Renal Outcome in Type 2 Diabetic Patients With or Without Coexisting Nondiabetic Nephropathies

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OBJECTIVE — To determine the risk factors for adverse renal outcome in type 2 diabetic patients who underwent renal biopsy and were followed-up longitudinally.

RESEARCH DESIGN AND METHODS — We examined 68 consecutive patients with type 2 diabetes during the period of 1985–1999 who underwent renal biopsy for proteinuria ≥1 g/day, renal involvement (proteinuria or renal impairment) at the absence of retinopathy, renal involvement with duration of diabetes <5 years, or unexplained hematuria of glomerular origin. Their clinical features and underlying renal lesion were correlated with the renal outcome after longitudinal follow-up. Three groups of patients were defined based on their renal pathology: group I consisted of 24 patients (35%) with diabetic glomerulosclerosis (DGS) alone, group II consisted of 13 patients (19%) with nondiabetic nephropathy (NDN) superimposed on DGS, and group III consisted of 31 patients (46%) with NDN alone without evidence of DGS.

RESULTS — After a mean follow-up of 123 months from the diagnosis of type 2 diabetes (74 months from the time of renal biopsy), univariate analysis showed that risk factors for reaching end-stage renal disease (requiring maintenance dialysis, or a serum creatinine [SCr] ≥700 μmol/l) included proteinuria ≥2 g/day ($P = 0.0087$), SCr >120 μmol/l ($P = 0.0005$), presence of retinopathy ($P < 0.00001$) at the time of biopsy, and biopsy showing DGS (groups I and II) ($P = 0.035$). On multivariate analysis, retinopathy was the only independent variable correlated with end-stage renal failure. This study also showed that the association of hematuria or proteinuria with the absence of retinopathy constitutes the strongest indication for a nondiabetic lesion (positive predictive values of 94%).

CONCLUSIONS — Patients with type 2 diabetes undergoing renal biopsy constitute a heterogeneous group by their clinical presentations and underlying pathology, but longitudinal studies on the renal outcome of these patients remain limited. Our study showed that renal biopsy is indicated in selective diabetic patients because of potentially treatable nephropathy and of a better prognosis than DGS.

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The prevalence of type 2 diabetes is rising rapidly among Asian populations, in part due to the westernization of diet and urbanization of lifestyle. It is estimated that by the year 2025, the prevalence of diabetes will reach 50 million in China alone (1). The high prevalence of renal involvement, despite correction for environmental factors among Asian type 2 diabetic patients, has recently been recognized, with up to 50% showing albuminuria as compared with 15% in Western populations (2–4). Data also suggested that Asian diabetic patients lose functional renal reserve earlier in the course of nephropathy than whites due to defective nitric oxide production (5). In our locality, diabetic nephropathy leading to maintenance dialysis has increased from 17% 10 years ago to 30% recently (6). The importance of recognizing factors predictive of renal outcome among this group of patients cannot be overemphasized.

Proteinuria is a strong predictive factor for renal failure and cardiovascular mortality in diabetic patients (7,8). However, renal biopsies from type 2 diabetic patients with proteinuria show that they comprise a heterogeneous group, as they are prone to other renal diseases such as hypertensive glomerulosclerosis, nondiabetic glomerulonephritis, e.g., IgA nephropathy, and other nephropathies (8–11). It has been estimated that up to one-third of diabetic patients who present with proteinuria are suffering from nondiabetic renal diseases (8–11). Nevertheless, studies on the effect of underlying pathology, other than diabetic glomerulosclerosis (DGS), on renal outcome are scattered and limited, and no longitudinal data are available for Asian patients, whose disease pattern might be different from the West (7–11). To determine the risk factors for adverse renal outcome, this study focused on the clinical features and underlying pathology of a group of type 2 diabetic patients who underwent renal biopsy and were followed-up longitudinally.

