Early Nephropathy Predicts Vision-Threatening Retinal Disease in Patients with Type I Diabetes Mellitus

RICHARD E. GILBERT,* CON TSALAMANDRIS,* TERRI J. ALLEN,* DEBORAH COLVILLE,† and GEORGE JERUMS*

Departments of *Medicine and †Ophthalmology, Austin and Repatriation Medical Centre, Heidelberg, Victoria, Australia.

Abstract. In type I (insulin-dependent) diabetes mellitus, nephropathy may be identified in its early stages by the development of persistent microalbuminuria. This longitudinal study sought to examine the development of vision-threatening retinal disease (VTRD) (proliferative retinopathy and clinically significant macular edema) in such patients with early and evolving diabetic kidney disease. Eighty patients with type I diabetes and at least 8 yr of longitudinal data were identified. Glycated hemoglobin and albumin excretion rate (AER) were measured every 3 mo. Ophthalmologic examination was performed at least yearly. Thirteen patients were identified as having evolving nephropathy by a progressive increase in AER and the presence of microalbuminuria during the study period. Sixty-seven patients remained persistently normoalbuminuric. VTRD developed in eight of 13 (62%) patients with evolving nephropathy compared with five of 69 (7%) patients who were persistently normoalbuminuric (P < 0.001) in the absence of any difference in long-term glycemic control or duration of diabetes between the two groups. Clinically significant macular edema (P < 0.05) and proliferative retinopathy (P < 0.01) were both more common in patients with evolving nephropathy. In such patients, AER was 150 ×/± 1.7 μg/min at the time of laser photocoagulation for VTRD. These data suggest that patients with type I diabetes and evolving nephropathy may be at higher risk of developing VTRD than patients who remain persistently normoalbuminuric despite similar long-term glycemic control and duration of diabetes. (J Am Soc Nephrol 9: 85–89, 1998)

Diabetes is a leading cause of both renal failure and blindness. Although all patients with diabetes develop glomerular histopathologic changes such as basement membrane thickening (1), only one-third develop clinical nephropathy (2). Similarly, although nonproliferative retinopathy eventually develops in virtually all patients with type I diabetes, vision-threatening retinal diseases (VTRD) such as maculopathy and neovascularization affect approximately 30% of patients (3,4). An association between retinopathy and nephropathy has been suggested in some (4,5), but not in other studies (6–8) of patients with type I diabetes. These studies have been mostly cross-sectional and potentially confounded by the effects of diabetes duration and long-term glycemic control.

In type I (insulin-dependent) diabetes mellitus, nephropathy may be identified in its early stages by the development of persistent microalbuminuria (9). However, the stage of evolution of nephropathy at which time neovascularization develops is uncertain, as is the association between nephropathy and sight-threatening maculopathy. The present study was undertaken to examine the relationship between such early, evolving nephropathy and the development of VTRD, both proliferative retinopathy and clinically significant macular edema (CSME). The study also sought to examine whether the relationship between VTRD and nephropathy could be explained entirely by glycemic control and diabetes duration or whether there may be, in addition, other factors involved in a common predisposition to both complications.

Materials and Methods

Patients

Starting in 1978, patients of the Austin and Repatriation Medical Centre diabetes clinic have been recruited for a study of evolving diabetic complications. Patients were seen every 3 mo for clinical management and measurement of urinary albumin excretion, plasma creatinine, BP, and glycated hemoglobin. Diabetic patients studied between 1978 and 1995 for whom there was at least 8 yr of longitudinal data were evaluated. Patients were designated as having type I diabetes if they had persistent ketonuria, weight loss on presentation, and insulin dependency within 1 mo of diagnosis. All other patients were deemed to have type II diabetes. Patients were classified as having evolving nephropathy on the basis of two criteria. First, patients were required to have developed persistent microalbuminuria during the study period as defined by an albumin excretion rate (AER) of 20 to 200 μg/min in two of three consecutive specimens (10). Second, such patients were also required to have an AER that progressed throughout the study period, as defined by a statistically significant positive regression between log_{10} AER and time (11). Because therapy with angiotensin-converting enzyme inhibitors may influence the rate of progression of both early (12) and late (13) nephropathy in type I diabetes, only data before the introduction of such therapy were included. Using these criteria, 98 patients with type I diabetes and 8 yr of longitudinal follow-up were identified. Eleven

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Correspondence to Dr. Richard E. Gilbert, Department of Endocrinology, Austin and Repatriation Medical Centre (Austin Campus), Studley Road, Heidelberg 3084, Victoria, Australia.
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of these patients were excluded because of concern that alterations in urinary albumin excretion may reflect causes other than diabetic kidney disease. These included recurrent urinary tract infections (n = 4), cardiac failure (n = 3), and other known renal diseases (n = 4). Other patients were excluded because they had overt nephropathy on initial specimens (n = 3) and were thus unsuitable for recruitment into a study of early, evolving diabetic kidney disease. Poor attendance excluded another four patients. Of the 80 remaining patients, 13 had evidence of evolving nephropathy and 67 remained persistently normoalbuminuric. The study protocol was approved by the Human Ethics in Research Committee of the Austin and Repatriation Medical Centre. Table 1 summarizes the clinical details of the two patient groups.

