Utilization of HbA1c in Screening Living Kidney Donors With Prediabetes

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ABSTRACT

Objectives. To study the outcome of living kidney donors with prediabetes and to evaluate the utilization of baseline HbA1c to identify donors at high risk for developing diabetes during the postdonation follow-up period.

Patients and methods. Living kidney donors with prospectively collected preoperative fasting glucose and HbA1c results were included in the study. Donors were categorized to the high-risk group when both results were in the prediabetic range, the low-risk group when only 1 result was in the prediabetic range, and the control group when both results were normal.

Results. Ninety-three donors were followed for 75.9 ± 23.3 months. A higher proportion of donors in the high-risk group progressed to diabetes compared with donors in the low-risk and control groups (31.3% vs 6.5% vs 0.0%, respectively; $P < .001$). Donors with prediabetes were not at a higher risk for new-onset hypertension (4.4% vs 10.0% vs 7.7%, in control, low-risk, and high-risk groups, respectively; $P = .519$) or microproteinuria (7.3% vs 10.3% vs 0.0%, in control, low-risk, and high-risk groups, respectively; $P = .478$) and exhibited equivalent postdonation renal function compared with donors with normal glucose metabolism.

Conclusions. HbA1c can identify donors with prediabetes who are at risk for progression to diabetes. Our results indicate that carefully accepted donors with prediabetes are not at increased risk of renal function deterioration in the immediate postdonation period.

KIDNEY transplantation, particularly from a living donor, is the treatment of choice for most patients with end-stage renal disease (ESRD). Kidney donors are thought to have normal life spans, health statuses that are similar to the general population, and excellent quality of life, without an excessive risk of ESRD [1]. However, as both living and deceased donor transplant kidneys are in short supply, many renal transplant centers are faced with evaluating potential living donors with risk factors for developing future kidney disease, a group of patients termed "medically complex living donors." This group includes donors with prediabetes [2]. Taler et al [3] recently reported that donors who exhibit glucose intolerance have increased from 7% to 22% over the past 5 decades.

Prediabetes is the term used for individuals whose glucose levels do not meet the criteria for type 2 diabetes mellitus (T2DM) but are too high to be considered normal. Individuals with prediabetes are at increased risk for T2DM [4]. T2DM is one of the most common comorbid risk factors for chronic kidney disease (CKD) and accounts for approximately 50% of acquired adult-onset ESRD [5].

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Major guidelines identify the presence of T2DM as an absolute contraindication to living kidney donation [6]. Data specific to the outcomes of living kidney donors with prediabetes is scarce, however, and recommendations regarding the candidacy of those with prediabetes for kidney donation are conflicting [7]. Given the increasing trend to accept candidates with prediabetes as living kidney donors, evaluation of long-term health outcomes in these individuals is warranted.

Two previous studies have reported favorable outcomes among living kidney donors with prediabetes [8,9]. These studies used either fasting plasma glucose (FPG) or an oral glucose tolerance test to screen for prediabetes or T2DM. The American Diabetes Association (ADA) guidelines acknowledge the HbA1c assay to be equally appropriate for diagnosing T2DM and recommend an HbA1c range of 5.7% to 6.4% (39–47 mmol/mol) as a criterion for prediabetes [4]. Using HbA1c in addition to impaired fasting glucose (IFG) has been shown to increase the power to predict the risk of developing T2DM [10]. To our knowledge, however, HbA1c has not yet been used in studies of living kidney donors with prediabetes. This study aimed to report the health outcomes of living kidney donors with prediabetes and evaluate the power of HbA1c in predicting adverse outcomes among these individuals.

PATIENTS AND METHODS

This study was approved by the Severance Hospital Yonsei University Health System Institutional Review Board. Among the living kidney donors included in our prospectively collected database, those with a preoperative HbA1c evaluation within a year before donation and with more than 36 months of follow-up after donation were included in the study. From March 2006 to December 2014, 93 donors who satisfied the inclusion criteria were enrolled in the study.

