

Prevalence of abnormal urinary albumin excretion in adolescents and children with insulin dependent diabetes: the MIDAC study

T H M Moore, J P H Shield on behalf of the Microalbuminuria in Diabetic Adolescents and Children (MIDAC) research group

Abstract

Objective—To examine the prevalence of microalbuminuria, defined as an albumin to creatinine ratio (UAC) equal to or greater than 2 mg/mmol in at least two of three early morning urine samples, in adolescents and children with insulin dependent diabetes mellitus.

Design—Centrally coordinated, cross sectional, multicentre study in paediatric diabetes outpatient clinics in the United Kingdom and Republic of Ireland.

Methods—Blood and urine samples collected between July 1997 and July 1998 were analysed at a central reference laboratory for HbA_{1c} using high performance liquid chromatography, and for urinary albumin and creatinine concentrations from which the UAC was derived (mg/mmol). Clinical data were collected locally and coordinated centrally.

Subjects—Patients, aged between 10 and 20 years, with insulin dependent diabetes mellitus for more than a year, attending diabetes outpatient clinics.

Results—A total of 1007 patients, comprising 69% of the eligible population of 1451, provided three early morning urine samples. Ninety eight (9.7%) had microalbuminuria using the currently accepted screening cut off of UAC \geq 2 mg/mmol in at least two of three early morning urine samples. Significantly more girls than boys and significantly more pubertal and postpubertal patients had abnormal albumin excretion. Microalbuminuria was not associated with raised blood pressure.

Conclusions—A prevalence of 9.7% for abnormal UAC was found in a cohort of 1007 children and adolescents aged 10–20 years. Thus a tenth of this national sample of young people were identified as being at particular risk of microvascular and later macrovascular disease.

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Keywords: microalbuminuria; insulin dependent diabetes mellitus; albumin to creatinine ratio; multicentre; puberty

Those who develop insulin dependent diabetes mellitus (IDDM) in childhood have an increased risk of diabetic nephropathy,¹ which can progress to end stage renal failure requiring dialysis and transplantation.² The presence of microalbuminuria is said to precede and

predict overt diabetic nephropathy,^{3 4} and in previous small studies it has been detected in 7–20% of young adults and children with IDDM.^{5–7} In a Swedish cohort, a quarter of diabetic youth under the age of 21 years had demonstrable microalbuminuria within 14 years of diagnosis.⁸ Overall it appears that the prevalence of microalbuminuria in childhood increases with the age of the population under study. Known risk factors for microalbuminuria in the young include poor long term glycaemic control, duration of diabetes, and possibly hypertension.^{9 10} The importance of hypertension in the initiation of diabetic renal pathology is unclear: however, once established, it undoubtedly accelerates the progression of renal disease.¹¹

MIDAC (microalbuminuria in diabetic adolescents and children) was set up to determine the cross sectional prevalence of microalbuminuria in a population of children and adolescents attending paediatric diabetes outpatient clinics in the United Kingdom and Republic of Ireland, thereby identifying the proportion at risk of morbid diabetic nephropathy in later life and assessing the factors likely to increase the risk of microalbuminuria, including glycaemic control and raised blood pressure. The project also set out to establish a network of diabetes clinics across the country that were willing to collaborate on future research strategies aimed at preventing the microvascular and macrovascular complications of the disease.

A ratio of urinary albumin to creatinine (UAC) equal to or greater than 2 mg/mmol in at least two of three consecutive early morning samples was used to determine microalbuminuria. This value was determined from a pilot study of 308 children tested for microalbuminuria using timed overnight urine collections and from work by Shield *et al.*¹²

Subjects, population, and methods

PATIENTS

Between July 1997 and July 1998, patients from 22 centres were recruited who had expressed an interest in an initial advertisement in the Royal College of Paediatrics and Child Health newsletter (see list of contributors at the end). Patient inclusion criteria were: age between 10 and 20 years and a duration of insulin treated diabetes of more than 1 year on 1 July 1997. Patients being treated for microalbuminuria, proteinuria, hypertension, or other medical conditions such as asthma were

Institute of Child Health, St Michael's Hill, Bristol BS2 8BJ, UK

J P H Shield

University of Bristol
T H M Moore

Correspondence to:
Dr Shield
email: j.p.h.shield@bris.ac.uk

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included. Patients were not excluded on the grounds of poor treatment compliance. Patients were not recruited if they were: taking renotoxic chemotherapy or had known renal disease other than that caused by diabetes mellitus. Informed consent was obtained from each of the patients recruited to the study. Ethics approval was obtained from the local ethics committees of all participating centres.

