# Epidemiology of Persistent Proteinuria in Type II Diabetes Mellitus

## Population-Based Study in Rochester, Minnesota

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**Clinical risk factors for nephropathy were assessed in a population-based study of Rochester, Minnesota, residents with diabetes mellitus initially diagnosed between 1945 and 1969 (incidence cohort). The 1031 Rochester residents with non-insulin-dependent diabetes mellitus (NIDDM) were followed through their complete medical records in the community to 1 January 1982. The prevalence of persistent proteinuria was 8.2% at the diagnosis of NIDDM. Among those initially free of persistent proteinuria, the subsequent incidence was 15.3/1000 person-yr. Twenty years after the diagnosis of diabetes, the cumulative incidence of persistent proteinuria was 24.6%. A proportional hazards model identified the following risk factors for persistent proteinuria in NIDDM: elevated initial fasting blood glucose ($P < .01$); older age at onset of diabetes ($P < .01$); male gender ($P = .05$); and presence of macrovascular disease ($P = .05$), diabetic retinopathy ($P = .05$), or glycosuria ($P = .07$) at the diagnosis of diabetes. Separate analyses controlling for attained age indicated no association between duration of NIDDM and the incidence of persistent proteinuria. Stratified analysis of the two most significant risk factors (fasting blood glucose and age) indicated that hyperglycemia was a stronger risk factor for proteinuria in younger diabetic subjects, perhaps because of a competing risk of death in the elderly diabetic patient. In contrast to a recently described decreasing secular trend of proteinuria in Danish insulin-dependent diabetes mellitus patients, there was no decrease over the past 40 yr in proteinuria risk in this NIDDM incidence cohort. *Diabetes* 37:405–12, 1988**

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Diabetes accounts for ~25% of new cases of end-stage renal disease in the United States, and the proportion of new patients with diabetes-related end-stage renal disease has increased ~300% since 1973 (1). Although nephropathy in non-insulin-dependent diabetes mellitus (NIDDM) has received little attention in the medical literature, the public health significance of this problem is indicated by the fact that ~50% of diabetic individuals enrolled in end-stage renal failure programs in the United States have NIDDM (2). Furthermore, proteinuria predicts early mortality in NIDDM (3). Early identification of NIDDM patients at high risk for nephropathy is therefore important in selecting candidates for intensified treatment.

With this ultimate objective in mind, we used the unique data resources provided by the Rochester Epidemiology Project to study the natural history of renal disease in a large population-based incidence cohort of Rochester, Minnesota, residents with NIDDM initially diagnosed in the period 1945–1969 (4). In this report, we estimate the prevalence of persistent proteinuria at the time of diagnosis of diabetes and, in those initially free of the condition, the subsequent incidence of persistent proteinuria. We also examine the influence of various potential risk factors on the development of persistent proteinuria. Finally, we assess secular trends in proteinuria incidence in NIDDM to determine whether the decreasing secular trend in nephropathy in insulin-dependent diabetes (IDDM) recently reported (5) also pertains to NIDDM.

### MATERIALS AND METHODS

The population of Rochester, Minnesota, is well suited for this investigation into the natural history of diabetes mellitus because comprehensive unit medical records for the residents are available, and these records are accessible through a centralized index of diagnoses made by essentially all medical-care providers utilized by the local population. This index includes the diagnoses made among out-

patients seen in clinic and office consultations, emergency room visits, house calls, or nursing home care as well as diagnoses recorded among hospital inpatients and at death. The potential of this data system for population-based studies has been described previously (6,7).

The original medical records of the patients identified through the index were retrieved and reviewed for an initial diagnosis of diabetes in the 25-yr period 1945–1969. The diagnostic criteria used for diabetes mellitus have been reported in detail previously (4) and required fasting hyperglycemia on two determinations >120 mg/dl (Folin-Wu method) for 1945–1958 or >110 mg/dl (autoanalyzer–ferrocyanide reductase technique) for 1959–1969 on whole venous blood. An oral glucose tolerance test was generally carried out when an equivocal fasting or postprandial blood glucose determination was obtained. At Mayo Clinic, the oral glucose tolerance test was performed by administering 1 g glucose/kg body wt and determining blood glucose concentrations at 0, 1, 2, and 3 h after the loading dose. Only the 1- and 2-h values were used for interpretation of the oral glucose tolerance test, and both values had to be elevated in comparison with age-specific standards (4) to make the diagnosis of diabetes mellitus. The criteria resulted in an incidence cohort of 1135 Rochester residents newly diagnosed with diabetes between 1945 and 1969. Although the criteria used here were somewhat more generous than those proposed by the National Diabetes Data Group (8), we have shown that the differences have little practical effect on the resulting clinical spectrum of diabetes or risk of microvascular complications (9). The characterization of a specific clinical type of diabetes generally followed National Diabetes Data Group recommendations, although, as explained in detail in a separate report (10), some modifications were required in the context of a retrospective study with extant medical records. The risk-factor analyses described pertain only to the patients with NIDDM ($n$ = 1031). IDDM ($n$ = 75) and secondary diabetes ($n$ = 29) incidence cases were excluded due to small numbers and consequent inadequate statistical power.