RESEARCH DESIGN AND METHODS

— Type 2 diabetic patients, as defined by the World Health Organization (12), with absence of ketosis-prone state (absence of significant ketonuria and insulin treatment started at least 1 year after diagnosis) were recruited in this study. Those patients with renal biopsy performed in our institution between 1984 and 1999 were reviewed. A total of 74 patients were identified, and 6

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Abbreviations: DGS, diabetic glomerulosclerosis; ESRF, end-stage renal failure; FGS, primary focal sclerosis; MCN, minimal change nephropathy; NDN, nondiabetic nephropathy; SCr, serum creatinine; TGF, transforming growth factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1 —*Distribution of different types of nondiabetic nephropathy*

Type of nondiabetic renal lesions	Coexisting with DGS (group II)	Not coexisting with DGS (group III)	Total
HTN	2	7	9
MCN	2	2	4
MGN	3	5	8
IgAN	3	10	13
FGS	0	2	2
MCGN	2	2	4
TMD	0	2	2
TIN	1	1	2
Total	13	31	44

HTN, hypertensive nephrosclerosis; IgAN, primary IgA nephropathy; MCGN, mesangiocapillary glomerulonephritis; MGN, membranous glomerulonephritis; TIN, tubulointerstitial nephritis; TMD, thin membrane disease.

were excluded because of advanced renal failure (serum creatinine [SCr] ≥530 μmol/l) at the time of renal biopsy, which showed end-stage nephrosclerosis. All of the remaining 68 patients were followed-up for a mean of 74 ± 41 months after the renal biopsy (123 ± 76 months after the diagnosis of diabetes) and had adequate pathological materials for the assessment of underlying renal pathology. The mean duration of diabetes before renal biopsy was 77.2 ± 63.9 months. Renal biopsy was performed for the following reasons: *1*) proteinuria ≥1 g/day; *2*) renal involvement (proteinuria or renal impairment) at the absence of retinopathy; *3*) renal involvement with duration of diabetes <5 years; or *4*) unexplained hematuria of glomerular origin. The biopsies were interpreted blindly by our renal pathologist. Morphological criteria of diabetic glomerular lesions included glomerular hyaline arteriolosclerosis; global mesangial sclerosis with or without Kimmelstiel-Wilson nodule or nodular mesangial sclerosis; exudative lesions such as "fibrin cap," "capsular drop," or "hyaline thrombus"; microaneurysm; uniform glomerular capillary basement membrane thickening (highlighted as linear accentuation under immunofluorescence study); or ultrastructural thickness ≥350 nm (11). The diagnosis of DGS was made when at least three of the above features were present. Based on the renal biopsy, patients were divided into three groups: group I (DGS alone), group II (DGS coexisting with nondiabetic nephropathy [NDN]), and group III (NDN without DGS, i.e., without any of the above features). Minimal change nephropathy (MCN) was diagnosed by the presence of podocyte fusion in electron microscopy and clinical response to prednisolone.

The clinical data and biochemical parameters at the time of renal biopsy and subsequent follow-up were studied. Fundoscopy examination was performed by an ophthalmologist or a physician, and diabetic retinopathy was defined as presence of proliferative or background changes. About 60–70% of patients were assessed by an ophthalmologist and the rest by physician alone. HbA_{1c} (reference range 5.1–6.4%) was measured by an automated ion-exchange chromatographic method (Bio-Rad, Hercules, CA). Hypertension was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg or taking antihypertensive drugs. Disease progression (rate of deterioration of renal function) was calculated by the regression coefficient of the yearly reciprocal SCr (1/SCr). The study end point was end-stage renal disease, which was defined as advanced renal failure requiring maintenance dialysis, or SCr ≥700 μmol/l. The patients were censored for the study of end points on 30 October 2000. Event rates were defined as the prevalence of end-stage renal disease at the censored date. Patients who did not reach 30 October 2000 were administratively censored and designated as the "preserved renal function group"

Statistical analysis

Statistical analysis was performed using SPSS version 10.0 for Windows (SPSS, Chicago). A χ^2 test or Fisher's exact test was used as appropriate to assess the association between or among the parameters. For parametric data, Student's *t* test and ANOVA were used to compare two and multiple parameters, respectively. For nonparametric data, Mann-Whitney tests and Kruskal *H* tests were used to compare two and multiple parameters, respectively. Kaplan-Meier analysis and Cox's regression analysis were used for analysis of factors associated with renal survival. *P* values <0.05 were considered as statistically significant.

