Microalbuminuria and Coronary Heart Disease in NIDDM

An Incidence Study

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In most survival studies in NIDDM, microalbuminuria (urinary albumin excretion rate 20–200 µg/min) predicts early mortality; in cross-sectional studies, it is associated with coronary heart disease (CHD) morbidity. It is unclear, however, whether microalbuminuria is a risk factor for the development of CHD or the result of it, and little is known of the factors that predispose to the development of microalbuminuria in NIDDM. We examined these issues in a 7-year prospective study of a hospital-based cohort comprising 146 white NIDDM patients without clinical albuminuria. Microalbuminuria was a significant risk factor for both all-cause mortality (relative risk 3.94, 95% CI 2.04–7.62) and CHD mortality (relative risk 7.40, 95% CI 2.94–18.7) when adjusted for age only. Its independent predictive power did not persist, however, in age-adjusted multivariable survival analysis that allowed for the other significant risk factors: male sex, preexisting CHD, high levels of glycated hemoglobin, and high serum cholesterol. Among men free of CHD at baseline, the independent risk factors for CHD morbidity and mortality were microalbuminuria, current smoking, high diastolic blood pressure, and high serum cholesterol (all $P < 0.05$). For the 100 NIDDM patients with normoalbuminuria at baseline, the incidence of microalbuminuria was 29% over the 7-year period. In that group, fasting plasma glucose, current smoking, preexisting CHD, and high initial urinary albumin excretion rate were risk factors for the development of microalbuminuria (all $P < 0.05$). When men and women were analyzed separately, preexisting CHD was a significant risk factor in men only. These results demonstrate that microalbuminuria predicts incident clinical CHD in men with NIDDM. Preexisting CHD is also a risk factor for incident microalbuminuria in men, however, suggesting that microalbuminuria and CHD are not causally related but rather reflect common determinants. *Diabetes* 47:1786–1792, 1998

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CHD, coronary heart disease; CV, coefficient of variation; ECG, electrocardiogram; OR, odds ratio; RIA, radioimmunoassay; RR, relative risk; SOR, standardized odds ratio; UAER, urinary albumin excretion rate; WHO, World Health Organization.

People with NIDDM are at markedly increased risk for coronary heart disease (CHD). Established major risk factors explain this risk only in part (1,2). In recent years, microalbuminuria has been recognized as a powerful and largely independent marker of vascular risk in diabetes (3,4). In IDDM, microalbuminuria is an early pointer to progressive renal disease and cardiovascular mortality (5–7). Microalbuminuria also predicts the development of clinical albuminuria in NIDDM (4), but its major prognostic implication, at least in white NIDDM patients, is the approximately doubled risk of mortality, largely from cardiovascular disease (8). This relationship appears to be independent of other established risk factors in most studies (3,4,9–14)—including an earlier 3-year follow-up for mortality in the present cohort (15)—but not in all (16–18). A significant association has also been found between CHD morbidity and increased urinary albumin excretion in cross-sectional NIDDM studies (19,20), but it is unclear whether microalbuminuria operates as an independent risk factor for the development of CHD or is the result of it. Moreover, reports on the factors that predispose NIDDM patients to the development of microalbuminuria are scarce, and findings differ between studies (14,21–25). Because the evolution of diabetic cardiovascular and renal disease is potentially modifiable, investigation of microalbuminuria's determinants is important. We undertook this 7-year follow-up study of a well-defined cohort of NIDDM patients to examine the role of microalbuminuria as a risk factor for the development of CHD morbidity and mortality and identify factors that predispose patients to the development of microalbuminuria.

RESEARCH DESIGN AND METHODS

The cohort was assembled from all patients with NIDDM attending the diabetes clinic at Lewisham Hospital, London, in 1984 and has been described in detail (15,19). NIDDM was defined using World Health Organization (WHO) criteria in subjects diagnosed at age >30 years who had no history of ketosis and did not require insulin in the first year after diagnosis. In brief, all 311 patients in the 31–64 age-range were asked to fast for 10–12 h overnight, collect a timed overnight urine sample, and attend the clinic the next morning. Of the 274 (88%) responders, 167 (61%) were of European (white), mostly British, ethnic origin, 86 (31%) were Afro-Caribbean, and 21 (8%) were South Asian. Patients underwent a standardized baseline assessment of cardiovascular and renal status and relevant risk factors. They were reexamined twice, a median (interquartile range) of 2.9 (2.6–3.0) and 7.1 (6.8–7.8) years later. This report is confined to the white NIDDM patients, in whom survivor response rates were 89% at 3 years and 95% at 7 years.

