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Early-onset microalbuminuria in children with type 1 diabetes in Kuwait.

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Abstract

Background and Aims: Kuwait has the third highest incidence rates of Type 1 Diabetes Mellitus (T1DM) in the world, which makes diabetic complications more likely. The aim of this study is to identify the prevalence of diabetic nephropathy among our pediatric population and its risk factors.

Methods: A total of 302 TIDM patients <15 years of age diagnosed at Mubarak Al-Kabeer hospital from January 2008 to December 2015 were recruited. Their demographic, clinical and biochemical data were reviewed including age, duration of diabetes, gender, Blood pressure, HBA1c, serum creatinine, microalbuminuria (MA), macroalbuminuria and eGFR.

Results: the Mean age of patients at diagnosis was 11.2 ± 3.6 years and the male to female ratio was 48:52. The duration of disease was <5 years in 65% and the mean serum creatinine was 42.2 ± 15.8 µmol/L and mean eGFR was 183.7 ± 54 mL/min/1.73 m^2. A total of 17 out of 140 patients had MA (12.1%). The majority (66%) of albuminuric patients had the disease for less than 5 years.

Macroabuminuria was reported in 1 patient (0.07%). Chronic kidney disease was not reported in any of the patients. Compared to normoalbuminuric patients, more female patients were Albuminuric (83%vs. 50%, *P*<0.01), had a significantly higher mean systolic blood pressure centiles (88.6 ± 5.9 vs. 76.7 ± 23.9, *P*<0.0001), higher mean diastolic blood pressure centiles (88.0 ± 5.2 vs. 69.4 ± 22.3, *P*<0.0001) and a higher mean HbA1c levels (13.8 ± 1.5% vs. 9.3 ± 2.0 *P*<0.0001).

Conclusion: Early-onset MA and hyper filtration are common in T1DM patients in Kuwait. Involvement of pediatric nephrologists in the care of T1DM patients should be considered in an attempt to prevent progression of DN.

Keywords: Type 1 diabetes mellitus, Microalbumiburia, Hyperfiltration, Chronic kidney disease.

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Introduction

Diabetic Nephropathy (DN) is one of the major microvascular complications of diabetes in types 1 and 2 [1,2]. The pathophysiological changes in diabetic nephropathy in children include: hyper filtration, microalbuminuria (MA) and worsening of renal function due to cellular and extracellular derangements in both glomerular ad tubule-interstitial compartments [3]. Subsequently, this may lead to End-Stage Kidney Disease (ESKD) in early adulthood requiring renal replacement therapy [4].

MA is considered one of the earliest markers of kidney damage and therefore should be monitored regularly in any diabetic patient. MA is rare to occur before onset of puberty even in diabetics with a long-standing disease [5,6]. Most endocrine units, which manage the care of children with T1DM, follow the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association's (ADA) guidelines in monitoring diabetic complications including nephropathy. The guidelines recommend that annual screening for MA should start at the age of 10 or at the onset of puberty if earlier or after 2-5 years of having diabetes [7-9]. Unfortunately,

these guidelines underestimate the risk of DN in patients younger than that recommended age or at diagnosis in young patients. T1DM is considered to be the result of a complex interplay between predisposed genes, immune system mediators, nutritional and environmental factors. Therefore, it is not surprising to find a wide variation in the incidence of T1DM in different populations. In our geographic area where consanguinity rate and first-cousin marriages are common cultural norms, genetic susceptibility to the disease remains an important factor in determining the course and the severity of T1DM including its complications [10].

In consistence with the global significant increase in incidence of T1DM of almost 3% per year, epidemiologic studies reported Kuwait to have the highest incidence of T1DM in the middle East among children ages <15 years and ranked it third in the international incidence rates of T1DM [11-13]. Therefore we anticipate a parallel increase in the rate of complications, including DN. This single-center study reports the prevalence of diabetic nephropathy in children with T1DM in Kuwait and explore the risk factors associated with it.

Patients and Methods

In this retrospective single-center study, all children <15 years of age diagnosed with T1DM at Mubarak Al-Kabeer University hospital between January 2008 and December 2015, were included. All subjects were registered in the pediatric department's registry and diagnosis of the disease was confirmed by a pediatric endocrinologist per the ISPAD and the American Diabetes Association guidelines [7,8]. Demographic, clinical and laboratory data of all patients was extracted from patients' medical records. Their data included age, gender, nationality, age at diagnosis and at the time of study, duration of T1DM, family history of T1DM. Blood pressure measurement, height and weight were extracted from the medical records, as well. Missing data was completed by calling the patients for a recent OPD visit. Glycemic control was assessed by mean level of HbA1c (%), fasting blood glucose (mmol/L) and number of Diabetic Ketoacidosis (DKA) admissions. Markers of renal involvement included microalbuminuria (mg/24 h), serum creatinine (µmol/L) and estimated Glomerular Filtration Rate (eGFR: ml/min/1.73m^2) calculated using the Schwartz formula [14].

