Screening for Diabetic Nephropathy in Teenage Diabetes

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Abstract:

Background: Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD). Epidemiological studies have demonstrated that diabetic nephropathy occurs in approximately one-third to one half of all diabetes and, today, diabetes is the most important cause of renal failure in the industrialized world. Recent studies have demonstrated that the onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions but these interventions would have their greatest impact if instituted at a point very early in the course of the development of this complication.

Objective: To screen the problem of diabetic nephropathy in teenage patients with type I diabetes Mellitus (TIDM), by detection of Microalbuminuria (MA) which consider the best predictor of high risk for developing diabetic nephropathy.

Patients and Methods: A cross-sectional design and a convenient sampling procedure were adopted to enroll 230 patients (118 males and 112 females) who met the inclusion criteria, from those attending the National Center for Treatment & Research of Diabetes in Al-Mustansirya Collage of Medicine-Baghdad during the period from the 1st of September 2006 to the end of December 2007. Micral test II was used to screen early morning (spot) urine samples for increased albumin excretion rate while the Schwartz formula made possible estimating the glomerular filtration rate (GFR) from serum creatinine and demographic characteristics. The results were used for evaluating the relationship between microalbuminuria and GFR. Some important risk factors including patient's age, disease duration, body mass index, and hypertension have also been evaluated with reference to the impact of hyperglycemia measured as the prevailing (HbA1c).

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Conclusion: Micro-albuminuria manifested by increased urinary albumin excretion was encountered in 47.82% of our teenage DM patients showing significant association with hyperfiltration state, increasing level of HbA1c, and hypertension. But not gender or body mass index.

Key words: Screening, Diabetic nephropathy, Teenage diabetes

Introduction

The classical long-term microvascular complications of diabetes mellitus (DM) are retinopathy, nephropathy, and neuropathy[1]. These complications affect quality of life and/or life expectancy. The classical definition of diabetic nephropathy (DN) is the progressive rise in urine albumin excretion coupled with increasing blood pressure, leading to declining glomerular filtration and eventually End Stage Renal Disease (ESRD) [2].The majority of future ESRD cases from diabetic nephropathy are preventable when early detection is done [3].

Microalbuminuria (MA) is the best predictor of high risk of developing diabetic nephropathy [4]. Thus, the detection of micro-albuminuria has played a key-role in the management of DM. Therefore a reliable easy test for routine screening for MA is desirable; such a test has been developed and marketed as Micral Test II [5].

MA is defined as a urinary albumin rate between 30 and 299mg/24hr urine collection or 20-199 microgram per minute in timed overnight urine collection, or albumin of 20-199 mg/l in (early morning urine sample)[6, 7]. MA is also called incipient DN to be differentiated from macro-proteinuria (overt DN) [8].

Epidemiological studies have demonstrated that DN occurs in approximately one-third to one half of all DM patients and, today, diabetes is the most important cause of renal failure in the industrialized world [6]. The prevalence, incidence and mortality of ESRD, and from all forms of cardio- vascular disease (CVD), are strikingly increased in persons with diabetes compared to those without diabetes in the world. [9,10]. In many studies from United States, Western European countries as well as many other regions of the world, *DN* has been reported as the main cause of ESRD. Variable prevalence rates have been reported in many countries. In United States, *DN* accounts for about 40 percent of new cases of ESRD. The incidence of ESRD caused by diabetes was 148 per million populations in the United States in 2001[11]. However, as for the Arab World, the prevalence of DN as a cause of ESRD varied in different countries, the highest rate is in Saudi Arabia (27.9%), while in Kuwait 21.2%, in Tunisia 11.4%, and the lowest is in Egypt (8.9%)[12,13,14,15]. Among the great world-wide interest in early detection of DN in DM patients, only few Iraqi studies have been documented [16,17,18,19,20] .

This study has been designed to explore this important problem among teenage diabetic patients as a first step to prevent ESRD.

Patients & Methods

This cross-sectional study was done in the National Center for Treatment & Research of Diabetes in Al-Mustansirya Collage of Medicine-Baghdad during the period from the 1st of September 2006 to the end of December 2007. A convenience sample was used to enroll 230 patients (118 males and 112 females) who met the inclusion criteria.

Inclusion Criteria for eligible patients are:

1- Patients with age of 13 to18 years.

2- The duration of the DM should be 5 years or more.

The study adapted the following exclusion criteria:

1- Presence of overt proteinuria.

2- Presence of Urinary tract infection (UTI).