Of the 167 patients, 162 (97%) provided a baseline urine sample. Sixteen patients were excluded from analysis: four each with hematuria, urinary tract infec-

tion, a single kidney, and clinical albuminuria. Of the remaining 146 patients, 71% took oral antidiabetic therapy, 5% injected insulin, and 24% used dietary treatment alone. These patients formed the cohort for examination of risk factors for all-cause mortality, as previously reported (15), and CHD mortality. To determine risk factors for development of new CHD, the 50 patients with baseline CHD were excluded, leaving 96 patients (39 women, 57 men). To study determinants of microalbuminuria, of the original 146 patients, 37 (25%) with baseline microalbuminuria were excluded. A further 9 patients (7 of whom had died) did not attend the clinic after the initial visit, leaving 100 eligible patients with baseline normoalbuminuria for analysis; there was no significant difference in any measured variable between the 9 patients who attended only the initial visit and the 100 eligible patients. In this analysis, we used 3-year values for the four patients who did not attend the 7-year examination and the nine who died before it. The Lewisham Hospital Ethics Committee approved the study. Patients received a full written explanation of the procedures.

Methods were as previously described and remained unchanged at all three examinations (15,19). Smoking habits were assessed at baseline only. Weight and height were measured in indoor clothes, and BMI was calculated. Questionnaires were used to collect information on past medical history, smoking habits, and cardiovascular symptoms. Arterial blood pressure (phases 1 and 5), taken in the sitting position with a standard clinical sphygmomanometer, was recorded as the mean of two measures. A resting 12-lead electrocardiogram (ECG) was recorded and analyzed according to the Minnesota code (26). Biochemical methods have been described (15). Fasting venous blood samples were collected, and the major serum lipoprotein classes VLDL, LDL, and HDL and HDL's major subfractions HDL_2 and HDL_3 were separated by ultracentrifugation. Serum total and lipoprotein fractional triglycerides and cholesterol were assayed by standard enzymatic methods. Total glycated hemoglobin (HbA_1) (reference range 4.9–7.5%) was measured by electroendosmosis. The interassay coefficient of variation (CV) was 5.2% at a mean HbA_1 of 10.9%. Because of technical problems (clotting due to insufficient mixing) in eight samples, results are available in only 138 of the 146 study patients. Plasma glucose was measured by a hexokinase method, and serum insulin by radioimmunoassay (RIA). The seven patients receiving injected insulin were not included in insulin assays. Urinary albumin concentration was measured by an RIA (interassay CV 8%) developed in this laboratory (27), and urinary albumin excretion rate (UAER) was calculated from the product of concentration and timed urine flow. Urine was cultured in samples positive for blood, protein, or nitrite on dipstick testing; if urinary tract infection was found, patients submitted new urine samples after appropriate therapy. A single overnight urine sample was obtained at baseline, but at least two samples were obtained at follow-up visits. If both UAER values did not fall in the same category of albumin excretion, another sample was obtained and the mean of the two values in a single category was used.

Definitions. The categories normoalbuminuria, microalbuminuria, and clinical albuminuria were defined by UAER <20 μg/min, 20–200 μg/min, and >200 μg/min, respectively (28). Current smokers were defined as those smoking one or more cigarettes per day, ex-smokers as those who in the past smoked at least three cigarettes per day for at least 2 years, and nonsmokers as all others. Hypertension was defined as a systolic blood pressure of ≥160 mmHg, diastolic pressure of ≥95 mmHg, or current antihypertensive therapy. CHD was defined as positive responses to the WHO cardiovascular questionnaire (26) (angina or past myocardial infarction) or by ECG Minnesota codes defining possible ischemia (1-3: 4-1, 4-2, or 4-3 if accompanied by 5-1, 5-2, or 5-3) or probable ischemia (1-1, 1-2, or 7-1). Underlying causes of death were obtained from death certificates supplied by the U.K. Office of National Statistics (one patient died abroad and a death certificate could not be obtained). Additional information was available from hospital clinical records. In those without clinical evidence of CHD at baseline, its new development was defined as CHD morbidity found at one or both of the two follow-up visits or death from CHD (International Classification of Diseases, 9th revision, codes 410–414). Patients who died of other causes were included in the group without CHD. In patients with normal UAER at baseline, the development of microalbuminuria was defined as a UAER ≥20 μg/min on at least two occasions at either of the two follow-up visits and includes those with clinical albuminuria. The incidence was expressed per 100 person-years. The period of risk extended from the date of the first examination to the date on which microalbuminuria was first detected or, in those in whom it did not develop, to the date of their final examination.