According to the American Diabetic Association, any patient with microalbuminuria was considered to have an early stage diabetic nephropathy [8]. Microalbuminuria was defined as albumin/creatinine ratio of 2.5-25 mg/mmol in Males and 3.5-25 mg/mmol in Females, or albumin excretion rate (AER) of 30-300 mg/24 h on 2 out of 3 early morning urine samples within 3-6 months of the first positive urine test [7]. The urine culture was checked concomitantly to exclude urinary tract infection as a cause of albuminuria. MA was checked using Immage immunochemistry System (Beckman Coulter-Washington DC-USA). Macro-albuminuria was defined as AER>300 mg/day [7]. Hyperfiltration was defined as eGFR>120 ml/min/1.73m^2 in children <12 years of age and >130 ml/min/1.73m^2 in children older than 12 years [15].

Blood pressure readings (mmHg) were obtained from the patients' medical records as it is usually checked by a trained nurse. BP measurements and interpretation of systolic and diastolic readings were expressed as BP percentiles (%) according to age and gender as per the fourth report on diagnosis of high blood pressure in children and adolescents 2004 [16]. All patients received treatment with multiple insulin injections with long acting insulin (Lantus) and short acting insulin (Novorapid) or regular Actrapid. Insulin was given in a dose of 0.7-1.0 IU/Kg/day in prepubertal children and 1.2-2 IU/Kg/day in pubertal patients as per ISPAD guidelines. A total of 132 patients were shifted to insulin pumps during the course of the disease. No patient was on Continuous Glucose Monitoring (CGM) as it was not popular among children.

Statistical Analysis

The data was analyzed using the Statistical Package for the Social Sciences version 23 (SPSS, Chicago IL, USA). Data of the different groups of subjects were presented as mean ± SD and comparison between studies groups were made by using Fisher's Exact test, chi-square or student *t*-test. The *P*-values were considered significant when <0.05. A Pearson correlation test was used to assess correlation between groups.

Results

From a total of 302 patients, Males constitutes 48% (n=145) and females 52% (n=157). The mean age of patients at the time of study was 11.2 ± 3.6 years (range: 1.7 to 15.0 years) and the mean age at onset of the disease was 7.4 ± 3.2 years (range: 1 month to 13.8 years). Mean duration of T1DM was 3.9 ± 2.4 years and 65% of patients had the disease for less than 5 years while the rest had it for 5-10 years. No patient had the disease for more than 10 years. Family history of T1DM was reported in 15.6%. Mean HbA1c level was 9.6 ± 2.3%. No significant difference was found when comparing mean HbA1c Levels in patients with disease duration of more and less than 5 years (*P*=0.484). The mean serum creatinine was 42.2 ± 15.8 µmol/L and hyper filtration was reported in 87% of the total patients with a mean eGFR of 183.7 ± 54 ml/min/1.73m^2.

Microalbuminuria was documented in 17 out of the 140 (12.1%) patients who had a urine test for microalbuminuria as per ISPAD and ADA guidelines, whereas only one patient (0.07%) had macroalbuminuria. The single patient who had macroalbuminuria was a 13 year old female who had the disease for more than 5 years with a poor glycemic control (mean HbA1c=13.6%) and was receiving daily insulin injections with poor compliance. No patient had chronic kidney disease. Table1 summarizes the

demographic and clinical data of all patients. Stratifying patients into two groups according to the presence of albuminuria, albuminuric patients (both with MA and macroalbuminuria) were found to have more Female patients (83%) compared to normoalbuminuric group (50.7%) ($P<0.01$). Moreover, albuminuric patients had a higher mean HbA1c (13.8 ± 1.5 vs 9.3 ± 2.0, $P \leq 0.0001$), higher mean systolic blood pressure percentiles

(88.6 ± 5.9 vs. 76.7 ± 23.9, $P=0.0001$) and higher mean diastolic blood pressure percentiles than normoalbuminuric patients (88.5 ± 5.0 vs. 69.4 ± 22.3, $P \leq 0.001$). No significant difference in eGFR was found between the two groups ($P=0.10$). Table 2 summarizes the results comparing the clinical and biochemical data of the two groups. Using Pearson regression analysis, no significant correlation was found between MA and HbA1c (r=0.032, P=0.711).

