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Frequency of Diabetic Nephropathy in Diabetic Children and Adolescents at Children Hospital of Zagazig University

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Abstract
Background:Diabetic kidney disease (DKD) is defined as kidney disease attributed to diabetes. Diabetic nephropathy (DN) is a common micro vascular complication of diabetes .DN develops in 15-20% of subjects with T1DM and in similar or higher percentage of T2DM patients, causing increased morbidity and premature mortality. American Diabetes Association (ADA) recommends screening for nephropathy 5 years after diagnosis for type 1 diabetes and at diagnosis for type 2 diabetes.Aim: To estimate the occurrence of diabetic nephropathy in children and adolescent diagnosed with diabetes Method: A case control study was carried on one hundred and fifty of children went to pediatrics clinics of zagazig university hospital. They were classified in to 75 diabetic children who were type 1DM for more than 4 years and their age less than 18 years old and 75 non diabetic children of the same gender and age. Both groups under go full history, clinical and laboratory investigations during the period from December 2018 to November 2019. Result: frequency of persistent microalbuminuria and hypertension among diabetic patients were 293 per 1000 and 160 per 1000patient respectively.Conclusion: Type1 diabetic children and adolescent are liable for the occurrence of early diabetic nephropathy so intensive diabetes therapy is needed, regular screening for MA and measurement and interpretation of BP and GFR
Key words: diabetes,diabetic nephropathy,microalbuminuria

Introduction: Type 1 diabetes mellitus (T1DM) commonly occurs in childhood or adolescence, although the rising prevalence of type 2 diabetes mellitus (T2DM) in these age groups is now being seen worldwide **(Bogdanović, 2008).**DKD is defined as kidney disease attributed to diabetes (versus chronic kidney disease, which may have numerous etiologies, including diabetes), **(ADA, 2015).**Diabetic nephropathy (DN) is

a common micro vascular complication of diabetes **(Lee et al., 2012).**DN develops in 15-20% of subjects with T1DM and in similar or higher percentage of T2DM patients, causing increased morbidity and premature mortality **(Bogdanović, 2008).**DN is a clinical syndrome characterized by the following: Persistent albumin-to-creatinine ratios >30 mg/g creatinine on three separate occasions is a useful marker of diabetic nephropathy **(ADA, 2015).** Progressive decline in the glomerular filtration rate (GFR) **(Tang et al., 2016).** Elevated arterial blood pressure (**Tang et al., 2016).**The American Diabetes Association recommends screening for nephropathy 5 years after diagnosis for type 1 diabetes and at diagnosis for type 2 diabetes. Screening includes urine albumin excretion (mg/g creatinine) **(ADA, 2015).**

Patients and methods:A case control study was carried out at Pediatric Endocrinology Unit of Children Hospital and Outpatient Pediatric Endocrinology Clinic ofZagazig University Hospital. The study was carried on150 child and adolescent over a period of one year from December of 2018to November 2019 after approval by the ethical committee of Zagazig University and informed consent was obtained from all parents. Children and adolescent were classified into two groups:

1-Diabetic group: This group comprised 75 children and adolescent primary diagnosed as diabetics. They were admitted for diagnosis, treatment and follow up at Pediatric Endocrinology Unit of Children Hospital and Outpatient Pediatric Endocrinology Clinic of Zagazig University Hospital. They were 38 (50.7%) males and 37(49.3%) were female. Their ages had a range from 6 to 15 years. Age of onset had a range 1-10 y. Positive family history were present in 20(26.7%) of children and adolescent.

2-Control group: This group comprised 75 of apparently healthy children andadolescentof comparable age and gender .They were attended at Pediatrics Outpatient Clinic of Zagazig University for preoperative evaluation for elective surgery.

Inclusioncriteria:

1-All children and adolescent of primaryDM.

2-Age of cases less than 18years.

3-Duration of DM more than 4years.

Exclusion criteria:

1- Newly diagnosed cases of primary DM.

2-Duration of DM less than 4 years

3- Patients of secondary DM.

4- Patients of Type 2 DM

All diabetic children and adolescents enrolled in the study will be subjected to the following:

1-Complete history taking asregarding: Age &sex, Family history of DM and renaldiseases, Onset of disease, course and admission to hospital byDKA, Initial

symptoms of DM (polydipsia, decreased weight, polyuria, diurnal and or nocturnal enuresis, urinary tract infection, fever, RD), Medications (Insulin therapy, antihypertensive drugs and vitamins).

