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Research Paper

High Frequency of Nephropathy Among the Iranian Children and Adolescents With Type 1 Diabetes

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ABSTRACT

Background: Type 1 Diabetes (T1D) is an autoimmune condition, in which the pancreas produces little or no insulin. Nephropathy is a serious T1D microvascular complication that is associated with high mortality and morbidity.

Objective: This study aimed to investigate the prevalence of diabetic nephropathy and comorbidities in children with T1D.

Methods: This cross-sectional study was conducted on 208 children (aged 1–18 years old) with T1D who were referred to the Qazvin endocrinology clinic from 2017 to 2019. Anthropometric, demographic, laboratory, and comorbidities data were collected.

Results: The Mean±SD age at diagnosis of diabetes was 7.59 years, and the Mean±SD HbA1c level of the study subjects was 8.68±1.42 mmol/mol. Out of 208 diabetic patients, 64 cases (30.7%) had diabetic nephropathy, of whom 53 cases (25.5%) had microalbuminuria and 11 cases (5.3%) had macroalbuminuria. Among the studied diabetic patients, 30 cases (14.45%) had hypothyroidism, 12 patients (5.8%) had celiac disease, and 14 patients (6.7%) had anemia. Retinopathy was not found in any of the patients. Moreover, variables, such as the duration of diabetes, puberty status, mean HbA1c levels, and age were significantly associated with diabetic nephropathy ($P<0.05$).

Conclusion: Mean HbA1c levels were significantly higher in patients with macroalbuminuria, which may corroborate the role of metabolic control of diabetes in the development of albuminuria.

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1. Introduction

Type 1 Diabetes (T1D) is one of the most common chronic diseases in children and its incidence is increasing all over the world. Diabetic Nephropathy (DN) occurs in 15-20% of patients with T1D [1]. The peak of diabetes onset is at the age of 2 to 6 years old, and the highest age for diabetes is 10 to 14 years old [2]. Chronic complications of diabetes can be generally classified into microvascular and macrovascular diseases [3]. DN is one of the most frequent and progressive microvascular complications of diabetes that leads to End-Stage Renal Disease (ESRD), and the mortality rate of T1D increases with the development of nephropathy in children and adolescents [4, 5]. Studies have confirmed the importance of persistent microalbuminuria as a risk factor for mortality and have shown that T1D patients without kidney disease have a long survival compared to the general population [6].

Recent studies have shown that despite the increase in the incidence of T1D, the number of T1D patients with nephropathy has decreased due to improvements in diabetes care. Risk factors for the development or progression of DN include poor glycemic (metabolic) control, duration of diabetes, puberty, age at onset, high blood pressure, smoking, hyperlipidemia, family history of diabetes, and genetic predisposition [7]. Microalbuminuria predicts the onset of DN and is associated with primary diabetic glomerulopathy. Among patients with T1D, microalbuminuria is often the first step in the development of macroalbuminuria and ultimately, ESRD [8].

The study aimed to estimate the prevalence of DN and other comorbidities in children with T1D for the first time in Qazvin, Iran.

2. Materials and Methods

The present cross-sectional study was performed on 208 children aged 1-18 years old diagnosed with T1D who were referred to Qazvin Endocrinology Clinic from 2017 to 2019. The inclusion criteria were the age of 1–18 years, diagnosis of T1D, and conducting 24-h urine albumin test. Exclusion criteria were the presence of other types of diabetes (type 2 diabetes, iatrogenic diabetes, and others), comorbidities that affect the complications of diabetes (leukemia, tuberculosis anemia, and heart disease), and incomplete information in the medical records. The sample size was calculated to be 192 according to the formula suggested by Al-Eisa et al. [9].

The minimum sample size was considered to be 192 participants with a 20% loss, we finally included 208 subjects. The data were analyzed by Chi-square and Mann-Whitney test and t-test using SPSS software v. 22. Also, descriptive data were reported as Mean±SD, frequency, and percentage. DN was defined based on the following criteria: 24-h urinary albumin between 30 and 300 mg (microalbuminuria) in two of three consecutive requested samples (within 3-6 months) and 24-h urinary albumin greater than 300 mg (macroalbuminuria) in one sample [10]. In the initial stage, a random urinary albumin test was requested for the patients, which is reported as milligrams of albumin per gram of urinary Creatinine (Cr). Macroalbuminuria (MA) is defined as urine albumin values 30 to 300 mg/gr creatinine, or urinary albumin/creatinine ratio 2.5-25 mg/mmol (men) or 3.5-25 mg/mmol (women) or albumin 30-300 mg/l in the early morning urine sample. In these conditions, a 24-h urine albumin test was requested [11].

