Prevalence of Microalbuminuria in Older-Onset Diabetes

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OBJECTIVE — To examine the prevalence of microalbuminuria and the relationships of microalbuminuria to blood pressure and other risk factors.

RESEARCH DESIGN AND METHODS — Individuals diagnosed with diabetes at ≥30 yr of age either taking insulin (n = 435) or not taking insulin (n = 363), who were participants in the population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy, were examined during 1984–1986. Random urine samples were collected and an agglutination inhibition test was used to determine the presence of microalbuminuria, which is defined as ≥0.03 g/L but <0.3 g/L.

RESULTS — The frequency of microalbuminuria was 29.2% in those individuals taking insulin and 22.0% in those not taking insulin. Microalbuminuria was significantly associated with the male sex, older age, higher systolic blood pressure, higher GHb, use of insulin, higher recent alcohol consumption, and a history of cardiovascular disease.

CONCLUSIONS — These findings suggest a relationship between controllable risk factors, blood pressure and GHb, and microalbuminuria in older-onset diabetic individuals.

Diabetes is an important cause of renal failure (1). In studies of people with both IDDM and NIDDM, urinary excretion of albumin has been found to be predictive of development of gross proteinuria and end-stage diabetic nephropathy (2–4). Recent data suggest that early intervention to control BP and hyperglycemia might reverse microalbuminuria and delay the subsequent development of diabetic nephropathy (5–10). We report the prevalence of microalbuminuria in a large population of people with older-onset diabetes and the relationship of microalbuminuria to sBP and dBP, smoking history, GHb, and other characteristics of the study population.

RESEARCH DESIGN AND METHODS

— The population for the Wisconsin Epidemiologic Study of Diabetic Retinopathy has been described in detail elsewhere (11–13). Participants for the study were selected from an 11-county area in southern Wisconsin. Lists of all diabetic patients cared for between 1 July 1979 and 30 June 1980 were provided by 452 of 457 primary-care physicians practicing in the area. After a chart review to determine whether eligibility criteria were met, a sample of 2990 people was selected, which included 1780 people who either took insulin (n = 824) or did not (n = 956) and whose diabetes had been diagnosed at ≥30 yr of age (older-onset). Of these, 1370 (77.0%) older-onset diabetic individuals participated in the first examination, which took place from 1980–1982 (12,13). Microalbuminuria was not determined at the time of the first examination.

A second examination was conducted between 1984–1986 in which 1007 older-onset diabetic individuals (567 taking insulin and 440 not taking insulin) were examined (14,15).

Procedures

Informed consent was obtained from all subjects. Pertinent parts of the ocular and physical examinations consisted of measuring height, weight, and BP (16); dilating the pupils; taking stereoscopic fundus photographs of 7 standard fields for each eye (17); and determining GHb levels (18). Measurements of total serum cholesterol (19) and HDL cholesterol (20) began later in the study and involved only 172 of the older-onset dia-

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; HDL, high-density lipoprotein; CVD, cardiovascular disease; BMI, body mass index; RR, relative risk; CI, confidence interval; OR, odds ratio.

Table 1—*The frequency of microalbuminuria and gross proteinuria in older-onset diabetic groups taking and not taking insulin participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (1984–1986)*

	Diabetic group taking insulin			Diabetic group not taking insulin		
	Males	Females	Total	Males	Females	Total
n	192	243	435	164	199	363
Proteinuria status (%)						
None	43.2	55.1	49.9	64.0	70.9	67.8
Microalbuminuria	33.3	25.9	29.2	22.6	21.6	22.0
Gross proteinuria	23.4	18.9	20.9	13.4	7.5	10.2

betic group taking insulin and 168 of those not taking insulin (21,22).

A standardized questionnaire was administered. A history of diuretic or other antihypertensive medication use, digoxin use, and a history of CVD and stroke was obtained from each participant. In addition, information on smoking history, alcohol consumption, and physical activity was obtained.

Random fresh urine samples were collected and tested for gross proteinuria by means of a reagent strip (Labstix, Ames, Elkhart, Indiana). Individuals whose urine samples contained ≥0.3 g/L of protein were considered to have gross proteinuria (23).