Two surgeons performed all donor nephrectomies by video-assisted mini-incisional surgery as previously reported [11]. Recorded donor characteristics, including age, sex, height, weight, body mass index, and body surface area were evaluated, as were the results of preoperative routine serum chemistry and HbA1c. Renal function was estimated using the CKD Epidemiology Collaboration creatinine equation to calculate estimated glomerular filtration rate (eGFR) pre- and postoperatively [12]. Urinalysis also was conducted to determine the presence of proteinuria. A urine microalbumin excretion rate of 30 to 300 mg/24 hr, urine microprotein excretion rate of 150 to 500 mg/24 hr, urine albumin-to-creatinine ratio of 30 to 300 mg/g, or urine protein-to-creatinine ratio of 150 to 500 mg/g was defined as microproteinuria. In accordance with in-house donor criteria, candidates with an eGFR < 80 mL/min/1.73 m^2 at baseline and those with diabetes or hypertension inadequately controlled by single medication were rejected as donors. Candidates with overt proteinuria exceeding the microproteinuria range also were excluded from donation.

The included patients were stratified into 3 groups by their preoperative FPG and HbA1c results. According to the ADA guidelines, prediabetes is defined as an FPG of 100 to 125 mg/dL or an HbA1c of 5.7% to 6.4%. Donors with both normal FPG and HbA1c results were included in the control donor group, whereas those with either an FPG or HbA1c result in the prediabetic range were included in the low-risk prediabetic donor group, and those with both FPG and HbA1c results in the prediabetic range were included in the high-risk prediabetic donor group. eGFR, FPG, microproteinuria, and the presence of new-onset diabetes or hypertension was assessed annually for at least 36 months. Donors who exhibited an FPG $\geq$ 100 mg/dL on more than 2 occasions during the follow-up period were considered to have persistent or new-onset IFG.

Continuous variables are expressed as means $\pm$ standard deviations and were compared using the 1-way analysis of variance test. Post-hoc tests were performed using a Bonferroni correction. Categorical variables are expressed as percentages and were compared using either the χ^2 test or Fisher exact test. Post-hoc tests for contingency tables were performed as described by Beasley and Schumacker [13]. A P value $< .05$ was considered significant. All statistical analyses were conducted in SPSS version 23 (IBM Corp, Armonk, NY, United States).

RESULTS

Of the 93 donors included in the study, 46 (49.5%) were included in the control donor group, 31 (31.6%) in the low-risk prediabetic donor group, and 16 (16.3%) in the high-risk prediabetic donor group. The donors were followed for a mean of 75.9 $\pm$ 23.3 months. Forty-five (48.4%) of the donors were men, and the mean age of all donors was 44.3 $\pm$ 12.9 years. Age and baseline triglyceride and low-density lipoprotein–cholesterol levels were significantly lower in the control group compared with the other 2 groups. Baseline FPG and HbA1c levels were significantly different in all 3 groups. Body mass index of all 3 groups were not significantly different and were quite normal (23.9 $\pm$ 2.6 kg/m^2). No other baseline characteristics were significantly different across the 3 groups (Table 1).

Five of 23 (21.7%) donors with IFG developed T2DM after donation, whereas only 2 out of 70 (2.9%) donors with normal fasting glucose developed T2DM ($P = .009$). Seven of 40 (17.5%) donors with HbA1c levels in the prediabetic range subsequently developed T2DM compared with 0 of 53 donors with normal HbA1c levels ($P = .002$). When prediabetic donors were stratified using both HbA1c and FPG, 5 of 16 (31.3%) donors in the high-risk group were diagnosed with T2DM at 70.9 $\pm$ 31.6 months after donation compared with 2 of 31 (6.5%) donors in the low-risk group (at 79.5 months and 87.1 months postdonation, respectively) and 0 of 46 donors in the control group. The risk of being diagnosed with T2DM after donation therefore was significantly higher in the high-risk group compared with the other 2 groups ($P < .001$) (Table 2). Survival analysis by log-rank test also confirmed that the high-risk group was significantly more likely to be diagnosed with T2DM after donation (high-risk vs low-risk, $P = .008$; high-risk vs control, $P < .001$; low-risk vs control, $P = .08$) (Fig 1). None of the donors in the high-risk group converted to normal fasting glucose during the follow-up period. Of the donors in the low-risk group with IFG, 4 of 7 (57.1%) converted to normal fasting glucose. Sixteen of 24 (66.7%) donors in the low-risk group without IFG, however, exhibited new-onset

