PREVALENCE OF MICROALBUMINURIA IN CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS TYPE I

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Abstract- Persistent microalbuminuria is predictive of nephropathy in patients with type I diabetes mellitus (DM) and has led to the development of screening programs and intervention studies. We report a longitudinal evaluation of urinary albumin excretion in 118 children with type I DM, attending a single clinic over a period of seven years. Collected blood and urine samples were analyzed for glycated hemoglobin (Hb $A1_c$), cholesterol, triglyceride (TG), creatinine and for 12 h urinary albumin and creatinine concentrations. Blood pressures were recorded and clinical data collected. Twenty– three (19.5%) children had persistent microalbuminuria (urine albumin 30-300 mg/24 h) on at least three consecutive occasions. Factors associated with microalbuminuria in diabetic children included longer duration of DM, higher mean age, higher mean Hb A1c, higher mean arterial blood pressure and higher cholesterol and TG levels ($P < 0.001$). Significantly more girls than boys and more pubertal and post pubertal patients had microalbuminuria but one patient developed microalbuminuria under the age of 11 years. In conclusion, microalbuminuria may appear as early as the prepubertal period, suggesting that metabolic control of DM is an important factor of diabetic nephropathy.

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Key words: Microalbuminuria, diabetes mellitus type I, screening.

INTRODUCTION

Epidemiologic studies have demonstrated that 20-30% of all patients with type I diabetes mellitus (DM) with disease duration of 20-30 years develop clinically significant renal disease (1). Diabetic nephropathy is the most common cause of end stage renal disease (ESRD) in the western world. Therapies to prevent or delay the progression of diabetic nephropathy are thus critical. (2) Diabetic nephropathy is a clinical condition characterized by persistent proteinuria, decline in glomerular function, hypertension and progression to ESRD. Among the complications of type I DM, nephropathy is a major life threatening complication (1-3).

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The presence of microalbuminuria is said to precede and predict overt diabetic nephropathy and is the most commonly used clinical marker, and can be seen in stage III of diabetic nephropathy. Several studies suggest that at these early stages progression of diabetic nephropathy can be prevented (1-3). Estimates of the prevalence of microalbuminuria in children vary between 7-28.2% in different studies (4-13).

The objective of this study was to find out the prevalence of microalbuminuria in children with type I DM attending a clinic of pediatrics endocrinology over a period of seven years. We assessed association between raised urinary albumin excretion and age at disease onset, duration of diabetes, pubertal status, glycemic control, lipid profile, insulin dose and blood pressure. An understanding of the development and progression of increased albumin excretion in childhood can guide the development of screening practices, and might have implication for disease control in childhood.

MATERIALS AND METHODS

A total of 118 children and adolescents (58 boys and 60 girls), mean age 12.4 ± 4 y attending the diabetic clinic at Imam Khomeini Hospital, Tehran, from June 1997 to September 2004 were included in the study. They were diagnosed as having type I DM on the basis of World Health Organization (WHO) criteria (14). Patients inclusion criteria were: age between 5 and 20 years and a duration of insulin treated diabetes of more than 1 year. Patients exclusion criteria were: 1) patients being treated for other medical conditions such as rheumatoid arthritis, 2) patients taking nephrotoxic chemotherapy or having known renal disease other than that caused by diabetes, 3) heavy exercise, 4) febrile disease and dehydration, and 5) urinary tract infection.

At a designated clinic visit, blood and urinary samples were collected and were analyzed at a central reference laboratory for Hb A1c, creatinine, cholesterol, triglyceride and for 12 h urinary albumin and creatinine concentration. Girls were asked not to collect urine during menses and any sample with hematuria was excluded from the results.

Urinary albumin and creatinine concentration was determined by an immunoturbidimetric assay (DAKO Instruments, Denmark Ltd). Twenty-four hour urinary albumin concentration used as a measure of urine albumin excretion and was considered raised if it was 30-300 mg/24 h on at least three consecutive occasions.

