Microalbuminuria in children and adolescent with type 1 Diabetes mellitus attending the diabetic center of children welfare teaching hospital.

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Summary:

Backgrounds: Despite advances in management of diabetes mellitus, it remains one of the major causes of morbidity and mortality, yet diabetic nephropathy is one of the main complications of diabetes mellitus. .Microalbuminuria is the beginning to the renal complications of diabetes mellitus; it is a significant index of early detection as well as monitoring the progression of diabetic nephropathy.

Aim of the study: to estimate the presence of microalbuminuria as predictor for nephropathy among children and adolescent with type1 diabetes mellitus and to study the effect of various factors on incidence of microalbuminuria in these patients.

Subjects and methods: this study was carried out in the Children Welfare Teaching Hospital/ Medical City over ten months period. Fifty patients with type 1 diabetes and fifty non-diabetic children matched for age and sex were included in the study as control group. History was taken, physical examination and investigations done for all subjects. Early urine samples were used to estimate albumin/creatinine ratio to detect microalbuminuria. Statistical analysis done using T test and chi square, P value < 0.05 regarded as statistically significant.

Results: out of 50 patients with type 1 diabetes, 35 (70%) had microalbuminuria. There was significant association between presence of microalbuminuria and increasing age (P value 0.04), increasing duration of diabetes (P value 0.03) and glycemic control level(P value =0.04).Seven (46.6%) patients with duration of diabetes <5 years had microalbuminuria, all of them had onset of diabetes before puberty. There was no significant difference between diabetic patients and controls and between microalbuminuria +ve and -ve diabetic patients in regards to systolic and diastolic blood pressure, body mass index and glomerular filtration rate.

Conclusions: All patients with microalbuminuria had normal blood pressure, and normal glomerular filtration rate, so we can detect the patients early before they develop overt nephropathy, hypertension and impaired renal function. Some of our patients with duration of diabetes < 5 years had microalbuminuria, all of them had prepubertal onset of diabetes.

Key words: Type 1 diabetes mellitus, microalbuminuria, diabetic nephropathy.

Introduction:

Despite advances in management of diabetes mellitus, nephropathy remains one of the major causes of morbidity and mortality, yet diabetic nephropathy is one of the main complications of diabetes mellitus (1, 2, 3, 4).Diabetic nephropathy affects 20-30% of patients with type 1Diabetes mellitus and 15-20% of type 2 Diabetes mellitus patients 20 years after onset. The mean 5-yr life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term type 1 DM may be due to nephropathy, which may account for about 50% of deaths (5).The risk of nephropathy increases with duration of diabetes, up until 25 -30 years duration (1,5) , degree of metabolic control , and genetic predisposition to essential hypertension (1,5,6). Microalbuminuria is the beginning to the renal complications of diabetes mellitus and it is the more reliable indicator of diabetic nephropathy which is a leading cause of death and disability in diabetic patient (7) and is heralded by progressive proteinuria ,hypertension and progressive   loss of renal function (1,2,3),and it precedes persistent proteinuria and represent a potentially reversible stage of diabetic nephropathy (4) , Diabetics in whom the urinary albumin excretion rate (AER) are in the range of (20-200microgram/min) or (30-300mg per day) are defined as having microalbuminuria(8,9)and they have a twenty fold increased likelihood to develop clinical proteinuria or overt nephropathy (Macroalbuminuria> 300mg per day of albumin) over the next 7-14 year(8,10) this will be associated with a diminished GFR within period of 7- 10 year, and only 50% of individual reach ESRD. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible (11). So it is now incumbent on clinicians to carefully monitor patients with DM for evidence of early renal disease, This involves regular screening for microalbuminuria (9). the timing for microalbuminuria screening depend on the