The fasting blood glucose value used herein was the first that met the diagnostic criteria for each patient. We used the method recommended by West et al. (11) for standardization of blood glucose values measured by the Folin-Wu and autoanalyzer–ferrocyanide reductase techniques to the glucose oxidase method, which has been employed at Mayo Clinic since 1972, and all values were expressed in terms of the latter. Relative weight at the diagnosis of diabetes was calculated with recommended height-weight tables (8). Therapeutic regimens were classified as insulin (with or without other therapy), oral agent (with or without diet but without insulin), or diet alone (no insulin or oral agents) as of the time of dismissal after the initial diagnosis and work-up. Diabetic complications were classified at the time of diagnosis of diabetes as a history of macrovascular disease (angina pectoris, myocardial infarction, stroke, transient ischemic attack, or peripheral vascular disease) or microvascular disease other than persistent proteinuria (diabetic retinopathy). The determination of glycosuria was based on the detection of glucose in a urine sample at the diagnosis of diabetes. A diagnosis of hypertension was made if the subject had two consecutive blood pressure readings >160/95 mmHg or was on antihypertensive drug therapy at the diagnosis of diabetes. Patients were also classified as "ever smokers" or "never smokers" as of the date of diagnosis of diabetes.

TABLE 1
Clinical characteristics of Rochester, Minnesota, residents with and without persistent proteinuria at time of diagnosis of NIDDM, 1945–1969

| | Persistent proteinuria at diagnosis ($n$ = 85) | | No persistent proteinuria at diagnosis ($n$ = 946) | |
|---|---|---|---|---|
| Characteristic | % | $n$ | % | $n$ |
| Sex | | | | |
| Men | 66 | 56 | 48 | 455 |
| Age (yr) | | | | |
| <30 | 2 | 2 | 3 | 24 |
| 30–49 | 6 | 5 | 19 | 178 |
| 50–59 | 26 | 22 | 25 | 234 |
| 60–69 | 26 | 22 | 28 | 269 |
| ≥70 | 40 | 34 | 25 | 241 |
| Fasting blood glucose (mg/dl) | | | | |
| ≥300 | 8 | 7 | 8 | 80 |
| 200–299 | 16 | 14 | 26 | 250 |
| <200 | 75 | 64 | 65 | 616 |
| Glycosuria | | | | |
| Yes | 72 | 61 | 79 | 748 |
| Relative weight | | | | |
| <1.00 | 12 | 10 | 8 | 80 |
| 1.00–1.19 | 31 | 26 | 28 | 262 |
| 1.20–1.39 | 24 | 20 | 34 | 323 |
| ≥1.40 | 34 | 29 | 30 | 281 |
| Macrovascular disease | | | | |
| Yes | 47 | 40 | 24 | 227 |
| Diabetic retinopathy | | | | |
| Yes | 1 | 1 | 3 | 26 |
| Hypertension | | | | |
| Yes | 66 | 56 | 44 | 413 |
| Smoking | | | | |
| Ever | 33 | 28 | 29 | 278 |
| Initial therapy | | | | |
| Insulin | 9 | 8 | 15 | 141 |
| Oral agents | 14 | 12 | 14 | 132 |
| Diet alone | 76 | 65 | 71 | 673 |

Each of the 1031 NIDDM incidence cases was followed for proteinuria through linked medical records until death, emigration from the community, or 1 January 1982. A diagnosis of persistent proteinuria was based on two consecutive random urine samples with at least grade 1 (40 mg/dl) protein that persisted until last follow-up. The diagnostic urine samples were generally morning specimens obtained during the course of routine medical care. The Mayo Clinic and its associated hospitals have used the sulfosalicylic acid method since 1940 to quantify urine protein. The institutional grading of urine protein concentration did not change during this time period. The prevalence of persistent proteinuria at the time initial diagnosis of diabetes mellitus was calculated as the proportion of patients whose persistent proteinuria was diagnosed before or within 6 mo after the diagnosis of diabetes. For those free of proteinuria at the diagnosis of diabetes, persistent proteinuria incidence density was determined with person-years analysis (12). The cumulative

