

Original articles

Renal function in diabetes mellitus

A G DAVIES, D A PRICE, R J POSTLETHWAITE, G M ADDISON, J L BURN,
AND B A FIELDING

*Royal Manchester Children's Hospital, Department of Child Health, Royal Manchester Children's Hospital,
and Department of Paediatrics, Bolton General Hospital*

SUMMARY Glomerular filtration rate, day and night-time albumin excretion, and blood pressure were estimated in 83 children with diabetes mellitus and compared with measures of glycaemic control, age, and duration of disease. Careful attention was paid to definition of normal values in age matched controls.

The glomerular filtration rate was greater than normal, and correlated with duration of disease, but not with albumin excretion or blood pressure. Daytime albumin excretion correlated with duration of disease and glycosylated haemoglobin, but not with age, glomerular filtration rate, or blood pressure. Night-time albumin excretion was significantly raised and correlated with duration of disease, glycosylated haemoglobin, mean blood sugar concentration, and M value but not with age, glomerular filtration rate, or blood pressure. Diastolic blood pressure was significantly raised but was not correlated with any other measured variable.

We have confirmed abnormalities of renal function in a children's diabetic clinic. The measurement of overnight albumin excretion rates may provide a sensitive early indicator of renal damage.

The long term prognosis for children with insulin dependent diabetes mellitus is poor. Approximately half will develop diabetic nephropathy which will eventually lead to end stage renal disease.¹ Abnormalities of renal function are known to occur in the early years after diagnosis²⁻³ and small increases in albumin excretion rates have been shown to be predictive of diabetic nephropathy in adult diabetic patients.⁴⁻⁵

Renal function in diabetic children has been less extensively studied.²⁻⁹ Less attention has been paid to definition of normal values in age matched controls, and to changing normal ranges during childhood. This paper presents a cross sectional analysis of all patients attending the diabetic clinic at the Royal Manchester Children's Hospital. The study began in 1982 as part of a long term study of renal function in diabetic children.

Methods

Patients. Ninety nine children attend the diabetic clinic at the Royal Manchester Children's Hospital

and all have insulin dependent diabetes mellitus. The mean age at the time of study was 11.6 years (range 1.0 to 17.6 years). The children were admitted to hospital for 24 hours for the study: the study was approved by the ethical committee and informed parental consent was obtained.

Renal function. Glomerular filtration rate was estimated using a ⁵¹chromium edetic acid (⁵¹Cr-EDTA) method¹⁰ with blood sampling at two and four hours.

Albumin excretion was estimated by 24 hour urine collection divided into day and night-time portions collected into bottles without preservative. The urine albumin concentration was estimated using a sensitive ELISA (enzyme linked immunosorbent assay) method¹¹ and the urine creatinine concentration was estimated using a semi-automated alkaline picrate method. All urine cultures were sterile.

Sitting blood pressure was measured in the right arm using a mercury sphygmomanometer with the appropriate sized cuff.

Glycaemic control. The mean blood sugar concentration and M value were calculated on capillary blood samples collected before and after breakfast, lunch, tea, at 11 pm, and at 3 am. The plasma glucose concentration was measured using a glucose oxidase system, and the M value¹² calculated using the formula:

$$M \text{ value} = \frac{\sum \left| 10 \times \log_{10} \frac{\text{plasma glucose}}{4.44} \right|^3}{n}$$

The glycosylated haemoglobin was measured using a Boehringer mini column method with aldimine inhibition.

Adequacy of collections. Complete data were collected on 83 (85%) children only, as two ⁵¹Cr-EDTA estimations were rejected for technical reasons and 14 urine collections were judged incomplete on the basis of the creatinine excretion expected for age.¹³ The mean duration of disease (3.6 years), age (11.7 years), and ⁵¹Cr-EDTA clearance (144 ml/minute per 1.73 m²) of the children not included in the analysis were not significantly different from the remainder of the study group.

Normal values. Albumin excretion rates were compared with a normal range established in 374 school children.¹⁴ The albumin excretion rate of the 1 year old child was within the appropriate local normal range. The geometric mean multiplied or divided by the square of the tolerance factor defined the normal range.