Statistical analysis. Statistical analysis was carried out using SAS (29). UAER, serum insulin, total triglycerides, and VLDL triglycerides were $\log_{10}$ transformed to normalize their skewed frequency distributions. The Cox proportional hazards model was used for the analysis of all-cause and CHD mortality because duration of follow-up until death was known with some precision. Clinical and laboratory variables were initially examined in bivariable models that adjusted for age. In assessing the importance of microalbuminuria as a causal risk factor, our analytical strategy was to examine the significance of microalbuminuria in a multivariable model that adjusted for other variables of importance. The selection procedure followed that described by Collett (30). Initially, we employed a backward elimination procedure. Microalbuminuria, age, and sex were entered along with all those variables that were significant (that is, conventionally significant [$P < 0.05$] or of borderline significance [$P \geq 0.05$ but $P \leq 0.10$]) at the bivariable level. Age, sex, and microalbuminuria were held in, the least significant variable was eliminated, and the significance of each variable remaining in the model was reevaluated. The procedure was repeated until all remaining variables were significant at $P < 0.05$. Finally, other variables that were considered of importance, even if not significantly related to all-cause or CHD mortality in the bivariable Cox analysis, were introduced into the models (since there was a possibility that they could be significant in a larger model by confounding) and included if $P < 0.05$. The results for continuous variables give the relative risk (RR) associated with a 1 SD increase in the risk factor. The development of new CHD and the development of microalbuminuria were analyzed with logistic regression because precise follow-up intervals were not known. Each variable was first entered in an age-adjusted bivariable model. All variables found significant at $P \leq 0.10$ were then entered in an age- and sex-adjusted multivariable model (age and sex were held in). The final models were obtained using the selection criteria described above for the Cox regression. These analyses were also performed separately in men and women. Full data were available for all 146 patients, except for eight with missing HbA_1 values. Since one of those eight patients subsequently died, the results in the multivariable models for all-cause mortality relate to 35 deaths (rather than 36) and multivariable models containing HbA_1 are based on 138 patients rather than the full 146.

RESULTS

Table 1 shows the baseline clinical and biochemical features of the 146 NIDDM patients and compares the characteristics in patients with and without baseline microalbuminuria and baseline CHD. Patients with microalbuminuria were characterized by longer duration of diabetes and higher BMI, serum cholesterol, fasting plasma glucose, prevalence of hypertension ($P < 0.05$), triglycerides, diastolic blood pressure, HbA_1, and prevalence of CHD ($P < 0.01$). Patients with CHD were characterized by higher systolic blood pressure and serum cholesterol ($P < 0.05$), longer duration of diabetes, and higher UAER, serum triglycerides, and prevalence of microalbuminuria and hypertension ($P < 0.01$).

All-cause mortality. During the median 7-year follow-up until January 1994, 36 (25%) of 146 patients had died, 23 (28%) of 82 men and 13 (20%) of 64 women, a nonsignificant difference ($P = 0.28$). In univariate survival analysis, baseline age was significantly related to all-cause mortality (RR 2.10, 95% CI 1.26–3.51). In age-adjusted bivariable survival analysis, the baseline variables significantly related to all-cause mortality were $\log_{10}$ UAER, microalbuminuria, male sex, known duration of diabetes, diastolic blood pressure, HbA_1, serum cholesterol, LDL cholesterol, $\log_{10}$ serum triglycerides, and $\log_{10}$ VLDL triglycerides (Table 2). All those variables were entered in a backward elimination Cox model, with age, microalbuminuria, and sex kept in by design. In the final model, which included age, sex, preexisting CHD, HbA_1, and serum cholesterol (Table 3), microalbuminuria was no longer significantly related to all-cause mortality (RR 1.15, 95% CI 0.47–2.84). The RR for continuous risk factors is that associated with an increase of 1 SD in the risk factor. For example, for all-cause mortality an increase in HbA_1 of 1.92 percentage units (that is, 1 SD) is associated with a relative risk of 1.42, that is, a 42% increase in risk (Table 3). When we entered other baseline variables (such as smoking and systolic blood pressure) that did not show a significant bivariable relation to all-cause mortality in the present study but were potentially related to mortality, there was no change in their significance in the final model.

