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Coronary heart disease and urinary albumin excretion rate in Type 2 (non-insulin-dependent) diabetic patients

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Summary. Associations between overnight urinary albumin excretion rate and prevalent coronary heart disease and its major risk factors were examined in a cross-sectional study of 141 Type 2 (non-insulin-dependent) diabetic patients. Mean albumin excretion rate was higher in men (geometric mean 13.5 μg/min; 95% confidence interval 10.3-17.6) than women (7.5 μg/min; 5.7-9.8, $p<0.01$). In diabetic men and women mean albumin excretion rate was higher in those with electrocardiographic and/or symptomatic evidence of coronary heart disease than in those without (men, 23.1 μg/min; 95% confidence interval 13.7-39.0 versus 10.6 μg/min; 7.9-14.2, $p<0.01$, women, 13.7 μg/min; 8.0-23.5 versus 5.4 μg/min; 4.2-6.8, $p<0.01$). Multiple logistic regression analysis was used to allow for confounding between variables. In the diabetic group as a whole, raised albumin excretion rate ($p<0.001$), gender ($p<0.05$) and systolic blood pressure ($p=0.06$) entered the "best" model for coronary heart disease prediction. In women, albumin excretion rate alone ($p<0.01$) and in men albumin excretion rate ($p<0.01$) and age ($p=0.05$) entered the "best" models. We conclude that albumin excretion rate is significantly associated with coronary heart disease morbidity after taking into account the confounding effects of raised blood pressure and other cardiovascular risk factors.

Key words: Urinary albumin excretion rate, coronary heart disease, Type 2 (non-insulin-dependent) diabetes mellitus.

Persistent proteinuria is associated with a greatly increased risk of death in patients with Type 1 (insulin-dependent) diabetes mellitus [1]. The majority of deaths are caused by renal failure, but a substantial minority are due to cardiovascular disease and this largely accounts for the excess cardiovascular mortality of Type 1 diabetic patients [2-4]. Patients with subclinical elevation of urinary albumin excretion (microalbuminuria) earlier in the course of Type 1 diabetes are at much increased risk of developing persistent proteinuria later [5-7].

Clinical proteinuria is common in Type 2 (non-insulin-dependent) diabetes, but renal failure is a much less prominent consequence than in Type 1 diabetes [8] and the major cause of the increased morbidity and mortality in Type 2 diabetes is cardiovascular disease [9].

Two studies in patients with Type 2 diabetes have shown that microalbuminuria is strongly predictive of all-cause (mainly cardiovascular) mortality [10-11], but it is not clear whether this is independent of, or whether it operates through, an association with other established risk factors for cardiovascular disease. We have therefore investigated associations between the rate of overnight urinary albumin excretion and indices of prevalent cardiovascular disease and its risk factors in a cross-sectional study of Type 2 diabetic patients.

Subject and methods

Patients

During 1985-1987 a sample of 276 Type 2 diabetic patients aged 35-64 years and attending Lewisham Hospital diabetic clinic was screened for selected indices of cardiovascular disease and several of its risk factors including overnight urinary albumin excretion rate (AER). Patients were invited to attend a special morning clinic after a 12-14 h overnight fast and asked to provide a timed overnight urine sample. Examination of the medical records of 1,010 diabetic patients attending Lewisham Hospital diabetic clinic in 1984 (defined as those patients whose hospital number appeared at least once on the weekly clinic lists for 1984) revealed 646 Type 2 diabetic patients. Of these patients, 310 were aged 65 years or more and were not included in this study while the remaining 336 patients aged 35-64 years were invited, in random order, to the screening clinic. Twenty-two of the latter patients were over 65 years by the time their screen was due and they were not included in the study.

Of the 314 diabetic patients invited to the clinic 276 (88%) attended. Of the 38 (12%) patients not attending, 3 were known to have died, 8 had moved out of the area, 10 were defaulters from the routine diabetic clinic since 1984 and the remaining 17 did not respond to a second letter of invitation. Of the 276 responders, 87 (32%) were of Afro-Caribbean ethnic origin, 20 (7%) were Indian Asians and 169 (61%) were of Europid, almost exclusively British, origin. Because of the possibility that ethnic origin affects susceptibility to diabetic complications, the present analysis is confined to the Europid patients.

