Microalbuminuria: associations with height and sex in non-diabetic subjects

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Abstract

Objectives—To study the association(s) between microalbuminuria and cardiovascular risk factors in non-diabetic subjects.

Design—Patients aged 40-75 years were randomly selected from a general practice list and invited to participate.

Setting—Health centre in inner city London.

Subjects—Of those invited, 1046 out of 1671 (62·6%) attended. Subjects were excluded for the following reasons: not being white (44); urinary albumin excretion rate >200 μg/min (3); having a urinary infection (5); taking penicillamine or angiotensin converting enzyme inhibitors (7); older than 75 (2); having diabetes (25); missing data on glucose concentration (1).

Main outcome measures—Glucose tolerance test results, albumin excretion rate from overnight and timed morning collections of urine; blood pressure; height.

Results—Mean albumin excretion rate was significantly lower in women than men (mean ratio 0·8, 95% confidence interval (0·69 to 0·91)). Mean albumin excretion rate was significantly associated with age, blood pressure, and blood glucose concentration (fasting, 1 hour, and 2 hour) in men and inversely with height. Men who had microalbuminuria in both samples were significantly shorter (by 5 cm (1·3 to 9·3 cm)) than those who had no microalbuminuria in either sample when age was taken into account. In the case of women only systolic pressure was significantly associated with albumin excretion rate.

Conclusions—Microalbuminuria and short stature in men are associated. Cardiovascular risk has been associated with both of these factors and with lower birth weight. The inverse association of microalbuminuria with height is compatible with the suggestion that factors operating in utero or early childhood are implicated in cardiovascular disease. The higher prevalence of microalbuminuria in men compared with women may indicate that sex differences in cardiovascular risk are reflected in differences in albumin excretion rate.

Introduction

In diabetic subjects, microalbuminuria predicts overt proteinuria and chronic renal failure[1 2] and has a powerful association with macrovascular disease that is unexplained by known cardiovascular risk factors.[3] Microalbuminuria is also found in non-diabetic subjects, with a prevalence ranging from 6·3% to 13%.[4-6] In a previous study in Islington an association was found between coronary heart disease and microalbuminuria in non-diabetic subjects independent of blood pressure; mortality at $3^{1/2}$ years in subjects with microalbuminuria was 24 times higher.[4] Height is inversely associated with risk of coronary heart disease,[7 8] and this observation has been considered evidence of factors acting in utero or in early childhood.[9] We examined the relation between albumin excretion rate, height, and other cardiovascular risk factors in non-diabetic white subjects aged 40-75 in north London.

Subjects and methods

Ethical approval for the study was obtained from the district ethics committee. The participants were recruited from a general practice in north London with a list size of around 8500 at the time of the study. A list of all patients aged 40-75 was obtained and those known to have diabetes were removed from it. Subjects were invited randomly by post to participate in the study. Patients with terminal illnesses were excluded from the study. Those who were eligible were advised that the screening procedure would take just over two hours and include blood tests, urine tests, measurement of height, weight, and blood pressure, and some questions about general health and current treatments. Those who did not respond to the first invitation were invited again in another letter. Anyone who defaulted was offered another appointment. The screening programme took place from May 1990 to September 1991.

SCREENING PROCEDURE

Participants were given a morning appointment and asked to fast from 2200 the preceding night. Compliance with this request was confirmed on arrival. After initial registration details had been completed blood pressure was taken with a random zero sphygmomanometer, and an oversize cuff (Hawksley Gelman, Lancing, Sussex) was used when appropriate; the fifth Korotkoff sound was taken as the measure of diastolic pressure. Venous blood was taken for fasting plasma glucose concentrations. A glucose load (75 g) (Fortical, Cow and Gate, Trowbridge, Wiltshire) was then given and further blood samples were taken after one and two hours for measurement of plasma glucose concentration.

Each subject filled in a questionnaire, which included items on serious illnesses and current treatments. The questionnaires were completed by the subject and checked by a researcher. If, however, the subject was unable to do this—for example, because of illiteracy or physical or mental impairment—the questionnaire was filled in by the subject's companion or the questions were asked orally by a researcher. Blood pressure was then measured for the second time on the same arm.