Table 1. Predonation Characteristics

	Control Donors (n = 46)	Low-Risk Donors With Prediabetes (n = 31)	High-Risk Donors With Prediabetes (n = 16)	*P* Value
Age, y	39.1 ± 13.1*	48.0 ± 11.3	51.9 ± 8.9	< .001
Male sex, No. (%)	25 (54.3)	11 (35.5)	9 (56.3)	.210
Follow-up duration, mo	77.4 ± 24.4	79.6 ± 19.7	64.8 ± 24.4	.099
HbA1c, %†	5.28 ± 0.22	5.81 ± 0.29	6.01 ± 0.24	< .001
Fasting plasma glucose, mg/dL†	88.4 ± 6.3	96.4 ± 11.2	110.8 ± 13.7	< .001
Baseline IFG, No. (%)	0 (0.0)	7 (22.6)	16 (100.0)	< .001
History of hypertension, No. (%)	1 (2.2)	1 (3.2)	3 (18.8)	.058‖
Body mass index, kg/m^2	23.6 ± 2.6	24.4 ± 2.3	23.9 ± 2.9	.373
Systolic BP, mm Hg	121.2 ± 11.8	124.9 ± 12.6	119.9 ± 9.0	.283
Diastolic BP, mm Hg	73.4 ± 10.4	77.0 ± 7.8	76.0 ± 10.0	.233
Hemoglobin, g/dL‡	14.2 ± 1.4	13.6 ± 1.2	14.8 ± 1.2	.012
Hematocrit, %	41.8 ± 4.2	42.0 ± 8.0	42.9 ± 3.1	.788
Total cholesterol, mg/dL	180 ± 34	196 ± 39	191 ± 38	.142
Triglyceride, mg/dL	92 ± 44*	124 ± 51	145 ± 48	.001
HDL cholesterol, mg/dL	57 ± 16	53 ± 13	51 ± 11	.402
LDL cholesterol, mg/dL§	96 ± 32	121 ± 34	117 ± 26	.013
Calcium, mg/dL	9.2 ± 0.4	9.1 ± 0.3	9.31 ± 0.3	.148
Uric acid, mg/dL	5.1 ± 1.3	4.5 ± 1.1	4.9 ± 1.4	.141
Creatinine, mg/dL	0.90 ± 0.17	0.82 ± 0.11	0.84 ± 0.16	.078
Estimated GFR (CKD-EPI), mL/min/1.73 m^2	101.9 ± 19.5	100.1 ± 20.3	99.4 ± 15.0	.879
Microproteinuria, No. (%)	2 (4.3)	2 (6.5)	1 (6.3)	1.000‖

Continuous variables are expressed as means ± standard deviations.
Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein.
*Age and triglyceride levels were significantly lower in control donors compared with the low-risk and high-risk groups.
†HbA1c and fasting plasma glucose were significantly different across all 3 groups.
‡Hemoglobin was significantly higher in the high-risk group compared with the low-risk group.
§LDL-cholesterol was significantly lower in the control group compared with the low-risk group.
‖The analysis was performed using the Fisher exact test.

IFG after donation, which was significantly higher than the control group ($P < .001$, odds ratio, 12.3, 95% confidence interval, 3.7–41.4). One (7.7%) donor in the high-risk group, 3 (10.0%) donors in the low-risk group, and 2 (4.4%) donors in the control group were diagnosed with hypertension after donation; the risk of developing hypertension was not significantly different across the 3 groups ($P = .519$) (Table 2).

The mean eGFR across all donors was 100.8 ± 18.9 mL/min/1.73 m^2 at predonation and 68.3 ± 14.9 mL/min/1.73 m^2 1 year after donation. eGFR was not significantly different at predonation or at any of the yearly follow-up visits across the 3 groups (Table 3). None of the donors in the high-risk group, 3 (10.3%) of the donors in the low-risk group, and 3 (7.3%) of the donors in the control group developed microproteinuria during the follow-up period; this risk was not significantly different across the 3 groups ($P = .478$) (Table 2). None of the donors progressed to ESRD during the study period.

DISCUSSION

The findings from this study indicate that living kidney donors with prediabetes have preserved renal function after donation and do not experience an increased risk of

Table 2. Postdonation Development of DM, HTN, Proteinuria, and Status of IFG.

