The Risk of Cardiovascular Disease Mortality Associated With Microalbuminuria and Gross Proteinuria in Persons With Older-Onset Diabetes Mellitus

Charles T. Valmadrid, MD, MPH; Ronald Klein, MD, MPH; Scot E. Moss, MA; Barbara E. K. Klein, MD, MPH

Background: Despite the numerous studies on the relation of albuminuria with increased risk of all-cause mortality in type 2 diabetes mellitus, it remains uncertain whether microalbuminuria and/or gross proteinuria are independent risk factors for cardiovascular mortality. Moreover, the association of albuminuria with cardiovascular mortality in people with type 2 diabetes mellitus has not been well described in US populations.

Objective: To estimate the relative risks (RRs) for the associations of microalbuminuria and gross proteinuria with cardiovascular disease mortality among persons with older-onset diabetes mellitus.

Methods: We conducted a prospective cohort study of 840 people with older-onset diabetes mellitus who provided urine samples in the 1984-1986 examination of a population-based study of diabetic persons. The presence of microalbuminuria was determined by an agglutination inhibition assay and gross proteinuria by a reagent strip. The main outcome was time to mortality from cardiovascular disease, as determined from death certificates.

Results: Of the 840 older-onset diabetic persons, 54.8% had normoalbuminuria, while 24.8% had microalbuminuria and 20.5% had gross proteinuria. During the 12-year follow-up (6127 person-years), we identified 364 deaths from cardiovascular disease. Compared with persons with normoalbuminuria, those with microalbuminuria and gross proteinuria had significantly higher risks of cardiovascular mortality. The RR as controlled for age, sex, glycemic control, insulin use, alcohol intake, physical activity, cardiovascular disease history, antihypertensive use, and retinopathy severity, was 1.84 (95% confidence interval [CI], 1.42-2.40) for those with microalbuminuria and 2.61 (95% CI, 1.99-3.43) for those with gross proteinuria. Further adjustment for other factors did not change the relations we found. When the end point used was mortality from coronary heart disease, stroke, or all causes, the increased risks were significant for both microalbuminuria (adjusted RRs [95% CIs], 1.96 [1.42-2.72], 2.20 [1.29-3.75], and 1.68 [1.35-2.09], respectively) and gross proteinuria (adjusted RRs [95% CIs], 2.73 [1.95-3.81], 2.33 [1.28-4.24], and 2.47 [1.97-3.10], respectively).

Conclusions: Results from our population-based study strongly suggest that both microalbuminuria and gross proteinuria were significantly associated with subsequent mortality from all causes and from cardiovascular, cerebrovascular, and coronary heart diseases. These associations were independent of known cardiovascular risk factors and diabetes-related variables.

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CARDIOVASCULAR DISEASE is the leading cause of death among individuals with type 2 diabetes mellitus.¹ Many follow-up studies involving patients with type 2 diabetes mellitus have demonstrated the relation of both microalbuminuria²-¹⁹ and clinical proteinuria²⁰-²⁸ with increased risk of mortality, which is largely due to cardiovascular diseases. However, some of these studies had a small number of participants or short follow-up periods. Whether their effects on cardiovascular mortality were independent of known cardiovascular risk factors and other variables related to diabetes¹⁵,¹⁶,¹⁹,²⁰,³⁰ or evident only in the earlier periods of follow-up as suggested by previous studies on total mortality,¹⁸,¹⁹ remains in question. Moreover, the excess risk of cardiovascular mortality associated with microalbuminuria or gross proteinuria in people with type 2 diabetes mellitus has not been well described, especially in US populations.

