Having One Kidney Does Not Accelerate the Rate of Development of Diabetic Nephropathy Lesions in Type 1 Diabetic Patients

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OBJECTIVE—Reduced nephron number is hypothesized to be a risk factor for chronic kidney disease and hypertension. Whether reduced nephron number accelerates the early stages of diabetic nephropathy is unknown. This study investigated whether the rate of development of diabetic nephropathy lesions was different in type 1 diabetic patients with a single (transplanted) kidney compared with patients with two (native) kidneys.

RESEARCH DESIGN AND METHODS—Three groups of volunteers were studied: 28 type 1 diabetic kidney transplant recipients with 8–20 years of good graft function, 39 two-kidney patients with duration of type 1 diabetes matched to the time since transplant in the one-kidney group, and 30 age-matched normal control subjects. Electron microscopic morphometry was used to estimate glomerular structural parameters on 3.0 ± 1.4 glomeruli per biopsy.

RESULTS—In the one- versus two-kidney diabetic subject groups, respectively, serum creatinine (means ± SD 1.3 ± 0.4 vs. 0.9 ± 0.2 mg/dl; $P < 0.001$), systolic blood pressure (133 ± 13 vs. 122 ± 11 mmHg; $P < 0.001$), and albumin excretion rate (median [range] 32.1 μg/min [2–622] vs. 6.8 μg/min [2–1,495] ; $P = 0.006$) were higher. There were no differences in the one- versus two-kidney diabetic subject groups, respectively, in glomerular basement membrane width (median [range] 511 nm [308–745] vs. 473 nm [331–814]), mesangial fractional volume (mean ± SD 0.30 ± 0.06 vs. 0.27 ± 0.07), mesangial matrix fractional volume (0.16 ± 0.05 vs. 0.16 ± 0.06), and mesangial matrix fractional volume per total mesangium (0.61 ± 0.07 vs. 0.64 ± 0.09). However, these glomerular structural parameters were statistically significantly higher in both diabetic subject groups compared with normal control subjects. Results were similar when patients receiving ACE inhibitors were excluded from the analyses.

CONCLUSIONS—Reduced nephron number is not associated with accelerated development of diabetic glomerulopathy lesions in type 1 diabetic patients. ***Diabetes*** **57:1707–1711, 2008**

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AER albumin excretion rate; GBM, glomerular basement membrane; Vv(MC/glom), mesangial cell fractional volume; Vv(Mes/glom), mesangial fractional volume; Vv(MM/glom), mesangial matrix fractional volume; Vv(MM/mes), mesangial matrix fractional volume per total mesangium.

Reduced nephron number has been proposed as a risk factor for and is implicated in association with diabetic nephropathy in humans (1), but direct studies so far have been unavailable or limited in numbers of diabetic subjects (2). This study investigates whether nephron number, decreased by approximately one-half, accelerates the early lesions of diabetic nephropathy by comparing the rate of development of glomerular lesions in kidneys exposed to the diabetic state for 8–20 years in patients with one transplanted kidney versus those with two native kidneys.

RESEARCH DESIGN AND METHODS

Transplant (one-kidney) group. Twenty-five type 1 diabetic patients received living related kidneys (eight HLA identical), and three received cadaveric transplants. All patients at least 8 years' posttransplantation with serum creatinine ≤2.5 mg/dl volunteering for studies of allograft diabetic nephropathy recurrence were included. These patients received transplants between 1969 and 1987 at the University of Minnesota. None received a pancreas transplant. All together, 8 patients were on cyclosporine, azathioprine, and prednisone; 3 were on cyclosporine and prednisone; 13 were on azathioprine and prednisone; 1 was on cyclosporine and azathioprine; 1 was on azathioprine; 1 was on cyclosporine; and 1 was on mycophenolate mofetil and prednisone. Six were receiving ACE inhibitors. All studies were approved by the Committee for the Use of Human Subjects in Research at the University of Minnesota.

Two-kidney group. Thirty-nine type 1 diabetic patient volunteers constituted the two-kidney group. All had at least 8 years duration of type 1 diabetes and serum creatinine ≤2.0 mg/dl and/or glomerular filtration rate ≥45 ml/min per 1.73 m^2; 2 received ACE inhibitors.

