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Sodium-lithium countertransport activity in red cells of patients with insulin dependent diabetes and nephropathy and their parents

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Abstract

Objective—To determine whether there are familial and genetic aspects of sodium-lithium countertransport activity in red cells in diabetic nephropathy.

Design—Case-control study.

Setting—Teaching hospital diabetic clinic.

Subjects—40 Patients with insulin dependent diabetes, both of whose parents were alive: 20 with persistent proteinuria and 20 with normal albumin excretion matched for age, duration of diabetes, and body mass index. All 80 parents.

Main outcome measures—Sodium-lithium countertransport activity in red cells and arterial blood pressure.

Results—Sodium-lithium countertransport activity in red cells was higher in the patients with proteinuria than in the patients with normoalbuminuria (mean (95% confidence interval) 0.47 (0.39 to 0.54) v 0.33 (0.28 to 0.38) mmol/l red cells/h respectively, $p=0.0036$; mean difference 0.14 (0.04 to 0.22)). The mean countertransport activity for the two parents of each patient was calculated, and from this the mean value for each group of parents was calculated; the value was higher in the parents of the patients with proteinuria than in the parents of the patients with normoalbuminuria (0.40 (0.32 to 0.48) v 0.30 (0.26 to 0.33) mmol/l red cells/h respectively, $p=0.016$; 0.10 (0.02 to 0.19)). Twenty eight of the parents of the patients with proteinuria compared with 12 of the

parents of the patients with normoalbuminuria had a countertransport activity that was above the median value in all 80 parents ($p<0.001$). Mean arterial blood pressure in the parents of the patients with proteinuria was related to that of their offspring ($r=0.46$; $p<0.01$). There was a positive correlation between the sodium-lithium countertransport activity in red cells in the parents and their offspring when all parents and patients were considered ($r=0.37$; $p<0.001$).

Conclusions—Increased sodium-lithium countertransport activity in red cells in the parents of diabetic patients with nephropathy provides further evidence that familial, and possibly genetic, factors related to a predisposition to arterial hypertension have a role in the susceptibility of diabetic renal disease.

Introduction

The factors that predispose a substantial subset of diabetic patients to the serious complication of diabetic nephropathy have not been elucidated. Although poor glycaemic control may play some part, it is unlikely to be the sole determinant.^{2,5} Recent work has shown that diabetic nephropathy clusters in families, the frequency of nephropathy in diabetic siblings of diabetic probands with nephropathy being five times that in diabetic siblings of diabetic probands without nephropathy.⁶ The importance of familial factors, and thus possibly heredity, has been further emphasised

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by the finding of a raised arterial pressure in the parents of insulin dependent diabetic patients with proteinuria.^{7,8} These observations have been complemented by the finding that sodium-lithium countertransport activity in red cells, a marker of risk for essential hypertension, is raised in insulin dependent diabetic patients with either microalbuminuria or established nephropathy.⁸⁻¹⁰ In the general population this countertransport activity is largely genetically determined,¹¹ and a positive correlation has consistently been reported between activities in parents and their offspring.¹²

To explore further the familial and hereditary components in the susceptibility to diabetic renal disease we investigated sodium-lithium countertransport activity in the red cells of insulin dependent diabetic patients with and without nephropathy and their parents.

Subjects and methods

The overnight urinary albumin excretion rate is screened regularly in all patients with insulin dependent diabetes attending our diabetic clinic. All of the patients with persistent proteinuria (defined as an overnight urinary albumin excretion rate $>150 \mu\text{g}/\text{min}$ in at least two consecutive collections in the absence of urinary sepsis, congestive cardiac failure, or any other overt renal disease) and all of those with persistent normoalbuminuria (defined as an overnight urinary albumin excretion rate $<15 \mu\text{g}/\text{min}$ in at least two out of three collections, to exclude persistent microalbuminuria) were asked to complete a family history questionnaire to identify those whose biological parents were both alive.

Twenty patients (12 men, eight women) with persistent proteinuria whose biological parents were both alive were identified; they were matched for age, duration of diabetes, and body mass index with 20 patients with normoalbuminuria (nine men, 11 women) whose biological parents were both alive who had been randomly selected from the larger group of diabetic patients with normoalbuminuria. All patients and parents were of European origin, and none of the parents were known to have hyperlipidaemia, thyroid disease, or diabetic nephropathy.

