Segmental Glomerulosclerosis in Pima Indians with Type 2 Diabetes

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ABSTRACT

Type 2 diabetes mellitus is widespread in the United States, and diabetic kidney disease is one of its most common complications. There is increasing evidence that podocyte injury is the initial pathologic change in diabetic nephropathy, and podocytopathy often manifests on renal biopsy as segmental sclerosis in other kidney diseases. The purpose of this study was to determine if segmental sclerosis is widespread in diabetic kidney disease. This study examined 1142 glomeruli from 61 Pima Indians who had diabetes for at least ten years. 24 patients were normoalbuminuric, 20 were microalbuminuric, and 17 were macroalbuminuric. The presence of segmental sclerosis was noted, as was global sclerosis. Segmental sclerosis was present in less than 2% of glomeruli. All glomeruli showed evidence of diabetic nephropathy including mesangial hypercellularity and invasion of mesangium into capillary loops. These data suggest that segmental sclerosis is not present in significant amounts in diabetic kidney disease. Rather, pathologic changes in the glomeruli of diabetic patients occur in a more diffuse pattern.

INTRODUCTION

Type 2 diabetes mellitus is increasingly common in the United States. In 2011, the National Institutes of Health estimated that 8.3 percent of the U.S. population had diabetes. One of the most common and serious complications of diabetes is diabetic nephropathy. Some populations are at very high risk of developing overt diabetic nephropathy. Pima Indians are one such high-risk population, with a rate of end-stage kidney disease 23 times that of the general population. Up to half of these patients develop overt nephropathy within 20 years of the onset of diabetes.

Diabetic nephropathy is increasingly recognized as a disease of the glomerular podocyte, with loss of glomerular podocytes on kidney biopsies and an increase in urinary podocyte excretion. Podocyte injury is also recognized to be the primary problem in focal segmental glomerulosclerosis (FSGS), a cause of non-diabetic kidney disease. Since both diseases affect the same cell, it may be possible to see segmental sclerosis in early diabetic nephropathy.. If segmental glomerulosclerosis occurs in diabetic kidneys, this would provide more evidence that podocytopathy is a primary problem in diabetic kidney disease.

METHODS

Kidney biopsies were obtained in Pima Indians who had consented to participate in a clinical trial (ClinicalTrials.gov number, NCT00340678). This study was approved by the review board of the National Institute of Diabetes and Digestive Kidney Diseases. Volunteers had diabetes for at least ten years. The pattern of glomerulo-sclerosis was assessed using light microscopy to identify segmental sclerosis. Sclerotic segments were identified based on the collapse of basement membrane and increase in mesangial matrix. The sclerosis had to be significantly more severe in one portion of the glomerulus in order to be classified as segmental sclerosis. Each glomerulus was classified as either exhibiting segmental sclerosis or not. Global sclerosis, defined as no open capillaries within the glomerulus, was also noted. The percentage of segmentally sclerosed glomeruli per subject was calculated, as was the percentage of globally sclerosed glomeruli per subject.

Clinical information was also obtained, including height, weight, serum creatinine, fasting plasma glucose, hemoglobin A1C, urinary albumin, glomerular filtration rate, and renal plasma flow.

The patients were split into three groups for statistical analysis: normoalbuminuria, which was defined as albumin-to-creatinine ratio (ACR) less than 30 mg/g; microalbuminuria, which was defined as ACR between 30 mg/g and 300 mg/g; and macroalbuminuria, which was defined as ACR 300 mg/g or greater.

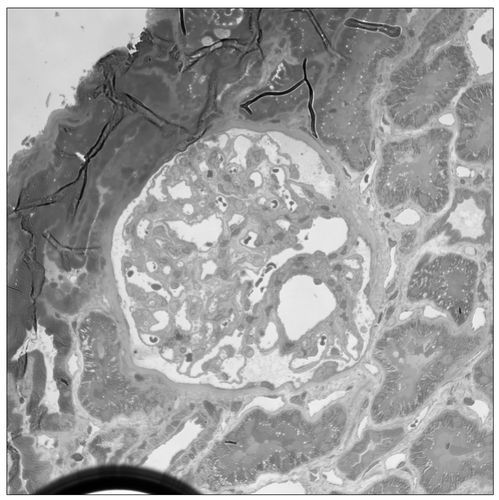

Figure 1: A glomerulus from a normoalbuminuric subject with diabetes duration of 11 years. Note diffuse mesangial hypercellularity and mesangial invasion into capillary loops.

