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Kidney Donors With Diabetes: Renal Biopsy Findings at Time of Transplantation and Their Significance

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Diabetes (DM) is an increasingly significant factor in renal transplantation. DM, both diagnosed and undiagnosed, is noted in as many as 9.3% of the US adult population.[1] According to the 2013 and 2015 Scientific Registry of Transplant Recipients Reports, about 8% of deceased donors have DM and up to 40% of kidneys from diabetic donors were discarded.[2,3]

DM is considered a contraindication of kidney donation by living donors.[4] Consideration on the impact of DM on organ allocation in deceased kidney donors is evolving. There have been various approaches to the allocation of marginal donor kidneys as their utilization has expanded. The first allocation scheme in 1987 introduced the concept of expanded criteria donor (ECD) defined as donors aged 60 years or older, or aged 50–59 years in the presence of at least 2 of 3 risk factors including cerebrovascular cause of death, history of hypertension, or serum creatinine >1.5mg/dL. Donor DM is not included as a risk factor in this scheme.[5,6] The new Kidney Allocation System implemented in 2014 utilizes the Kidney Donor Profile Index based on 10 donor factors to assign a risk score for posttransplant graft survival. Donor DM carries a heavyweight in this scoring.[5-7] Donor DM has been an important reason for the discard of donor's kidneys. Using UNOS data until 2008, Sung et al reported a discard rate of 39%, 57%, and 21% for diabetic donors, diabetic donors of EDC, and diabetic donors of standard criteria donor (SCD), respectively.[8]

Against this background, diabetic donor kidneys account for a small but significant percentage of transplanted kidneys ranging from 3.5% to 6.5%.[6,9-11] Few studies have evaluated the outcome of transplanted kidneys from diabetic donors, all concurring that diabetic donor kidneys have either no impact on long-term graft or recipient survival, or confer only a small risk for failure. Although much insight was achieved, all of these studies display some limitations, reflecting their retrospective nature utilizing incomplete data from national registries. Mostly unknown are the status of diabetic nephropathy (DN) in these donated kidneys, its evolution after transplantation in relation to posttransplant DM, and its impact on graft outcome.

The current study aims to address some of these considerations.

MATERIALS AND METHODS

Records of all deceased kidney donors at the J.C. Walter Transplant Center, The Houston Methodist Hospital, between January 2006 and December 2014 were reviewed to identify the donors with DM. Out of 749 donors, 46 (6.1%) had DM. Postperfusion biopsy of the transplanted kidneys was performed in 26 recipients. Posttransplant renal biopsies were also performed in these recipients for evaluating changes of renal functions or for surveillance in high-risk recipients. These biopsies are the focus of this study. This study is approved by the institutional review board.

The biopsies are subjected to light microscopy (LM) including hematoxylin & eosin, Periodic acid-Schiff, Masson's trichrome, and methenamine silver stains; and immunofluorescent stains, including IgG, IgA, IgM, C3, C4, C1q, kappa light chain, lambda light chain, and C4d. Electron microscopy (EM) was done both prospectively and retrospectively, including measurement of the thickness of the glomerular basement membrane (GBM) according to a method described by Haas.[12] Thickened GBM, a diagnostic change of DN, was defined as a thickness of >430 and 395 nanometers for male and female, respectively. Systematic examination was performed with special attention to the features of DN. The diabetic changes were graded on a scale of 0–IV, as defined by the Renal

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Pathology Society[13]: class 0 = no diabetic changes by LM or EM; class I = no obvious LM changes, but thickening of the GBM by EM; class IIa = mild mesangial expansion by LM; class IIb = marked mesangial expansion by LM; class III = nodular mesangial sclerosis; and class IV = advanced diabetic glomerulosclerosis with global sclerosis in >50% of glomeruli. Changes other than DN were also recorded. Follow-up biopsies were evaluated in the same manner.

The profiles of donors and recipients and their clinical/laboratory information around the time of transplantation with special attention to those pertinent to the diabetic status, were obtained from hospital medical records, United Network of Organ Sharing registry, and family members. Up-to-date follow-up, including graft outcome and recipient outcome, was established. For donors, the diagnosis of DM and its estimated duration were made through communication with family members, old medical records, and data from national registries. For recipients, the diagnosis criteria included a fasting plasma glucose level of at least 126 mg/dL or a random plasma glucose level of at least 200 mg/dL and a hemoglobin A1c of at least 6.5%.

RESULTS

Postperfusion Renal Transplant Biopsy Findings

Twenty-six postperfusion biopsies were performed from 26 transplanted kidneys from 25 deceased diabetic kidney donors (2 kidneys from a single donor, cases 8 and 9, Tables 1–4). DN was not seen in 20 biopsies, even after EM study (Renal Pathology Society class 0[12,13]) (Figure 1A and B). One biopsy showed no LM changes of DN, but EM showed thickened GBM (495+/–27 nanometers) (class I) (Figure 2A and B). Five biopsies showed DN of class IIa, characterized by mild mesangial sclerosis and hypercellularity, with thickened GBM (569+/–51 nanometers) (Figure 3A and B). None of these biopsies showed class IIb, class III, or class IV lesions.

