

Manchester *et al* from Denver reported a series of 257 pregnancies which were complicated by suspected fetal abnormality on ultrasonography.¹ Thirty seven per cent of the infants born had additional anomalies not detected by prenatal ultrasonography, and the authors concluded that prenatal diagnoses based on ultrasonography were remarkably accurate but were insensitive to associated anomalies in individual cases. Our study confirms this, a revised diagnosis being made in 53 (40%) of such cases.

We believe that examination of midtrimester fetuses by a clinical geneticist is a worthwhile service and improves diagnosis, which in turn benefits the diagnostic teams and parental counselling. It is best carried out by a clinician experienced in dysmorphology, used to normal variations in the appearance of fetuses at various stages in gestation, and familiar with rare dysmorphic syndromes. The collaboration of cytogeneticists and paediatric pathologists is important in defining the full extent of the anomalies in order to arrive at the final post-termination diagnosis, on which the parents will base their future reproductive decisions.

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Microalbuminuria as predictor of increased mortality in elderly people

Else Marie Damsgaard, Anders Frøland, Ole Dan Jørgensen, Carl Erik Mogensen

Abstract

Objective—Correlation of the urinary albumin excretion rate and the risk of death among elderly subjects.

Design—216 Subjects aged 60-74 whose urinary albumin excretion rate had been determined were followed up 62-83 months later.

Setting—Municipality of Fredericia, Denmark.

Subjects—223 People who had been selected as control subjects for diabetics found during a systematic screening for diabetes of all people aged 60-74 living in the municipality of Fredericia, Denmark. Of these subjects, 216 had an extensive clinical and biochemical examination within a few weeks of selection.

Main outcome measure—Death.

Results—The median urinary albumin excretion rate was 7.52 µg/min. Eight of those with a rate below the median died compared with 23 with a rate equal to or greater than the median ($p=0.0078$). The median albumin excretion rate in the 31 who died was 15.00 µg/min. Cardiovascular disease was the most common cause of death in both groups. A multivariate regression analysis of survival data was performed using the proportional hazards model. Besides albumin excretion rate, male sex, serum creatinine concentration, and hypertension were found to be of prognostic value.

Conclusions—The association between the albumin excretion rate and mortality that has been described in recent years in patients with diabetes mellitus may be present in elderly people in general, even when other known risk factors are taken into account.

Introduction

Excretion of urinary albumin above 20 µg/min (microalbuminuria)¹ is strongly prognostic of disease and death in diabetes mellitus.²⁻⁸ The association between albumin excretion and the risk of death is also

present when other risk factors such as male sex, age, obesity, ischaemic heart disease, hypertension, smoking, and raised blood lipid concentrations are taken into account.^{1,3,5} Microalbuminuria is also associated with hypertension⁹ and increased cardiovascular morbidity in people who are not diabetic.^{5,10} We followed up a cohort of subjects drawn from the population of Fredericia¹¹ who were recruited to serve as controls for a cohort of diabetics aged 60-74 found during population screening. We followed up the subjects who were not diabetic for 62 to 83 months, or to death, and evaluated their urinary albumin excretion and other possible risk factors for death.

Subjects and methods

From 1 February 1981 to 31 October 1982 all people aged 60-74 living in the municipality of Fredericia, Denmark, were invited to have their blood glucose concentration measured after fasting overnight. The participants were also interviewed about a possible history of diabetes. Details of the sampling procedure and characteristics of those who did not respond have been described.¹¹ We invited 5699 people to participate, 5292 (92.9%) of whom accepted. Of these, 236 gave a history of diabetes. All the people screened were numbered consecutively, and for each diabetic subject a control was defined as the person with the nearest following number who was of the same sex and age (within one year) and whose fasting blood glucose concentration was below 7.0 mmol/l. Altogether 223 (94.5%) controls consented to further examination. Table I gives the age and sex distributions of this control group (the study population) and the corresponding total population of the municipality. All subjects were asked to have an extensive clinical and biochemical examination.

The blood and urine of subjects were sampled not later than three weeks after the initial screening. Venous blood obtained after subjects had fasted was tested for glucose, serum creatinine, triglyceride, total

Department of Medicine,
Fredericia Hospital,
Fredericia, Denmark
Else Marie Damsgaard, MD,
senior registrar
Anders Frøland, MD,
consultant

Department of Clinical
Physiology, Odense
Hospital, Odense,
Denmark
Ole Dan Jørgensen, MD,
registrar

Department of Medicine,
Aarhus Kommunehospital,
University of Aarhus,
Aarhus, Denmark
Carl Erik Mogensen, MD,
professor

Correspondence to:
Dr Else Marie Damsgaard,
Institute of Clinical
Genetics, J B Winsløvsvej
17, 5000 Odense C,
Denmark.

