Predictors of Microalbuminuria in Individuals with IDDM

Pittsburgh Epidemiology of Diabetes Complications Study

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OBJECTIVE — To examine the relationships between microalbuminuria and the development of overt diabetic nephrology, elevated blood pressure, and a more atherogenic lipid profile; and to identify risk factors for the development of microalbuminuria in individuals with IDDM. Microalbuminuria has been associated with the subsequent development of overt diabetic nephropathy in individuals with IDDM. It is associated with elevated blood pressure and a more atherogenic lipid profile, but the temporal relationship between the development of microalbuminuria and the changes in these factors is unclear.

RESEARCH DESIGN AND METHODS — Baseline characteristics were examined in 256 individuals with IDDM who had normal albumin excretion (urinary AER ≤20 μg/min in ≥2 timed urine collections) and were re-examined 2 yr later.

RESULTS — At follow-up, 24 had developed microalbuminuria (AER 20–200 μg/min in ≥2 timed urine collections) and 1 had developed overt nephropathy (AER >200 μg/min). Overall, the significant independent predictors of microalbuminuria were HbA_1 ($P < 0.001$), low-density lipoprotein ($P < 0.01$), duration of IDDM ($P < 0.05$), and systolic blood pressure ($P = 0.05$). Sex-specific analyses showed HbA_1, age, and baseline AER were particularly important for men; whereas, for women, the main predictors were duration of IDDM and triglycerides. Duration-specific analyses showed that HbA_1 was an important predictor both for individuals with < and >20-yr duration. Low-density lipoprotein cholesterol was more important for subjects with shorter durations; whereas triglycerides were important for those with longer durations.

CONCLUSIONS — These results suggest that glycemic control, age or duration of IDDM, disturbed lipids, and possibly elevated blood pressure all may contribute to the development of microalbuminuria; and, further, that the adverse cardiovascular risk profile seen in individuals with overt nephropathy may begin to develop even before the detection of microalbuminuria.

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IDDM, insulin-dependent diabetes mellitus; AER, albumin excretion rate; BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; EDC, Epidemiology of Diabetes Complications; CV, coefficient of variation; CI, confidence interval; BMI, body mass index; LDL, low-density lipoprotein; apoB, apoprotein B; apoA-I, apoprotein A-I; apoA-II, apoprotein A-II.

Microalbuminuria appears to be a predictor of overt diabetic nephropathy (1–4), which is the leading cause of end-stage renal disease in the U.S. (5), and a leading cause of death (6) and cardiovascular disease (7) in individuals with IDDM. Whether all individuals with microalbuminuria will necessarily progress to overt nephropathy is not known. However, it is clear that all individuals with overt nephropathy must pass through the stage of microalbuminuria; thus, a clearer understanding of the etiology and early natural history of microalbuminuria is central to the possible prevention of this major complication. A key issue is whether the elevated BP (4,8–10) and more atherogenic lipid profile (11–13) seen in microalbuminuric individuals are results, or potential causes, of microalbuminuria. Determining whether these factors predict microalbuminuria will help establish intervention strategies at the earliest possible stage.

RESEARCH DESIGN AND METHODS

— This study is based on the population of the EDC study (14,15). This is a 10-yr prospective study in which the participants are evaluated every 2 yr. This report focuses on 256 individuals who were normoalbuminuric at baseline, 1986–1988 (cycle 1), and returned for follow-up (cycle 2) examination. Subjects were diagnosed with IDDM at <17 yr of age during 1950–1980 and are not under the care of the investigators.

Approximately two weeks before their scheduled clinic appointment, participants were sent urine containers and instructions in the proper collection of a 24-h and an overnight urine specimen. At the beginning of the clinic appointment, the participants were instructed to completely empty their bladders; this void was collected and is referred to as the preclinic sample. A timed postclinic (~4-h) collection also was obtained over the course of the clinic visit. Thus, for

most subjects, all urine collections were made within a 2-wk period.