**Ophthalmologic Evaluation**

Ophthalmologic examinations were performed by one of four qualified ophthalmologists associated with the Hospital Diabetes Clinic. Each involved ophthalmologist had substantial experience in the diagnosis and treatment of diabetic retinal disease and was unaware of the patient’s renal status or glycated hemoglobin (HbA1c). All participating ophthalmologists used criteria elaborated by the Diabetic Retinopathy Study (DRS) (14,15) and the Early Treatment of Diabetic Retinopathy Study (ETDRS) (16) for the diagnosis of proliferative retinopathy and CSME, respectively. The frequency of eye examinations was based on the Preferred Practice Patterns of the American Academy of Ophthalmology (17), such that patients with no or minimal retinopathy were seen every 12 mo, patients with macular edema that was not clinically significant were seen every 4 to 6 mo, and patients with severe nonproliferative retinopathy were seen every 3 mo. Patients were identified as having VTRD by the ophthalmologist’s recommendation for laser photocoagulation due to CSME or neovascularization. Laser therapy was initiated within 4 wk of the diagnosis of CSME or proliferative retinopathy. The development of VTRD was considered a study end point and was related to AER measured within 3 mo of the diagnosis of VTRD.

**Laboratory Techniques**

Urinary albumin was measured by a coated tube RIA technique with an interassay coefficient of variation of 10.9% (18). Clinical and laboratory data obtained during periods of acute metabolic compensation, such as ketoacidosis, pregnancy, or while receiving treatment for urinary tract infection, were excluded from analysis. Hemoglobin A1 (HbA1c; nondiabetic range, 5 to 7.5%) was measured by the thiobarbituric acid technique (19) from 1978 to 1981 and by column chromatography preceded by a dialysis step after 1981. There was a close correlation between the two methods (r = 0.90, n = 35, P < 0.001), and a conversion formula was derived so that results could be pooled for statistical analysis (20). HbA1c measured by the thiobarbituric acid technique was converted to equivalent values for column chromatography by the equation y = 0.8x + 1.2, in which y denotes the column chromatography result and x is the value obtained by the thiobarbituric acid technique.

**Statistical Analyses**

All analyses were performed using the Stat-View SE + Graphics package (Abacus Concepts, Berkeley, CA) on an Apple Macintosh IIcx computer (Apple Computer, Cupertino, CA). Because of a positively skewed distribution, AER was logarithmically transformed before statistical analysis and expressed as the geometric mean ± standard deviation. Comparisons between groups of patients evolving diabetic nephropathy and those who were persistently normoalbuminuric were performed by ANOVA. To compare the number of patients who developed VTRD, Fisher’s exact test and Kaplan–Meier life table analysis were used. A P value < 0.05 was considered statistically significant.

**Results**

Duration of diabetes, initial HbA1c measurements, and mean HbA1c values for the entire study period were similar in patients with evolving nephropathy and those who remained persistently normoalbuminuric.

VTRD developed in 13 of 82 (16%) patients overall; five (6%) were due to maculopathy and eight (10%) were due to neovascularization. However, the number of patients with VTRD was significantly influenced by the presence or absence of nephropathy. VTRD was found in eight of 13 (62%) patients with evolving nephropathy compared with five of 67 (7%) persistently normoalbuminuric patients (P < 0.001; Figures 1 and 2). Five of 13 (38%) patients with evolving nephropathy developed proliferative retinopathy compared with three of 67 (4%) persistently normoalbuminuric patients (P < 0.01; Figure 1). CSME developed in three of 13 (27%) patients with evolving nephropathy and in two of 67 (7%) persistently normoalbuminuric patients (P < 0.05; Figure 1). The duration of diabetes at which VTRD developed was similar in patients with evolv-

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<th>Characteristic</th>
<th>Persistently Normoalbuminuric</th>
<th>Evolving Nephropathy</th>
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<tr>
<td>n</td>
<td>67</td>
<td>13</td>
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<tr>
<td>Sex (male/female)</td>
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<td>12/1</td>
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<tr>
<td>Age at diagnosis (yr)</td>
<td>22 ± 1</td>
<td>29 ± 3b</td>
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<td>AER (µg/min)</td>
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<td>13.2 ×/± 1.4c</td>
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<td>Plasma creatinine (µmol/L)</td>
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<td>Systolic BP (mmHg)</td>
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<td>Diastolic BP (mmHg)</td>
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*HbA1c, hemoglobin A1c; AER, albumin excretion rate.

b P < 0.05.

c P < 0.01.
ing nephropathy and those who were persistently normoalbuminuric (Table 2). There was no difference in mean HbA1 or duration of diabetes between patients with VTRD and those without in the group as a whole.