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cholesterol, very low density lipoprotein, low density lipoprotein, and high density lipoprotein concentrations and for C peptide concentration before and six minutes after an intravenous injection of 1 mg of glucagon.¹² Blood glucose concentration was measured by a hexokinase method,¹³ plasma lipoproteins by centrifugation and electrophoresis,¹⁴ and C peptide concentrations by radioimmunoassay.¹⁵ Creatinine was determined by Jaffe's kinetic method with a Beckman Astra analyser. Urine tests were performed within one week of the blood sampling and the subjects were again fasting or had had a light meal and had drunk at most 500 ml of water during the preceding four hours. After voiding they drank 200 ml of water, waited for one hour, and then voided again. This second urine

specimen was frozen and later analysed for albumin by radioimmunoassay¹⁶ and for creatinine.

The participants were asked to complete a Rose questionnaire¹⁷ on the symptoms of angina pectoris and were interviewed about their smoking habits. Their height and weight were measured without shoes and overcoat, and blood pressure was measured in the right arm with an electronic sphygmomanometer (Kontron 3000) after the subjects had rested supine for 10 minutes. Diastolic blood pressure was taken as that at the disappearance of the Korotkoff sounds (phase V). A 12 lead resting electrocardiogram was recorded with the subjects sitting before and after exercise and was interpreted according to the Minnesota code.¹⁷ A six lead exercise electrocardiogram was recorded at minute intervals during a bicycle test in the sitting position. Men started at a power of 50 W and women at 25 W, the workload being increased stepwise until subjects were exhausted or stopped the test for other reasons.¹⁸

Body mass index was calculated as weight (kg)/(height (m))², and hypertension was defined as a systolic blood pressure ≥ 160 mm Hg, diastolic pressure ≥ 95 mm Hg, or treatment for hypertension. Ischaemic heart disease was diagnosed if a person had one or more of the following signs: angina pectoris; previous myocardial infarction verified during admission to hospital; important changes in the resting electrocardiogram (Minnesota code 1.1-1.3, 4.1-4.4, 5.1-5.3, 7.1); ST segment changes of ≥ 1 mm during exercise; or ST items, T items, or left bundle branch block after exercise (Minnesota code 11.1-5, 12.1-4, 14.1).

All urine specimens were tested for the presence of leucocytes by a test strip (Cytur).¹⁹ If the strip yielded a positive result a fresh urine specimen was examined by microscopy and the urine was incubated for 48 hours if more than three leucocytes were seen. Urinary tract infection was diagnosed if the urine contained more than 10^5 bacteria/ml.

All subjects were traced through the national register at the beginning of 1988. If a subject had died before 31 December 1987 the date of death was recorded and information on the cause of death was sought from hospital records, necropsy records, and death certificates. The observation period was defined as the number of days from the date of the population screening in 1981-2 to the date of death or 31 December 1987.

STATISTICAL METHODS

Statistical analysis was performed with χ^2 tests, log rank tests, and proportional hazards analyses.²⁰ For the log rank tests and proportional hazards analyses the continuous variables (see table III) were divided into two groups: those with values equal to or above the median (scored 1) and those below (scored 0). The discontinuous variables (see table IV) were grouped into classes such that being male, smoking, and having ischaemic heart disease and urinary tract infection scored 1 and the opposite scored 0. Although the categorisation of the continuous variables in the proportional hazards analysis may have led to some loss of statistical power, it avoided the assumption of linearity and kept the scoring simple. Additional tests showed that the continuous variables were non-linear and that no simple scoring was possible.

Proportionality was checked by stratification and observing a constant vertical difference (independent of time) between plots of estimates of the logarithm of the integrated hazard for each stratum. The risk factors considered in the proportional hazards model were all entered into a first model. This model was reduced by removing the variable causing the least change in significance. This principle was continued

TABLE I—Sex and age distributions (expressed as numbers (percentages) of study population and corresponding total population of municipality of Fredericia on 1 January 1982

Age (years)	Study population			Total population		
	Men	Women	Men:women	Men	Women	Men:women
60-65	28 (31)	36 (27)	0.78	1128 (42.5)	1189 (37.2)	0.95
65-69	28 (31)	45 (34)	0.62	858 (32.4)	1046 (32.7)	0.82
70-74	33 (37)	53 (40)	0.62	666 (25.1)	964 (30.1)	0.69
Total	89	134	0.66	2652	3199	0.83