The large cohort of persons with older-onset diabetes mellitus in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) offers the opportunity to investigate the role of proteinuria in cardiovascular disease mortality in a US population. The aims of the present

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SUBJECTS AND METHODS

STUDY SAMPLE AND PROCEDURES

The WESDR has been described in detail in earlier articles. Participants in this population-based study of diabetic persons were selected from an 11-county area in southern Wisconsin. Lists of all diabetic patients cared for from July 1, 1979, to June 30, 1980, were obtained from 452 of 457 primary care physicians practicing in the area. Eligibility criteria were determined from a systematic chart review, of which a representative sample of 2990 people was chosen for the baseline examination from 1980 to 1982. This included all 1210 patients with type 1 diabetes mellitus who were taking insulin (diagnosed before the age of 30 years) and a probability sample of 1780 persons with older-onset diabetes mellitus (diagnosed at 30 years of age or later). Follow-up interviews and/or examinations were done in 1984-1986, 1990-1992, and 1995-1996. The subject of these analyses was the older-onset group, of which 1370 participated in the baseline examination. Of these, 1.5% refused to participate in the 1984-1986 follow-up examination, and 0.4% were lost to follow-up, 1.2% had an interview only, and 24.8% of the original cohort had died. The analyses in this report were on the remaining 987 persons who returned for the follow-up examination done in 1984-1986, when information on microalbuminuria was first obtained.

Pertinent parts of the 1984-1986 examination consisted of standardized methods for measuring height, weight, and blood pressure; dilating the pupils and taking stereoscopic color fundus photographs of 7 standard fields for determining the presence and severity of diabetic retinopathy; and taking blood samples for standardized measurements of glycosylated hemoglobin, serum creatinine, and plasma C peptide for the whole cohort and total serum cholesterol and high-density lipoprotein cholesterol (HDL-C) for a subset of the cohort. The glycosylated hemoglobin A1c microcolumn results of the WESDR were related to the Diabetes Control and Complications Trial (DCCT) glycosylated hemoglobin A1c values, by the following equation: DCCT = 0.003 + 0.935 \times WESDR. Serum creatinine was measured by the modified Jaffe reaction using a centrifugal analyzer (Cobas FARA; Roche Diagnostics System, Division of Hoffmann-LaRoche, Nutley, NJ) and standard reagents (Boehringer Mannheim Diagnostics, Indianapolis, Ind). The imprecision of the creatinine assay was determined as 2.73% (SD, ±0.03%) and 1.45% (SD, ±0.09%) on the basis of repeated (\( n = 140 \)) measurement controls, with values of 97 \( \mu \)mol/L (1.1 mg/dL) and 546 \( \mu \)mol/L (6.2 mg/dL), respectively. The method was determined to be linear to more than 1760 \( \mu \)mol/L (20.0 mg/dL). Single-voided, casual, fresh urine samples were collected for the determination of microalbuminuria and gross proteinuria. Microalbuminuria was defined as having urinary albumin concentrations of at least 0.03 g/L using an agglutination inhibition assay (AlbuScreen; Cambridge Life Sciences, Cambridge, England); and gross proteinuria was defined as having urinary protein concentrations of at least 0.3 g/L using a reagent strip (Labstix; Ames Division, Miles Inc, Elkhart, Ind). A structured interview was administered for questions on smoking, physical activity, and intake of alcohol, aspirin, digoxin, nitroglycerin, and medications for the control of blood glucose and blood pressure. Any questions regarding medication use were verified by a physician’s report. All procedures were performed in a mobile van in or near the city in which the participants lived or, if not possible, in other settings, such as a clinic, hospital, nursing home, or home. The study was approved by the Human Subjects Committee of the University of Wisconsin, Madison.

ASCERTAINMENT OF DEATHS FROM CARDIOVASCULAR DISEASES

Mortality from cardiovascular disease was ascertained from ongoing mortality surveillance of the WESDR cohort, which consisted of reviews of daily newspaper obituaries and regular contact with study participants and their relatives, designated contact persons, or physicians. Deaths were confirmed with death certificate data from annual requests made to the Wisconsin Center for Health Statistics, Section of Vital Statistics. For this study, state mortality records through 1996 have been searched. The names of persons who had moved out of Wisconsin and those who had been lost to follow-up or were suspected to have died were submitted for matching against Wisconsin death records and the National Death Index. For each match made, a copy of the death certificate was secured from the appropriate state. Only deaths that had been confirmed by death certificates were included in the definition of cardiovascular mortality. Persons who were thought to be deceased but for whom a death certificate could not be obtained were considered to be alive as of the last contact date they were known to be alive. Death certificates were collected and coded by trained nosologists using the International Classification of Diseases, Ninth Revision (ICD-9). Deaths were classified as due to cardiovascular disease when hypertensive heart disease, ischemic heart disease, heart failure, and/or cerebrovascular disease (ICD-9 codes 402, 404, 410-414, 428, 430-438) were mentioned as the underlying or contributory cause of death listed on the death certificates. Our preliminary analysis involving deaths due to cardiovascular disease as the “underlying cause” of death showed results similar to those based on “any mention” of cardiovascular disease as a cause of death on the death certificates, as was shown by others who conducted studies with general populations. Because of this and the advantage of having a higher number of events over those based solely on the underlying cause of death, this article presents the findings using any mention of cardiovascular disease as the end point.

