MICROALBUMINURIA IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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ABSTRACT

Diabetic nephropathy is the most important cause of increased morbidity and premature mortality in patients with type 1 diabetes mellitus. Detection of microalbuminuria helps to carry out early interventions to halt the progression of early stages of diabetic nephropathy to advanced renal disease. In this study the albumin: creatinine ratio was estimated in 70 children and adolescents with type 1 diabetes mellitus and 74 non-diabetic subjects attending Basrah Maternity and Children Hospital over one-year period *(from the first of June 2001 till the end of May 2002)*, their ages ranged from 16 month-18 year. Albumin: creatinine ratio on early morning urine samples, HbA_{1C}, blood pressure measurements and growth measures were recorded. Microalbuminuria (albumin: creatinine ratio 30-300mg/g) was present in 41.42% of patients with type 1 diabetes mellitus, while macroalbuminuria (albumin: creatinine ratio > 300mg/g) was detected in one patient (1.42%). Factors associated with a raised albumin: creatinine ratio compared with normoalbuminuric patients (albumin: creatinine ratio < 30 mg/g) with type 1 diabetes mellitus include longer duration of diabetes mellitus (P-value < 0.01), poor glycemic control reflected by raised HbA_{1C} (P-value <0.001), and older age of diabetic patients (P-value <0.05). Microalbuminuria was not associated with body mass index, gender and systolic and diastolic blood pressure. These results stress the need for routine monitoring of diabetic patients for microalbuminuria and the importance of improved glycemic control in these patients.

INTRODUCTION

Diabetes mellitus is one of the most frequent chronic diseases in childhood, the seriousness of which is still often not recognized, although the complications that the condition implies can be very damaging as well as costly and are often brought on by a lack of knowledge about the condition and lack of care[1]. Diabetic nephropathy is the most important cause of increased morbidity and premature mortality in patients with type 1 diabetes[2]. The cumulative incidence of diabetic nephropathy is 25-40% in type 1 and 10-15% in Type 2 diabetes[3,4]. Diabetic nephropathy may be functionally silent for long periods (10-15 years)[5]. The first manifestation of diabetic nephropathy is microalbuminuria, an elevated albumin excretion rate (AER). The presence of persistent microalbuminuria predicts progression to gross proteinuria within 6-14 years[6]. Microalbuminuria is well recognized as a risk factor for the development of diabetic nephropathy in adults, but its natural history is less clear in children and adolescents[7]. The microalbuminuric (MA) phase, or incipient diabetic nephropathy is defined as a urinary albumin excretion rate of 20-200 mg/min (30-300 mg/day)[8]. Diabetics with MA have a 20-fold increased likelihood of developing clinical proteinuria *(> 300mg/day of albumin)* or a diminished glomerular filtration rate within a period of 10 years. A number of factors e.g. strenuous exercise, high blood pressure, urinary tract infection, menstrual bleeding and very poor control of diabetes elevate albumin excretion rate[9,10]. Microalbuminuria is the most reliable indicator of diabetic nephropathy, it also predicts the development of cardiovascular diseases in diabetes[11]. Because there is no specific treatment for diabetic nephropathy and it is a leading cause of death and disability[5], in addition to it's decisive importance to long term prognosis of diabetes[12], it is now incumbent on clinicians to carefully monitor patients with diabetes for evidence of early renal disease. This involves regular screening for MA, which is an important intermediary end point that correlates strongly with future advanced renal disease retinopathy and mortality[8,13].

This study was carried out to estimate the frequency of MA among children and adolescents with type 1 and to investigate the influence of sex, age, duration of diabetes, body mass index, blood pressure and glycemic control on MA in these patients.

SUBJECTS AND METHODS

SUBJECTS

This study was carried out over one year period *(from the first of June 2001 till the end of May 2002)*. The study included children who were admitted to Basrah Maternity and Children Hospital for the management of diabetes or consulting the outpatient department for monitoring of diabetes mellitus. Seventy

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patients with type 1 *(36 males and 34 females)* were investigated, their ages ranged from 16 months to 18 years. Full medical history was recorded and the following data were collected: date of admission or consultation, age, sex, residence, duration of diabetes, frequency of hospitalizations, dietary history, insulin dose (U/kg), cause of referral, complaints, family history of diabetes mellitus or renal diseases and drug history. Physical examination was carried out for each patient and it included: general examination; including vital signs *(pulse rate, respiratory rate, temperature, and blood pressure)*, growth measurements *(weight, length or height)*, and examination for periorbital or peripheral oedema, in addition to systemic examinations. Body mass index was measured as weight *(in kilograms)* divided by the square of the height *(in meters)*. Seventy-four non-diabetic children matched for age and sex *(39 males and 35 females)* were included in the study as a control group. They were selected randomly from children consulting the outpatient department for minor illness like upper respiratory tract infections. The following data were collected: date of consultation, age, sex, residence, cause of referral, complaints, past medical and surgical history. Physical examination was carried out including vital signs *(including blood pressure measurement)*, growth parameters like *(body weight, height or length)*, BMI and systemic examination. An informed consent was obtained from at least one of the parents of patients and controls before they were recruited in the study.