Effect of follow-up time. The effect of microalbuminuria as a risk factor for all-cause mortality appeared to diminish with time. Thus the age- and sex-adjusted RR of 3.69 (95% CI 1.84–7.42) in the present 7-year analysis with 36 deaths was

TABLE 1
Baseline clinical and laboratory findings in NIDDM patients by microalbuminuria and CHD

	Microalbuminuric	Normoalbuminuric	With CHD	Without CHD	All patients
n (M/W)	37 (28/9)	109 (54/55)	50 (25/25)	96 (57/39)	146 (82/64)
Age (years)	59 (55–62)	58 (53–63)	59 (56–63)	58 (51–62)	59 (53–63)
Known duration of diabetes (years)	6 (3–10)*	4 (2–7)	7 (4–10)†	3 (2–6)	5 (2–9)
BMI (kg/m^2)	30.2 (28.1–33.8)*	28.6 (24.9–32.1)	30.2 (27.3–33.2)	28.6 (25.1–32.1)	29.0 (25.6–32.6)
Urinary albumin excretion (μg/min)	67.8 (29.9–98.5)†	5.8 (3.8–9.9)	16.5 (5.5–68.0)†	6.6 (4.2–12.4)	7.3 (4.4–20.8)
Fasting plasma glucose (mmol/l)	10.5 (8.2–13.0)*	8.8 (7.6–10.6)	9.5 (7.5–13.3)	9.0 (7.8–11.5)	9.1 (7.6–11.8)
HbA_1 (%)	9.7 (8.6–11.0)†	8.3 (7.3–10.0)	9.1 (8.0–10.4)	8.7 (7.5–10.2)	8.9 (7.5–10.3)
Systolic blood pressure (mmHg)	154 (132–158)	142 (128–154)	150 (138–158)*	142 (127–154)	144 (130–154)
Diastolic blood pressure (mmHg)	88 (82–92)†	82 (72–90)	85 (76–92)	82 (74–88)	84 (76–90)
Serum cholesterol (mmol/l)	6.74 ± 0.26*	6.05 ± 0.12	6.61 ± 0.21*	6.02 ± 0.13	6.22 ± 0.12
Serum triglycerides (mmol/l)	2.39 (1.87–3.75)†	1.68 (1.11–2.50)	2.14 (1.50–3.15)†	1.74 (1.06–2.50)	1.91 (1.20–2.72)
Prevalence					
Microalbuminuria	—	—	22 (44)†	15 (16)	37 (25)
Coronary heart disease	22 (59)†	28 (26)	—	—	50 (34)
Current smoking	13 (35)	37 (34)	15 (34)	35 (36)	50 (34)
Hypertension	22 (59)*	41 (38)	31 (62)†	32 (33)	63 (43)

Data are means ± SE, median (interquartile range), or *n* (%). *P < 0.05, †P < 0.01 for micro- versus normoalbuminuria and for those with versus those without CHD.

lower than that found after only the first 3 years of follow-up with 14 deaths (RR 8.97, 95% CI 2.69–29.9) (14). This suggests that microalbuminuria may be a predictor of short-term mortality only.

Coronary heart disease mortality. Of the 36 deaths, 20 were due to CHD, 15 (18%) among the 82 men and 5 (8%) among the 64 women, a difference of borderline significance (P = 0.07). Of 18 patients with microalbuminuria, 13 (72%) died from CHD compared with 7 (39%) of 18 with normoalbuminuria (P < 0.05). In univariate survival analysis, baseline age had an association of borderline significance with CHD mortality (RR 1.71, 95% CI 0.93–3.14). In age-adjusted bivariable survival analysis, the baseline variables significantly related to CHD mortality were essentially the same as those for all-cause mortality and included microalbuminuria (Table 2). Microalbuminuria was also a significant predictor of CHD mortality in separate bivariable analysis in men and women. Multivariable analysis was carried out as described above for all-cause mortality, with the same variables in the initial model. The final model contained age, male sex, preexisting CHD (kept in the model by design even though P = 0.068), serum cholesterol, and HbA_1 (Table 3); microalbuminuria did not emerge as a significant independent risk factor for CHD mortality (RR 1.83, 95% CI 0.56–6.04).

Incidence of new CHD events. Features of the group of 96 patients (57 men, 39 women) free of CHD at baseline are

TABLE 2
Risk factors for all-cause and CHD mortality in NIDDM patients after adjustment for age only

	All-cause mortality	CHD mortality
Sex (M = 1, F = 0)	1.79 (0.90–3.57)	2.92 (1.05–8.10)
Known duration of diabetes (years)	1.30 (0.97–1.75)	1.53 (1.05–2.24)
Microalbuminuria (yes/no)	3.94 (2.04–7.62)	7.40 (2.94–18.7)
Log_{10} UAER (μg/min)	1.70 (1.27–2.28)	2.27 (1.53–3.36)
Preexisting CHD (yes/no)	2.63 (1.36–5.10)	2.66 (1.10–6.43)
Diastolic blood pressure (mmHg)	1.35 (0.96–1.89)	1.62 (1.02–2.58)
HbA_1 (%)	1.57 (1.16–2.12)	1.81 (1.24–2.65)
Serum cholesterol (mmol/l)	2.08 (1.50–2.89)	2.35 (1.51–3.67)
LDL cholesterol (mmol/l)	2.03 (1.42–2.91)	2.01 (1.24–3.28)
Log_{10} triglycerides (mmol/l)	1.60 (1.14–2.24)	1.99 (1.24–3.19)
Log_{10} VLDL triglycerides (mmol/l)	1.57 (1.09–2.26)	2.08 (1.27–3.41)

