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ORIGINAL ARTICLE

Pentosidine and Renal Resistance Index Are Potential Early Predictors of Diabetic Nephropathy in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Background: Diabetic nephropathy (DN) is the primary cause of end-stage renal disease in children with type 1 diabetes mellitus (T1DM), and it can be prevented. Therefore, it is critical to identify children who are at risk of developing DN as soon as possible. Diabetic nephropathy (DN) can be diagnosed using pentosidine and renal resistance index.

Aim of this study: to elaborate the significance of serum pentosidine and renal resistance index as early indicators of Diabetic kidney disease (DKD) in type1 diabetes mellitus(T1DM) pediatric patients.

Methods: This cross-sectional study was conducted on 48 diabetic children at the pediatric outpatient clinics of Zagazig University Hospitals. Comprehensive assessments included medical history, physical examinations, renal resistance index using doppler sonography, and laboratory tests, including hemoglobin A1C (HbA1C), serum creatinine, microalbuminuria, and serum pentosidine.

Results: Serum pentosidine had high diagnostic accuracy for early-stage diabetic nephropathy, with a sensitivity of 90%, a specificity of 97.4%, and an area under the curve (AUC) of 0.964. The mean renal index measured by Doppler sonography was 0.68, indicating a significant relationship with early-stage diabetic kidney disease. The pentosidine and mean resistance index were significantly positively correlated with age, duration of the disease, estimated glomerular filtration rate, and HbA1C.

Conclusion: The serum pentosidine level and renal resistance index are reliable early predictors of renal damage in pediatric patients with type 1 diabetes mellitus. To avoid progression to end-stage renal disease, it is crucial to identify children at risk promptly and initiate preventative measures.

Keywords: pentosidine, renal resistance index, diabetic nephropathy, children, type 1 diabetes mellitus.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) with juvenile-onset has become much more common during the past ten years, especially in children under the age of five [1]. Persistent proteinuria greater than 500 mg/24 h or albuminuria larger than 300 mg/24 h are indicators of diabetic nephropathy (DN) [2]. Nearly half of all new occurrences of end-stage renal disease (ESRD) in the USA are caused by DN, which continues to be the primary cause of ESRD in the Western world [3]. However, only a tiny percentage of T1-DM patients go on to develop ESRD [1]. Early structural and functional renal abnormalities occur in less than 1% of the juvenile population [4], even though overt DN is uncommon in children with type-1 or type-2 diabetes. [3]

All T1-DM patients appear to have structural changes of diabetes in the glomerulus; some develop

these changes very slowly, while others develop them so quickly that in as little as ten years, overt DN results. Patients with T1-DM have glomerular lesions prior to the start of DN clinical symptoms. [5] Even in the early stages of DN, Doppler sonography may be a valuable complementary test in the assessment process [6]. In actuality, it appears that functional changes in endothelial control over vascular tone and wall contact with circulating cells characterize the early stages of vascular involvement. An accurate, non-invasive method of assessing arterial function is renal Doppler monitoring of renal index (RI), which is especially helpful in the early detection of vascular involvement [7]. Doppler ultrasonography can identify the high renal resistance index (RI) that may exist in the early stages of diabetic nephropathy (DN) before microalbuminuria develops [8].

A non-enzymatic Maillard process involving the free amino groups of proteins and carbohydrates, such as arginine and lysine residues, produces reactive derivatives. These groups go through a series of intricate processes that result in the complex group of irreversible molecules known as AGEs, which cause the complex illness known as metabolic syndrome [7]. It was discovered that the production of these compounds was caused by the covalent interaction between the free amino and thiol groups in proteins and methylglyoxal (MG) and glyoxal on one side [9]. Pentosidine is a well-established biomarker for the creation and accumulation of advanced glycation end products (AGEs), which play a critical role in the development of diabetes and vascular disorders [10].

The use of pentosidine as a check would give diabetic patients a powerful long-term glycemic management tool that can significantly affect glycated hemoglobin levels. Spectrophotometry, ELISA, HPLC, and mass spectrometry are among the techniques used to analyze pentosidine, a fluorescent agent [11]. Among the chemically defined AGEs, pentosidine is one of the best molecules found in humans. Previous research has found a relationship between diabetes patients' thicker and stiffer arterial walls and elevated serum pentosidine levels [12]. In essence, oxidation and glycosylation can lead to the production of pentosidine. One possible explanation for the raised pentosidine plasma level in diabetes is increased oxidative stress. In diabetic kidney disease, plasma pentosidine is highly correlated with decreased GFR, elevated oxidative stress, and inflammatory conditions[13].

The gold standard study design for estimating predictive value would be a prospective cohort study with sufficient follow-up time between outcomes. However, in this particular case, there is a problem with such a perfect study design: The trial should extend at least that long to examine a substantial sample of patients who developed a specified outcome since DN occurs after 20 to 30 years on average [14]. While doing such a study is feasible [15, 16], it would need a 20–30 year wait period for results that could enhance the management of children with DM-T1. Our study's goal was to evaluate the relationship. Thus, this study aimed to assess the significance of serum pentosidine and renal resistance index as early indicators of DKD in T1DM pediatric patients.

We hypothesize that the pentosidine and Renal Resistance Index play a role in diagnosing DKD. Therefore, we aimed to assess their significance as early indicators of DKD.

Therefore, the current study aims to assess the relationship between pentosidine and kidney problems in DN patients.