COLLECTION OF BLOOD AND URINE SAMPLES

At a designated clinic visit, a 5 µl sample of blood was drawn from a finger prick into a heparinised capillary tube and immersed in 1 ml stabilising solution of EDTA and KCl in a sealable vial (BioRad blood collection system).¹³ The vials were posted to the central reference laboratory where HbA_{1c} was measured using high performance liquid chromatography (HPLC).¹⁴ The normal range for HbA_{1c} was defined as 3.2–4.8% based on the mean ± 2 SD from an adult population of 200 people, male and female, with normal urea, creatinine, and fructosamine. The interassay coefficient of variation (CV) for HbA_{1c} was 3–6% and the intra-assay CV was 1–5% for an HbA_{1c} of 4%. The interassay CV for an HbA_{1c} of 7.5% was 2–6% and the intra-assay CV was 1–5%.

Each patient was asked to collect a mid-stream early morning urine specimen on three consecutive days, each of volume 10 ml. Patients posted the three samples of urine to the central laboratory in appropriate packaging in a prepaid envelope. Girls were asked not to collect urine during menses and to wait for three days after the last day of bleeding before commencing collection. Urine samples were stored at 4°C in the laboratory; samples were not frozen, as this is known to affect the measured concentration of albumin in urine.^{15,16} The concentration of albumin in the urine was determined by an immunoturbidimetric assay¹⁷ using a Cobas Mira spectrophotometer, and the concentration of urinary creatinine by a method modified from that of Jaffé using a Technicon RA500 spectrophotometer.¹⁸ The UAC was calculated for each patient for each collection.

The interassay CV for an albumin concentration of 41.5 mg/ml was 5.6%. The intra-assay CV for a mean albumin concentration of 40.5 mg/ml was 1.8%. The interassay CV for a creatinine concentration of 4.7 mg/ml was 7.0%, and for a creatinine concentration of 9.0 mg/ml it was 3.6%. The intra-assay CV for a mean creatinine concentration of 3.6 mg/ml was 0.73% and for a mean creatinine concentration of 16.8 mg/ml was 0.66%. All consumables associated with the collection of urine and blood were supplied to the regional centres by the central study coordinator.

PUBERTAL STATUS

Pubertal status was described for each patient at the start of the study using the scale: 1, prepubertal (puberty not yet started); 2, pubertal (puberty started); 3, postpubertal (in girls, two years after menarche; in boys, growth velocity of 2 cm or less per year).

BLOOD PRESSURE

Korotkoff phases I and V were measured in the supine position after five minutes rest using a standard sphygmomanometer.

STATISTICAL ANALYSIS

Standard deviation scores (SDS)—that is, the number of standard deviations that a given data point is from the mean of a normative population—were calculated for blood pressure using the data from a normative population of 28 043 European children and adolescents aged 10–19 years.¹⁹ SDS allow direct comparison of blood pressure while taking into account effects of age and sex. In the case of body mass index (BMI), the “lms” method was used to calculate the SDS based on the new United Kingdom standards for growth²⁰ using the revised (September 1996) coefficients from Cole. Kolmogorov-Smirnov goodness of fit tests were used to determine if distributions were Gaussian. For data conforming to a Gaussian distribution, Student’s *t* tests and analysis of variance were used to compare means. Non-Gaussian data was analysed using the non-parametric Mann-Whitney U test (two groups) or Kruskal-Wallis one way analysis of variance (for more than two groups). Proportions were analysed using χ^2 . The significance level used throughout was 5%. To assess the interactive effects of predictor variables associated with microalbuminuria, these data were further assessed using logistic regression analysis.