RESULTS — Among the 68 type 2 diabetic patients studied, 24 (35%) had DGS alone (group I), 13 (19%) had DGS coexisting with NDN (group II), and 31 (46%) had NDN alone without DGS (group III). Table 1 shows the different types of NDNs diagnosed. Among groups II and III, four patients received 8–24 weeks of prednisolone therapy (one primary focal sclerosis [FGS], one mesangiocapillary glomerulonephritis, one MGN, and one coexisting DGS and MCN). Only one patient with pure FGS showed near-complete response, with proteinuria decreasing from 10 to 1.3 g/day associated with preservation of renal function at the end of follow-up (SCr 136 μmol/l). The other three patients progressed to end-stage renal failure (ESRF) despite therapy, which is higher in prevalence when compared with those without immunosuppressive treatment (75 vs. 15% reached ESRF, $P = 0.02$).

Comparisons of baseline clinical feature of patients with different renal diagnosis

Table 2 depicts the clinical features of the three groups of patients with different renal lesions. There was no difference in sex distribution, age, amount of proteinuria at biopsy or follow-up, presence of hematuria at biopsy, prevalence of usage of ACE inhibitor, BMI, HbA_{1c}, and serum cholesterol level at biopsy among the three groups.

Patients with DGS (groups I and II) tended to have a higher degree of proteinuria than those without DGS (group III), but the difference did not reach statistical significance. Moreover, DGS patients (groups I and II) had a significantly longer history of diabetes before biopsy, higher SCr level at the time of biopsy, and higher prevalence of renal impairment (SCr of ≥120 μmol/l), insulin usage, hypertension, and retinopathy at the time of biopsy. However, mean blood pressure was higher in group II patients than in group I or III patients.

Table 2 —*Clinical features and biochemical characteristics of the patients with different renal pathologies*

Clinical features	Group I: DGS only	Group II: DGS with NDN	Group III: NDN only	*P*
n (%)	24 (35)	13 (19)	31 (46)	
M/F (*n*)	14/10	9/4	15/16	NS
Age (years)	49.0 ± 11.6	48.7 ± 16.5	48.4 ± 13.5	NS
Duration of diabetes prior to biopsy (months)	99.6 ± 69.7*	94.3 ± 78.7	52.6 ± 42.0	0.031
Proteinuria at biopsy (median g/day)	2.10	2.50	1.90	NS
Proteinuria ≥2 g at biopsy (%)	58.3	69.2	48.4	NS
Proteinuria at follow-up (median g/day)	2.60	2.30	2.00	NS
SCr at biopsy (μmol/l)	167 ± 105*	176 ± 79†	140 ± 44	0.004
SCr ≥120 μmol/l at biopsy (%)	54.2*	53.8†	19.4	0.014
Hypertension at biopsy (%)	87.5	92.3	64.5	0.048
Blood pressure at follow-up (mmHg)	101 ± 11‡	111 ± 13†	101 ± 10	0.037
On ACE inhibitor (%)	60.9	84.6	63.3	NS
BMI at biopsy (kg/m^2)	24.9 ± 3.9	25.4 ± 9.5	25.6 ± 6.1	NS
HbA_{1c} at follow-up (%)	7.47 ± 2.59	8.99 ± 1.94	7.47 ± 2.19	NS
Prevalence on insulin (%)	50	39	16	0.02
Total cholesterol at biopsy (mmol/l)	5.9 ± 1.3	5.3 ± 1.6	5.7 ± 2.1	NS
Retinopathy at biopsy (%)	70.8*	38.5†	9.7	0.000
Hematuria at biopsy (%)	35.3	23.1	35.5	NS

Data are means ± SD, unless otherwise indicated. *Significant difference between groups I and III; †significant difference between groups II and III; ‡significant difference between groups I and II. NS, not significant.

