Concomitance of Diabetic Retinopathy and Proteinuria Accelerates the Rate of Decline of Kidney Function in Type 2 Diabetic Patients

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OBJECTIVE — To evaluate the rate of progression of renal disease in proteinuric type 2 diabetic patients with and without retinopathy.

RESEARCH DESIGN AND METHODS — Thirty-eight proteinuric type 2 diabetic patients with diabetic retinopathy and 27 without were enrolled in an observational study for the evaluation of rate of glomerular filtration rate (GFR) decline and followed up for a median period of 6 years. GFR was determined at least once per year, and blood pressure, glycated hemoglobin, and proteinuria were determined every 4 months.

RESULTS — Although the two groups had comparable GFR, albuminuria, blood pressure, and HbA_{1c} at entry of the study, the rate of decline of GFR was higher in type 2 diabetic patients with retinopathy (-6.5 ± 4.4 ml/year) than in those without (-1.8 ± 4.8 ml/year; $P < 0.0001$). Protein and albumin excretion rate increased significantly in patients with retinopathy, while they did not change in those without. Mean blood pressure between the two groups of patients were similar both at entry and during the follow-up, although the proportion of patients treated with at least two antihypertensive drugs was higher in patients with retinopathy. On a multiple regression analysis, only mean blood pressure and proteinuria were significant determinants of progression of renal disease in type 2 diabetic patients with retinopathy.

CONCLUSIONS — The rate of progression of renal disease in proteinuric type 2 diabetic patients with retinopathy is faster than that observed in those without retinopathy. The screening for retinopathy identifies patients at high risk for rapid deterioration of kidney function.

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Diabetic nephropathy is the leading cause of end-stage renal disease in the U.S., and it is responsible for 42% of all new cases (1); a similar trend has been reported in Europe. Type 2 diabetes contributes to almost 50% of diabetic patients joining end-stage renal failure program (2). Although the bulk of evidence suggests that the course of renal disease might be similar in type 1 and type 2 diabetes (3), the risk factors and the clinical course of renal disease in type 2 diabetic patients are not clearly defined yet.

Proteinuria, a common finding in type 2 diabetes, is often observed in patients with no evidence of diabetic retinopathy: 20–45% of type 2 diabetic patients with proteinuria do not show retinal diabetic lesions. While a 14% prevalence of macroalbuminuria has been reported in a cross-sectional study of 549 type 2 diabetic patients, only 45% of the macroalbuminuric patients also had some degree of retinopathy (4). In another population-based study of 840 type 2 diabetic patients, 20.4% of 172 macroalbuminuric patients had no diabetic retinopathy (5). In two recent pharmacological trials that enrolled >3,000 type 2 diabetic patients with nephropathy, one-third of the subjects did not show diabetic retinopathy (6,7).

To make the picture even more complex, it has been suggested that 25–50% of type 2 diabetic patients may have kidney alterations not necessarily related to their diabetic condition. This finding seems to occur more frequently in those patients who have no sign of diabetic retinopathy (8). Thus, the absence of any retinal involvement might suggest a pathologic renal process independent of the deleterious effect of hyperglycemia, and that might have a different time course and different response to common factors known to accelerate the decline of kidney function. Nonetheless, to our knowledge, no studies have investigated whether the progression of renal disease is different in type 2 diabetic patients with and without retinopathy. The present study was then undertaken to evaluate the impact of retinopathy on the rate of progression of renal disease in proteinuric type 2 diabetic patients, with normal or mild elevation of their serum creatinine concentration.

RESEARCH DESIGN AND METHODS

— Between 1988 and 1996, all type 2 diabetic patients attending the Diabetes Outpatient Clinic of the Padova University Hospital who met the inclusion criteria listed below were invited to participate in a follow-up observational study for regular determinations of glomerular filtration rate (GFR). Inclusion criteria included the following: type

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Abbreviations: GFR, glomerular filtration rate; WHO, World Health Organization.