RESULTS

A total of 61 subjects were available for analysis, with a total of 1142 glomeruli and an average glomeruli-per-subject of 18.7 (range, 5-58). All glomeruli showed evidence of increased mesangial expansion consistent with diabetic nephropathy, even in the normoalbuminuric group (Figure 1). The results of exact Wilcoxon and Fisher's tests are shown in Table 1 and Spearman correlations are shown in Table 2.

Segmental sclerosis was present in at least 1 glomerulus in 12 of the 61 subjects (Fgure 2; compare with Figure 1), but in less than 2% of the total glomeruli examined. As expressed as a percentage of the glomeruli per subject, segmental sclerosis did not correlate with any other morphometric or physiologic variable.

Table 1: Subject characteristics

	Normo- (n=24)	Micro- (n=20)	Macro- (n=17)	*P* value		
Fraction female	18/24	14/20	9/17	[a]0.7456	[b]0.3277	[c]0.1877
Age (years)	48.4±11.6	47.0±8.7	47.1±7.6	[a]0.3588	[b]0.3646	[c]0.2957
Duration (years)	13.9±4.1	16.9±6.9	20.2±6.2	[a]0.0647	[b]0.0324	[c]<.0001
BMI (kg/m^2)	37.7±8.9	34.2±7.3	34.9±7.4	[a]0.0964	[b]0.3874	[c]0.1264
HbA1c (%)	8.1±2.0	9.2±2.2	9.6±2.0	[a]	[b]0.2321	[c]0.0075
FPG (mg/dL)	170.8±65.1	213.1±93.3	211.6±100.4	[a]0.0895	[b]0.4077	[c]
ACR (mg/g)	11.4 (4.8-25.8)	60.5 (34.0-194.3)	1031.7 (357.6-8869.6)	§	§	§
GFR (ml/min)	132.0±55.2	163.9±48.2	104.7±43.8	[a]0.0064	[b]<.0001	[c]0.0272
RPF (ml/min)	536.2±198.0	695.8±210.2	556.3±161.8	[a]0.0028	[b]0.0165	[c]0.3522
FF	0.25±0.03	0.24±0.04	0.19±0.12	[a]0.2758	[b]<.0001	[c]<.0001
%GS	9.1±11.1	12.0±11.6	29.6±33.1	[a]0.1405	[b]0.0815	[c]0.0153
%SS	0.92±2.2	1.8±4.1	2.0±5.0	[a]0.2136	[b]0.4373	[c]0.3135
MPGV (m^3)	5473696.2±1449615.7	6235675± 2008038.8	6907679.1± 3748522.9	[a]0.0776	[b]0.2033	[c]0.0369
MGGV (m^3)	1422671.4±1905551.01	2510112.4± 3665191.4	2693301.1± 2660071.0	[a]0.0526	[b]0.1998	[c]0.0338
FIA (%)	0.26±0.06	0.27±0.06	0.40±0.12	[a]0.3069	[b]<.0001	[c]<.0001

Table 1. Patient characteristics at biopsy from 61 Pima Indians with type 2 diabetes mellitus. P values are shown for [a]normo vs. micro-, [b]micro- vs. macro-, and [c]normo- vs. macroalbuminuric groups. P values less than 0.05 are shown in bold. Data are means ± SD, median (range), or percent. §ACR values by group are different by definition.