Data are RR (95% CI). Results are from Cox proportional hazards analysis. For continuous variables, RRs are standardized to a change of 1 SD (duration = 4.2 years, log_{10} UAER = 0.52, log_{10} triglycerides = 0.26, log_{10} VLDL triglycerides = 0.37, diastolic blood pressure = 10.7 mmHg, HbA_1 = 1.92%, cholesterol = 1.38 mmol/l, LDL cholesterol = 1.09 mmol/l).

TABLE 3
Risk factors for all-cause and CHD mortality in NIDDM patients in multivariable analysis

	All-cause mortality	CHD mortality
Age (years)	2.42 (1.31–4.46)	2.01 (0.94–4.30)
Sex (M = 1, F = 0)	2.77 (1.17–6.52)	3.82 (1.16–12.6)
Microalbuminuria (yes/no)	1.15 (0.47–2.84)	1.83 (0.56–6.04)
Preexisting CHD (yes/no)	2.28 (1.05–4.96)	2.72 (0.93–7.94)
HbA_1 (%)	1.42 (1.02–1.96)	1.53 (1.01–2.32)
Serum cholesterol (mmol/l)	2.13 (1.49–3.06)	2.50 (1.50–4.17)

Data are RR (95% CI). Results are final models from Cox proportional hazards analysis. Variables entered initially in the backward elimination model were log_{10} UAER, microalbuminuria, sex, age, known duration of diabetes, diastolic blood pressure, HbA_1, serum cholesterol, LDL cholesterol, log_{10} triglycerides, and log_{10} VLDL triglycerides. For continuous variables, RRs are standardized to a change of 1 SD (age = 8.0 years, HbA_1 = 1.92%, serum cholesterol = 1.38 mmol/l).

TABLE 4
Risk factors for CHD morbidity and mortality in men with NIDDM who were free of CHD at baseline

	Age-adjusted	Multivariable-adjusted
Microalbuminuria (yes/no)	7.16 (1.71–29.9)	10.0 (1.63–61.4)
Current smoking (yes/no)	3.58 (1.10–11.6)	6.53 (1.37–31.1)
Diastolic blood pressure (mmHg)	2.26 (1.12–4.53)	3.21 (1.21–8.52)
Serum cholesterol (mmol/l)	1.74 (0.97–3.13)	2.31 (1.01–5.29)
Log_{10} serum triglycerides (mmol/l)	1.64 (0.93–2.88)	—
Hypertension (yes/no)	3.14 (0.98–10.1)	—

Data are OR (95% CI). Results are age adjusted. Variables considered in logistic regression analysis were microalbuminuria, diastolic blood pressure, current smoking, serum cholesterol, log_{10} serum triglycerides, and hypertension. For continuous variables, ORs are standardized to a change of 1 SD (diastolic blood pressure = 9.8 mmHg, serum cholesterol = 1.20 mmol/l, log_{10} serum triglycerides = 0.28).

shown in Table 1. In this group there were 40 new cases of CHD, a cumulative incidence of 42% over the 7-year period. Evidence of new CHD was based on death from CHD (8 men, 1 woman), angina pectoris or history of myocardial infarction (6 men, 3 women), one of the latter plus ECG abnormalities (3 men, 1 woman), or ECG changes alone (6 men, 12 women). In age-adjusted bivariable logistic regression with new CHD morbidity and mortality as outcome, the significant risk factors were microalbuminuria (odds ratio [OR] 6.11, 95% CI 1.66–22.4) and UAER (standardized odds ratio [SOR] 1.83, 95% CI 1.15–2.94). Log_{10} serum triglycerides (SOR 1.53, 95% CI 0.99–2.37) and log_{10} serum insulin (SOR 1.57, 95% CI 0.99–2.47) were of borderline significance. In age- and sex-adjusted multivariable analysis including microalbuminuria, log_{10} UAER, log_{10} triglycerides, and log_{10} serum insulin, only microalbuminuria was significant in the final model (OR 7.14, 95% CI 1.86–27.3). Only one woman, however, had baseline microalbuminuria and was also initially free of CHD (she later had a nonfatal myocardial infarction). It was therefore not possible to reliably examine the predictive ability of microalbuminuria for new CHD in women or extrapolate results to both men and women. In men (Table 4), the significant age-adjusted risk factors for new CHD were diastolic blood pressure, current smoking, and microalbuminuria (OR 7.16, 95% CI 1.71–29.9). Serum cholesterol, log_{10} serum triglycerides, and hypertension were of borderline significance, but neither HbA_1 nor fasting plasma glucose was significantly associated with new CHD risk. In multivariable analysis, the final model contained microalbuminuria (OR 10.0, 95% CI 1.63–61.4), current smoking, diastolic blood pressure, and serum cholesterol. Age was also significant in this model (SOR 3.25, 95% CI 1.26–8.37).