Blood pressure was compared with standards established in 17 874 children.¹⁵ Two standard deviations from the mean defined the normal range.

Glomerular filtration rate was compared with a normal range established in 28 children.⁶ We used a value of 97 ± 16 ml/minute per 1.73 m² for the 1 year old child.¹⁶ Two standard deviations from the mean defined the normal range.

Statistical methods. The albumin excretion rates were logarithmically transformed to ensure normality¹⁴ and the distribution of values was found to be log normal whether the data were examined for boys, girls, or as a single group. The antilogarithm of the mean of the logarithmically transformed data, expressed in conventional units, is the geometric mean and the antilogarithm of the standard deviation is the tolerance factor. Multiplying or dividing the geometric mean by the tolerance factor, or the square of the tolerance factor, is the equivalent of

adding and subtracting one or two standard deviations in a normally distributed population.

The distribution of all other values was found to be normal.

Conventional parametric statistics were used. Stepwise regression with the day or night-time albumin excretion rate as the dependent variable was calculated after exclusion of the other albumin variable because of their mutual interdependence. Chi squared or Fisher's exact probability tests were used where appropriate. Standard deviation scores were calculated for albumin excretion rates and blood pressure because the normal ranges of these variables are partly age and sex dependent.

All tests of significance were two tailed. A probability of less than 0.01 was taken as significant for multiple correlations but otherwise a probability of less than 0.05 was taken as significant.

Results

Population characteristics. The means, standard deviations, and ranges are shown in Table 1 for the whole group. There was no sex difference for any of the variables. There were 43 boys and 40 girls.

Glomerular filtration rate. The mean glomerular filtration rate was significantly raised (P < 0.001). Forty two (51%) children had a ⁵¹Cr-EDTA clearance greater than two standard deviations above the mean. The mean duration of disease for children with an increased ⁵¹Cr-EDTA clearance was 5.4

Table 1 Characteristics of study population (n=83)

Variable	Mean	(SD)	Range
Age (years)	11.6	—	1.0-17.6
Duration of disease (years)	4.6	—	0.1-13.6
Mean plasma glucose (mmol/l)	12.9	(4.2)	3.6-21.4
M value (mmol/l)	136	(79)	6.1-323
Glycosylated haemoglobin (%)	10.4	(2.3)	5.4-15.8
Systolic blood pressure (mm Hg)	110	(12)	75-136
Systolic blood pressure standard deviation score	-0.04	(1.05)	-1.9-+3.0
Diastolic blood pressure (mm Hg)	71	(10)	45-95
Diastolic blood pressure standard deviation score	+0.81	(0.97)	-1.2-+3.7
⁵¹ Cr-EDTA clearance (ml/minute per 1.73m ²)	137	(25)	80-192
Albumin excretion rate, daytime standard deviation score	-0.04	(1.27)	-2.6-+5.7
Albumin excretion rate, night time standard deviation score	+0.73	(1.57)	-2.7-+8.2
	<i>Geometric mean</i>	<i>Tolerance factor</i>	<i>Range</i>
Albumin excretion rate (µg/minute per 1.73m ²)			
Daytime	6.5	2.9	0.9 to 580
Night time	4.7	2.7	0.5 to 441

Conversion—SI to traditional units: plasma glucose 1 mmol/l ≈ 18 mg/100 ml.

years compared with 3-6 years for the remainder of the group ($P<0.05$).

The ^{51}Cr -EDTA clearance correlated positively with duration of disease ($r=0.30$, $p<0.005$) and the partial correlation, controlled for age, of ^{51}Cr -EDTA clearance with duration remained significant ($r=0.29$, $P<0.005$). Clearance of ^{51}Cr -EDTA was not significantly correlated with age, albumin excretion rates, or measures of glycaemic control. There was no significant correlation between ^{51}Cr -EDTA clearance and albumin excretion or ^{51}Cr -EDTA clearance and glycosylated haemoglobin, mean blood sugar concentration, or M value when the patients were divided into groups according to whether they had had diabetes for more than, or less than, five years.

Stepwise addition of variables showed that only duration of disease was predictive of ^{51}Cr -EDTA clearance ($P<0.005$).