To be classified into one of the categories of normoalbuminuria (AER ≤20 μg/min), microalbuminuria (AER 20–200 μg/min), or overt nephropathy (AER >200 μg/min), an individual must have had at least two urine collections with an AER in the corresponding range (16). One woman at cycle 1 with overt nephropathy, which was attributable to pregnancy, was excluded.

Urinary albumin concentrations were measured within 1 mo of storage at −20°C using an immunonephelometric technique (17,18). This assay has a sensitivity of 0.0004 g/L, an intra-assay CV of 3%, and an interassay CV of 9.5%. Urinary creatinine concentrations were measured using an Ektachem 400 Analyzer (Eastman Kodak Co., Rochester, NY). As incomplete bladder emptying, inaccurate timing of urine collections, and the discarding of voids during the course of timed urine collections all can affect the accuracy of urine-collection parameters, the adequacy of each collection was determined by referring to its measured creatinine excretion. If a urine sample was deemed inadequate (197 of 1379 samples [14%] for the 256 participants presented, both cycles combined), the AER was calculated from the product of the urinary albumin/creatinine ratio of that sample and the calculated 24-h creatinine excretion (based on the participant's age and sex). The albumin/creatinine ratio also was used to calculate an AER for the preclinic urine if another AER was needed because an individual's nephropathy status could not be determined based on the other urine collections (n = 18 at cycle 1, all classified as normoalbuminuric; and 24 at cycle 2, with 20 normoalbuminuric and 4 microalbuminuric).

BP was measured 3 times after a 5-min rest in the sitting position using a Random Zero Sphygmomanometer (Hawksley, England). The mean of the second and third readings was used. Hypertension was defined as sBP >140 mmHg and/or dBP >90 mmHg, and/or taking antihypertensive medication. A positive family history of hypertension was defined as reported hypertension in a first-degree relative in a questionnaire. Smoking history and information regarding the use of oral contraceptives were elicited via questionnaire. The methods used for other measurements have been described earlier (19).

As the length of time between cycle 1 and cycle 2 evaluations varied somewhat among participants, incidence rates were measured as incidence density. The statistical significance of differences in group means (those who progressed to microalbuminuria or overt nephropathy versus those who remained normoalbuminuric) was tested using the Mann-Whitney U test statistic. Multiple logistic regression analyses were used to identify significant independent predictors of microalbuminuria.

RESULTS— At cycle 1 of the EDC study, nephropathy status could be determined in 649 individuals: 170 had overt nephropathy and 140 had microalbuminuria (22 of whom regressed to normal at cycle 2). In addition, 339 (52%) were normoalbuminuric at cycle 1. Of these 339 subjects, 256 could be classified by nephropathy status 2 yr later at cycle 2 (76 did not return, and 7 could not be classified because of incomplete data). Those classified and those not classified at follow-up did not differ by sex or duration of IDDM; however, those that were classified were older than those not classified (age at cycle 1: 25.7 vs. 23.6 yr, $P < 0.05$): Of these 256 individuals, 231 (90.2%; 115 men, 116 women) were again normoalbuminuric at cycle 2, 24 (9.4%; 9 men, 15 women) were microalbuminuric at cycle 2, and 1 (0.4%; woman) had overt nephropathy (but not renal failure) at cycle 2. This yielded an overall incidence density of microalbuminuria (including the woman with overt nephropathy) of 4.8 cases/100 person-yr of follow-up. Whereas for those with a duration <20 yr, incidence density was 3.5%; and, for those with duration >20 yr, it was twice as high (7.3%). For men, the incidence density was 3.6, and for women, the incidence density was 5.9 cases/100 person-yr of follow-up. The baseline characteristics of those who developed microalbuminuria or overt nephropathy were compared with those who did not, stratifying by duration (Tables 1 and 2). Compared with individuals who were normoalbuminuric at both cycles, those who progressed from normoalbuminuria to microalbuminuria or overt nephropathy had, at cycle 1, higher levels of HbA_1, serum triglycerides, and apoB. For those with duration <20 yr, LDL-cholesterol and apoA-I concentrations also were higher in those who progressed, whereas apoA-II and fibrinogen concentrations were higher in progressors with a duration >20 yr. Age, duration, and BP showed only weak nonsignificant increases. Those who progressed to microalbuminuria were not (either overall or by duration group) more likely to have ever been a smoker compared with those who did not progress (33 vs. 27%, overall, respectively) or to have a positive family history of hypertension (56 vs. 41%, overall, respectively). Table 3—which presents relative risks for developing microalbuminuria by specified levels of risk factors—confirms these duration-specific results from Tables 1 and 2, namely that increased HbA_1 (relative risk 3.6), LDL cholesterol (2.5), triglycerides (3.1), apoA-I (2.6), and apoB (3.4) all are associated with progression to microalbuminuria. Multiple logistic regression analyses showed HbA_1, LDL cholesterol, duration of IDDM, and sBP were significant independent predictors of microalbuminuria overall. LDL cholesterol was particularly important in the model for shorter-duration (< 20 yr) subjects, whereas triglycerides and sBP ($P = 0.06$) were predictive in longer-duration subjects (Table 4).

