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Diabetes after Kidney Donation

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Abstract

Kidney donors, similar to the general population, are at risk for development of type 2 diabetes mellitus (T2DM). The course of donors who develop T2DM has not been studied. We surveyed 3777 kidney donors regarding the development of T2DM. Of the 2954 who responded, 154 developed T2DM 17.7 ± 9.0 years after donation. The multivariable risk of development of T2DM was associated with type 1 DM in the recipient, male gender and body mass index $>30 \text{ kg/m}^2$ at time of donation. Compared to age, gender, duration after donation and body mass index (BMI)-matched non-diabetic donor controls; diabetic donors were more likely to have hypertension (70.8% vs. 36.2%, $p = 0.005$), proteinuria (18.8% vs. 3.9%, $p < 0.0001$) but had a similar serum creatinine. eGFR change after T2DM development was $-0.80 \pm 0.94 \text{ mL/min/year}$, -0.70 ± 0.86 in nondiabetic donors with similar duration after donation and $-0.61 \pm 0.76 \text{ mL/min/year}$ in age, gender, BMI and duration after donation matched nondiabetic donor controls. These preliminary and short-term data demonstrate that factors associated with T2DM in kidney donors are similar to those in the general population and donors screened carefully at the time of donation do not appear to have an acceleration of diabetic kidney disease.

Keywords

diabetes mellitus; donation; kidney

Introduction

Diabetes mellitus is the leading cause of end-stage renal disease (1). Its prevalence will more than likely increase as the prevalence of type 2 diabetes mellitus (T2DM) increases in parallel with the rise of obesity in the general population (2).

T2DM has a strong genetic component and 30% of those afflicted with it develop kidney damage (3). Therefore, some transplant centers decline kidney donors with a strong family history of type 2 diabetes, due to theoretical concerns regarding the possible additive effect of hyperfiltration that is instigated by diabetes and reduction in renal mass (4–6). Yet it is unknown whether development of T2DM after donating a kidney leads to a higher risk of experiencing acceleration in glomerular filtration rate (GFR) decay when compared to nondiabetic donors or diabetics with two kidneys.

Herein, we report on the donors' risk of developing T2DM, compare kidney function in diabetic donors to that of age, gender, duration after donation and body mass index (BMI)-

matched nondiabetic donors and assess whether diabetic donors are vulnerable to a faster decay in GFR when compared to nondiabetic donors.

Materials and Methods

Between January 1, 1963 and March 31, 2009, 3825 donor nephrectomies were performed at the University of Minnesota. At several times in the last three decades, we have attempted to contact all donors to ascertain their health status. In the last 7 years, we have begun a comprehensive multistep approach to locate all kidney donors (including review of medical records, utilizing phone and internet directories and also the help of the recipients). Those known to be alive and with available contact information were sent a survey regarding development of T2DM after donation. The survey included the following questions:

1. Were you ever told you have diabetes? If you answered yes, please answer the following questions:
 - a. How old were you when you were diagnosed with diabetes?
 - b. Are you currently taking insulin, a pill to lower your blood sugar (glucose) or both?
 - c. Are you controlling your blood sugars by diet only?
2. Do you have hypertension (high blood pressure)? If yes, are you taking medications to lower your blood pressure and when did you start taking them?
3. Were you ever told you have protein in the urine? When?

The University of Minnesota program has no policy that excludes donors with family history of T2DM. We counsel the offspring of a type 2 diabetic individual about their lifetime risk for the condition and have generally accepted such donors if their age at the time of evaluation was at least 10 years beyond the age at which their parent developed T2DM. Potential donors who have two diabetic parents, have multiple siblings with T2DM in addition to a diabetic parent or more than one immediate family member with type 2 diabetic kidney disease are strongly discouraged from donating, particularly if they are African-American or Hispanic. Moreover, prior to 2002, all potential donors wishing to donate to a family member with diabetes had to have a normal glucose tolerance test. After 2002, only those with more than one immediate family member with T2DM, women with history of gestational diabetes and those with fasting blood sugar ≥ 99 mg/dL underwent GTT. Donors with BMI >35 kg/m² are encouraged to lose weight and are generally not accepted till their BMI is less than 30 kg/m².

