Microalbuminuria and coronary heart disease in non-diabetics

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Summary: Microalbuminuria (or urinary albumin excretion rates (AER) above normal limits) is associated with coronary heart disease (CHD) particularly in diabetics. To determine the sensitivity and specificity of AER for CHD in a non-diabetic population we prospectively studied 115 consecutive patients undergoing coronary angiography and 66 undergoing exercise electrocardiography (ECG). There was no relationship between AER and the severity of CHD determined by angiography (Gensini-scored). While microalbuminuria (AER > 20 µg/minute) was 91% specific it had low sensitivity (12%). Microalbuminuria is not a sensitive indicator of CHD in a non-diabetic population.

Introduction

Increasing evidence suggests that microalbuminuria excretion of abnormal levels of urinary albumin, undetectable by reagent strips, usually expressed as albumin excretion rate (AER) is of pathological significance. It is strongly prognostic of renal failure, proliferative retinopathy and cardiovascular mortality in patients with insulin-dependent and non-insulin-dependent (NIDDM) diabetes mellitus.^{1–7} Recently, an association between microalbuminuria and all causes of mortality in non-diabetic subjects has also been demonstrated.^{8,9} In the Islington Diabetes Survey, Yudkin *et al.*¹⁰ reported that microalbuminuria was a predictor of coronary heart disease (CHD) in non-diabetic subjects.

This study was undertaken to examine the strength of the suggested association between microalbuminuria and CHD in a cross-section of non-diabetic patients with angiographically or exercise electrocardiographically proven CHD, particularly to determine if it is predictive of the severity of coronary ischaemia.

Subjects and methods

A timed overnight urine collection was obtained from 115 consecutive, non-diabetic (normal fasting glucose) patients (age 57 ± 10 years, 95 male), undergoing coronary angiography. A midstream

urine was examined to exclude urinary tract infection as a cause of microalbuminuria. Time of bladder voiding before retiring was noted. All nocturia and first-morning urine was collected. Total volume and collection time were noted.

Samples were Dipstix-tested (Ames Division, Miles Lab.) to rule out gross proteinuria and haematuria, and 61 were randomly neutralized to pH = 7 before being frozen at –18°C. They were assayed within 4 months using an immunoturbidimetric assay,^{11–13} coefficient of variation (CV) = 3.5% and 6.3% at 5 mg/l and 80 mg/l, respectively. Forty-four random samples were also analysed by radioimmunoassay,¹⁴ CV = 2.7% and 3.9% at 5 and 80 mg/l, respectively and there was a highly significant correlation ($r = 0.98$) between these two methods.

A distinct group of 63 consecutive patients (age 55 ± 9.5 years, mean ± s.d., 43 males) gave random urine samples before and after exercise electrocardiogram (ECG). The bladder was emptied before exercise, and a modified Bruce Protocol used. No fluid was allowed prior to taking the post-exercise sample, as forced diuresis may interfere with true AER.¹⁵

Major cardiovascular risk factors were assessed on all patients. Hypertension was defined as blood pressure ≥ 150/90 mmHg. Fasting total cholesterol, blood glucose, past and current smoking history, family history of coronary heart disease and current drug therapies were noted. Cine-angiography was analysed by a radiologist, blinded to the other results, according to the Gensini Score.¹⁶ Resting ECG was analysed according to

the Minnesota Code¹⁷ for evidence of coronary heart disease.

Logarithmic transformation was applied to AER values, which showed a positively skewed distribution. Multiple regression analysis was performed to study the independent influence of one variable on AER or Gensini Scores.

Results

Of the 115 patients undergoing angiography, 13 had microalbuminuria. There was no difference between AER values of neutralized and non-neutralized samples. Although the mean Gensini Score was 14.9 (range 0–84), a score of four or more indicates > 75% occlusion of a major vessel and is taken to indicate significant coronary heart disease. The sensitivity of an AER value of > 20 µg/minute for the presence of coronary heart disease (Gensini > 4) was only 12% in this study. Specificity of AER of < 20 µg/minute for the absence of CHD (Gensini < 4) was 91%. The positive predictive value of AER > 20 µg/minute was 77%. No association was found between AER and Gensini Scores (Spearman's rank correlation coefficient, $\rho = 0.163$, $P > 0.1$). Neither did AER increase with more widespread vessel involvement.

Subjects with microalbuminuria (AER > 20 µg/minute), were compared to those with normal levels ($n = 102$). These groups (Table I) were well matched for age, sex, current treatment regimens, body-mass index (BMI) and proportion of smokers. Serum creatinine levels were higher in the higher AER group but there was no association with CHD, blood pressure or cholesterol history nor family history of CHD.

Table I Comparison of patients with AER > and < 20 µg/minute ($x \pm s.d.$)

Variable	AER > 20 µg/minute ($n = 13$)	AER < 20 µg/minute ($n = 110$)	P value
Age (years)	61 (7)	57 (10)	NS
Sex (% male)	85%	76%	NS
Gensini Score	17.04	14.78	NS
(+) Minnesota	62%	57%	NS
Smokers	77%	74%	NS
Hypertension	46%	24%	0.08
Cholesterol > 6.2 mmol/l	31%	39%	NS
Family history of coronary heart disease	70%	53%	NS
Serum creatinine (µmol/l)	118.69 (23.3)	94.65 (31.4)	0.001
Body mass index	25.88 (2.0)	25.21 (3.0)	NS

NS = not significant.

