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Epidemiology and Risk Factors of Diabetic Nephropathy in Children and Adolescents

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Abstract

Background: Diabetes mellitus is the most common childhood metabolic disease whose prevalence has been increasing worldwide in recent decades. Diabetic nephropathy is one of the most important chronic complications of both types of diabetes (type one and two), which seriously increases the morbidity and mortality of diabetes. The present study evaluated the epidemiology and risk factors of diabetic nephropathy in children with diabetes in the northwestern region of Iran.

Method: In this cross-sectional study, 80 diabetic children, 33 (41.3%) males and 47 (58.7%) females with a mean age of 16.69± 4.50 years at the time of assessment, have been identified, evaluated, and followed up in the endocrinology clinic of Tabriz Children's Hospital from 2000 to 2015. The patients were divided into two groups based on the presence or absence of micro- or overt albuminuria, and different variables were compared between the two groups to determine risk factors.

Results: The mean age at the diagnosis was 7.75 ± 3.69 and the mean duration of diabetes was 8.98± 4.07 years. Good glycemic control was presented in 19 (23.8%), microalbuminuria in 36 (45%), overt albuminuria in 1 (1.3%), and retinopathy in 5 (6.3%) of patients; 7 (8.8%) had hypertension. Chronic kidney disease was found to be stage I in 90% and stage II in 10% of the patients. There was a significant difference between cases with and without albuminuria in terms of age at the time of the study (p=0.003), duration of diabetes (p=0.02), and serum cholesterol level (p=0.04). Linear Regression test showed that «the age at diagnosis» has a significant ability to predict the incidence of albuminuria (p = 0.03).

Conclusion: Due to the significant frequency of poor glycemic control in children and adolescents and the high prevalence of albuminuria in them, it is recommended to evaluate the renal function in diabetic children, especially in older patients, those with longer duration of diabetes or poor glycemic control.

Key Words: Children, Diabetes mellitus, Microalbuminuria, Nephropathy.

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1- INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most common metabolic disease in childhood and adolescence whose incidence has increased worldwide in recent decades. According to reports from the United States, the prevalence of diabetes mellitus is about 2 cases per thousand school-age children (1-3). One of the most important chronic and persistent complications of both types of diabetes (type I and type II) is the renal glomerular disease, known as diabetic nephropathy (DN), and as declared by worldwide reports, DN can affect 10% to 50% of diabetic patients within 5 to 10 years from the onset of diabetes. The main feature of DN is microangiopathy involving the kidney, gradually causing proteinuria by damaging the capillary bed of the renal glomeruli over a period of time. The onset of DN is usually accompanied by changes in the renal function such as increased renal blood flow and glomerular filtration (Hyperperfusion - Hyperfiltration) as well as the enlargement of the kidneys, where appropriate treatment at this stage, can usually reverse the changes (1-5); however, if left untreated, protein excretion begins in the form of microalbuminuria and manifests itself with increased blood pressure toward albuminuria, which is accompanied by decreased glomerular filtration. This stage is usually irreversible so that within 15 to 20 years after the diagnosis of diabetes and despite conventional treatments, end-stage renal disease (ESRD) develops and the patient needs dialysis or a kidney transplant (1-5). These events strongly deteriorate the prognosis of diabetes and will ultimately trouble the patient by increasing the morbidity and mortality along with raising treatment costs (6-9). The normal course of detectable DN in type 1 diabetes begins with the development of microalbuminuria (30-300 mg of albumin in 24-hour urine) which can occur even less than 5 years after the onset of diabetes. This stage of primary nephropathy is more likely in patients with a GFR above 150 ml/min. Overt proteinuria (more than 300 mg of albumin in 24-hour urine) usually occurs in patients with diabetes lasting between 5 and 10 years. Hypertension usually occurs at the same time. The appearance of persistent proteinuria and hypertension indicates irreversible overt nephropathy (10-15).

Considering that a significant number of children with diabetes in northwest Iran are being treated and followed up in the pediatric endocrine clinic affiliated with Tabriz Children's Hospital and that no coherent and comprehensive study on various aspects of diabetic nephropathy in this group of children has been conducted, the present study aimed to evaluate the epidemiology and identify the risk factors for diabetic nephropathy in children with diabetes in the northwestern region of Iran. However, the information obtained from this study can be used in the development and/or optimization of executive protocols for the long-term care of children with diabetes all over the world.