Predictive factors of NDN in type 2 diabetic patients with renal involvement

We also assessed the clinical features that predicted the presence of NDN in type 2 diabetic patients at the time of biopsy. Absence of retinopathy alone has a sensitivity of 81.8%, a specificity of 70.8%, and a positive predictive value of 83.7%. SCr ≤120 μmol/l (absence of impaired renal function), by itself, has a sensitivity of 70.5%, a specificity of 54.2%, and a positive predictive value of 73.8%. However, proteinuria ≥2 g/day, hematuria, and hypertension all had poor predictive values for NDN. Nevertheless, when combining absence of retinopathy with proteinuria ≥2 g/day or with hematuria at the time of biopsy, positive predictive values of 94.4 and 92.9%, respectively, were observed.

Renal prognosis among the patients with different renal lesions

Figure 1 depicts the trend of renal function over time among the three groups of patients. Patients in groups I and II had more rapid deterioration of renal function than group III patients ($P < 0.05$). However, there was no significant difference in the rate of deterioration between group I and II patients ($P = 0.19$). Other clinical factors correlated with significant disease progression included presence of retinopathy ($P < 0.0001$), proteinuria ≥2 g/day ($P < 0.0001$), and hypertension at time of biopsy ($P = 0.0006$). However, SCr ≥120 μmol/l did not correlate with rate of renal function deterioration.

Figure 2 depicts cumulative survival rates (percentage of patients not reaching ESRF) over time. Group III patients had higher renal survival rates than group I and II patients ($P < 0.05$). At the time of censor, event rates (end-stage renal disease) were 38, 30, and 16.1% for groups I, II, and III, respectively. Other clinical features significantly correlated with renal outcome included presence of retinopathy (56%, $P < 0.0001$), SCr ≥120 μml/l (46.2%, $P = 0.001$), and proteinuria ≥2 g/day (49.5%, $P = 0.009$). Presence of hypertension, hematuria, and usage of ACE inhibitor, however, did not affect renal survival. When considering the effect of ACE inhibitor on the DGS patients, the event rate in treated patients was 28.0% and appeared to be lower than the nontreated patients, whose event rate was 63.6%; however, the *P* value did not reach statistical significance. Multivariate analysis of the following factors: sex, age, BMI, cholesterol level, mean blood pressure, baseline creatinine and proteinuria, presence of DGS, and HbA_{1c} showed that independent risk factors for reaching renal end points were presence of DGS, increased mean blood pressure, baseline SCr level, and degree of proteinuria ($P < 0.05$). However, when retinopathy was included in the analysis model, it was found to be the only independent variable correlated with ESRF.

CONCLUSIONS

— Among type 2 diabetic patients with renal biopsy performed, the prevalence of nondiabetic renal disease in the literature varies widely, from 12 to 45%, depending on the selection criteria and populations being studied (9,11,13–15). Although renal biopsy policy may vary between institutions, diabetic patients with renal involvement not readily ascribed to diabetes alone are often selected to undergo the procedure. These selected patients probably only represent a minority of the diabetic population, accounting for 5% of our renal biopsy cases. Despite such a selection, the renal biopsy in this series of 68 patients with type 2 diabetes permitted the distinction of three groups of renal lesions associated with different prognostic features. In this study, only 54% of patients demonstrated DGS (groups I and II), whereas 65% of the subjects demonstrated a nondiabetic glomerular lesion or