Sixteen of the patients with proteinuria were taking drugs for arterial hypertension, including β blockers, calcium antagonists, angiotensin converting enzyme inhibitors, vasodilators, and loop diuretics. None of the patients with normoalbuminuria were taking any drugs other than insulin. Of the 80 parents, 13 were taking antihypertensive drugs, including β blockers, calcium antagonists, angiotensin converting enzyme inhibitors, vasodilators, and thiazide and loop diuretics; none of them were taking any oestrogen, progesterone, or amiloride. Three of the parents in each group were known to have diabetes.

All 120 subjects were studied in the morning in the fasting state. The diabetic patients withheld their morning insulin injection until after the procedure, and all subjects (patients and parents) taking antihypertensive drugs were asked to stop them at least 36 hours before the assessment. Subjects were weighed

in indoor clothing without shoes, and their height was measured. Blood pressure (phases I and V) in the right arm was measured twice to the nearest 2 mm Hg with a standard sphygmomanometer by one observer; measurements were made with the subject supine after 10 minutes' rest. Mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure and the mean of the two measurements used for calculation.

A blood sample was taken from all subjects for measurement of plasma glucose concentration (glucose oxidase method, Yellow Springs Instruments, Yellow Springs, Ohio). Glycated haemoglobin concentration was measured by electroendosmosis (Corning Chemical, Palo Alto, California) in only the diabetic patients. Sodium-lithium countertransport activity in red cells was measured in all subjects as described previously.⁹ Urinary albumin concentration was measured by radioimmunoassay¹³ in timed overnight collections made within three months of the measurement of sodium-lithium countertransport activity in the diabetic patients. Glomerular filtration rate was assessed by clearance of edetic acid labelled with chromium-51 and expressed in $\text{ml}/\text{min}/1.73\text{m}^2$.¹⁴

The study was approved by the hospital's ethical committee.

Student's *t* test was used to compare normally distributed data, Wilcoxon's rank sum test to compare non-normally distributed data, and χ^2 tests with Yates's correction to compare discrete variables. Correlation coefficients were calculated by using the Pearson product moment correlation.¹⁵

Results

The patients with and without nephropathy had similar glycaemic control as assessed by the fasting blood glucose concentration (median (range) 11.4 (2.0-19.9) *v* 9.7 (5.2-21.0) mmol/l respectively) and glycated haemoglobin concentration (8.5 (6.5-13.5) *v* (8.2 (6.0-11.0) %), but the mean supine blood pressure was higher in the patients with proteinuria (106 (72-123) *v* 86 (73-100) mm Hg, $p<0.001$). By selection the urinary albumin excretion rate was higher in the group with proteinuria (geometric mean 314 (range 170-589) *v* 6.7 (4.8-9.2) $\mu\text{g}/\text{min}$). Similarly, the glomerular filtration rate was lower in the patients with proteinuria (mean 72 (15-125) *v* 127 (97-154) $\text{ml}/\text{min}/1.73\text{m}^2$). Age, duration of diabetes, and body mass index were similar in the two groups of patients (table).

The two groups of parents were well matched for age and body mass index (table). Fasting blood glucose concentration was similar in the two groups (mean 5.0 (4.0-13.2) mmol/l in the parents of the patients with proteinuria *v* 5.0 (3.2-18.7) mmol/l in the parents of the patients with normoalbuminuria). Mean blood pressure was also similar in the two groups of parents (99 (77-121) *v* 98 (89-118) mm Hg respectively), but more of the parents of the patients with proteinuria were taking antihypertensive treatment (eight *v* five), though the difference did not achieve significance.

Sodium-lithium countertransport activity in red cells was significantly higher in the patients with proteinuria than in those with normal albuminuria (mean (95% confidence interval) 0.47 (0.39 to 0.54) *v* 0.33 (0.28 to 0.38) mmol/l red cells/h respectively, $p=0.0036$; difference between means 0.14 (0.04 to 0.22)). The mean countertransport activity for the two parents of each patient was calculated, and then the mean of these values was calculated for each of the two groups of parents (mid-parental value). The activity was higher in the parents of the patients with proteinuria (0.40 (0.32 to 0.48) *v* 0.30 (0.26 to 0.33) mmol/l red cells/h, $p=0.016$; 0.10 (0.02 to 0.19)). When all 40

Details of diabetic patients with and without proteinuria and their parents. Values are means (ranges)