Patients in the two-kidney group were matched for duration, defined as time from onset of type 1 diabetes to renal biopsy in the two-kidney group and time from transplant to renal biopsy in the one-kidney group. The groups were also matched for sex of the donor. The control subjects were 30 living kidney donors matched for age (mean ± SD 33.3 ± 7.7 years) and sex (15 female) with the two-kidney group.

Clinical studies. While admitted to the general clinical research center, trained nurses measured blood pressure multiple times by oscillometric monitoring. Hypertension was defined as mean blood pressure levels ≥140/90 mmHg or the use of antihypertensive medications. A1C was measured by high-performance liquid chromatography, serum creatinine by an automated Jaffé reaction method, and urinary albumin excretion rate (AER) by immunoassay in at least one, but usually two, 24-h sterile urine collections.

Renal biopsy morphometric studies. Renal tissues were obtained by percutaneous biopsy in the diabetic subject groups and by intra-operative kidney biopsies performed before kidney removal in control subjects. Tissues were processed for electron microscopy as described (3). Sections 1-μm thick were used to select the centermost, nonsclerotic glomerulus in each block. All tissues were masked before study. Per biopsy, 3.0 ± 1.4 glomeruli (range 1–7) were photographed at a final magnification of 3,900× to produce photomontages of the entire glomerular profile. Montages were blindly screened for changes suggestive of transplant glomerulopathy (4–7) and such cases were excluded.

The photomontages were used to estimate mesangial fractional volume [Vv(Mes/glom)] by point counting (3,8). Random systematic images at 12,000×, representing ~15–20% of the glomerular cross section, were used to estimate the mesangial matrix fractional volume [Vv(MM/glom)] and mesan-

TABLE 1
Subject characteristics

	One-kidney group	Two-kidney group	Control group	*P*
n	28	39	30	
Kidney sex (*n*)				
Female	13	22	15	NA
Male	15	17	15	
Patient age (years)	49 ± 8	32 ± 9	33 ± 8	<0.001
Kidney age (years)	38 ± 13	32 ± 9	33 ± 8	0.048
Diabetes duration (years)*	13 ± 4	14 ± 3		NA
Systolic blood pressure (mmHg)	133 ± 13†	122 ± 11		<0.001
Diastolic blood pressure (mmHg)	73 ± 8†	74 ± 8		NS
Hypertension (*n*)	22	7		<0.001
On ACE inhibitor (*n*)	6	2		
A1C (%)‡	8.4 ± 1.1	9.0 ± 1.8		NS
Serum creatinine (mg/dl)	1.3 ± 0.4	0.9 ± 0.2§		<0.001
Urinary albumin excretion (μg/min)‖	32.1 (2–622)	6.8 (2–1,495)		0.006
Renal transplantation (*n*)				
Living	25			
Cadaver	3			
On cyclosporine (*n*)	13			

Results of continuous variables are means ± SD or median (range). *Diabetes duration in the one-kidney group is defined as the duration from kidney transplant to kidney biopsy; in the two-kidney group it is defined as the duration from type 1 diabetes onset to kidney biopsy. †Blood pressure measurements were available in 25 patients. ‡A1C was available in 26 patients from the one-kidney group and in 36 patients from the two-kidney group. §Serum creatinine was available in 37 patients. ‖Urinary albumin excretion was available in 24 patients from the one-kidney group and was logarithmic transformed prior to statistical analysis. NA, not applicable; NS, not significant.

gial cell fractional volume [Vv(MC/glom)] (3). Mesangial matrix fractional volume per total mesangium [Vv(MM/mes)] is the ratio of mesangial matrix to total mesangium (mesangial matrix and mesangial cell), or Vv(MM/glom)/[Vv(MM/glom) + Vv(MC/glom)] (9). These 12,000× images were also used to measure glomerular basement membrane (GBM) width using the orthogonal intercept method (10).

Statistics. SPSS (version 12.0; SPSS, Chicago, IL) for Windows was used. Data are presented as means ± SD, except for non-normally distributed AER and GBM width, which were expressed as median (range) and logarithmically transformed before analysis. Clinical parameters were compared using unpaired independent *t* tests. ANOVA, followed by least significant difference post hoc test, was used to compare the structural parameters among the groups. χ^2 test was used to analyze categorical variables. Clinical and structural parameters were also analyzed after excluding patients on ACE inhibitors.