In the men, those who progressed to microalbuminuria were significantly older (30.1 vs. 24, $P < 0.05$), and

Table 1—*Host characteristics at cycle 1 by cycle 2 status stratified by duration of IDDM at cycle 1*

	Normoalbuminuric at cycle 2	Microalbuminuric* at cycle 2	*P* value
Sex (*n* [% male])			
<20 yr IDDM duration	159 (54.7)	12 (33.3)	NS
≥20 yr IDDM duration	72 (38.9)	13 (38.5)	NS
Age at diagnosis (yr)†			
<20 yr IDDM duration	8.9 ± 4.2	9.6 ± 4.4	NS
≥20 yr IDDM duration	7.6 ± 4.0	7.9 ± 4.3	NS
Age (yr)†			
<20 yr IDDM duration	21.7 ± 5.7	22.8 ± 4.3	NS
≥20 yr IDDM duration	33.4 ± 5.2	35.2 ± 5.9	NS
Duration of IDDM (yr)†			
<20 yr	12.8 ± 3.6	13.1 ± 4.0	NS
≥20 yr	25.7 ± 3.9	27.2 ± 4.1	NS
HbA_1 (%)†			
<20 yr IDDM duration	10.2 ± 1.7	12.2 ± 2.7	<0.05
≥20 yr IDDM duration	9.3 ± 1.3	10.5 ± 1.3	<0.01
BMI (kg/m^2)†			
<20 yr IDDM duration	22.9 ± 3.5	23.8 ± 3.3	NS
≥20 yr IDDM duration	23.6 ± 2.5	23.1 ± 2.8	NS
AER (μg/min)‡			
24 h			
<20 yr IDDM duration	9 (0.5–87)	10 (5–29)	NS
≥20 yr IDDM duration	9 (1–117)	13 (3–35)	NS
Overnight			
<20 yr IDDM duration	6 (1–48)	8 (4–21)	NS
≥20 yr IDDM duration	6 (0.5–46)	8 (2.5–12)	NS
Postclinic			
<20 yr IDDM duration	7 (2–105)	7 (5–32)	NS
≥20 yr IDDM duration	8 (1–58)	11 (3–26)	NS

*Includes one subject with normoalbuminuria at cycle 1 and overt nephropathy at cycle 2.
†Data are means ± SD.
‡Data are median (range).

had significantly higher levels of HbA_1 (11.6 vs. 9.9%, $P < 0.01$), sBP (121 vs. 110 mmHg, $P < 0.05$), LDL cholesterol (3.39 vs. 2.56 mM, $P < 0.01$), triglycerides (1.74 vs. 0.94 mM, $P < 0.05$), apoB (1.16 vs. 0.90 g/L, $P < .01$), and fibrinogen (3.19 vs. 2.45 g/L, $P < 0.05$). They also had a significantly higher postclinic AER (12 vs. 8 μg/min, $P < 0.05$). Multiple logistic regression analyses (using a maximum of eight independent variables) showed that HbA_1, age, and postclinic AER were significant independent predictors of microalbuminuria, with LDL cholesterol remaining in the model at $P = 0.07$ (Table 4).