2- MATERIALS AND METHODS

In this cross-sectional analytical study, 80 children with diabetes (of any type) have been diagnosed by pediatric endocrinologists, treated and followed up in the pediatric endocrinology clinic affiliated with Tabriz Children's Hospital (a university hospital working as a referral center for sick children in Northwest Iran) during the past 15 years. Sampling was done by a convenient counting method so that all diabetic patients of the center who met the inclusion criteria were enrolled in this study.

The studied diabetic children were divided into two groups based on the presence of albuminuria in the 24-hour collected urine sample, considering the definition of microalbuminuria and overt albuminuria: a group "without albuminuria" including

diabetic patients without nephropathy or in the latent stages of nephropathy and the other group "with albuminuria" to the extent of microalbuminuria or overt albuminuria, including diabetic patients in both inevitable or advanced stages of nephropathy. The routine clinical and laboratory information of the studied children provided during their clinical follow-up was extracted from their medical records and reviewed. Different findings were compared between the two groups with and without albuminuria.

2-1. Inclusion and Exclusion Criteria

Inclusion criteria encompassed the diabetic patients aged less than 18 years old at the time of diagnosis of diabetes with at least 5 years passing the initial diagnosis of diabetes, and accepted the conditions to participate in clinical and laboratory evaluations with the written consent of the patient or their parents. The exclusion criteria included having a history less than 5 years from the onset of diabetes, the presence of any (former or current) vascular or renal disease not related to diabetes, age of 18 or more at the time of diagnosis of diabetes, and dissatisfaction of the patient or their parents to participate in the study.

2-2. Data analysis

Statistical data analysis was performed using SPSS16 software. In addition to descriptive statistical methods (including frequency, percentage, mean and standard deviation), the chi-square test and Fisher's exact test were used to compare qualitative variables, and the Independent t-test was used for quantitative variables. The Linear Regression test was performed to evaluate the determinants of albuminuria. The significance level was considered at the p-value less than 0.05.

3- RESULTS

A total of 80 diabetic children and adolescents were evaluated. The youngest and oldest patients were 8 and 29 years old at the time of evaluation, respectively. **Fig. 1** shows the age distribution of the patients, who were 33 (41.3%) males and 47 (58.7%) females. The mean age of the patients at the time of diagnosis was 7.75±3.69 years. The youngest and oldest patients at the onset of diabetes aged 1.5 and 16 years, respectively.

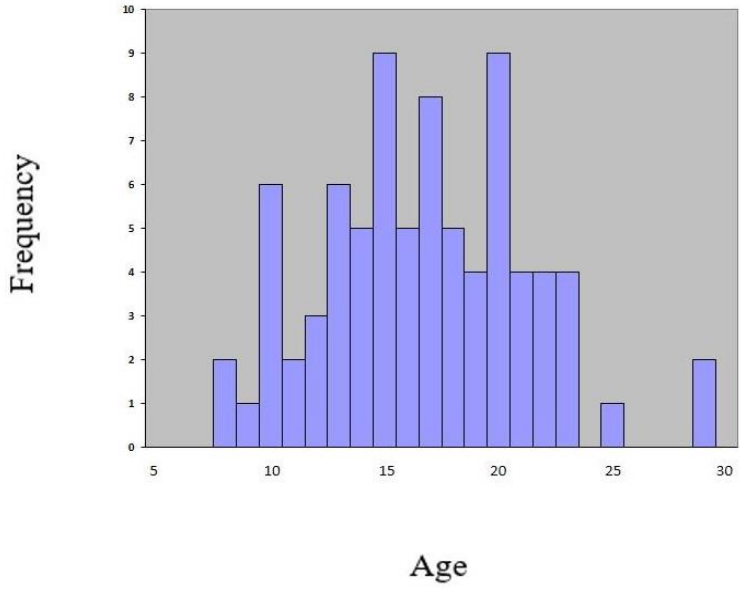

Fig. 1: Age distribution of children and adolescents (years - at the time of assessment)

The mean duration of diabetes was 8.98±4.07 years, with the shortest and longest duration of diabetes being 5 and 21 years, respectively. The mean weight of the patients was 54.86±14.52 kg. The lightest and heaviest patients weighed 22 and 79 kg, respectively.