RESULTS

Of the 987 participants in the 1984-1986 examination, 9 individuals had undergone dialysis and 138 individuals had missing information on microalbuminuria and/or gross proteinuria, leaving 840 participants in...
DATA ANALYSIS

Participants were grouped into the following proteinuria categories based on their urinary test results: normoalbuminuria (persons with negative test results for both microalbuminuria and gross proteinuria), microalbuminuria (those testing negative for gross proteinuria but testing positive for microalbuminuria), and gross proteinuria.

After examining the frequency distribution of all variables, the associations between the proteinuria groups and possible confounding variables were assessed by χ² analysis and analysis of variance. Mortality rates were expressed as the number of deaths from cardiovascular disease per 1000 person-years accrued for each cohort member. This was based on the length of follow-up, calculated as the number of days from the date of the 1984-1986 examination to the date of death, date of last contact, or December 31, 1996, whichever was earliest. The relation of proteinuria and subsequent mortality from cardiovascular disease was examined with Kaplan-Meier analysis. To evaluate whether mortality differed by proteinuria groups, the log-rank test was used. Multivariate analysis was performed using Cox proportional hazards regression, with 2 indicator variables created for the groups with microalbuminuria and gross proteinuria, which compared them with the group with normoalbuminuria. Initial analyses involved adjustments for age and sex, and subsequent procedures further controlled for diabetes-related variables, other cardiovascular risk factors, and presence of comorbid conditions or their markers. The diabetes-related variables we examined included diabetes duration, insulin intake, oral glucose-lowering agent use, plasma C peptide levels (categorized as <0.03, 0.03-0.29, and ≥0.30 nmol/L), and glycemic control (grouped as “excellent,” “good,” and “take action” based on glycosylated hemoglobin values of <7.5, 7.5-8.6, and ≥8.7%, respectively, which corresponded to the current recommendations for glycemic control using hemoglobin A₁c. Cardiovascular risk factors included cigarette smoking (classified as never, former, current), physical activity (categorized as engaging in regular physical activity for ≥3, 1-3, or 0 times per week), education (<12, 12, >12 years of school completed), alcohol intake (classified as never drinkers, past-year nondrinkers, and drinkers with alcohol intake of <2 g/d, 2-13 g/d, and ≥14 g/d), body mass index (calculated as weight in kilograms divided by the square of the height in meters), systolic and diastolic blood pressures, history of hypertension (defined as systolic blood pressure of ≥160 mm Hg or a diastolic of ≥95 mm Hg or taking antihypertensive medications), and intake of medications such as aspirin and antihypertensive agents. The comorbid conditions (or their markers) we examined included the presence of peripheral neuropathy symptoms (defined as self-reported loss of tactile sensation in hands or feet or decreased ability to feel the hotness or coldness of things), the presence and severity of diabetic retinopathy (grouped into none, mild to early nonproliferative, moderate to severe nonproliferative, and proliferative retinopathy, based on fundus photographs graded in masked fashion using a modified Air–Lee House classification system) and history of cardiovascular disease (defined as having prior angina, myocardial infarction or stroke, or intake of nitroglycerin or digoxin). Variables were successively entered in Cox regression models, which adjusted for age, sex, and glycemic control, starting from diabetes-related variables, to other cardiovascular risk factors, and finally, to comorbid conditions or complications, while retaining those that remained independently related to cardiovascular mortality. For a subset (n = 400) of the total study sample for whom we had measurements on HDL-C, total cholesterol, and the ratio of total cholesterol to HDL-C, we repeated our multivariate analyses including each of these variables.