These biopsies also showed other changes (Table 2), including arterionephrosclerosis (14 biopsies), interstitial fibrosis and tubular atrophy >15% of cortical tissue area (8 biopsies), acute tubular necrosis (4 biopsies), myoglobin casts (2 biopsies), incidental IgA nephropathy (1 biopsy), and incidental rare glomerular capillary thrombi, perhaps related to organ preservation (1 biopsy).

Donor Profiles

The clinical information of the 25 donors are summarized in Table 3. They included: age 18–70 years (mean 47); male/female ratio 12/13; ethnic distribution: 16 Hispanic, 5 white, 3 African American, and 1 Asian; EDC in 8; history of hypertension in 19; obesity (body mass index >30) in 11. By design, all 25 donors had DM with variable durations (unknown in 7, 15 y in 9, 6–10 y in 7, and >10 y in 2). There was an overlapping of the duration of DM among different classes of DN (Table 1).

Recipient Profiles

The clinical information of the 26 recipients are summarized in Table 4. They included: included: age 33–71 years (mean 57); male/female ratio 16/10; ethnic distribution: 8 Hispanic, 4 white, 11 African American, and 3 Asian. Before transplantation, hypertension was diagnosed in 24 recipients and DM in 15, with 14 of them having both and obesity (BMI >30) in 8. The causes of end-stage renal disease included hypertension in 10, DM in 8, hypertension and DM in 3, glomerulonephritis in 2, polycystic kidney disease in 1, and unknown in 2.

The levels of histocompatibility were widely variable (Table 4). Although delayed graft function was noted in 7 recipients, all grafts recovered. Thymoglobulin induction was achieved in 16 recipients, and maintenance immunosuppression included tacrolimus in each recipient with added mycophenolate and/or steroid in some recipients (Table 4).

At most recent follow-up (36–136 mo), 4 recipients died, all of cardiovascular complications, with functional renal grafts. The remaining 22 recipients were alive with functional grafts in 21 and 1 failed graft 54 months posttransplant probably due to progressive interstitial fibrosis and tubular atrophy (case 15; Table 4). Protein excretion (urine protein/creatinine ratio) was normal in 4; increased, albeit of low levels (0.1–0.83), in 19; and reached high levels in three recipients (1.40, 1.42, and 1.7, cases 11, 15, and 20; Table 4). The serum creatinine at follow-up of these 3 recipients were 1.8, 8, and 2.7 mg/dL, respectively. The last follow-up transplant biopsies of these recipients showed polyomavirus nephropathy in one (case 11) and arterionephrosclerosis with interstitial fibrosis and tubular atrophy in all 3, but not DN (Table 2). DM was present in 15 recipients before transplantation. After transplantation, DM persisted in 14, regressed in 1, and developed *de novo* in 6, for a total of 20 recipients with posttransplant DM (Tables 4 and 5). Hypertension noted in 24 recipients pretransplant, was diagnosed in 23 after transplantation. Several diseases were also noted in these recipients after transplantation, affecting some but not all patients, including hyperparathyroidism, hyperlipidemia, metabolic syndrome, urinary or nonurinary infection, atherosclerosis, obesity, cirrhosis, and gastroesophageal reflux. However, these diseases did not seem to impact the course of DN.

TABLE 1.

Diabetic changes in 26 postperfusion biopsies of transplanted kidneys

Diabetic nephropathy RPS class (0–IV)[a]	Number of Bx	Duration of diabetes in donors (number of donors)
0 (no LM or EM changes)	20	Unknown (7), 1–5 y (8), 6–10 y (3), >10 y (2)
I (no LM changes, but GBM thickening by EM)	1	6–10 y (1)
IIa (mild mesangial expansion by LM)	5	1–5 y (1), 6–10 y (3[b])
IIb (marked mesangial expansion by LM)	0	Not applicable
III (mesangial nodules)	0	Not applicable
IV (sclerotic glomeruli)	0	Not applicable

[a]See text (Method) for the classification scheme for diabetic nephropathy.
[b]Two kidneys from the same donor, cases 8 and 9 in Tables 2–4.
Bx, biopsy; EM, electron microscopy; GBM, glomerular basement membrane; LM, light microscopy; RPS, Renal Pathology Society.