	Control Donors (n = 46)	Low-Risk Donors With Prediabetes (n = 31)	High-Risk Donors With Prediabetes (n = 16)	*P* Value
New-onset T2DM	0 (0.0)	2 (6.5)	5 (31.3)*	< .001†
New-onset HTN	2/45 (4.4)	3/30 (10.0)	1/13 (7.7)	.519†
Postdonation microproteinuria	3/41 (7.3)	3/29 (10.3)	0/16 (0.0)	.478†
New-onset IFG	6/43 (14.0)	20/31 (64.5)	16/16 (100.0)	< .001
IFG conversion to normal FPG		4/7 (57.1)	0/16 (100.0)	< .02†
New-onset IFG	6/43 (14.0)	16/24 (66.7)		< .001

Data are represented as number (%).
Abbreviations: DM, diabetes mellitus; FPG, fasting plasma glucose; HTN, hypertension; IFG, impaired fasting plasma glucose; T2DM, type 2 diabetes mellitus.
*The high-risk group was more likely to be diagnosed with T2DM after donation compared with the low-risk and control groups.
†The analysis was performed using the Fisher exact test.

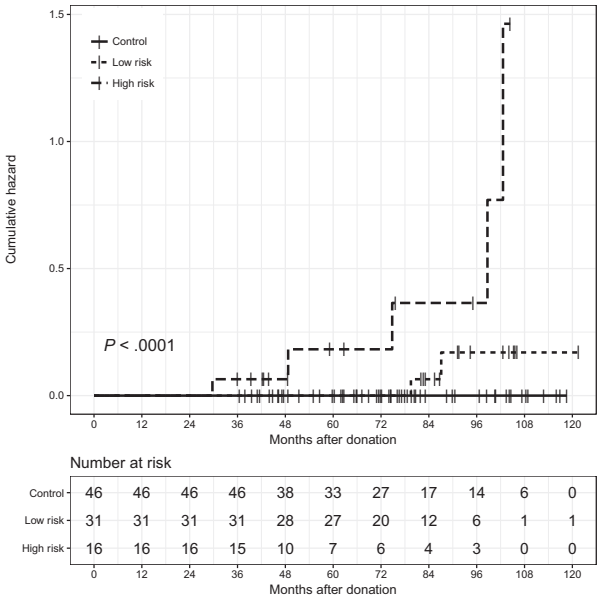

Fig 1. The cumulative risk of diabetes after kidney donation. The high-risk group was significantly more likely to be diagnosed with diabetes after donation compared with the low-risk and control groups (high-risk vs low-risk, $P = .008$; high-risk vs control, $P < .001$; low-risk vs control, $P = .08$).

developing microproteinuria compared with normal donors. Our study also shows that predonation HbA1c combined with FPG can be used to stratify the risk of donor candidates with prediabetes: donors with prediabetes who have both FPG and HbA1c in the prediabetic range are considered high-risk for developing T2DM and are less likely to convert to normal fasting glucose compared with low-risk donors with only 1 abnormal indicator for prediabetes. Despite this higher risk, however, preservation of renal function was similar among high-risk, low-risk, and normal donors.

Recent attention has focused on living kidney donation because of the long wait time for deceased donor kidneys. Many renal transplant centers now routinely accept kidneys from "complex living donors" who exhibit risk factors for developing future kidney disease [14]. Donors with prediabetes are included in this group of patients, and current guidelines do not provide clear recommendations for living kidney donation in this population because of insufficient evidence. Most transplant centers will deny candidates with diabetes, but many will accept candidates with prediabetes. Taler et al [3] studied 8951 live kidney donations at 3 large US transplant centers across 5 decades and reported that the proportion of donors with glucose intolerance rose from 7% in 1963–1974 to 22% in 1997–2007. Other studies, however, have reported abnormal glucose metabolism as the primary reason for declining a candidate donor, highlighting the need for uniform guidelines on screening candidates with prediabetes [15].

The main concern with accepting donors with prediabetes is their risk of developing T2DM, which may potentially lead to diabetic nephropathy and progression to ESRD. The number of adults with prediabetes is expected to increase worldwide, which will lead to a higher number of donor candidates presenting with prediabetes at predonation evaluation. Each year, approximately 5% to 10% of people with prediabetes convert to T2DM; according to an ADA expert panel, up to 70% of individuals with prediabetes will eventually develop diabetes [16]. The lifetime risk of developing nephropathy in T2DM is approximately 30%, which is the leading cause of ESRD [5,15]. HbA1c is now widely used in addition to FPG and oral glucose tolerance tests to screen for T2DM and prediabetes. Patients with prediabetes who exhibit both IFG and prediabetic HbA1c levels are at an increased risk of progressing to T2DM compared with those patients in whom only 1 factor is abnormal [10,17]. In our study, this increased risk for progression to T2DM after donation was also demonstrated in living kidney donors with both FPG and HbA1c in the prediabetic range (high-risk group) compared with donors with only 1 abnormal factor (low-risk group) or no abnormal factors (control group). Furthermore, 66.7% of donors with prediabetic HbA1c values and normal fasting glucose during predonation converted to IFG during the postoperative follow-up period. Thus, evaluating HbA1c during kidney donation screening can provide further information regarding the risk of developing abnormal glucose metabolism postdonation.