Albumin excretion rates. The standard deviation score for the daytime albumin excretion rate was not significantly different from normal. Table 2 shows that daytime albumin excretion correlated with duration of disease and glycosylated haemoglobin, but not with age, mean blood sugar concentration, M value, ^{51}Cr -EDTA clearance, or blood pressure. The partial correlation coefficient of daytime albumin excretion with glycosylated haemoglobin, controlled for duration of disease, was not significant ($r=0.25$).

The standard deviation score for night-time albumin excretion was raised. Table 2 shows that night-time albumin excretion correlated with duration of disease, mean blood sugar, M value, and glycosylated haemoglobin but not with ^{51}Cr -EDTA clearance or blood pressure. The partial correlation coefficient of night-time albumin excretion with glycosylated haemoglobin, controlled for duration of disease, was significant ($r=0.34$, $P<0.001$).

Table 2 Pearson correlation coefficients for albumin excretion rates

	Daytime	Night-time
Duration of disease†	0.29**	0.29**
Age†	NS	NS
Mean blood glucose	NS	0.41***
M value	NS	0.40***
Glycosylated haemoglobin	0.31**	0.40***
Systolic blood pressure	NS	NS
Diastolic blood pressure	NS	NS
^{51}Cr -EDTA clearance	NS	NS

* $P<0.01$, ** $P<0.005$, *** $P<0.001$.

†Calculation of Pearson correlations was performed using standard deviation scores after logarithmic transformation of the original data.

Day and night-time albumin excretion rates were strongly correlated ($r=0.72$, $P<0.001$). Stepwise addition of variables showed that duration of disease ($P<0.05$) and glycosylated haemoglobin ($P<0.05$) were predictive of daytime albumin excretion, and that duration of disease ($P<0.02$), M value ($P<0.05$), and glycosylated haemoglobin ($P<0.001$) were predictive of night-time albumin excretion.

Children with raised albumin excretion. The night-time albumin excretion rates for the diabetic children are shown in the Figure. Regression lines for the normal population are also shown.¹⁴ Thirteen children had a raised night-time albumin excretion, and four of these had a raised daytime albumin excretion rate. No other child had raised daytime albumin excretion rates.

Table 3 shows that the 13 children with raised night-time albumin excretion rates had a significantly increased age ($P<0.01$), duration of disease ($P<0.01$), mean blood sugar concentration ($P<0.001$), M value ($P<0.01$), and glycosylated haemoglobin ($P<0.001$) compared with the remainder of the diabetic patients, but did not have significantly different blood pressure or ^{51}Cr -EDTA clearance.

Nine of the 30 children who had had diabetes for more than five years had a raised night-time albumin excretion rate. Assuming that two children would be

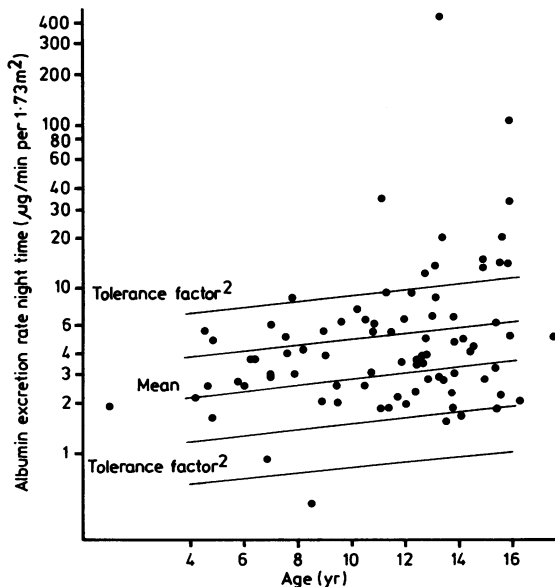


Figure Night-time albumin excretion rate for the diabetic children superimposed upon the normal range of albumin excretion in normal school children.