Information on height, weight, sex, age, Body Mass Index (BMI), birth weight, positive family history of T1D, duration of T1D, age at the time of diagnosis, puberty status, and age of menstruation was extracted from medical files. In addition, laboratory data, including HbA1c levels (at least four samples), levels of vitamin D, GFR, Cr, and 24-hour urinary albumin/random urinary albumin, as well as comorbid conditions, such as celiac disease and hypothyroidism, were recorded in the checklist. The duration of T1DM was calculated from the time of diagnosis of T1DM.

Patients were divided into four groups based on the BMI-age percentile Clinical Growth Charts (CDC): Under 5th percentile (underweight), 5th to 85th percentile (normal weight), 85th to 96th percentile (overweight), and more than 95th percentile (obese) [12]. Puberty status for girls and boys was defined based on Tanner's stages 1 through 5 [13]. HbA1c concentration, as a measure of blood sugar in the last three months, was assessed by High-Performance Liquid Chromatography (HPLC) [14].

If a patient tested positive for IgA/anti-Tissue Transglutaminase (anti-TTG) antibody and IgA/anti-endomysial antibody, celiac disease was suspected and confirmed by a small intestine biopsy [15]. According to the USA Endocrine Society recommendations, vitamin D levels less than 20 ng/mL are considered vitamin D deficiency, levels between 20 and 30 ng/mL indicate vitamin D insufficiency, and levels more than 30 ng/mL are considered normal [16]. Hypothyroidism was diagnosed with a Thyroid-Stimulating Hormone (TSH) of more than 10 IU/dl. [17, 18]. Anemia was defined based on hemoglo-

bin levels less than normal according to age and sex [19]. Diabetic retinopathy was also included in the checklist based on the results of an eye examination by a retinal ophthalmologist. Estimated Glomerular Filtration Rate (GFR) (creatinine clearance) was calculated using the following Equation 1 [20]:

1. GFR (ml/min per 1.73 m²)=0.43 [Height (cm)/S_{Cr} (mg/dl)]

3. Results

In the present study, a total of 208 children with T1D were investigated. Demographic and anthropometric data, laboratory features, and comorbidities are shown in Table 1. About 85 (40.9%) subjects were boys. The Mean±SD age of the subjects was 12.52±3.92 (3.08-18) years. The Mean±SD birth weight of the patients was 3.20±0.49 kg (2.00-4.90). The Mean±SD duration of diabetes in patients was 4.39±2.56 years, and the Mean±SD age at diagnosis of diabetes was 7.59±3.27 years (0.17–15.67). The frequency and the mean of HbA1c, Cr and GFR, BMI, puberty status, and family history of T1D in the participants as shown in Table 1. In terms of vitamin D levels, 20 (9.6%), 136 (65.4%), and 52 (25%) patients had vitamin D deficiency, vitamin D insufficiency, and normal level of vitamin D_3, respectively. Also, 30 patients (14.45%) had hypothyroidism due to Hashimoto's thyroiditis and 12 patients (5.8%) had celiac disease. Retinopathy was not found in any of the patients. Regarding the prevalence of DN, 64 patients (30.7%) had DN, of whom 53 cases (25.5%) had microalbuminuria and 11 cases (5.3%) had macroalbuminuria. The age of the studied children showed a significant difference between the two groups (P<0.001). The mean age of the macroalbuminuria and microalbuminuria groups was 15.46 and 14.66 years, respectively, and in the normoalbuminuria group was 11.4 years. There was a significant difference in the duration of diabetes between the two groups (P=0.003). The mean duration of the disease in the macroalbuminuria and microalbuminuria groups was 5.87 and 5.13 years, respectively; however, in the normoalbuminuria group, it was 4.01 years (Figure 1).

There was a significant relationship between puberty status and nephropathy (P<0.001). Totally, 77.4% of the children with microalbuminuria and 90.9% of the children with macroalbuminuria were in the post-pubertal stage (Figure 2), while only 42% of the participants in the normoalbuminuria group were in this stage.

The HbA1c, creatinine, and GFR ranges in patients were (5-9.40%), (0.35-1.36 mg/dl), and (20-90 ml/min), respectively. A significant difference was observed between the two groups in terms of HbA1c levels (P=0.009). Therefore, it can be concluded that HbA1c affects the development of DN. The Mean±SD levels of HbA1c were 9.74±1.48 mmol/mol in the macroalbuminuria group, 8.90±1.28 mmol/mol in the microalbuminuria group, and 8.51±1.43 mmol/mol in the normoalbuminuria group.