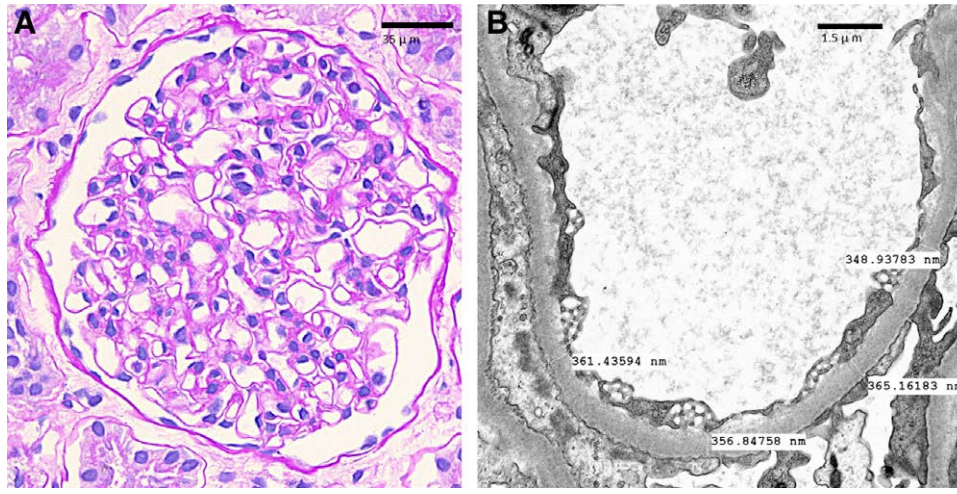

FIGURE 1. Absence of diabetic nephropathy (class 0). A, No significant glomerular changes (Periodic acid–Schiff stain ×200). B, Electron microscopy shows normal mesangial areas and glomerular basement membrane of normal thickness (×3000).

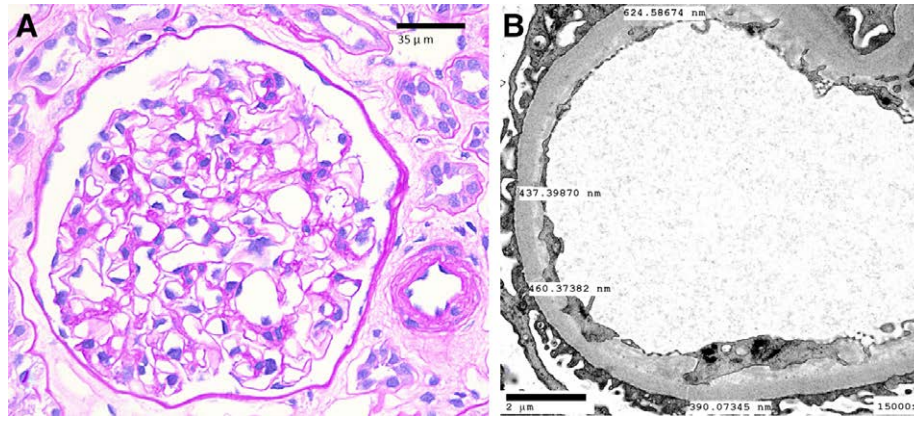

FIGURE 2. Class I diabetic nephropathy. A, No significant glomerular changes by LM (Periodic acid–Schiff stain ×200). B, Electron microscopy shows thickened glomerular basement membrane (×3000). LM, light microscopy.

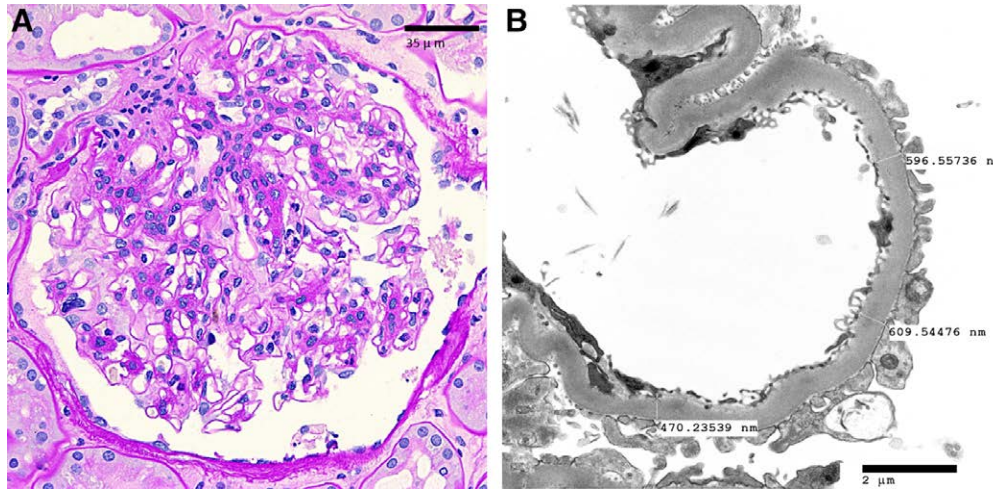

FIGURE 3. Class IIa diabetic nephropathy. A, Mild mesangial sclerosis and hypercellularity by LM (Periodic acid–Schiff stain ×200). B, Electron microscopy shows thickened glomerular basement membrane (×3000). LM, light microscopy.

Follow-up Biopsies

Follow-up biopsies (1–6 biopsies /recipient) were done for 17 recipients. Focus was aimed at the most recent follow-up biopsies (at 5–342 wk, mean 41) to evaluate the evolution of DN (Table 5) against the background of the DM status of the recipients.