TABLE 2
Incidence of persistent proteinuria by clinical characteristics of Rochester, Minnesota, residents at time of diagnosis of NIDDM, 1945–1969, followed for persistent proteinuria to 1982

| Characteristic | Persistent proteinuria | |
|---|---|---|
| | *n** | Rate† |
| Sex | | |
| Men | 83 | 16.5 |
| Women | 81 | 14.3 |
| Age (yr) | | |
| <30 | 1 | 2.6 |
| 30–49 | 23 | 8.0 |
| 50–59 | 55 | 18.3 |
| 60–69 | 45 | 16.0 |
| ≥70 | 40 | 24.6 |
| Fasting blood glucose (mg/dl) | | |
| ≥300 | 26 | 39.0 |
| 200–299 | 45 | 17.1 |
| <200 | 93 | 12.6 |
| Glycosuria | | |
| Yes | 138 | 16.5 |
| No | 26 | 11.2 |
| Relative weight | | |
| <1.00 | 14 | 20.9 |
| 1.00–1.19 | 38 | 13.2 |
| 1.20–1.39 | 52 | 13.8 |
| ≥1.40 | 60 | 17.8 |
| Macrovascular disease | | |
| Yes | 40 | 26.8 |
| No | 124 | 13.5 |
| Diabetic retinopathy | | |
| Yes | 8 | 36.3 |
| No | 156 | 14.9 |
| Hypertension | | |
| Yes | 71 | 17.8 |
| No | 93 | 13.9 |
| Smoking | | |
| Ever | 48 | 13.7 |
| Never | 116 | 16.1 |
| Initial therapy | | |
| Insulin | 35 | 24.3 |
| Oral agents | 16 | 13.5 |
| Diet alone | 113 | 14.0 |

*No. of cases of persistent proteinuria.
†Incidence density (per 1000 person-yr).

incidence of persistent proteinuria was estimated using the Kaplan-Meier product limit method (13). The statistical significance of differences in incidence rates and cumulative incidence was assessed with the method of Fleiss (14) and with the Armitage test for linear trend (15). The relative influence of various clinical characteristics on the risk of subsequent persistent proteinuria was evaluated with proportional hazards models (16,17). To assess the competing risk of death in patients with hyperglycemia, we examined Kaplan-Meier survival curves for patients at varying levels of age and glycemia.

## RESULTS

**Clinical characteristics at diagnosis of diabetes.** Clinical characteristics at the time of initial diagnosis of NIDDM are shown in Table 1. Only 85 of 1031 (8.2%) NIDDM patients had persistent proteinuria diagnosed before or within 6 mo after their initial diagnosis of diabetes. Although this low prevalence precludes a rigorous comparison, NIDDM patients with persistent proteinuria at the diagnosis of diabetes were more likely to be male, older, and hypertensive and were more likely to have macrovascular complications.

**Univariable analyses.** Among those free of persistent proteinuria at the diagnosis of NIDDM, the subsequent incidence was 15.3/1000 person-yr. To determine the influence of the various factors on the risk of subsequent persistent proteinuria, we first evaluated each characteristic by itself. The incidence of subsequent persistent proteinuria in each clinical group is shown in Table 2. Factors associated with a statistically significant increased risk ($P < .05$) of persistent proteinuria among patients with NIDDM who were free of persistent proteinuria at diagnosis ($n = 946$) were as follows: male gender, older age at diagnosis of diabetes mellitus, higher fasting blood glucose level at diagnosis, glycosuria, macrovascular disease, diabetic retinopathy, hypertension, and initial insulin therapy. The cumulative incidence of per-

TABLE 3
Cumulative incidence of persistent proteinuria at various times of follow-up by clinical characteristics of Rochester, Minnesota, residents at time of diagnosis of NIDDM, 1945–1969, followed for persistent proteinuria to 1982

| Characteristic | Cumulative incidence of persistent proteinuria (%) | | | |
|---|---|---|---|---|
| | Duration of diabetes (yr) | | | |
| | 5 | 10 | 15 | 20 |
| Sex | | | | |
| Men | 7.5 | 12.6 | 21.8 | 26.5 |
| Women | 8.5 | 14.1 | 18.6 | 23.0 |
| Age (yr) | | | | |
| <30 | 4.2 | 4.2 | 4.2 | |
| 30–49 | 4.0 | 8.2 | 11.3 | 12.3 |
| 50–59 | 8.9 | 12.4 | 21.3 | 31.9 |
| 60–69 | 6.4 | 13.7 | 23.7 | 25.1 |
| ≥70 | 13.1 | 21.9 | 26.8 | 32.7 |
| Fasting blood glucose (mg/dl) | | | | |
| ≥300 | 20.0 | 27.8 | 37.4 | |
| 200–299 | 9.9 | 16.3 | 21.8 | 24.4 |
| ≤199 | 5.2 | 10.6 | 17.4 | 20.8 |
| Glycosuria | | | | |
| Yes | 8.7 | 14.3 | 21.0 | 26.3 |
| No | 4.2 | 10.1 | 16.8 | 18.4 |
| Relative weight | | | | |
| <1.00 | 14.9 | 16.9 | 25.3 | |
| 1.00–1.19 | 5.8 | 10.2 | 18.9 | 21.0 |
| 1.20–1.39 | 8.2 | 13.6 | 17.9 | 21.7 |
| ≥1.40 | 7.9 | 14.9 | 22.1 | 29.1 |
| Macrovascular disease | | | | |
| Yes | 15.7 | 22.9 | 28.5 | |
| No | 6.0 | 11.2 | 18.0 | 23.0 |
| Diabetic retinopathy | | | | |
| Yes | 27.9 | 34.4 | | |
| No | 7.5 | 12.9 | 19.5 | 24.2 |
| Hypertension | | | | |
| Yes | 7.0 | 15.8 | 21.9 | 27.5 |
| No | 8.7 | 12.1 | 19.1 | 23.1 |
| Smoking | | | | |
| Ever | 6.4 | 10.5 | 19.5 | 22.2 |
| Never | 8.7 | 14.7 | 20.2 | 25.8 |
| Initial therapy | | | | |
| Insulin | 17.6 | 24.6 | 29.0 | 34.3 |
| Oral agents | 8.1 | 13.0 | 19.0 | |
| Diet alone | 6.1 | 11.3 | 18.5 | 23.8 |