3- Presence of Haematuria, Ketonuria.

4- Pregnancy in female patients.

5- Acute febrile illness.

6- After heavy exercise and heavy meal.

In the 1st visit (first contact with the patient), data collection was done by taking a complete medical history, followed by full clinical examination. A General urine examination (GUE) was done for each patient by collecting freshly voided urine sample to test the presence of protein, cells, and blood casts, using a dipstick technique (Multistix 10, SG, Bayer, Bridgend, UK), to exclude proteinuria (strip result of □30 mg/dl), UTI, haematuria, and ketonuria. Ineligible patients were excluded.

Informed consent was obtained from each eligible patient or from their parents. The participant was provided with screw capped plastic containers. He was asked to put the containers at the bedside during the night, and collect an early morning sample immediately, after awakening and bring it on the same day after collection. The patients were instructed not to clean the containers by any detergent.

Each patient was instructed to come, for the next visit, fasting with the early morning urine sample collected as described earlier.

In the second visit, fasting blood samples were taken for various laboratory tests at the laboratories of the centers above.

The data were collected by direct patient's interview and from surveying their medical records. The following data were reported; name, age, gender, occupation (student, worker, idle), type and duration of the disease, smoking, (smokers were defined as never smoking, smokers, ex-smokers) as recorded in the patient's medical records or by asking the patients himself.

General physical examination was done for each patient including vital signs (pulse rate, respiratory rate, temperature, and blood pressure), growth parameters (body weight, height), with full systemic examination. Height was calculated from the anthropometric measurements standing height measurement (CMS weighing equipment LTD, England).The patient stood shoeless with the heels and back in contact with the vertical column of the scale. Weight measurement was done by digital weight scale, Seca, Australia. Before each measurement the digital scale was adjusted to zero, the patient was asked to take-off his or her shoes and jackets before weighing, and the weight was taken to the nearest fraction of Kg (to the closest 0.1 Kg) .

BMI was calculated as weight per height^2 (squared height) where weight is in kilogram and height in meter which can be plotted on standard BMI tables according to Official Centers for Disease Control growth chart [21]. A BMI over 95th percentile indicates overweight, while between 85th-95th percentiles is at risk, and below 5th percentile is underweight.

Blood pressure measurement was done by standard mercury Sphygmo-manometer (Speide and Keller, GmbH & Co. miniature 300 B, Germany) was used with an appropriately sized cuff for age which should cover 2/3rd of the upper arm of the patient who was adequately rested for about 10 minutes, the systolic BP (Korotkoff phase 1) and diastolic BP (Korotkoff phase 5) were recorded. The patient had an average of at least two recordings taken two minutes apart. By using specific percentile chart of blood pressure for boys & girls, readings above the 95th percentile were considered hypertensive. [22].

Laboratory Investigations:

In the 2nd visit the following laboratory investigations were done for the eligible patients.

1- Micral Test: Micral Test II (Roche diagnostic GmbL, Mannheim, Germany) is an immunological strip, highly sensitive and specific, gold labeled, optically read test for the immunological, semi-quantitative in vitro determination of urinary albumin from 0 up to concentration of 100 mg/L. MA was considered to be present if urinary albumin excretion rate (AER) in spot (first morning urine sample) was 20-199 mg/l. Micral test strips should be stored at + 2°C to + 8°C, the test strips are stable up to the expiry date even after the pack has been opened. After being taken out of the refrigerator the strips are stable for six months if stored at room temperature up to 30°C.

The early morning urine sample was tested immediately after receiving it; the test strip

was immersed in the urine in such a way that the level of immersion is just between the two black bars which are present on the test strip. The test strip was withdrawn out after 5 seconds, then the test strip was placed across the top of the urine container and was read after one minute. The intensity of the colour produced is proportional to the albumin concentration in the urine. The colour formed is compared with the reference standard chart on the vial. There are four colour blocks, reflecting categories of albumin concentration of (0, 20, 50, 100 mg/L) (off-white, light pink, medium pink, and pink), respectively. According to the manufacturer, the colour corresponding to 20 mg/L or more was considered positive (presence of MA), and recorded positive when at least two of the three consecutive morning urine tested produce a reaction colour corresponding to 20mg/l albumin threshold for micro-albuminuria or more.[6, 11, 20].