To check for possible effect modification, stratified analyses were performed on subgroups of participants defined by specific risk factors. Likelihood ratio tests were used to test for interactions in the proportional hazards models.

To further quantify the excess risk of cardiovascular disease mortality associated with the severity of clinical proteinuria, the risk in persons with gross proteinuria was further analyzed according to the presence or absence of possible renal insufficiency, defined as having a serum creatinine level of 176 µmol/L (2.0 mg/dL) or greater. Because gross proteinuria found in the 1984-1986 examination could be isolated, data on the presence of gross proteinuria in the 4 years before that examination (ie, in the 1980-1982 examination of the WESDR) were used to analyze separately the risk associated with (persistent) gross proteinuria found during both the 1980-1982 and 1984-1986 examinations. The presence of gross proteinuria was assessed in the same manner in both examinations.

We also checked whether any associations of microalbuminuria and gross proteinuria were evident only for short-term cardiovascular mortality by comparing the RR's across different lengths of follow-up (12-year vs 10-year, 8-year, and 6-year follow-up) or whether these relations would disappear when persons who died during the first 5 years were successively removed from the analysis, as suggested in previous studies. Finally, the risks associated with microalbuminuria and gross proteinuria were also calculated for other end points, including coronary heart disease (CHD) mortality, stroke mortality, and all-cause mortality. Coronary heart disease mortality was defined as any mention of CHD (ICD-9 codes 410-414.9) and stroke mortality as any mention of stroke (ICD-9 codes 430-438.9) as a contributory cause of death on the death certificate.

The proportionality assumption for the Cox regression models was tested (using time-dependent covariates defined by the interaction between time and the proteinuria indicator variables) and met. Hazard ratios were reported as RRs with 95% confidence intervals (CIs). The analyses were done using SAS version 6.12 software (SAS Institute, Cary, NC).

the final study sample. Compared with those in the final study sample, individuals who had missing data on urinary protein levels were older (mean age, 72.9 vs 67.9 years) and had lower blood pressures (mean systolic/diastolic pressures, 138.8/72.8 vs 143.3/75.7 mm Hg) and body mass indexes (mean, 27.2 vs 29.4 kg/m²). They also had a higher rate of cardiovascular disease history (49.6% vs 40.4%). They were essentially similar with respect to all the other variables we examined.

Of the 840 persons in the final study sample, 54.8% had no evidence of microalbuminuria or gross protein-
vascular diseases, and use of aspirin and antihypertensive agents. No clear patterns were observed for the other variables.

During follow-up of up to 12 years (6127 person-years), we identified 364 deaths from cardiovascular disease. The overall cardiovascular disease mortality rate for the study cohort was 59.4 per 1000 person-years. The rate for those with normoalbuminuria was 36.9 per 1000 person-years, whereas the rates for those with microalbuminuria and gross proteinuria were 85.5 and 123.0 per 1000 person-years, respectively.

Compared with older-onset diabetic persons and normoalbuminuria, diabetic persons with microalbuminuria and gross proteinuria had significantly higher risks of death from cardiovascular disease ($P < .001$) (Figure). The age- and sex-adjusted RRs progressively increased across increasing levels of proteinuria (Table 2). Additional adjustments for significant diabetes-related variables and cardiovascular disease risk factors, which included glycemic control, insulin use, alcohol intake, physical activity, history of cardiovascular disease, intake of antihypertensive agents, and the presence and severity of diabetic retinopathy, showed that the associations for increasing proteinuria levels remained significant. The RRs (95% CIs) were 1.84 (1.42-2.40) and 2.61 (1.99-3.43) for those with microalbuminuria and gross proteinuria, respectively. Further control for other factors, which were not independently related to cardiovascular mortality in the presence of all variables in the earlier model, did not change the significant associations observed. In a subset of 400 persons with older-onset diabetes mellitus who had complete information on HDL-C and total cholesterol, similar multivariate models that included HDL-C, total cho-