Table 3 Patients with a raised night-time albumin excretion rate compared with the remainder of the study group (values, mean (SD))

Variable	Raised excretion (n=13)	Normal excretion (n=70)	P value
Sex (boys:girls)	9:4	34:36	NS
Age (years)	13.9 (2.4)	11.2 (3.4)	<0.01
Duration of disease (years)	6.9 (4.1)	4.2 (3.3)	<0.01
Mean blood glucose (mmol/l)	16.4 (2.3)	12.4 (4.3)	<0.001
M Value (mmol/l)	198 (53)	124 (78)	<0.01
Glycosylated haemoglobin (%)	12.3 (2.0)	10.0 (2.1)	<0.001
Systolic blood pressure standard deviation score	-0.03 (0.75)	-0.04 (1.10)	NS
Diastolic blood pressure standard deviation score	+1.11 (0.98)	+0.75 (0.97)	NS
⁵¹ Cr-EDTA clearance ml/min per 1.73m ²	140 (24)	136 (24)	NS

expected to have an albumin excretion rate more than two standard deviations above the mean, this is significant ($P<0.05$).

Systolic and diastolic blood pressure. The diastolic blood pressure was significantly raised. Systolic and diastolic blood pressures were not significantly correlated with any other variables. Two children had increased systolic blood pressure and these two plus eight others had increased diastolic blood pressure.

Glycaemic control. There was a positive correlation ($r=0.28$, $P<0.01$) between duration of disease and glycosylated haemoglobin. There was no significant correlation between duration of disease and the mean blood sugar concentration or M value.

Discussion

We have examined three separate physiological variables, namely glomerular filtration rate, blood pressure, and albumin excretion. Each variable has a wide scatter which is partly due to the cross sectional nature of the study, and inter-relations may be weaker than they would be in a longitudinal study. It remains clear, however, that each variable behaves differently when related to glycaemic control and duration of disease implying a degree of disassociation between glomerular filtration rate, blood pressure, and albumin excretion.

The glomerular filtration rate was raised, and correlated with duration of disease but not with albumin excretion, blood pressure, or glycaemic control. The glomerular filtration rate was raised in

51% of the children; the mean of 137 ml/minute per 1.73m² compares well with that of Brøchner-Mortensen *et al.*,⁶ who reported a mean of 138 ml/minute per 1.73m² using a multiple sampling ⁵¹Cr-EDTA clearance technique, and Dahlquist *et al.*,⁷ who gave a mean of 138 ml/minute per 1.73m² using an inulin clearance technique. Our mean differs from that of Ellis *et al.*⁸ whose mean rate of 123 ml/minute per 1.73m² was established using creatinine clearance. The patients of Ellis *et al.*⁸ had a longer duration of diabetes (mean 6.7 years) and there may be methodological problems¹⁷ with the estimation of glomerular filtration rate using creatinine clearance in diabetic patients because acetoacetate can form pseudo-creatinine complexes. Dahlquist *et al.*⁷ found no correlation between creatinine and inulin clearances.

Experimentally, an acute increase in the blood glucose concentration leads to an increased glomerular filtration rate.¹⁸ We were unable to document a relation between glycaemic control and glomerular filtration rate in the whole group, or when the patients were divided into groups of differing disease duration. Dahlquist *et al.*⁷ showed a weak correlation between glycaemic control and glomerular filtration rate in diabetic children whose duration of disease was less than five years. In that study there was no correlation between glycaemic control and glomerular filtration rate in children with duration of disease between five and 10 years, and a negative correlation in children whose duration of disease was greater than 10 years. Our own study data, however, indicate that the positive correlation between glomerular filtration rate and duration is not explicable in terms of worsening metabolic control.

Daytime albumin excretion was not greater than normal but night-time albumin excretion was raised. The mean albumin excretion rate is difficult to compare directly with other studies because of differing collection periods or failure to correct for surface area. Dahlquist *et al.*⁷ and Ellis *et al.*⁸ give results of 24 hour urine collections as mg/24 hours ignoring the day and night-time differences in albumin excretion rates.¹⁴ Brøchner-Mortensen *et al.*⁶ give a geometric mean albumin excretion rate for a daytime three hour collection period as 6.0 µg/minute per 1.73m² and this compares well with our geometric mean daytime albumin excretion rate of 6.5 µg/minute per 1.73m². Dahlquist *et al.*⁷ and Ellis *et al.*⁸ found increased 24 hour albumin excretion in diabetic children, but Brøchner-Mortensen *et al.*⁶ found no difference between diabetic and normal children. Dahlquist *et al.*⁷ and Ellis *et al.*⁸ have probably obtained high night-time values in the 24 hour collection period which increased the mean

