Prevalence and Associated Features of Albuminuria in Koreans With NIDDM

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OBJECTIVE — To determine the prevalence and the associated features of microalbuminuria and overt proteinuria in Korean subjects with non-insulin-dependent diabetes mellitus (NIDDM) attending a hospital clinic.

RESEARCH DESIGN AND METHODS — A total of 631 Korean outpatients with NIDDM were studied cross-sectionally for the presence of albuminuria and other micro- and macrovascular complications. Urinary albumin excretion rate (AER) was determined in timed overnight urine samples. Subjects were divided into three groups: no nephropathy (AER <20 μg/min), microalbuminuria (AER 20–200 μg/min), and overt proteinuria (AER >200 μg/min).

RESULTS — Increased AER was present in 34% of our patients: 20% had microalbuminuria and 14% had overt proteinuria. Of patients with diabetes duration ≥15 years, 35% had overt proteinuria. Most (82%) patients with overt proteinuria had retinopathy. Although the prevalence of microalbuminuria as a whole did not differ according to diabetes duration, the prevalence of microalbuminuria in the patients with retinopathy increased with diabetes duration. The microalbuminuric patients without retinopathy (diabetes duration <5 years) were characterized by higher prevalence of hypertension and previous obesity, higher plasma triglyceride level, and lower plasma high-density lipoprotein cholesterol level.

CONCLUSIONS — The prevalence of overt proteinuria in Korean NIDDM patients with a long diabetes duration was higher than that reported in Caucasians. Our data also suggest that the clinical meaning of microalbuminuria may be different based on the presence or the absence of retinopathy. Microalbuminuria in patients with retinopathy most probably would reflect diabetic nephropathy. In contrast, some recent-onset NIDDM patients with microalbuminuria in the absence of retinopathy had features of syndrome X.

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AER, albumin excretion rate; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVA, cerebrovascular accident; dBP, diastolic blood pressure; HDL, high-density lipoprotein; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; PVD, peripheral vascular disease; sBP, systolic blood pressure.

Several reports, including the World Health Organization Multinational Study of Vascular Disease in Diabetes, indicate ethnic/racial variations in the prevalence of various vascular complications of diabetes (1–4). Macrovascular complications, such as coronary heart disease (CHD) and peripheral vascular disease (PVD), are rare in Asian populations when compared with Caucasians (1), whereas the prevalence of albuminuria has been reported to be higher in Asian populations (1,5,6).

Microalbuminuria is a well-established marker for incipient nephropathy in patients with insulin-dependent diabetes mellitus (IDDM) (7). In contrast, the meaning of microalbuminuria in non-insulin-dependent diabetes mellitus (NIDDM) is complex. Microalbuminuria progresses to overt proteinuria in NIDDM patients, but not as consistently as it does in IDDM patients (8,9). The presence of microalbuminuria in NIDDM patients is closely linked to cardiovascular disease and mortality (8,10–12). Studies reporting the association of microalbuminuria with hypertension, dyslipidemia, obesity, and insulin resistance in NIDDM, as well as in prediabetic subjects, even suggested that this may be a feature of syndrome X, rather than a consequence of diabetes (13–16). The clinical meaning of microalbuminuria in Asian subjects with NIDDM remains to be established.

This cross-sectional study was undertaken to ascertain the prevalence of microalbuminuria and overt proteinuria in Korean NIDDM patients and to determine the associated features of albuminuria.

RESEARCH DESIGN AND METHODS

— This study was performed in NIDDM patients attending a diabetes clinic of a university hospital (the Asan Medical Center) in Seoul, South Korea. The diagnosis of NIDDM was based on clinical characteristics that included *1*) no past history of ketoacidosis, 2) diagnosis of diabetes after 30 years of age, and 3)

treatment by diet and/or oral hypoglycemic agents or fasting serum C-peptide values >0.30 nmol/l in the insulin-requiring patients (17).

Over a 3-month period from April to June 1993, 745 consecutive patients who were 30–75 years old were screened for eligibility to participate in the study. Of these, 35 were excluded from the study because they had malignancy, chronic liver disease, or another disabling disease. Of the remaining 710 patients, 682 (96%) agreed to participate in the study. Of these patients, 58% were receiving oral hypoglycemic agents, 24% were receiving insulin, and 18% were treated by diet alone. All patients gave their informed consent.