Height was measured without shoes and subjects were weighed wearing only light clothing on a balance with attached height measure (Seca). Body mass index was calculated as weight divided by the height squared (kg/m^2).

A timed urine sample was obtained at the time of screening from all subjects and was tested with dipsticks for protein and blood and additionally for leucocytes and nitrites in the second half of the recruitment phase. When there was evidence of possible urinary tract infection, urine was sent for culture. A second, overnight, sample was requested from all subjects.

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ASSAY METHODS

Plasma glucose concentration was measured by a glucose oxidase technique (Beckman, Brea, California). Urinary albumin excretion was measured by an inhouse modified competitive enzymoimmunoassay,[10] which was validated against a commercial radioimmunoassay (r=0·96; Pharmacia-LKB, Milton Keynes). Albumin excretion rate was calculated from this, and the mean of the two results (timed and overnight samples) after logarithmic transformation was used in the analyses except when indicated.

CLASSIFICATION CRITERIA FOR ANALYSES

Diabetes—Glucose intolerance and diabetes were defined by the criteria of the World Health Organisation.[11] Diabetes mellitus is classified as a venous plasma glucose concentration during a 75 g oral glucose tolerance test of greater than or equal to 7·8 mmol/l (fasting) or 11·1 mmol/l (two hours after the load).

Blood pressure—The means of the two systolic and diastolic blood pressures were used in the analyses.

Microalbuminuria—Subjects were classified as having microalbuminuria if they had an albumin excretion rate of 20-200 µg/min detected in either or both of the urine samples.

DATA ENTRY AND STATISTICAL ANALYSIS

The data were entered into a computer database using the Smartware II software package and analysed using the statistical package for the social sciences (SPSS). Albumin excretion rate was $\log_e$ transformed because the distribution was skewed. Logistic regression was used for analysis of dichotomous variables and multiple linear regression for continuous data.

SUBJECTS

By the end of the screening programme 1671 eligible people had been sent letters asking to participate in the study; 1046 of them attended (62·6%). Of the nonattenders, 57 (3·4%) defaulted, 67 (4%) refused, and

TABLE I—*Results of regression analysis of albumin excretion rate ($\log_e$ transformed) adjusted for age in men*

Variable	Regression coefficient (95% confidence interval) per unit $\log_e$ AER	% Of variation (R^2)	p Value for R^2
Blood glucose (mmol/l):			
Fasting	0·25 (0·04 to 0·45)	3·5	≤0·0007
1 h	0·07 (0·03 to 0·12)	4·6	≤0·0001
2 h	0·12 (0·04 to 0·19)	4·3	≤0·0002
Blood pressure (mm Hg):			
Systolic (mm Hg)	0·01 (0·01 to 0·02)	6·6	≤0·0001
Diastolic (mm Hg)	0·02 (0·01 to 0·03)	7·0	≤0·0001
Height (cm)	-0·02 (-0·03 to -0·01)	3·8	≤0·0004

TABLE II—*Mean values (95% confidence intervals) for height, glucose concentration, and blood pressure by category of microalbuminuria in men*

Variable	p Value (analysis of covariance)	Microalbuminuria in:		
		Both samples	One sample	Neither sample
Height	0·026	168 (164 to 172)	172 (170 to 174)	173 (172 to 174)
Blood glucose (mmol/l):				
Fasting	0·031	5·0 (4·7 to 5·3)	5·1 (4·9 to 5·3)	4·9 (4·8 to 5·0)
1 h	0·080	8·7 (7·2 to 10·2)	8·3 (7·5 to 9·1)	7·6 (7·3 to 7·9)
2 h	0·020	5·1 (4·3 to 5·9)	5·6 (5·1 to 6·1)	4·9 (4·7 to 5·1)
Blood pressure (mm Hg):				
Systolic	0·0001	139·3 (129·0 to 149·0)	126·2 (121·0 to 132·0)	118·8 (117·0 to 121·0)
Diastolic	0·0001	81·4 (74·7 to 88·1)	76·7 (72·8 to 80·6)	70·7 (69·4 to 72·0)