TABLE II—Cause of death among subjects whose urinary excretion rate had been determined

Case No	Sex	Age at death (year)	Albumin excretion ($\mu\text{g}/\text{min}$)	Cause of death	Source of information
1	M	68	55.0	Myocardial infarction	Necropsy
2	M	72	14.4	Myocardial infarction	Necropsy
3	M	77	55.9	Myocardial infarction	Necropsy
4	M	78	86.0	Myocardial infarction	Necropsy
5	M	73	32.5	Myocardial infarction	Hospital record
6	F	67	4.4	Myocardial infarction	Hospital record
7	M	79	343.6	Myocardial infarction	Hospital record
8	F	78	8.7	Heart disease	Death certificate
9	F	75	5.0	Found dead. Previous myocardial infarction	Death certificate
10	M	72	21.8	Found dead. Previous myocardial infarction	Death certificate
11	M	68	34.7	Found dead. Previous myocardial infarction	Death certificate
12	M	72	4.3	Found dead. Heart disease presumed	Death certificate
13	M	72	71.5	Cerebral haemorrhage	Hospital record
14	F	79	2.0	Cerebral thrombosis	Death certificate
15	F	66	41.1	Subarachnoid haemorrhage	Necropsy
16	M	76	21.6	Bronchitis	Hospital record
17	M	80	11.8	Carcinoma of the prostate	Hospital record
18	F	74	25.1	Carcinoma of the stomach	Hospital record
19	M	70	18.2	Carcinoma of the urinary bladder	Necropsy
20	M	76	5.0	Carcinoma of the urinary bladder	Necropsy
21	M	63	10.5	Carcinoma of the urinary bladder	Hospital record
22	M	75	2.1	Carcinoma of the urinary bladder	Hospital record
23	F	76	4.3	Carcinoma of the colon	Hospital record
24	M	75	12.6	Carcinoma of the lung	Hospital record
25	M	69	160.6	Carcinoma of the pancreas	Hospital record
26	F	74	12.6	Lymphatic leukaemia	Hospital record
27	M	77	17.0	Suicide	Death certificate
28	F	76	162.3	Found dead. No information on previous disease	Death certificate
29	M	73	6.2	Found dead. No information on previous disease	Death certificate
30	M	70	13.5	Found dead. No information on previous disease	Hospital record
31	F	67	15.0	Unknown. Died abroad	

TABLE III—Characteristics of continuous variables studied (populations were divided at median for log rank tests on mortality)

	Median (quartiles)	Total No of subjects examined	No of subjects who died with values:		p Value of log rank test
			Equal to or above the median*	Below the median†	
Age	68.1 (63.6, 71.3)	223	20	15	NS
Fasting blood glucose (mmol/l)	4.55 (4.22, 4.91)	223	23	12	0.03
Stimulated C-peptide (nmol/l)	1.38 (0.98, 1.77)	223	19	16	NS
Urinary albumin excretion rate ($\mu\text{g}/\text{min}$)	7.52 (4.77, 14.85)	216	23	8	0.002
Body mass index (kg/m^2)	24.90 (22.44, 27.68)	223	17	18	NS
Triglycerides (mmol/l)	1.21 (0.88, 1.65)	223	23	12	0.001
Total cholesterol (mmol/l)	6.57 (6.03, 7.40)	223	21	14	NS
Very low density lipoproteins (g/l)	1.40 (1.00, 1.99)	223	18	17	NS
Low density lipoproteins (g/l)	4.91 (4.29, 5.67)	223	18	17	NS
High density lipoproteins (g/l)	3.80 (3.10, 4.90)	223	12	23	NS
Serum creatinine ($\mu\text{mol}/\text{l}$)	92.6 (82.3, 101.8)	223	29	6	0.0001
Creatinine clearance (ml/min) (1.73 m ² surface area)	80.55 (68.95, 96.40)	216	19	16	NS

*Proportional hazards analysis score=1.

†Proportional hazards analysis score=0.

TABLE IV—Characteristics of discontinuous variables (populations were divided according to stated groups for log rank tests on mortality)

	Total No of subjects examined	No (%) of subjects in each group	No who died	p Value of log rank test
Sex	223			<0.0001
Male*		89 (40)	24	
Female†		134 (60)	11	
Ischaemic heart disease	223			0.02
Present*		87 (39)	20	
Absent†		136 (61)	15	
Hypertension	223			0.0002
Present*		71 (32)	20	
Absent†		152 (68)	15	
Urinary infection	223			NS
Present*		16 (7)	4	
Absent†		207 (93)	31	
Smoking	223			NS
Present*		108 (48)	19	
Formerly or never†		115 (52)	16	

*Proportional hazard analysis score=1.