Among 20 recipients in whom the postperfusion biopsies showed no DN (class 0), follow-up biopsy was not done in 8. DM was noted in 4 and 5 of these recipients pre- and post-transplant, respectively. Follow-up biopsies, done in 12 recipients, showed no DN (class 0) in 9 and DN in 3 (class I in 2 and class IIa in 1). For the 9 recipients without DN in follow-up

TABLE 2.

Renal transplant biopsy findings: postperfusion and follow-up biopsies

	Postperfusion biopsy		Follow-up biopsy	
Case #	DN+	Other diagnoses	DN+	Other diagnoses
1	0	ArN	0	ArN
2	0	ArN	I	ArN
3	0	ATN	Not done	Not done
4	0	ATN	Not done	Not done
5	I	ArN	Not done	Not done
6	IIa	ArN	IIb	IFTA 80%
7	0	None	0	ArN; IFTA (15%)
8[a]	IIa	ArN	IIb	ArN, IFTA (30%)
9[a]	IIa	ArN	IIa	ArN, IFTA (15%)
10	0	None	0	Glomerulitis, transplant glomerulopathy, IFTA (40%)
11	0	None	0	Polyomavirus nephropathy, IFTA (25%)
12	0	None	0	Severe chronic rejection, IFTA (70%)
13	IIa	ArN	IIa	Transplant glomerulopathy, antibody-mediated rejection
14	0	None	Not done	Not done
15	0	ATN, myoglobin casts, ArN	0	ArN, IFTA (20%)
16	0	None	0	None
17	0	None	Not done	Not done
18	0	ATN	I	ArN, IFTA (20%)
19	0	ATN, myoglobin casts	IIa	ArN, IFTA (50%)
20	IIa	None	IIa	ArN, IFTA (30%)
21	0	ATN, rare glomerular capillary thrombi	0	IFTA (10%)
22	0	ArN	Not done	Not done
23	0	None	Not done	Not done
24	0	None	Not done	Not done
25	0	IgA nephropathy	0	ArN, IFTA (60%)
26	0	None	Not done	Not done

[a]Same donor.

ArN, arterionephrosclerosis; ATN, acute tubular necrosis; DN+, RPS diabetic nephropathy class (0, Ia, IIa, and IIb; see text for detailed description); IFTA, interstitial fibrosis and tubular atrophy (% of cortical tissue affected); RPS, Renal Pathology Society.

biopsies, pre- and posttransplant DM were present in 5 and 66 recipients, respectively. For the 3 recipients in whom DN developed in follow-up biopsies, DM was present in 2 recipients before transplantation but developed in all 3 recipients after transplantation (Table 5).

Among the 6 recipients in whom the postperfusion biopsies showed DN, follow-up biopsy was not done in 1. The follow-up biopsies, done in the other 5 recipients, showed no DN of the same class in 3 (class IIa/class IIa) and mild progression in 2 (class IIa/class IIb, Figure 4A and B). Among these 5 recipients, pretransplant DM was present in 4, but developed in all 5 after transplantation (Table 5).

Other significant changes in these 17 most recent follow-up biopsies (Table 2) included aterionephrosclerosis (9 biopsies), interstitial fibrosis and tubular atrophy >25% of cortical tissue (8), glomerulitis (1), polyomavirus nephropathy (1), severe chronic rejection (1), transplant glomerulopathy (2), and chronic antibody-mediated rejection (1).

DISCUSSION

To the best of our knowledge, this is the first study that comprehensively evaluates the renal changes of diabetic donor kidneys at the time of transplantation and its posttransplant evolution.[6,8-10,14]

We found that diabetic donor kidneys account for 6.1% of all kidney transplants in our center. This frequency is similar to those derived from national registry studies (3.5%, 6.4%, and 5.6%) by Ahmad, Mohan, and Cohen, respectively,[6,9,10] reflecting a standard practice of organ allocation for diabetic donors.

Our findings may have implications for the utilization of renal biopsy in the decision to accept or discard the donor's kidneys. About 8% of deceased donors have DM and up to 40% of kidneys from diabetic donors were discarded.[2,3] Renal changes in pretransplant biopsies are often reported to be the main cause of this discard.[8] The findings leading to this decision are mostly the severity of glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arterial intimal thickening. Changes referable to DN were not included as a criterion for rejection. The current study found that DN is not seen or is only mild in postperfusion biopsies from donors with DM even of long duration (>10 y). However, these biopsies often show significant arterionephrosclerosis, and interstitial fibrosis/tubular atrophy, reflecting the presence of hypertension (in 73% of diabetic donors). These observations thus lend support to the validity of the current morphological criteria within the general scheme for organ allocation,[15] which does not include changes referable to DN. It is noted that in the most recent kidney donor allocation scheme, which correlates with graft outcome, donor DM is not only one of the 10 evaluated factors, but also carries a heavy scoring weight.[5,7] The discrepancy of the significant impact of donor DM on graft outcome and the frequent absence of DN in diabetic donor kidneys noted in our study is of considerable interest. It suggests that donor DM adversely impacts graft outcome through mechanisms distinct from the renal tissue injury seen in DN.