Development of microalbuminuria. Baseline clinical and biochemical features of the 109 NIDDM patients (54 men, 55 women) with initial normoalbuminuria are shown in Table 1. Of those patients, 9 did not return for a further visit, leaving 100 patients for follow-up analysis; the baseline characteristics of those 100 were closely comparable to the initial group of 109. After a median of 3 years of follow-up, 13 patients (6 men, 7 women) had developed microalbuminuria. After a median of 7 years, a further 16 patients (9 men, 7 women) had developed microalbuminuria. Of those patients, 6 (all women) had progressed to clinical albuminuria by the end of follow-up. Thus, 29 patients (15 men, 14 women) had developed microalbuminuria or clinical albuminuria, a cumulative incidence of 29% over the 7-year period or 4.6 cases per 100 person-years.

Risk factors associated with the development of microalbuminuria. The age-adjusted risk factors significantly associated with the development of microalbuminuria in logistic regression analysis were fasting plasma glucose (SOR 1.87, 95% CI 1.17–3.00), UAER (SOR 1.97, 95% CI 1.20–3.23), and HbA_1 (SOR 1.76, 95% CI 1.10–2.83). Risk factors of borderline significance were current smoking (versus those who never smoked) (OR 3.07, 95% CI 0.93–10.2), low serum HDL cholesterol (SOR 1.51, 95% CI 0.92–1.95), and log_{10} triglycerides (SOR 1.44, 95% CI 0.92–2.26). Systolic blood pressure (SOR 1.33, 95% CI 0.80–2.21), diastolic blood pressure (SOR 1.25, 95% CI 0.81–1.95), preexisting CHD (OR 1.90, 95% CI 0.73–4.96), and hypertension (OR 1.10, 95% CI 0.49–3.06) were not significantly related to the outcome. Baseline factors significantly associated with the development of microalbuminuria in age- and sex-adjusted multivariable analysis (Table 5) were fasting plasma glucose, UAER, and current smoking. We examined the effect of entering other baseline variables in the model, such as preexisting CHD and arterial blood pressures, that did not themselves show a significant bivariable relation to development of microalbuminuria but were potentially related in larger models. Doing so resulted in a final model that also contained preexisting CHD as a risk factor for development of microalbuminuria (OR 3.61, 95% CI 1.09–11.9). Men and women were also analyzed separately, although numbers were small. In men, the bivariable risk factors significant at $P \leq 0.10$ (UAER, preexisting CHD, glucose, HDL cholesterol, and serum triglycerides) were initially entered in an age-adjusted multivariable model, in which other potential risk factors that were not in themselves significant in bivariable analysis, such as current smoking, were later examined as well. In the final model, plasma glucose, current smoking, and preexisting CHD (OR 27.8, 95% CI 2.89–267.0) emerged as significant risk factors for the development of microalbuminuria; UAER was of only borderline significance in this model. In women, only plasma glucose emerged as significant in the final multivariable model. Overall, the results in men indicate that on the one hand, preexisting CHD precedes the development of microalbuminuria, but on the other hand, microalbuminuria precedes the development of CHD.

DISCUSSION

The findings of most previous retrospective (3,4,9) and prospective (10–14) survival studies in NIDDM subjects, including an earlier short-term follow-up for mortality in the present cohort (15), have suggested that microalbuminuria is an independent risk factor for all-cause and CHD mortality. The present 7-year prospective study confirms that after adjustment for age only, microalbuminuria is a strong predictor for all-cause and CHD mortality. Microalbuminuria's predictive power did not persist, however, in statistical analyses allowing for the effects of the other important risk factors—preexisting CHD, serum cholesterol, and glycated hemoglobin. The findings of other recent prospective studies have also cast some doubt on microalbuminuria's status as an

TABLE 5
Multivariable risk factors associated with the development of microalbuminuria in NIDDM patients