	Diabetic patients		Parents	
	With proteinuria	With normoalbuminuria	Of patients with proteinuria	Of patients with normoalbuminuria
No	12M, 8F	9M, 11F	20M, 20F	20M, 20F
Age (years)	31 (24-42)	31 (18-42)	62 (48-79)	62 (42-80)
Duration of diabetes (years)	20 (11-36)	18 (10-28)		
Body mass index (kg/m^2)	24 (19-31)	24 (19-29)	27 (16-46)	26 (19-38)

values obtained in each parental group were considered the mean was still significantly higher in the parents of the patients with proteinuria (0.40 (0.34 to 0.46) v 0.30 (0.26 to 0.33) mmol/l red cells/h, $p=0.0023$; 0.10 (0.03 to 0.18)). The median sodium-lithium countertransport activity in red cells in all 80 parents was 0.35 mmol/l red cells/h. Twelve of the parents of the patients with normoalbuminuria had values above this (both parents of two patients and one parent of eight patients). In contrast, 28 of the parents of the patients with proteinuria had values above the median (both parents of 10 patients and one parent of eight patients); this difference was highly significant ($\chi^2=11.25$; $p<0.001$; odds ratio 5.4).

There was a significant correlation between blood pressure in the parents of the patients with proteinuria and that in their offspring ($r=0.46$, $p<0.001$). Sodium-lithium countertransport activity in red cells showed a correlation between the parents and their offspring when both groups of parents and patients were considered ($r=0.37$; $p<0.001$) (figure).

Correlation between sodium-lithium countertransport activity in red cells in 40 diabetic patients and mean value of this activity in each patient's parents (mid-parental value). Values are expressed as mmol/l red cells/h ($\times 10^3$)

Discussion

The observation that diabetic nephropathy develops in only about one third of patients with insulin dependent diabetes⁵ has led investigators to search for familial, and possibly genetic, factors that may predispose patients to, or protect against, this complication. Recently a familial clustering of diabetic renal disease has been reported⁶ and two studies have suggested that a familial predisposition to arterial hypertension may contribute to the susceptibility to diabetic nephropathy.^{7,8} Moreover, an increased maximum velocity of the sodium-lithium countertransport in red cells, a marker of risk for essential hypertension,¹⁶⁻¹⁸ has been shown in patients with insulin dependent diabetes and proteinuria.⁸⁻¹⁰ The contribution of environmental rather than familial or genetic factors to this abnormality of the cell membrane cation transporter, however, remains a matter for debate.¹⁹⁻²³

Our findings, as well as confirming that sodium-lithium countertransport activity in red cells is increased in diabetic patients with proteinuria, show for the first time that this activity is significantly increased in the parents of these patients, thus strongly supporting the view that familial, and possibly hereditary, elements are centrally important in this phenomenon. In the general population familial aggregation and high heritability of the sodium-lithium countertransport activity in red cells have been reported. Several studies have estimated that as much as 80-90% of the individual variance in this activity can be accounted for by inheritance,^{11,12} and a model with a

major gene or a polygenic transmission, or both, has been proposed.¹¹ Our data, although obtained from a small sample, seem to support this view of an intermediate form of inheritance. Interestingly, both parents of 10 of the 20 patients with proteinuria but both parents of only two of the 20 patients with normoalbuminuria had a sodium-lithium countertransport activity that was above the median for all 80 parents.

All the parents were white and of similar age and body weight; moreover, none were known to have hyperlipidaemia, diabetic nephropathy, or thyroid disease and none were pregnant. Thus ethnic and environmental factors that may affect sodium-lithium countertransport activity in red cells¹⁹⁻²³ are unlikely to have accounted for the observed difference.

Although the overlap in the sodium-lithium countertransport activity in red cells between the two groups of parents and offspring suggests that a raised activity is not the only factor responsible for the development of nephropathy, our findings indicate that a strong familial factor, possibly related to the genesis of arterial hypertension, operates in the susceptibility to diabetic kidney disease.