TABLE 3.
Donor information

Case #	Age (y)	Race	Sex	Cause of death	BMI	HBP	DM duration	Peak Cr (mg/dL)	Terminal Cr (mg/dL)
1	56	Hispanic	M	CVA	25.5	Yes	Unknown	0.7	0.7
2	56	Hispanic	M	Trauma	25.5	Yes	Unknown	0.7	0.7
3	35	White	M	Gunshot wound	77.9	Yes	6–10 y	2.5	2
4	18	Hispanic	F	CVA	39.4	No	1–5 y	3	2
5	51	Hispanic	M	Stroke	22.5	Yes	6–10 y	1.3	1.3
6	66	Hispanic	F	Stroke	39	Yes	6–10 y	1	1
7	45	White	M	CVA	27.5	Yes	6–10 y	0.8	0.6
8[a]	47	Hispanic	M	Trauma, anoxia	43.1	Yes	6–10 y	1.1	1
9[a]	47	Hispanic	M	Trauma, anoxia	43.1	Yes	6–10 y	1.1	1
10	67	Black	F	CVA	30.2	Yes	Unknown	2.1	1.1
11	48	Hispanic	F	Gunshot wound	29.3	Yes	Unknown	1	0.5
12	48	Hispanic	F	Stroke	29.3	Yes	Unknown	1	0.5
13	44	Black	M	CVA	23.1	Yes	6–10 y	1.1	0.8
14	28	Hispanic	M	Trauma	23.2	No	Unknown	1.1	0.6
15	42	Hispanic	F	Stroke	26.7	Yes	6–10 y	2.2	1,2
16	54	White	M	CVA	34	No	Unknown	2.4	1.3
17	32	Hispanic	F	Head trauma	26.7	No	>10 y	2.2	0.9
18	32	Hispanic	F	CVA	26.7	No	>10 y	2.2	0.9
19	30	Hispanic	F	Anoxia	34.4	Yes	1–5 y	1.7	1.6
20	60	White	M	Head trauma	33.9	Yes	1–5 y	1.1	0.6
21	54	Asian	F	Asphyxiation	39	Yes	1–5 y	2.5	2.5
22	72	Hispanic	F	Stroke	31.1	No	1–5 y	0.7	0.6
23	45	Hispanic	F	Stroke	24.6	Yes	1–5 y	1	0.7
24	22	Hispanic	F	Head trauma	23.9	No	1–5 y	1.1	0.7
25	57	Black	M	Stroke	33.9	Yes	1–5 y	2.4	2
26	70	White	M	Stroke	29.1	Yes	1–5 y	1.2	0.8

[a]Same donor.
BMI, body mass index; Cr, serum creatinine; CVA, cerebrovascular accident; DM, diabetes mellitus; HBP, high blood pressure.

Diabetic donor kidneys are increasing accepted. Several studies addressing the outcome of this type of kidney transplant support this trend. Mohan et al[10] compared 3058 diabetic donors with 90 933 nondiabetic donors and reported that the 10-year graft survival rate were 43% (diabetic + ECD), 55% (diabetic + SCD), 50% (nondiabetic + ECD), and 65% (nondiabetic + SCD), respectively. They concluded that SCD diabetic donors provide better grafts than nondiabetic ECD donors and worse than diabetic donors with ECD, but the risks of graft loss are all small compared to the ideal situation. Most recently, Cohen et al evaluated 9074 diabetic donors and 152 555 nondiabetic donors and noted a modest difference in the overall graft survival (10-y survival rate of 37% vs 50%).[6] However, DM in recipient imparts a significant risk for graft loss (25% for diabetic donor/diabetic recipient vs 37% for diabetic donor/nondiabetic recipient or nondiabetic donor/diabetic recipient). In the current study, diabetic donor kidneys enjoy good outcome. Whereas 4 recipients died of causes other than DN per ser, with functional grafts, other 22 recipients were alive at last follow-up with functional grafts in 21.