Outcomes

COMPLIANCE WITH THE MIDAC STUDY

From a total of 1233 patients who agreed to participate, 1007 compliant patients, a mean of 72% of each clinic population, returned urine samples. To avoid sampling bias, each centre attempted to ask every eligible patient (*n* = 1451) at their clinic to participate in the study: in the event, 1329 were asked (a mean of 85% of eligible patients per clinic) and 122 patients were not, because of non-attendance at clinic during the study period or insufficient recruitment time during a busy clinic. Clinical data and blood samples were also available for 226 non-compliant patients—that is, those recruited in clinic who did not subsequently return urine samples. The non-compliant patients had higher log HbA_{1c} values than the compliant ones (7.83 *v* 7.19%; *p* < 0.0001), but the duration of diabetes and age were similar. Some 96 patients declined to participate (7%); reasons included being too busy with work or school, not wanting to handle urine samples, and lack of interest in participating.

POPULATION

In comparison with the United Kingdom (non-diabetic) standard,²⁰ the MIDAC patients had significantly higher BMI (SDS mean difference = 0.61; 95% confidence interval (CI) 0.551 to 0.670; *p* < 0.001). Although of a similar height, they were heavier (SDS mean difference = 0.48; 95% CI 0.42 to 0.54; *p* < 0.0001). The MIDAC study group as a

Table 1 Clinical data of compliant patients

	Boys	Girls	p Value
n	498 (49.5%)	509 (50.5%)	NS
Age (years) (median, range)	13.9 (10.1–19.6)	14.0 (10.4–20.2)	NS
Duration (years) (median, range)	5.8 (1.3–17.5)	6.0 (1.0–19.9)	NS
Pubertal status			
Prepubertal	97 (19.5%)	34 (6.7%)	
Pubertal and postpubertal	401 (80.5%)	474 (93.3%)	<0.001
HbA _{1c} (%) (geometric mean, range)	7.14 (4.2–13.1)	7.26 (3.7–16.8)	NS
Insulin dose (unit/kg/24 h) (median, range)	0.98 (0.25–2.42)	1.05 (0.17–3.03)	<0.0001
Systolic BP (mm Hg)* (mean (SD))	113.4 (13.6)	112.5 (12.9)	
Standard deviation scores for systolic BP (mean (SD))	−0.237 (1.009)	−0.070 (1.146)	0.015
Diastolic BP (mm Hg)* (mean (SD))	65.0 (11.7)	66.6 (11.6)	
Standard deviation scores for diastolic BP (mean (SD))	0.305 (1.10)	0.529 (1.236)	0.003
BMI (kg/m ²) (mean (SD))	20.1 (3.1)	21.7 (3.6)	
Standardised scores for BMI (mean (SD))	0.542 (0.925)	0.678 (0.994)	0.025
Standardised scores for height (mean (SD))	0.395 (0.984)	0.557 (1.021)	0.01

*n=1004, BP not available for three patients.
BP, blood pressure; BMI, body mass index.

whole had higher diastolic blood pressure and lower systolic blood pressure than the normative European cohort¹⁹ ($p < 0.0001$).

Age, duration of diabetes, and HbA_{1c} were similar for boys and girls. Girls had a higher insulin dose, of doubtful clinical relevance (median 1.05 *v* 0.98 units/kg/day; $p < 0.0001$), systolic (SDS mean difference = 0.167; 95% CI 0.3 to 0.033; $p < 0.02$) and diastolic (SDS mean difference = 0.22; 95% CI 0.368 to 0.079; $p < 0.005$) blood pressure, and BMI (SDS mean difference = 0.136; 95% CI 0.2255 to 0.018; $p = 0.025$) than boys (table 1). There was a significant difference in the proportion of each sex classified as prepubertal, pubertal/postpubertal. There were fewer prepubertal girls (χ^2 , $p < 0.001$; table 1), presumably explained by the age group of patients in the study and the earlier age of onset of puberty in girls than boys.

