Abnormal Albuminuria as a Predictor of Mortality and Renal Impairment in Chinese Patients With NIDDM

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OBJECTIVE — Microalbuminuria predicts mortality in non-insulin-dependent diabetes mellitus (NIDDM), but its association with deterioration of renal function remains more controversial than in insulin-dependent diabetes mellitus (IDDM). Using albumin-to-creatinine ratios (ACRs) in random spot urine samples is a convenient method for evaluating albuminuria. We studied prospectively the predictive values of albuminuria in NIDDM when assessed by this urine measurement.

RESEARCH DESIGN AND METHODS — Between 1991 and 1992, we restudied the clinical and biochemical status of 403 Chinese NIDDM patients recruited in 1989 after a follow-up period of 26.6 ± 3.2 months (mean ± SD). Spot urine ACR was measured on two occasions and microalbuminuria was defined as a mean ACR between 5.6 and 38 mg/mmol.

RESULTS — From the original cohort, 29 patients had died mostly because of cardiovascular events with or without renal failure. The overall relative risk of death in patients with abnormal albuminuria was 7.1 ($P < 0.001$) (microalbuminuria: 3.7, $P = 0.04$; macroalbuminuria: 11, $P < 0.001$). On multivariate analysis, the independent predictive factors for mortality were plasma creatinine (wald = 12.1, $P < 0.001$) and glucose concentrations (wald = 10.4, $P < 0.001$) in the normo- and microalbuminuric patients ($n = 11$) and age (wald = 4.4, $P = 0.03$) and plasma creatinine (wald = 8.2, $P < 0.01$) in the macroalbuminuric group ($n = 18$). In the survivors ($n = 374$), baseline spot urine ACR was independently associated with 2-year spot urine ACR in the normo- ($P < 0.001$), micro- ($P < 0.01$), and macroalbuminuric groups ($P = 0.01$). In addition, baseline spot urine ACR was independently related to 2-year plasma creatinine ($P = 0.01$) in the macroalbuminuric group. The rates of change of the reciprocal of plasma creatinine ($\Delta[Cr]^{-1}$) were -27.3 ± 62.5, -43.4 ± 68.6, and $-108.8 \pm 98.81 \cdot \mu mol^{-1} \cdot month^{-1}$ in the normo-, micro-, and macroalbuminuric groups, respectively ($P < 0.001$). The $\Delta[Cr]^{-1}$ was independently and inversely related to the baseline spot urine ACR ($P < 0.001$) and 2-year systolic blood pressure ($P < 0.001$).

CONCLUSIONS — Abnormal albuminuria as indicated by a random spot urine ACR >5.6 mg/mmol predicts increased mortality and is associated with the progression of albuminuria and deterioration of renal function in Chinese NIDDM patients.

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ACR, albumin-to-creatinine ratio; $\Delta[Cr]^{-1}$, rate of change of the reciprocal of plasma creatinine; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; UAE, urinary albumin excretion.

Microalbuminuria predicts the progression of nephropathy and renal failure in insulin-dependent diabetes mellitus (IDDM) (1) and mortality in non-insulin-dependent diabetes mellitus (NIDDM) (2). Renal failure is responsible for a significant number of deaths in non-Caucasian NIDDM patients (3). The relationship between microalbuminuria and subsequent renal deterioration in NIDDM, however, remains controversial (3). Albumin-to-creatinine ratios (ACRs) in spot urine samples correlate well with albumin excretion in timed urine collections and can be used to quantify proteinuria (4). We used random spot urine samples to examine the natural history of albuminuria in a cohort of Chinese NIDDM patients and its relationship with subsequent mortality and deterioration in renal function.