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age of onset of diabetes, in prepubertal onset of diabetes; the screening will be after 5 year of onset or at the age of 11 years ,and annually thereafter(5,8) Pubertal onset of diabetes; 2 years after onset and annually thereafter (5,12). Some diseases or conditions may cause microalbuminuria including: hypertension ,UTI ,CHF ,fever and intensive exercise (1,3,13,14), menstrual bleeding, vaginal discharge, glomerulonephritis,orthostatic proteinuria(8) Obviously if such factors are present the finding of microalbuminuria does not necessarily imply incipient diabetic nephropathy (12,15). Screening for microalbuminuria can be performed by three methods (16,17): 1) Measurement of the albumin-to-creatinine ratio in a random spot collection . 2) Twenty four-hr collection with creatinine, allowing the simultaneous measurement of creatinine clearance. 3) Timed (e.g., 4-h or overnight) collection. The first method is often found to be the easiest to carry out in an office setting, generally provides accurate information, and is therefore preferred; first-void or other morning collections are best because of the known diurnal variation in albumin excretion, but if this timing cannot be used, uniformity of timing for different collections in the same individual should be employed (16). There is also marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3- to 6-month period should show elevated levels before designating patient as having microalbuminuria .The role of annual microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy and blood pressure control. Many experts recommend continued surveillance to assess both response to therapy and progression of disease. In addition to assessment of urinary albumin excretion, assessment of glomerular function is important in patients with diabetic kidney disease (16). The use of urine albumin to urine creatinine ratio (which is a ratio between two measured substance) is preferable since it is unaffected by variation in urine concentration (18). The normal urine albumin to creatinine ratio: - In men is less or equal to 17 mg/g. In women is around 25 mg/g. Microalbuminuria= 30-300 mg albumin/g creatinine.   Macroalbuminuria = >300 mg albumin / g creatinine (19). Primary efforts should focus on optimizing glycemic control early in the course of diabetes especially in higher risk patients (10). Detection of microalbuminuria and the use of Angiotensin converting enzyme (ACE) inhibitors have been shown to delay the onset and progression of nephropathy in type 1 diabetes mellitus (7),The aim of this study was to estimate the presence of microalbuminuria as predictor for nephropathy among children and adolescent with type1 diabetes mellitus and to study the effect of various factors on incidence of microalbuminuria in these patients.

Patients and methods:
This prospective study was carried out over ten months period

(from the first of March 2011 till the end of December 2011) .It included 50 children who had type1diabetes for at least 4 years and who were admitted to Children Welfare Teaching Hospital / Medical City for the management of diabetes and those consulting the diabetic clinic for monitoring of their diabetes .The following data were collected: age (date of birth), date of admission or consultation, date of onset of diabetes and so duration of diabetes was calculated, sex, dose of insulin U/Kg /day ,family history of diabetes mellitus or renal diseases ,and history of other diseases or complications related to diabetes mellitus .Physical examination was carried out for each patient, which includes:Temperature, blood pressure, height, weight, body mass index, examination for periorbital or peripheral oedema, limited joint mobility, and systemic examination was done. Fifty non-diabetic children matched for age and sex were included in the study as control group. They were selected randomly from children consulting the outpatient department for minor illness like upper respiratory tract infection. The following data were collected: Date of consultation, age, sex, complaints and past medical and surgical history. Physical examination was carried out for each patient, which includes: Temperature, blood pressure, height, weight, body mass index, examination for periorbital or peripheral oedema, and systemic examination was done. Blood pressure was measured by using sphygmomanometer with appropriate cuff size for age and using CDC (central diseases control) age specific percentile of blood pressure in boys and girls , and considered hypertensive when the reading above the 95th percentile for age.Body Mass Index calculated by the following formula: BMI=weight (Kilogram)/(height in meter) (5)we use central diseases control(CDC) chart for body mass index-for –age percentiles and children >2 year old with a BMI ≥ 95th percentile meet the criterion for (obesity) ,and those with BMI between 85th and 95th percentiles fall in the(overweight) range (20). Limited joint mobility (LJM) was assessed by using prayer maneuver; patients were asked to approximate the palmer surfaces of the fingers in a praying position with the fingers fanned and the wrists flexed. If the patient failed to approximate the palmer surfaces completely, the examiner attempted to extend the fingers passively. Equivocal ,or unilateral , findings or simply a sense of resistance without limitation was classified as no LJM .The failure of any joint to make contact was classified as LJM (21).Any febrile child was excluded from study. An informed consent was obtained from at least one of the parents of patients and controls before they recruited in the study. Blood samples were collected as follows:- two milliliters were taken into vacuum collection tube containing EDTA and thoroughly mixed for estimation of HbA1c and another four milliliters of blood were centrifuged and the serum was used for estimation of albumin, urea and creatinine. Early morning urine samples were collected from patients and controls, which were analyzed for estimation of urinary albumin, urinary creatinine, and albumin-creatinine ratio,

were calculated accordingly.