As children with diabetes enter puberty at similar ages to their non-diabetic peers,²¹ we examined at what age diabetic children start to deviate from normative cohort blood pressure. Diastolic blood pressure of prepubertal diabetic children (boys and girls) was similar to that of their normative counterparts; however, postpubertal and pubertal children with diabetes had raised diastolic blood pressure: mean difference Z score 0.34 ($p < 0.0001$) for boys and 0.56 ($p < 0.0001$) for girls. Diabetic boys had significantly lower systolic blood pressure than the normative cohort: mean difference Z score 0.4 ($p < 0.0001$) for prepuber-

tal boys and 0.2 ($p < 0.001$) for pubertal and postpubertal boys. The systolic blood pressure of diabetic girls did not differ from the norm.

UAC

Compared with the normoalbuminuric MIDAC population, patients with microalbuminuria were more likely to be pubertal or postpubertal ($p < 0.05$), older (median 14.7 *v* 13.9; $p < 0.001$), with a longer duration of diabetes (7.8 *v* 5.6 years). BMI, insulin dose, and systolic and diastolic blood pressure were similar (table 2). Most microalbuminuric patients were female (73%; table 2). Of those identified as having an abnormal UAC in this study, only six (6%) had been previously identified, and three of these were receiving treatment with angiotensin converting enzyme inhibitor.

Distribution of HbA_{1c} was positively skewed, but rendered Gaussian by a log transformation. The mean HbA_{1c} of patients with microalbuminuria was higher than that of those with normoalbuminuria (geometric mean 7.76 *v* 7.15; $p < 0.001$; table 2). There were five patients with haemoglobinopathies, for whom it was not possible to obtain a value for HbA_{1c}.

There appeared to be a significant difference between the numbers of patients who were prepubertal with microalbuminuria and those in puberty or postpubertal (table 3). Analysis of the three pubertal states and sex in a logistic regression model alone showed girls were 2.5 times more likely to have microalbuminuria

Table 2 Clinical data for normoalbuminuric and microalbuminuric patients (univariate analysis)

	Normoalbuminuric	Microalbuminuric	p Value
n	909 (90.3%)	98 (9.7%)	<0.001
Gender			
Male	471 (51.8%)	27 (27.5%)	<0.0001
Female	438 (48.2%)	71 (72.5%)	
Age (years) (median, range)	13.9 (10.1–20.2)	14.7 (10.6–19.6)	<0.001
Duration (years) (median, range)	5.6 (1.1–19.9)	7.8 (1.7–15.9)	<0.001
Pubertal status			
Prepubertal	126 (13.9%)	5 (5.1%)	
Pubertal and postpubertal	782 (86.1%)	93 (94.9%)	<0.05
HbA _{1c} (%) (geometric mean, range)	7.15 (3.7–16.8)	7.76 (4.3–12.5)	0.001
Insulin dose (unit/kg/24 h) (median, range)	1.01 (0.17–3.01)	1.03 (0.58–3.03)	NS
Systolic BP (mm Hg) (mean (SD))	112.7 (13.1)	115.6 (14.5)	
Standard deviation scores for systolic BP (mean (SD))	−0.171 (1.070)	0.023 (1.193)	NS
Diastolic BP (mm Hg) (mean (SD))	65.7 (11.6)	67.6 (12.2)	
Standard deviation scores for diastolic BP (mean (SD))	0.402 (1.17)	0.572 (1.251)	NS
BMI (kg/m ²) (mean (SD))	21.0 (3.4)	21.7 (3.7)	
Standardised scores for BMI (mean (SD))	0.614 (0.955)	0.581 (1.030)	NS
Standardised scores for height (mean (SD))	0.034 (1.058)	−0.104 (1.178)	NS

BP, blood pressure; BMI, body mass index.