	All subjects	Men	Women
n	100	49	51
Fasting plasma glucose (mmol/l)	2.27 (1.33–3.88)	3.93 (1.35–11.5)	2.28 (1.14–4.55)
Log_{10} UAER (μg/min)	1.84 (1.09–3.11)	—	—
Current smoker (yes/no)	3.72 (1.23–11.3)	10.9 (1.27–92.8)	—
Preexisting CHD (yes/no)	3.61 (1.09–11.9)	27.8 (2.89–267.0)	—

Data are OR (95% CI). Results are age and sex adjusted in the all-subjects group and are from logistic regression analysis. For continuous variables, ORs are standardized to a change of 1 SD (plasma glucose = 2.86, log_{10} UAER = 0.28). In separate analysis in men and women, results are age adjusted. In men, SD for plasma glucose = 2.71 mmol/l and for log_{10} UAER = 0.23; in women, SD for plasma glucose = 3.00 mmol/l. Variables initially considered in the backward elimination analysis were fasting plasma glucose, HbA_1, log_{10} UAER, and current smoking.

independent risk factor for macrovascular death in NIDDM (16–18). An important finding of this study is that, at least in men, CHD and microalbuminuria are shown to precede each other, suggesting that both disorders are downstream expressions of some common etiology.

Our finding that microalbuminuria is not an independent risk factor for all-cause and CHD mortality in NIDDM is largely attributable to the confounding effect of other important cardiovascular risk factors. In earlier longitudinal studies of an association between microalbuminuria and early mortality (3,4,9), neither baseline cardiovascular status nor plasma lipids were taken into account. Our study shows that these factors help explain the predictive power of microalbuminuria. The way in which preexisting CHD is defined may also be relevant. Although Neil et al. (11) found that microalbuminuria was a significant risk factor for all-cause and CHD mortality in NIDDM, there was no significant univariate association between baseline CHD and all-cause mortality. Since their definition of CHD rested on symptomatic evidence alone without systematic use of ECGs, the effect of baseline CHD may have been underestimated. Similarly, MacLeod et al. (12) found age, baseline CHD, and UAER to be risk factors for all-cause mortality in multivariable analysis in NIDDM, but ECGs were not performed and plasma lipids were not assessed.

In our earlier 3-year follow-up report in the present NIDDM cohort, microalbuminuria emerged as a significant predictor of all-cause mortality in multivariable survival analysis (15). Why, then, is microalbuminuria apparently no longer an independent risk factor for mortality when follow-up is extended to 7 years? A possible reason is that microalbuminuria is only a predictor of short-term mortality, as Damsgaard et al. have suggested (31). Our study findings are in accord with that proposal, in that the age- and sex-adjusted RR of microalbuminuria for all-cause mortality of the first 3 years of follow-up is less than that of the full 7-year period. Another explanation may be that our earlier study, based on a 3-year follow-up and only 14 fatal events, did not have the statistical power to identify other, weaker, risk factors that have now emerged as more significant after 7 years of follow-up and 36 fatal events; two such factors in this study are glycated hemoglobin and sex. It is notable that when the same risk factors used in multivariable survival analysis in the 3-year study (where glycated hemoglobin and sex had not been included)—that is, microalbuminuria, age, preexisting CHD, hypercholesterolemia (serum cholesterol ≥6.5 mmol/l), and hypertriglyceridemia (fasting triglycerides ≥2.3 mmol/l)—were examined in the same way after 7 years of follow-up, microalbuminuria remained a significant, apparently independent, predictor of all-cause mortality. If, however, sex and glycated hemoglobin were also taken into account in the multivariable analysis, the independent predictive power of microalbuminuria was lost (results not shown). Other recent prospective studies have also found evidence that poor glycemic control is a risk factor for mortality in NIDDM (13,14), and several possible mechanisms by which hyperglycemia could accelerate the atherosclerotic process have been suggested (32,33).

Microalbuminuria was found to be a risk factor for the development of CHD morbidity and mortality in NIDDM men free of CHD at recruitment. That finding extends our earlier observation of a cross-sectional association between raised UAER and CHD prevalence in this cohort (19). Age, diastolic blood pressure, smoking, and serum cholesterol were also CHD risk factors, but the predictive power of microalbuminuria was independent of them. Although microalbuminuria preceded the development of clinical CHD in our study, we cannot exclude the possibility that sub-clinical CHD might already have been present in the patients with microalbuminuria. In IDDM patients, microalbuminuria has recently been shown to be associated with silent myocardial ischemia (34). It was therefore important to examine which factors predisposed patients to the development of microalbuminuria in NIDDM.