Microalbuminuria was determined by an agglutination inhibition assay (AlbuScreen, Cambridge Life Sciences, Cambridge, England). Details of the procedures have been described previously (23). A positive test measured albumin in urine at concentrations of ≥0.03 g/L.

Urine samples from 457 older-onset diabetic participants taking insulin and 366 not taking insulin were tested for both gross proteinuria and microalbuminuria. However, 22 of these diabetic individuals taking insulin and 3 not taking insulin were excluded because they either had blood in their urine or were on dialysis, leaving 435 diabetic individuals taking insulin and 363 not taking insulin providing the prevalence data for this study.

Definitions

All characteristics were defined by responses and measurements at the time of the second examination during the period from 1984 through 1986. Hypertension was defined as a mean sBP ≥160 mmHg, a mean dBP ≥95 mmHg, and/or a history of hypertension with use of hypertensive medication at any age. Smokers were defined as individuals who had smoked >100 cigarettes in their lifetime. Current and ex-smokers were distinguished by whether or not they were currently smoking. Alcohol consumption history was also used to determine average consumption in the past year and in the past week. BMI was determined by dividing the measured weight in kilograms by the measured height in meters squared.

To determine retinopathy status, all fundus photographs were graded using a modification of the Airlie House Classification scheme that specified 9 levels of retinopathy (12,14). Participants were classified using the more severely involved eye. Briefly, level 10 represents no retinopathy; levels 21, 31, 41, and 51 represent minimal to severe nonproliferative retinopathy; and levels 60, 65, 70, and 80 represent increasing stages of proliferative retinopathy.

Statistical analysis

Analyses were limited to data collected at the examination of 1984 through 1986. Student's *t* test statistics and RR were calculated for univariate comparisons between groups. Tests of trends were performed by the Mantel-Haenszel procedure (25). Multiple logistic regression was used to describe the associations of several variables with microalbuminuria controlling for potential confounders. All statistical analyses were performed using SAS software (26,27).

RESULTS — Microalbuminuria ($P = 0.02$) and gross proteinuria ($P < 0.0001$) occurred more frequently in diabetic individuals taking insulin compared with those not taking insulin (Table 1). In individuals taking insulin, men had a higher proportion of any proteinuria (gross proteinuria and microalbuminuria), 56.7%, than women, 44.8% ($P < 0.05$). No other significant differences betwen men and women were observed. For all following analyses, the 91 diabetic individuals taking insulin and the 37 diabetic individuals not taking insulin who had gross proteinuria were excluded, and the 2 diabetic groups were combined; this resulted in a sample size of 670 participants.

The frequency of microalbuminuria increased with increasing age from 17.5% in those 36–49 yr of age, to 37.5% in those ≥80 yr of age (Mantel-Haenszel test for trend, $P < 0.005$, Table 2). The frequency of microalbuminuria increased with longer duration of diabetes (Mantel-Haenszel test of trend, $P < 0.001$, Table 2).

A significant trend was observed for an increase in the percentage of positive tests for microalbuminuria with an increase in sBP (Mantel-Haenszel test of trend, $P < 0.001$, Table 2). Diabetic individuals in the highest quartile for sBP were about twice as likely to have a positive test for microalbuminuria as were those in the lowest quartile. The RR of microalbuminuria for diabetic individuals with hypertension compared with those without hypertension was 1.37 (95% CI 1.08–1.73).

Individuals with GHb in the highest quartile were 1.52 times (95% CI

Table 2—*Relationship of prevalence of microalbuminuria to various characteristics in older-onset diabetic individuals (1984–1986)*