Although the optimal outcome of diabetic donor kidney is perhaps multifactorial, we hypothesize that the good preservation of renal tissue in the presence of DM is 1 significant factor. The current literature is nebulous in this aspect. We could not identify any study evaluating the renal biopsy findings from diabetic donors around the time of transplantation.[6,8-10,14] Furthermore, all the pertinent major studies obtained data from national registries with no information on pre- or posttransplant biopsies. Our study demonstrates that renal changes characteristic for DN are most often not seen and, when seen, are rather mild in kidneys from diabetic donors. In addition, the presence or absence of DN in diabetic donors, as well as the DN class reflecting its severity, does not seem to correlate with the duration of DM. These findings are in keeping with previous native renal biopsy studies in diabetic patients. Although DM is common (10% of adult population in the United States),[1] its involvement of kidney, that is, DN, is less frequent (10%–30% of diabetic patients).[16,17] The development of DN along the clinico-morphologic pathway in native kidneys is fairly understood. Advanced DN is often manifested by impaired renal function and progressively heavy proteinuria, which are reasons for declining kidney donation. This stage of DN often requires a long duration of DM (often >10 y), and the renal biopsies tend to show typical changes of DN, often class IIb, III, or IV, together with severe interstitial fibrosis/tubular atrophy and arteriosclerosis/hyalinosis.[16] However, the renal changes in the diabetic patients without or with only minor clinical manifestation are variable, but often inconspicuous, as shown by several renal biopsy studies within this clinical background.[18] Absence of significant proteinuria and preserved renal function are 2 requirements for kidney donor acceptance. Donors with DM but without significant clinical manifestations, therefore, may show little changes in their kidney biopsies, as shown in the current study, in keeping with the known evolution of DN in native kidneys. It should, however, be emphasized that at least in native kidney, clinicopathologic discrepancy has been noted, as shown by a recent autopsy study in which DN, even of advanced classes, may develop without any clinical

TABLE 4.

Recipient information

Case #	Age at Tx (y)	Race	Gender	BMI	Cause of ESRD	HTN pre-Tx	DM pre-Tx	Dialysis type	Dialysis duration (y)	PRA (%)	DGF	Thymo induction	Maint immunosup	Follow-up (mo)	Recipient status	Graft status	HBP post-Tx	DM post-Tx	HbA1c (mg/dL)	Cret at follow-up	Prot at follow-up
1	60	Hispanic	F	26		Yes	Yes	H	3	86	No	Yes	T + M	93	Alive	Functional	No	Yes	6.5	1.8	1+
2	59	Black	M	32	HBP + DM	Yes	Yes	H	5	3	Yes	Yes	T + M	93	Dead (CVA)	NA	Yes	Yes	6.3	NA	NA
3	43	Hispanic	F	28	GN	Yes	No	H	2	0	Yes	Yes	T	75	Alive	Functional	Yes	Yes	5.8	1,1	0.21
4	73	White	F	28	HBP	Yes	No	H	2	18	No	No	T	70	Alive	Functional	No	No	5.1	0.68	2+
5	64	Black	F	21	HBP	Yes	No	H	2	4	No	Yes	T	66	Alive	Functional	Yes	Yes	6.1	1.2	0.15
6	67	Asian	M	28	DM	Yes	Yes	P	2	0	No	No	T	65	Alive	Functional	Yes	Yes	7.3	0.9	0.56
7	57	White	F	30	Unknown	Yes	No	H	3	100	Yes	Yes	T + S	61	Alive	Functional	Yes	Yes	5.5	1.9	0.83
8	36	Asian	F	36	DM	Yes	Yes	H	4	98	No	Yes	T + M	58	Alive	Functional	Yes	Yes	7.7	1.3	0.02
9	53	Hispanic	M	28	HBP	Yes	No	H	2	0	No	No	T + M + S	58	Alive	Functional	Yes	Yes	6.6	1.4	0.1
10	66	Hispanic	M	33	GN	No	No	H	8	0	No	No	T + M	57	Alive	Functional	Yes	No	5.2	1.6	0.03
11	68	White	F	31	HBP	Yes	Yes	P	3	99	No	Yes	T + M	56	Dead (MI)	NA	Yes	Yes	5.8	1.8	1.42
12	37	Black	F	34	HBP	Yes	No	H	4	61	Yes	Yes	T + M	56	Dead (MI)	NA	Yes	No	4.9	1.2	0.8
13	62	Black	M	21	HBP	Yes	Yes	H	7	50	No	Yes	T + M + S	55	Alive	Functional	Yes	Yes	7.8	2,1	0.65
14	33	Hispanic	F	28	DM	Yes	Yes	H	10	0	No	No	T + M	54	Alive	Functional	Yes	No	6	0.73	0.02
15	54	Black	M	27	DM	Yes	Yes	H	3.5	0	No	Yes	T + M + S	54	Alive	Failed	Yes	Yes	6.7	8	1.4
16	70	Black	F	26	HBP	Yes	No	H	2	68	Yes	Yes	T + M	54	Alive	Functional	Yes	No	8	1.32	0.1
17	59	Black	M	22	HBP	Yes	No	H	3.5	0	No	No	T + M + S	52	Alive	Functional	Yes	No	5	1.1	0.13
18	59	Hispanic	M	32	DM	Yes	Yes	H	1.5	0	No	Yes	T + M	52	Dead (CVA)	NA	Yes	Yes	6,6	1.2	0.1
19	49	White	M	32	Unknown	Yes	No	H	2	0	No	Yes	T + M	46	Alive	Functional	Yes	Yes	6.5	2.2	0.16
20	63	Black	M	29	DM	Yes	Yes	H	6.5	0	Yes	No	T + M + S	46	Alive	Functional	Yes	Yes	9.2	2.7	1.7
21	57	Black	M	28	HBP	Yes	Yes	H	4	0	No	Yes	T + M + S	35	Alive	Functional	Yes	Yes	8.9	1.37	0.56
22	71	Asian	M	25	PKD	Yes	No	P	0.5	0	No	Yes	T + M + S	25	Alive	Functional	Yes	Yes	6.5	0.98	0.02
23	68	Hispanic	M	28	DM	No	Yes	H	2.5	0	No	No	T + M + S	24	Alive	Functional	No	Yes	Lost	Lost	Lost
24	63	Hispanic	M	27	HBP + DM	Yes	Yes	H	6	4	Yes	Yes	T + M + S	21	Alive	Functional	Yes	Yes	7.8	1	0.1
25	50	White	M	32	DM	Yes	Yes	H	3	0	No	No	T + M + S	20	Alive	Functional	Yes	Yes	8.9	1.5	0.68
26	52	Black	M	31	HBP	Yes	Yes	P	1.1	36	No	Yes	T + M + S	17	Alive	Functional	Yes	Yes	NM	0.9	0.16

