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Risk Factors of Diabetic Nephropathy Among A Group of Iraqi Children with Type 1 Diabetes Mellitus

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Abstract

Background Diabetic nephropathy is the major cause of end-stage kidney disease in patients with diabetes mellitus.

Objective To identify risk factors for occurrence of Diabetic nephropathy among group of Iraqi children with type 1 diabetes mellitus.

Methods A cross-sectional study was conducted at Department of Chemistry and Biochemistry, and department of Pediatrics, College of Medicine, Al-Nahrain University from November 2019 to April 2020. Total of 80 children with diabetic nephropathy were divided into two groups: 40 patients without diabetic nephropathy and 40 patients with diabetic nephropathy. Blood and urine samples were taken for biochemical tests.

Results Each of age, duration of diabetes mellitus, fasting blood sugar and HbA1c were significantly associated with diabetic nephropathy. However, duration showed higher predictive value (OR = 18.69, 95% CI = 5.48-63.74, p<0.001). Very low-density lipoprotein (VLDL-c) was the most powerful lipid test as predictor for diabetic nephropathy (OR = 15.07, 95% CI = 3.98-57.1, p<0.001). Albumin-creatinine ratio was the most powerful renal function test predictor for diabetic nephropathy (OR = 107.6, 95% CI = 20.3-569.6, p<0.001). When all variables were entered in multivariate regression model, only 3 (out of 14) remained significantly associated with the development of diabetic nephropathy. Of those, albumin creatinine ratio >25 mg/g was the most powerful independent predictor (OR = 11.78, 95%CI = 7.45-42.82, p = 0.009). In contrast, estimated glomerular filtration rate, was a negative predictor of diabetic nephropathy (OR = 0.26, 95% CI = 2.79-18.93, p = 0.026). HbA1c level >9% was a positive predictor of diabetic nephropathy (OR = 4.15, 95% CI = 3.88-36.91, p value = 0.031).

Conclusion Albumin creatinine ratio and estimated glomerular filtration rate, are the strongest predicting factors for development and progression of diabetic nephropathy in Iraqi children with type 1 diabetes mellitus.

Keywords Diabetes mellitus, diabetic nephropathy, children, risk factors

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List of abbreviations: BMI = Body mass index, DBP = Diastolic blood pressure, eGFR = Estimated glomerular filtration rate, FBS = Fasting blood sugar, HbA1c = Glycated hemoglobin, HDL = High-density lipoprotein, LDL = Low-density lipoprotein, SBP = Systolic blood pressure, TG = Triglycerides, VLDL = Very low-density lipoprotein, uACR = Urinary albumin to creatinine ratio

Introduction

Diabetes mellitus (DM) is metabolic disorder that characterized by chronic hyperglycemia and glycosuria, which

results from insulin deficiency that caused by autoimmune destruction of pancreatic beta cells (T1DM) [1].

T1DM usually occurs in adolescents with a peak begin around puberty [2]. The American Diabetes Association (ADA) in 2020, have issued DM diagnostic criteria [3].

Diabetic nephropathy (DN) is one of the microvascular complications, which represents the major cause of end-stage renal disease in DM patients [4]. DN occurs in 20% to 40% of all diabetic cases [5,6]. ADA (2019) guidelines for screening of chronic kidney disease (CKD) in diabetic patients, and The Kidney Disease: Improving Global Outcomes (KDIGO) recommends annually at least, assessing urinary albumin/creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) in patients with T1DM with duration ≥5 years, and in all patients with T2DM and hypertension. ACR is considered more sensitive and dependable biomarker to identify the patients who are at a risk for progression to DN [7].

Albuminuria is defined as above than 30 mg/day of albumin urine excretion, and is the initial sign of DN or cardiovascular dysfunction [8,9].

Numerous epidemiological studies show that ethnicity, family history, elevated blood pressure, hyperglycemia, dyslipidemia, obesity, and insulin resistance are the main risk factors of DN and other putative risk factors involve elevated glycosylated hemoglobin level (HbA1c), proteinuria and smoking [10].

This study was conducted to identify risk factors for occurrence and progression of DN among group of Iraqi children with T1DM.

Methods

This cross-sectional study was conducted at the Diabetic Pediatric Clinic in Al-Imamein Al-Kadhimein Medical City, Ibn Al-Balady Children and Maternity Hospital and Al-Ramadi Teaching Hospital for Gynecology and Pediatrics from November 2019 to April 2020.