There was also no significant difference between the two groups in terms of gender, age at diagnosis of diabetes, BMI, vitamin D_3 level, the mean age at the onset of menstruation, mean Cr level, GFR, celiac disease, and hypothyroidism (Tables 2 and 3).

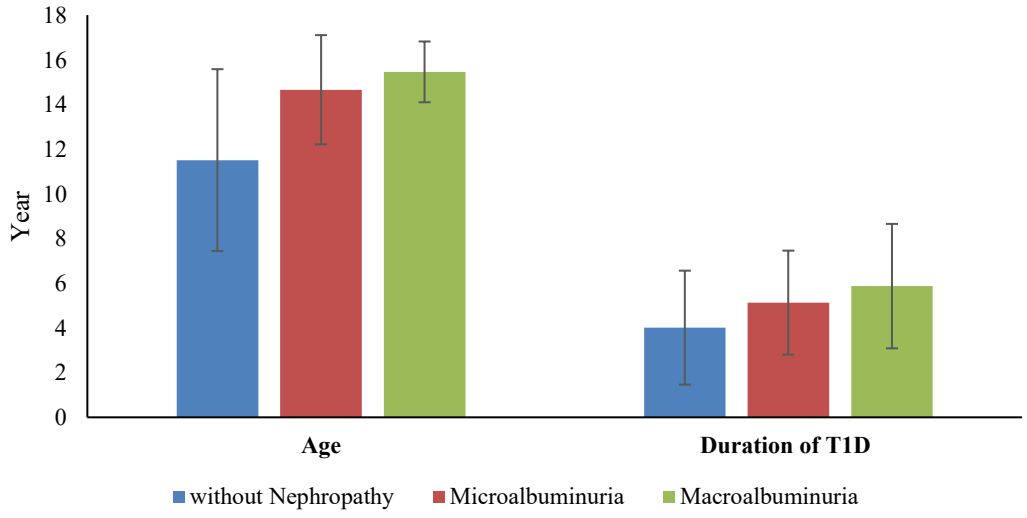

Figure 1. The mean age and duration of Type 1 Diabetes (T1D) in three studied groups

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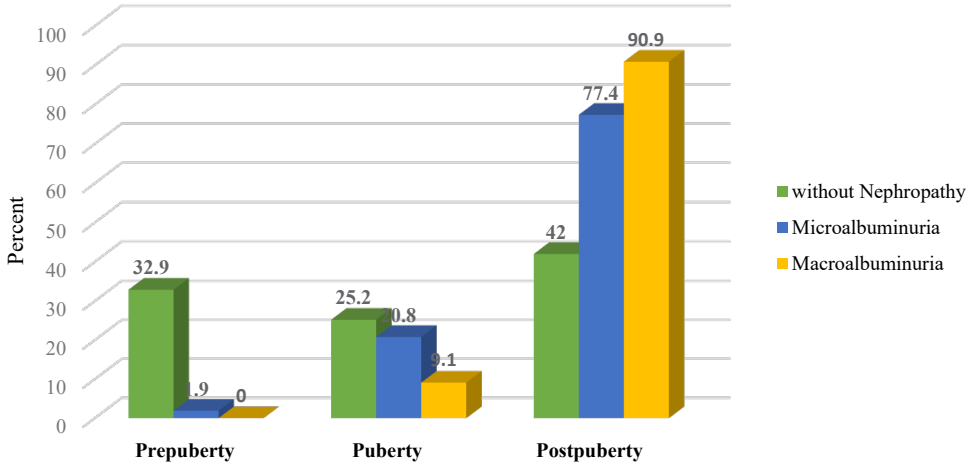

Figure 2. Puberty status in diabetic patients with and without nephropathy

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4. Discussion

In the present study, approximately one-third of 208 studied patients had DN, of whom 53 cases (25.5%) had microalbuminuria and 11 cases (5.3%) had macroalbuminuria. Among the diabetic patients, 30 patients (14.45%) had hypothyroidism, and 12 patients (5.8%) had celiac disease. In addition, 25 patients (12%) had anemia. Retinopathy was not found in any of the patients. As a result, the duration of diabetes, puberty status, mean HbA1c levels, and age were significantly associated with DN.