Comparing patients with coronary heart disease ($n = 81$) to those without ($n = 34$) these groups were well matched for age, BMI, blood pressure–cholesterol, smoking status and most drug groups (Table II). At an AER cut-off of 20 µg/minute no difference was present between those with and without heart disease. Similarly the AER values were not different between these groups (Table II). As expected a much greater proportion of patients with CHD were male and had a family history of CHD. Patients with CHD were more likely to be on calcium antagonists but otherwise CHD was not significantly associated with other risk factors or drug groups. An ischaemic Minnesota Code was significantly associated with Gensini Scores ($P < 0.05$).

In patients undergoing exercise electrocardiography, a positive stress test (defined by onset of ST depression or T-wave inversion during or up to 5 minutes post-exercise, or the occurrence of chest pain relieved by sublingual nitrates) was obtained in 27 subjects. In 10 patients the urinary albumin was elevated (> 20 mg/l) prior to exercise. There was a highly significant postexertional increase (10.7 ± 2.7 to 70.5 ± 9.5 mg/l, $P < 0.001$) in the urinary excretion of albumin. The degree of increment expressed as the difference in creatinine-corrected albumin concentration in post- and pre-exercise samples, was not related to positivity of the stress test or to the stage of Bruce Protocol at which the test was terminated.

Table II Comparison of patients with angiographically proven coronary heart disease (CHD) to those without (mean $\pm$ s.d.)

Variable	CHD ($n = 81$)	Non-CHD ($n = 34$)	P value
Age (years)	57.2 (10.1)	57.8 (9.7)	NS
% male	84%	64%	< 0.03
Smoking	77%	67%	NS
Systolic BP (mmHg)	128.8 (16.6)	129 (15.6)	NS
Diastolic BP (mmHg)	81.2 (10.3)	81.4 (11.9)	NS
AER (µg/minute)	12.9 (24.3)	11.0 (24.9)	NS
Serum cholesterol (mmol/l)	5.9 (1.1)	5.6 (0.8)	NS
Family history CHD	65%	32%	< 0.001
Serum creatinine (µmol/l)	103.3 (25.9)	84.2 (17.9)	< 0.001
Body mass index	25.4 (2.8)	24.7 (2.6)	NS
Calcium antagonist	49%	27%	< 0.05

NS = not significant; BP = blood pressure.

Discussion

Microalbuminuria is now firmly established as a useful screening test to predict the development of nephropathy in diabetics.¹⁻⁷ Recent population screening studies^{10,18} raised the possibility that microalbuminuria may be indicative of CHD. Our data in non-diabetic patients with angiographically or stress test-proven disease suggests that sensitivity and positive predictive value of AER for CHD are poor. Furthermore we did not find any relationship between AER and the severity of atheromatous lesions at angiography.

A number of factors may contribute to this discrepancy with the earlier studies of Yudkin *et al.*¹⁰ and Damsgaard *et al.*¹⁸ Firstly, the Islington Diabetes Survey may have recorded a spuriously high prevalence of CHD by using the WHO questionnaire to define CHD, relying in some cases on subjects' own history of angina or myocardial infarction, as chest pain frequently is falsely positive for CHD even if guided by WHO criteria.¹⁹ Secondly, subjects in the population screening study were not examined for asymptomatic urinary tract infection. Thirdly, subjects with CHD were significantly older than those deemed free of CHD. Subsequently, Damsgaard *et al.*¹⁸ showed an association between AER and overall mortality in elderly non-diabetic subjects (aged 60–74 years). It is therefore possible that the association between AER and CHD reported by Yudkin *et al.* may in part reflect an age effect.

The Islington Diabetes Survey population was also significantly biased on the basis of self-selection as 45% of those with CHD had impaired glucose tolerance or frank diabetes, compared with 25% of the group without CHD.¹⁰ In addition, both systolic and diastolic blood pressure was significantly higher in those with CHD and as hypertension is associated with microalbuminuria,²⁰ this may also be contributory.

There is increasing evidence that patients with insulin resistance and hypertension are more likely to have microalbuminuria than those with normal

glucose tolerance and systemic blood pressure.^{21,22} Glucose intolerance with hyperinsulinaemia may be a common denominator in the associated subgroup of patients with NIDDM, hyperlipidaemia, hypertension and microalbuminuria. Since our population excluded patients with diabetes, the association of AER with coronary heart disease in earlier studies may be explained in part through diabetes and glucose intolerance.

We confirmed Damsgaard's association of AER with serum creatinine noting a strong association between CHD and serum creatinine. Damsgaard also reported that creatinine predicted mortality and that heart disease was the commonest cause.¹⁸

There was a particularly strong association between family history of CHD and angiographic evidence of CHD. The strength of this association may be influenced by relatives themselves having risk factors for CHD such as excessive smoking, hypertension, hypercholesterolaemia, but we have not studied this.

Our exercise study confirms the postexertional increment in microalbuminuria;^{15,23} however, no pattern between the level of increase and result of the exercise test was noted. Neither was exertional microalbuminuria related to the level of physical activity achieved on the modified Bruce Protocol. It has been shown that angiotensin converting enzyme inhibitors reduce resting and exercise induced microalbuminuria.^{24,25} Perhaps individual differences in intraglomerular haemodynamics during exercise determines the degree of post-exertional microalbuminuria which may be mediated by renal prostaglandins.²⁶

In conclusion, we were unable to find an association between AER levels and established CHD. While there is evidence from other community studies that AER may be an indicator of overall mortality in older subjects over 60 years, this may reflect rising systolic blood pressure and glucose intolerance in the elderly. The value of AER as an independent specific marker of CHD in the younger non-diabetic patient population is not established.

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