### Table 1. Characteristics of Persons With Older-Onset Diabetes Mellitus Who Had Data on Microalbuminuria and Gross Proteinuria in the 1984-1986 Examination of the Wisconsin Epidemiologic Study of Diabetic Retinopathy*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population (N = 840)</th>
<th>Normoalbuminuria (n = 460)</th>
<th>Microalbuminuria (n = 208)</th>
<th>Gross Proteinuria (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>67.9 ± 11.0</td>
<td>66.8 ± 11.1†</td>
<td>69.8 ± 10.3†</td>
<td>68.8 ± 11.3†</td>
</tr>
<tr>
<td>Male, %</td>
<td>45.0</td>
<td>40.4†</td>
<td>48.6†</td>
<td>52.9†</td>
</tr>
<tr>
<td>Diabetes duration, mean ± SD, y</td>
<td>15.1 ± 7.9</td>
<td>13.5 ± 7.1†</td>
<td>16.4 ± 8.0†</td>
<td>17.6 ± 8.6†</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, mean ± SD, %</td>
<td>9.3 ± 1.9</td>
<td>9.1 ± 1.9†</td>
<td>9.6 ± 1.9†</td>
<td>9.6 ± 1.9†</td>
</tr>
<tr>
<td>Using insulin, %</td>
<td>56.1</td>
<td>47.0†</td>
<td>62.5†</td>
<td>72.7†</td>
</tr>
<tr>
<td>Using oral hypoglycemic agent, %</td>
<td>34.2</td>
<td>39.6†</td>
<td>30.3†</td>
<td>24.4†</td>
</tr>
<tr>
<td>Plasma C peptide, mean ± SD, nmol/L</td>
<td>1.02 ± 0.92</td>
<td>1.03 ± 0.83</td>
<td>0.98 ± 0.90</td>
<td>1.05 ± 1.15</td>
</tr>
<tr>
<td>Body mass index, mean ± SD, kg/m²</td>
<td>29.4 ± 6.0</td>
<td>29.6 ± 6.1</td>
<td>29.6 ± 5.8</td>
<td>28.5 ± 5.7</td>
</tr>
<tr>
<td>Systolic blood pressure, mean ± SD, mm Hg</td>
<td>143.3 ± 22.8</td>
<td>138.9 ± 20.0†</td>
<td>147.4 ± 22.9†</td>
<td>150.2 ± 26.9†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean ± SD, mm Hg</td>
<td>75.7 ± 12.0</td>
<td>75.5 ± 11.3</td>
<td>75.5 ± 12.0</td>
<td>76.4 ± 13.6</td>
</tr>
<tr>
<td>Current or former smoker, %</td>
<td>47.2</td>
<td>46.1</td>
<td>44.0</td>
<td>54.1</td>
</tr>
<tr>
<td>Current alcohol drinker, %</td>
<td>57.0</td>
<td>60.4</td>
<td>54.8</td>
<td>50.6</td>
</tr>
<tr>
<td>Physical activity less than once per week, %</td>
<td>67.9</td>
<td>62.5†</td>
<td>72.5†</td>
<td>76.7†</td>
</tr>
<tr>
<td>Education =12 y, %</td>
<td>74.9</td>
<td>72.8</td>
<td>79.8</td>
<td>74.3</td>
</tr>
<tr>
<td>With retinopathy, any grade, %</td>
<td>66.5</td>
<td>57.9†</td>
<td>74.9†</td>
<td>79.6†</td>
</tr>
<tr>
<td>With peripheral neuropathy, %</td>
<td>32.8</td>
<td>27.3†</td>
<td>35.4†</td>
<td>44.2†</td>
</tr>
<tr>
<td>History of cardiovascular disease, %</td>
<td>40.4</td>
<td>32.5†</td>
<td>46.1†</td>
<td>54.4†</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>65.9</td>
<td>61.1†</td>
<td>72.1†</td>
<td>71.4†</td>
</tr>
<tr>
<td>Using aspirin, %</td>
<td>26.9</td>
<td>24.8</td>
<td>27.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Using antihypertensive agents, %</td>
<td>52.3</td>
<td>48.7</td>
<td>55.8</td>
<td>57.6</td>
</tr>
</tbody>
</table>