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

2 diabetes (according to World Health Organization [WHO]criteria); age <75 years; persistent proteinuria (albumin excretion rate ≥300 mg/24 h in at least three timed urine collections in the absence of urinary infection or hematuria); absence of heart failure or unstable angina; serum creatinine <150 μmol/l; and absence of any clinical or laboratory evidence of other kidney or renal tract disease. A microscopic examination of the urinary sediment and ultrasonography of the kidneys were performed in all patients before the entry into the study. Presence of hematuria and evidence of obstructive uropathy and of scarred or asymmetric kidneys were exclusion criteria.

Among a population of ~1,000 type 2 diabetic patients regularly attending the Diabetes Outpatient Clinic, 85 consecutive type 2 diabetic patients were identified as having persistent proteinuria. Fifteen proteinuric patients were excluded because of advanced renal failure, obstructive uropathy, and severe heart or liver failure. Seventy consecutive type 2 diabetic patients met the inclusion criteria and accepted to participate in the study. Each patient gave his/her volunteer consent before entering the study. The study protocol was approved by the local ethics committee.

The patients were seen at 3-month intervals for regular clinical evaluation, while GFR was measured annually by means of the determination of ^{51}Cr-EDTA plasma clearance over 5 h as previously described (9). To estimate the rate of decline of GFR, at least three GFR measurements were required. Supine blood pressure was measured by a standard mercury sphygmomanometer and calculated as the average of three readings obtained in four different times per year. Mean blood pressure was calculated as diastolic pressure plus one-third of the pulse pressure. The examination of the fundus oculi was performed once a year by direct ophthalmoscopy after pupillary dilatation by a single trained ophthalmologist, and patients were classified on the basis of absence or presence (background or proliferative) of retinopathy. Retinopathy status was confirmed by fluorescein angiography 1 year after the enrollment into the study. Background retinopathy was diagnosed in the presence of microaneurisms, hemorrages, exudates, and intra-retinal microvascular abnormalities. Proliferative retinopathy was diagnosed when new vessels, glial proliferation, preretinal or vitreous hemorrages, or scars of photocoagulation (known to have been directed at new vessels) were present. Fundus oculi was then re-evaluated once per year. The presence of cardiovascular disease was defined by at least one of the following: *1*) a positive WHO questionnaire for cardiovascular disease; *2*) a positive history of cardiovascular disease, corroborated by medical records; or *3*) Q wave criteria for previous myocardial infarction. Cerebrovascular disease was defined as a history of stroke or transient ischemic attacks, and peripheral vascular disease was defined as a history of intermittent claudication, rest pain, gangrene, or amputation or as having an abnormal ankle-to-arm ratio (<0.8).

Total urinary protein and albumin excretion, HbA_{1c}, serum creatinine, cholesterol, and triglyceride levels were measured at least twice a year during the follow-up period. Total urinary protein and albumin excretion were measured by the Biuret and nephelometric method (Behring Nephelometer Analyzer; Behring, Marburg, Germany), respectively. HbA_{1c} was determined on a venous blood specimen by high-performance liquid chromatography (normal values <5.9%). Serum creatinine concentration was assessed by a kinetic Jaffé method, and serum cholesterol and triglyceride levels were assessed by conventional laboratory technique.

Table 1—*Baseline characteristics of proteinuric type 2 diabetic patients according to retinopathy status.*

	Patients with retinopathy	Patients without retinopathy
Number of men/women	38 (30/8)	27 (21/6)
Retinopathy (*n*)		
Background/Proliferative	18/20	0
Age (years)	57 ± 8	55 ± 8
Duration of diabetes (years)	12 ± 10	9 ± 7
BMI (kg/m^2)	27 ± 3	29 ± 4
HbA_{1c} (%)	8.9 ± 2	8.5 ± 2
Total serum cholesterol (mmol/l)	6.7 ± 3.5	6.5 ± 2.4
Serum triglycerides (mmol/l)	2.6 (0.6–19.3)	2.8 (0.9–8.4)
Treatment for diabetes (*n*)		
Oral hypoglycemic agents	18	18
Insulin	20	9
Blood pressure (mmHg)		
Systolic	159 ± 21	154 ± 18
Diastolic	90 ± 10	89 ± 9
Receiving antihypertensive treatment (*n*)		
ACE inhibitors	23	16
Diuretics	20	13
Calcium-channel blockers	9	2
α-Blockers	10	8
	6	1
Duration of hypertension (years)	5 ± 6	5 ± 5
Smokers (*n*)	8	3
Follow-up (years)	5.96 (2–10)	6.13 (2–10)

Data are means ± SD or median (range).