RESULTS

Clinical characteristics. Sex and duration of renal exposure to type 1 diabetes were, by design, similar in the two diabetic subject groups, whereas kidney and patient age were greater in the one-kidney subjects (Table 1). Systolic blood pressure, serum creatinine, and AER were higher in the one-kidney group. A1C was comparable (Table 1). All but one of the group comparisons were similar when patients on ACE inhibitors were excluded; kidney age was no longer statistically different.

Morphometric findings. GBM width, Vv(Mes/glom), Vv(MM/glom), and Vv(MM/mes) were not different in the one- versus two-kidney group (Table 2 and Fig. 1*A–D*). These parameters were greater in the diabetic versus the normal control groups. Vv(MC/glom) was slightly higher in the one- versus two-kidney and the control groups (Table 2 and Fig. 1*E*). Similar results were obtained when patients on ACE inhibitors were excluded; however, Vv(MC/glom) was no longer significantly different from control subjects (Fig. 1*E*).

DISCUSSION

This study used unbiased quantitative morphometric techniques to evaluate whether nephron number affects the rate of development of early diabetic nephropathy lesions in type 1 diabetes. Because transplant patients have one kidney versus two in nontransplant patients, this creates two groups in which nephron number, on average, is twice as high in the two-kidney group.

Diabetic nephropathy lesions reoccur in the renal allograft (11–17). The incidence of clinically significant diabetic nephropathy lesions in transplant kidney biopsy samples ranges from 0.4 to 1.8% (13–17). Early pathologic

TABLE 2
Glomerular structural parameters

	One-kidney group	Two-kidney group	Control group	ANOVA *P*
n	28	39	30	
GBM width (nm)	511 (308–745)*	473 (331–814)	314 (250–479)†	<0.001‡
Vv(Mes/glom)	0.30 ± 0.06§	0.27 ± 0.07	0.20 ± 0.04†	<0.001
Vv(MM/glom)	0.16 ± 0.05*	0.16 ± 0.06	0.09 ± 0.02†	<0.001
Vv(MC/glom)	0.10 ± 0.02‖	0.09 ± 0.02	0.09 ± 0.02¶	0.015
Vv(MM/Mes)	0.61 ± 0.07*	0.64 ± 0.09	0.51 ± 0.06†	<0.001

Results of continuous variables are means ± SD or median (range). *P = NS comparing one-kidney vs. two-kidney groups. †$P < 0.0001$ comparing one-kidney group vs. control group and two-kidney group vs. control group. ‡Nonparametric variables log transformed prior to statistical analysis. §P = NS (0.082) comparing one-kidney vs. two-kidney groups. ‖$P = 0.005$ comparing one-kidney vs. two-kidney groups. ¶$P = 0.03$ comparing one-kidney group vs. controls, P = NS comparing two-kidney group vs. controls.

