months)	47 (39.5)	35 (29.0)	0.25
Length of stay (days)	9.3 (14) [6]	7.2 (2.7) [6]	0.80
Cold ischemia time (hours)	22 (9.8)	20 (10.6)	0.40
Anastomotic time (minutes)	49 (15.2)	47 (11.5)	0.70
PRA	11.8 (23.8)	17.6 (33.4)	0.90
Follow-up (months)	39.2 (14.7)	42 (16.4)	0.21
Donor age (years)	42 (17)	44 (15)	0.50
Re-transplant			0.50
Yes	13 (10%)	3 (10%)	
No	122 (90%)	27 (90%)	
Gender			0.80
Female	49 (36%)	9 (30%)	
Male	86 (64%)	21 (70%)	
Race			0.70
Black	52 (39%)	11 (36.7%)	
Hispanic	38 (28%)	11 (36.7%)	
White	34 (25%)	7 (23.3%)	
Other	11 (8%)	1 (3.3%)	
Type of diabetes			0.05
Type I	4 (3%)	6 (20%)	
Type II	111 (82%)	22 (73.3%)	
Unclassified	20 (15%)	2 (6.7%)	
Diabetic medications			0.40
Insulin	92 (68%)	23 (77%)	
OHA	21 (15%)	4 (13%)	
Both	18 (13%)	3 (10%)	
Type of graft			0.26
SCD	93 (69%)	16 (53%)	
ECD	27 (20%)	9 (30%)	
DCD	15 (11%)	5 (17%)	
Donor type			0.18
Deceased donors	70 (52%)	17 (57%)	
Living donors	65 (48%)	13 (43%)	

Data presented as mean (standard deviation) [median] or count (percentage). PRA – Panel Reactive Antibody; OHA – Oral Hypoglycemic Agent; SCD – Standard Criteria Donor; ECD – Extended Criteria Donor; DCD – Donation after Cardiac Death.

Table 3. Outcome measures by HbA_{1c} Level.

	HbA _{1c} ≤7.7% (135 patients)	HbA _{1c} >7.7% (30 patients)	p-Value
Documented noncompliance			0.40
Yes	35 (25.9%)	5 (16.7%)	
No	100 (74.1%)	25 (83.3%)	
Failed graft			0.20
Yes	30 (22.2%)	4 (13.3%)	
No	105 (77.8%)	26 (86.7%)	
Rejection episodes			0.30
Yes	20 (14.8%)	2 (6.7%)	
No	115 (85.2%)	28 (93.3%)	
Low immunosuppressant level			0.30
Yes	63 (46.7%)	18 (60.0%)	
No	72 (53.3%)	12 (40.0%)	

Data presented as count (percentage).

Table 4. Mean HbA_{1c} levels by outcome measure.

	Mean HbA _{1c}	p-Value
Failed graft		0.40
Yes	6.6%	
No	6.5%	
Rejection episodes		0.80
Yes	6.6%	
No	6.5%	
Medication noncompliance		0.70
Yes	6.6%	
No	6.4%	

transplant and which patients are at high risk for organ rejection or failure [1]. Currently, this is done through widely variable preoperative evaluation and screening practices, including assessment of compliance with dialysis visits, drug screening, socioeconomic status, family support, and documented history of medical noncompliance, in order to determine if a patient will be compliant in the post-transplant period [10]. Pre-transplant HbA_{1c} levels are also used in the assessment of patient compliance prior to transplant listing, despite a paucity of data to support a standard cutoff value or its relationship to kidney transplant outcomes.