Of the 169 Europid patients, 162 (96%) submitted a timed overnight urine collection. Urine was cultured in samples found to be positive for protein or blood on dipstick testing (respectively by Albustix, Ames Division, Miles Laboratories, Stoke Poges, Bucks, UK and BM-5L sticks, Boehringer Corporation, London (Ltd), East Sussex, UK). All urine samples were stored in aliquots at −40 °C and these were retrospectively screened for evidence of infection with the nitrite test (N-Labstix, Ames). Exclusions from the analysis (21 patients) were made on the basis of haematuria (3 men, 4 women), evidence of urinary tract infection (10 women, with 2 women showing both haematuria and infection) or clinical proteinuria (defined by an albumin excretion rate ≥200 μg/min). The 4 male patients defined as clinically proteinuric all had ECG and/or cardiovascular questionnaire evidence of coronary heart disease (3 had ECG and questionnaire evidence and 1 had ECG changes alone). No patient had chronic congestive cardiac failure as diagnosed by clinical examination, history and drug therapy. The remaining 141 patients form the basis of the present analysis. Of these patients 52% were receiving sulphonylureas, 36% biguanides (with 19% receiving both) and 4% insulin, while 26% were treated by dietary advice alone.

Procedures

For collection of the urine sample, a two litre plastic container (containing 0.5 ml of 1% sodium merthiolate as preservative) was posted to each patient a few days prior to their clinic visit. Clear instructions on how to collect a timed overnight urine sample were enclosed and patients were asked to bring the whole sample to the clinic with them. The timing of the collection was checked with each patient and urine volume measured. Aliquots of urine were then stored at −40 °C for subsequent assays.

Venous blood samples were collected, without stasis, while the patient rested supine. Weight and height were measured in indoor clothing and without shoes and the body mass index calculated. Standard questionnaires on past medical history, smoking habits, alcohol consumption and the WHO cardiovascular questionaire [12] were administered. Arterial blood pressure was measured on the right arm with a standard clinical sphygmomanometer (cuff size 14 cm × 42 cm, diastolic 5th phase) by the same observer after at least 10 min of rest; 2 blood pressure measurements were made in the sitting position (with 1 min and raising of the arm between) and the mean of these was recorded. A resting 12-lead ECG was recorded and analysed according to the Minnesota Code [13].

Laboratory methods

Urinary albumin concentration was estimated by radioimmunoassay [14] (between-batch coefficient of variation 8%). Albumin excretion rate (AER, μg/min) was calculated from the product of timed urine volume (ml/min) and albumin concentration (μg/ml). Major serum lipoprotein classes were separated by preparative ultracentrifugation [15]. Serum total and lipoprotein fractional triglyceride and cholesterol concentrations were assayed by enzymatic methods (Boehringer, Mannheim, FRG) using a Cobas-Bio centrifugal analyser, (Roche, Welwyn Garden City, Herts, UK). Glycated haemoglobin (HbA_1) was assayed by electroendosmosis after removal of the unstable adduct (Ciba-Corning, Halstead, Essex, UK) (laboratory reference range 4.9-7.5%). Plasma creatinine was assayed by a kinetic Jaffé method and plasma glucose by an automated hexokinase method (Roche).

Definition of terms

Smokers were defined as those currently smoking one or more cigarettes per day. Alcoholic beverage users were defined as those who reported consuming one or more drink units per week (where a drink unit is defined as 285 ml of beer or lager, 115 ml of wine or 25 ml of spirit). Hypertension was defined as a systolic blood pressure of ≥160 mmHg and/or a diastolic blood pressure of ≥95 mmHg (WHO) [16]. For the purposes of this study a further discrete variable hypertension and/or treatment was defined by a comination of the above WHO definition and/or a current history of antihypertensive therapy (i.e. systolic BP≥160 and/or diastolic BP≥95 and/or anti-hypertensive treatment). Coronary heart disease (CHD) was considered present either by the appropriate responses to the cardiovascular questionaire or by ECG Minnesota codes 1-3, 5-1, 5-2, 5-3 (possible ischaemia) or 1-1, 1-2, 7-1 (probable ischaemia) or both. The study was approved by the Lewisham Hospital Ethics Committee.

Statistical analysis

Anonymous data were entered at the University of London Computer Centre and analysed using the statistical package SAS [17]. AER and serum triglyceride values were $\log_{10}$ transformed because of their positively skewed frequency distribution (although log AER distribution was not fully normalised by this transformation). The hypothesis for the equality of two independent sample means was tested by unpaired Student's t-test and the equivalent hypothesis for two independent sample proportions by the standard chi-square test. Associations between AER and a selection of continuous variables were measured using Spearman's rank correlation coefficient.