RESEARCH DESIGN AND METHODS

— A total of 453 NIDDM patients were recruited in 1989 from the Diabetes Clinic of the Prince of Wales Hospital. The methodologies used in the baseline cross-sectional study have been described previously (5). They were recalled 2 years later between 1991 and 1992 and restudied using the same methodology, including the measurement of ACRs in random sterile spot urine samples on two separate occasions, between 8 and 16 weeks apart (5). In addition, fasting plasma cholesterol and triglyceride concentrations were measured. For validation of spot urine ACRs and 24-h urinary albumin excretion (UAE), 501 pairs of concurrent sterile random spot urine samples and 24-h urine collections were made in 167 Chinese NIDDM patients recruited separately for a clinical trial (6). The laboratory assays for the various measurements have been described previously (5). In 1989, total HbA_1 was measured by gel electrophoresis (Ciba Corning Diagnostics) (reference range: 6.5–8.5%). From 1990 on, HbA_{1c} was measured by automated ion-exchange chromatographic methods (Bio-Rad) (ref-

Table 1—*The clinical and biochemical characteristics of NIDDM patients at recruitment in 1989 and at 2-year follow-up in 1991*

	Baseline	Follow-up
Body mass index (kg/m^2)	24.5 ± 3.7	24.3 ± 3.7
Systolic blood pressure (mmHg)	146 ± 26	137 ± 21‡
Diastolic blood pressure (mmHg)	79 ± 12	77 ± 10‡
Fasting plasma cholesterol (mmol/l)	—	5.6 ± 1.4
Fasting plasma triglyceride (mmol/l)	—	2.6 ± 2.2
HbA_1 (%)	10.8 ± 2.6	11.6 ± 3.0*‡
Plasma creatinine (μmol/l)	78 (47–565)	87 (52–947)‡
Spot urine ACR (mg/mmol)	3.6 (35.7–89.3)	4 (0.24–1,012.3)
Normoalbuminuria	56.1 (208)	57.2 (214)
Microalbuminuria	25.1 (94)	22.7 (85)
Macroalbuminuria	18.7 (72)	20.1 (75)

Data are means ± SD (*n*) or median (range). Baseline fasting plasma cholesterol and triglyceride levels were not measured. *Transformed from HbA_{1c} based on the conversion factor: $HbA_{1c} = 0.65 \times HbA_1 + 0.86$; ‡$P < 0.001$.

erence range: 5.1–6.4%). The conversion factor used to allow comparison was $HbA_{1c} = (0.65 \times HbA_1) + 0.86$. Total cholesterol and triglyceride levels were measured enzymatically with commercial reagents automated on a centrifugal analyzer (Encone Baker). There was good linear correlation between the 501 pairs of spot urine ACR and 24-h UAE values ($r = 0.82$, $P < 0.0001$, $\log[ACR] = 0.83 \times \log[UAE] - 1.1$). Based on the regression analysis, normo-, micro-, and macroalbuminuria were defined as an ACR <5.6, 5.6–38, and >38 mg/mmol, respectively. The progression of renal function was estimated by the rate of change of the reciprocal of plasma creatinine ($\Delta [Cr]^{-1}$).

Statistical Analysis

The analysis was performed using the ABstat (version 6.01, Anderson Bell) and Statistical Package for Social Sciences (version 4.0) statistical packages. The mean values of all parameters at both visits were used for analysis. Plasma creatinine concentrations and spot urine ACRs were logarithmically transformed before analysis because of skewed distributions. All data are expressed as mean ± SD or median (range) as appropriate. Student's *t* test, analysis of variance with Scheffe's test, and Mann-Whitney tests were used for comparisons as appropriate. Relative risks with 95% confidence intervals (Taylor series) were compared between groups using Fisher's exact χ^2 test. Spearman's correlation analysis and stepwise multiple regression analysis were used to test the associations between different variables. Multivariate analysis by stepwise logistic regression modeling was used to identify the most significant and independent variables for mortality as indicated by the Wald value. A *P* value <0.05 (two-tailed) was considered to be significant.