2-Thorough clinical examination including: Weight , height and body massindex, Bloodpressure., Type of insulin therapy &control of bloodsugar., Laboratory investigation, including: Fasting and postprandial bloodsugar, Urineanalysis, Complete blood picture., Liver function test: Total protein and albumin, Kidney function test: blood urea nitrogen, creatinine,-Urine albumin-to-creatinine ratio., Hb-A1C, Estimated GFR.

Blood samples: Venousbloodwascollectedfromeachsubjectafter12hoursfastingby cleanvenipunctureusingdisposableplasticsyringeandsubsequentlydivided into:1ml of blood was taken on EDTA tube, ethylene diamine tetra-acetic salt (1.2mg/mL) as an anticoagulant, it was used for the glycosylated hemoglobin 3ml of blood was taken on plain tube (without anticoagulant) for serum separation. The tube was left at room temperature for 30 minutes till coagulation, and then was centrifuged (at 1500 rpm for 15 minutes). The resultant serum was used for clinical chemistry tests.

Clinicalchemistry tests:Fastingbloodglucose (mg/dl), CBC, Albumin, Total protein, Urea, Creatinine (mg/dl).

Analytical Methods: The followingtestswere done usingBiosystemA15auto-analyzer by appropriate chemicalprinciples:

1. **Blood glucose Level:**By glucose oxidase enzymatic colorimetric method, in which oxidation occursinthe presence of glucose oxidase***(Carlet al.,2006)***.
2. **Creatinine:** Bymodified Jaffé reaction. ***(Myersetal.,2006)***.
3. **Glycosylated hemoglobin (HbA1c):**Determinationofglycohemoglobinwasdone inbloodbyIonExchange Resinmethod.Glycosylatedhemoglobinhasbeendefinedoperationallyas thefastfractionhemoglobinsHbA1(HbA1a,A1b,A1C)whichelutefirst during+columnchromatographyasit employsaweakbindingcationexchange thannon-glycosylatedhemoglobin.TheratiooftheabsorbanceofHbA1c and totalHbofthecontrolandtestisusedtocalculatethepercentHbA1cofthe samplebyusingspectrophotometryat415nm***(Nathan etal.,1984).***

Statistical analysis

The collected data were computerized and statistically analyzed usingSPSS program (Statistical Package for Social Science) version 24.0 (SPSSInc., 2007). For the statistical calculations data coding was done. Qualitative (categorical) data were represented as frequencies and percentages, Chi -Square test (χ^2) and fisher exact test were carried outfor testing the association between the qualitative data frequencies. Quantitative (numerical) data were represented as mean and standard deviation (SD), student's t-test was used to detect difference between groups which were normally distributed or median and inter quartile ranges (IQRS), Mann-

Whitney test was used to detect the difference between groups which were not normally distributed.

The test results were considered significant when p-value ≤ 0.05, highly significant when p-value ≤ 0.01 and non-significant when p-value > 0.05 .All p values are two-tailed. **(Levesque, 2007)**

Cutoff level: The median value of control was used as the cutoff level.

Results: In the current study, age of patients was ranged from 6 to 15years with mean 10.5years. Age of onset was ranged from 1 to 10 years with mean 4.38 years and duration of disease more than 4 years.

There was a no significant difference between the studied groups regarding gender or age. (**Table1**)

There was a highly significant difference between the studied groups regarding weight and BMI. There was a statistically non-significant difference between the studied groups regarding height.**(Table2**)

Age of onset of diabetes among patients in our study ranged from 1 to 10 years with mean 4.38 and number of DKA ranged from 0 to 3 times. (**Table3**)

Positive family history for DM group was 20 (26.7%) of children and adolescent included in study. (**Table3**)

Persistent microalbuminuria for DM group was present for 29.3% of children and adolescent included in study.(**Table3**)

Prevalence of persistent microalbuminuria among diabetic patients as one of clinical nephropathy**=** (patients with persistent microalbuminuria/ Total diabetic patients) *1000**=** 22/75*1000=293/1000 ***(Table3)***

Hypertension for DM group was present for 16 % of children and adolescent included in study.

Prevalence of hypertension among diabetic patients as one of clinical nephropathy = (patients with hypertension/Total diabetic patients) *1000= 12/75*1000=160/1000 ***(Table3)***

There was a highly significant difference between the studied groups regarding fasting blood glucose and glycosylated hemoglobin (significantly higher in diabetic group).(**Table 4**)

There was a no significant difference between the studied groups regarding hemoglobin. There was a highly significant difference between the studied groups regarding TLC and platelet count (significantly higher in Control group).(**Table 5**)

There was a significant difference between them regarding serum albumin, total protein, BUN and eGFR. There was a non-significant difference between the studied groups regarding serum creatinine. (**Table 6**)