METHODS

Blood samples were collected after an over night fast as follows: two ml. were taken into a vacuum collection tube containing EDTA and thoroughly mixed, specimens can be stored up to seven days at 2-8^{o}C, for estimation of HbA_{1C} *(using ion-exchange high performance liquid chromatography)*, another four ml of blood were centrifuged and the serum was used for glucose and albumin estimations, these investigations were done for diabetic patients only. Early morning urine samples were collected from patients who have been admitted after stabilization of the blood sugar and general condition, and patients consulting the outpatient department. For controls, early morning urine samples were also collected from children consulting the hospital from 8-10 am. Urine samples were freezed in the refrigerator and analyzed thereafter for estimation of urinary albumin, urinary creatinine and albumin-creatinine ratio *(ACR)*, in the Biochemistry Department, College of Medicine, University of Basrah. General urine examination and urine culture was done for all patients, those with urinary tract infections were excluded from the study. Albumin-creatinine ratio *(ACR)* was used as a measure of urinary albumin excretion and was considered raised if it was ≥ 30 mg/g.

Statistical analysis

Chi-square (X^2) test was carried out to determine the relative importance of various variables. T-test was carried out to compare between two samples proportions. P-value less than 0.05 was considered as statistically significant (S), value less than 0.01 was considered to be highly significant (HS), and less than 0.001 as extremely significant (ES).

RESULTS

The study has included 70 patients with type 1 diabetes mellitus, and 74 non-diabetic children as a control group. (Table-1) illustrates that there was no significant difference between patients and controls in regard to sex, age, BMI, systolic blood pressure and diastolic blood pressure, and as expected the HbA_{1C} was significantly higher in diabetic children compared to non-diabetic controls, P-value <0.001. The same table also reveals that the mean albumin-creatinine ratio was significantly higher in diabetic patients compared to controls.

Table 1. Clinical and biochemical characteristics of the studied groups.

Parameters		Patients (n=70)	Control (n=74)	P-value+
Sex+	*Male*	36	39	
	Female	34	35	
Age (years)*	9.78 ± 4.04	9.78 ± 4.04	9.5 ± 3.5	NS
BMI*	15.42 ± 2.21	15.42 ± 2.21	16.31 ± 4.32	NS
Systolic blood* pressure (mm Hg)	108.5 ±11.43	108.5 ±11.43	106 ± 0.31	NS
Diastolic blood* pressure (mm Hg)	68.07 ± 9.02	68.07 ± 9.02	65.32 ± 8.08	NS
HbA_{1C} (%)*	10.24 ± 2.38	10.24 ± 2.38	5.8 ± 1.25	ES
ACR (mg/g) *	53.1 ± 76.3	53.1 ± 76.3	11.11 ± 5.82	ES

***Values were expressed as mean ± SD (tested by t-test)**
+X^2- test was utilized.

Total patients with type 1 diabetes included in this study were 70 cases; 29(41.42%) were found to have MA (ACR 30-300 mg/g) and 40(57.14%) with normoalbuminuria. The study also has detected one patient (1.44%) with macroalbuminuria (ACR > 300 mg/g).
The ages of MA positive type 1 diabetic patients have ranged from 56 months to18 years. The study has demonstrated that the frequency of MA is increasing with advance age of diabetic patients, the frequency was ranging from 11% *(one child out of nine)* in patients less than 5 years old to 75% (six out of eight) in patients older than 15 years, the difference was statistically highly significant, (Table-2). Out of 29 patients with MA, 16 were males and 13 were females. There was no statistically significant association between sex of patients and the development of MA (P-value > 0.05).