BMI, body mass index; Cret, serum creatinine (mg/dL); CVA, cerebrovascular accident; DGF, delayed graft function; DM, diabetes; ESRD, end-stage renal disease; GN, glomerulonephritis; H, hemodialysis; HBP, hypertension; Lost, lost to follow-up; Maint Immunosup, maintenance immunosupression; MI, myocardial infarct; M, mycophenolate; NA, not applicable; NM, hemoglobin A1c not measured but blood glucose repeatedly >200 mg/dL; P, peritoneal dialysis; PKD, polycystic kidney disease; PRA, panel reactive antibodies; Prot, urine protein/creatinine ratio; S, steroid; T, tacrolimus; Thymo, thymoglobulin; Tx, transplant.

TABLE 5.

Diabetic nephropathy in postperfusion biopsies and follow-up biopsies: correlation with diabetes in 26 recipients

Diabetic nephropathy status		Diabetic nephropathy RPS class (0-IV)[a] in postperfusion and F/U biopsies	Diabetic status in recipients	
Postperfusion biopsies (26)	F/U biopsies (17)		Pretransplant	Posttransplant
No DN (8)	F/U biopsy not done	0/No follow-up biopsy	Yes diabetes in 4/8 cases	Yes diabetes in 5/8 cases
No DN (9)	No DN (9)	0/0	Yes diabetes in 5/9 cases	Yes diabetes in 6/9 cases
wNo DN (3)	Yes DN (3)	0/I (case 2[b])	Yes diabetes	Yes diabetes
		0/I (case 18)	Yes diabetes	Yes diabetes
		0/IIa (case 19)	No diabetes	Yes diabetes
Yes DN (5)	Yes DN (5)	IIa/IIb (case 6)	Yes diabetes	Yes diabetes
		IIa/IIa (case 9)	No diabetes	Yes diabetes
		IIa/IIa (case 13)	Yes diabetes	Yes diabetes
		IIa/IIa (case 20)	Yes diabetes	Yes diabetes
Yes DN (1)	F/U biopsy not done	I/No follow-up biopsy (case 5)	No diabetes	Yes diabetes

[a]See text (Method) for the classification scheme for diabetic nephropathy.
[b]These are the case numbers in Tables 2–4.
DN, diabetic nephropathy; F/U, follow-up; RPS, Renal Pathology Society.

manifestations.[16] This discrepancy may explain the presence in the current study of mild but established DN in a few postperfusion biopsies in diabetic donors fulfilling clinical criteria for acceptance. These discrepancies also put in focus the potential role of pretransplant biopsy for diabetic donors in at least selected clinical settings.[19]

The posttransplant evolution of donor kidney DN is of considerable interest for at least 2 major reasons: potential reversibility of the renal changes and high incidence of diabetic donor kidneys transplanted into diabetic recipients.

Reversibility of the renal changes characteristic for DN has been evaluated in experimental models. Pugliese et al[20] noted that pancreas transplant prevented the development of streptozocin-induced DN in Lewis rats and induced the reverse the DN of 4-month duration, but failed to do so for DN of 8-month duration. Pichaiwong et al[21] found that advanced DN in a model of leptin deficiency ob/ob mouse was completely reversed by leptin replacement. However, Steffes et al[22] reported a failure of pancreas transplant to reverse DN in Lewis rats of 7-month duration.