In the women, those who progressed to microalbuminuria (or overt nephropathy) had a longer duration of IDDM, which was not significant univariately (21.0 vs. 17.9 yr, $P = 0.12$), and significantly higher levels of HbA_1 (11.2 vs. 9.9%, $P < 0.05$), triglycerides (1.29 vs. 0.82 mM, $P < 0.01$), apoA-I (1.48 vs. 1.38 g/L, $P < 0.05$), and apoA-II (0.48 vs. 0.44 g/L, $P < 0.05$). Multiple logistic regression analyses (using a maximum of five independent variables) showed that duration of IDDM and triglycerides were significant independent predictors of microalbuminuria, with HbA_1 remaining in the model at $P = 0.08$ (Table 4). Thus, time-related variables (age in men, IDDM duration in women), along with HbA_1, are the major common risk factors in both men and women. Though triglycerides were significant in women and LDL cholesterol in men, because sex lipid interaction terms were not significant in the overall model, it remains unclear whether the lipoprotein association truly differs by sex.

CONCLUSIONS— This study revealed an incidence density of microalbuminuria of 4.8 cases/100 person-yr of follow-up. The twofold higher incidence in those with a duration >20 yr is particularly interesting; although, given the small number of cases (13), these duration-specific rates cannot be considered definitive. The incidence of microalbuminuria is not well established and, for the most part, incidence data must be extrapolated from studies designed to investigate other hypotheses. Four other studies were found from which incidence data could be derived (Table 5). Compared with these studies (20–23), the present study found a similar incidence rate. The lower rates in Jerums et al.'s (20) study probably were a result of 40% of the participants being newly diagnosed. The reason for the higher rates in Raal et al.'s (23) study is not clear.

One major problem with any study of microalbuminuria is that of definition. The critical lower limits of microalbuminuria have varied from 15 (short-term collection) (3) to 70 g/min (24-h collection) (4). Note that, although AER is reduced at night, the best predictive cutoff in the study that used overnight urines was still 30 g/min (1). In view of this variability, we have adopted a compromise proposed by a group of investigators (16). That is, microalbuminuria corresponds to an AER of 20–200 μg/min; although it should be noted that results may vary if different limits were chosen for the various types of samples. Another factor that may influence results, is the potential survivor

Table 2—*Risk factors at cycle 1 by cycle 2 status stratified by duration of IDDM at cycle 1*

Risk factors: <20 yr IDDM duration ≥20 yr IDDM duration	Normoalbuminuric at cycle 2	Microalbuminuric* at cycle 2	*P* value
sBP (mmHg)			
<20 yr IDDM duration	106 ± 10	109 ± 9	NS
≥20 yr IDDM duration	111 ± 11	118 ± 14	NS
dBP (mmHg)			
<20 yr IDDM duration	68 ± 8	69 ± 7	NS
≥20 yr IDDM duration	71 ± 8	73 ± 5	NS
Hypertension			
<20 yr IDDM duration	0/159	0/12	—
≥20 yr IDDM duration	5/72 (6.9)	3/13 (23.1)	NS
HDL cholesterol (mM)			
<20 yr IDDM duration	1.40 ± 0.26	1.45 ± 0.26	NS
≥20 yr IDDM duration	1.50 ± 0.39	1.40 ± 0.31	NS
LDL cholesterol (mM)			
<20 yr IDDM duration	2.56 ± 0.59	3.31 ± 0.83	<0.01
≥20 yr IDDM duration	2.72 ± 0.59	3.10 ± 0.88	NS
Triglycerides (mM)			
<20 yr IDDM duration	0.94 ± 0.51	1.43 ± 0.89	<0.05
≥20 yr IDDM duration	0.76 ± 0.35	1.47 ± 1.06	<0.001
Apoproteins (g/L)			
apoA-I			
<20 yr IDDM duration	135 ± 17	144 ± 17	<0.05
≥20 yr IDDM duration	138 ± 18	146 ± 15	NS
apoA-II			
<20 yr IDDM duration	44 ± 9	47 ± 8	NS
≥20 yr IDDM duration	43 ± 8	49 ± 8	<0.05
apoB			
<20 yr IDDM duration	88 ± 23	106 ± 26	<0.05
≥20 yr IDDM duration	93 ± 23	106 ± 25	0.06
Fibrinogen (g/l)			
<20 yr IDDM duration	2.7 ± 0.8	2.7 ± 0.4	NS
≥20 yr IDDM duration	2.5 ± 0.7	3.1 ± 1.3	<0.05