†Proportional hazard analysis score=0.

TABLE V—Results of proportional hazards analysis

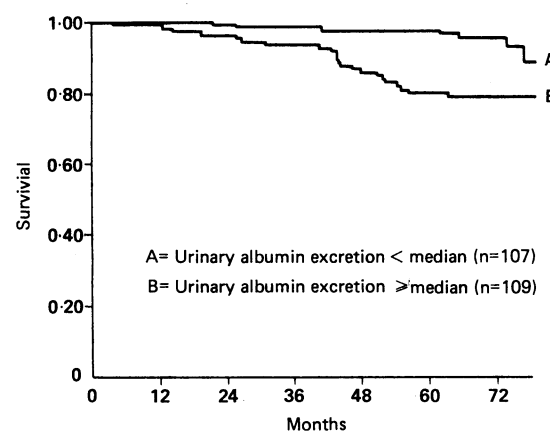
Risk factor	Regression coefficient	Standard error	p Value	Odds ratio (95% confidence interval)
Urinary albumin excretion rate	1.080	0.415	0.009	2.94 (1.31 to 6.64)
Serum creatinine	1.425	0.513	0.006	4.16 (1.52 to 11.36)
Male sex	0.824	0.424	0.051	2.28 (0.99 to 5.23)
Hypertension	1.119	0.376	0.003	3.06 (1.46 to 6.40)

until no further variables could be removed without causing a significant change of the model. The models were compared by using likelihood ratio tests (5% significance level).

Results

The urinary albumin excretion rate was determined in 216 subjects, 31 of whom died during the observation period. The median excretion rate was 7.52 µg/min (25% and 75% centiles 4.77 and 14.85 µg/min). Among the 107 subjects with excretion rates below the median value eight died, and among those with values equal to or above the median 23 died ($\chi^2=7.08$, $p=0.0078$). Four subjects excreted more than 200 µg albumin/min, and one of these died during the observation period. The median excretion rate in those who died was 15.00 µg/min (25% and 75% centiles 6.20 and 41.10 µg/min). The figure shows the survival curves for the groups with low and high excretion.

Information on the cause of death was obtained for all those who died, except one who died abroad (table II). Eight of 15 subjects who had an excretion rate below 15.00 µg/min died from cerebrovascular disease or suddenly from coronary artery disease, as did 10



Survival curves for subjects aged 60-74 in municipality of Fredericia, Denmark, according to whether urinary albumin excretion rate was below or at or above median value (7.52 µg/min)

of 16 who had rates ≥ 15.00 µg/min. A log rank test showed that male sex, serum creatinine concentration, hypertension, albumin excretion rate, ischaemic heart disease, serum triglyceride concentration, and fasting blood glucose concentration were significantly associated with death (tables III and IV). All risk factors were included in proportional hazards analyses, and albumin excretion, male sex, serum creatinine concentration, and hypertension were then found to be significantly associated with death (table V).

Discussion

We followed up 223 subjects aged 60-74 for 62 to 83 months; 35 died. Further analysis showed that three times as many people whose urinary albumin excretion rate was equal to or above the median (7.52 µg/min) died compared with those who had rates below the median. In the Framingham study a cohort aged 50-62 at entry into the study was followed up for 16 years²¹; proteinuria (≥ 0.2 g/l) increased the mortality threefold. In our study only four people (one of whom died) had an albumin excretion rate above 200 µg/min, suggesting that the excess mortality in subjects who had an albumin excretion rate above the median value was not due to proteinuria. Yudkin *et al* recently reported that microalbuminuria was a strong risk factor in people who are not diabetic.¹⁰ In their study 24 out of 149 subjects observed for an average of 3.6 years had an albumin excretion rate above 20 µg/min initially; in all, nine subjects died, of whom six had had an excretion rate above 20 µg/min. Yudkin *et al* reported that a urinary excretion rate above 20 µg/ml strongly predicted the presence of ischaemic heart disease and peripheral vascular disease. Their population was younger than ours (60 *v* 68). In a previous report we discussed the association between microalbuminuria and hypertension in the population described in this paper and found a slight association.⁹