Statistical analysis

Values represent means ± SD, but values for protein excretion rate and plasma triglyceride concentrations are expressed as median (range), owing to skewed distribution. In each patient, all measurements performed during the entire follow-up period were used to calculate the mean values. Linear regression analysis was used to assess the rate of decline in GFR by using all the available readings for each patient (median 7, range 3–12). For normally distributed variables, groups were compared by unpaired Student's *t* test, while the Mann-Whitney *U* test was used for non–normally distributed variables. Survival function estimates were calcu-

Table 2—*Renal function, mean blood pressure, and metabolic parameters at entry, during follow-up, and at the end of the study in type 2 diabetic patients with and without retinopathy*

	Type 2 diabetic patients with retinopathy			Type 2 diabetic patients without retinopathy		
	At entry	During follow-up	At exit	At entry	During follow-up	At exit
Serum creatinine (μmol/l)	100 ± 27	—	174 ± 118*	93 ± 24	—	108 ± 38*
GFR (ml · min^{-1} · 1.73 m^{-2})	88 ± 30	—	61 ± 29	88 ± 29	—	75 ± 28*
Protein excretion (g/24 h)	1.08 (0.5–3.5)	1.4 (0.3–8.6)*	1.7 (0.4–10.5)*	0.93 (0.5–2.6)	0.75 (0.2–4.52)	0.80 (0.3–6.95)
Albuminuria (mg/24 h)	530 (302–2,400)	743 (95–4,890)*	822 (104–5,430)*	394 (310–1,580)	405 (85–2,954)	421 (100–4,251)
Mean blood pressure (mmHg)	113 ± 9	112 ± 9	114 ± 13	111 ± 11	111 ± 10	111 ± 15
HbA_{1c} (%)	8.9 ± 2.3	8.8 ± 1.4	9.2 ± 2	8.6 ± 1.7	8.9 ± 1.6	8.7 ± 2
Serum cholesterol (mmol/l)	6.7 ± 3.5	5.9 ± 2.1*	5.7 ± 1.9*	6.5 ± 2.4	5.7 ± 2.0*	5.7 ± 1.8*
Serum triglycerides (mmol/l)*	2.6 (0.6–5.4)	1.9 (0.4–5.5)*	2.0 (0.6–4.6)*	2.8 (0.9–8.4)	2.0 (0.5–6.2)*	1.8 (0.8–22.5)*

Data are means ± SD or median (range). *$P < 0.01$ vs. entry values.

lated using the Kaplan-Meier method. The χ^2 test was used to analyze differences in the proportion of patients receiving antihypertensive treatment. Multivariate regression analysis of putative progression promoters was performed with the rate of decline in GFR as a dependent variable. The following putative progression promoters were included into the model: mean blood pressure, proteinuria, HbA_{1c}, cholesterol, retinopathy, and smoking. Values for proteinuria were logarithmically transformed before analysis, because of their positively skewed distribution. The R^2 value was adjusted for the number of variables introduced into the model. A P value of <0.05 was considered statistically significant. All calculations were performed using SPSS (SPSS, Chicago).

RESULTS — Five type 2 diabetic patients (three with and two without retinopathy), in whom only two determinations of GFR were available because of loss to follow-up, were excluded from the analysis. Demographic and clinical data at entry into the study were comparable in the remaining 65 type 2 diabetic patients with and without retinopathy (Table 1). All insulin-treated lean patients had a glucagon test performed, and all of them had a stimulated C-peptide value >0.60 pmol/ml. GAD antibody assay was performed in 25 patients with and in 14 without retinopathy. None of the patients tested for GAD were antibody-positive.