Data are means ± SD. Risk factors are < 20 yr IDDM duration and ≥ 20 yr IDDM duration.
*Includes 1 subject with normoalbuminuria at cycle 1 and over nephropathy at cycle 2.

bias for longer-duration subjects, i.e., some of the sicker individuals may have died earlier. Indeed, 147 subjects, otherwise eligible for EDC, died before recruitment started (15). This may explain why certain risk factors (e.g., LDL cholesterol) may be a stronger predictor in shorter-duration subjects (e.g., those with a high LDL cholesterol may be more likely to die earlier).

The significant independent predictors of microalbuminuria found in this study are summarized in Table 4. Of all the risk factors examined, glycemic control was the only one found to be a predictor of microalbuminuria in both men and women, and at short and long durations. This and time-related variables (age in men and IDDM duration in women) appeared to be the most important predictors of the development of microalbuminuria. Duration of IDDM generally has been the strongest risk factor for overt nephropathy (14,24), but has not always shown an association with microalbuminuria (9).

Previous data on the relationship between glycemic control and microalbuminuria are equivocal. Some studies have reported a significantly higher HbA_{1c} in microalbuminuric individuals (4,8,10), whereas others have reported no significant difference (25). We have reported previously that at a duration of 5 yr of IDDM, girls (but not boys) with microalbuminuria had a higher mean HbA_1 since diagnosis than those without (26). At a longer duration of IDDM, this study has found glycemic control plays a stronger predictive role in men than women. Thus, it appears that poor glycemic control may accelerate the development of microalbuminuria in both sexes, but that this acceleration occurs earlier in women.

Some studies (27,28)—although not all (29)—have shown that poor glycemic control in the first years of IDDM is associated with the subsequent development of persistent proteinuria or overt nephropathy. Other studies have shown that achieving strict metabolic control via continuous subcutaneous insulin infusion has a beneficial effect of slowing or preventing the progression of diabetic nephropathy in microalbuminuric individuals (30,31)—but not in individuals who have already reached the stage of persistent proteinuria (32). These studies suggest that a point of no return is reached in the development of diabetic nephropathy, after which glycemic control plays less of a role.

This study, showing that glycemic control is a predictor of microalbuminuria, provides important confirmation of these earlier studies by documenting for the first time the predictive power of glycemic control in the context of many other risk factors in an epidemiological population of IDDM individuals. These results also add support to those who advocate monitoring for microalbuminuria, a stage at which intensive efforts to achieve good glycemic control may be of benefit.

Table 3—*Relative risks for developing microalbuminuria over 2-yr period by baseline risk factors*

	Cut points		Relative risk (95% CI)
	Low risk	High risk	
HbA_1 (%)	<10	≥10	3.56 (1.47–8.63)
sBP (mmHg)	≤120	>120	1.43 (0.53–3.90)
dBP (mmHg)	≤80	>80	0.42 (0.06–2.98)
HDL cholesterol (mM)	≥1.29	<1.29	1.12 (0.53–2.40)
LDL cholesterol (mM)	<2.59	≥2.59	2.47 (1.06–5.74)
Triglycerides (mM)	<1.13	≥1.13	3.14 (1.51–6.49)
Apoproteins (g/L)			
apoA-I	<1.40	≥1.40	2.63 (1.18–5.87)
apoA-II	< .45	≥ .45	2.07 (0.95–4.50)
apoB	<1.00	≥1.00	3.40 (1.60–7.24)
Fibrinogen (g/L)	<2.50	≥2.50	2.23 (0.97–5.16)