Table 3 Relation between pubertal status and the development of microalbuminuria

Pubertal status	Percentage with normal albumin excretion	Percentage with abnormal albumin excretion
Girls		
Prepubertal	94 (32/34)	6 (2/34)
Pubertal	86 (279/323)	14 (44/323)
Postpubertal	83 (126/151)	17 (25/151)
Boys		
Prepubertal	97 (94/97)	3 (3/97)
Pubertal	94 (314/333)	6 (19/333)
Postpubertal	93 (63/68)	7 (5/68)

Values in parentheses are the numbers of patients.

than boys ($p < 0.001$; adjusted odds ratio 2.53; 95% CI 1.6 to 4.0). Furthermore, analysis between pubertal groups showed odds ratios of 2.2 (95% CI 0.8 to 5.5; $p = 0.1$) for puberty compared with prepuberty, and 2.8 (95% CI 1.0 to 7.4; $p < 0.05$) for postpubertal children compared with prepubertal children. There was no significant interaction between sex and pubertal status in defining the risk for microalbuminuria, with both showing independent association with risk. However, backwards stepwise logistic regression analysis used to assess whether the predictor variables (log HbA_{1c}, pubertal status, duration, sex, and age) were independently related to microalbuminuria resulted in a loss of age and pubertal status, whereas log HbA_{1c} (4.387 (1.289) (coefficient (SE); $p < 0.001$), duration (0.102 (0.030); $p < 0.001$), and sex (odds ratio for girls 2.64; 95% CI 1.62 to 4.28; $p < 0.0001$) remained in the model.

BLOOD PRESSURE

Using the accepted definition of severe hypertension in childhood systolic and/or diastolic blood pressure equal to or greater than the 95th percentile for age and sex²⁰: 13 patients (1.3%) had severe systolic and diastolic hypertension, of whom three had microalbuminuria; 125 (12.5%) had severe diastolic hypertension only, 11 of whom had microalbuminuria; 27 (2.7%) had severe systolic hypertension only, three of whom had microalbuminuria.

Discussion

This is the largest cross sectional evaluation to date of microalbuminuria in childhood diabetes, enrolling a national sample of children attending routine diabetes clinics. The cross sectional analysis has identified about 10% of participating children and adolescents with microalbuminuria. The association with poorer glycaemic control suggests that the real level may be higher, given the characteristic of non-compliers to have higher HbA_{1c} values. The mean duration of diabetes in this study population was six years, and from other studies we believe that it is reasonable to predict that the cumulative prevalence will further increase with increasing disease duration.^{9 10} The actual value of 9.8% is similar to recent results from the Oxford Regional Prospective study of childhood diabetes (ORPS), which identified, in a truly representative sample with much greater ascertainment, an incidence of

12.8% at a median duration of five years.²² It is important to note the 3:1 ratio of girls to boys with microalbuminuria in this cohort, similar to that recently described for Liverpool,⁹ Oxfordshire,²² and Germany,²³ confirming that the development of microalbuminuria is accelerated in girls.²⁴ Both the Liverpool and Oxfordshire studies identified a number of children with IDDM developing microalbuminuria before the onset of puberty.^{9 22} MIDAC also identified a small number of prepubertal children (3.8%; one in 20 of all cases) developing microalbuminuria. The statistical evidence possibly points to an undefined permissive effect for abnormal albumin excretion acting throughout and after pubertal development. The prepubertal children are unusual, given the reported natural history of diabetic nephropathy, and may represent other underlying renal pathologies associated with IDDM, such as autoimmune glomerulonephritis,²⁵ thus justifying further renal investigation. There was a surprising lack of association between blood pressure and microalbuminuria. Although hypertension may aggravate the pathophysiology of renal disease in diabetes, it does not seem to be a prerequisite for the development of microalbuminuria, as suggested by other studies.^{26 27} However, simply measuring blood pressure in clinic may not identify aberrant blood pressure that can only be found by 24 hour monitoring.²⁸