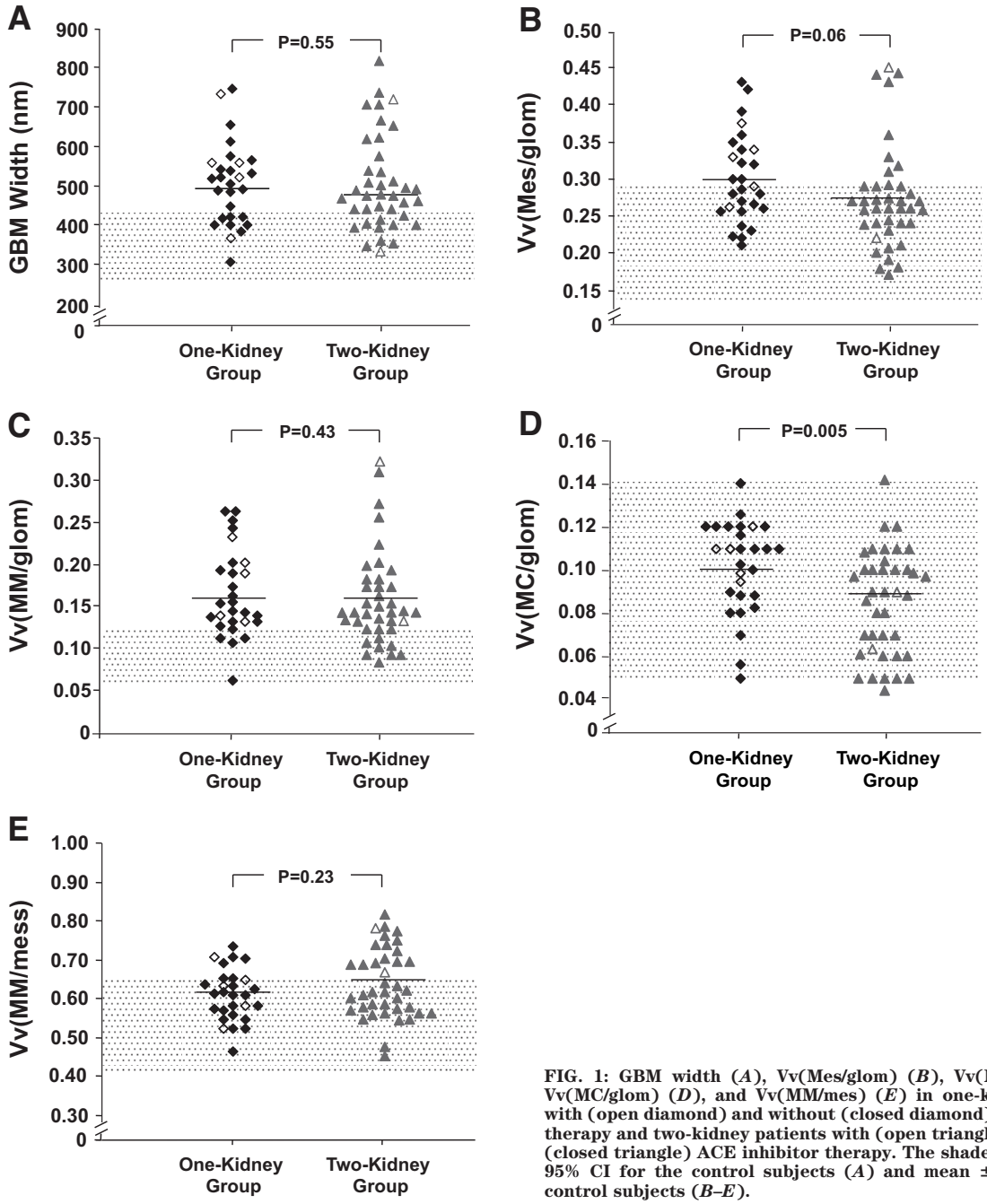

FIG. 1: GBM width (*A*), Vv(Mes/glom) (*B*), Vv(MM/glom) (*C*), Vv(MC/glom) (*D*), and Vv(MM/mes) (*E*) in one-kidney patients with (open diamond) and without (closed diamond) ACE inhibitor therapy and two-kidney patients with (open triangle) and without (closed triangle) ACE inhibitor therapy. The shaded area is 5 and 95% CI for the control subjects (*A*) and mean ± 2 SD for the control subjects (*B–E*).

lesions in allograft diabetic nephropathy follow a course similar to native diabetic nephropathy in type 1 diabetic patients. Although glomerular volume increases at 6 months were greater in type 1 diabetic versus nondiabetic renal transplant recipients, this early glomerular enlargement did not predict the later development of diabetic glomerulopathy lesions (18). Increases in GBM width and Vv(Mes/glom) are discernable within 2–10 years after kidney transplant (12,17,19,20). Their rate of development, however, is highly variable, ranging from very slow to allograft failure as early as 8 years posttransplantation (20). However, the major causes of allograft loss in type 1 diabetic renal transplant recipients are chronic allograft nephropathy, death, or acute rejection. Recurrent and de novo allograft diabetic nephropathy are rarely documented as a cause of end-stage renal disease in the first two decades after renal transplantation. This variability is only partially explained by glycemia (17) and may represent variable responses of the transplant kidney to type 1 diabetes. Our previous study did not suggest that diabetic nephropathy lesions develop faster in type 1 diabetic patients with allografts than in patients with two native kidneys (11); however, the imprecision of the light microscopy methods used did not allow firm conclusion.