As part of our ongoing efforts to study long-term consequences of kidney donation, we have, at intervals asked all donors to get serum creatinine and urinary protein measurements at their primary care provider's office. For those with measured serum creatinine level, we estimated GFR (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation (7). We have previously shown that this model offers the most precise GFR estimate in former kidney donors (8,9).

For the determination of the prevalence of hypertension, eGFR and proteinuria, diabetic donors were matched (1:1) on age, gender, years from donation and BMI at donation to donors who did not develop diabetes. All diabetic and nondiabetic controls were white.

To address whether the rate of eGFR change is accelerated in diabetic donors, we studied diabetic donors who had multiple serum creatinine measurements obtained after T2DM development and that were at least 1 year apart. eGFR change in these diabetic donors was compared to two groups:

1. Five hundred and twenty-two nondiabetic donors who also had multiple serum creatinines available in the same time frame the diabetic donors' onset of T2DM (i.e. 15 years after donation).
2. Fifty-six nondiabetic donors matched on age, gender, BMI and duration after donation who also had multiple creatinine measurements available. This group is a subset of the 522 nondiabetic donors mentioned earlier.

These studies were performed after approval by the University of Minnesota Institutional Review Board.

Statistical method

Categorical variables were compared using the chi-square or Fisher's exact test. Continuous variables were compared utilizing the unpaired *t*-test. A Cox proportional hazard model was used to study the predictors for the development of type 2 diabetes, utilizing variables ascertained at the time of donation. Variables entered in this model were age, gender, BMI, type 1 DM in the recipient, type 2 DM in the recipient, serum creatinine and smoking status. Results from these models are expressed as adjusted hazard ratio and their 95% confidence intervals. The unadjusted hazard ratios are also provided. All other results are expressed as mean $\pm$ SD, unless otherwise specified. $p < 0.05$ was considered significant. SAS 9.1 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Of the 3825 who underwent uninephrectomy for kidney donation as of March 31, 2009, 48 also donated a partial pancreas and, therefore, were not included in the analyses. Of the remaining 3777: 293 have died, 555 did not send back any health updates in the last four years and 2929 have responded to our surveys (Figure 1). In total, 154 donors reported developing T2DM; 129 from the 2929 currently alive donors, 17 of 293 deceased donors with available information prior to death and 8 of the 555 donors with no recent health updates reported having T2DM, as well. Therefore, we have diabetes information on 2945 donors (2929 + 17 deceased + 8 with no recent contact). The cause of death is unknown for 40% of the donors, cardiovascular disease in 19% and cancer in 20%. Only two donors were listed to have died of diabetes-related complications. In addition, 11 donors have developed ESRD requiring dialysis or transplantation and none was due to diabetic kidney disease.

Total population

Characteristics of donors with and without diabetes and nonresponders are shown in Table 1. Donors with diabetes were more likely to be smokers, were more likely to have a BMI greater than 30, and their serum creatinine measurements at the time of donation were slightly higher than those of their nondiabetic counterparts. Nonresponders donated more recently, were least likely to have ever smoked cigarettes and least likely to have donated to a recipient with T2DM. The majority, 80% of nondiabetic responders, donated prior to 2002, when glucose tolerance testing was required in high risk individuals.

Risk factors for diabetes

The Cox regression analysis assessing the various risk factors (at time of donation) for diabetes development revealed that donating to a family member with type 1 diabetes; HR 2.97 (95% CI 1.93–4.56), $p < 0.001$, and to a lesser extent, but not statistically significant T2DM; HR 3.07 (95% CI 0.92–10.23), $p = 0.07$, were associated with the future risk of developing T2DM (Table 2). A BMI greater than 30; HR 2.97 (95% CI 1.93–4.56), $p < 0.001$ and male gender; HR 1.76 (95% CI 1.12–2.76), were also strongly associated with the development of diabetes. Donors who were over the age of 45 were slightly more likely to

develop diabetes; HR 1.46 (95% CI 0.97–2.19), $p = 0.07$. Neither serum creatinine nor smoking status at donation were predictive of the future risk of T2DM.