2- Glomerular Filtration Rate (GFR) was measured using the Schwartz formula utilizing the proportionality between GFR and height/serum creatinine was used to provide an estimate of GFR based on a constant multiplied by the child's height divided by serum creatinine. The formula GFR = KL/Pcr can be used to estimate GFR in infants, children, and adolescents. GFR is expressed in ml/min per 1.73m^2 BSA. (L: represents body length in cm, Pcr: represent plasma creatinine concentration in mg per dl, and K: is a constant). Schwartz equation is :

$$C_{Cr}\ (\mathrm{mL/min/1.73\ m^2}) = \frac{0.55 \times Height\ (cm)}{S_{Cr}\ (mg/dL)}$$

C_{Cr} : Indicates creatinine clearance; S_{Cr}, : Serum creatinine.

In the Schwartz equation, the constant K is directly proportional to the muscle component of body, and varies with age and sex, the value of K to be used in premature infants through the first year of life is 0.33, and in full term infants and (<1 year of age) is 0.45,[92] in children up to 13 years old is 0.55 and also in adolescent girls. And in adolescent boys the value of the constant changes to 0.7. The estimated GFR can easily be calculated by going to http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.. Normal GFR cutoff value ≥90 ml/min/1.73m^2, and hyperfiltration ≥130 ml/min/1.73m^2 [23, 24, 25].

3- Serum Creatinine: Serum creatinine was measured by using Jaffe's method (Rolf Greiner, Biochema GmbH, Germany). Reference value (0.7- 1.3 mg/dl)(24).

4- Blood Urea: Blood urea was measured with (Urease-GLDH (Glutamate dehydrogenase), Rolf Greiner Biochemica . GmbH. Germany). Reference Range for teenage from (18-45)mg/dl .(24).

5- Assessment of Glycemic Control: Glycosylated haemoglobin was measured as hemoglobin A1c (105). HbA1c was measured by high performance liquid chromatography (HPIC) system, Bio-Rad lab. USA. To assess the glycaemic control the study group was classified by the age of the patient and the level of HbA_1c [26].

Glycemic Control	7 - 12 years	*> 12 years*
good	6.5-8 %	*< 6.5 %*
Fair	>8-9 %	*6.5- 8 %*
Poor	*> 9%*	*> 8 %*

Statistical analysis was done using SPSS version 10.0 under windows XP Statistical methods were used in order to analyze and assess the results, they include the d**escriptive statistics** (Frequencies, percentages, tables and graphical presentation) and inferential statistics (Chi-squared test, student t-test). A p-value less than 0.05 were

considered statistically significant, and less than 0.001 considered highly significant.

Results

A total of 230 teenage patients with type I diabetes mellitus. The sample is comprised of 118 males (51.30%) and 112 females (48.70%) with a male / female ratio of 1.05. Micral Test was positive in 47.82% of patients (as shown in table 1). The percentages of micro-albuminuria in males and females were 43.22% and 52.67% respectively. The difference did not achieve statistical significance.

According to the estimated GFR, most of the participants had normal GFR (61.74%), Those below normal GFR constituted 19.56%, and hyper filtrating patients constitute 18.69% of the studied subjects (89.48% were male), the difference was statistically significant.

The micro-albuminuria in relation to the level of estimated GFR showed that 60.46% of hyper filtrating patients with positive Micral test. As well as normal GFR was higher in Micral negative cases (58.26%) than Micral positive cases (40.14%). As seen from the same table the frequency of the below normal GFR was higher in Micral positive cases, than in Micral negative cases; (60%) vs. (40%). The difference proved to be statistically significant as shown in table 2.

Patients with duration of <10 years were more in Micral negative group (55.77%). While those with disease duration of ≥10 years were more in Micral positive group (81.81%).The difference was statistically significant. as shown in table 3**.**

Table (1): Distribution of the studied sample regarding Micral test results and gender

Gender	Micral Test		Total	X^2-test	*P. value*
	- ve	+ve			
Male	67	51	118	2.060	*0.151*
Female	53	59	112		
Total	*120*	*110*	*230*		

Table (2): Distribution of the studied sample regarding Micral test results and the GFR.

GFR (ml/min/1.73 m^2)	Micral test		Total	X^2-test	*P. value*
	- ve	+ve			
≥ 130	17	26	43	**8.787 DF = 2**	***0.012***
90-129	85	57	142		
<90	18	27	45		
Total	*120*	*110*	*230*		

Table (3): Distribution of the studied sample regarding Micral test results and disease duration.