The follow-up period was similar in the two groups. At the end of follow-up, eight patients with retinopathy progressed from background to proliferative retinopathy (and required laser therapy), while only three patients in the group without retinopathy at baseline developed minimal retinal changes (background retinopathy).

Systolic blood pressure, proteinuria, and albuminuria were slightly higher in patients with retinopathy at entry, though the difference was not statistically significant (Tables 1 and 2). At entry, 60% of patients in both groups were on antihypertensive treatment (13 patients with and 6 patients without retinopathy were treated with one drug; 8 patients with and 10 without retinopathy were treated with two drugs; and 2 patients with retinopathy were taking three drugs). Almost all patients received ACE inhibitors either alone or in combination with diuretics or calcium-channel blockers and diuretics (Table 1). All patients were prescribed an ACE inhibitor after the first determination of GFR.

Serum creatinine levels rose significantly in both groups of patients, but the levels measured at the end of the follow-up period were significantly higher in type 2 diabetic patients with retinopathy (Table 2). Similarly, while there was no difference at entry, GFR was significantly lower in type 2 diabetic patients with retinopathy at the follow-up end point (Table 2). Figure 1 illustrates the individual figures for GFR decline. Although GFR decline varied considerably among patients, the rate of decline was much greater in patients with than in those without retinopathy (−6.5 ± 4.4 vs. −1.8 ± 4.8 ml/year; $P < 0.0001$). There was no difference in GFR decline in patients with background retinopathy compared with those with proliferative retinopathy at entry (−6.0 ± 7.6 vs. −6.9 ± 3.3 ml/year; NS). Of the patients with retinopathy, 10 had a doubling or more of serum creatinine during follow-up. None of the patients in the group without retinopathy had doubling of baseline serum creatinine. In patients with retinopathy, total protein excretion and albumin excretion rate increased significantly during the follow-up, while they did not change in those without (Table 2). In both groups, there was no significant change of mean blood pressure over the whole study period (Table 2). However, at the end of follow-up period, the proportion of patients taking more than one antihypertensive drug was significantly higher in those with than in those without retinopathy ($P < 0.01$). In particular, in the retinopathy group, 25 patients required two agents and 13 required three or more agents. On the contrary, in the patients without retinopathy, 17 patients required two drugs, 2 required three or more drugs, and 8 required only one drug. Two out of these eight patients withdrew ACE inhibitor treatment during the follow-up period because of symptomatic low blood pressure values.

As far as the metabolic parameters are concerned, HbA_{1c} levels remained constant during the follow-up, with no difference between the two groups of patients (Table 2). A significant reduction in total plasma cholesterol and triglyceride concentrations was observed in patients both

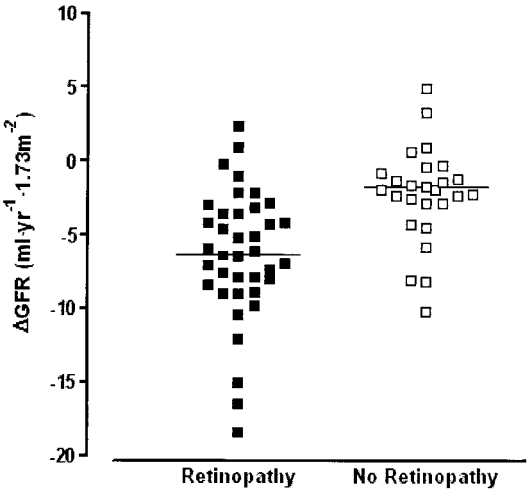

Figure 1—*Individual values of GFR decline in 38 proteinuric type 2 diabetic patients with and in 27 without retinopathy.*

with and without retinopathy (Table 2). Ten patients in each group were treated with statins during the follow-up period.