Donors with diabetes

For the 154 donors who developed diabetes, mean age ($\pm$ SD) at time of donation was 39.8 ± 11.4 years and the diagnosis of diabetes occurred 17.7 ± 9.0 years after donation. Characteristics of these donors are shown in Table 3; the majority were white and 47% donated to a sibling or other family member (Table 3). The cause of ESRD in the recipient was type 1 diabetes in 33%, hypertension in 35%, T2DM in 10%, polycystic kidney disease in 5% and other in 15%. Of the 154, 20% had a positive family history for T2DM. Current Hb_{A1c} was available in 51 donors and it was $8.0 \pm 7.8\%$ and a third were receiving oral hypoglycemic agents.

Of the 154 diabetic donors, 71% developed hypertension requiring treatment 17.6 ± 8.9 years after donation; almost at the same time they were told they have diabetes. Actual blood pressure readings were available in 126 donors and they were 128 ± 16 mmHg for systolic blood pressure and 75 ± 10 mmHg for diastolic blood pressure. Serum creatinine was available in 126 of the diabetic donors (following diagnosis) and it was 1.26 ± 0.40 mg/dL with an eGFR of 58.8 ± 16.7 mL/min/1.73m²; 7.7 ± 7.0 years after the development of diabetes (Table 4). Regarding proteinuria, 29 donors (18.8%) were told they have proteinuria. The percentage with proteinuria was verified by obtaining the urine analysis results which confirmed the presence of +1 dipstick positive proteinuria. Furthermore, in 20 local diabetic donors who were able to come back to the University of Minnesota, we were able to measure the urinary albumin/creatinine ratio (ACR) at our laboratory and it was 68.7 ± 176.85 mg/g, 75% were normoalbuminuric (using ACR <17 mg/g creatinine for men and 25 mg/g creatinine for women), 20% were microalbuminuric and 10% were macroalbuminuric (Table 4). Time from development of type 2 diabetes to ACR measurement in these 20 donors was 5.1 ± 7.2 years.

When compared to the age, gender, duration after donation and BMI-matched nondiabetic donor controls, we found that donors who developed T2DM had an increased prevalence of hypertension (71% vs. 36.3%; $p = 0.005$) and were also more likely to be proteinuric (18.8% vs. 3.9%, $p < 0.0001$). Quantitative proteinuria information was available in 14 nondiabetic controls. The average ACR was 61.8 ± 181.1 mg/g and a similar proportion (i.e. 71%) was normoalbuminuric (Table 4).

Longitudinal eGFR change

Of the 154 donors who developed diabetes, 64 donors had multiple serum creatinine measurements available after the diagnosis of diabetes was made. To address whether these 64 donors were different than the rest of the diabetic donors, they were compared to the remaining 90 diabetic donors with no serial measurements on baseline demographics that included age, gender, time from donation, BMI and relation to the recipient, among others, and they were not different (data not shown). They, however, were more likely to be hypertensive (91%), 19% were proteinuric, their BMI at the time of last follow-up was 31.6 ± 7.0 kg/m² and an average of 15.5 ± 8.8 years had elapsed from donation to the development of T2DM. The annual eGFR change in these donors was -0.80 ± 0.9 mL/min/1.73m² (range -2.99 – 1.63). The annual change of eGFR in 522 donors without diabetes and 15 years after donation was -0.70 ± 0.86 mL/min/year, range $(-4.99$ – 2.19 , $p = 0.43$, vs. those with diabetes). To strengthen this analysis, we matched 56 donors out of the above 522 nondiabetic donors to the 64 diabetic donors on age, gender, BMI and duration after donation and found their rate of eGFR change to be almost indistinguishable; 0.61 mL/min/year.

Finally, seven diabetic donors had multiple serum creatinine measurements before and after the development of diabetes that allowed us to compare pre- and postdiabetes eGFR slopes. Prior to development of T2DM, it was -0.88 ± 0.67 mL/min/year (range -1.96 to -0.21) and after developing the condition it was -1.10 ± 5.6 mL/min/year (range -10.8 – 7.3), $p = 0.93$.