Diagnosis of DM of all patients was according to ADA (2020) [3].

The study group was divided into two groups:

1. Normoalbuminuria (without DN): N = 40 (22 male and 18 female) included patients with uACR <30 mg/g creatinine.
2. Microalbuminuria (with DN): N = 40 (22 male and 18 female) included patients with uACR = 30-299 mg/g creatinine.

Patient with chronic inflammatory condition (autoimmune disease, systemic Lupus Erythematosus), other renal disease, liver disease, malnourished children and malignancies were excluded.

Ethical approval was taken from parents of children involved in this study. The protocol of study was approved by the Scientific Committee of Department of Pediatrics, College of Medicine, Al-Nahrain University.

Five milliliters of venous blood were obtained from each fasting (8 hour fast) patient. Also freshly voided morning urine samples were collected from each patient.

Blood and urine samples were immediately transferred to Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, for biochemical tests using LINEAR kits (Spain).

Normal reference values of blood chemistries were applied accordingly [11]. Determination of the stage of CKD was done by calculating the eGFR using Schwartz formula [12].

Statistical analysis

All data were analyzed with statistical package for social sciences (SPSS). Continuous variables were express as Mean±standard deviation (SD) and analyzed with independent student t-test. Categorical variables were expressed as number and percentage and analyzed with Chi-square. Univariate and multivariate logistic regressions were used to predict the factors associated with the development DN. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of eGFR and uACR with T1DM. The area under the curve (AUC) provides a useful tool to compare different biomarkers. Whereas an AUC value close to 1 indicates an excellent diagnostic and

predictive marker. Pearson's correlation was used to explore the possible correlation between different quantitative variables in diabetic patients with and without DN. Odds ratio (OR) used to measure association between an exposure and an outcome. A p ≤0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the patients

The mean±SD of age of diabetic patients with DN significantly was higher than diabetic patients without nephropathy (P <0.001). In contrast, there were no significant differences between the two groups in body mass index (BMI), gender distribution, systolic and diastolic blood pressure P >0.05. However, patients with DN showed significantly higher fasting blood sugar (FBS), HbA1c and duration of than patients without DN as shown in table (1).

Table 1. Demographic and clinical characteristics of the patients

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value
Age (years)	Mean±SD	11.6±3.04	13.7±2.52	0.001
BMI (kg/m^2)	Mean±SD	19.35±0.85	19.56±1.24	0.380
Gender	Male N (%) Female N (%)	22 (55%) 18 (45%)	22 (55%) 18 (45%)	1.000
Duration (years)	Mean±SD	2.83±1.15	8.35±3.72	<0.001
SBP (mmHg)	Mean±SD	118.5±9.82	123.0±11.47	0.423
DBP (mmHg)	Mean±SD	78.0±7.12	82.75±9.2	0.391
FBS (mg/dl)	Mean±SD	229.9±42.77	278.23±40.03	<0.001
HbA1c (%)	Mean±SD	8.97±0.95	9.76±1.01	0.031

Values are expressed as mean ± standard deviation, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, HbA1c: glycated hemoglobin

Lipid profile

The mean±SD of cholesterol, triglycerides (TG), low-density lipoprotein (LDL-c) and very low-density lipoprotein (VLDL-c) in diabetic patients with DN was significantly higher than that of patients without DN (P <0.001). In contrast, patients without DN had significantly higher level of high-density lipoprotein (HDL-c) than those with DN as shown in Table (2).

Table 2. Lipid profile of the patients

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value
Cholesterol (mg/dl)	Mean±SD	154.9±19.0	174.6±17.56	<0.001
TG (mg/dl)	Mean±SD	117.83±26.95	150.98±28.09	<0.001
LDL-c (mg/dl)	Mean±SD	91.08±16.6	112.09±16.12	<0.001
VLDL-c (mg/dl)	Mean±SD	23.56±5.39	30.1 9± 5.62	0.018
HDL-c (mg/dl)	Mean±SD	38.57±13.3	32.60±13.75	0.044

Values are expressed as mean ± standard deviation, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Renal functions tests

All parameters included in renal function tests (urea, creatinine, and ACR) were recorded in higher level in patients with DN than those without DN, with highly significant differences. In contrast, eGFR was significantly lower in patients with DN compared to those without DN P <0.001 and significantly lower levels of serum albumin, P <0.021 (Table 3).