*For more detailed description of variables, see the “Subjects and Methods” section.
†Values were significantly different ($P < .05$) among the 3 groups (normoalbuminuria, microalbuminuria, and gross proteinuria) using analysis of variance for continuous variables and $\chi^2$ analysis or Fisher exact test for binary variables. The $P$ values were <.01 for age, sex, glycosylated hemoglobin, and hypertension history; <.001 for oral hypoglycemic agent use, physical inactivity, and peripheral neuropathy; and <.0001 for diabetes duration, insulin use, systolic blood pressure, retinopathy, and cardiovascular disease history. The rates were of borderline significance for physical inactivity ($P = .06$) and use of antihypertensive agents ($P = .07$).
lesterol, or the ratio of total cholesterol to HDL-C still showed significantly higher risks for the groups with microalbuminuria and gross proteinuria (data not shown). In separate analyses of all these models, we also consistently found that the risk of cardiovascular mortality in those with gross proteinuria was significantly greater than in those with microalbuminuria.

We also examined variables, including sex, hypertension history, smoking status, insulin intake, glycemic control, and cardiovascular disease history, for their potential to modify the direct relation between levels of proteinuria and fatal cardiovascular disease. Not one was significant as an interaction variable.

To determine the risk associated with the severity of nephropathy, we further analyzed those with gross proteinuria according to the presence or absence of possible renal insufficiency. Table 3 shows that diabetic patients with proteinuria who had serum creatinine levels of at least 176 µmol/L (2.0 mg/dL) had a substantially higher risk of cardiovascular disease mortality compared with those with normoalbuminuria. To separate those with possible isolated gross proteinuria, we additionally analyzed the risk of older-onset diabetic patients who tested positive for gross proteinuria in both the 1984-1986 and 1980-1982 examinations, also finding a greater risk for fatal cardiovascular disease in this subgroup (Table 4). When persons who died during the first 5 years were removed from the proportional hazards regression analysis, the associations of microalbuminuria and gross proteinuria with cardiovascular mortality remained highly significant. The adjusted RRs (95% CIs), which controlled for all variables listed in the multivariate models in Table 2, were 2.30 (1.58-3.44) for microalbuminuria and 2.75 (1.75-4.31) for gross proteinuria. Similarly, the associations remained significant for shorter periods of follow-up. For example, the adjusted RRs (95% CIs) for microalbuminuria and gross proteinuria were 1.76 (1.32-2.33) and 2.57 (1.94-3.42), respectively, after 10 years of follow-up and 1.69 (1.18-2.43) and 2.73 (1.94-3.85), respectively, after 6 years of follow-up.

When the end point used was CHD mortality, stroke mortality, or total mortality, the risks associated with microalbuminuria and gross proteinuria remained significantly higher compared with the risk associated with normoalbuminuria (Table 5).

**Table 2. Mortality Rates and Relative Risks for Death From Cardiovascular Disease (CVD) According to Proteinuria Status in 840 Persons With Older-Onset Diabetes Mellitus, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1984-1996**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normoalbuminuria (n = 460)</th>
<th>Microalbuminuria (n = 208)</th>
<th>Gross Proteinuria (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths from CVD</td>
<td>146</td>
<td>113</td>
<td>105</td>
</tr>
<tr>
<td>CVD mortality rate, per 1000 person-years</td>
<td>36.9</td>
<td>85.5</td>
<td>123.0</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00 (Reference)</td>
<td>2.23 (1.74-2.86)</td>
<td>3.66 (2.82-4.75)</td>
</tr>
<tr>
<td>Multivariate model 1 RR (95% CI)†</td>
<td>1.00 (Reference)</td>
<td>2.02 (1.57-2.60)</td>
<td>3.16 (2.42-4.12)</td>
</tr>
<tr>
<td>Multivariate model 2 RR (95% CI)‡</td>
<td>1.00 (Reference)</td>
<td>1.84 (1.42-2.40)</td>
<td>2.61 (1.99-3.43)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk as estimated by the hazard ratio using Cox proportional hazards regression comparing each proteinuria status group with older-onset diabetic persons who had normoalbuminuria; CI, confidence interval. For definition of variables, see the “Subjects and Methods” section.

†Multivariate model 1 was adjusted for age, sex, glycemic control, insulin use, alcohol intake, and physical activity.