Discussion

Uninephrectomy is followed by a rapid increase in renal plasma flow and GFR. In fact, GFR increases by 70% within 1 week of donation (10). In addition, a substantial proportion of subjects with either types 1 and 2 diabetes undergo hyperfiltration (5,11). The compensatory increase in GFR observed in the setting of reduced renal mass and diabetes has been linked to the progressive nature of kidney disease (6). Of concern is the possibility of a multiplicative adverse action of the hyperfiltration from donating a kidney and the hyperfiltration observed in diabetes. However, in case series of diabetic patients with either unilateral agenesis or unilateral nephrectomy, none suffered accelerated kidney function in the remaining kidney (12–14). Silveiro et al. studied type 2 nonliving donor diabetic patients who had undergone uninephrectomy (single-kidney diabetes, $n = 20$; duration of diabetes, 8.5 ± 7 years) comparing renal function versus nondiabetics who had undergone uninephrectomy (single-kidney nondiabetic, $n = 17$) and versus type 2 diabetics having 2 kidneys ($n = 184$; duration of diabetes, 10 ± 7 years) (15). The single-kidney and two-kidney type 2 diabetic patients were matched for age, sex and BMI. Microalbuminuria was noted in a higher proportion of single-kidney diabetics (40%) than single-kidney nondiabetics (18%) or two-kidney diabetics (20%). Macroalbuminuria was noted in a higher proportion of single-kidney diabetics (30%) than single-kidney nondiabetics, but there was no difference between single-kidney diabetics (30%) and two-kidney diabetics (23%). Of importance, renal function at the time of the study was not different for single-kidney patients, whether or not they had diabetes. More recently, Chang et al. examined clinical and morphologic differences between kidney biopsies from 28 subjects with type 1 diabetes who received renal transplants and 39 subjects with diabetes and two functioning kidneys and found no difference between the mesangial matrix volume; the hallmark of diabetic nephropathy, in subjects with one kidney compared to those with two kidneys (16). To our knowledge, this is the first detailed report on outcome after development of T2DM in former kidney donors. Okamoto et al. reviewed the records of 444 kidney donors who donated between 1985 and 2000 and underwent 75 g oral glucose tolerance test (17); 71 were found to have impaired glucose tolerance or diabetes. After a mean follow-up of 83 ± 78 months (range 6–212), seven of 65 survivors with impaired glucose tolerance at the time of donor evaluation became frankly diabetic. No end-stage renal disease was reported in the 71 individuals, their survival was similar to the rest of the donor cohort but no information was provided on their level of kidney function or protein excretion. Our data suggests that the prevalence and risk factors for T2DM in kidney donors are not different than what is observed in the general population. The emergence of type 1 DM as an associated factor for the development of T2DM in the donor and the only marginal nonstatistical association with type 2 DM in the recipient are rather surprising. We suspect that the former may be due to the fact that some of the recipients diabetes type was misclassified as type 1 DM if using insulin was the main criteria for such a label. There was a higher prevalence of smoking in the donors who developed diabetes. Possibly due to the small number of donors studied, smoking was not a significant risk factor for T2DM in both the adjusted and unadjusted analyses. Several large prospective studies have raised the possibility of an association with type 2 DM and in a large meta-analysis composed of 25 prospective cohort studies, smokers were 40% more likely to develop diabetes (95% CI 1.3–1.6) (18–23). The lack of association we observed here may also be due to the clustering of other habits in smokers such as lack of physical activity or unhealthy eating habits that were not captured in our surveys.

Diabetic donors had a comparable degree of albuminuria and hypertension in the first decade of diabetes to what has been generally described in subjects with diabetes and two kidneys in the first few years of type 2 diabetes development (2,3,24). Diabetic donors, however, are twice more likely to be hypertensive than age, gender, duration of follow-up and BMI-matched nondiabetic donor controls but this frequency of hypertension is, again, similar to type 2 individuals with two kidneys (2,3,24).