Many risk factors apart from microalbuminuria are supposed to influence morbidity and mortality in diabetics and non-diabetics. We included total cholesterol and high density lipoprotein concentrations in the risk factors we studied as they have been shown to be related to cardiovascular disease in people aged 49 and over.²² Low density lipoprotein concentrations are positively associated with coronary artery disease in non-diabetics,²³ and triglyceride and very low density lipoprotein concentrations may play a part in the development of vascular disease.²⁴ C peptide concentration was included as a risk factor because hyperinsulinaemia is associated with a high prevalence of cardiovascular disease.²⁵⁻²⁷

To evaluate the relative importance of the risk factors in our study log rank tests were performed on each variable. All risk factors were included in a proportional hazards analysis, and albumin excretion, male sex, serum creatinine concentration, and hypertension were found to be significantly associated with death. In a Danish study of the association between microalbuminuria and mortality in non-insulin dependent diabetic patients⁴ a proportional hazards analysis showed that albumin excretion, age, duration of diabetes, and serum creatinine concentration were of significance. It has been suggested that the urinary albumin excretion rate reflects the vascular state of an individual.²⁸ In our study, however, more than half of the subjects died from coronary artery disease or cerebrovascular disease or were found dead irrespective of their albumin excretion rate.

In conclusion, the association between urinary albumin excretion rate and mortality that has been described in diabetes mellitus seems also to be present in elderly people in general when other known risk factors are taken into account.

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Screening for prolonged incubation of HTLV-I infection in British and Jamaican relatives of British patients with tropical spastic paraparesis

J K Cruickshank, J H Richardson, O St C Morgan, J Porter, P Klenerman, J Knight, A L Newell, P Rudge, A G Dalglish

Department of Medicine and Retrovirus Research Group, Northwick Park Hospital and Clinical Research Centre, Harrow HA1 3UJ

J K Cruickshank, MD, senior registrar
J H Richardson, PHD, research fellow
A L Newell, BSC, research officer
P Rudge, FRCP, consultant neurologist
A G Dalglish, FRACP, head of group

Faculty of Medicine, University of West Indies, Kingston 7, Jamaica
O St C Morgan, FRCP, professor
J Knight, medical student

Medical School, University of Oxford, Oxford
J Porter, medical student
P Klenerman, medical student

Correspondence to: Dr Cruickshank.

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Abstract

Objective—To compare the prevalence of antibody to and proviral DNA of the retrovirus HTLV-I in relatives of 11 British patients with tropical spastic paraparesis who had migrated from Jamaica before they developed symptoms, and to examine factors possibly related to transmission of HTLV-I.

Design—Migrant, family study. Antibody state was determined by several methods and confirmed by western blotting; the polymerase chain reaction was used to detect proviral DNA.

Setting—Britain and Jamaica.

Subjects—All available first degree relatives: those born and still resident in Jamaica (group 1); those born in Jamaica who migrated to Britain (group 2); and index patients' children who were born and resident in Britain (group 3). All had been breast fed and none had had blood transfusions.

Results—Of the 66 living relatives, 60 were traced. Seroprevalence among those born in Jamaica (irrespective of current residence) was 22% (10/46; 95% confidence limits 9 to 34%) compared with zero among British born offspring (0/14) and was higher in group 2 at 33% (7/21; 12 to 55%) than in group 1 at 12% (3/25; 0 to 25%). (Patients in group 1 had the greatest mean age.) Proviral DNA was not detected in any subject negative for HTLV-I antibody, making prolonged viral incubation in those negative for the antibody unlikely.

Conclusion—In this sample factors related to

place of birth and early residence were more important in transmission of HTLV-I than maternal or age effects. In areas with a low to moderate prevalence policies of preventing mothers who are carriers of the virus from breast feeding would be premature.

Introduction

The human T cell leukaemia lymphoma virus type I (HTLV-I) has been aetiologically related to the adult T cell leukaemia lymphoma syndrome¹ and, more recently, to tropical spastic paraparesis.²⁻⁴ Both diseases occur primarily in the major areas where HTLV-I is endemic—south western Japan and the Caribbean—but also develop in migrants from these regions.⁵⁻⁸ The cumulative lifetime risk of developing either disease in otherwise healthy people with antibodies against HTLV-I has been estimated at between 2% and 7% and rises with age.⁹⁻¹¹ Oddly, the risk of adult T cell leukaemia lymphoma is consistently greater in male carriers of HTLV-I than in female carriers, while that of tropical spastic paraparesis is greater in females and reflects the sex ratio of seroprevalence of HTLV-I in the population.

Known routes of HTLV-I transmission include transfusion with infected cellular blood products, sexual activity, and perinatal transmission from mother to child.¹²⁻¹⁴ Whether breast feeding or other perinatal routes are responsible is uncertain but of considerable