Table 3. Renal functions tests of the patients

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value
B. Urea (mg/dl)	Mean±SD	33.62±3.79	40.92±4.78	<0.001
S. Creatinine (mg/dl)	Mean±SD	0.72±0.14	1.04±0.21	<0.001
S. Albumin (g/dl)	Mean±SD	4.08±0.35	3.35±0.38	0.021
eGFR (ml/min)	Mean±SD	109.22±8.81	84.35±12.28	<0.001
uACR (mg/g)	Mean±SD	18.28±4.32	52.69±39.48	<0.001

Values are expressed as mean ± standard deviation, eGFR: Estimated glomerular filtration rate, uACR: Urinary albumin to creatinine ratio

Predictors of DN

Univariate logistic regression test was used to find out the predication value of each parameter that showed significant variation between patients with and without DN. Through this test, the OR with its corresponding 95% CI were calculated.

Demographic and clinical predictors

Each of age, duration of DM, FBS and HbA1c were significantly associated with DN. However, duration showed higher predictive value followed by FBS, and HbA1c as shown in table (4).

Table 4. Demographic variable as predictors for diabetic nephropathy

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value	Odds ratio (95%CI)
Age (years)	≤12 N (%)	22 (55%)	11 (27.5%)	0.012	3.22 (1.27-8.19)
	>12 N (%)	18 (45%)	29 (72.5%)		
Duration (years)	≤5 N (%)	36 (90%)	13 (32.5%)	<0.001	18.69 (5.48-63.74)
	>5 N (%)	4 (10%)	27 (67.5%)		
FBS (mg/dl)	≤250 N (%)	30 (75%)	11 (27.5%)	<0.001	7.91 (2.92-21.43)
	>250 N (%)	10 (25%)	29 (72.5%)		
HbA1c (%)	≤9 N (%)	26 (65%)	10 (25%)	<0.001	5.57 (2.12-14.65)
	>9 N (%)	14 (35%)	30 (75%)		

FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin

Lipid profile as predictor for DN

Each of cholesterol, LDL-c and VLDL-c was significantly associated with development of DN, with VLDL-c was the most powerful predictor compared with the other two components. In contrast, HDL-c was inversely associated with the development of DN (OR =

0.04, 95% CI = 0.01-0.15, P <0.001) as shown in table (5).

Table 5. Lipid profile as predictor for diabetic nephropathy

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value	Odds ratio (95%CI)
Cholesterol (mg/dl)	≤165 N (%) >165 N (%)	26 (65%) 14 (35%)	13 (32.5%) 27 (67.5%)	<0.001	3.86 (1.53-9.75)
TG (mg/dl)	≤150 N (%) >150 N (%)	26 (65%) 14 (35%)	13 (32.5%) 27 (67.5%)	<0.001	3.86 (1.53-9.75)
LDL (mg/dl)	≤100 N (%) >100 N (%)	26 (65%) 14 (35%)	9 (22.5%) 31 (77.5%)	< 0.001	6.4 (2.89-17.15)
VLDL (mg/dl)	≤30 N (%) >30 N (%)	37 (92.5%) 3 (7.5%)	18 (45%) 22 (55%)	< 0.001	15.07 (3.98-57.1)
HDL (mg/dl)	≤35 N (%) >35 N (%)	4 (10%) 36 (90%)	29 (72.5%) 11 (27.5%)	< 0.001	0.04 (0.01-0.15)

TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Renal function tests as predictors for DN

For those parameters which were positively associated with DN (urea, creatinine, and ACR), the ACR was the most powerful predictor for DN. On the other hand, eGFR had a greater prediction value than albumin as a negative predictor for development of DN, Table (6).

Table 6. Renal function tests as Predictors for diabetic nephropathy

Variables		Without Nephropathy (N=40)	With Nephropathy (N=40)	P value	Odds ratio (95%CI)
B. urea (mg/dl)	≤35 N (%) >35 N (%)	28 (70%) 12 (30%)	2 (5%) 38 (95%)	< 0.001	44.33 (9.18-214.06)
S. Creatinine (mg/dl)	≤0.9 N (%) >0.9 N (%)	35 (87.5%) 5 (12.5%)	11 (27.5%) 29 (72.5%)	< 0.001	18.45 (5.85-59.23)
S. Albumin (g/dl)	≤3.5 N (%) >3.5 N (%)	4 (10%) 36 (90%)	27 (67.5%) 13 (32.5%)	< 0.001	0.05 (0.02-0.18)
eGFR (ml/min)	≤95 N (%) >95 N (%)	4 (10%) 36 (90%)	34 (85%) 6 (15%)	< 0.001	0.02 (0.01-0.08)
uACR (mg/g)	≤25 N (%) >25 N (%)	38 (95%) 2 (5%)	6 (15%) 34 (85%)	< 0.001	107.6 (20.3-569.6)

eGFR: Estimated glomerular filtration rate, uACR: Urinary albumin to creatinine ratio