Patients collected a timed overnight urine sample for the measurement of albumin excretion rates (AERs) by radioimmunoassay (Diagnostic, Los Angeles, CA). This was repeated 4 weeks later. Normoalbuminuria was considered to be present if urinary AER was consistently <20 μg/min. Patients were recalled for a third urine sample if the results of the initial two were inconsistent. Microalbuminuria was defined as a mean of AER between 20 and 200 μg/min and overt proteinuria as a mean AER >200 μg/min (18). Urinary tract infection, if present, was treated, and the urine collection was then repeated.

All participants were examined and interviewed by one of the authors (K.-U.L.) for past and present evidence of myocardial infarction, angina pectoris, cerebrovascular accident (CVA), and PVD. Blood pressure (BP) was measured after a 10-min rest in sitting position, with a standard 12.5-cm cuff mercury sphygmomanometer. Diastolic BP (dBP) was recorded at the disappearance of the Korotkoff sounds (phase V). Arterial hypertension was defined as systolic BP (sBP) ≥160 mmHg and/or dBP ≥95 mmHg or if the patient was on antihypertensive therapy.

Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) (kg/m^2) was calculated from these measurements. Each subject was also asked to recall his or her maximum weight and weight at diagnosis, and the corresponding BMI was calculated from the recalled weight divided by the current height. We defined obesity as a BMI >25 kg/m^2 (19).

Dorsalis pedis artery pulse was carefully checked. Those who had symptoms and signs suggesting PVD underwent segmental BP measurement with a Doppler ultrasound device (20) to document the lesion. A 12-lead ECG was recorded and was coded using the Minnesota codes (21). CHD was diagnosed if the ECG showed signs of probable myocardial infarction (Minnesota code 1.1–2) or possible myocardial ischemia (Minnesota code 1.3, 4.1–4.5, 5.1–5.3, or 7.1). The patients with symptoms suggestive of CHD underwent a treadmill test, thallium scan, and/or coronary angiography to document the lesion. Those patients in whom CHD was confirmed with these tests were separately classified as "confirmed CHD."

Fundus examination was performed by an ophthalmologist after mydriasis. The findings were graded as follows: *1*) no signs of diabetic retinopathy, 2) nonproliferative retinopathy, or 3) proliferative retinopathy.

Plasma glucose, triglyceride, and total cholesterol levels were measured using an autoanalyzer with enzymatic techniques. High-density lipoprotein (HDL) cholesterol was measured after heparin and manganese chloride precipitation (22). HbA_1 was measured by affinity chromatographic method (Isolab, Akron, OH; normal range: 4–8%). Plasma C-peptide level was measured by radioimmunoassay (Daiichi, Tokyo, Japan).

Statistical analysis

Values are given as means ± SD (ranges). Statistical analysis was performed using SAS computer software (SAS, Cary, NC). To compare continuous variables, Student's *t* test or analysis of variance followed by Duncan's multiple-range test was used. For evaluating frequencies, a chi-squared test was used. To account for the effect of duration of diabetes in comparison of complications, we performed a stratified Mantel-Haenszel analysis using intervals of known diabetes duration of 0–4, 5–9, 10–14, 15–19, and >20 years. All *P* values reported are for two-sided tests, and results were considered significant if $P < 0.05$.

RESULTS — Of 682 patients, 15 patients were excluded because of microscopic hematuria. An additional 36 were excluded because a second or third urine specimen could not be obtained. Complete data are presented for 631 patients.

Increased AER was present in 34% of our NIDDM subjects: 20% had microalbuminuria and 14% had overt proteinuria (Table 1). The number of men and women in each category of AER was not significantly different. Known diabetes duration was longer in patients with overt proteinuria or with microalbuminuria compared with patients with normoalbuminuria. BMI was lower in patients with overt proteinuria compared with patients with normo- or microalbuminuria. The prevalence of hypertension increased with increasing albuminuria. sBP and dBP were higher in untreated patients with microalbuminuria or with overt proteinuria compared with patients with normoalbuminuria. Plasma total cholesterol and triglyceride levels were higher and HDL cholesterol level was lower in patients with overt proteinuria compared with patients with normo- or microalbuminuria.

The prevalence of retinopathy and PVD increased with increasing albuminuria (Table 2; *P* values were determined after adjustment for known diabetes duration by Mantel-Haenszel analysis). Of patients with overt proteinuria, 82% had evidence of retinopathy. CHD was associated with overt proteinuria when based on Minnesota ECG codes, but not when based on symptoms and other measures to confirm its presence.