‡Multivariate model 2 was adjusted for the same variables as in multivariate model 1 as well as history of CVD, intake of antihypertensive agents, and the presence and severity of diabetic retinopathy.

**Table 3. Mortality Rates and Relative Risks for Death From Cardiovascular Disease (CVD) According to Levels of Severity of Proteinuria in 840 Persons With Older-Onset Diabetes Mellitus, Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1984-1996**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normoalbuminuria (n = 460)</th>
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<td>36.9</td>
<td>85.5</td>
<td>123.0</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00 (Reference)</td>
<td>2.25 (1.76-2.88)</td>
<td>3.39 (2.59-4.44)</td>
</tr>
<tr>
<td>Multivariate model 1 RR (95% CI)†</td>
<td>2.04 (1.58-2.62)</td>
<td>2.94 (2.23-3.87)</td>
<td>7.10 (3.97-12.70)</td>
</tr>
<tr>
<td>Multivariate model 2 RR (95% CI)‡</td>
<td>1.86 (1.43-2.43)</td>
<td>2.42 (1.82-3.21)</td>
<td>5.97 (3.36-10.60)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk as estimated by the hazard ratio using Cox proportional hazards regression comparing each proteinuria status group with older-onset diabetic persons who had normoalbuminuria; CI, confidence interval. For definition of variables, see the “Subjects and Methods” section.

†The group with gross proteinuria was further subdivided according to possible renal insufficiency, defined as having a serum creatinine level of at least 176 µmol/L (2.0 mg/dL).

‡Multivariate model 1 was adjusted for age, sex, glycemic control, insulin use, alcohol intake, and physical activity.

§Multivariate model 2 was adjusted for the same variables as in multivariate model 1 as well as history of CVD, intake of antihypertensive agents, and the presence and severity of diabetic retinopathy.

**COMMENT**

In this population-based prospective study, we have shown that older-onset diabetic persons with microalbuminuria or gross proteinuria had higher risks of death from cardiovascular disease and all causes in general and...
from CHD and stroke in particular compared with diabetic persons with normoalbuminuria. Despite the initial relation between proteinuria levels and some cardiovascular risk factors at baseline, some of which were seen in previous studies, the increased risks were independent of several factors related to diabetes, cardiovascular disease, and survival.

Despite the numerous studies on the prognostic significance of urinary albumin excretion in diabetic and nondiabetic settings, there have been few epidemiologic data on the specific association between microalbuminuria and cardiovascular or coronary mortality in type 2 diabetes mellitus. Earlier studies on microalbuminuria in type 2 diabetes mellitus have focused mainly, if not solely, on total mortality. Subsequently, significant estimates of RRs for the association of microalbuminuria with deaths from cardiovascular disease and CHD were reported. A 1997 meta-analysis reported a summary odds ratio for microalbuminuria and cardiovascular mortality or morbidity of 2.0 (95% CI, 1.4-2.7) as pooled from 6 European studies; however, only 1 study included in the overview presented RR estimates that corrected for potentially confounding factors. Interestingly, a study in Japan found no difference in the cardiovascular death rates between diabetic patients with normoalbuminuria and those with microalbuminuria. Moreover, other studies in Europe, Australia found that the associations of microalbuminuria or urinary albumin excretion with coronary, cardiovascular, macrovascular, or all-cause mortality were not independent of common cardiovascular and diabetes-related variables. Our multivariate analyses showed that persons with older-onset diabetes mellitus and microalbuminuria had a significant 1.8-fold increase in the risk for cardiovascular death and a 2-fold increase in the risk for CHD mortality compared with older-onset diabetic persons with normoalbuminuria.
vascular disease risk factors, including hyperinsulinemia.

tes mellitus. Albuminuria is associated with many cardio-
count for the relation between urinary protein excretion
and cardiovascular mortality due to cardiovascular disease.

Moreover, when the group with gross protein-
uria was characterized further by serum creatinine val-
ues to indicate possible renal insufficiency or by the
presence of gross proteinuria 4 years before the current
examination to indicate possible longer-term “expo-
sure” to clinical proteinuria, the risks for both coronary
data not shown) and cardiovascular mortality were in-
creased substantially. Our data also showed that both mi-
croalbuminuria and gross proteinuria significantly pre-
dicted long-term mortality due to cardiovascular disease.