The prevalence of coronary heart disease was similar at both entry into the study (7 patients with vs. 5 patients without retinopathy) and the end of the study (20 patients with vs. 12 patients without retinopathy). However, 12 patients with retinopathy (32%) died during the follow-up period as opposed to one death among those without retinopathy ($P < 0.05$). The latter and nine of the patients with retinopathy died from acute myocardial infarction. Finally, three patients with retinopathy died from stroke. Two of them were on dialysis replacement therapy.

On a multiple linear regression analysis, both mean blood pressure during the follow-up (β −0.44; $P = 0.003$) and proteinuria at entry into the study (β −0.36; $P = 0.02$) appeared to be independently associated with the rate of decline in GFR in type 2 diabetic patients with retinopathy ($F = 8.83$; adjusted $R^2 = 0.33$), while no significant association was found between GFR decline and any putative progression promoters (mean blood pressure, proteinuria, HbA_{1c}, cholesterol, and smoking) in type 2 diabetic patients without retinopathy.

To further evaluate the role of retinopathy on renal disease progression, multiple linear regression analysis was performed on all patients data pooled together: retinopathy (β −0.37; $P = 0.0008$), mean blood pressure during the follow-up (β −0.28; $P = 0.0078$), and proteinuria at entry into the study (β −0.31; $P < 0.0061$) were independently associated with the rate of decline in GFR ($F = 10.82$; adjusted $R^2 = 0.38$). Although BMI was lower, diabetes duration was longer, and the prevalence of insulin treatment was higher in patients with retinopathy, none of these variables were related to GFR decline.

CONCLUSIONS — Our results suggest that the concomitance of nephropathy and diabetic retinopathy is associated with a faster decline of renal function and greater mortality in type 2 diabetic patients. This occurred despite no significant difference in blood pressure, metabolic control, and plasma lipid profile. Our prospective cohort study was long-term and the requirements to obtain a valid determination of GFR decline have been fulfilled: the applied GFR method has a good accuracy and precision; at least three GFR determinations were performed; and the observation period was extended to at least 2 years (10).

Several mechanisms may account for the worse outcome of patients with retinopathy. In microalbuminuric type 2 diabetic patients, Fioretto et al. (11) showed that atypical patterns of renal lesions (mainly tubulointerstitial and arteriolar changes) were present in 30–40% of these patients. Biopsy studies have suggested that as much as 30% of proteinuric type 2 diabetic patients may not have typical diabetic lesions and that these nontypical lesions are more frequent in proteinuric individuals with no sign of diabetic retinopathy (8,12). A normal glomerular structure was also found in 18% of type 2 diabetic patients with proteinuria but without retinopathy (12). A recent article has demonstrated that the course of kidney function and albuminuria in type 2 diabetic patients with persistent albuminuria and with nondiabetic glomerular patterns is less rapid than in the patients with diabetic nephropathy and similar to the rate of decline observed in our patients without retinopathy (13). In the majority of the studies, however, patients were referred to the nephrologist for kidney biopsies for clinical indications; thus, many of these renal biopsies were presumably performed because of an unusual clinical course (14). A large autopsy study on type 2 diabetic patients did not confirm such a high incidence of nondiabetic renal lesions (15). Nondiabetic nephropathy is therefore unlikely to account completely for a slower loss of kidney function in type 2 diabetic patients without retinopathy. Recently, a study applying an unbiased indication for kidney biopsy in macroalbuminuric type 2 diabetic patients found that 94% of patients had diabetic glomerulosclerosis and that retinopathy was associated with Kimmenlstiel-Wilson nodules, but not with mesangial sclerosis lesions (16). This article raises the possibility that retinopathy is correlated with more advanced glomerular pathology and that diabetic glomerulosclerosis may be caused by different pathogenetic mechanisms. In a group of 65 consecutive proteinuric type 2 diabetic patients, Ruggenenti et al. (17) found that the progression of renal disease was consistently predicted by baseline urinary protein excretion rate but was independent from the pattern of underlying glomerular lesions. Unfortunately, no data regarding the prevalence of retinopathy were given in this study.