In this retrospective study, HbA_{1c} was tested to determine if it is a valid predictor of compliance with non-diabetic post-transplant medications in diabetic ESRD patients. Based on a previous study that showed non-ESRD diabetic patients with HbA_{1c} above 7.7% were at higher risk of noncompliance with diabetic medications compared to those with HbA_{1c} below this value, 7.7% was chosen as a cutoff for this study [12]. Graft outcomes, rejection episodes, documented noncompliance, and low therapeutic medication levels were used to assess patient compliance and were compared with the preoperative HbA_{1c} level. This study did not show any significant difference between those with HbA_{1c} level above or below 7.7% in the outcome variables of interest. Interestingly, the mean HbA_{1c} (6.5%) for patients that received a kidney transplant at our institution was less than the mean HbA_{1c} (7.2%) for adult diabetic patients in the United States, using the Center for Disease Control data for the same period (see Table 5). The difference in the mean HbA_{1c} levels could be a result of the improved glycemic control seen in ESRD due to decreased insulin excretion and decreased insulin requirements compared with the general diabetic population [20,21,22]. Additionally, several factors have been shown to cause variations in measured HbA_{1c} levels in patients with ESRD, including anemia, blood transfusion, race, age, hemoglobinopathies, hemodialysis, and the administration of erythropoietin [23,24]; therefore, pre-transplant HbA_{1c} level should be interpreted with caution. Alternatively, glycated albumin is not significantly affected by these factors and could be a better marker of glycemic control in this patient population [25]; however, the use of alternative biomarkers such as

Table 5. Comparison of HbA_{1c} levels in CDC data and this study.

	Minimum	25 th %ile	Mean	Median	75 th %ile	Maximum
CDC data	3.9	6.0	7.2	6.7	7.8	18.0
This study	4.5	5.6	6.5	6.3	7.2	11.5

fructosamine and glycated albumin outside the research setting has not been sufficiently validated and may be unreliable if there is hypoalbuminemia. For these reasons, the use of correction factor for HbA_{1c} measurement in patients on dialysis has been proposed [26] and may be better.

Looking specifically at the patients with HbA_{1c} levels above 10%, the cutoff value typically used by our program for transplant listing, we observed 1 graft loss, giving a 33.3% overall graft failure for this group. The graft loss was preceded by 2 rejection episodes (acute antibody mediated rejection and acute cellular rejection), and later followed by death from a pulmonary embolism. Another important observation is that all patients with HbA_{1c} levels above 10% had unexplained low immunosuppressant levels. Although this is a very small group, the data points towards a trend with poor post-transplant outcomes and compliance compared to those with HbA_{1c} below 10%. Additional research in centers that do not use HbA_{1c} of 10% as a cutoff for listing patients may give more information.

There are several factors that may play a role in the lack of correlation observed between pre-transplant glycemic control and post-transplant compliance. Glycemic control is influenced by several factors beyond medication compliance which may be more difficult for a patient to control, including diet and exercise. Additionally, appropriate glycemic control often requires finger-stick glucose monitoring, medication calculations, and insulin injections multiple times per day, whereas post-transplant medication compliance usually only requires a patient to take the appropriate immunosuppressant and prophylactic medications by mouth once or twice per day. The variability of pre-transplant HbA_{1c} and the many factors that may affect it further support the findings from this study that patients should not be excluded from listing based on pre-transplant HbA_{1c} levels alone.

Limitations of this study include its retrospective design and selection bias for patients who are more likely to be compliant by our current institutional listing criteria. As a result, the number of patients with elevated pre-transplant HbA_{1c} level was relatively small. Another limitation is that HbA_{1c} levels may not be as meaningful in the ESRD population as compared to the general diabetic population [27–29]. Future studies evaluating the association between glycated albumin or corrected HbA_{1c} on post-transplant compliance may offer further information. Additionally, it is not part of our institutional protocol to perform routine biopsies after transplant; however, in an institution where this is performed, it may give more information on the correlation between pre-transplant glycemic control and post-transplant graft outcomes. Furthermore, it is possible that a longer follow-up period would affect the outcomes of graft rejection or failure. The value of this study is that it is the first study to look at the relationship between pre-transplant HbA_{1c} and post-transplant compliance, and it demonstrates that pre-transplant HbA_{1c} level is not predictive of post-transplant compliance and outcomes; this may limit the unnecessary exclusion of diabetic patients struggling with glycemic control from listing for transplant.

Conclusions

This retrospective study found no correlation between elevated pre-transplant HbA_{1c} levels, defined as HbA_{1c} >7.7%, and post-transplant medication compliance in diabetic ESRD patients undergoing renal transplant. The findings from this study may better inform transplant programs when deciding on selection criteria for transplant listing. Further prospective studies are needed to better evaluate the role of HbA_{1c} in transplant outcomes.

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