There was a significant difference between the studied groups regarding serum triglycerides, total, HDL and LDL cholesterol. (**Table 7**)

Table (1): Comparison between studied groups regarding demographic characteristics:

Demographic characteristics	Groups		Test	
	Diabetic group N=75 (%)	Control group N=75 (%)	χ^2/t	P
Gender:				
Male	**38 (50.7)**	**48 (64)**	**2.725**	**0.099**
Female	**37 (49.3)**	**27 (36)**		
Age (years):				
Mean ± SD	**10.56 ± 2.61**	**10.44 ± 2.31**	**0.307**	**0.758**
Range	**6 – 15**	**7 – 15**		

t Independent sample t testχ^2Chi square test

There is statistically non-significant difference between the studied groups regarding gender or age

Table (2) Comparison between the studied groups regarding anthropometric measures:

Measurements	Groups		Test	
	Diabetic group	Control group	T	P
Weight (kg):				
Mean ± SD	**36.53 ± 7.74**	**33.2 ± 9.24**	**2.395**	**0.018***
Range	**24 – 53**	**22 – 51**		
Height (cm):				
Mean ± SD	**138.65 ± 11.9**	**133.4 ± 19.87**	**1.694**	**0.052**
Range	**108 -161**	**100 – 160**		
BMI(kg/m^2):				
Mean ± SD	**19.35 ± 1.44**	**18.6 ± 2.06**	**2.573¥**	**0.011***
Range	**16.5 – 22.6**	**16.3 – 22**		

¥Mann Whitney test t independent sample t test

Table (3) Distribution of patients according to disease-specific criteria:

	N=75
Age of onset(/year):	
Mean ± SD	**4.387 ± 2.508**
range	**1 – 10**
Number of DKA:	
Median	**0**
Range	**0 – 3**
Family history:	
negative	**55 (73.3)**
positive	**20 (26.7)**

Persistent microalbuminuria(mg/dl):	
Negative	**53 (70.7)**
Positive	**22 (29.3)**
Hypertension(mmhg):	
Negative	**63 (84)**
Positive	**12 (16)**

Table (4) Comparison between the studied groups regarding glycemic profile:

Glycemic profile	Groups		Test	
	Diabetic group	Control group	T	P
Fasting blood sugar (mg/dl)				
Mean ± SD	**135.12 ± 8.47**	**87.08 ± 14.3**	**16.306**	**<0.001****
Range	**126 – 255**	**65 – 126**		
HbA1c(mmol/mol):				
Mean ± SD	**6.97 ± 0.35**	**5.55 ± 0.56**	**18.622**	**<0.001****
Range	**6.6 -7.9**	**4.3 – 6.3**		

t Independent sample t test

Table (5) Comparison between the studied groups regarding CBC:

CBC	Groups		Test	
	Diabetic group	Control group	T	p
Hemoglobin (g/dl)				
Mean ± SD	**11.78 ± 1.27**	**12.09 ± 0.99**	**-1.659**	**0.099**
Range	**8 – 13.5**	**9.9 – 13.5**		
TLC (10^3/ mm^3):				
Mean ± SD	**5.27 ± 1.93**	**6.19 ± 1.44**	**-3.309**	**0.001****
Range	**2.5 -9.5**	**2.2 – 9.5**		
Platelet count(10^3/mm^3):				
Mean ± SD	**301.19 ± 95.51**	**344.81 ± 87.55**	**-2.917**	**0.004***
Range	**130 -550)**	**80 –550**		

Z Mann Whitney test t independent sample t test

Table (6) Comparison between the studied groups regarding liver and kidney function tests:

Parameters	Groups		Test	
	Diabetic group	Control group	T	P
Total protein (g/dl)				
Mean ± SD	**6.08 ± 0.3**	**6.19 ± 0.81**	**-2.388**	**0.018***
Range	**5.5 – 6.8**	**5.8 – 6.6**		
Serum albumin (g/dl)				
Mean ± SD	**3.81 ± 0.44**	**4.05 ± 0.24**	**-4.082**	**<0.001****

Range	**3 – 4.5**	**3.5 – 4.6**		
Creatinine (mg/dL):				
Mean ± SD	**0.69 ± 0.11**	**0.68 ± 0.2**	**0.532**	**0.602**
Range	**0.5 – 0.9**	**0.3 – 0.9**		
BUN (mg/dL):				
Mean ± SD	**22.73 ± 8.49**	**19.16 ± 6.96**	**2.819**	**0.005***
Range	**11 – 53**	**12 – 43**		
eGFR (g/dl)				
Mean ± SD	**115.58 ± 8.56**	**121.96 ± 5.93**	**-5.309**	**<0.001****
Range	**101.06 – 138.6**	**110 – 131**		