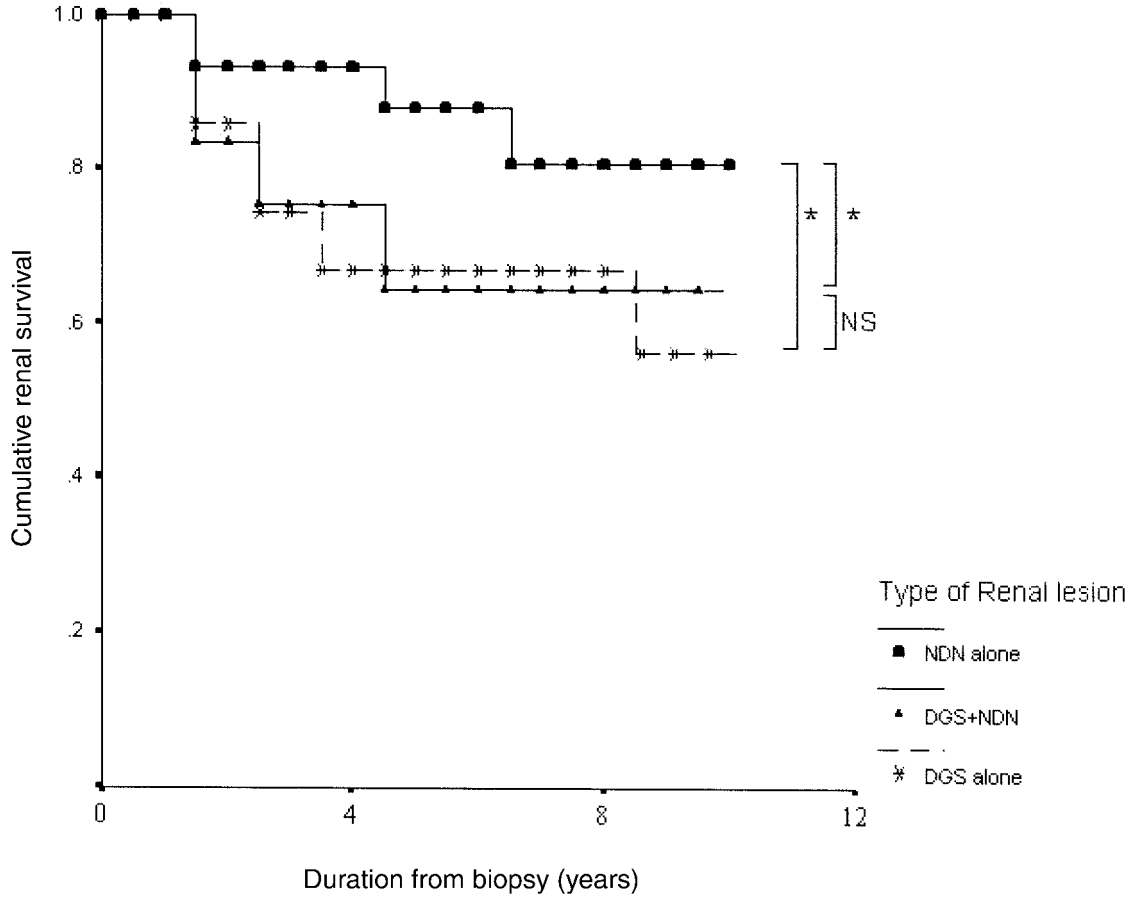

Figure 1—*Deterioration of renal function among patients with different renal pathologies. Slope of decline of 1/SCr for group I: mean* $-1.9 \pm 1.5 \times 10^{-3}$*; group II: mean* $-1.3 \pm 1.2 \times 10^{-3}$*; and group III: mean* $-0.5 \pm 1.0 \times 10^{-3}$*.* $P = 0.19$ *(not significant [NS]), group I versus group II;* $*P = 0.013$*, group II versus group III;* $\#P < 0.0001$*, group I versus group III.*

nephropathy (NDN, groups II and III). The mechanisms implicated in the development of NDN in diabetic patients with or without DGS remained speculative (9,11,13–16). The predisposition of DGS to superimposed nephritis has been attributed to enhanced exposure of antigenic cellular components, triggering immune responses (17). Others, however, found no difference in the prevalence of NDN between patients with and without diabetes and that the coexistence of a different glomerulonephritis in the diabetic kidney may be merely coincidental (11,18).