The prevalence of proteinuria in 128 donors with available measurements was 18.8% by self-report and 25% by the urinary albumin/creatinine ratio obtained in 20/154 donors. This prevalence is higher than the usual rates of albuminuria encountered in kidney donors but similar to subjects with diabetes with two kidneys. Garg et al. quantified the pooled incidence of proteinuria in 42 studies of kidney donors comprising 4793 donors and found it to be 12% (95% CI 8–16%) (25). In addition, we have recently measured the urinary albumin/creatinine ratio in 255 kidney donors, of whom only 3.1% have T2DM, who were at least 12.2 ± 9.2 years after donation and found that 12.7% were albuminuric (26). These observations suggest that the higher prevalence of proteinuria in the diabetic donors is unrelated to donation itself, but probably represents the presence of underlying diabetic renal involvement and possibly hypertension. While the proportion with normoalbuminuria was similar between diabetic and non-diabetic donor controls, only 3.9% of nondiabetic donors reported proteinuria suggesting that diabetes is responsible for the higher prevalence (18.8%) of proteinuria. This finding needs to be confirmed in a larger group of individuals. We, unfortunately, do not have information on retinopathy, kidney biopsy information or other end organ damage from diabetes which would make diabetic renal involvement a more likely reason for this increased albuminuria. In addition, quantitative proteinuria data was only available in 20/154 diabetic donors and 14/154 matched controls.

In donors who had multiple serum creatinines available, the rate of GFR decline is not accelerated when compared to nondiabetic donors, and is similar to the rate observed in two-kidney diabetic subjects with hypertension and microalbuminuria (27). Interestingly, diabetic donors had a urinary albumin excretion rate of 68.7 ± 176.8 mg/g; very comparable to the 35 mg/day reported by Parving et al. (27) in their study of microalbuminuric hypertensive type 2 individuals with roughly a similar duration of diabetes.

The mean time from donation to development of T2DM in our donor population was 17.7 ± 9.0 years. Importantly, our policy prior to 2002 was to do an oral glucose tolerance test on all potential donors with positive family history for diabetes; all 154 donors described in this report donated before 2002. Our median follow-up of donors after development of diabetes was 7.7 ± 7.0 years. It takes many years to develop diabetic renal changes and our conclusions are, therefore, limited to the first decade after type 2 diabetes development. Data from the United Kingdom Prospective Diabetes Study (UKPDS) indicate that it takes an average of 10 years from the diagnosis of type 2 diabetes for 25% of subjects with diabetes to develop microalbuminuria. Based on statistical modeling, the median time with normoalbuminuria before progressing to microalbuminuria is 19 years; the median time with microalbuminuria before progressing to macroalbuminuria is 11 years and the median time with macroalbuminuria before progressing to nephropathy is 10 years (28). Therefore, longer follow-up is certainly needed. Finally, one may interpret the comparable level of eGFR seen in diabetic and nondiabetic donors as an early sign of progressive renal disease in the diabetic individuals. One would expect that diabetic donors have undergone hyperfiltration and the fact that their eGFR is the same as nondiabetics may be reflective of a drop in their renal function.

There are other limitations to our data. The cause of death was missing in 40% of all donors. We have information on only 2945 of our kidney donors; therefore, true incidence of

diabetes could not be precisely determined. In our detailed studies of 255 randomly selected kidney donors, the prevalence of T2DM was 3.1% (26). In the current analysis, the overall prevalence was 5.2% in those who responded and 4.0% in the entire pool of 3777 donors. We are also limited by survival bias (we do not have information on type 2 diabetes in the majority of donors who have passed away), and also by response bias as responders are certainly different and in this analysis were more likely to have ever smoked and were heavier at donation. Data from the general population clearly indicates that a significant percentage, at least 25%, of people may not be aware of the presence of diabetes and hypertension and thus our report may underestimate these two conditions (3,24). The prevalence of diabetes in our donors (5.2%) is lower than the 9.8% that is observed in non-Hispanic whites (3). However, our donors were screened at the time of donation and so may be a selected subgroup.

Our population consisted of mainly white kidney donors and therefore we could not assess whether ethnicity plays a factor in the development of type 2 diabetes after donation and information on family history of type 2 DM in nondiabetic donors was not captured. Most importantly, reporting on proteinuria was by self-report and dipstick protein assessment which are clearly inferior to quantitative methods and only a small fraction of donors had quantitative measurement of proteinuria.