Table (7) Comparison between the studied groups regarding lipid profile:

Lipid profile	Groups		Test	
	Diabetic group	Control group	t	p
Triglyce1rides (mg/dl)				
Mean ± SD	**159.59 ± 24.38**	**79.23 ± 11.69**	**25.738**	**<0.001****
Range	**92 – 198**	**65 – 100**		
Total Cholesterol (mg/dL):				
Mean ± SD	**228.8 ± 30.83**	**149.6 ± 17.27**	**19.408**	**<0.001****
Range	**160 – 280**	**125 – 188**		
LDL cholesterol (mg/dL):				
Mean ± SD	68.17 ± 10.84	42.76 ± 11.65	24.93	<0.001**
Range	50 –85	25 – 75		
HDL cholesterol (mg/dL):				
Mean ± SD	87.79 ± 5.05	161.56 ± 25.13	-13.831	<0.001**
Range	80 – 95	130 -550		

Discussion

DKD represents a major component of the health burden associated with type 1 and type 2 diabetes. Many patients with progressive DKD follow a classical albuminuria-based pathway **(Radcliffe et al., 2017).**

The average incidence of diabetic nephropathy is high (3% per year) during the first 10 to 20 years after diabetes onset (Magee et al., 2017). Typically, it takes 15 years for small blood vessels in organs like kidney, eyes and nerves to get affected. It is estimated that more than 20 and up to 40% of diabetic patients will develop CKD (Papadopoulou-Marketou et al., 2018).

The primary goal of diabetic nephropathy treatment is to prevent microalbuminuria from progressing to macroalbuminuria and an eventual reduction in renal function and associated heart disorders. Consequently, intensive glycaemic control,

antihypertensive treatment by blocking RAAS system and lipid-modifying statin therapy are the main cornerstones of treatment **(Oltean et al., 2017).**

Our study was designed to estimate the occurrence of diabetic nephropathy in children and adolescent diagnosed with diabetes.

In the current study, 38(50.7%) cases were male and 37(49.3%) were female. This denotes slightly dominance of male sex in agree with another study in Egypt carried by **Hassan et al., 2019** but with the highest percentage (66.6%) cases were male than female 10 (33.3%).

In the current study, age of patients was ranged from 6 to 15years with mean 10.5years. Age of onset was ranged from 1 to 10 years with mean 4.38 years and duration of disease more than 4 years. Our results were supported by Gardner et al., 1997 and Daneman et al.,1999,they reported that children under three to five years of age with type I diabetes comprise a small proportion of all those with this disorder. Less than 1% of all children are diagnosed in the first year of life, and less than 2% of children attending large pediatric diabetes centres fall into the under three-year age group. Although, other studies documented type 1DM can occur at any age, type 1diabetes has a bimodal distribution with one peak at 4 to 6 years of age and a second at early puberty (10 to 14 years of age) **Al-Herbish et al.,2008.**

Our study showed a highly significant difference between the studied groups regarding weight and BMI. **da Costa et al., 2016** supported our results, as children and adolescents with type 1 diabetes have risk of developing overweight/obesity and cardio metabolic risk factors. Monitoring weight gain is an important aspect in the care of children and adolescents with T1DM, especially among those of younger age and with higher doses of insulin.

Positive family history for our patients was 26.7% .In agree with **Šipetić et al., 2014** who supported our result and reported that risk of type 1 diabetes was significantly associated with a positive family history for type 1 diabetes.

Frequency of DKA in the present study was ranged from 0 to 3 from onset of disease known until time of study. The lower rates of DKA noticed in the current study compared to the previous reports may be due to better awareness of the disease by the community and easy access to health care. **Rewers et al., 2008** reported that frequency of DKA at the onset of the disease correlates inversely with the incidence of Type 1 diabetes and is more common if there is negative family history, poor socioeconomic conditions, less desirable health insurance coverage, and lower parental education. **Habib,2005** published in a local study done in the northwest of Saudi Arabia, DKA was diagnosed in 55.3% at the onset of the disease and girls were found to present in DKA more frequently than boys, with a ratio of 1.4:1.