There is little question that BP is elevated, although still within the normal range, in IDDM individuals with microalbuminuria compared with normoalbuminuric IDDM individuals (4,8,9). However, whether BP rises before or after the development of microalbuminuria has been debated considerably. Two other studies of normoalbuminuric IDDM individuals monitored prospectively to identify incident cases of microalbuminuria, and that document BP changes, have been fully reported. Mathiesen et al. (21) found no difference in BP between those who did and those who did not develop persistent microalbuminuria until the third year of microalbuminuria, indicating that BP elevation is secondary to the initiation of diabetic nephropathy. Raal et al. (23) found no difference in BP at baseline between individuals who remained normoalbuminuric and those who later progressed to microalbuminuria; however, they found the development of microalbuminuria was accompanied by a rise in dBP, indicating that BP elevation and the development of microalbuminuria are concurrent events. Another study (33) was based on IDDM subjects with a duration of 15–21 yr, selected on the basis of retinopathy status. BP readings abstracted from clinic records for these patients during adolescence or young adulthood were not higher in those who had microalbuminuria when compared with control subjects. However, a further study (34), which followed 137 normoalbuminuric IDDM subjects with a mean duration of 14 yr for 4 yr, found that those who progressed to microalbuminuria had higher mean BP at baseline as well as a higher AER and HbA_{1c}. Unlike this study, a history of smoking also was predictive (34). Unfortunately, lipid measures were not reported. This study, therefore, is consistent with this U.K. study and suggests that BP may rise before the detection of microalbuminuria and may even serve as a predictor of its development. We do not believe that antihypertensive medication use influenced these results because 98% of the participants were not taking such medication at baseline and only 3 participants (2 with microalbuminuria) started taking BP medication between exams. In addition, BP medication use was not a significant predictor in the multiple logistic regression analyses.

Several studies have compared, cross-sectionally, lipid levels between normoalbuminuric and microalbuminuric IDDM individuals (11–13), including the recent baseline analysis of renal function in the Diabetes Control and Complications Trial (35). Only one of these studies found microalbuminuric individuals had a significantly higher mean level of LDL cholesterol (13); however, in studies that included a group with overt nephropathy (11,12), the level of LDL cholesterol in the microalbuminuria group fell in between the levels in the normoalbuminuria and overt nephropathy groups. The same was true for total cholesterol, apoB, and triglycerides. It is well established that individuals with overt nephropathy have higher total and LDL cholesterol and triglyceride levels (7,11,12).

The major new finding of this study is that LDL cholesterol and triglycerides levels, although in the normal range, are elevated in those destined to later become microalbuminuric. This raises a new and important potential avenue for prevention (i.e., lipid correction). The potential that raised cholesterol is involved in the pathogenesis of microalbuminuria is supported by both animal experimental studies and clinical studies, which have been reviewed recently (36). These studies suggest a number of similarities between atherosclerosis and glomerulosclerosis, in particular the presence of lipid-filled monocytes in both atherosclerotic plaques and the mesangium, and similar proliferation of vascular smooth muscle cells (atherosclerosis) and mesangial cells (glomerulosclerosis).

Sodium lithium countertransport activity traditionally has been viewed as a genetic marker for predisposition to essential hypertension (37). This activity has received increased attention in diabetic individuals since Krolewski et al. (38) and Mangili et al. (39) reported it as elevated in individuals with diabetic nephropathy, including individuals with microalbuminuria. This has led to the hypothesis that genetic predisposition to hypertension determines who develops renal complications. However, these studies were cross-sectional, and sodium lithium countertransport activity has been positively correlated with factors

Table 4—*Multiple logistic regression results: overall, by sex and IDDM duration*