Table 2. ***Age distribution of diabetic patients in relation to MA.***

Age	Total number of cases	Ma + ve cases (%)
< 5 years	9	1 (11.11)
5- < 10 years	22	5 (22.72)
10- < 15 years	30	17 (56.66)
≥ 15 years	8	6 (75)
Total	*69*	29 (42.02)

X^2 –test was utilized
P-value < 0.01

The clinical and biochemical characteristics of type 1 diabetic patients were presented in (Table-3). The ages of diabetic patients included in this study have ranged from 16 months to18 years, while the duration of diabetes has ranged from newly diagnosed disease to 14 years. The ages of diabetic patients with MA has ranged from 56 months to 18 years, while the duration of the disease has ranged from 9 months to 14 years. Table-3 also shows that there was a significant association between MA and age of patients, duration of disease and diabetes control, as the mean age of diabetic patients with MA, duration of diabetes mellitus and HbA_{1C} level were significantly higher compared with MA negative cases. While systolic and diastolic blood pressure and BMI show no statistically significant differences in both groups.

Table 3. ***Selected clinical and biochemical characteristics of patients with type 1 diabetes mellitus***

Parameters	MA + ve cases (n=29)	MA - ve cases (n=40)	P-Value+
Age (years) *	10.77 ± 3.87	8.6 ± 3.7	S
Duration of diabetes (years)*	4.44 ± 3.40	2.37 ± 2.59	HS
BMI*	15.43 ± 2.44	15.41 ± 2.04	NS
Systolic blood pressure (mmHg)*	109 ± 12.86	107 ± 10.82	NS
Diastolic blood pressure (mmHg)*	67.5 ± 11.36	66.57 ± 9.08	NS
HbA_{1C} (%)*	11.57 ± 2.60	9.12 ± 1.45	ES
ACR (mg/g)*	98.44 ± 94.66	14.91 ± 8.41	ES

***Values were expressed as mean ± SD**
+ t-test was utilized

Selected clinical and biochemical variables among diabetic males and females with MA were presented in (Table-4). This table shows that there was no statistically significant difference between males and females with MA in relation to age, duration of diabetes, BMI, blood pressure and ACR. However, there was a statistically significant difference in the level of HbA_{1C} among both sexes; females with MA have a significantly higher HbA_{1C} level compared to males.

The duration of type 1 diabetes mellitus in patients with MA has ranged from 9 months to 14 years. The study has revealed that the frequency of MA increases with increasing duration of diabetes mellitus. The frequency of MA has ranged from 23% in patients with a duration of diabetes mellitus < 2 years to 65% in patients with a duration of diabetes 5-10 years. Two patients have a duration of diabetes more than 10 years, both of them have microalbuminuria.

About 45% of diabetic patients included in the study have a HbA_{1C} level < 9 %, 33.3% with a level between 9-12% and only 21.7% have a level > 12%. The frequency of MA was 19.4% in patients with good control, 43.5% in patients with fair control and 86.7% in patients with poor glycemic control.

Table 4: ***Selected clinical and biochemical variables among males and females with MA.***

Parameters	Male (n= 16)	Female (n = 13)	P- value +
Age (years) *	10.36 ±4.68	12.15 ± 1.95	NS
Duration of diabetes (years)*	3.58 ± 2.71	5.7 ± 4.01	NS
BMI*	15.47 ± 2.69	15.38 ± 2.11	NS
Systolic blood pressure (mmHg)*	111.25 ± 13.65	113.46 ± 9.65	NS
Diastolic blood pressure (mmHg)*	68.12 ± 12.51	71.15 ± 6.50	NS
HbA_{1C} (%)*	10.36 ± 2.98	12.16 ± 2.66	S
ACR (mg/g)*	107.74 ± 113.40	84.31 ± 59.06	NS

***Values were expressed as mean ± SD**
+ t-test was utilized

DISCUSSION

Diabetic nephropathy (DN) is the major life-threatening complication of type 1 diabetes mellitus. The availability of methods for detecting MA has allowed the study of urinary albumin excretion rates in diabetics well before clinically persistent proteinuria develops. Therefore, detection of MA is of crucial importance to define strategies and carry out interventions for the prevention of decline in kidney function[14]. In this study, MA was identified in 41.42% of type 1 diabetic patients who have consulted Basrah Maternity and

Children Hospital. The frequency of MA was investigated in many countries especially developed countries[15-21], the lowest rate was reported in Finland being 6%[20] and the highest rate was reported in Egypt being 38.1%[16]. The frequency of MA in our study was higher than other studies, this difference can be explained by; firstly: other studies had measured the frequency of persistent MA (MA positive in two out of three consecutive urine samples in 2-3 months interval[1], which therefore had excluded the transient form of MA, while in our study we measured the MA in spot urine sample and this can not differentiate between the two forms of MA. Many studies have shown that up to 50% of MA can revert to normal[15,22]. An example of these studies is the study that was done in Canada[15], where transient MA was present in 11% and persistent MA in 25% of all diabetic patients included in the study with initial MA[15]. Secondly, in our study 70% of diabetic patients were recruited from the pediatric ward (admitted cases), therefore causing selective bias towards patients with worse diabetic control.