Table 1—*Clinical characteristics of patients with NIDDM in relation to urinary AER*

	Normoalbuminuria	Microalbuminuria	Proteinuria
n	420	124	87
Urinary AER (μg/min)	6 ± 5 (1–19)	71 ± 52 (21–195)	446 ± 185 (258–761)
Age (years)	55.5 ± 10.2	56.7 ± 10.4	60.7 ± 8.8†
Sex (M/F)	203/217	63/61	51/36
Known duration of diabetes (years)	6.7 ± 6.1	9.2 ± 7.6*	14.4 ± 7.7†
Diet/OHA/insulin (%)	19/58/23	17/59/24	16/54/30
BMI (kg/m^2)	24.3 ± 3.0	24.7 ± 3.3	23.4 ± 2.8†
Fasting plasma glucose (mmol/l)	9.2 ± 2.5	9.3 ± 2.9	9.0 ± 3.0
HbA_1 (%)	10.9 ± 3.6	11.0 ± 3.1	10.9 ± 3.5
Cholesterol (mmol/l)	5.40 ± 1.10	5.50 ± 1.20	5.95 ± 1.55†
Triglyceride (mmol/l)	2.2 ± 1.5	2.3 ± 1.6	2.7 ± 1.6†
HDL cholesterol (mmol/l)	1.25 ± 0.30	1.20 ± 0.30	1.15 ± 0.40†
Percentage with hypertension	38	53*	56*
Percentage receiving antihypertension treatment	22 (92/420)	29 (36/124)	45 (39/87)†
sBP (mmHg) in untreated patients	137 ± 23	150 ± 21*	161 ± 20†
dBP (mmHg) in untreated patients	85 ± 9	88 ± 11*	89 ± 10*

Data are means ± SD (ranges). OHA, oral hypoglycemic agent. * Significantly different from normoalbuminuric group. † Significantly different from normo- and microalbuminuric groups.

The prevalence of overt proteinuria increased with diabetes duration (Fig. 1). Of the patients with diabetes duration ≥15 years, 35% had overt proteinuria. In contrast, the prevalence of microalbuminuria did not change significantly according to diabetes duration. However, the prevalence of microalbuminuria in the patients with retinopathy increased after 10 years' duration of diabetes. Of patients with microalbuminuria and overt proteinuria, 88 and 90%, respectively, with diabetes duration ≥15 years had retinopathy.

Most (76%) microalbuminuric patients with known diabetes duration <5 years did not have retinopathy. Clinical data for these patients and normoalbuminuric patients with diabetes duration <5 years are compared in Table 3. Microalbuminuric patients without retinopathy were characterized by higher BMI, higher sBP and dBP, higher plasma triglyceride level, lower plasma HDL cholesterol level, and higher prevalence of hypertension and previous obesity.

CONCLUSIONS — The association between increased urinary albumin excretion and other micro- and macrovascular complications is well known in NIDDM patients (23,24). In our study, we used clinical assessment of retinopathy and a sequential algorithm for measurement of PVD. Both of these measures may have led to a considerable misclassification. With this limitation in mind, the present study shows that increased urinary albumin excretion is associated with longer duration of diabetes, dyslipidemia, and higher prevalence of retinopathy, PVD, and hypertension.

Our study confirmed the previous report that CHD is relatively rare in Asian subjects with NIDDM (1). The prevalence of CHD in each category of urinary AER was consistently lower in Korean NIDDM patients when compared with a previous study in Caucasians (10, 12, and 26% vs. 22, 26, and 46%, respectively) (23). This low rate of CHD in Asian NIDDM patients

Table 2—*Prevalence of various complications in relation to urinary AER in NIDDM patients*

	Normoalbuminuria	Microalbuminuria	Proteinuria
n	420	124	87
Retinopathy	21	50*	83*‡
Nonproliferative	20	39*	48†
Proliferative	1	11*	34*‡
CHD	10	12	26
Probable and possible	5	9	19*
Confirmed	5	3	7
CVA	6	11	17†
PVD	3	7†	17*§
Hypertension	38	53†	56†

Data are percentages of *n*. *P* values were determined after adjustment for known diabetes duration by Mantel-Haenszel analysis. * $P < 0.001$ vs. normoalbuminuric group; † $P < 0.05$ vs. normoalbuminuric group; ‡ $P < 0.001$ vs. microalbuminuric group; § $P < 0.05$ vs. microalbuminuric group.