CONCLUSIONS

MIDAC has inherent limitations given the incomplete ascertainment and cross sectional nature of patient sampling. In addition, there is a widely acknowledged inherent variation over time of urinary albumin excretion rates.^{10 22} However, a significant proportion of children and adolescents aged 10–20 in this cohort have microalbuminuria. If one accepts that persisting microalbuminuria represents a risk factor for diabetic nephropathy and most major long term complications such as retinopathy,²⁹ neuropathy,³⁰ stroke, and myocardial infarction,^{31 32} then we have identified a major health care problem which requires urgent clinical attention. The mean HbA_{1c} in patients with microalbuminuria was higher than in those with normal urinary albumin excretion, suggesting that the most obvious first treatment option is to improve glycaemic control.³³ However, given the well documented problems of lifestyle regulation and compliance in optimising control, especially in this age group,³⁴ we need to develop alternative and simple interventional strategies to improve outcome. A number of studies in adults with diabetes have shown positive benefits from the introduction of angiotensin converting enzyme inhibitors in relation to overt nephropathy and microalbuminuria.^{35 37} Similar trials in childhood and adolescence are now urgently needed, the MIDAC group providing the framework for such interventions.

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- The MIDAC research group consists of the following. Steering committee: Professor J D Baum, Department of Child Health, Institute of Child Health, Bristol (Professor Baum died on); Dr P Betts, Southampton General Hospital, Southampton; Dr D B Dunger, Department of Paediatrics, John Radcliffe Hospital, Oxford; Dr S A Greene, Department of Child Health, Ninewells Hospital, Dundee; Dr I G Jefferson, Department of Paediatrics, Hull Royal Infirmary, Hull; Dr D A Price, Department of Child Health, Royal Manchester Children's Hospital, Manchester; Dr K Robertson, Royal Hospital for Sick Children, Glasgow; Dr J P Shield Department of Child Health, Institute of Child Health, Bristol; Dr P G F Swift, The Children's Hospital, Leicester Royal Infirmary, Leicester; Dr R J Young, Department of Endocrinology, Hope Hospital, Salford Royal Hospitals Salford. Participating centres: Dr D J Carson and Dr H Tenny, Royal Belfast Hospital for Sick Children Belfast; Dr W H Lamb, The General Hospital, Bishop Auckland; Dr J W Gregory, University Hospital of Wales, Cardiff; Professor H Hoey, National Children's Hospital, Dublin; Dr K Noyes and Dr C J H Kelnar, Royal Hospital for Sick Children, Edinburgh; Dr P J Smith, City Hospital, Stoke on Trent; Dr K Robertson, Royal Hospital for Sick Children, Glasgow; Dr I G Jefferson, Hull Royal Infirmary, Hull; Dr A J Bradbury, Wythenshawe Hospital, Manchester and Duchess of York Children's Hospital, Manchester; Dr D A Price, Royal Manchester Children's Hospital, Manchester; Dr M S Kibirige, South Cleveland Hospital, Middlesbrough; Dr J H Baumer, Derriford Hospital, Plymouth; Dr A McAulay, Poole Hospital, Poole; Dr C A Mackenzie, Dr K J Price, and Dr J K H Wales Sheffield Children's Hospital, Sheffield; Dr C M McCowen, North Tees Hospital, Stockton; Dr J King and Dr A J Salisbury, Princess Margaret Hospital, Swindon; Dr M Webster, Taunton and Somerset Hospital, Taunton; Dr F R J Hinde, Princess Royal Hospital, Telford; Dr S T Jones, Pinderfields General Hospital, Wakefield; Dr A S Ahuja, Royal Albert Edward Infirmary, Wigan; Dr E Crowne, Royal Hospital for Sick Children, Bristol; Dr S Court and Dr D Matthews, Royal Victoria Infirmary, Newcastle upon Tyne. Laboratory staff at the Department of Chemical Pathology, Bristol Royal Infirmary: Ms F Bridgeman, research technician; Dr C P Pennock, clinical pathologist; Dr J Scott, chemical pathologist; Dr J Stone, chemical pathologist. Research coordinator: Ms T H Moore, University of Bristol. Statistics advisor: Dr L Hunt, University of Bristol.
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