At the time of laser photococagulation in patients with evolving nephropathy, AER was 150 ×/± 1.7 µg/min. Within the group of patients with evolving nephropathy, AER was higher in patients with VTRD (149 ×/± 1.7 versus 30 ×/± 1.4 µg/min; P < 0.05). Patients with evolving nephropathy were more likely to be men (P = 0.06) and have a later age of onset of diabetes (Table 2). During the study period, AER progressed in patients with evolving nephropathy such that six progressed from normoalbuminuria to microalbuminuria, five progressed from microalbuminuria to macroalbuminuria, and two progressed from normoalbuminuria through microalbuminuria to macroalbuminuria. In association with increased AER, at the end of the study period, plasma creatinine was higher in patients with evolving nephropathy when compared with baseline values and with values of persistently normoalbuminuric patients (Tables 1 and 2).

All patients were normotensive at study entry. BP rose in patients with evolving nephropathy (Table 2). At the end of the study period, eight of 13 (62%) patients with evolving nephropathy received antihypertensive therapy with thiazides (n = 4), β-blockers (n = 2), and prazosin (n = 4). In contrast, only seven of 67 (10%) persistently normoalbuminuric patients (P < 0.001, versus patients with evolving nephropathy) required antihypertensive treatment. Drugs used included β-blockers (n = 5), thiazides (n = 3), prazosin (n = 3), and α-methyldopa (n = 1).

**Discussion**

The present study demonstrates a concordance between the development of nephropathy and vision-threatening diabetic retinopathy. This relationship applied to both CSME and proliferative retinopathy. No differences in long-term glycemic control or duration of diabetes were found between patients with evolving nephropathy and those who remained persistently normoalbuminuric, suggesting a common predisposition to the development of both nephropathy and VTRD in certain patients with type I diabetes.

Serial measurement of the AER may be useful in following the evolution of diabetic nephropathy from normoalbuminuria through microalbuminuria to macroalbuminuria (21). The stage during this process at which VTRD develops is important if microalbuminuria is to be useful as an adjunctive means of identifying patients at high risk of visual as well as renal disease. In the present study, no patient with evolving nephropathy developed VTRD before the onset of microalbuminuria. Indeed, the mean AER at the time VTRD developed was 150 µg/min, which is in the higher part of the microalbuminuric range. Thus, patients may be identified as being at high risk of VTRD by the development of incipient nephropathy (persistent microalbuminuria), reinforcing their need for vigilant follow-up.

Although the present study documents that 62% of patients with evolving nephropathy develop VTRD compared with only 7% of persistently normoalbuminuric patients, the latter group accounted for approximately four-fifths of the study group. Thus, VTRD still develops in many patients with type I diabetes without evidence of kidney disease, reflecting the multiple pathogenetic influences in the development of diabetic complications and the need for ophthalmologic surveillance in all diabetic patients.

Although the pathologic and clinical features of proliferative retinopathy and clinically significant maculopathy are very different, both may result in blindness in patients with type I and type II diabetes. Although their pathogeneses are poorly understood, recent studies have implicated the endothelial-specific mitogen vascular endothelial growth factor in the pathogenesis of retinal neovascularization in diabetes (22). In addition to its mitogenic action, vascular endothelial growth factor induces vascular hyperpermeability and may thereby also contribute to capillary exudation as occurs in diabetic maculopathy (23), providing a possible pathogenetic link be-
tween these two retinal disorders. Despite the clinical importance of maculopathy, several studies on diabetic complications classify retinopathy as either absent, nonproliferative, or proliferative (24). This procedure classifies macular disease as nonproliferative despite the far worse visual prognosis of clinically significant maculopathy compared with other nonproliferative changes such as the presence of microaneurysms. The relationship between nephropathy and macular disease in type I diabetes has been examined previously only in a small cross-sectional study (7). Among 17 patients with maculopathy in that study, six (35%) had normoalbuminuria, seven (41%) had microalbuminuria, and four (23%) had macroalbuminuria.