The influence of these nondiabetic lesions on the renal outcome in diabetic patients has not been well established, and most of the data available are based on cross-sectional study design (11,13,16, 17). Our study demonstrated that type 2 diabetic patients with DGS have a significantly worse renal outcome than those without DGS. In addition, it also confirmed the previous notion that the renal outcome of patients with DGS is not altered by a coexisting nephropathy (11,19), at least with the spectrum of NDN that was seen. The renal outcome in diabetic patients with NDN varies and depends on the specific type of nondiabetic renal lesion, but the small number of each subtype in this study does not permit further subgroup analysis. In our study, only four patients received prednisolone for coexisting and pure nondiabetic renal disease, and their outcome appears to be worse than those without immunosuppressive agents. Diabetic patients were probably less likely than their nondiabetic counterparts to receive immunosuppressive agents (most commonly prednisolone), unless histology and clinical course point toward an aggressive course (e.g., necrotizing or cresenteric lesions, or severe nephrotic state due to nondiabetic lesions) because of the tendency of hyperglycemia and infection. Our data are therefore too limited to conclude whether an immunosuppressive agent is altering the clinical outcome. Nevertheless, our study showed that although uncommon, some nondiabetic renal diseases do respond well to specific treatment and should not be missed.

This study confirms the accepted view that absence of retinopathy or diabetes of short duration should raise the possibility of a nondiabetic lesion and hence a renal biopsy (11,19–21). We also showed that the combination of absence of retinopathy with hematuria or proteinuria ≥ 2 g/day constitutes the most sensitive marker for NDN and is thus a strong indicator for biopsy. Also, hematuria is not a good indicator of NDN. Although retinopathy has been strongly correlated with the presence of DGS, discordance in the occurrence of the two complications is not uncommon, and it has been suggested that the two complications show dissimilar genetic predisposition (22–24). We