TABLE III—*Multiple regression analysis of albumin excretion rate ($\log_e$ transformed) with height, blood glucose concentration, systolic blood pressure, and age in men*

	Height	2 h Blood glucose	Systolic pressure	Age	Constant
Regression coefficient	-0·02	0·08	0·01	0·0006	2·20
95% Confidence interval	-0·03 to -0·0007	0·002 to 0·16	0·005 to 0·02	-0·011 to 0·012	1·42

Total R^2=8·4%, p≤0·0001.

TABLE IV—*Regression analysis of factors associated with height in men (systolic pressure and blood glucose concentration two hours after a glucose load) with adjustment for age*

Variable	Regression coefficient (95% confidence interval)	R^2 (%)	p Value for R^2
Systolic pressure (mm Hg)	-0·231 (-0·456 to -0·007)	20·1	≤0·0001
2 h blood glucose (mmol/l)	-0·029 (-0·048 to -0·010)	10·1	≤0·0001

501 (30%) did not respond. Subjects were excluded from this analysis for the following reasons: (*a*) they were not white (44), (*b*) albumin excretion rate was greater than 200 µg/min (three), (*c*) they had evidence of urinary infection (five), (*d*) they were taking penicillamine or angiotensin converting enzyme inhibitors (seven), (*e*) they were older than 75 (two), (*f*) they had diabetes (25), and (*g*) data on glucose concentrations were missing (one). Thus a total study population of 959 remained, comprising 536 women and 423 men.

Results

The prevalence of microalbuminuria (albumin excretion rate 20-200 µg/min) was 8·9% (81/913) in urine samples taken two hours after the glucose load and 5·8% (47/812) in the overnight samples, with 2·5% (19/774) showing microalbuminuria on both occasions. The prevalence of microalbuminuria differed significantly between men and women in the overnight sample (8·9% v 3·3%, p<0·001) but not in the two hour sample (10·7% v 7·4%, p<0·1). Men had a significantly higher mean albumin excretion rate than women (p≤0·001; mean ratio 0·80 (95% confidence interval 0·69 to 0·91). The correlation of albumin excretion rate between the two urine samples was 0·46 (n=774, p<0·001). Because of the substantial differences in albumin excretion rate between the sexes, we analysed data for men and women separately.

Among the women mean albumin excretion rate ($\log_e$ transformed) decreased slightly with age (r= -0·08, p=0·08), but among the men it increased with age (r=0·16, p<0·003). All analyses were therefore adjusted for age.

MEN

Table I shows the associations of blood pressure, blood glucose concentration, and height with albumin excretion rate adjusted for age in the men (the percentage of variation, R^2, has been adjusted for the number of variables in the regression equation).

Analysis of covariance was used to test for mean differences in three categories of microalbuminuria: none on both occasions, microalbuminuria in one urine sample, and microalbuminuria in both samples (MM). The results are shown in table II. Mean height was significantly different in the group with microalbuminuria in both samples compared with the group with no microalbuminuria in both samples (difference between means 5 cm (1·3 to 9·3)).

Age, height, systolic blood pressure, and blood glucose concentration at 2 hours accounted for 8·4% of the variation in mean albumin excretion rate. The regression equation including all four variables is shown in table III. The strength of the relation between height and albumin excretion rate was reduced but remained significant when age, blood glucose concentration, and blood pressure were included in the equation.

Other associations of height are shown in table IV.

WOMEN

Table V shows the associations of blood pressure, blood glucose concentration, and height with albumin excretion rate adjusted for age in the women. Only the association with systolic blood pressure was significant.