	At risk (*n*)	With micro-albuminuria (%)	RR (95% CI)
Age (yr)			
36–49	40	17.5	1.00 (—)
50–59	117	23.9	1.37 (0.65–2.88)
60–69	210	29.0	1.66 (0.82–3.36)
70–79	223	36.3	2.07 (1.04–4.16)
≥80	80	37.5	2.14 (1.03–4.45)
Duration of diabetes (yr)			
5–9	258	23.3	1.00 (—)
10–14	155	31.0	1.33 (0.96–1.84)
15–19	72	38.9	1.67 (1.16–2.40)
20–24	116	35.3	1.51 (1.09–2.11)
≥25	69	43.5	1.87 (1.32–2.64)
Sex			
Female	381	27.8	1.00 (—)
Male	289	34.9	1.25 (1.00–1.57)
GHb (%)			
5.0–7.9	172	24.4	1.00 (—)
8.0–9.0	168	30.4	1.25 (0.88–1.77)
9.1–10.4	163	31.3	1.28 (0.91–1.82)
10.5–17.1	164	37.2	1.52 (1.10–2.12)
HDL cholesterol (mM)			
0.30–0.80	85	37.6	1.00 (—)
0.85–1.05	87	25.3	0.67 (0.43–1.06)
1.10–1.30	83	27.7	0.74 (0.47–1.15)
1.35–3.25	85	24.7	0.66 (0.41–1.04)
sBP (mmHg)			
87–127	167	20.4	1.00 (—)
128–140	167	24.6	1.21 (0.81–1.80)
141–154	166	34.9	1.71 (1.19–2.46)
155–232	166	44.0	2.16 (1.53–3.05)
dBP (mmHg)			
44–67	159	31.4	1.00 (—)
68–75	179	30.2	0.96 (0.70–1.32)
76–83	166	28.3	0.90 (0.64–1.26)
84–117	161	34.2	1.09 (0.80–1.49)
Recent alcohol consumption			
Nondrinker	494	30.4	1.00 (—)
Light drinker	78	23.1	0.76 (0.50–1.16)
Moderate drinker	74	36.5	1.20 (0.86–1.67)
Heavier drinker	23	47.8	1.57 (1.00–2.46)
History of CVD			
No	425	26.6	1.00 (—)
Yes	237	39.7	1.49 (1.20–1.86)
History of diuretic use			
No	327	27.5	1.00 (—)
Yes	343	34.1	1.24 (0.99–1.56)
History of amputation			
No	646	29.7	1.00 (—)
Yes	24	62.5	2.10 (1.51–2.93)
Diabetic retinopathy			
None	250	20.4	1.00 (—)
Minimal nonproliferative	258	31.8	1.56 (1.15–2.11)
Moderate to severe nonproliferative	103	45.6	2.24 (1.62–3.09)
Proliferative diabetic retinopathy	54	42.6	2.09 (1.41–3.10)

1.10–2.12) as likely to have microalbuminuria present as those whose GHb were in the first quartile. The trend for an increase in the percentage of positive tests for microalbuminuria with an increase in GHb (Mantel-Haenszel test of trend, $P < 0.05$) was significant (Table 2). Individuals with a history of recent, heavy alcohol consumption were 1.57 times as likely to have microalbuminuria present compared with nondrinkers. However, the trend was not significant ($P = 0.15$).

Sex, a history of CVD, a history of amputation, and having more severe retinopathy were significantly associated with the presence of microalbuminuria ($P < 0.05$) (Table 2). There was no relationship of microalbuminuria with dBP (Table 2), HDL cholesterol (Table 2), BMI or height, smoking history, past alcohol consumption or drinking history, history of physical activity, total serum cholesterol, or C-peptide (data not shown).

Because of the interrelationship of many of these factors, we performed a multivariate logistic regression analysis with presence of microalbuminuria as the dependent variable. All individuals with gross proteinuria were excluded from the analyses. There were 199 diabetic individuals with and 446 without microalbuminuria in the model. Insulin use was forced into the model, because it was related to both GHb and microalbuminuria. Because CVD is a possible cause of microalbuminuria, we controlled for it and a history of digoxin use. Other variables considered were sex, age at examination, sBP and dBP, duration of diabetes, GHb, alcohol consumption or drinking history, smoking history, and history of physical activity. Higher sBP, being male, older age at examination, a positive history of CVD, using insulin, higher GHb, and higher recent alcohol consumption were associated with the presence of microalbuminuria ($P < 0.05$) (Table 3). We reran the models, excluding a history of CVD or insulin use, and found no change in the relation-