Where no data are reported, there were <10 patients remaining under follow-up.

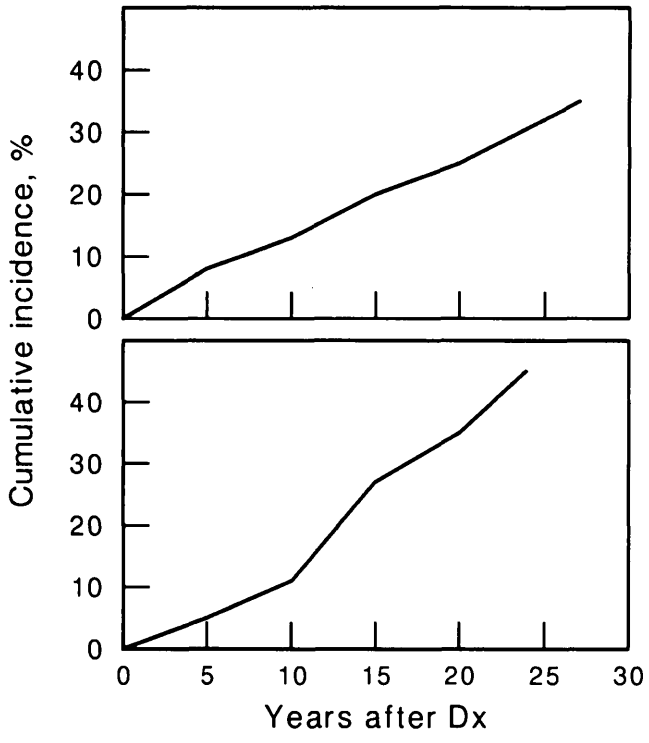


**FIG. 1. *Top*: cumulative incidence (%) of persistent proteinuria among residents of Rochester, Minnesota, with NIDDM diagnosed from 1945 to 1969 and followed for proteinuria to 1982 (all curves terminate before $n < 10$). *Bottom*: cumulative incidence (%) of persistent proteinuria among residents of Rochester, Minnesota, with IDDM diagnosed from 1945 to 1969 and followed for proteinuria to 1982 (all curves terminate before $n < 10$). Dx, diagnosis.**

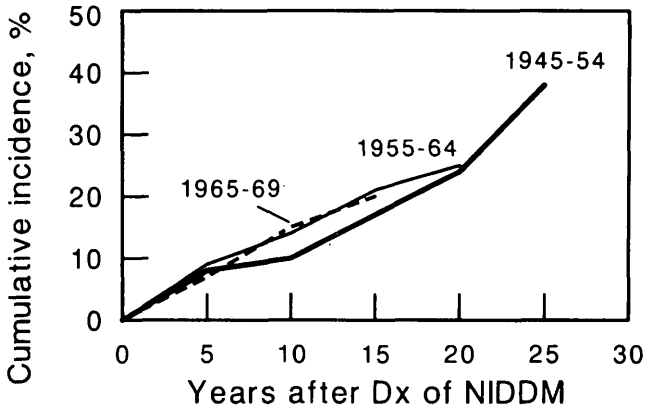


**FIG. 2. Cumulative incidence (%) of persistent proteinuria by year of diagnosis (Dx) of NIDDM for residents of Rochester, Minnesota, with NIDDM diagnosed from 1945 to 1969 and followed to 1982 for proteinuria (all curves terminate before $n < 10$).**

sistent proteinuria among patients with various characteristics reflected the findings described above (Table 3).