Risk factor (at cycle 1)	Coefficient	Coefficient/SE	P value
Men and women combined			
HbA_1	0.5315	3.767	<0.001
LDL cholesterol	0.0252	2.722	<0.01
Duration of IDDM	0.0828	2.372	<0.05
sBP	0.0428	1.938	0.05
BP-lowering medication	−0.5370	−0.407	NS
Men			
HbA_1	1.0591	2.713	<0.01
Age	0.2057	2.336	<0.05
AER (postclinic)	0.2783	2.180	<0.05
LDL cholesterol	0.0444	1.804	0.07
Women			
Duration of IDDM	0.0987	2.379	<0.05
Triglycerides	0.0139	2.101	<0.05
HbA_1	0.3064	1.743	0.08
IDDM duration < 20 yr			
LDL cholesterol	0.3650	2.919	<0.01
HbA_1	0.4390	2.709	<0.01
IDDM duration > 20 yr			
Triglycerides	0.0217	2.591	<0.01
HbA_1	0.6417	2.249	<0.05
sBP	0.0579	1.905	0.06

Individuals who were normoalbuminuric at both cycles were coded as 0, and individuals who were normoalbuminuric at cycle 1, but had microalbuminuria or overt nephropathy at cycle 2, were coded as 1.

such as total cholesterol, triglycerides, and apoB (40,41)—which also are elevated in IDDM individuals with microalbuminuria and overt nephropathy.

Unfortunately, measurement of sodium lithium countertransport activity was available for only 51 individuals in this study, 4 of whom developed microalbuminuria. Although the difference in the means of those who progressed (0.41 mmol lithium/L red blood cell/h) compared with those who did not (0.37 mmol lithium/L red blood cell/h) was much smaller than the previous studies (37,38), our sample size is too small to draw any conclusions. Some studies have noted that sodium lithium countertransport activity is increased only in those hypertensive individuals with a positive family history of hypertension (42,43). Therefore, the lack of a significant difference in the prevalence of a positive family history of hypertension between the two groups in this study may relate to the lack of difference in sodium lithium countertransport activity. Another study has failed to find elevated sodium lithium countertransport activity in IDDM individuals with nephropathy, but data on family history of hypertension were not presented (44).

An alternative hypothesis, the Steno hypothesis (45), suggests two factors (genetic predisposition and glycemic control) lead to complications, but proposes that the genetic component is a genetically conferred susceptibility to the deleterious effects of hyperglycemia rather than a predisposition to hypertension. Both theories imply the existence of a subgroup of individuals who are at risk; and, that this subgroup is identifiable by a genetically determined characteristic. They cite this subgroup as comprising the 35–45% of IDDM individuals who are commonly reported to develop nephropathy. Previously published data from the EDC study—which reported a combined prevalence of microalbuminuria and overt nephropathy at ≥30-yr duration of IDDM of 84% in men and 59% in women—suggest that most IDDM individuals will develop some form of nephropathy with time (14). It might, therefore, be more prudent to search for factors that accelerate the development of nephropathy rather than search for a genetically determined

Table 5—*Studies reporting incidence data for microalbuminuria*

	Normoalbuminuric at baseline (*n*)	Developed microalbuminuria (*n*)	Length of follow-up (yr)	Incidence density (cases/100 person-yr of follow-up)		
				All	Men	Women
Jerums et al. (20) (1987)	48	4	mean 7.8	~1.1	~1.2	~0.9
Mathiesen et al. (21) (1990)	205	15	2	3.7	3.5	3.8
Rudberg (22) (1991)	53	15	8	3.5	?	?
Raal et al. (23) (1992)	39	7	mean 2.2	~8.2	~6.5	~10.1
Present study	256	25	mean 2	4.8	3.6	5.9

subgroup at risk. Indeed, a wide range in the rate of progression of albuminuria has been noted (46).

This investigation found glycemic control and time-related variables (age or duration of IDDM) were the most important predictors of microalbuminuria. A new finding is the predictive role for LDL cholesterol, which has pathogenetic relevance and preventive potential. A weaker role for BP and familial hypertension was found compared with some previous studies, although sodium lithium countertransport activity data was only available on a small group. Thus, though factors such as age and duration of IDDM cannot be modified, this study suggests that good glycemic control, correction of even modest LDL-cholesterol elevations, and low-normal BP (intervention strategies that require formal clinical trial evaluation) may help prevent, slow, or delay the development of diabetic nephropathy.

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