Duration of diabetes(yr)	Micral test		Total	X^2-test	*P. value*
	- ve	+ve			
<10	116	92	208	11.265 DF = 1	*0.001*
≥10	4	18	22		
Total	*120*	*110*	*230*		

Most of the participants were normotensive (80.87%). Isolated systolic hypertension (HT) was not found in any patient. The percentages of cases with diastolic and combined systolic and diastolic HT were higher in Micral positive group (72% and 68.42% respectively), than in Micral negative .

As shown from table (5), the majority of cases were within the normal range of the BMI (86.08%). While those classified as abnormal BMI subdivided further into at risk (8.52%) followed by the underweight (4.32%), and the overweight (1.08%). Comparisons between Micral +ve and -ve cases with regard to normal and abnormal BMI (including overweight, underweight, at risk), were statistically not significant.

Table (4): Distribution of the studied sample regarding Micral test results and Blood pressure.

Clinical Characteristics		Micral test		Total	X^2-test	*P. value*
		- ve	+ve			
Normal BP		107	79	186	11.220 DF = 2	*0.004*
Hypertension	**Diastolic HT**	7	18	25		
	Systolic and Diastolic HT	6	13	19		
	Total	*120*	*110*	*230*		

Table (5): Distribution of the studied sample regarding Micral test results and BMI.

BMI	Micral Test			X^2-test	*P value*
	+ve	-ve	Total		
Normal	106	92	198	1.057 DF = 1	*0.304*
Abnormal	14	18	32		
Total	*120*	*110*	*230*		

Table 6 shows that more than half of the participants had poor glycemic control (58.69%) with the poorest level of HbA1c documented in Micral (+ve) cases (65.45%), compared to Micral (-ve) cases, (29.16%), the difference was statistically significant.

There were no statistically differences in the means of serum creatinine and blood urea in both groups as shown in table 7.

Table (6): Distribution of the studied sample regarding Micral test results and different HbA_{1c} levels

HbA_{1c}%	Micral Test II		Total	X^2-test	*P-value*
	(-ve)	(+ve)			
Good	35	10	45	14.802 DF = 2	*0.001*
Fair	22	28	50		
Poor	63	72	135		
Total	*120*	*110*	*230*		

Table (7): Distribution of the studied sample regarding Micral test results and S. creatinine and blood urea levels.

Bl. level Mg/dl	Micral Test		t-test	*P value*
	+ve Mean ± SD	-ve Mean ± SD		
S. creatinine	0.878 ± 0.157	0.882 ± 0.114	0.004	*0.9987*
Bl. urea	27.57 ± 8.55	26.60 ± 7.14	0.9293	*0.3537*
Total	*120*	*110*	*230*	

Discussion

Diabetic Nephropathy (DN) is the major life-threatening complication of DM and occurs in 20-40% of the patients, it is the single cause of end stage renal disease (ESRD). The first manifestation of DN is an increase in the urinary albumin excretion (UAE) in the range of 20-199 mg/L in (spot) early morning urine sample or 30-299mg/24 hr. or 300microgram per minute termed as micro-albuminuria (MA).[27]

MA strongly predicts DN, the progression of which may be reduced or prevented by early detection. However once MA appears the fatal outcome is predictable [28], therefore, a crucial goal in prevention would be to demonstrate factors early during the disease which may indicate the progression to MA and then to the ESRD [6].

The prominent finding of the current study was the detection of MA in 110 out of 230 patients (47.82 %), this result exceeded the figures reported by some of the previous studies.[17, 29, 30], but less than Hana T., in which she found 48.70 % of DM patients had MA [20]. Of substantial concern is the marked variability in the occurrence of MA among DM patients in previous studies (range from 12.7% to 42%). A number of complex variables could have accounted for those differences including study location, background genetics, population, selection criteria, MA definition, methods of laboratory investigation, and other factors. The other reason for such discrepancy in the occurrence of MA among different countries may be attributed to a more defective diabetic control in DM patients, which may be related to many factors: As the type of insulin regime (conventional or intensive), dietary management, exercise, and the cornerstone of management "patient's education".

In this study we use Schwartz formula to estimate the GFR. The method is easy and convenient for both the investigator, and the patient, with the advantage of rapid determination of the GFR, reasonable accuracy, less invasive than other methods, and the avoidance of urine collection, especially for age groups like those enrolled in this study [31, 32, 33]. Several previous cross sectional and prospective studies have demonstrated that hyper filtration is frequently detectable DM patients [18,25,32] In this study

18.69% of the patients had increased levels of GFR (Hyper filtration), which was in accordance with the results reported by Hana and Rajic et al.[20,34].