This work was done in the biochemistry department of teaching laboratories of medical city. The kits which were used for detection of microalbuminuria were not available in teaching laboratory of medical city so we bought them from the market.

GFR estimation done by applying the following formula: K* height (cm)/serum creatinine (mg/dl) (Where K=0.55 in children and adolescent girls, and K=0.70 in adolescent boy) (22).Regarding glycemic control,we took the HbA1c as indicator for glycemic control in which we have either: Good control with (HbA1c= 6- 7.9), Fair controls with (HbA1c= 8- 9.9),and Poor control with (HbA1c ≥ 10)(5).Spss program was used for statistical calculation*chi-square (X2) test was carried out to determine the relative importance of various variables.

*T-test was carried out to compare between two samples proportion.*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 was included 50 patients with type 1 diabetes mellitus and 50 non-diabetic children as control group (table 1).

Table 1: The means of clinical and biochemical characteristics of the studied groups.

Parameters(mean)*	Patients =50	Control=50	p- value
Age(years)	12.5	10.68	0.1 (NS)
BMI	18.2	18.7	0.5 (NS)
Systolic blood pressure(mmHg)	102.4	97	0.11 (NS)
Diastolic blood pressure(mmHg)	55.8	52.8	0.2 (NS)
Albumin creatinine ratio (mg/gm.)	133	16.1	0.0001 (HS)
GFR (ml/min/1.73 m2)	131.6	121.7	0.2 (NS)

*Values were expressed as mean and t-test was utilized.

This table illustrates that there was no significant difference between patients and controls in regard to (age, BMI, systolic blood pressure, diastolic blood pressure and GFR). It also reveals that the mean albumin-creatinine ratio was significantly higher in diabetic patients compared to controls. The age of the fifty diabetic patient included in this study ranged from 6-18 years with mean (12.58±3.04 years); while the duration of diabetes ranged from 4-14 years with mean (6.3±2.3 years).Thirty five (70%) of diabetic patients were found to have microalbuminuria.

Table 2: The means of clinical and biochemical characteristics of patients with type 1 diabetes mellitus according to presence of microalbuminuria.

Parameters (mean)*	Microalbuminuria +Ve	Microalbuminuria -Ve	p-value
Age(years)	13.1	11.2	0.04 (S)
Duration of diabetes(years)	6.6	5.2	0.04 (S)
HbA1c (%)	10.7	9.2	0.05 (S)
BMI	18.7	17.2	0.1 (NS)
Systolic blood pressure (mmHg)	103.7	99.3	0.3 (NS)
Diastolic blood pressure (mmHg)	56.4	50	0.14 (NS)
Albumin/ creatinine ratio in urine (mg/g)	178	٢٧	0.0001 (HS)
GFR	42.3	47.7	0.3 (NS)

*values were expressed as mean and t-test was utilized.

Table(2)shows that there was a significant association between microalbuminuria and age of patients ,duration of diabetes mellitus ,HbA1c, and it shows high significant association with albumin/creatinine ratio compared with(-Ve) microalbuminuria patients. While BMI ,GFR ,systolic and diastolic blood pressure show no significant difference in both groups. No one in this study were obese so we took the mean of BMI, also no one have B.P(systolic or diastolic) ≥ 95th , so we took the mean for systolic and diastolic B.P. The GFR for all patients were normal.Twenty-five of patients that included in our study were male, 16(64%) of them had microalbuminuria. The other 25 patients were female, 19(76%) of them had microalbuminuria (table 3).

Table 3: The sex distribution of diabetic patients in relation to presence of microalbuminuria

Gender	Microalbuminuria +Ve No. (%)	Microalbuminuria –Ve No. (%)	Total No. (%)
Male	16 (64%)	9 (36%)	25 (50%)
Female	19 (76%)	6 (24%)	25 (50%)

P-value = 0.5(NS).