Table 2: Spearman correlations

	GFR	ACR	% GS	% SS	FIA	MPGV	MGGV	BMI	Age (years)	Dur	RPF	FF	HbA1C (%)	FPG
GFR	1.0	-0.12285 (0.3456)	-0.32461 (0.0107)	0.08088 (0.5355)	-0.30465 (0.0190)	0.26171 (0.0416)	0.29722 (0.0200)	0.05992 (0.6465)	-0.39323 (0.0017)	-0.33818 (0.0077)	0.83273 (<.0001)	0.44490 (0.0003)	0.26056 (0.0425)	0.34880 (0.0059)
ACR		1.0	0.30443 (0.0171)	-0.04568 (0.7267)	0.43805 (0.0005)	0.25436 (0.0479)	0.29722 (0.0200)	-0.15442 (0.2347)	-0.15362 (0.2372)	0.37234 (0.0031)	0.14532 (0.2638)	-0.44553 (0.0003)	0.33896 (0.0075)	0.22605 (0.0798)
% GS			1.0	-0.09954 (0.4453)	0.31335 (0.0157)	-0.08650 (0.5074)	0.63647 (<.0001)	0.10359 (0.4269)	0.33438 (0.0084)	0.40736 (0.0011)	-0.25469 (0.0476)	-0.20805 (0.1076)	-0.24518 (0.0568)	-0.25212 (0.0500)
% SS				1.0	-0.08170 (0.5384)	0.03337 (0.7985)	0.13905 (0.2852)	-0.05741 (0.6603)	0.01570 (0.9044)	-0.14545 (0.2634)	0.12214 (0.3484)	-0.09261 (0.4778)	0.10547 (0.4185)	-0.11716 (0.3685)
FIA					1.0	-0.03060 (0.8181)	0.29552 (0.0231)	-0.18180 (0.1682)	0.24977 (0.0564)	0.41377 (0.0011)	-0.07057 (0.5953)	-0.49077 (<.0001)	0.16381 (0.2151)	0.00102 (0.9939)
MPGV						1.0	-0.00252 (0.9846)	0.04469 (0.7324)	-0.20830 (0.1072)	0.00502 (0.9693)	0.30465 (0.0170)	-0.05685 (0.6634)	0.09535 (0.4648)	0.09335 (0.4743)
MGGV							1.0	-0.03046 (0.8158)	0.14834 (0.2539)	0.29270 (0.0221)	-0.12994 (0.3182)	-0.10238 (0.4324)	-0.03399 (0.7948)	-0.04698 (0.7192)
BMI								1.0	0.15394 (0.2362)	-0.05939 (0.6494)	0.02332 (0.8584)	-0.09519 (0.4656)	-0.35666 (0.0048)	-0.25527 (0.0471)
Age (years)									1.0	0.38318 (0.0023)	-0.43099 (0.0005)	-0.05738 (0.6605)	-0.40268 (0.0013)	-0.45445 (0.0002)
Dur										1.0	-0.19466 (0.1328)	-0.31148 (0.0145)	0.00918 (0.9440)	-0.04816 (0.7125)
RPF											1.0	-0.05309 (0.6845)	0.25258 (0.0495)	0.29941 (0.0191)
FF												1.0	0.09046 (0.4881)	0.15750 (0.2254)
HbA1C (%)													1.0	0.80227 (<.0001)
FPG														1.0

Table 2. Spearman correlations (p-values) between physiologic and morphometric variables in 61 Pima Indians with type 2 diabetes mellitus. P values less than 0.05 are shown in bold.

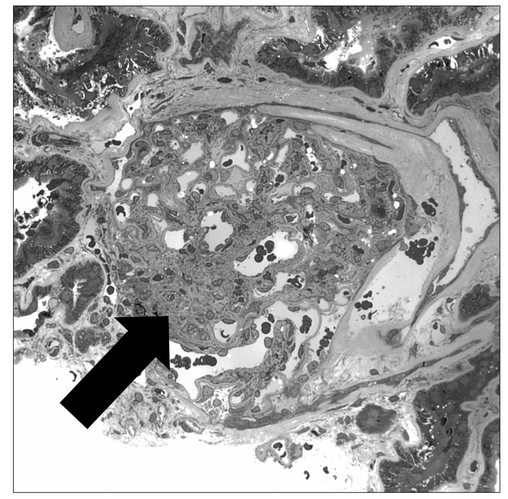

Figure 2: A glomerulus showing segmental sclerosis. Arrow shows segmental increase in mesangial matrix and collapse of capillary loops..

DISCUSSION

The aim of this study was to evaluate whether segmental sclerosis is widely present in diabetic nephropathy. Less than 2% of glomeruli studied showed evidence of segmental sclerosis. Notably, all the glomeruli showed evidence of diabetic nephropathy, as manifested by mesangial expansion, even in the normoalbuminuric subjects.

Duration of diabetes was significantly longer in the macroalbuminuria versus the normoalbuminuria group, but the average age across the three groups was not significantly different. These data support previous findings that long duration of diabetes is a significant predictor of kidney disease.

Global sclerosis correlated negatively with glomerular filtration rate and renal plasma flow and positively with albumin-to-creatinine ratio, fractional interstitial area, age, and duration of diabetes. These data suggest that global sclerosis is a marker of kidney disease progression. Previous studies have indicated that globally sclerosed glomeruli are eventually reabsorbed and disappear, so it is possible that global sclerosis was underestimated using this method.

CONCLUSION

Pathologic changes in glomeruli of diabetic patients occur before microalbuminuria develops. Changes visible on light microscopy include mesangial hypercellularity and invasion of mesangium into capillary loops. Segmental sclerosis is present only in a very small portion of diabetic glomeruli (<2%), and it is not possible to predict which patients will develop segmental sclerosis based on clinical characteristics.