Children were considered to have normal albuminuria if it remained < 30 mg/24 h. Glycated hemoglobin was measured as Hb A1c using column chromatography. The normal range for Hb A1c in non diabetic subjects was considered 3.9-6.4%. Serum total cholesterol and TG were analyzed using an automated analyzer (Vital Scientific, Spankeren, Netherlands). Blood pressure was measured in the supine position after five minutes rest using a standard sphygmomanometer with an appropriate pediatric cuff. Pubertal status was determined according to Marshal and Tanner staging.

The data were analyzed using the SPSS software. Differences between the groups were evaluated by the Chi squared and Student *t* test. Difference were considered significant when $P < 0.05$.

RESULTS

From 118 study participants, 23 (15 girls, 8 boys; 19.5%) children had microalbuminuria in three consecutive occasions over a period of one year (Table 1). The mean age of the patients with microalbuminuria (16.26 ± 1.68 y) was significantly higher ($P < 0.001$) than the mean age of the children with normal albuminuria (11.3 ± 4.4 y). The onset of microalbuminuria in 22 of 23 children was after puberty and in 1 patient it occurred before puberty. The youngest subject with microalbuminuria was a 10.5 years old girl.

Table 1. Clinical data for normoalbuminuric and microalbuminuric patients with type I diabetes mellitus*

Feature	Normoalbuminuric patients (n = 95)	Microalbuminuric Patients (n = 23)
Age at onset of diabetes (year)	6.4 ± 3.3	7.6 ± 2.5
Diabetes duration (year)	5.2 ± 3.4	8.7 ± 3.2†
Age at completion of study (years)	11.3 ± 4.4	16.26 ± 1.68†
Insulin dose (U/kg)	1.5 ± 0.137	1.4 ± 0.72†
Hb Alc (%)	7.1 ± 0.77	9.3 ± 1.8†
Cholesterol (mg/dl)	143.5 ± 37.6	178.5 ± 2.9†
Triglyceride (mg/dl)	137.96 ± 34.9	218.9 ± 92.1†
Systolic blood pressure (mmHg) **	108 ± 9	138 ± 10†
diastolic blood pressure (mm Hg) **	70 ± 8	94.5 ± 10†

*Data are presented as mean ± SD.
†$P < 0.001$ was considered statistically significant by *t* test.
** Thirty-five age matched patients without microalbuminuria compared with patients with microalbuminuria.

The mean duration of diabetes in patients with microalbuminuria (8.7 ± 3.2 y) was significantly higher than the subjects with normal albuminuria (5.2 ± 3.4 y) ($P < 0.001$). The age at the onset of diabetes in patients with microalbuminuria was 7.6 ± 2.5 years and in subjects with normal albuminuria was 6.4 ± 3.3 years ($P = 0.237$). The dose of insulin in group with microalbuminuria was significantly higher (1.4 ± 0.72 U/kg) than the group without microalbuminuria (1.5 ± 0.137 U/kg) ($P < 0.001$).

The mean of TG (218.9 ± 92.1 mg/dl), cholesterol (178.5 ± 2.9 mg/dl) and Hb Alc (9.3 ± 1.8) were significantly higher ($P < 0.001$) in group with microalbuminuria than the group with normal albuminuria (TG, 137.96 ± 34.9 mg/dl; cholesterol, 143.5 ± 37.6 mg/dl; and Hb Alc, 7.1 ± 0.77).

Mean systolic and diastolic blood pressures were significantly ($P < 0.001$) higher in microalbuminuric patients (138 ± 10 and 94.5 ± 10 mmHg, respectively) compared to the age matched normoalbuminuric diabetic group (n = 35; 108 ± 9 and 70 ± 8 mm Hg, respectively).

DISCUSSION

In type I DM, much of the excess morbidity and mortality, caused by cardiovascular disease and end stage renal failure, occur in individuals with diabetic nephropathy (1-3).

We describe our observation in a population of 118 children and adolescents with type I DM followed longitudinally over a period of seven years. A cumulative prevalence of 19.5% with microalbuminuria has been identified in participating subjects. Estimates of the point prevalence of microalbuminuria in childhood vary between 7% and 28.2% in various reports (Table 2). The wide range of prevalence in various studies may be due to difference in ethnic groups (genetic factors are believed to be responsible for the development of diabetic nephropathy), methodology and definition of microalbuminuria, population size, length of follow up and mean age of study population.