Multivariate regression

When all variables were entered in multivariate regression model, only 3 (out of 14) remained significantly associated with the development of DN. Of those, ACR >25 mg/g was the most powerful independent predictor (OR = 11.78, 95%CI = 7.45-42.82, P = 0.009). In contrast, eGFR, was a negative predictor of DN (OR = 0.26, 95%CI = 2.79-18.93, P = 0.026). HbA1c level >9% was a positive predictor of DN (OR = 4.15, 95% CI = 3.88-36.91) as shown in table (7).

Table 7. Multivariate regression

Variables	P value	Odds ratio (95%CI)
Age (>12 years)	0.112	3.26 (2.71-13.67)
Duration (>5 years)	0.097	2.18 (1.91-17.53)
FBS (>250 mg/dl)	0.107	3.31 (2.24-21.81)
HbA1c (>9%)	0.031	4.15 (3.88-36.91)
Cholesterol (>165 mg/dl)	0.219	4.44 (1.09-38.73)
LDL-c (>100 mg/dl)	0.181	3.92 (2.98-26.51)
VLDL-c (>30 mg/dl)	0.285	1.89 (1.07-13.98)
HDL-c (≤35 mg/dl)	0.107	0.68 (3.65-22.87)
Blood urea (>35 mg/dl)	0.088	4.32 (2.11-17.67)
Serum creatinine (>0.9 mg/dl)	0.071	2.27 (1.16-21.28)
Serum albumin (≤3.5 g/dl)	0.114	0.34 (2.08-24.41)
eGFR (≤95 ml/min)	0.026	0.26 (2.79-18.93)
uACR (>25 mg/g)	0.009	11.78 (7.45-42.82)

FBS: Fasting blood sugar, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, eGFR: Estimated glomerular filtration rate, uACR: Urinary albumin to creatinine ratio

Diagnostic value

According to the results of multivariate regression, ROC curve was used to assess the diagnostic value of all variables, which showed a significant association with the development of DN.

Glycated hemoglobin (HbA1c):

The AUC was 0.732, 95% CI = 0.622-0.841, P <0.001. The sensitivity and specificity of the test at cut off value of HbA1c = 9.1% were 0.75 and 0.65, respectively (Figure 1).

Urinary albumin/creatinine ratio (uACR)

The area under the curve (AUC) was 0.968, 95% CI = 0.936 - 0.999, P < 0.001. The sensitivity and specificity of the test at cut off value of uACR = 24.5 mg/g were 90% for each (Figure 2).

Estimated glomerular filtration rate

The AUC was 0.938, 95% CI = 0.883-0.993, P <0.001. The sensitivity and specificity of the test at cut off value of eGFR = 97 ml/min were 90% and 85% respectively (Figure 3).