Information in human is even more limited, with, to the best of our knowledge, only 3 small studies. Mauer and Fioretto studied the effect of pancreas transplant (without renal transplant) on DN in the native kidneys in 13 patients with type 1 DM. They reported that DN was not changed at 5 years, but reversibility even in cases of initial advanced DN (RPS class III) was achieved at 10 years.[23,24] Abouna et al[25] reported the absence of DN at 7 months posttransplant in both transplanted kidneys from a deceased donor with DM for 17 years and with DN in pretransplant biopsy. Harada et al[26] reported 3 living kidney donors with DM lasting 2–5 years, who fulfilled clinical criteria for donation including absence of proteinuria and normal renal function. The pretransplant kidney donor biopsies showed mild DN (class I in 2 and class IIa in 1). Transplant biopsies at 1 year posttransplant showed resolution of DN including normalization of GBM thickness. Collectively, these studies indicate that knowledge in this area is limited, but suggest that reversibility of DN is possible, at least for early lesions and against specific clinical backgrounds.

The current study, although with a limited number of cases, represents the largest study on posttransplant evolution of donor kidney DN. It suggests that DN, at least in early stages, can be stable, or progress albeit rather slowly. These observations, made against some limitations, including the small number of cases (6/26 biopsies), absence of advanced DN, and relatively short follow-up duration, require further confirmatory studies. Factors that impact this evolution have not

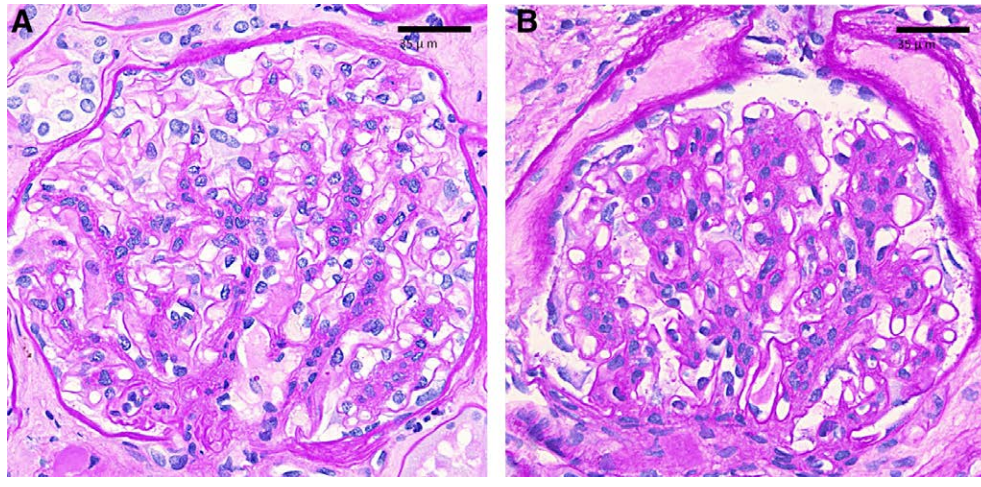

FIGURE 4. Development of diabetic nephropathy from class IIa in postreperfusion biopsy. A, Class IIb in follow-up biopsy. B, Periodic acid–Schiff stain ×200.

been elucidated. Nevertheless, posttransplant DM seems to be an important condition, being present in all cases with stable or progressive posttransplant DN. How the diabetic status in the recipients impacts the posttransplant evolution of donor kidney, DN remains poorly understood. Thirty-eight percent, 44%, and 50% of recipients of diabetic donor kidneys are diabetic themselves, as noted previously[6,10] and in the current study. This high incidence of DM in renal transplant recipients reflects not only the persistence of pretransplant DM, but also de novo DM. De novo DM develops in 4%–25% of kidney transplant recipients[27] and in 6/26 recipients in the current study. De novo DM may be due to several factors, including the diabetogenic effect of steroid and tacrolimus, the latter used in all recipients in the current study. Recipient DM imparts significantly increased risk of graft loss, and this risk is even more pronounced in cases of diabetic donor kidneys.[6] Several factors have been implicated as the causes of this adverse effect, including impaired infection control, increased cardiovascular complications, and increased alloreactivity.[28] How DN, either donor-related, recurrent, or de novo, in the transplanted kidneys fits in this scheme is unknown. Our study is the first addressing this concern. This study, though relatively small, suggests that diabetic donor kidneys with or without DN, transplanted into a diabetic recipient, may not develop DN during the posttransplant period at least in short term, or develop into a mild/early form of DN, that by itself may not significantly impact graft outcome. Pertinent to this issue is how pancreas or islet transplantation affects the transplanted kidneys for DN. Several studies have suggested that pancreas/islet transplantation did confer protective effects, including attainable glycemic control, attenuated diabetic vascular complications, and better renal transplant survival.[29-33]

In summary, DN is noted in a small percentage of diabetic donor kidneys. When this occurs, the DN is often mild and in early stages. After transplantation, DN in diabetic donor kidneys may stabilize or progress with a mild increase in severity and at a slow pace. In cases DN is not present in diabetic donor kidneys, DN often does not develop in posttransplant, even in diabetic recipients. This study suggests that diabetic donor kidneys with or without DN may not by itself impart significant adverse effect of graft survival, an observation that requires confirmatory evaluation of a larger number of cases with longer follow-up.

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