The average total daily dose of insulin was $0.96\pm0.34_{unit/kg}$, with the lowest and highest rates being 0.3 and 2.3, respectively. The mean systolic blood pressure was $113.27\pm11.74_{mmHg}$. The lowest and highest measures were 90 and 140_{mmHg}, respectively. The mean diastolic blood pressure was $73.71\pm8.61_{mmHg}$. The lowest and highest measures were 60 and 100 mmHg, respectively. According to the standard tables for determining hypertension considering age, weight, and sex, 7 (8.8%) of the subjects had hypertension.

Table 1 displays the laboratory findings in the studied children and adolescents. Accordingly, the mean glomerular filtration rate (GFR) was $110.15 \pm 31.76_{ml/min}$. The lowest and highest rates were 70 and $286_{ml/min}$, respectively. The mean corrected GFR (GFRc: $ml/min/1.73_{m^2}$) was 128.31±47.46. The lowest and highest rates were 69.96 and 390.02, respectively.

Table-1: Laboratory findings in children and adolescents

Variable	Mean	Standard Deviation	Lower	Upper
Hemoglobin (g/dL)	69/13	32/1	8/5	16/2
HbA_1c (%)	5/8%	62/1	6/5%	/13%5
24-hour urinary microalbumin (mg/day)	55/16	7/42	2	304
24-hour urinary creatinine (mg/day)	97/908	379/84	240	900
Blood creatinine (mg/dL)	0/85	0/15	0/5	1/4
24-hour urine volume (ml)	1497/75	565/46	560	4000
Blood urea level (mg/dL)	23/81	6/91	8/4	44
Triglycerides (mg/dL)	87/28	43/05	30	234
Cholesterol (mg/dL)	162/20	35/76	65	250

Glycemic control was determined based on Hemoglobin-A1c (HbA1c) measurement and classified as good (HbA1c<7.5%), intermediate (HbA1c=7.5–9.5%), and poor (HbA1c>9.5%) (3, 13). The glycemic control was good in 19 (23.8%) cases and intermediate or poor in 61 (76.2%) patients. Microalbuminuria (30 to 300 mg/day) was present in 36 cases (45%) and overt albuminuria in 1 case (1.3%). In total, albuminuria was present in 37 cases (46.3%). Dyslipidemia was also present in 2 (2.5%) of the patients.

We found diabetic vascular complications including diabetic retinopathy in 5 cases (6.3%) and hypertension in 7 cases (8.8%). There was chronic kidney disease (CKD) stage-I in 29 cases (36.3%) and stage-II in 8 cases (10%). Findings were compared between cases with and without albuminuria.

Tables 2 and **3** show the comparison of demographic findings and the comparison of laboratory findings between cases with and without albuminuria, respectively. The albuminuria group had a significantly older mean age and longer duration of diabetes compared to the group without albuminuria. In both groups, poor glycemic control was common, with this rate being higher in the albuminuria group. However, their difference was not statistically significant (p = 0.19).

Table-2: Comparison of demographic findings and clinical evaluations between cases with and without albuminuria

Demographic findings and clinical evaluations		With albuminuria 37 (46.3%)	Without albuminuria 43 (53.7%)	P-value
Gender	Male	(7/29%) 11	(2/51%) 22	06/0
	Female	(3/70%) 26	(8/48%) 21	
Mean Age at check-in (years)		15/4±27/18	39/4±32/15	003/0 *
Mean Age at diagnosis (years)		57/3±24/8	/3±33/777	0/27
Mean Duration of diabetes (years)		/4±08/1027	/3±03/867	02/0 *
Daily Insulin (IU)		41/0±03/1	26/0±90/0	1/0
Systolic blood pressure (mmHg)		63/11±83/112	95/11±65/113	76/0
Diastolic blood pressure (mmHg)		98/8±43/74	33/8±09/73	49/0
Hypertension		(5/13%) 5	(7/4%) 2	24/0
Intermediate or poor glycemic control		(8/83%) 31	(8/69%) 30	19/0
Dyslipidemia		(7/2%) 1	(3/2%) 1	9/0
Diabetic retinopathy		(8/10%) 4	(3/2%) 1	17/0

*significant

Table-3: Comparison of laboratory findings between cases with and without albuminuria