Frequency of hypertension was 16% in present study as one of clinical syndrome of diabetic nephropathy. In agree with Downie and collages were reported that the prevalence of hypertension in children with type 1 diabetes to be between 6% and 16%. This potentially modifiable cardiovascular risk factor may go undiagnosed and

undertreated, particularly in children with type 1 diabetes. Recent updated Canadian clinical practice guidelines recommended blood pressure screening every 2 years in children with type 1 diabetes as well as routine use of ambulatory blood pressure monitoring. Risk factors for hypertension in type 1diabetes include poor glycemic control, overweight and obesity and genetic predisposition for hypertension (**Downie et al., 2018).**

Microalbuminuria has been established as an early marker of progressive kidney disease in diabetes starting at pediatric age and currently albumin excretion rate (AER) remains the best available noninvasive predictor for diabetic nephropathy and should be measured regularly according to established guidelines (**ADA,2018a).** In the current study revealed prevalence of persistent microalbuminuria was 293 per 1000 patient. Frequency of persistent microalbuminuria was 29.3% of diabetic patient included in study as one of clinical syndrome for diagnosis DN. In agree with **(Alleyn et al.,2010)** who reported that microalbuminuria, or incipient DN is the most common abnormal finding in diabetic children and adolescents, whereas overt proteinuria is found in less than 1–1.5% of pediatric patients. Also, (**Chowta et al., 2009)** reported that the first clinical sign of renal dysfunction in patients with DM is generally microalbuminuria. The degree of microalbuminuria determines the progression of diabetic nephropathy. It may reflect the renal manifestation of a global vascular dysfunction. So, (**Afkarian 2015**) recommended that all diabetics warrant ongoing assessment of kidney function and screening for the earliest manifestations of renal injury.

Zhang et al., 2018 reported that early morphological signs of renal damage include nephromegaly and a modified Doppler, but the degree of damage is best ascertained from proteinuria and GFR. Our study showed a significant difference between DM group and control group regarding eGFR. Our result can be explained by Afkarian , 2015 who reported that loss of glomerular filtration rate, does not occur until adulthood, kidney biopsies show DKD structural changes as early as 1.5–5 years after the onset of type 1 diabetes. Earliest clinical sign of DKD, e.g. increased urine albumin excretion, commonly appears during childhood and adolescence and presents an important opportunity to detect and intervene on early DKD, perhaps more successfully than later in the disease course. Also**, Molitch et al., 2010** documented that albuminuria is a sensitive marker and the strongest predictor of diabetic kidney disease that usually develops before the GFR is impaired and increases the risk that the GFR will fall. Once the clinical manifestations, including the development of persistent microalbuminuria, are present the structural injury is often far advanced.

Moreover, albuminuria and an impaired GFR are strong additive risk factors for cardiovascular disease and death **Ninomiya et al.,2009**. The prevention of albuminuria by means of intensive diabetes therapy is therefore a cornerstone of recommendations that encourage tight glycemic control in patients with type 1 diabetes (**and ADA,2011).** Involvement of pediatric nephrologist in the care of diabetic children and adolescents should include advising on administration and interpretation of screening

for MA and measurement and interpretation of GFR and BP, as well as evaluation and treatment of patients with renal dysfunction or atypical features (**NKF, 2012).**

Although microalbuminuria is a confirmatory test for diagnosis of diabetic nephropathy with Type 1 DM do not all patients progress to overt proteinuria and end-stage renal disease, Many studies have shown regression to normoalbuminuria in 40–60% of patients. HbA1c <8.0%, lower systolic BP, and low cholesterol and triglyceride levels were independently associated with regression (**Perkins et al., 2003).**

Current study showed a highly significant difference between the studied groups regarding fasting blood glucose and glycosylated hemoglobin. As known as DM is diagnosed by testing the level of sugar or HbA1C in the blood (**Chiang et al., 2014**). Target A1C goal may vary depending on your age and various other factors, but the ADA generally recommends that A1C levels be below 7 percent, which translates to an estimated average glucose of 154 mg/dL (**ADA, 2018 a).**

There was a significant difference between the studied groups regarding serum triglycerides, cholesterol, HDL and LDL. In agree with **Bhambhani et al., 2015** who reported that diabetics' patients were more prone for dyslipidemia which is one of the common disorders is seen in diabetes patients. The frequencies of the high cholesterol, high TG and high LDL levels were higher in the diabetic group, which could cause cardiovascular disorders. **ADA, 2018 b** recommended that if lipid levels are abnormal, initial therapy should consist of optimizing glucose control and initiating restricting saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day). After age 10 years, consider adding a statin if, despite 6 months of medical nutrition therapy and lifestyle changes, LDL cholesterol remains greater than 160 mg/dL (4.1 mmol/L) or LDL cholesterol remains greater than 130 mg/dL (3.4 mmol/L) with one or more cardiovascular disease risk factors present.

Conclusion:

Type1 diabetic children and adolescent are liable for the occurrence of early diabetic nephropathy so intensive diabetes therapy is needed, regular screening for MA and measurement and interpretation of and BP and GFR.

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