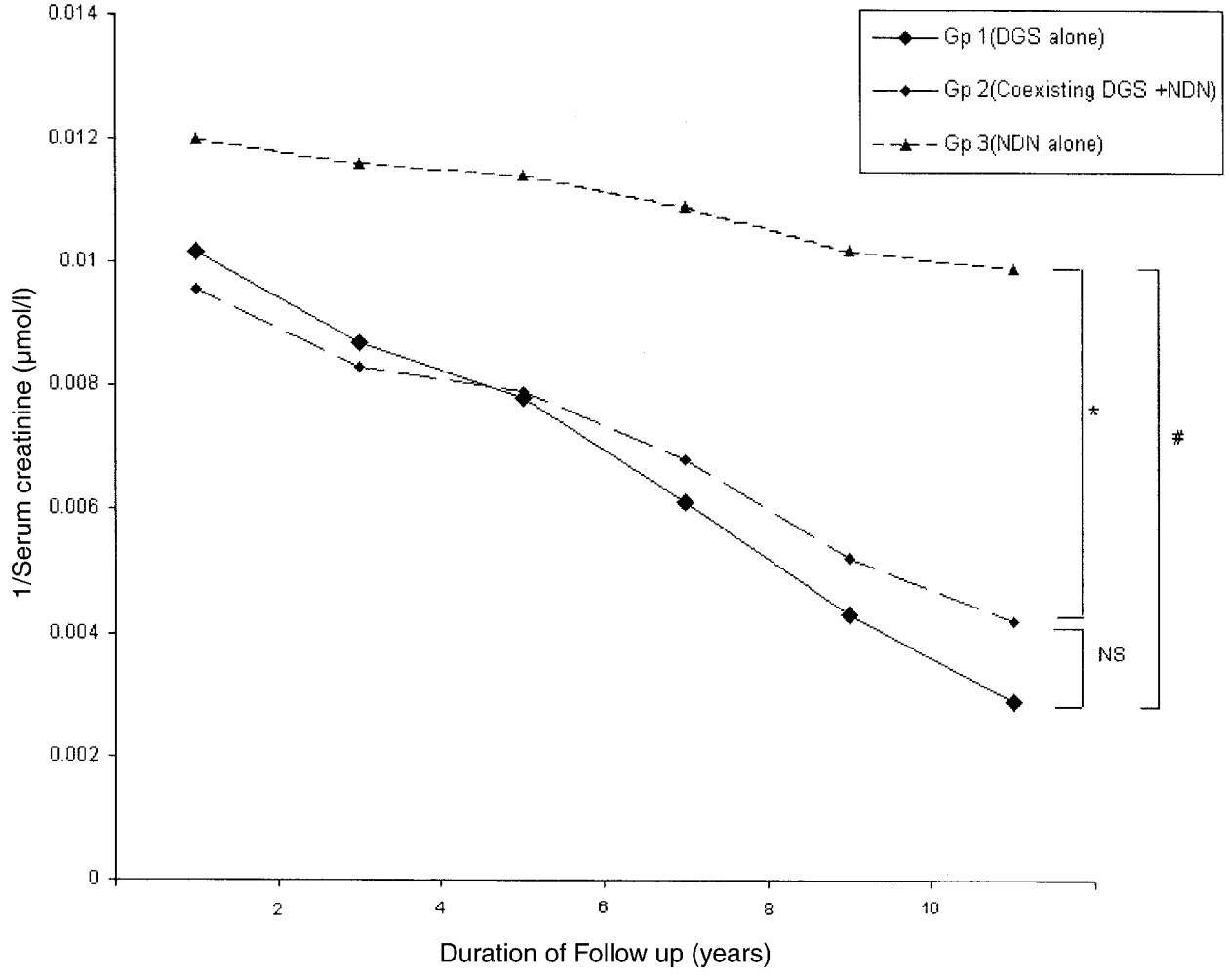

Figure 2—*Renal survival of the three groups of patients with different renal pathology. Percentage of patients not reaching ESRF. *P < 0.05.*

found that 40.5% of patients with DGS did not have retinopathy, and 13.6% of diabetic patients with retinopathy did not have DGS but had NDN instead. In our study, 70.8 and 38.5% of patients with DGS alone and DGS coexisting with NDN, respectively, had retinopathy. The low prevalence of retinopathy among the latter group may reflect a selection bias for renal biopsy. Nevertheless, retinopathy is still the single most important predictor for disease progression and adverse renal outcome.

Proteinuria >2 g/day was associated with disease progression and adverse renal outcome, independent of the underlying renal lesion. The magnitude of proteinuria probably reflects the severity of underlying renal disease, and proteinuria per se is tubulotoxic. Thus, the prognostic value of proteinuria >2 g/day applies not only to diabetic patients in general but also to those with superimposed or isolated nondiabetic renal lesions (8,9,15). This finding is in accordance with a study from the West (8), which showed that the degree of proteinuria is an independent predictor for adverse renal outcome among type 2 diabetic patients, despite potential different patterns of renal disease among different races.

Contrary to the reported beneficial effects of ACE inhibitor on diabetic nephropathy, we observed no significant difference in the renal outcome between treated and nontreated patients (21,25). Such a result can be explained by the potential selection bias that occurred in the nonrandomized study design. However, when we compared the effects of ACE inhibitor among patients with DGS, treated patients had a lower risk for end-stage disease, although the difference fell short of statistical significance.

Blood pressure control is of primary importance in the prevention of progression of renal disease in both diabetic and nondiabetic renal lesions. Although glycemic control is important in the management of diabetic renal disease, no data are available on the effect of glycemic control on progression of nondiabetic renal disease in diabetic patients. Hyperglycemia has been shown to induce transforming growth factor (TGF)-β production in the kidney or in cultured mesangial or tubular cells (26). Because TGF-β is a common mediator of progression of all renal diseases (27), the potential adverse effect of hyperglycemia on renal function in this group of patients cannot be excluded.

This study has emphasized that among patients with type 2 diabetes, renal complications may be frequently due to a heterogeneous nondiabetic lesion. This nondiabetic lesion may occur alone or may be superimposed on underlying

DGS, which is associated with different renal outcome and probably associated with treatment modalities. This study advocates a higher degree of suspicion in patients with type 2 diabetes for the need of a renal biopsy, and the association of proteinuria or hematuria with the absence of retinopathy represents a strong indication for such a procedure. Patients with biopsy-confirmed DGS or significant proteinuria, >2 g/day, are at highest risk for adverse renal outcome, and more aggressive treatment is warranted. However, since most patients were initially selected for renal biopsy because there was a clinical suspicion of underlying nondiabetic renal disease, the results cannot be readily extrapolated to the general population of diabetic patients with renal disease.

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