Multiple logistic regression analysis was performed on selected variables with CHD as the outcome. The objective was to find the linear combination of parameters which best describe the data. The maximum likelihood estimate (MLE) of a parameter represents the linear relation between a specified variable and the logit of the outcome variable CHD allowing for the joint effect of all the other linear parameters (variables) in the current model. The "best" models were chosen using the stepwise option of the LOGIST procedure [18]. For a variable to be included in the model at a particular step in the regression the statistic for the MLE must be the largest of all the variables not in the current model and be significant at the 10% level. Similarly, for a variable to be excluded from the model the statistic for the MLE must be the smallest of all the variables in the current model and not be significant at the 10% level. The choice of significance level for variable entry or exit from the current model is arbitrary.

There has been some debate as to the appropriateness of the deviance (minus twice the log likelihood) as a measure of goodness of fit [19] when modelling ungrouped binary data. The question of how well the "best" model fits the data is partly answered by comparing the deviance of the "best" model with some other model which has more parameters and remains fixed. Equivalent information on the lack of fit of the model is supplied by the LOGIST procedure when either the stepwise or backward options are invoked. An efficient score chi-square statistic is calculated which tests the joint significance of all variables not in the current model.

Results

Biometric, clinical and biochemical features of the diabetic group are shown in Table 1. Men and women did not differ significantly in respect of mean age, known duration of diabetes, glycated haemoglobin (% HbA_1) or plasma glucose but mean body mass index (BMI) was significantly higher in women than men ($p<0.05$). Mean overnight AER was markedly higher in men

than women ($p<0.01$). There were no significant sex differences in mean arterial blood pressure, the prevalence of hypertension (WHO) or in the prevalence of hypertension when anti-hypertensive treatment was taken into account (hypertension and/or treatment). Thirty-five percent of diabetic patients (34% men, 36% women) were receiving anti-hypertensive medication while 11% (9% men, 14% women) were hypertensive according to WHO criteria but were untreated. Mean serum total cholesterol and HDL-cholesterol concentrations were significantly higher in women than men ($p<0.05$ and $p<0.001$ respectively) but serum total triglycerides did not differ between the sexes. Plasma creatinine concentration was significantly higher in men than women ($p<0.001$). The proportions of men and women who were current smokers (as defined) did not differ. However, there was a marked difference in the proportions of alcohol consumers (as defined) with prevalence in men exceeding that in women ($p<0.001$). The proportions of patients receiving different treatments for their diabetes did not differ between men and women.

Table 1. Biometric, clinical and biochemical features of the Type 2 (non-insulin-dependent) diabetic patients (mean ± SD unless otherwise stated)

	Men	Women
Number	82	59
Age (years)	56 ± 8	57 ± 8
BMI (kg/m^2)	28 ± 4[b]	30 ± 5
Duration of disease (years)	6 ± 4	5 ± 4
HbA_1 (%)	8.8 ± 1.8	9.3 ± 2.1
Glucose (mmol/l)	9.5 ± 3.0	10.2 ± 3.3
AER (μg/min)[a]	13.5 (10.3-17.6)[c]	7.5 (5.7-9.8)
(range)	(2.5-176)	(1.2-163)
Systolic BP (mmHg)	141 ±19	146 ±20
Diastolic BP (mmHg)	83 ±10	81 ±11
Hypertension prevalence (%)	21 ± 4	20 ± 5
Hypertension and/or treatment	43 ± 5	49 ± 6
Prevalence (%)		
Triglycerides (mmol/l)[a]	2.00 (1.73-2.30)	1.79 (1.53-2.07)
Cholesterol (mmol/l)	5.63 ± 1.20[b]	6.08 ± 1.31
HDL-Cholesterol (mmol/l)	0.98 ± 0.23[d]	1.16 ± 0.35
Creatinine (μmol/l)	88.6 ±15.8[d]	72.0 ±17.1
Smoking	37 ± 5	35 ± 6
Alcohol Consumption	51 ± 6[d]	10 ± 4

[a] geometric mean and 95% confidence interval; [b] $p<0.05$, [c] $p<0.01$, [d] $p<0.001$ for men versus women

Coronary heart disease and its associations

Thirty-three percent (46) of patients showed ECG and/or cardiovascular questionnaire (CVQ) evidence of CHD. CHD was present in 30% (25) of diabetic men (CVQ evidence alone = 4, ECG evidence alone = 14, ECG + CVQ = 7) and 36% (21) of diabetic women (CVQ = 4, ECG = 15, ECG + CVQ = 2) but the difference in frequency of CHD did not achieve statistical significance.