RESULTS — Of the 453 NIDDM patients originally studied in 1989, the status of 403 was reevaluated at a mean follow-up period of 26.6 ± 3.2 months between 1991 and 1992. A total of 374 patients (131 men [35%], ages 54.2 ± 12.5 years) with a mean duration of diabetes of 5.5 ± 4.8 years in 1989 were restudied. Table 1 summarizes their clinical and biochemical characteristics at baseline and follow-up. Blood pressure was lower, but both renal function and glycemic control had deteriorated at the time of restudy. It was confirmed that the other 29 patients had died (15 men, 14 women); 6 were confirmed through informants and the remainder through hospital medical records. The majority died from a combination of cardiovascular events (3 of 4 in normoalbuminuric, 6 of 7 in microalbuminuric, and 11 of 18 in macroalbuminuric groups) and/or renal failure (1 of 7 in microalbuminuric and 5 of 18 in macroalbuminuric groups). For cardiovascular events, cerebrovascular accident was the cause of death in 8 patients and ischemic heart disease in 11. Deceased patients were older, less obese, had higher baseline systolic blood pressure, and worse glycemic control and renal function than the survivors (Table 2). Compared with normoalbuminuric patients, the overall relative risk of death in patients with abnormal albuminuria was 7.1 (2.5–19.9, $P < 0.001$); microalbuminuria: 3.7 (1.1–12.4, $P = 0.04$); and macroalbuminuria: 11 (3.8–31.6, $P < 0.001$). On multivariate analysis, the independent predictive factors for mortality were plasma creatinine (wald = 12.1, $P < 0.001$) and glucose concentrations (wald = 10.4, $P < 0.001$) in the normo- and microalbuminuric patients ($n = 11$) and age (wald = 4.4, $P = 0.03$) and plasma creatinine (wald = 8.2, $P < 0.01$) in the macroalbuminuric group ($n = 18$).

Using multivariate analysis with age, duration of diabetes, blood pressure, lipid profiles, renal function, and glycemic indexes as independent variables, baseline spot urine ACR ($R^2 = 0.74$, $F = 456.6$, $P < 0.001$) was independently associated with 2-year spot urine ACR ($\beta = 0.80$, $P < 0.001$) and plasma creatinine ($\beta = 0.11$, $P < 0.01$) in the whole group. In the normoalbuminuric subjects ($R^2 = 0.29$, $F = 25.3$, $P < 0.001$), baseline spot urine ACR was related to age ($\beta = 0.15$, $P = 0.02$), 2-year spot urine ACR ($\beta = 0.44$, $P < 0.001$), and HbA_{1c} ($\beta = 0.13$, $P = 0.04$). Baseline spot urine ACR ($R^2 = 0.18$, $F = 11.3$, $P < 0.01$) was associated with 2-year spot urine ACR ($\beta = 0.36$, $P < 0.01$) in both micro- and macroalbuminuric subjects ($\beta = 0.36$, $P < 0.01$). In the macroalbuminuric group ($R^2 = 0.31$, $F = 15.2$, $P < 0.001$), baseline spot urine ACR was independently related to 2-year plasma creatinine ($\beta = 0.31$, $P = 0.01$).

Table 2—*The baseline clinical characteristics and biochemical data of decreased NIDDM patients compared with those confirmed to be alive at 2 years*

	Deceased	Alive
n	29	374
Sex (M/F)	15/14 (5:5)	138/243 (4:6)
Age (years)	66.8 ± 10.9	53.7 ± 12.8‡
Body mass index (kg/m^2)	22.9 ± 3	24.5 ± 3.7*
Systolic blood pressure (mmHg)	159 ± 32	143 ± 27†
Diastolic blood pressure (mmHg)	82 ± 14	79 ± 12
Random plasma glucose (mmol/l)	12.3 ± 6.5	10.3 ± 4.1†
HbA_1 (%)	11.5 ± 3.5	10.9 ± 3.2
Plasma creatinine (μmol/l)	131 (65–527)	78 (47–565)‡
Spot urine ACR (mg/mmol)	94 (3.7–696.4)	3.5 (0.3–754.3)‡
Normoalbuminuria (%)	13.8 (4)	57.2 (214)
Microalbuminuria (%)	24.1 (7)	22.7 (85)
Macroalbuminuria (%)	62.1 (18)	20.1 (75)

Data are means ± SD (*n*) or median (range). *$P < 0.02$; †$P < 0.01$; ‡$P < 0.001$.