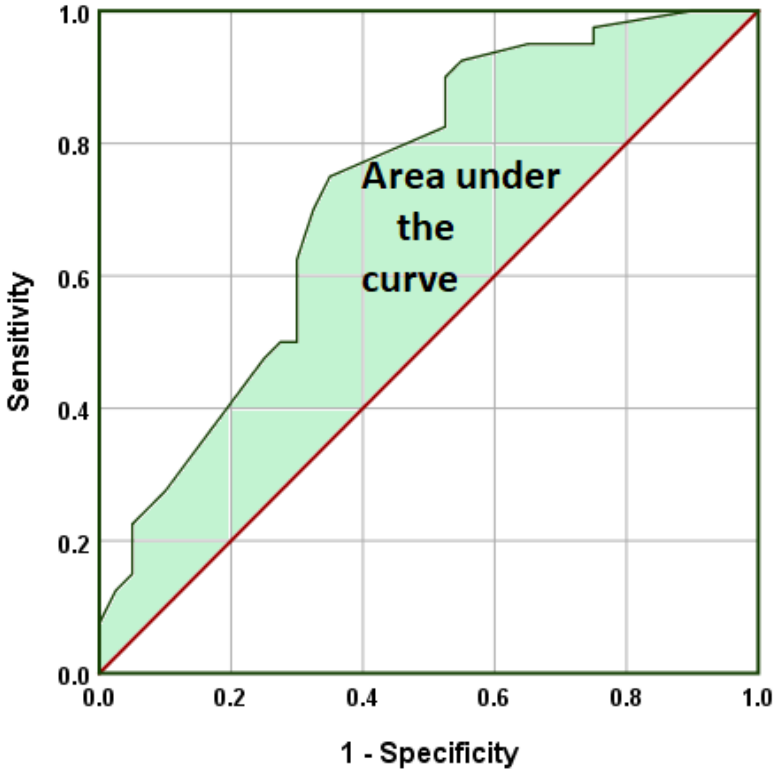

Figure 1. Receiver operating characteristic curve for HbA1c% in the context of detection of nephropathy in patients with T1DM

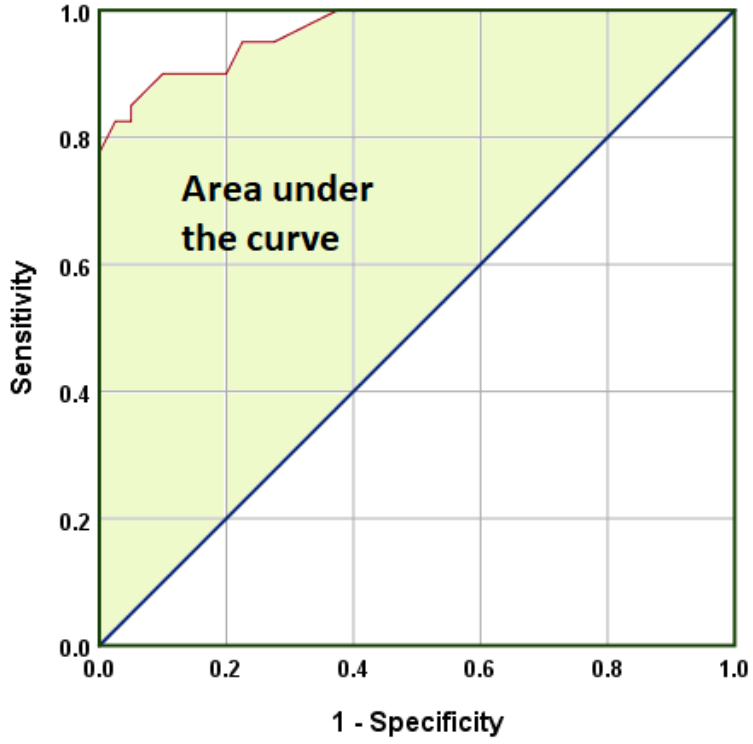

Figure 2. Receiver operating characteristic curve for urinary albumin/creatinine ratio (uACR) in the context of detection of nephropathy in patients with T1DM