In this study, one patient has macroalbuminuria (ACR > 300 mg/g), this patient is 13 years old, with a duration of diabetes of 7 years and HbA_{1C} level of 12%. He had not complained of edema or hypertension and has normal renal function tests.

The mean age for MA patients was 10.77±3.87 and for normoalbuminuric patients was 8.6±3.7. This difference in mean age of both groups was statistically significant. In addition to that, the frequency of MA increases significantly with increasing age of diabetic patients, this result is in agreement with other studies in other countries like Italy[17], Finland[20], UK[23-25] and France[26] which had revealed that the age is a risk factor for development of MA and onset of diabetic nephropathy. In a longitudinal study done in UK, it was found that the cumulative probability for developing MA was 40% after 11 years of age[27]. Differences in IGF-I levels and androgens, accompany development of MA at puberty, the presence of MA was associated with lower free IGF-I levels, higher testosterone standard deviation score[28]. In addition, puberty is a time of exaggerated physiological insulin resistance, and higher growth hormone have been found in adolescents with type 1 diabetes in association with higher albumin excretion. The influence of sex on MA was investigated in many studies with variable results. In this study there was no significant difference in the frequency of MA among both sexes. This result is in agreement with the result of other study done in Denmark[29] which has shown that the prevalence of MA was significantly associated only with age and diastolic blood pressure. While other studies had concluded that female sex is a risk factor for development of MA[20,21,27], and one study in India had concluded that MA is more common in males[19]. Duration of diabetes was one of the most important risk factors for development of MA and progression to overt nephropathy. In our study it was found that the mean duration of diabetes mellitus in patients with MA is 4.44±3.40 years which is significantly higher from that of normoalbuminuric patients 2.37±2.59 years (P-value = 0.005). These results were in agreement with the results of other studies done in Italy[17], UK[18,27], and Australia[30]. A study from UK[18] had demonstrated that the cross-sectional prevalence of raised ACR was 12.9% at 1 year, 18.3% at 5 years and 33% at 10 years after diagnosis. There were 6 patients with MA in our study with duration of diabetes below 2 years, the age of these patients were ranging from 8 to 16 years, two of them were less 12 years and the rest were older than 12 years, the above results of development of MA with shorter duration of diabetes can be explained by the impact of puberty as an important independent risk factor for the development of MA. This result is supported by the results of other studies done in Italy[17], Finland[20], and France[26] which had revealed that puberty is involved in the appearance of MA. The influence of blood pressure on MA in children with type 1 diabetes mellitus was evaluated and there was no significant difference between microalbuminuric and normoalbuminuric patients in relation to the mean systolic and diastolic blood pressure. Various studies have revealed conflicting results, some of these studies did not show any significant role of blood pressure on MA[20], while others have revealed hat high blood pressure especially diastolic pressure is one of important predictors of developing MA[21,23, 31]. It is possible that blood pressure only increases in relation to onset of microalbuminuria, either

shortly before or after, and thus only is a short-term risk factor. Another possibility is that the changes in blood pressure initially are so small that they are not detectable with a baseline office measurement and that 24-h ambulatory blood pressure measurements are necessary to demonstrate their presence[9,32]. Few studies have investigated the association between MA and BMI. In our study, there was no significant difference in BMI among diabetic patients and control, and between microalbuminuric and normoalbuminuric patients. This results is in agreement with the result of the study done in Denmark[29] while this result was in contrast to studies in Finland[20], and Sweden[31], who had demonstrated that patients with MA have a higher BMI than normoalbuminuric patients and controls. Insulin resistance is associated with both central obesity and microalbuminuria and may play a prominent mediating role[33]. Glycemic control is one of the important predictors of the development of MA in type 1 DM. In this study, the mean HbA_{1C} of MA patients was 11.57±2.60 which was significantly higher than that of the normalbuminuric patients 9.12±1.45 ($P< 0.001$). Also the study has shown that the frequency of MA increases significantly with the increase in the level of HbA_{1C}. Other studies also have concluded that HbA_{1C} is a determinant risk factor for MA[24], and that poor glycemic control predisposes to MA[15,18,21,34,35]. From this study it can be concluded that routine monitoring of children with type 1 diabetes mellitus should be carried out using albumin: creatinine ratio on an early morning sample as it is a simple and reliable technique in clinical practice, in addition monitoring should be extended to those in early stage of the disease and those who still prepubertal. Continued follow up of children with raised albumin: creatinine ratio is important to identify those with persistent microalbuminuria and those with transient microalbuminuria and to clarify whether they will follow a benign course or will progress ultimately to nephropathy.

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