To our knowledge, only 2 previous studies have investigated long-term health outcomes in living kidney donors with prediabetes. Okamoto et al [9] were the first to report

Table 3. Annual Postdonation Estimated Glomerular Filtration Rate

Postdonation eGFR (mL/min/1.73 m^2)	All Donors (n = 93)	Control Donors (n = 46)	Low-Risk Donors With Prediabetes (n = 31)	High-Risk Donors With Prediabetes (n = 16)	*P* Value
At 1 y	68.3 ± 14.9 n = 76	69.5 ± 14.7 n = 35	70.1 ± 17.1 n = 25	62.8 ± 10.4 n = 16	.255
At 2 y	71.1 ± 14.4 n = 71	73.2 ± 15.6 n = 32	71.9 ± 15.4 n = 23	66.0 ± 8.9 n = 16	.257
At 3 y	72.6 ± 15.8 n = 74	75.2 ± 17.8 n = 36	72.5 ± 14.7 n = 22	67.1 ± 11.2 n = 16	.238
At 4 y	74.9 ± 15.6 n = 57	77.8 ± 18.1 n = 27	72.7 ± 11.8 n = 21	71.5 ± 15.3 n = 9	.421
At 5 y	77.6 ± 17.6 n = 52	81.8 ± 19.1 n = 24	74.0 ± 15.9 n = 21	74.0 ± 16.1 n = 7	.283
At 6 y	75.8 ± 17.9 n = 39	80.4 ± 22.3 n = 17	71.2 ± 11.7 n = 16	74.9 ± 17.2 n = 6	.339
At 7 y	77.5 ± 15.0 n = 23	79.6 ± 13.0 n = 9	78.8 ± 18.7 n = 10	69.2 ± 6.6 n = 4	.501
At 8 y	81.7 ± 17.2 n = 20	80.3 ± 19.7 n = 12	88.5 ± 12.0 n = 6	69.6 ± 3.0 n = 2	.386

Abbreviation: eGFR, estimated glomerular filtration rate.

on kidney donors with pre-existing abnormal glucose metabolism. These authors conducted a cross-sectional survey to study Asian kidney donors with glucose intolerance. Donors were evaluated by an oral glucose tolerance test predonation. A total of 409 donors with a mean follow-up period of 123 ± 81 months were included in this study, including 24 donors with a T2DM glucose intolerance pattern (120-minute blood sugar ≥ 200 mg/dL) and 41 donors with a prediabetic glucose intolerance pattern (120-minute blood sugar 140–200 mg/dL). The study reported that donors with glucose intolerance were not at an increased risk of perioperative complications. Survival rates also were equivalent across all subgroups. During long-term follow-up, donors with prediabetes were not at an increased risk of developing renal dysfunction compared with donors with normal glucose metabolism (2.4% vs 6.7%, respectively), but were more likely to be diagnosed with T2DM (9.8% vs 2.4%, respectively). This study therefore suggests that kidney donation from a donor with glucose intolerance is acceptable. Evidence regarding postdonation renal dysfunction is limited in this study, however, because the assessment relied on survey self-report rather than proteinuria or GFR measurements.

More recently, Chandran et al [8] reported on donors with predonation IFG. The authors studied 45 kidney donors with IFG and matched control donors with normal fasting glucose. Among the donors with IFG, 15.6% developed T2DM, but more than half (57.8%) reverted to normal fasting glucose. The authors estimated a 7-fold increased risk of developing overt diabetes within 10 years of donation among patients with IFG compared with those with normal fasting glucose at the time of nephrectomy. Donors with IFG had a preserved GFR, and their rates of albuminuria were similar to those of matched controls at 10 years postdonation. Donors with IFG also were not at an increased risk of developing ESRD.