A number of explanations have been proposed to ac-
count for the relation between urinary protein excretion
and cardiovascular morbidity or mortality in type 2 dia-
tebes mellitus. Albuminuria is associated with many cardio-
vascular disease risk factors, including hyperinsulinemia
and insulin resistance. Microalbuminuria can also be
a risk marker of established cardiovascular disease. Inter-
estingly, a recent study provided subgroup findings in men
that showed that although microalbuminuria could pre-
cede the development of CHD in patients with type 2 dia-
tebes mellitus, CHD could also precede the development
of microalbuminuria, suggesting that both factors could re-
sult from common determinants. Perhaps the most plau-
sible of all mechanisms linking albuminuria to cardiovas-
cular disease is the concept that albuminuria is a marker
of extensive endothelial dysfunction or generalized vascu-
lopathy, which may lead to heightened atherogenic states.
Previous studies have described the associa-
tion of microalbuminuria with impairment of fibrinolytic
capacity and increased plasma levels of von Willebrand fac-
tor and transcapillary loss of albumin. Whether or not these
are the actual mechanisms involved, it remains important
to address the issue of preventing the unwanted burden
associated with albuminuria in diabetes. Current evidence
from clinical trials of patients with type 2 diabetes mell-
tus suggests that tight blood pressure control may reduce
the risk of microalbuminuria in patients with hyperten-
sion and that angiotensin-converting enzyme inhibition
with enalapril maleate can prevent or delay the progres-
sion of microalbuminuria to overt nephropathy in normo-
tensive persons. Although it remains to be seen whether
angiotensin-converting enzyme inhibitors and other anti-
hypertensive agents can similarly influence the risk of car-
diovascular events, older-onset diabetic persons with al-
buminuria may significantly profit from aggressive efforts
to correct contributing risk factors such as hyperglyc-e-
mia, hypertension, dyslipoproteinemia, smoking, obesity,
and physical inactivity.

Bias seemed unlikely to greatly account for the ob-
erved associations in our study. Differential follow-up was
not likely given the uniform vital status follow-up pro-
ducts used by staff masked to the participants’ albumi-

nuria status. The assignment of causes of death was also made
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tus collected in the study. It is possible that selective mor-
tality, as well as our methods to ascertain the presence of
microalbuminuria and gross proteinuria, could have af-
A large number of studies involving patients with type 2 diabetes mellitus showed higher risks
for overall mortality associated with clinical proteinuria or macroalbuminuria, but few presented RR estimates
for cardiovascular or coronary mortality. Others found no or weak associations with microalbuminuria. Our
study unequivocally showed a graded increase in the risk for cardiovascular and CHD mortality associated with
proteinuria. Moreover, when the group with gross proteinuria was characterized further by serum creatinine values
to indicate possible renal insufficiency or by the presence of gross proteinuria 4 years before the current
examination to indicate possible longer-term “exposure” to clinical proteinuria, the risks for both coronary
(data not shown) and cardiovascular mortality were increased substantially. Our data also showed that both mi-
croalbuminuria and gross proteinuria significantly predicted long-term mortality due to cardiovascular disease.

A number of explanations have been proposed to account for the relation between urinary protein excretion
and cardiovascular morbidity or mortality in type 2 diabetes mellitus. Albuminuria is associated with many cardio-
vascular disease risk factors, including hyperinsulinemia and insulin resistance. Microalbuminuria can also be
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that showed that although microalbuminuria could precede the development of CHD in patients with type 2 diabetes
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tensive persons. Although it remains to be seen whether angiotensin-converting enzyme inhibitors and other anti-
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albuminuria may significantly profit from aggressive efforts to correct contributing risk factors such as hyperglyc-
emia, hypertension, dyslipoproteinemia, smoking, obesity, and physical inactivity.

Bias seemed unlikely to greatly account for the observed associations in our study. Differential follow-up was
not likely given the uniform vital status follow-up procedures used by staff masked to the participants’ albumin-
uria status. The assignment of causes of death was also made without any knowledge of the participants’ exposure sta-

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