The $\Delta[Cr]^{-1}$ was −27.3 ± 62.5, −43.4 ± 68.6, and −108.8 ± 98.8 liter · μmol^{-1} · month^{-1} in the normo-, micro-, and macroalbuminuric subjects, respectively ($P < 0.001$ between normo- and macroalbuminuric groups, $P < 0.001$ between micro- and macroalbuminuric groups). The $\Delta[Cr]^{-1}$ ($R^2 = 0.17$, $F = 33.8$, $P < 0.001$) was independently related to baseline spot urine ACR ($\beta = -0.31$, $P < 0.001$) and 2-year systolic blood pressure ($\beta = -0.19$, $P < 0.001$). In the normoalbuminuric subjects ($n = 208$), 28 (13.5%) patients progressed to microalbuminuria ($n = 26$) or macroalbuminuria ($n = 2$). In the microalbuminuric subjects ($n = 94$), 29 (31%) became normoalbuminuric and 17 (18.1%) became macroalbuminuric. In the macroalbuminuric subjects ($n = 72$), 11 (15.3%) became microalbuminuric and 3 (4.2%) became normoalbuminuric.

CONCLUSIONS— In Caucasians, the incidence of end-stage renal failure is estimated to be 15 times greater in IDDM than in NIDDM (7). However, proteinuria and renal failure are disproportionately more prevalent among non-Caucasian NIDDM patients (3), including African-Americans (8), Hispanics (9), Pima Indians (10), Asian Indians (11), and Chinese. The propensity for coexistent hypertension is an important factor for this racial predilection for NIDDM-related renal disease (3). The predictive value of microalbuminuria in renal deterioration is more controversial in NIDDM than in IDDM (3). In the present study, we found that the rate of deterioration of renal function was independently related to baseline albuminuria and blood pressure. Furthermore, the baseline spot urine ACR predicts the progression of albuminuria, irrespective of its severity, although its relationship with rising plasma creatinine was predominant in the macroalbuminuric group. However, given the progressive nature of albuminuria, eventual deterioration in renal function may be expected in patients with less severe albuminuria. Nevertheless, varying regression and deterioration of albuminuria was also observed in the present study, in particular within the microalbuminuric group. Although the possibility of misclassification of the albuminuric status based on random spot urine ACRs cannot be excluded, aggressive antihypertensive treatment (12) and glycemic control (13) are known to reduce proteinuria and slow the deterioration of renal function. Although the use of antihypertensive medications was not monitored in these patients, a proportion of patients seen in 1989 required antihypertensive therapy, explaining their lower blood pressure after 2 years. Despite this, albuminuria continued to increase, although one can postulate that this rate of increase might have been attenuated by the treatment. The introduction of antihypertensive therapy might also explain the improvement of albuminuria in some patients, especially those with microalbuminuria. Among the deceased, the majority died from atherosclerotic events with or without renal failure, and it is not surprising that age and plasma creatinine predicted mortality in those patients who had established renal damage reflected in macroalbuminuria. However, even in those with normo- or microalbuminuria, poorer glycemic control and higher plasma creatinine concentrations were still highly significant predictors of mortality.

Our data suggest that abnormal albuminuria as indicated by a random spot urine ACR >5.6 mg/mmol predicts mortality and is associated with progression of albuminuria and deterioration of renal function in Chinese NIDDM patients.

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