Discussion

Despite the increasing incidence of T1DM globally, the trend over the past decade was that the incidence of DN has become substantially lower than reported historically due to the new advancements in DM management including insulin pumps. In this study we reported a high prevalence of diabetic nephropathy among T1DM patients, which was around 12%. Compared to international rates, this result was far more than reported in many countries worldwide including 3.3% in USA in 2015, 5% in UK and 3.3% in German diabetic children [17-19]. These were comparable to 13% reported in west Australian children with T1DM and 13.4% reported in Indian children [20,21].

Numerous previous reports had supported that diabetic nephropathy, as other microvascular complications, only started after 5 years of onset of T1DM [8]. It was rare before puberty even in diabetics of long disease duration [5,6]. The increased risk of MA as the earliest sign of DN was related to diabetes duration, therefore the American Diabetic Association, ISPAD and Kidney Disease [22-24]: Improving Global Outcome (KDIGO) guidelines have recommended that annual screening for microalbuminuria should only be done after 5 years of diagnosis of T1DM [7-9]. However, according to our results, 65% of patients with diabetic nephropathy had T1DM for less than 5 years. This interesting finding, which is peculiar to our population, raises many queries regarding the need for early and more frequent screening for MA irrespective of age or duration of the disease. It is not clear whether this early-onset MA progresses to macro albuminuria or not as a long term studies are still lacking. The need for nation-wide and larger scale studies are essential to assess the cost-effectiveness of such early and frequent screening.

Poor glycemic control is a well-known risk factor of diabetic nephropathy. The finding of a higher mean HbA1c in our albuminuric patients which supports the fact that MA is, most likely, due to poor glycemic control. Nevertheless, it is believed that the accelerated early-onset DN cannot solely be explained on the basis of poor glycemic control and other factors, such as genetic and environmental, might play a major role in its pathogenesis.

Despite the high prevalence of microalbuminuria in our patients, the incidence of Macro albuminuria in our patients was low. This is not surprising as many studies had shown that microalbuminuria was proved to be a dynamic process when it develops, it can remain static, advance towards proteinuria, but most frequently it regresses towards normal levels of albumin excretion [25-29]. In previous studies, Perkins et.al. had shown that MA was likely to remit in 50% of case over 6 years, whereas the risk of progression to proteinuria was only 15% [30]. The mean duration of follow-up in our patients was not long enough to check for remission or reversibility of MA in our patients. As macroalbuminuria was found to be

Table 1. *Demographic and clinical data of patients with type1 diabetes mellitus*

Demographical data:	
Total Number	302
Gender: Male	145 (48.0%)
Female	157 (52.0%)
Nationality: Kuwaiti	186 (61.6)
Non-Kuwaiti	116 (38.4%)
FHx of T1DM	47 (15.6%)
FHx of HTN	139 (46.0%)
Mean age at study (years)	11.2 ± 3.6
Mean age at diagnosis of T1DM (years)	7.4 ± 3.1
Mean duration of T1DM (years)	3.9 ± 2.4
Diabetic control signs:	
Mean FBG (mmol/L)	12.1 ± 6.0
Mean HbA1c (%)	9.6 ± 2.3
Mean no. of DKA admissions	0.6 ± 1.1
Microalbuminuria (mg/day)	16.0 ± 91.2
Abbreviations: FHx: Family History; T1DM: Type 1 Diabetes Mellitus; HTN: Hypertension; FBG: Fasting Blood Sugar; HbA1c: Hemoglobin A1c; DKA: Diabetic Ketoacidosis	

Table 2. *Demographic and clinical characteristics of T1DM patients with and without albuminuria*