In summary, the risk factors for the development of T2DM in kidney donors is similar to the general population and donors who develop it have rates of albuminuria that are higher than nondiabetic donors, which may be suggestive of early diabetic kidney disease. Importantly, when compared to nondiabetic donors, diabetic donors in the first decade of diabetes development did not exhibit an increased risk for accelerated kidney disease. Therefore, declining donors with positive family history of type 2 diabetes, if screened with oral glucose tolerance, may not be fully justified but larger studies and, more importantly, longer follow-up are needed. All kidney donors, particularly those with a positive family history for diabetes, should be strongly advised to maintain weight control.

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Figure 1.
Study participants.

Table 1

Characteristics of diabetic, non-diabetic and non-responding donors

	Responders with diabetes	Responders without diabetes	Non-responders	p-Value
n	154	2914	709	
Follow-up (years)	24.4 ± 8.4	14.0 ± 11.1	11.8 ± 11.1	0.01
White	95%	97%	96%	0.85
Women	49.4%	56.7%	48.7%	0.08
Age at donation 18–45 years	68.2%	67.7%	68.7%	0.96
History of smoking (ever)	54.6%	38.8%	17.9%	0.0001
Serum creatinine at donation (mg/dL)	0.95 ± 0.19	0.91 ± 0.18	0.91 ± 0.2	0.04
BMI at donation >30 kg/m ²	25.3%	17.2%	19.5%	0.02
Type 1 diabetes in recipient	22.1%	23.7%	19.0%	0.64

Table 2

Risk factors for development of type 2 diabetes

Variable at donation	Unadjusted		Adjusted	
	Hazard Ratio (95% C.I.)	p-Value	Hazard Ratio (95% C.I.)	p-Value
BMI >30 kg/m ²	3.33 (2.19–5.08)	<0.0001	2.97 (1.93–4.56)	<0.0001
Type 1 diabetes in recipient	3.07 (1.97–4.80)	<0.0001	2.77 (1.75–4.38)	<0.0001
Type 2 diabetes in recipient	2.46 (0.75–8.06)	0.14	3.07 (0.92–10.23)	0.07
Men	1.35 (0.93–1.97)	0.11	1.76 (1.12–2.76)	0.01
Donor age >45 years	1.53 (1.03–2.28)	0.04	1.46 (0.97–2.19)	0.07
Serum creatinine (mg/dL)	0.95 (0.65–1.39)	0.80	0.79 (0.50–1.24)	0.31
Smoking (ever vs. none)	1.22 (0.84–1.77)	0.31	1.21 (0.82–1.76)	0.34

Table 3

Clinical characteristics of kidney donors with post-donation type 2 diabetes

n	154
Age at donation	39.8 ± 11.4 years
Men	50.6%
White	95%
Time from donation to type 2 diabetes	17.7 ± 9.0 years
Age at time of type 2 diabetes diagnosis	57.5 ± 12.6 years
Relationship to recipient	
Sibling	47%
Mother	18%
Father	19%
Other	16%
Most recent fasting glucose (n = 63), mg/dL	130 ± 59
Most recent Hb _{A1c} (n = 51)	8.0 ± 7.8%
Anti-diabetic strategy	
Diet	36/154 (23%)
Oral hypoglycemia agents	52/154 (34%)
Oral hypoglycemic agents and insulin	19/154 (12%)
Unknown	47/154 (31%)

Table 4

Blood pressure and kidney function in diabetic donors and non-diabetic matched * donor controls

	Diabetic donors	Non-diabetic donor controls
n	154	154
Duration of follow-up (years)	24.4 ± 8.4	24.3 ± 8.3
Self-reported hypertension †	71%	36.3%
Last Serum creatinine (mg/dL)	1.26 ± 0.40 (n = 126)	1.30 ± 0.30 (n = 112)
Last eGFR (mL/min/1.73m ²)	58.8 ± 16.7 (n = 126)	59.3 ± 18.5 (n = 112)
Years from diabetes to creatinine measurement	7.7 ± 7.0	N/A
Self-reported proteinuria	29/154 (18.8%)	6/154 (3.9%) **
Albumin/creatinine ratio (mg/g)	68.7 ± 176.8 (n = 20)	61.8 ± 181.1 (n = 14)
Normoalbuminuric	15/20 (75%)	10/14 (71%)

* Diabetic donors were matched 1: 1 to non-diabetic donors on age, gender, duration after donation and BMI at donation.

† p = 0.005

** p < 0.0001