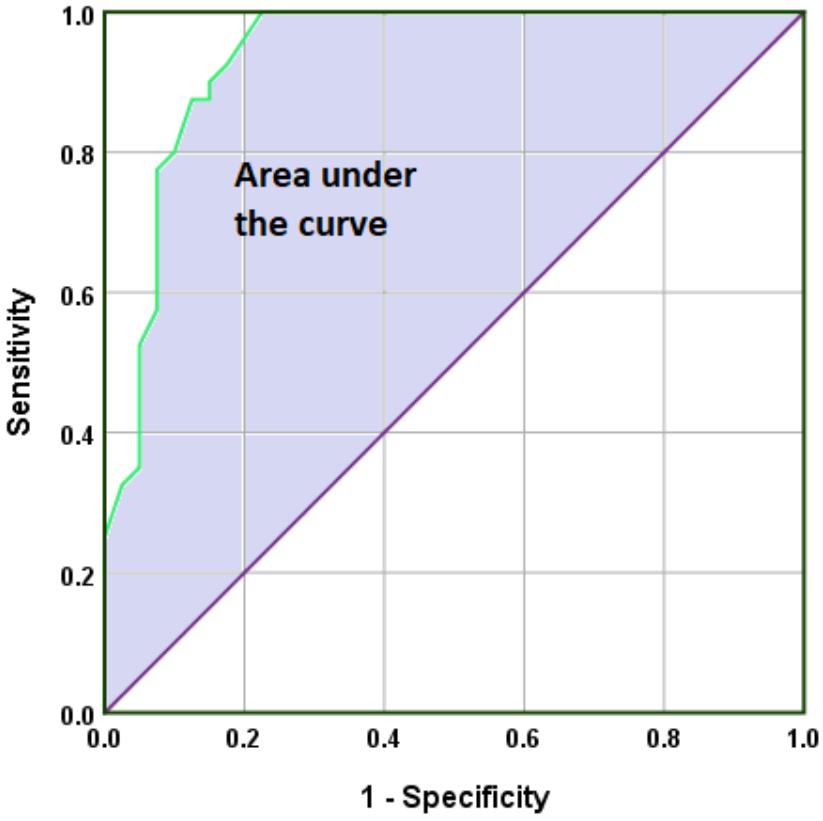

Figure 3. Receiver operating characteristic curve for estimated glomerular filtration rate (eGFR) in the context of detection of nephropathy in patients with T1DM

Discussion

Demographic and clinical characteristics of the patients

Several studies reported that the longer duration of DM and higher HbA1c level were significantly higher in children with Microalbuninuria when compared with normoalbuminuria children [13-19].

Several studies highlighted the effect of older age and longer duration of diabetes as predictor for nephropathy in T1DM patients [13,20,21].

Longer disease duration with longer exposure to hyperglycemia induce advanced glycation end products accumulation and leads to renal endothelial cells dysfunctions, so hyperglycemia is the driving force for the development of DN [17,22].

It has been argued that poor glycemic control in adolescents is directly proportionate to increasing age. This may be correlated to physiologic insulin resistance because of increased sex steroids, growth hormone and reduced free insulin-like growth factor [23].

Compared to other studies, systolic and diastolic blood pressure and BMI showed no statistically significant differences were found in both groups [13,16,24]. In Aljabri et al. (2013) study, there was no significant difference in gender with DN [18]. This result agrees with present study.

Regarding lipid profile, several studies found higher readings of cholesterol, TG, LDL-c and VLDL-c in patients with DN compared to patients without DN. increased cholesterol and LDL-c levels have been proven to be risk factors for DN [16,19, 25,26].

cholesterol is associated with persisted microalbuminuria in adolescents with T1DM [25]. The finding of significant decreased in HDL-c concentration in children with DN compared with normoalbuminuria patients was similar to three studies [19,27,28]. Another study showed that glycemic control significantly influenced

changes in lipid levels except HDL-c. The adverse effect of glycemic control could be due to glycation of lipoproteins, with subsequent reduction of their catabolism and to stimulation of transfer of cholesteryl esters from HDL-c to apolipoprotein B-containing lipoproteins [29]. Abnormal lipid profiles could cause tubule damage via deposition of lipids in renal tubule and may also develop in association with inflammation in vessel wall, therefore patients with hyperlipidemia shows higher ACR [30].

The changes in eGFR typically reflect derangement of renal function due to injury, with increasing the damage of the kidney, leading to decrease in the elimination of the creatinine and urea from the blood [21].

The present study was agreed with Zhang et al. (2019) who found hypoalbuminemia is frequently present in most patients with DN; the lower serum level of albumin was associated with the reduced renal function in patients with DN [31].

Renal function tests and HbA1c as predictors for DN

The current study showed that uACR is the most powerful predictor for DN followed by eGFR and HbA1c. Sueud et al. (2019) reported that the ACR has an excellent diagnostic power and it is a precise biomarker with best specificity, good sensitivity and acceptable accuracy in predicting the severity of nephropathy in patients with diabetes [32].

Two studies reported microalbuminuria was not only as an indicator of DN risk but also as a strong predictor of its progression, and albuminuria remain one of the strongest risk factors for progression of renal disease. ACR improves risk stratification and predicts CKD progression and mortality. Albuminuria and eGFR independently predicted kidney disease progression and the combination of both markers was superior to predict those subjects as highest risk for ESRD development [33,34].

In conclusion, ACR and eGFR are the strongest predicting factors for development and progression of DN in Iraqi children with T1DM but there many associated but inadequately controlled risk factors that need to be followed.

Understanding the relationship among the risk factors for DN in children and adolescents with T1DM helps us to take earlier steps for slowing down CKD.

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Author contribution

All authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data, as well as the writing of the manuscript.

Conflict of interest

The authors declare there is no conflict of interest.

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