The levels of the variables in Table 1 were then compared for men and women with and without CHD. Variables showing a significant association with CHD are shown in Table 2. Mean AER was significantly higher in diabetic patients with CHD than in those without in both men and women ($p<0.01$). Men with CHD were older ($p<0.01$), had significantly longer duration of disease ($p<0.05$) and significantly higher mean systolic blood pressure ($p<0.01$); duration of disease and systolic pressure in women and diastolic pressure in men and women did not differ significantly between those with and without CHD.

The percentage prevalence of WHO defined hypertension did not differ significantly between men and women with and without CHD (men, 32 ± 9 versus 16 ± 6, women, 29 ± 10 versus 16 ± 6 respectively). However, the proportion of patients on anti-hypertensive therapy (without reference to measured arterial blood pressure) was considerably higher in both men and women with CHD (men, 60 ± 10 versus 23 ± 6 (%) $p<0.01$, women, 67 ± 10 versus 18 ± 6, $p<0.01$). The proportion of patients classified by the combined variable hypertension and/or treatment (as defined) was also significantly higher in men and women with CHD compared to those without ($p<0.05$ and $p<0.01$ respectively) (Table 2). No other variables listed in Table 1 were found to differ significantly between diabetic patients with and without CHD whether male or female, nor were there any significant differences in the proportions of patients receiving different treatments for their diabetes.

Table 2. Associations with coronary heart disease (CHD) in Type 2 diabetic patients (mean ± SD unless otherwise stated)

	Number	Albumin excretion rate[a] (μg/min)	Age (years)	Duration of disease (years)	Systolic blood pressure (mmHg) (%)	Hypertension and/or treatment (% prevalence)
Men with CHD	(25)	23.1(13.7-39.0)[c]	59 ± 4[c]	7 ± 4[c]	149 ± 18[c]	64 ± 10[b]
Men without CHD	(57)	10.6 (7.9-14.2)	54 ± 9	5 ± 4	137 ± 19	33 ± 6
Women with CHD	(21)	13.7 (8.0-23.5)[c]	57 ± 6	6 ± 5	150 ± 18	76 ± 9[c]
Women without CHD	(38)	5.4 (4.2- 6.8)	56 ± 8	5 ± 4	143 ± 21	34 ± 8

[a] geometric mean and 95% confidence interval, [b] $p<0.05$, [c] $p<0.01$ for those with CHD versus those without

Table 3. Spearman correlation coefficients with albumin excretion rate in Type 2 diabetic patients

Variable	Patient group Correlation coefficient (number)		
	All patients	Men only	Women only
Body mass index	0.109 (139)	0.298[b] (80)	−0.008 (59)
Duration of disease	0.287[c] (139)	0.156 (82)	0.437[c] (57)
Systolic blood pressure	0.093 (140)	0.191 (82)	0.026 (58)
Diastolic blood pressure	0.101 (140)	0.281[a] (82)	−0.191 (58)
HbA_1	0.347[c] (134)	0.469[c] (79)	0.267[a] (55)
Plasma glucose	0.290[c] (138)	0.298[c] (82)	0.337[a] (56)
Serum triglycerides	0.214[a] (139)	0.242[a] (82)	0.122 (57)
VLDL-triglycerides	0.208[a] (138)	0.234[a] (82)	0.091 (56)
HDL-cholesterol	−0.243[b] (138)	−0.218[a] (82)	−0.098 (56)
Plasma creatinine	0.197[a] (136)	0.107 (81)	−0.017 (55)

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Table 4. Variables predictive of coronary heart disease (CHD) in Type 2 diabetic patients using multiple logistic regression analysis (all patients)

"Best" model $n=130$ (42 CHD cases)

Variable	Beta coefficient	Standard error	Probability
Log AER	1.558	0.423	0.0002
Gender	−0.919	0.447	0.0400
Systolic blood pressure	0.021	0.011	0.0611

Score statistic = 7.87 with 12 degrees of freedom ($p>0.5$); Sensitivity = 40.5%, Specificity = 89.8%