The overall cumulative incidence of persistent proteinuria by duration of NIDDM is shown in Fig. 1 (*top*). The decreasing slope of the cumulative incidence curve indicates that the incidence of proteinuria decreased with duration of diabetes. We therefore assessed the duration data in the context of aging by evaluating proteinuria incidence density by age group and years of follow-up, where the effect of duration was taken into account (Table 4). The incidence of persistent proteinuria increased with age ($P < .01$, Armitage test for linear trend) and was not associated with duration of diabetes ($P > .20$). In contrast, the incidence of proteinuria increased with duration in IDDM (Fig. 1, *bottom*), although this finding must be interpreted with caution given the few IDDM patients free of proteinuria at diagnosis ($n = 72$).

The secular trend in the incidence of persistent proteinuria was examined univariably in Fig. 2. There is no evidence of a relationship between the incidence of proteinuria and year of diagnosis of NIDDM in Rochester residents.

**Multivariable analyses.** Because the univariable relationships described above may have been confounded or modified by other study variables, a multivariable proportional hazards analysis was used to identify factors at the time of diagnosis of diabetes that might be independently predictive of the development of subsequent persistent proteinuria (16). In addition to presentation of the univariable and full multivariable models, the most parsimonious multivariable model [based on consideration of validity (12), precision (12), and the model $R$ statistic (17)] is shown in Table 5. The proportional hazards model identified male gender, older age at diagnosis of diabetes, elevated fasting blood glucose level, glycosuria, macrovascular disease, and diabetic retinopathy as important independent risk factors for the development of persistent proteinuria among patients with NIDDM. Although age and level of hyperglycemia at the time of diagnosis of diabetes seemed to be the most important

TABLE 4
Incidence of persistent proteinuria by age at diagnosis of persistent proteinuria and duration of diabetes for Rochester, Minnesota, residents with NIDDM, 1945–1969, followed for persistent proteinuria to 1982

| Follow-up period (yr) | Age group (yr) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 | | 30–49 | | 50–59 | | 60–69 | | 70+ | | Total | |
| | Rate* | Person-yr† | Rate | Person-yr | Rate | Person-yr | Rate | Person-yr | Rate | Person-yr | Rate | Person-yr |
| 0–4 | 10.7 | 94 | 9.8 | 714 | 13.9 | 938 | 18.1 | 1160 | 25.0 | 1080 | 17.3 | 3985 |
| 5–9 | 0 | 49 | 2.4 | 424 | 12.8 | 626 | 10.0 | 904 | 17.0 | 1117 | 11.9 | 3120 |
| 10–14 | 0 | 18 | 0 | 219 | 5.3 | 380 | 24.4 | 573 | 19.3 | 934 | 16.0 | 2124 |
| 15–19 | 0 | 0 | 0 | 67 | 6.5 | 154 | 19.1 | 262 | 14.6 | 547 | 13.6 | 1029 |
| 20+ | 0 | 0 | 0 | 12 | 0 | 59 | 35.5 | 113 | 24.5 | 245 | 23.3 | 429 |
| Total | 6.2 | 161 | 5.6 | 1436 | 11.1 | 2157 | 17.6 | 3012 | 19.9 | 3923 | 15.3 | 10,687 |

*Incidence density (per 1000 person-yr).
†Person-years of observation.

TABLE 5
Proportional hazards models for development of persistent proteinuria by clinical characteristics of Rochester, Minnesota, residents at time of diagnosis of NIDDM, 1945–1969, followed for persistent proteinuria to 1982

| | Univariable | | Full multivariable | | Reduced multivariable | | |
|---|---|---|---|---|---|---|---|
| Clinical characteristics | Coefficient | *P* | Coefficient | *P* | Coefficient | *P* | $\chi^2$ |
| Sex* | .1418 | .36 | .3201 | .08 | .3073 | .05 | 3.73 |
| Age (yr) | .0293 | <.01 | .0278 | <.01 | .0255 | <.01 | 13.11 |
| Fasting blood glucose (mg/dl) | .0045 | <.01 | .0042 | <.01 | .0040 | <.01 | 31.53 |
| Glycosuria† | .3806 | .08 | .3726 | .08 | .3853 | .07 | 3.22 |
| Relative wt‡ | .0606 | .48 | .1105 | .24 | | | |
| Macrovascular disease† | .6688 | <.01 | .3885 | .05 | .3924 | .05 | 3.86 |
| Diabetic retinopathy† | .8654 | .02 | .6888 | .06 | .7112 | .05 | 3.82 |
| Hypertension† | .2486 | .12 | .0186 | .92 | | | |
| Smoking† | −.1578 | .36 | .1141 | .54 | | | |
| Time since diagnosis of diabetes (yr) | −.0058 | .66 | .0129 | .35 | | | |
| Initial therapy§ | .5391 | .01 | .2895 | .22 | | | |