Variable (Mean Values)	With albuminuria	Without albuminuria	P-value
Hemoglobin (g/dl)	60/1±38/13	98/0±96/13	05/0
HbA1c (%)	85/1±68/8	40/1±35/8	37/0
24-hour urinary creatinine (mg/day)	89/442±04/979	54/308±68/848	12/0
Blood creatinine (mg/dL)	17/0±90/0	13/0±81/0	02/0*
24-hour urine volume (ml)	16/712±59/1549	01/398±41/1414	15/0
Urea level (mg/dl)	52/7±18/25	18/6±62/22	09/0
Triglycerides (mg/dL)	06/46±72/90	59/40±32/84	51/0
Cholesterol (mg/dL)	06/34±78/170	91/35±81/154	04/0*

*significant

There was also a remarkable difference between the two groups in terms of creatinine and blood cholesterol levels. Dyslipidemia was present in 1 case (2.7%) of the albuminuria group and 1 case (2.3%) without albuminuria; there was no significant difference between the two groups, by using Fisher's exact test (p=0.9). Although it seems that CKD stage-II is more common in albuminuric cases, no significant statistical difference was observed between the two groups using Fisher's exact test (p = 0.13). **Table 4** shows the results of the Linear Regression test, based on which only age could significantly predict the incidence of albuminuria.

4- DISCUSSION

Diabetic nephropathy (DN) is the leading cause of death in young patients with type 1 diabetes (10-13). Due to advances in the early diagnosis and treatment of DN, its management has become much more effective, currently beginning as early as the appearance of microalbuminuria. Nephropathy occurs in 35-45% of cases of type 1 diabetes (10-

15). Micro and macroalbuminuria are important markers for early and progressive diabetic kidney disease (7). The normal course of detectable DN in type 1 diabetes begins with the development of microalbuminuria (30-300$_{mg}$ albumin in 24-hour urine), probably happening 5 years after the onset of diabetes or even earlier. Proteinuria (above 300$_{mg}$ of albumin in 24-hour urine) is usually seen in patients with diabetes lasting for 5 to 10 years. Hypertension usually begins at this interval and, together with the appearance of persistent proteinuria, is an indicator of overt nephropathy (10-15).

Table-4: Results of linear regression test

Variables	Odds Ratio	Confidence interval 95%		P-value
		Lower	Upper	
Age	29/0	06/0-	002/0-	03/0 *
Diabetes duration	02/0	03/0-	03/0	87/0
Cholesterol level	18/0	006/0-	00/00	09/0

*significant

In the present study, 80 children and adolescents with diabetes were evaluated for nephropathy, whose mean ages at the time of diagnosis and assessment were 7.75±3.69 and 16.69±4.50 years, respectively, with a mean duration of diabetes of 8.98±4.07 years. Similarly, in the study of Raile et al., the mean age at the time of diagnosis was 9.94 years in the age range of 5.8-14.3 years (17).

According to the Diabetes Control and Complications Trial (DCCT) study, poor glycemic control is a dominant risk factor for DN (18). In addition, another study has shown that accurate, complete, and on-time treatment of diabetes delays both the onset and progression of DN in patients (19, 20).

In addition to HbA1c, retinopathy, dyslipidemia, hypertension, and male gender have been reported in various studies as risk factors in DN development in patients with type 1 diabetes (21-25). The effect of sex on the incidence of nephropathy is age-dependent. In adolescents, the female sex increases the risk of microalbuminuria (23-25), while in adults and in cases of chronic and advanced diabetes, men are at higher risks of kidney disease (22-26).

Although in the present study there was a significant difference between cases with and without albuminuria in terms of age at the time of the study, duration of diabetes, and cholesterol, only the age factor was able to predict albuminuria. No difference was observed between cases with and without albuminuria in terms of the incidence of dyslipidemia and sex. In the study of Razavi et al., the microalbuminuric group had a higher mean age at the time of the study and a longer duration of diabetes than the group without microalbuminuria (11).

In a cohort study by Krolewski et al. on 292 patients, it was found that patients with severe uncontrolled hyperglycemia in the first 15 years of diabetes were 4.5 times more likely to develop resistant proteinuria (27).

In Mathiesen et al.'s study, 20% of patients had microalbuminuria (28). Al-Hermi et al. diagnosed DN to a lesser extent in 10 patients (31%), which was associated with microalbuminuria in two cases and overt proteinuria in 8 cases (29). Morgensen and Christensen evaluated the role of

microalbuminuria in predicting the incidence of DN in children. Fourteen out of the 43 studied patients (32.5%) had primary microalbuminuria, 12 (27.9%) of whom developed overt proteinuria after a few years. The patients, who eventually developed proteinuria, initially had elevated GFR and higher blood pressure (30).