Table 5. Variables predictive of coronary heart disease (CHD) in Type 2 diabetic patients using multiple logistic regression analysis (men only)

"Best" model $n=78$ (22 CHD cases)

Variable	Beta coefficient	Standard error	Probability
Log AER	1.367	0.510	0.007
Age	0.084	0.043	0.052

Score statistic = 7.62 with 12 degrees of freedom. ($p>0.5$); Sensitivity = 40.9%, Specificity = 87.5%

Table 6. Variables predictive of coronary heart disease (CHD) in Type 2 diabetic patients using multiple logistic regression analysis (women only)

"Best" model $n=52$ (20 CHD cases)

Variable	beta coefficient	Standard error	Probability
Log AER	2.114	0.799	0.008

Score statistic = 7.88 with 12 degrees of freedom ($p>0.5$); Sensitivity = 45.0%, Specificity = 84.4%

Correlations with AER

There were a number of statistically significant correlations between AER and other continuous variables (Table 3): for the group as a whole these included duration of disease, HbA_1, plasma glucose, serum total and VLDL-triglycerides, serum HDL-cholesterol (inverse correlation), and plasma creatinine. In diabetic men, body mass index, diastolic blood pressure, HbA_1, glucose, total and VLDL-triglycerides and HDL-cholesterol (inversely) were significantly correlated with AER, while in women the only significant correlations were for duration of disease, HbA_1 and glucose.

Multiple logistic regression analysis

In view of the above correlations with AER and the probable further inter-relationships between the variables showing significant associations with CHD, the data were submitted to multiple logistic regression analysis. Because of missing values only 130 patients (78 men, 52 women) contribute to the logistic regression model. The univariate correlations between serum total triglycerides and VDL-triglycerides and between serum total cholesterol and LDL-cholesterol were extremely high and therefore total serum triglycerides and cholesterol were used in most analyses. Log_{10} AER, systolic and diastolic pressures, serum triglycerides and cholesterol and HDL-cholesterol, presence of smoking, HbA_1, age, gender, duration of disease, any alcohol consumption and treatment (rather than using specific treatment groups, two variables were defined - sulphonylureas and biguanides - each denoting presence of drug in question) were regressed simultaneously on CHD - the dependent variable.

The maximum likelihood estimate of the beta coefficient and its standard error are shown in Table 4 for all patients and in Tables 5 and 6 for men and women separately. The probability of rejecting the null hypothesis, that a beta coefficient equals zero, incorrectly, has been calculated for each variable. At the bottom of each table is shown the efficient score chi-square statistic, the number of degrees of freedom and the sensitivity and specificity of a predicted outcome. Table 4 shows the variables entering the "best" model when all patients were considered. Albumin excretion rate and gender were significantly associated with CHD with systolic blood pressure just failing to achieve conventional levels of significance. When plasma glucose was substituted for HbA_1, age ($p=0.078$) displaced systolic blood pressure and weakened the predictive value of gender ($p=0.076$) but did not alter AER ($p=0.0002$). When the discrete variable "hypertension (WHO)" was substituted for the continuous blood pressure variables only AER ($p=0.0007$) and age ($p=0.056$) entered the "best" model. The substitution of the discrete variable "hypertension and/or treatment" for arterial blood pressures gave a model where only AER ($p=0.014$) and "hypertension and/or treatment" ($p=0.006$) were significant predictors of CHD.

Gender differences

The associations with CHD shown in Table 2 appeared to differ in men and women and gender

emerged in some models of CHD prediction. Multiple logistic regression analysis was therefore carried out for the sexes separately. In men (Table 5) the "best" model included only AER and age as significant predictors of CHD and there was no change in this whichever combination of independent variables was used. In women (Table 6) AER emerged as the only significant associate of CHD when arterial blood pressures were used and when HbA_1 was an independent variable. Substitution of plasma glucose for HbA_1 gave a "best" model that included AER ($p=0.004$) and glucose ($p=0.08$). Models were not changed by substituting "hypertension (WHO)" for the continuous blood pressure variables. However, substitution of "hypertension and/or treatment" for arterial pressures gave "best" models that included only this wider definition of hypertension ($p=0.017$) and AER ($p=0.012$). The substitution of VLDL-triglycerides and LDL-cholesterol for total serum triglycerides and cholesterol respectively did not change any of these models.