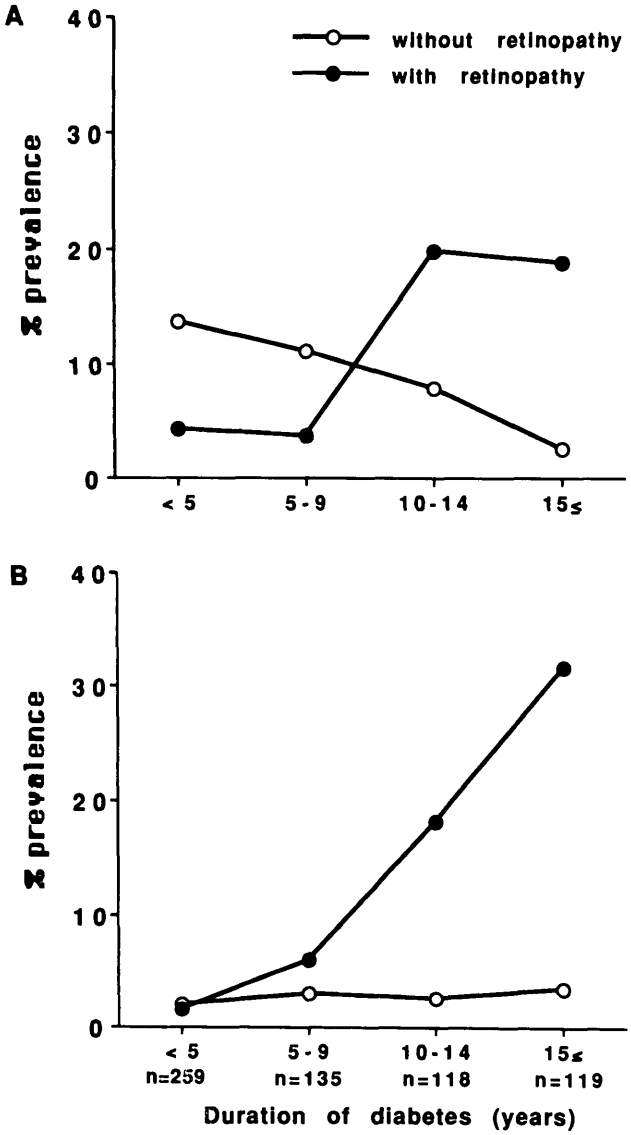

Figure 1—*Prevalence of microalbuminuria (A) and overt proteinuria (B) in Korean subjects with NIDDM with or without retinopathy, according to duration of diabetes.*

may explain the ethnic difference in the prognosis for albuminuric NIDDM patients. In Caucasian subjects, the major cause of death in albuminuric NIDDM patients is cardiovascular diseases (11,12). In contrast, Sasaki et al. (6) reported that renal disease is the predominant cause of death in albuminuric NIDDM patients in Japan.

Mechanisms responsible for the low rate of CHD in Korean NIDDM patients remain to be determined. One possible explanation would be that obesity (25) is relatively uncommon in this population. The mean BMI of our NIDDM patients (24.3 kg/m^2) was much smaller than that reported in the Caucasian populations (27–29 kg/m^2) (11,14,23,24). Studies performed in Caucasians and African Americans with NIDDM reported that BMI was higher in patients with microalbuminuria or overt proteinuria than in patients with normoalbuminuria (23,26). Such an association between albuminuria and obesity was not found in our patients.

Several studies in Caucasian populations reported that ~50–60% of NIDDM patients with overt proteinuria did not have retinopathy (12,23,27). In contrast, 82% of Korean NIDDM patients with overt proteinuria had retinopathy. This feature is similar to what is observed in Caucasian IDDM patients (28). The relative contribution of diabetic nephropathy as a cause of proteinuria cannot be estimated accurately without kidney biopsy. However, recent data indicate that nearly all proteinuric NIDDM patients with diabetic retinopathy have pathological evidence of diabetic nephropathy, while the chance for diabetic nephropathy is 50% in proteinuric patients without retinopathy (29).

The overall prevalence of overt proteinuria in our patients was similar to that reported in Caucasians (23,27,30). However, the prevalence of proteinuria in the patients with a longer duration of diabetes was somewhat higher in Korean subjects with NIDDM. Studies in Caucasians showed that 19–26% of NIDDM patients with diabetes duration ≥15 years have overt proteinuria (23,30). Our results report that 35% of Korean NIDDM patients with known diabetes duration ≥15 years have overt proteinuria. A previous study in Japan reported an even higher 20-year cumulative incidence (>50%) of overt proteinuria (6). Together with the high rate of retinopathy in proteinuric patients, the prevalence of diabetic nephropathy in Asian NIDDM patients would be higher than that in Caucasians.