albumin excretion rate to above normal values. Our findings of normal daytime albumin excretion rates and raised night-time rates explain the apparent lack of agreement in previous studies. Recently, and independently, Rowe *et al*⁹ reported a raised night-time albumin excretion rate in 86 diabetic children when compared with 36 normal children. There was no correction for surface area but their geometric mean of 3.2 µg/minute compares well with our geometric mean of 4.7 µg/minute per 1.73m². We would advocate the use of urinary collections divided into day and night-time portions in future studies.

Albumin excretion rates were correlated with duration of disease and glycaemic control, but not with glomerular filtration rate or blood pressure. There was no correlation between the standard deviation scores for day or night-time albumin excretion and age. Our findings contrast with those of Rowe *et al*⁹ who document a correlation between night-time albumin excretion and age which may be partly due to the normal rise of albumin excretion with age.¹⁴ The calculation of standard deviation scores takes account of the age effect seen in normal children. Rowe *et al*⁹ also report that night-time albumin excretion correlates positively with glycosylated haemoglobin and with duration of disease.

The positive correlations between day or night-time albumin excretion and glycosylated haemoglobin and between night-time albumin excretion rate and the M value or mean blood sugar concentration contrast with the findings of Dahlquist *et al*⁷ and Ellis *et al*,⁸ neither of whom showed a correlation between albumin excretion and glycaemic control. The relation remains significant for night-time albumin excretion, when controlled for duration of disease, showing that the effect acts independently of duration of disease. The differences between this study and those of Dahlquist *et al*⁷ and Ellis *et al*⁸ may reflect methodological differences. Firstly, there are difficulties in estimating albumin excretion exemplified by the differences between normal and diabetic population means given by Dahlquist *et al*⁷ (10.4 and 21.5 to 38.0 mg/24 hours respectively) and Ellis *et al*⁸ (5.5 and 10.1 mg/24 hours respectively). Secondly, there may be genuine differences between populations.¹⁹ Additionally, Ellis *et al*⁸ used an unusual method of patient selection whereas we studied an entire clinic population.

Diastolic blood pressure was greater than normal but was not significantly associated with any other variable. There are many difficulties inherent in the interpretation of blood pressure measurements; the procedure is open to observer bias, and blood pressure 'tracks' poorly in normal and diabetic²⁰ children.

The increase in glycosylated haemoglobin with increasing duration of disease probably reflects improved control during remission, and these findings are in agreement with those of Dahlquist *et al*,⁷ who noted a negative correlation between C-peptide concentration and duration of disease, and C-peptide concentration and glycosylated haemoglobin. It is worth noting that the average standard of glycaemic control with conventional treatment in children's diabetic clinics is poor.

Thirteen children had a raised night-time albumin excretion rate; they have had diabetes for longer and have worse glycaemic control. We know the development of diabetic nephropathy is partly dependent on duration of disease, but whether duration is as important a variable when looking for subtle renal function changes which may be predictive of the development of nephropathy is not known. It is likely that the group of children with high night-time albumin excretion rates include some of the children who will develop nephropathy but one isolated measure of albumin excretion will probably not define all of the children who will develop this.

In conclusion, we have confirmed abnormalities of renal function in diabetic children. The glomerular filtration rate correlated with duration of disease but not with other variables associated with renal function. Albumin excretion correlated with disease duration and glycaemic control but not with blood pressure or ⁵¹Cr-EDTA clearance. Blood pressure was not correlated with any other variable. The measurement of albumin excretion rates, especially overnight, may provide a sensitive early indicator of renal damage but the glomerular filtration rate and blood pressure do not seem to be such discriminatory markers. Longitudinal studies are essential to determine whether an improvement in the poor metabolic control seen in diabetic children can reduce abnormally high albumin excretion rates and the incidence of diabetic nephropathy.

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Correspondence to Dr A G Davies, Department of Child Health, Royal Manchester Children's Hospital, Manchester M27 1HA.

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