In other prospective studies almost two-thirds of the patients had hyper-filtration [35, 36]). Out of the 43 hyper filtrating patients, 26 (60.46%) were micro-albuminuric, implying a hyper filtration process even before the appearance of MA, a finding which may indicate that elevated GFR is an early process in the pathogenesis of DN in DM patients. Those patients with hyper filtration may be at particular risk of developing DN,[18] hence detecting hyper filtration at an early stage may be of prime importance.[14]. Askar[18] reported that the mean GFR was significantly higher in normo-albuinuric patients than in the control and micro-albuminuric groups.

Rudberg et al.[35] and Dahlquist et al.[37] reported that half of the hyper filtrating patients developed MA, the same result found by Askar[18] which indicates that glomerular hyper filtration increases the risk of developing MA (Incipient Diabetic Nephropathy).

In a two retrospective studies done by Mogensen,, [38] Mogensen, and Christensen,[39] as well as a follow-up study by Chiarelli et al,[33] they showed a strong prediction value for hyper filtration on the occurrence of MA.

Duration of diabetes was one of the most important factors for development of DN [13]. The MA was significantly associated with increased duration of DM. These results were in agreement with the findings of the other studies [18,20,35,37]. Bangstad et. al.[40] found that their patients developed hyperfilitrate after two and a half years from the onset of T1DM, and MA after 3-5 years. Rudberg et al.[35] recorded that high GFR after more than 8 years of diabetes predicted the development of nephropathy independently of the degree of metabolic control. These results indicate that the elevated GFR in T1DM even in the stage of normo-albuminuria can be an important risk factor for future MA and DN[35]. Warran et al. [41] reported that 6% of their patients developed MA within 1-3 years of diabetes, but they suggested that there is a rapid increase during two intervals, 1st and 3rd decade of DM. Thus the results indicate that MA does occur in TIDM patients with duration less than 5 yrs especially with poor glycemic control.

It was shown from this study 44 of the 230 T1DM patients (19.13%) had hypertension, a finding which approximates the results of an Iraqi study done by Dahar [17] but is higher than another Iraqi study done by Askar[18] in which he documented 7% of his patients had hypertension. Abdullah et al.[42] found 5.3% of the T1DM Yemeni patients had hypertension, while in a longitudinal study performed by Parving et al.[43] 30% of the T1DM were found to have hypertension. In all the above studies, including ours, the association between HT and presence of MA was significant indicating HT is an important risk factor for DN.

Regarding BMI, the majority of cases were within the normal range of the BMI. No significant difference was found between Micral +ve and -ve groups (between patients with and without MA), this result was in agreement with Atiya[16] and Abdullah et al.[42].

In this study 65.45% of the Micral (+ve) group had the poorest level of HbA1c, this result was in agreement with the studies.[20,29,35,41,45]. Glycemic control is one of the important predictors of development of MA in TIDM patients, as a risk factor for the onset and progression of MA.[4,8,11]. The famous DCCT study,[44] came to the conclusion that in both the primary and secondary-prevention component of that trial, the patients who received intensive treatment had a statistically significant reduction in the cumulative incidence of MA as compared with the patients who received conventional treatment , the distinctly different risk factors of MA in patients with low HbA1c value, and those with high values suggest that diabetes damage the kidney through several mechanisms. The mechanisms operating below the threshold HbA1c values of less than 8.1 percent seem to be independent of the level of hyperglycemia and may be influenced by other components of the diabetic milieu for example, abnormalities in plasma insulin concentrations. At high blood glucose concentrations, MA is most likely caused by deleterious effects of hyperglycemia on cell functions and extracellular structures such as the basement membrane and mesangial matrix.

There was no significant difference in the means of S. Creatinine and blood urea in the two studied groups (Micral positive and negative), this result was similar to the results of Finne P. et al.[45], where he stated that although there was a decrease in GFR, the S. Creatinine remained normal, the same result was found by Svensson et al.[46].

Chiarelli et al.[33] reported that S. Creatinine remain unchanged both in T1DM patients with normal or raised GFR, and in all T1DM patients S. Creatinine values were within the normal range, which is consistent with the current study. The reason for this result, as stated by the clinical practice guidelines for chronic kidney disease [31], GFR must decline to approximately half the normal level before the S. Creatinine concentration rises above the upper normal limit.

The conclusion of this study is MA manifested by increased urinary albumin excretion was encountered in 47.82% of our teenage DM patients showing significant association with hyper

filtration state, increasing level of HbA1c, and hypertension, but not gender, or body mass index. The blood urea and S creatinine remain unchanged in early state.

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