Table 3—*Logistic regression analyses*

Characteristic	OR (95% CI)	Microalbuminuria more likely if:
sBP (per 10 mmHg)	1.23 (1.13–1.34)	Higher
Sex (0 = female, 1 = male)	1.55 (1.08–2.25)	Male
Age at examination (per 10 yr)	1.34 (1.11–1.61)	Older
History of CVD (0 = no, 1 = yes)	1.80 (1.24–2.59)	Present
Using insulin (0 = no, 1 = yes)	1.81 (1.25–2.63)	Uses
GHb (per 2%)	1.30 (1.07–1.58)	Higher
Recent alcohol consumption (per 0.5 oz/day)	1.26 (1.01–1.59)	Higher

ships of GHb or sBP and microalbuminuria (data not shown). Because of the finding of a significant relationship between microalbuminuria and HDL cholesterol and because HDL cholesterol was measured in fewer patients, a model was also evaluated with insulin use, BP, sex, age, history of CVD, serum HDL cholesterol, and total serum cholesterol included. An inverse relationship between microalbuminuria and serum HDL cholesterol was observed (OR for each mM 0.54; 95% CI 0.27–1.09), which was of borderline significance ($P = 0.08$).

CONCLUSIONS — The prevalence of microalbuminuria was 29.2% in diabetic individuals taking insulin and 22.0% in those not taking insulin. Despite differences in methods of collection, detection of microalbuminuria, and characteristics of the groups studied, these frequencies of microalbuminuria are generally comparable with those reported by others in studies of older-onset diabetic people (28–34).

In our population, microalbuminuria was related to higher sBP, but not dBP. This is consistent with the work of some (29–31,34), but not others (28,35). Jerums et al. (36) reported no relationship of BP to the development of microalbuminuria or gross proteinuria in older-onset diabetic individuals. Shigeta et al. (37) demonstrated a concomitant elevation of sBP but not dBP in NIDDM patients who developed microalbuminuria over a 3-yr period; BP remained unchanged in patients who did not develop microalbuminuria. Although treatment with antihypertensive agents can reduce urinary albumin excretion in both IDDM and NIDDM patients, this may be caused by a direct effect of lowered BP on albumin excretion, independent of kidney disease (7,9,10,31). It is not certain whether the relationship of BP to the development of microalbuminuria, possible progression to gross proteinuria, and diabetic nephropathy is etiological. Long-term, longitudinal studies and clinical trials in older-onset diabetic individuals are necessary for further understanding of this relationship.

A consistent positive relationship between hyperglycemia and microalbuminuria has been found in studies of younger-onset IDDM patients (5,6,8, 23,29,38–40), but not in older-onset NIDDM patients (29–31,33–35,41,42). In this study, after controlling for other factors, an association between hyperglycemia was detected, as measured by GHb and microalbuminuria. Further longitudinal data are necessary to explore this relationship.

Most studies in IDDM patients have shown an association of diabetic nephropathy with abnormalities in serum lipids (43–47). This relationship has not been consistently found in NIDDM patients (30,48,49). In this study, an inverse relationship, of borderline significance ($P = 0.08$), between microalbuminuria and HDL cholesterol was established. Data from a prospective study by Niskanen et al. (50) suggest that microalbuminuria may precede the development of lipoprotein abnormalities in NIDDM patients.

After controlling for other factors, recent alcohol consumption, but not cigarette smoking, was associated with the presence of microalbuminuria. The reason for the relationship with alcohol is not clear. Alcohol consumption was associated with decreased frequency of late microvascular complications in one study (51) and unrelated to gross proteinuria in another study of IDDM patients (52).

Conclusions regarding this study must be made with caution. The methods used to collect (a single, randomly voided urine specimen) and store urine (frozen at 5–24 mo at −20°C until testing) and the precision and sensitivity of the test (qualitative agglutination test) used to measure microalbuminuria may have affected the prevalence of microalbuminuria (23,53,54). Nevertheless, in this study sBP and GHb were associated with microalbuminuria. Population-based longitudinal data are necessary to further understand the relationship of potential risk factors to the development and progression of microalbuminuria.

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