Arterial blood pressure was similar in the two groups of parents, but a higher proportion of the parents of the patients with proteinuria were taking antihypertensive treatment. The association between the sodium-lithium countertransport activity in red cells and arterial pressure is complex, and recent evidence suggests that increased activity is more specific for a subset of hypertensive patients who are at increased risk of renal and cardiovascular complications, having a family history of hypertensive and cardiovascular disease.^{24,25}

The pathogenic mechanism by which a familial, and probably genetic, predisposition to an increased sodium-lithium countertransport activity in red cells contributes to renal disease in diabetes remains to be elucidated. This transporter is believed to be a mode of operation of the physiological sodium-hydrogen antiport, a ubiquitous cell membrane cation transport system that has a role in regulating reabsorption of sodium by renal proximal tubules and growth and reactivity to various vasoactive and growth factors of smooth muscle and mesangial cells.²⁶⁻³⁰ A genetically determined hyperresponsiveness of this system, as recently suggested by in vitro studies,³¹ to the hormonal and metabolic disturbances of diabetes, could be implicated in the pathogenesis of the haemodynamic and structural abnormalities associated with arterial hypertension and renal disease in diabetes.

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Prediction of hip fracture in elderly women: a prospective study

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Abstract

Objective—To assess the relative importance of osteoporosis of the os calcis, cognisance, and mobility in the risk of subsequent fracture of the hip in elderly women.

Design—Prospective study of elderly women in residential care over two years.

Setting—21 Private or 38 local authority residential homes for the elderly and 4 geriatric hospitals in Doncaster and Hull.

Subjects—1414 Ambulant women aged over 69, in private or local authority residential care or geriatric care. Those who had had bilateral hip surgery were excluded.

Main outcome measures—Broad band ultrasonic attenuation (BUA) index, Clifton assessment procedures for the elderly test (for cognisance), and mobility on a six point scale, and fracture of the hip in the subsequent two year period.

Results—73 Women fractured their hip during the two years. Their mean age was not significantly different from that of the women who did not have a fracture (85.3 (SD 5.6) v 83.9 (6.3); $p=0.07$), but their mean BUA index (40.3 (19.3) v 50.9 (22.2) db/MHz), and score for cognisance (median 19 (interquartile range 10.5-27.0) v 24 (17-30)) were significantly lower (both $p<0.001$). These variables had independent associations with fracture of the hip. Women with fractures had a significantly lower score for the psychomotor component of the cognisance test (4.5 (1.8) v 7 (2-10); $p<0.0025$ and were significantly more mobile (1 (1-3) v 3 (1-6); $p<0.02$). Subdividing women according to high, medium, and low scores for BUA index and cognisance testing disclosed a high risk group (118 women) with low BUA index and cognisance score, whose incidence of fracture was 12.8%; in the group at lowest risk (136 women) with high BUA index and cognisance score, the incidence of fracture was only 1.5% (relative risk 8.4 (95% confidence interval 2.0 to 35.5)). Further analysis showed that those most at risk were, additionally, most mobile but that less mobile women with good cognisance had a low incidence of fractures, regardless of the BUA index, (1.2%, high index, v 0.9%, low index).

Conclusions—Elderly women most at risk of sustaining hip fractures were those with low BUA index, low cognisance test score, and high mobility. Improving bone strength and cognisance in elderly women may reduce their incidence of hip fracture.

Introduction

About a fifth of orthopaedic beds are occupied by patients with fracture of the hip.¹ The incidence has doubled in the past 25 years, and as the number of elderly people in the population continues to increase there is justifiable concern about this modern orthopaedic epidemic.² Retrospective studies suggest that osteoporosis is a risk factor for hip fracture,^{3,4} but the propensity to fall and the neuromuscular response may be equally important.⁵

We conducted a prospective study in a population of 1414 elderly women in residential care to assess the relative importance of osteoporosis (measured by a new ultrasound technique), cognisance, and mobility as risks for subsequent fracture.

Subjects and methods

We invited women aged 70 or above living in private residential homes or local authority homes for the elderly or in geriatric care within the catchment areas of Doncaster and Hull Royal Infirmaries to participate in the study. Women who were unable to walk with assistance and those who had had previous bilateral hip surgery were excluded.

Broad band ultrasonic attenuation (BUA) of the os calcis was used to assess osteoporosis with an Osteosonics Ultrasonic Bone Analyser 1001.⁶ The foot was placed in a water bath and seated on a heel plate. An anthropometric ankle measurement ensured that the os calcis was centred between transmitting and receiving ultrasound transducers. By subtracting a water trace it was possible to measure in decibels a linear increase in ultrasonic attenuation with increasing frequency over the range 0.2 to 0.6 MHz.⁷ The rate of increase of attenuation (in dB/MHz) was used as the index of assessment and is referred to hereafter as the BUA index. The technique is portable,

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