Discussion

Two earlier studies in Type 2 diabetic patients have suggested that subclinical increases in urinary albumin excretion are predictive of increased cardiovascular mortality [10–11]. We undertook the present study to define the relationship between overnight AER and the prevalence of coronary heart disease in representative hospital out-patients with Type 2 diabetes; we also wished to explore further the association between AER and other major cardiovascular risk factors (e.g. arterial blood pressure, serum lipids) and to assess its role as a risk factor for CHD independently of them. In the present study we confirmed the link between AER and CHD, finding the mean AER to be significantly higher in Type 2 diabetic patients with symptoms or ECG signs of CHD than in those without; AER was 2-fold higher in affected men and women.

This study and the previous investigations do not, of course, establish a direct causal link between a raised AER and increased CHD risk. Both may be due to a common factor and elevated arterial pressure would be a prime candidate for this. Several recent studies have reported significant elevation of arterial pressure accompanying microalbuminuria [20–21] and in the earliest study of AER in newly detected glucose intolerant subjects a significant correlation was found between AER and blood pressure [22]. In the 10-year follow-up of the Whitehall study of asymptomatic hyperglycaemic subjects, AER at baseline was significantly higher in those who died than in the survivors [23]; after taking into account the accompanying elevated baseline systolic blood pressure in multivariate analysis AER did not emerge as a significant independent predictor of mortality (although systolic blood pressure did). Any appraisal of AER as a determinant of cardiovascular prognosis in diabetes must therefore take account of blood pressure as a potentially important confounding variable. A further association of similar importance is the relation between AER and serum lipid concentrations demonstrated for the first time in this study. The additional univariate correlations between AER and HbA_1 and plasma glucose and between AER and duration of diabetes may cause further confounding. Positive correlations between urinary protein excretion and both glycaemic control and diabetes duration have been previously noted [8]. The use of multiple regression analysis allows to some extent for these associations. When used for analysing the group as a whole and after initially including all of the variables measured in the logistic regression equation only AER, systolic blood pressure and gender were found to retain a significant association with the indices of CHD morbidity, but age displaced systolic pressure when plasma glucose was used as an alternative measure of glycaemic control to HbA_1.

We found a strong univariate association between CHD and the prevalence of hypertension only when those who qualified because of anti-hypertensive treatment were included with those with raised arterial pressure; the association persisting in multiple regression analysis. However, AER remained a significant associate of CHD in multiple regression analysis whether continuous or discrete blood pressure variables were used and whether anti-hypertensive therapy was considered or not.

Gender emerged as a predictor of CHD, despite little difference in prevalence of CHD between men and women in this study. This may be partly due to the marked sex difference in AER found in this study. Since differences between the sexes in risk factors for arterial disease have been noted in other studies [24], the associations with CHD were examined in men and women separately. In men, AER and age were the only variables predictive of CHD in all models, whichever combination of independent variables were used. In women, as in men, AER emerged as a significant predictor of CHD in all analyses in the present study.

For women, when plasma glucose was substituted for HbA_1, glucose emerged in "best" models of CHD prediction. Glucose intolerance is associated with an enhanced risk for CHD in prospective studies but this does not appear to be independent of other risk variables [9], while any association in diabetic patients is confounded by considerations of treatment. When considered as a discrete variable including those treated by anti-hypertensive therapy irrespective of arterial pressure, hypertension joined AER in, but did not displace it from, "best" models of CHD prediction.

While the sex difference in plasma creatinine observed in these Type 2 diabetic patients is in accord with that observed in non-diabetic subjects [25], the sex difference in AER found in the present study (mean levels in men exceeded those in women) has not been

previously reported. Given the known preponderance of male compared to female diabetic patients with nephropathy [26], and since sub-clinical elevation of AER is predictive of future clinical proteinuria in both Type 1 [5-7] and Type 2 [11] diabetic patients, a sex difference in AER is not unexpected although it is unexplained. The findings suggest that gender should be taken into account in the analysis and interpretation of AER in Type 2 diabetes.

Our finding of significant associations between AER and CHD morbidity in this cross-sectional study supplements and in part explains the predictive power of microalbuminuria for cardiovascular mortality in earlier studies. Despite differing mean levels of AER between diabetic men and women, the association between AER and CHD was present in both sexes and appeared to be independent of established risk factors for cardiovascular disease. The mechanism of these associations between albumin excretion rate, coronary heart disease and certain of its risk factors requires further investigation.

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