Previous studies have indicated that the onset of microalbuminuria before puberty occurs only rarely and consequently screening for microalbuminuria should be recommend for children over 12 years of age (15-17). There are only a few reports of diabetic children who develop diabetic nephropathy in prepubertal period (18-20). In a longitudinal study by Rudberg *et al.*, three of 159 children developed persistent microalbuminuria at less than 12 years of age (21). Both Liverpool as well as MIDAC studies identified a number of children with diabetes developing microalbuminuria before the onset of puberty (11, 22). In another study by Jones *et al.*, 15 of 233 children developed microalbuminuria before puberty (8). We have found that in one of the 23 children with persistent microalbuminuria, onset was before puberty as assessed by Marshal and Tanner staging.

Table 2. Prevalence of microalbuminuria in type I diabetic children in different studies

Author (Ref No)	Year	No of Patients	Prevalence (%)
Jorner *et al.*[4]	1992	351	12.5
Baak *et al.* [5]	1993	70	16
Mathiesen *et al.* [6]	1995	209	15
Bruno *et al.* [7]	1996	211	7
Jones *et al.* [8]	1998	233	14.6
Patel *et al.* [9]	1998	90	12.5
Moore *et al.* [10]	1999	419	4.29
MIDAC group[11]	2000	1007	9.7
Schaltz *et al.* [12]	2001	494	12.5
Viswanthan *et al.* [13]	2002	95	28.2
Present study	2006	118	19.5

These suggest that children with diabetes are at risk of developing increased albumin excretion before puberty and this would warrant regular screening. The association of increasing urinary albumin excretion in type I diabetes in childhood and the duration of disease has been demonstrated in some studies (21, 23, 24) but not in others (17, 25).

We found no significance difference between microalbuminuric and normal albuminuric patients in age at diagnosis but there was a significant difference between the two groups with respect to the age of the children at the end of study ($P < 0.001$). However, the older age in children with microalbuminuria at completion of the study reflects the longer duration of diabetes in this group (8.7 vs. 5.2 years).

It is important to note that 1.9:1 ratio of girls to boys with microalbuminuria in this study was similar to those described for MIDAC and Pittsburgh research groups (11, 26), confirming that the development of microalbuminuria is accelerated in girls.

In agreement with MIDAC study (11), we also found an association of raised urinary albumin excretion with poorer glycemic control (mean of Hb Alc, 9.3 vs. 7.1 in microalbuminuric and normal albuminuric patients, respectively.

Patients with microalbuminuria had significantly higher mean cholesterol and TG levels and received higher doses of insulin compared to patients with normal albuminuria. Again these show poorer glycemic control in patients with microalbuminuria suggesting that the most obvious first treatment option is to improve glycemic control.

An increase in blood pressure is associated with increase in urinary albumin excretion in both adults and children (17, 26). There is controversy as to whether an increase in blood pressure precedes or is a result of the development of microalbuminuria (27). The association of microalbuminuria and hypertension in childhood has been demonstrated in some studies (8) but not in others. Using routine clinic blood pressure measurements, we found significantly higher systolic and diastolic blood pressures at the end of study period compared to the age matched normal albumin excretion diabetic children. Angiotensin converting enzyme (ACE) inhibitors delay the progression of diabetic nephropathy by normalizing glomerular capillary pressure independent of their antihypertensive effect in hypertensive and normotensive adults with diabetes (17, 24). There are few data on the use of ACE inhibitors in childhood diabetes although they have been shown to halt or reverse the progression of microalbuminuria in a small group of normotensive children with microalbuminuria (17). Similar trials in childhood and adolescence are now urgently needed. However, given the well documented problems of life style regulation and compliance in optimizing control especially in this age group, we need to develop alternative and simple interventional strategies to improve outcome. Monitoring should be extended to those in the early stages of the disease and those who are still prepubertal.

Conflict of interests

The authors declare that they have no competing interests.

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