*0 = female, 1 = male; †0 = no, 1 = yes; ‡0 = <1.00, 1 = 1.00–1.19, 2 = 1.20–1.39, 3 = ≥1.40; §0 = diet on oral agents, 1 = insulin.

risk factors for the development of persistent proteinuria, stratified modeling indicated that the importance of hyperglycemia as a risk factor varied with age. We therefore dichotomized age (<60 and ≥60 yr) and constructed Kaplan-Meier survival curves for survival free of proteinuria for those <60 and ≥60 at the three tertiles of glycemia (Fig. 3). In patients <60 yr, those with higher initial levels of glycemia were at higher risk for the development of persistent proteinuria (Fig. 3, *top*). In patients ≥60 yr, however, higher initial levels of glycemia did not correlate as strongly with an increased risk of proteinuria (Fig. 3, *bottom*). This may have resulted from differential survival in younger and older patients with hyperglycemia, because higher initial levels of glycemia were more strongly associated with decreased survival in patients ≥60 yr of age than in those <60 yr of age at NIDDM diagnosis (Fig. 4).

## DISCUSSION

At the time of diagnosis of NIDDM, ~10% of Rochester, Minnesota, residents had persistent proteinuria (prevalence cases). Although there are few studies of urinary protein

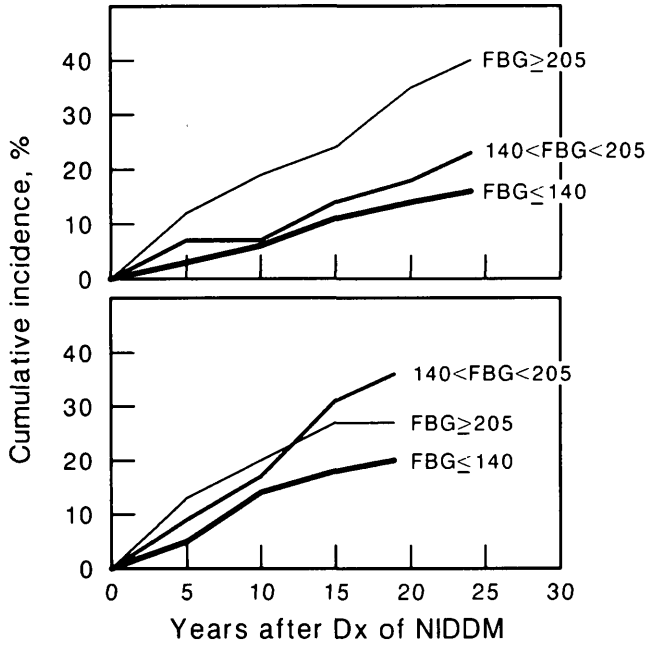


**FIG. 3. *Top*: cumulative incidence (%) of persistent proteinuria by level of initial fasting blood glucose (FBG) for Rochester, Minnesota, residents <60 yr of age with NIDDM diagnosed from 1945 to 1969 and followed for proteinuria to 1982 (all curves terminate before $n < 10$). *Bottom*: cumulative incidence (%) of persistent proteinuria by level of initial FBG for Rochester, Minnesota, residents ≥60 yr of age at diagnosis of NIDDM from 1945 to 1969 and followed for proteinuria to 1982 (all curves terminate before $n < 10$). Dx, diagnosis.**

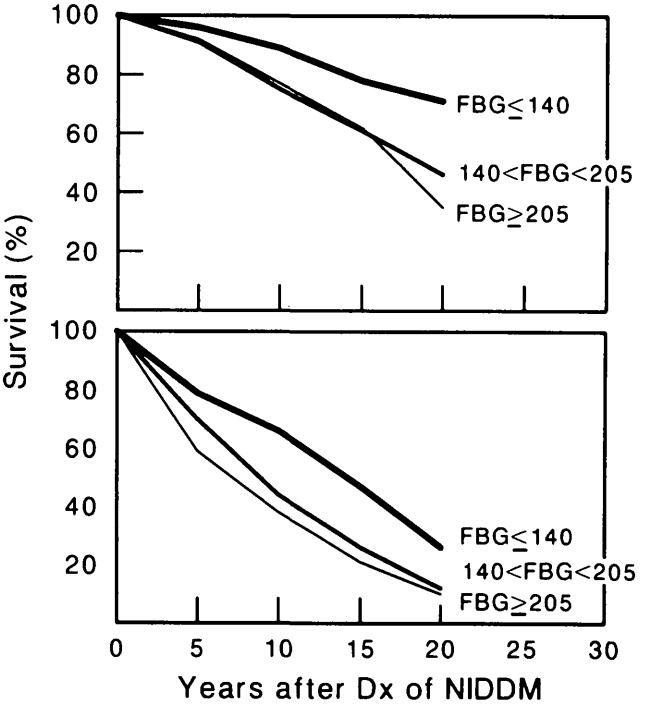


**FIG. 4 *Top*: survival after diagnosis (Dx) of NIDDM by initial fasting blood glucose (FBG) for residents of Rochester, Minnesota, <60 yr of age at diagnosis of NIDDM from 1945 to 1969 and followed for death to 1982 (all curves terminate before $n < 10$). *Bottom*: survival after diagnosis of NIDDM by initial FBG for residents of Rochester, Minnesota, ≥60 yr of age at diagnosis of NIDDM from 1945 to 1969 and followed for death to 1982 (all curves terminate before $n < 10$).**