Variable	Regression coefficient (95% confidence interval)	% Of variation R^2	p Value for R^2
Blood glucose (mmol/l):			
Fasting	0·061 (−0·096 to 0·218)	0·4	0·17
1 h	0·010 (−0·032 to 0·051)	0·2	0·23
2 h	0·037 (−0·024 to 0·098)	0·5	0·12
Blood pressure (mm Hg):			
Systolic	0·008 (0·003 to 0·012)	2·7	0·001
Diastolic	0·007 (−0·001 to 0·015)	0·8	0·06
Height	0·006 (−0·006 to −0·018)	0·5	0·14

Discussion

We found a prevalence of microalbuminuria of 8·9% in a single urine sample two hours after a glucose load. This is lower than the prevalence of 13·3% found by Haffner et al in Mexican-Americans[5] and higher than the prevalence of 6·3% in the Winocour study in Newcastle,[6] but it is similar to the 9·4% found in the previous Islington study.[4] Ethnic differences, age of subjects, selection bias, and different assay methods may have contributed to the differences. However, the Newcastle study defined microalbuminuria according to more rigorous criteria (albumin concentration greater than 20 μg/ml in conjunction with a ratio of albumin to creatinine concentration of greater than 3·5) and found a prevalence of 2·2%, which is similar to the prevalence of microalbuminuria of 2·5% detected in the two samples combined in our study.

We found that in men microalbuminuria was inversely associated with height and directly associated with blood glucose concentration (fasting and two hours after a glucose load) and systolic and diastolic blood pressures; in women microalbuminuria was directly associated with systolic pressure. Blood pressure and impaired glucose tolerance in adults are inversely related to birth weight and contribute to the increased cardiovascular risk associated with low birth weight.[9] This study also shows that, in men but not women, blood glucose concentration and blood pressure are inversely associated with height, which is in turn influenced by birth weight and early childhood environment.[12] An inverse association of height with risk of coronary heart disease has been found,[7 8] and as microalbuminuria, blood glucose concentration, and blood pressure are negatively associated with height in men, these factors may have a role in the raised cardiovascular risk which accompanies short stature. The association of microalbuminuria with short stature suggests that the factors determining adult height

may also influence renal structure or function in men.

Absolute differences in cardiovascular risk between men and women are not explained by conventional risk factors.[13] The higher albumin excretion rate in men might suggest that factors responsible for the increased cardiovascular risk in men also influence urinary albumin excretion. Males may be more affected by factors operating during the later stages of pregnancy as they gain more weight than females during the third trimester.[14] If microalbuminuria, height, blood pressure, and glucose intolerance are in part determined by factors operating in the later stage of pregnancy, this could explain the coincidence of these abnormalities in adulthood, their association with cardiovascular risk, and the difference between the sexes in prevalence of coronary heart disease and various associated factors.

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ONE HUNDRED YEARS AGO

"PEA-SOUP" FOGS.

Dr. Poore lectured to a large audience at the Sanitary Institute on February 8th on a subject of much importance to all Londoners. After some interesting facts relating to the great fog of Christmas, 1891, which lasted 100 hours and was responsible for the death of about 1,400 persons, Dr. Poore stated that London fogs were really due not so much to smoky chimneys as was generally supposed, but to climatic conditions. The primary causes of fog were saturation, coldness, and stagnation of the air. Of these three, the last mentioned—the most serious from the point of view of health—was the only one which could be to any extent controlled by us. The average daily motion of the air, it was stated, was 300 miles. During the fog above mentioned the air at Greenwich was moving at the rate of 49 miles a day; but in the streets of our city the high buildings and the absence of straight and open thorough-

fares so interfered with the current as to produce absolute stagnation. Thus for 100 hours London was breathing and rebreathing the same air with the direst results. Smoky fires certainly aggravated the evil; but, even if perfect combustion could be ensured, the deleterious nature of the fog would not be lessened as much as was popularly imagined. Analysis of fog deposit showed that 33 per cent. of it was of metallic origin, and was, therefore, quite independent of fires, while the sulphuric, carbonic, and other acids would result equally from perfect as from faulty combustion. The chief means of minimising the evil would be to keep people apart, to prevent overcrowding by the construction of high buildings, and to open up wide, straight thoroughfares in different directions so as to allow the air currents to move unchecked.

(BMJ 1893;i:369.)