In the study of Lutale et al., while evaluating the children with diabetes, it was observed that microalbuminuria and macroalbuminuria were present in 12% and 1% of patients, respectively (31). The prevalence of albuminuria in diabetic patients is a function of the duration of diabetes. According to the European Diabetes Prospective Complications Group (EURODIAB), the cumulative incidence of microalbuminuria in patients with type1 diabetes was 12.6% over 7.3 years (32, 33). But in the 18-year follow-up in Denmark, it was 33% (33) and in the Bramlage study, it was 19% (34).

In the present study, microalbuminuria and macroalbuminuria were present in 45% and 1.3% of children, respectively. In Razavi et al.'s study, 14.3% of patients had microalbuminuria (11). In Raile et al.'s study, out of 27805 patients with type 1 diabetes, 919 (3.3%) were microalbuminuric and 78 (0.28%) were microalbuminuric (17).

In general, the risk factors involved in the development of DN are divided into two groups: changeable (such as glycemic control, hypertension, dyslipidemia, diet, and smoking) and unchangeable (such as duration of diabetes, puberty, gender, genetics, and constitutional factors) (35, 36). The incidence of microalbuminuria in the present study was higher than in other studies, which can be attributed to the higher prevalence of underlying risk factors such as poor glycemic control in our cases.

In our study, good glycemic control was found in only 19 (23.8%) of patients, meaning that 61 (76.2%) had intermediate or poor glycemic control. However, in terms of the mean HbA1c level, there was no significant difference between cases with and without albuminuria (8.68±1.85 and 8.35±1.40, respectively). The rate of good glycemic control was higher in group without albuminuria than in albuminuric group [13 patients (30.2%) versus 6 patients (16.2%), respectively], however, this difference was not statistically significant, which could be due to the high prevalence of poor glycemic control in the general population of diabetic children.

In a similar way, in the study of Al-Hermi et al., the mean HbA1c for DN patients was 11.8% versus 10.2% for the non-nephropathic group, showing no significant difference between the two groups (29). In the study of Lutale et al., no significant difference was observed in terms of glycemic control between cases with and without microalbuminuria (31). However, it should be noted that the amount of the HbA1c is a reflection of the status of glycemic control in recent months in each patient, while the effect of lack of glycemic control in the development of DN is related to a longer period of recent past years in each patient.

In our study, hypertension and retinopathy were more frequent in cases with microalbuminuria than in cases without microalbuminuria, although the difference was not statistically significant. In the study by Mathiesen et al., arterial blood pressure increased in the microalbuminuric group compared with the non-albuminuric group. However, the two groups had a similar frequency of retinopathy (28). In the study of Al-Hermi et al., no cases of retinopathy were reported in the studied patients (29). In Raile et al.'s study, risk factors for microalbuminuria included the duration of diabetes, HbA1c, LDL, and blood pressure, while childhood-onset of

diabetes was a protective factor. Male sex was associated with the development of macroalbuminuria (17).

4-1. Limitations of the study

It should be noted that the significant role of these risk factors in the development of DN (such as lack of glycemic control) in multicenter studies with a larger number of patients and longer follow-ups has been proven, but the limited number of patients participating in our study and its cross-sectional method can be mentioned as main limitations of the present study.

5- CONCLUSION

Due to the high frequency of albuminuria in children and adolescents with diabetes and the relatively high prevalence of poor glycemic control in them, periodic monitoring of renal function in all diabetic children, especially older patients, longer diabetes and poor glycemic control is recommended.

6- ETHICAL CONSIDERATIONS

It is worth noting that only the patients whose parents or themselves read the informed written consent and signed it voluntarily participated in this study. The information collected for this study was entirely based on the standard care of patients with diabetes, subsequently, no tests, assessments, or additional costs in excess of the patient's needs were imposed on them. All information was confidentially gathered and reviewed, and no names or addresses of the patients were disclosed. The method of this study has been approved by the Ethics Committee of the Vice Chancellor for Research of Tabriz University of Medical Sciences.

7- ACKNOWLEDGMENTS

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