excretion in NIDDM at the time of diagnosis, Mogensen and others (18,19) have shown that newly diagnosed NIDDM patients with controlled blood glucose have abnormal exercise-induced proteinuria. This observation suggests that impaired glomerular permeability is present at the time of NIDDM diagnosis. In nondiabetic populations the prevalence of proteinuria is variable, ranging from 2 to 15% (20,21). We were unable to estimate the proportion of proteinuria due to diabetes, because proteinuria prevalence data are not available for the general population of Rochester.

However, most patients were free of proteinuria at the time of diagnosis of NIDDM. In this group, 25% developed persistent proteinuria by 20 yr of diabetes. There have been few comparative studies of diabetic nephropathy in NIDDM patients. Pirart (22), in a study of diabetic patients from several Brussels referral hospitals and clinics, found the prevalence of nephropathy, as defined by proteinuria, to be ~15% at 25 yr. It is not possible to specifically determine the cumulative incidence of proteinuria at different time intervals from the Brussels data. However, the relatively low proteinuria prevalence reported by Pirart may be due to the use of different methods for measuring urinary protein excretion or to the younger age of patients in the Brussels referral cohort. It is unlikely that we have overestimated the incidence of persistent proteinuria, because *1*) urine and blood glucose values obtained during hospitalizations were excluded, and *2*) the study design required two consecutive urinalyses with grade 1 proteinuria in addition to the persistence of proteinuria in the final urinalysis in the medical record. Our secular trend assessment of proteinuria risk is unlikely to have been distorted by measurement bias, because the Mayo Clinic used the same method for measuring and grading proteinuria over the 40-yr duration of the study.

This study identified age as a major risk factor for the development of persistent proteinuria, but the effect of age, independent of diabetes, on the incidence of persistent proteinuria has not been well defined. Although renal anatomic and physiologic changes occur with aging (23), permeability changes have been less clearly identified, and little information is available on protein excretion in the elderly. The importance ascribed to age in this study may thus reflect, in part, a higher frequency of proteinuria in older patients from causes other than diabetes. Nonetheless, the development of persistent proteinuria in NIDDM appears to be more strongly associated with aging than with the duration of diabetes. This is in contrast to findings in IDDM for our Rochester cohort and in other studies where proteinuria incidence increases with disease duration for at least two to three decades (24). Prior prevalence studies of NIDDM and proteinuria have also found the prevalence of proteinuria to increase with duration of diabetes (25,26). Because it has been shown that diabetic prevalence patients are more likely to have microvascular complications than are incidence cases (27), it is likely that this disparity reflects differences in prevalence and incidence data, which result in selection biases such as Neyman bias (28,29). Because asymptomatic glucose intolerance may precede the development of symptomatic NIDDM by several years (30), it is also possible that imprecision in the estimation of data of onset of NIDDM may obscure the relationship between duration of NIDDM and proteinuria incidence. Although we do not have data regarding the time interval from the last prior normal blood glucose to the date of NIDDM diagnosis by our study criteria, the median duration of community medical record before NIDDM diagnosis is >30 yr. Therefore, we are confident that we have identified the earliest point in the routine clinical care of Rochester residents when glycemic diagnostic criteria were fulfilled for NIDDM.

Initial degree of hyperglycemia was also identified as a major risk factor for the development of persistent proteinuria. Consistent with this finding was the increased risk associated with glycosuria. The relationship between hyperglycemia and proteinuria has been described in other studies (11,25,26). A significant correlation between the initial level of hyperglycemia and subsequent proteinuria was found in the Pima Indian diabetic population (31), and a similar relationship has recently been reported for retinopathy in Rochester NIDDM subjects (32). However, the importance of hyperglycemia as a risk for the development of proteinuria varied with age. Individuals <60 yr of age at NIDDM diagnosis who had higher initial levels of glycemia were at greater risk for developing persistent proteinuria. For individuals ≥60 yr of age at NIDDM diagnosis, higher levels of initial glycemia were less predictive of the development of persistent proteinuria due to the competing risk of death in the hyperglycemic elderly group.