This table shows that there was no significant association between gender of patients and development of microalbuminuria.The age range of type1 diabetic patients who had +Ve microalbuminuria was from 6-18 years (table 4).

Table 4: The age distribution of diabetic patients in relation to microalbuminuria.

Age (In years)	Microalbuminuria +Ve		Microalbuminuria −Ve		Total	
	No.	(%)	No.	(%)	No.	(%)
5 - ≤10	5	(41.6 %)	7	(58.4%)	12	(24%)
>10 -≤15	24	(77.4%)	7	(22.6%)	31	(62%)
>15 - ≤20	6	(85.7%)	1	(14.3%)	7	(14%)

P-value = 0.04 (S)

This table demonstrates that there was significant association between the frequency of microalbuminuria and increasing age in patients with type 1diabetes mellitus.
The duration of type 1 DM in patients with microalbuminuria ranged from 4-14 years (table 5).

Table 5: The distribution of diabetic patients according to duration of diabetes

Duration (In years)	Microalbuminuria +Ve		Microalbuminuria −Ve		Total	
	No.	(%)	No.	(%)	No.	(%)
≤ 5	7	(46.6%)	8	(53.4%)	15	(30%)
>5 - ≤10	26	(78.8%)	7	(21.2%)	33	(66%)
>10 - ≤15	2	(100%)	0	(0.0%)	2	(4%)

P-value =0.03 (S)

This table shows that the frequency of microalbuminuria increase with increasing duration of diabetes mellitus, and this difference was statistically significant.Out of 15 patients with duration of <5 years,Seven (46.6%) had microalbuminuria,all of them had onset of diabetes before puberty ,and 100% of patients with duration > 10 years had microalbuminuria.

Table 6: The distribution of diabetic patients according to glycemic control.

HbA1c (%)	Microalbuminuria +Ve		Microalbuminuria −Ve		Total	
	No.	(%)	No.	(%)	No.	(%)
6 -7.9 %	7	(53.8%)	6	(46.2%)	13	(26%)
8 -9.9%	10	(58.8%)	7	(41.2%)	17	(34%)
≥ 10%	18	(90%)	2	(10%)	20	(40%)

P-value =0.04 (S).

This table revealed that the frequency of microalbuminuria is significantly associated with glycemic control level as 90% of patients with poor glycemic control had microalbuminuria.
We found that 7/35 (20%) microalbuminuria +ve patients with HbA1c level between 6-7.9%, 10/35 (28.6%) patients with HbA1c level between 8-9.9%, and 18/35 (51.4%) patients with HbA1c level ≥10.
Other results were found including 7 (14%)patients with type 1 diabetes mellitus had limited joints mobility all of them had microalbuminuria(100%).

Discussion:
Diabetic nephropathy and cardiovascular disease are among the most   common causes of mortality and morbidity in DM patient (23,24). Microalbuminuria is the earliest sign of diabetic nephropathy and the simplest index for early detection of DM related renal complications (2).
 Microalbuminuria was identified in 70% of type 1diabetic patients who had been included in this study. This result was high compared with that was recorded in many countries especially developed countries such as Republic of Ireland 9.7%(25), U.K. 12.8% (26), USA 23% (4), Canada 32% (27) , Iran 30%(1)and in a study which was done in the Basra Maternity and Children Hospital in Iraq 42% (8). This high result in our study can be explained by the small sample size and the presence of some bias in selecting patients as we included only those patients who had diabetes for more than 4 years and 74% of them had fair to poor blood glucose control. the frequency of microalbuminuria shows significant increase with increasing age of diabetic patients (41.6%) in children between 5-10 years, up to (85.7%) in adolescent between 15-20 years ,which is statistically significant ,this result agrees with other studies like the study which done in Amsterdam(28), Australia(29) , Hungaria (30) and Iraq (8) But it disagrees with a study done in USA(4), and in the Netherlands(31), which showed no significant difference regarding age. This difference in the results can be related to the difference in the sample size, and the difference in age group that have been taken in our study.The influence of gender on microalbuminuria in this study shows no significant difference in the frequency of microalbuminuria among both sex .This result agrees with the result of other studies like that done in Iraq (8, 32), Netherland (31), but differs from study which done in Mumbai (33) which shows that microalbuminuria is more common in male, and from a study done in Iran (34) which shows that microalbuminuria is significantly more in girls than boys. These results may be related to the difference in the sample studied.Duration of diabetes in our study had significant effect on incidence of microalbuminuria in patients with type1diabetes mellitus ,the mean of duration in microalbuminuria +ve was 6.6 years which is significantly different from the mean of microalbuminuria −ve patients 5.2 (p-value 0.04). Microalbuminuria was found in (46.6%) of patients <5 years ,(78.8%) within 5-10 years of diabetes and(100%) within 11-15 years with (p-value 0.03).These results are in agreement with the results of other studies done in Iraq (8,32) ,USA(4) ,Italy (35) ,Iran (34) ,Germany (36) ,Lyon(37), and Hungaria(30).Glycemic control in our study (which assessed by HbA1c level) shows significant association with microalbuminuria in patients with diabetes mellitus. The mean HbA1c of microalbuminuria +ve patients was 10.7% which is significantly different from that of microalbuminuria -ve patients 9.2% (p-value 0.05). In our study we found that the frequency of microalbuminuria   increase significantly