Most studies of nephron number and diabetic nephropathy risk were based on estimates of nephron number endowment from both weight and length data (1,21–23). A single study using unbiased stereological glomerular counting found no difference in glomerular number between 64 patients with overt diabetic nephropathy and normal control subjects (24). As expected, the one-kidney patients were older than the two-kidney patients. Serum creatinine was higher in the one-kidney group, which was not surprising considering that these were single-kidney

patients and that 46% of the one-kidney patients were receiving cyclosporine. The one-kidney patients had higher systolic blood pressure and a greater incidence of hypertension. This could be related to prednisone, cyclosporine therapy, or the presence of diseased native kidneys. The greater AER in the one-kidney group may not reflect diabetic nephropathy in the renal allograft alone because albuminuria may have also emanated from the diseased native kidneys, and not all kidney transplant recipients had native nephrectomy. These explanations are highly likely, as numerous studies in type 1 diabetes have clearly shown that hypertension and increased AER follow the development of advanced glomerulopathy lesions and are rare in their absence (25–28).

GBM width and Vv(Mes/glom) were higher in both diabetic subject groups than in the control group, consistent with previous reports of recurrence of diabetic glomerular lesions in the renal allograft (29). The Vv(MM/glom) and the Vv(MM/mes) were also increased in the diabetic patients versus control subjects but were not different between the two diabetic subject groups. Mesangial matrix accumulation is a major component of diabetic glomerulopathy (30). These changes are, in fact, characteristic of diabetes and different from those seen in other diseases where mesangial expansion is mainly due to increases in the mesangial cellular compartment, such as type 1 membranoproliferative glomerulonephritis (9) and transplant glomerulopathy (5). Glomeruli were carefully screened to avoid the inclusion of patients with transplant glomerulopathy in this study. However, if mesangial matrix increase in the one-kidney patients was in part attributable to chronic allograft nephropathy, this would be further evidence against acceleration of diabetic nephropathy lesions in these patients.

The slight increase in mesangial cell fractional volume [Vv(MC/glom)] in the one- versus two-kidney patients and the control subjects could be the consequence of subtle allograft changes related to transplantation. However, similar and also unexplained group differences in Vv(MC/glom) were seen between different centers in a type 1 diabetic nephropathy natural history study (8) and is likely of little biological significance.

An important assumption is that a patient with a kidney transplanted into a diabetic environment has the same risk of diabetic nephropathy as the general type 1 diabetic population. This assumption could be wrong on at least three accounts. First, the risk of diabetic nephropathy may not be restricted to tissue responses to diabetes but may be related to systemic factors which could be more prominent among the transplant patients, who all demonstrated susceptibility to severe diabetic nephropathy. Second, the majority of transplant patients received living related donor kidneys. It is possible that diabetic nephropathy susceptibility genes are more common in these related donors. Third, the one-kidney patients had higher blood pressure. These factors might be expected to accelerate lesions in the one-kidney group, and this was not found.

The transplant patients received immunosuppressive medications that could blunt inflammation, which has been hypothesized as contributing to diabetic nephropathy. The link between inflammation and diabetic nephropathy risk is primarily with the later stages of diabetic nephropathy; although this study focused on the development of the early lesions, the study design does not allow complete exclusion of this possibility. Notably, however, 5 years of immunosuppressive therapy in pancreas transplant recipients cured of diabetes was not associated with improvement in the diabetic nephropathy lesions in their native kidneys (31).

The one-kidney patients had excellent overall graft function considering the mean posttransplant time of 13 years. Thus, it did not appear that the recurrence of diabetic nephropathy lesions in these patients was associated with progressive graft dysfunction and accelerated graft loss 8–20 years posttransplant. This could be due to selection bias, as one-kidney patients with serum creatinine >2.5 mg/dl were excluded from these studies. However, two-kidney patients with serum creatinine >2.0 mg/dl were also excluded, and these criteria were used because, at these late stages, diabetic nephropathy is characterized by advanced glomerular sclerosis. Moreover, as noted above, diabetic nephropathy per se is an uncommon cause of graft failure in the first 2 decades following renal transplantation (13); therefore, it is unlikely that selection bias played an important role in these studies. Although hypertension and ACE inhibitor treatment were more prevalent in the one-kidney patients, the study results were similar when subjects on ACE inhibitors were excluded from the analyses.

This study found that early diabetic nephropathy lesions occurring in the renal transplant are not different from those in the native kidneys of patients with type 1 diabetes. These results show that reduced nephron number is not a major risk factor for development of early diabetic glomerular lesions. However, it is quite possible that reduced nephron number could be associated with accelerated progression from established diabetic nephropathy to terminal uremia.

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