HbA1c is known to be a risk factor for retinopathy and nephropathy in children and adults with T1D. In this regard, Lind et al. [21] showed that the increased level of HbA1c effectively increased the risk of retinopathy and microalbuminuria. In the present study, the mean HbA1c level of diabetic patients was 8.68, and the mean HbA1c level of the macroalbuminuria group was 9.7. Moreover, the prevalence of microalbuminuria and macroalbumin-

Table 1. Distribution of the laboratory data, mean BMI, puberty status, and family history of T1D patients

Variables		Mean±SD/No.(%)
HbA1c (%)		8.68±1.42
Cr (mg/dl)		0.78±0.18
GFR (ml/min)		87.77±20.35
BMI-age percentile	Underweight	9(4.30)
	Normal	147(70.70)
	Overweight	44(21.20)
	Obese	8(3.80)
Puberty status	Pre puberty	48(23.20)
	Puberty	48(23.20)
	Post puberty	111(53.60)
Family history of T1D	Yes	9(4.33)
	No	199(95.67)

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T1D: Type 1 Diabetes; SD: Standard Deviation; BMI: Body Mass Index; HbA1c: Hemoglobin A1c; Cr: Creatinine; GFR: Glomerular Filtration Rate

Table 2. Comparison of quantitative variables in patients with and without nephropathy

Variables	Mean±SD		P
	T1D Without Nephropathy (n=144)	T1D With Nephropathy (n=64)	
Age (y)	11.51±4.069	14.80±2.30	<0.001
Diagnosis age (y)	7.30±4.51	7.90±2.64	0.319
Duration of T1D (y)	4.01±2.55	5.25±2.40	0.001
Age at the onset of menstruation in girls (y)	12.59±1.11	12.75±1.28	0.655
HbA1c (%)	8.50±1.86	9.06±1.98	0.090
Cr (mg/dl)	0.76±0.17	0.81±0.18	0.112
GFR (ml/min)	90.80±23.29	98.39±27.70	0.081

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T1D: Type 1 Diabetes; SD: Standard Deviation; HbA1c: Hemoglobin A1c; Cr: Creatinine; GFR: Glomerular Filtration Rate

uria in our study was 5.3% and 25.5%, respectively. No case of retinopathy was found in our study. The results of this study were not in line with those of Lind et al. Therefore, genetic and racial factors may affect the incidence and prevalence of retinopathy, and further investigation is needed in this area.

In the study by Alleyn et al. [22], the percentage of women with persistent microalbuminuria was significantly higher than that of women without persistent microalbuminuria (75% vs. 52%). In addition, mean HbA1c levels were significantly higher in individuals with persistent microalbuminuria (9.1) than in those without mi-

Table 3. Comparison of qualitative variables in patients with and without nephropathy (n=144)

Variables		No.(%)		P
		T1D Without Nephropathy	T1D With Nephropathy=64	
Sex	Male	64(44.40)	21(32.8)	0. 128
	Female	80(55.60)	43(67.2)	
Body Mass Index-age percentile	Underweight	7(4.90)	2(3.1)	0.924
	Normal	101(70.10)	46(71.9)	
	Overweight	30(20.80)	14(21.9)	
	Obese	6(4.20)	2(3.1)	
Vit D_3	Deficiency	8(10.10)	4(8.5)	0.398
	Insufficiency	48(60.80)	34(72.3)	
	Normal	23(29.10)	9(19.1)	
Puberty status	Pre puberty	47(32.90)	1(1.6)	< 0.001
	Puberty	36(25.20)	12(18.8)	
	Post puberty	60(42.00)	51(79.7)	
Celiac disease	Yes	8(5.60)	4(6.3)	1.000
	No	136(94.40)	60(93.8)	
Hypothyroidism	Yes	14(10.40)	18(27.27)	0.168
	No	121(89.60)	48(72.73)	

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croalbuminuria (8.7). Persistent microalbuminuria was significantly associated with the duration of diabetes only in older children (13-18 years). There was no significant difference between the subjects with and without persistent microalbuminuria in terms of age, duration of diabetes, BMI z-score, and puberty status. The mean level of HbA1c was the only important predictor of persistent microalbuminuria. The general characteristics of the study population were similar to those of the present study.

In our study, the percentage of girls in the nephropathy group was higher (69% vs. 55%); however, no significant association was found between gender and nephropathy (microalbuminuria), which is not consistent with the results of above-mentioned study. Puberty status and age were among the variables that were significantly associated with nephropathy (microalbuminuria) in our study; however, these findings were not in line with those of Alleyn. In our study, HbA1c and the duration of diabetes were significantly associated with nephropathy.