with increase level of HbA1c (poor glycemic control) .This result agrees with others studies which done in Iraq(8,32), Lebanon(38),USA(4), and U.K(26), but differs from result of a study in Iran(8) which shows no correlation between HbA1c level>8% and microalbuminuria .The association of increased blood pressure with microalbuminuria in patients with type 1 diabetes mellitus was evaluated and there was no significant difference between microalbuminuria +ve patients and microalbuminuria –ve patients in relation to mean systolic and diastolic blood pressure. This result agrees with result of a study done in Iraq(8), USA(4), U.K(26), but it differs from the result of a study that done in national diabetic center in Iraq(32)which shows statistical significant difference related to the systolic and diastolic hypertension between microalbuminuria +ve and –ve patients (p-value<0.001). and this difference may related to difference in sample size (1106) with type 1 diabetes mellitus, age of patients and duration of their diabetes .The influence of BMI on microalbuminuria was taken in our study and there was no significant difference in BMI between diabetic patients and controls (p-value=0.5), and between microalbuminuria +ve and –ve patients (p-value=0.1).This result agrees with the result of the study done in Iraq (8), USA (4) and Australia (29).Regarding limited joint mobility, 7 (14%) with type 1diabetes mellitus had limited joints mobility, all of them had microalbuminuria (100%), this result agrees with the result of a study done in Germany (21), which regard LJM as early marker for microalbuminuria.The GFR values for all patients in this study who have microalbuminuria +ve where normal ,this result agrees with the result of study which is done in India which shows that kidney filtration function usually remains normal during the microalbuminuria phase of nephropathy(39).

Conclusions:
Microalbuminuria has significant relation to the age of diabetic patients, the duration of diabetes and the glycemic metabolic control of the disease, some of our patients with duration of diabetes < 5 years had microalbuminuria, all of them had pre pubertal onset of diabetes, there was association between Limited joint mobility and microalbuminuria, and all patients with microalbuminuria had normal blood pressure(systolic and diastolic) with normal GFR.

Recommendations:
So early detection and management of microalbuminuria is very important and screening for microalbuminuria should be done for all diabetic patients even before 5 years after onset of diabetes especially if they had poor control of their disease, and finding of microalbuminuria in screening test should be followed by 2 other tests in period of 3- 6 months in order to demonstrate the presence of persistent microalbuminuria. Strict glycemic control (by diet and insulin) with good monitoring of glucose level should be ensured in every diabetic

patient to prevent or reduce the incidence of nephropathy, and Limited joint mobility can be used as rapid clinical test for early detection of microalbuminuria and nephropathy.

Author's contributions:
Dr munib alzubaidi and Dr. ali abd alhussien: study conception, study design, drafting of manuscript.
Dr. ali abd alhussien : acquisition of data analysis
Dr. munib alzubaidi: interpretation of data and critical revision

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