Whether the occurrence of microalbuminuria is a function of diabetes duration has been a matter of controversy (5,23,31,32). In our study, the prevalence of microalbuminuria as a whole did not show significant variation according to diabetes duration. However, quite similarly to what is observed in other microvascular complications (33), the prevalence of microalbuminuria in the patients

Table 3—*Clinical characteristics of microalbuminuric patients without retinopathy and normoalbuminuric patients (diabetes duration <5 years)*

	Normoalbuminuria	Microalbuminuria	*P* value
n	202	35	—
Urinary AER (μg/min)	5 ± 5 (2–19)	48 ± 33 (21–175)	—
Age (years)	50.7 ± 11.1	51.1 ± 10.8	NS
Sex (M/F)	90/102	19/16	NS
Known duration of diabetes (years)	1.9 ± 1.3	2.1 ± 1.7	NS
BMI (kg/m^2)	24.3 ± 2.8	26.0 ± 3.2	0.001
BMI at diagnosis (kg/m^2)	25.1 ± 2.9	27.2 ± 3.0	0.0001
Maximum BMI (kg/m^2)	26.3 ± 2.8	28.2 ± 3.3	0.0004
Age at maximum BMI (years)	43.9 ± 10.1	44.0 ± 10.4	NS
Percentage receiving antihypertensive treatment	21 (42/202)	31 (11/35)	NS
sBP (mmHg) in untreated patients	136 ± 23	148 ± 22	0.02
dBP (mmHg) in untreated patients	83 ± 13	90 ± 12	0.01
Fasting plasma glucose (mmol/l)	9.2 ± 2.5	9.5 ± 3.0	NS
HbA_1 (%)	10.9 ± 3.7	11.3 ± 4.4	NS
Cholesterol (mmol/l)	5.50 ± 1.20	5.70 ± 1.10	NS
Triglyceride (mmol/l)	2.3 ± 1.8	3.0 ± 2.0	0.04
HDL cholesterol (mmol/l)	1.25 ± 0.30	1.10 ± 0.30	0.007
Percentage obese	43	60	NS
Percentage previously obese	71	90	0.01
Percentage hypertensive	38	68	0.001

Data are means ± SD (ranges).

with retinopathy increased sharply after 10 years of diabetes duration.

Of Korean NIDDM patients with known diabetes duration <5 years, 18% had microalbuminuria. This may be due to a long unrevealed duration of diabetes (34), but causes other than diabetic nephropathy may be responsible (29). Studies reporting the association of microalbuminuria with hypertension, dyslipidemia, obesity, and insulin resistance in NIDDM patients as well as in nondiabetic subjects suggest that this may be a feature of syndrome X (13–16). Most of our patients with microalbuminuria and known diabetes duration <5 years did not have retinopathy. These patients tend to have a higher plasma triglyceride level, a lower HDL cholesterol level, and a higher prevalence of hypertension and previous obesity, which suggests that microalbuminuria in some of these patients may be a feature of syndrome X.

The clinical implication of these findings would be that some microalbuminuric NIDDM patients without retinopathy may benefit by measures that improve metabolic profiles of syndrome X. In accordance with this notion, Dubois et al. (35) recently reported on two cases of nondiabetic glomerulopathy in which the decrease in blood lipid levels was associated with a decrease in proteinuria. However, it should be noted that there are no data available yet regarding the renal pathology of microalbuminuric NIDDM patients with or without retinopathy.

In conclusion, microalbuminuria and overt proteinuria are frequently observed in Korean subjects with NIDDM. The prevalence of overt proteinuria in patients with long diabetes duration was higher than that reported in Caucasians. As reported previously, albuminuria was associated with other vascular complications. However, the pattern of association was different from that in Caucasians. Most patients with overt proteinuria had retinopathy. In contrast, the prevalence of CHD in Korean subjects with NIDDM was consistently lower than that reported in Caucasians in all three categories of AER. Our data also suggest that the clinical meaning of microalbuminuria may be different based on the presence or the absence of retinopathy. Microalbuminuria in the presence of retinopathy most probably would reflect diabetic nephropathy. On the other hand, some recent-onset NIDDM patients with microalbuminuria in the absence of retinopathy had features of syndrome X.

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