In a study conducted by Al-Agha et al. on children with T1D, the prevalence of microalbuminuria was reported to be 11% [23]. In the present study, the duration of diabetes, HbA1c levels, and puberty status were associated with microalbuminuria, which is consistent with the results of the mentioned study in Table 2. However, the BMI percentile was not significantly associated with albuminuria, and this finding is not in agreement with the results of the study by Al-Agha et al. The prevalence of nephropathy (microalbuminuria and macroalbuminuria) in our study was 30.8%, which is higher compared to the mentioned studies. The reason for this discrepancy may be genetic factors and poor metabolic control due to late referral of patients as a result of poverty, lack of health insurance, self-monitoring, and a long distance from experienced medical centers. Thus, further studies with a larger sample size are needed in this area.

The prevalence of persistent microalbuminuria in studies varies from 2% to 20%. This variation in the prevalence of microalbuminuria may be due to differences in the study populations, such as mean age, duration of diabetes, glycemic control, and duration of follow-up ranging from 1.5 to 9 years [24].

Orzan et al. reported that 18.3% of children and adolescents with T1D were positive for anti-TPO antibodies [25]. In the present study, the prevalence of hypothyroidism (Hashimoto's thyroiditis) in diabetic children (14.45%) was similar to that of the study by Orzan et al.

Mollazadegan et al. evaluated the risk of kidney disease in patients with both celiac disease and T1D compared to patients with only T1D [26]. They reported that patients with celiac disease and T1D had a higher risk of progressing to chronic kidney disease compared to patients who only had T1D. For chronic kidney disease, the Hazard Ratio (HR) was more pronounced after ten years of celiac disease. In the present study, the prevalence of celiac disease was higher in cases of kidney disease, which was in line with the results of the study by Mollazadegan et al.

The results of previous studies have indicated an inverse relationship between vitamin D levels and diabetic complications [27, 28]. These findings are understandable due to the role of vitamin D in immunity, β cell function, and insulin sensitivity. In the study by Xiao et al., the association between vitamin D deficiency and DN in China was investigated [27]. Patients with diabetic nephropathy were grouped according to the stage of DN. The level of 25 (OH) D in patients with DN was lower than the control group and showed a gradual decline with the increase of the stage of diabetic nephropathy. Also, Usluogullari et Al. reported that vitamin D deficiency is associated with microvascular complications in diabetic patients [28]. In the present study, there was no significant association between vitamin D levels and stages of DN, which was not in line with the results of Xiao et al. The probable cause of this discrepancy could be the high prevalence of vitamin D deficiency in Iran, which has caused both groups to have insufficient amounts of vitamin D or the sample size of the study is possibly not sufficient; therefore, conducting related studies with more samples will be beneficial.

The prevalence of microalbuminuria and macroalbuminuria in our study was 25.5% and 5.3%, respectively, which were higher than the mentioned studies. The reason for this discrepancy might be due to poor metabolic control and the effect of genetic factors. This variation in the prevalence of microalbuminuria may be related to differences in the study population, such as age range, duration of diabetes, and glycemic control among others.

In this study, the mean levels of HbA1c were significantly higher in patients with macroalbuminuria, which may confirm the role of the quality of metabolic control of diabetes in inducing urine albuminuria. In our study, we did not find any cases of retinopathy, which may be due to genetic and racial factors and requires further investigation. One of the positive points of our study was the relationship between albuminuria, pubertal stage, and associated comorbidities, however, lipid levels were not investigated.

5. Conclusion

DN was very common in our patients; thus, we recommend that similar studies with a larger sample size and

greater geographical distribution (in other regions of Iran) be carried out. Other variables, including triglycerides and cholesterol, can be also investigated.

Ethical Considerations

Compliance with ethical guidelines

After obtaining approval from the Ethics Committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1399.225), all the collected data were analyzed anonymously and remained confidential. This study was conducted in accordance with the Helsinki Declaration of Ethics.

Conflict of interest

The authors declared no conflict of interest.

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None of the authors have any potential conflicts of interest associated with this research.

Authors' contributions

Conceptualization and Supervision: Fatemeh Saffari; Methodology: Banafsheh Arad; Investigation, Writing – original draft, and Writing – review & editing: All authors; Data collection: Nadia Talati and Ali Homaei; Data analysis: Victoria Chegini and Ali Homaei; Funding acquisition and Resources: Fatemeh Saffari and Banafsheh Arad.

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