Male gender was found to be a moderately important predictor of proteinuria in NIDDM. A recent report of proteinuria in IDDM also found an increased incidence in men (5). Prior prevalence studies of proteinuria in NIDDM have not found a significant association with male gender (11,25). However, such prevalence data are misleading, because they are restricted to examination of previously diagnosed diabetic individuals who have survived to a given point in time, and proteinuria is a powerful predictor of survival (3). It is of interest that a study of streptozocin-induced diabetic glomerulopathy in rats suggests that sex steroids may play a role in the pathogenesis of diabetic complications (33). Additionally, renal failure is more common in nondiabetic men than women (1,34).

Although the number of patients with retinopathy present at the diagnosis of diabetes was small, this study nonetheless identified diabetic retinopathy as an important predictor of subsequent proteinuria. Many other studies also have shown a strong relationship between these two microvascular complications (22,35), although diabetic retinopathy has not been previously assessed as a specific risk factor for proteinuria in NIDDM. The presence of retinopathy at the time of diagnosis of NIDDM suggests that such individuals have had subclinical disease for a significant length of time before the diagnosis of diabetes or that they may have a special susceptibility to microvascular complications. We have previously identified hyperglycemia at the time of NIDDM diagnosis as a risk factor for retinopathy. However, other risk factors for retinopathy, including disease duration, obesity, and <60 yr age at time of diagnosis (32), were not identified as risk factors for proteinuria.

The presence of hypertension at the time of diagnosis of NIDDM was not a significant risk factor for the development of proteinuria in this Rochester incidence cohort. We also had similar results for the relationship between hypertension

and proteinuria risk when blood pressure was examined as a continuous variable (systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure). Other studies have shown an association between hypertension and proteinuria (36) but have not identified hypertension at the diagnosis of diabetes as a major risk factor for subsequent proteinuria. Examination of this relationship is difficult, however, because hypertension can cause proteinuria and renal insufficiency; because hypertension is a feature of progressive diabetic nephropathy as well as other forms of renal disease; and because blood pressure, particularly systolic blood pressure, increases with age. Thus, assessment of a possible causal relationship between hypertension and the development of proteinuria in NIDDM is complex. There is, however, evidence that protein excretion in diabetic subjects correlates with blood pressure (36), and intervention studies have clearly shown that treatment of hypertension in diabetic subjects decreases the amount of protein excretion (37) and slows the rate of renal impairment (37,38). Therefore, effective treatment of patients with hypertension after the diagnosis of diabetes may explain the absence of a relationship between hypertension and subsequent proteinuria in this study. Forty-two of the 81 incidence cases with hypertension were on antihypertensive drug therapy at the diagnosis of diabetes, whereas 75 of the 117 hypertensive subjects at last follow-up were on antihypertensive drug therapy. Also, diabetic patients with hypertension have a higher risk of death from ischemic heart disease and thus are selected out of the NIDDM population at risk for proteinuria (39).

The risk of persistent proteinuria did not decline over the period studied in this 1945–1969 Rochester NIDDM incidence cohort, in contrast to the recently reported decline in the incidence of persistent proteinuria in IDDM over a similar interval (5). Although the Danish study did not specifically identify causes for the declining incidence of persistent proteinuria in IDDM, the authors speculated that improvement in the management of IDDM may have been responsible. Although the Rochester NIDDM data do not indicate a reduction in the incidence of persistent proteinuria, this does not necessarily imply less progress in the management of NIDDM. Retinopathy risk, for example, has declined in this same NIDDM cohort (32). A more likely explanation is that proteinuria is a less specific finding in NIDDM than it is in IDDM, and that factors independent of diabetes, e.g., comorbidity and aging, are relatively more important risk factors for proteinuria. Additionally, a decline in cardiovascular mortality (40), the primary cause of death in NIDDM patients (39), may have resulted in survival of more patients into the older age groups at greater risk for proteinuria.

We have shown that older age and level of hyperglycemia at the time of diagnosis of NIDDM are the most important of the measured risk factors for the development of persistent proteinuria. Other important risk factors were male gender, glycosuria, diabetic retinopathy, and macrovascular disease. However, the utility of these data is still uncertain, because the relationship of persistent proteinuria to renal insufficiency and/or failure has not been established in NIDDM, although studies have shown that proteinuria is a powerful predictor of survival in diabetic (3) and nondiabetic subjects (41). We are currently investigating the relationship between persistent proteinuria and end-stage renal disease in the Rochester NIDDM cohort. Identification of risk factors for persistent proteinuria and elucidation of the relationship between proteinuria and end-stage renal disease in NIDDM will be applied clinically to select patients at higher risk of morbidity and mortality, in whom it may be possible to intensify treatment and modify risk factors. Clinical trials will be required to determine whether modification of proteinuria risk factors actually decreases the risk of proteinuria in NIDDM and whether such interventions have any influence on survivorship or the risk of end-stage renal disease in NIDDM.

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