	Normoalbuminuric group (n=284)	Microalbuminuric and Macroalbuminuric group (n=18)	*P*-value
Demographical data			
Gender (M/F)	140/144	13 May	0.09/0.09
Nationality (K/NK)	175/108	7 Nov	1.00/1.00
FHx of T1DM	43 (15.1%)	4 (22.2%)	0.49
FHx of HTN	131 (46.1%)	8 (44.4%)	1
Mean age at study (years)	11.2 ± 3.6	11.9 ± 3.1	0.42
Mean age at diagnosis of T1DM (years)	7.3 ± 3.2	7.6 ± 3.0	0.69
Mean duration of T1DM (years)	3.9 ± 2.4	4.3 ± 1.9	0.48
Signs of diabetic control:			
Mean FBG (mmol/L)	12.2 ± 6.0	14.1 ± 5.4	0.19
Mean HbA1c (%)	9.3 ± 2.0	13.8 ± 1.5	<0.0001
Mean no. of DKA admissions	0.6 ± 1.1	1.1 ± 1.5	0.18
Blood Pressure			
Systolic blood pressure percentile (%)	76.7 ± 23.9	88.6 ± 5.9	<0.0001
Diastolic blood pressure percentile (%)	69.4 ± 22.3	88.0 ± 5.2	<0.0001
Lipids			
Total Cholesterol (mmol/L)	4.6 ± 1.0	4.9 ± 1.1	0.22
LDL (mmol/L)	2.7 ± 0.7	3.0 ± 0.9	0.08
HDL (mmol/L)	1.4 ± 0.4	1.4 ± 0.2	1
TG (mmol/L)	1.2 ± 1.8	0.9 ± 0.7	0.13
Kidney function markers			
eGFR (ml/min/1.73M^2)	182.5 ± 53.7	204.0 ± 54.4	0.1
Creatinine (µmol/L)	42.5 ± 16.0	38.1 ± 11.8	0.25
Urea (mmol/L)	3.6 ± 1.5	3.3 ± 1.2	0.4

Abbreviations: M: Male; F: Female; K: Kuwaitis; NK: Non-Kuwaitis; FHx: Family History; T1DM: Type 1 Diabetes Mellitus; HTN: Hypertension; FBG: Fasting Blood Sugar; HbA1c: Hemoglobin A1c; DKA: Diabetic Ketoacidosis; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglyceride; eGFR: Estimated Glomerular Filtration Rate

rare in our subjects (0.07%), chronic kidney disease was subsequently not reported in any patient. CKD develops in late stages of DN after a long-standing disease, which was not applicable to any of our patients as none of them had the disease for more than 10 years duration. Higher levels of eGFR correlate with the presence of glomerular hyper filtration, a pathological stage of diabetic nephropathy that is powerful predictor of adverse outcomes [31]. It is associated with incipient loss of kidney function as well as higher risk of mortality [32,33].The estimated glomerular filtration rate (eGFR) is hypothesized to be a precursor of intra-glomerular hypertension preceding albuminuria by many years and subsequently leading to it [15,34]. In this study, hyper filtration rate was reported to be 87%, which was higher in albuminuric patients than those without it. This prevalence is much higher than the commonly reported rate in many studies which usually ranges from 40-60% [35].

Male gender was found to be a risk factor for diabetic nephropathy in adult diabetic patients while female gender was a risk factor in adolescent patients with T1DM [36]. Studies on German and Swiss children with T1DM concluded that male gender is a risk factor of DN [37,18]. Our finding was inconsistent with previous studies as DN was found to be more common in females in their pre-adolescent age. Females constitute almost half of our studied population (52%); therefore, this result cannot be attributed to gender bias in recruited patients.

DN is believed to be a multifactorial disease and it appears that multiple pathways interact and are involved in a process that is likely genetically regulated [10,38-39]. Therefore, further studies to elucidate any association of DN in our Arab population with specific genetic factors such as ACE gene D/D polymorphism or HLA typing is warranted.

Since the major part of this study was retrospective, we faced many limitations such as the difficulty to retrieve some of the patients' data. Some patients had to be called to complete missing data or BP readings. Some patients were transferred to the adult medical care and therefore had to be followed up at the medical side.

Conclusion

Early-onset MA and hyper filtration are both common complications in pediatric population with T1DM. Female gender and poor glycemic control were found to be major risk factors of DN in our patients. Early screening for MA starting at time of diagnosis is recommended to avoid further complications. Involvement of pediatric nephrologists early in the care and management TIDM patients should be considered in an attempt to prevent progression of diabetic nephropathy. Further studies at a larger scale are warranted to clearly define the factors leading to early DN in our pediatric population.

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Ethical Approval

This study was approved by the Joint Committee for Protection of Human Subjects in Research of the Faculty of Medicine, Kuwait University and Kuwait Institute of Medical Specializations (KIMS), Ministry of Health, Kuwait. Informed consent was obtained from the study subjects and/or their care givers as per regulations of the Ethics Committees.

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