The association between overt nephropathy and proliferative retinopathy in type I diabetes is well described (25). However, the extent to which this relationship is dependent on a tendency for poor glycemic control in both groups is unclear. A relationship between proliferative retinopathy and microalbuminuria was first reported by Mogensen, although the long-term glycemic control in the study groups was not described (26). In a cross-sectional study of 50 patients, Barnett and colleagues reported a higher prevalence of retinopathy (nonproliferative + proliferative) in patients with type I diabetes and microalbuminuria (4). However, the microalbuminuric group also had significantly worse glycemic control as indicated by an HbA1c 1.7% higher than in the normoalbuminuric group. This may be particularly important in light of the findings of the Diabetes Control and Complications Trial, in which a similar difference in long-term glycemic control was associated with an approximate doubling of the risk of developing retinopathy and microalbuminuria (27). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) 996 younger-onset insulin-treated diabetic patients (presumably mostly with type I diabetes), both microalbuminuria and overt nephropathy were strongly associated with proliferative retinopathy (3). However, this relationship no longer persisted after controlling for other risk factors such as glycated hemoglobin. Furthermore, in the Pittsburgh Epidemiology of Diabetic Complications Study (EDC), much of the concordance between retinopathy and nephropathy was thought to be the result of common effects of glycemic control and diabetes duration (28).

In the present study, long-term glycemic control (as measured by the frequent measurement of HbA1c) and diabetes duration patients were similar in patients with progressively increasing albuminuria and those who remain persistently normoalbuminuric. The mean study duration of 11 yr suggests that glycemic control before study entry is unlikely to explain the differences in VTRD between patients with evolving nephropathy and those who remain persistently normoalbuminuric. These results are not in conflict with previous studies or with the findings of the Diabetes Control and Complications Trial, in which progression of early retinopathy was associated with glycemic exposure (29). However, once diabetic renal disease has evolved from the stage of microalbuminuria to that of overt nephropathy, intensified glycemic control may not alter the rate of disease progression (30). Similarly, in patients with advanced retinopathy and previously poor long-term glycemic control, intensified treatment may result in an initial worsening of retinopathy (31). Hence, a slow approach to improvement in glycemic control and frequent ophthalmologic review are advised (17). The present study suggests that a predisposition for the development of microvascular complications may influence the risk of developing both nephropathy and VTRD in patients with type I diabetes. Indeed, this may explain, in part, the phenomenon whereby some patients develop microvascular complications despite good glycemic control and others with very poor glycemic control are not afflicted with nephropathy or VTRD.

At the end of the study period, patients with evolving nephropathy, in addition to being more likely to develop VTRD, also had higher BP and were more likely to be receiving antihypertensive therapy than those who remained persistently normoalbuminuric. This finding is akin to that of the cross-sectional EURODIAB study, in which a relationship between BP and retinopathy was found in patients with an elevated urinary AER (32). These findings suggest that retinopathy may be included with nephropathy in its relationship with BP. Furthermore, it is possible that in addition to their renoprotective actions, angiotensin-converting enzyme inhibitors (not used in the present study) may also exert a beneficial effect on the progression of retinopathy independently of their BP-lowering action, as suggested by a study in type II diabetic patients (33).

The present study did not address the issue of the rate of development of diabetic retinopathy in general. Such a study would require assessment of retinopathy by the use of appropriately verified fundus photography. Instead, the study sought to determine whether the measurement of urinary AER may be useful in identifying patients at high risk of VTRD. Both proliferative retinopathy and clinically significant maculopathy represent well defined clinical entities that account for most of the visual morbidity in diabetes and that, fortunately, in many instances may be effectively treated with laser photocoagulation. Although the number of patients who developed VTRD in the present study is small, the number of patient-years examined in this longitudinal study is not. Moreover, the level of statistical significance ($P < 0.001$) between the number of patients with VTRD in the two study groups suggests that the likelihood of a type 1 error is small. The proportion of patients who had microalbuminuria or proliferative retinopathy at the end of the study period was similar to those described in other clinic-based reports of patients with type I diabetes (32). However, it is likely that the prevalence of both VTRD and renal disease in diabetic patients treated in a community setting would be less than that in hospital-based clinics, reflecting the likelihood of the latter to recruit and continue to care for patients with the long-term complications of diabetes. Further longitudinal community-based studies may yield additional information that assists in determining the most appropriate interval between ophthalmic assessments, based in part on their renal status.

In summary, the results of the present study suggest that patients with type I diabetes and evolving nephropathy may be at higher risk of developing VTRD and that such patients may
be identified by the development of persistent microalbuminuria.

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References