In our study, among men and women with normal UAERs at baseline, poor glycemic control, smoking, preexisting CHD, and the baseline level of UAER itself were significant independent risk factors for the development of microalbuminuria. The cumulative incidence of microalbuminuria was 29% over the 7-year period, equivalent to 4.6 cases per 100 person-years. That incidence is similar to the 5-year incidence of 23% recently reported in Danish NIDDM patients (25). Higher incidence rates have been reported in certain ethnic groups with NIDDM, such as in Japanese (35) and Pima Indians (36).

Poor glycemic control emerged as a significant risk factor for the development of microalbuminuria, in accord with findings in IDDM (37,38), but results from prospective studies of NIDDM patients have been less consistent (14,23–25). As has been observed in IDDM patients (37,38), we found the initial level of UAER in NIDDM patients to be positively related to the risk of developing microalbuminuria. Patients destined to develop albuminuria may have albumin excretion

rates that are rising faster through the normal range, or they may exhibit intrinsically higher initial UAERs as a marker of susceptibility. Diabetic nephropathy occurs in familial clusters (39), and nondiabetic first-degree relatives of patients with increased UAERs and NIDDM have recently been shown to have raised UAERs (40), observations consistent with the hypothesis that heredity helps to determine susceptibility to diabetic nephropathy.

For the first time in a prospective study, smoking was found to be associated with the development of microalbuminuria in NIDDM patients, in keeping with some earlier cross-sectional data (20). In IDDM, smoking has also been shown to be a risk factor for development of microalbuminuria (38) and has been implicated, in some studies, in the progression of established nephropathy (41). Perhaps surprisingly, our study showed no relation between baseline levels of arterial blood pressure or the prevalence of hypertension and the onset of microalbuminuria. This observation contrasts with results of prospective studies in IDDM (37,38,42), but there is some controversy in NIDDM, with studies reporting either an important influence of baseline blood pressure (24) or no effect (14,23,25).

In view of the finding that microalbuminuria was a risk factor for incident CHD in men, factors predicting the development of microalbuminuria were also examined separately in men and women. In multivariable analysis in men, preexisting CHD, fasting plasma glucose, and current smoking were significant risk factors for the development of microalbuminuria; in women, fasting plasma glucose was the only significant risk factor. However, as numbers were small and confidence intervals wide, these findings must be interpreted with caution. Gall et al. (25) also noted a higher prevalence of preexisting CHD among NIDDM patients who subsequently developed incipient or overt nephropathy.

Given that microalbuminuria precedes the development of new CHD and preexisting CHD precedes the development of microalbuminuria in male NIDDM patients in our study, it can be hypothesized that each occurs as a result of a common determinant. A number of different mechanisms could be postulated to link CHD to microalbuminuria, including insulin resistance (43), a generalized increase in vascular permeability (44), endothelial dysfunction (45,46), and alterations in the atherogenicity of lipoprotein particles in the presence of hyperglycemia (47). It is unknown, however, whether a reduction of UAER in NIDDM patients with microalbuminuria is associated with a reduction in CHD incidence.

One has to accept that NIDDM patients recruited in a hospital setting may not be representative of all such patients in the population, although when our study began in 1984 most NIDDM patients in the U.K. were being treated in hospital diabetes clinics. As in most studies initiated in that period, our baseline classification of UAER was based on measurements in a single timed overnight urine collection. During the follow-up, however, at least two values of UAER had to be in the same category before classification was made. Because of its relatively small sample size and number of events, this study has limited power in identifying weaker risk factors. Also, because the risk factors for development of new CHD and development of microalbuminuria varied depending on whether men, women, or all patients were used in the model and because confidence intervals were wide, our findings can be regarded as suggestive but not conclusive.

In conclusion, in men free of clinical CHD at study entry, microalbuminuria is a significant predictor for CHD morbidity and mortality. On the other hand, preexisting CHD in men, but not in women, is a risk factor for development of microalbuminuria. In the presence of preexisting CHD and other major risk factors, microalbuminuria loses its independent predictive power for all-cause and CHD mortality. These observations suggest that microalbuminuria may not be causally related to CHD, but that both microalbuminuria and CHD may be the result of some common determinant of vascular injury.

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Author Queries (please see Q in margin and underlined text)

Q1: “diagnosed at age >30 years” correct?>

Q2: Please clarify the sentence. It does not match the statistics for the microalbuminuria study (2 nonattenders, 7 deaths), and similar data for the CHD study were not stated above. Is this information for the overall cohort?>

Q3: Calculation of BMI correct?>

Q4: Edits to the sentence okay?>