The results of our study are consistent with these previous studies in that donors with prediabetes were not at immediate risk of renal function deterioration after a kidney donation. Furthermore, our study has identified that a predonation analysis of HbA1c in addition to FPG can stratify a donor's risk of developing T2DM during the postdonation period: when both factors were in the prediabetic range, 31.3% of donors developed T2DM during a follow-up period of 64.8 ± 24.4 months, which is a higher proportion than has been reported in previous studies (9.8%–15.6%). Furthermore, none of these high-risk prediabetic donors reverted to normal fasting glucose during the study period, implying that they were at continuous risk of developing T2DM.

Glomerular hyperfiltration is also a concern when accepting donor candidates with prediabetes. Hyperfiltration is a well-recognized early renal change in diabetic nephropathy. Patients with prediabetes have a higher prevalence of hyperfiltration compared with subjects with normal glucose metabolism [18]. After donating a kidney, the remaining contralateral kidney is known to undergo compensatory hypertrophy and glomerular hyperfiltration, [19–21] raising concerns that patients with prediabetes may be at higher risk for new-onset or aggravated glomerular hyperfiltration and renal dysfunction postdonation. Animal models suggest that nephrectomy in rats with diabetes leads to functional and morphologic damage of the remaining kidney [22,23]. Results from clinical studies provide conflicting evidence. For example, Silveiro et al [24] reported an increased risk of developing albuminuria after nephrectomy in patients with T2DM compared with patients without T2DM, but Chang et al [25], who compared patients with type 1 DM who had either 1 or 2 kidneys, concluded that reduced nephron number is not associated with an accelerated development of diabetic glomerulopathy. In our study, we did not find an increased risk for developing microproteinuria in donors with prediabetes compared with donors in the control group.

Our study and previous studies therefore did not find a reduction in renal function after donation in donors with pre-existing prediabetes. Donors who are diagnosed as T2DM may be at risk of developing diabetic nephropathy during longer follow-up periods, however. Ibrahim et al [26] studied donors who developed T2DM after kidney donation. In their initial study, 154 of 2954 surveyed donors developed T2DM at 17.7 ± 9.0 years after donation. During the first decade after developing DM, donors were not at an increased risk for accelerated kidney disease but had higher rates of albuminuria [26]. The same group recently reported that the development of diabetes results in a faster rate of GFR decline than is observed in nondiabetic donors but only if both hypertension and proteinuria are present. Although these results indicate that T2DM is not associated with an increased risk of ESRD, the authors presumed that ESRD may develop during a longer follow-up period if the diabetic donor had microalbuminuria, suggesting that this subgroup of donors are at risk of accelerated renal function loss [27]. This study also suggests, however, that a diagnosis of T2DM itself does not pose a risk to donors, and the risk of deteriorating to ESRD remains low after a T2DM diagnosis. Nonetheless, results from a longer follow-up period in donors with diabetes are not yet available, and therefore the risk of ESRD remains a concern that needs to be addressed during predonation counseling when the candidate presents with prediabetes. The results of our study can offer more accurate guidance by stratifying the risk of developing T2DM after kidney donation.

There are some limitations to our study. The small sample size is a main limitation. Although the number of included donors with prediabetes was similar to previous studies, further stratification of these donors into high- and low-risk groups led to a smaller sample size within each group. The data were collected in a prospective manner and longitudinal follow-up data were available, however, which are strengths compared with previous studies. Another limitation is that all donors were of Asian descent; our results therefore may not be generalizable to other populations. The HbA1c measurements are known to be different in other ethnic

populations, which should be considered when applying our results to such populations. As previously described, the relatively short follow-up period is another limitation of the study. Longer follow-up is needed to provide long-term safety data among donors with prediabetes.

In conclusion, donors with both IFG and elevated HbA1c compared with donors with only IFG or elevated HbA1c are at a higher risk of being diagnosed as T2DM during follow-up after donating a kidney. The high-risk donors who did not progress to T2DM were not likely to revert to normal fasting glucose and thus were at continuous risk of developing T2DM. All donors with prediabetes exhibited preserved renal function and were not at increased risk of developing proteinuria after donation. Based on these results, we conclude that donors with prediabetes are not at an increased risk during the immediate postdonation period and can be safely accepted as donors after appropriate counseling and education. Donors with prediabetes should be counseled that prediabetes is a reversible state and presented with lifestyle modifications and other strategies that will prevent progression to diabetes.

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