The rate of GFR decline found in our series of patients is very similar to that found in a group of 26 type 2 diabetic patients with a biopsy confirmed diabetic glomerulosclerosis (18). It is of note that 9 of those 26 patients had no retinopathy and that their GFR decline was significantly lower than in patients with retinopathy (8.5 ± 6.0 vs. 0.41 ± 1.9 ml/year; $P < 0.001$) (18). These findings strongly support the hypothesis that, in the absence of retinopathy, isolated diabetic nephropathy has a better outcome and is

associated with a lower risk of progression to end-stage renal disease.

Our data provide further support to the close relationship between presence of diabetic retinopathy and abnormal increase in urinary albumin excretion (19,20). The patients with retinopathy had a significant increase in proteinuria, whereas the patients without had a stable protein excretion. Proteinuria is assumed to be an independent risk factor for the progression of renal diseases (21), and a progressive rise in proteinuria is an important clinical marker to identify those diabetic patients at high risk of rapid deterioration of renal function.

The rate of decline in GFR observed in type 2 diabetic patients with retinopathy was slower than that reported in untreated type 1 diabetic patients (12–15 ml $\cdot$ min^{-1} $\cdot$ year^{-1}) (22). All of our patients were hypertensive and were treated, mainly with ACE inhibitors in combination with diuretics or calcium-channel blockers. Nonetheless, blood pressure control was not optimal, though similar in the two groups during the study period. The greater proportion of patients with retinopathy who required more than one antihypertensive drug in comparison with those without indicates the presence of a more severe hypertension in this subset of proteinuric type 2 diabetic patients. The beneficial effect of antihypertensive treatment on the progression of diabetic nephropathy in type 1 and type 2 diabetic patients is well documented (6,7,23). Therefore, the possibility that a more aggressive therapy could have induced a further reduction of the rate of progression of renal disease should not be discounted.

No relationship among HbA_{1c}, plasma lipids, and the decline in GFR was found in our study. Both the relatively small number of patients and an overriding effect of blood pressure and proteinuria may account for this unexpected observation (21,24). These same factors might explain the lack of any association with lipid control. It is unlikely that the use of statins may have affected our results, since the GFR decline in the 10 patients with retinopathy treated with statins was again significantly greater than that observed in the 10 patients without retinopathy treated with statins (-6.3 ± 0.75 vs. -1.4 ± 0.70 ml/year; $P < 0.01$).

Our observation does have clinical implications. The importance of a careful and extensive screening for diabetic retinopathy is a powerful tool in reducing the burden of severe visual impairment together with glycemic control (25,26). Our data now provide evidence that screening for diabetic retinopathy might provide an important information for defining the risk for progression toward advanced kidney failure and cardiovascular mortality in type 2 diabetic patients. It is intriguing that 12 patients in the retinopathy group over the 6-year median follow-up died of acute myocardial infarction or stroke as compared with 1 individual in the group without retinopathy, in spite of a similar incidence of coronary events. Though larger number are needed to draw a definite conclusion, a role for diabetic retinopathy as a marker for diabetes outcome could be considered. Recently, two prospective cohort studies showed that the presence of visual impairment caused by diabetic retinopathy is a risk factor for death from cardiovascular disease in type 2 diabetic patients (27,28). This excess mortality in diabetic patients with retinopathy may partly explain the relatively low number of subjects developing end-stage renal disease. The identification of diabetic individuals with retinopathy or at risk of developing it would be of importance in the determination of the intervention needed to reduce the progression of renal and cardiovascular disease. Our observation may also be of importance in interpreting and/or planning clinical trials on renal protection in type 2 diabetes.

In conclusion, lack of retinopathy in diabetic patients with clinical proteinuria is associated with a better renal and cardiovascular prognosis, independently of blood pressure levels and metabolic control. We suggest that retinopathy is a powerful marker of the progression of renal damage in type 2 diabetic patients with proteinuria.

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