METHODS

We conducted this cross-sectional study at Zagazig University Children's Hospital's Nephrology and Endocrinology Unit during the period from January 2024 to July 2024 on 48 children with T1DM. For their children to participate, the parents or guardians gave their written, informed consent. The consent was proved by the medical ethical committee of Zagazig University Hospital (IRB number 11100-11-9-2023).

- ***Inclusion criteria*** were patients with T1DM between the ages 6 and 18 years with at least 5 years from the onset of diabetes mellitus.
- ***Exclusion criteria*** included patients with other endocrinal disorders, congenital or acquired heart diseases and renal diseases, patients with surgical intervention of thyroid gland, and patients with chronic illness or chronic drug therapy causing kidney injury.

Every patient had the following procedures: a thorough history taking, a thorough abdominal and general examination, including anthropometric measurements (weight, height, and BMI), and a renal examination focusing on signs of edema, renal failure, and blood pressure. Systolic and diastolic blood pressure readings were taken three times for each participant using a calibrated sphygmomanometer and the proper cuff. Depending on age, sex, and body height, the European Society of Hypertension's criteria were followed to calculate the pressure gradation [17].

Laboratory investigations:

Early morning, urine samples were collected from children and teenagers diagnosed with T1DM. Five milliliters of venous blood were drawn and placed in vacuum tubes. The samples intended for biochemical investigation underwent a 15-minute, 1500 rpm centrifugation. Following this, the serum was extracted and kept cold until further examination.

Hemoglobin A1C (HbA1C) was determined by the agglutination reaction method of monoclonal antibodies, with the normal range being 4.5-6.5%. Serum creatinine levels were measured using an Architect C8000 analyzer and an alkaline picrate kinetic technique. The particle enhanced turbidimetric inhibition immunoassay, or PETINIA, was used to assess the amount of microalbumin [18]. The diet was modified for renal disease. The Schwartz formula was used to determine eGFR regarding the normal range of 80-130 ml/min/1.73 m^2. eGFR = k x (height in cm) ÷ serum creatinine. [19]

Special investigations:

Renal resistance index (RI) and pentosidine were the two early prognostic markers of DKD that we used.

Renal Resistance Index (RI):

The RI, computed using the formula RI = (peak systolic velocity - end-diastolic velocity) / peak systolic velocity, can be used to measure resistance to blood flow.

Every one of the chosen cases underwent a B-mode ultrasonographic examination of both kidneys in order to rule out other renal illnesses and evaluate the size, shape, and echogenicity of the kidneys. Additionally, a Toshiba Nemio Medical System 3.5 MHZ convex transducer was used to perform color Doppler ultrasonography assessment of the intra-renal arteries.

Children were fasted for around three hours before being assessed in the prone position. The inter-lobar arteries were color-positioned before the Doppler sample volume was placed. All waveforms were measured on the greatest Doppler scale using the lowest pulse repetition frequency that prevents aliasing, and a low wall filter was employed. The transducer's angle was adjusted to provide the clearest and largest waveform amplitude. Each vessel's three subsequent cardiac cycles were recorded. After manually choosing the maximum systolic and diastolic velocities, the ultrasound unit's inbuilt software was used to compute the RI. RI was obtained for the three waveforms of the three vessels at the three different sites (upper, middle, and lower zones). The mean value for each kidney was then determined. Each patient's left and right kidneys showed comparable patterns and statistics. To prevent inter-observer variability, the same examiner conducted each Doppler examination. A normal RI for adults and children six years of age and up is less than 0.7 [12].

Pentosidine:

Enzyme-linked immunosorbent assay (ELISA) was utilized to measure pentosidine with the Human Pentosidine (PTD) ELISA Kit Instructions and ELISA Kit Catalog Number 201-12-0005. In order to measure the amount of human pentosidine, we first added patient serum to a well that had been pre-coated with a monoclonal antibody of human pentosidine, followed by the addition of biotin-labeled pentosidine antibodies combined with streptavidin-HRP to form an immune complex, then incubation at 37 °C for 60 minutes was done, followed by washing steps to eliminate any remaining uncombined enzyme. After adding Chromogen, Solutions A and B, the liquid's color turned blue, and after adding the stop solution (H2SO4), yellow was produced by the acidic reaction. Ultimately, using the Tecan Austria GmbH spectrophotometry reader (5082 Grodig, Austria, REF 16039400), the optical density (OD) of the plate at 450 nm wavelength was measured within 15 minutes of adding the stop solution. The linear regression equation for the standard curve was determined based on the concentration of the standards and the associated OD values. Then, the concentration of the corresponding sample was determined by applying the OD values of the sample to the regression equation.

There was a positive correlation between the sample's concentration of the human substance pentosidine and its color chroma. The detection of human (PID) using this ELISA kit is based on the double-antibody sandwich approach.

STATISTICAL ANALYSIS

Version 26 of the SPSS (Statistical Package for the Social Sciences) program was used to analyze the data. The Spearman rank correlation coefficient, ROC curve, independent sample t-test, chi-square test, Fisher exact test, Mann-Whitney test, and linear regression analysis were all employed. $P \leq 0.05$ was chosen as the level of statistical significance. There was a highly significant difference if $p \leq 0.001$.

RESULTS

The 48 patients included in this study ranged in age from 6.5 to 17 years, with a mean age of 12.15 years. Approximately 52.1% of them were males, and 52.1% of them were from rural regions. Approximately 6.2% had a positive renal family history, and 58.3% had a positive family history of diabetes. In terms of presentation, 91.7% had polyuria, polydipsia, and polyphagia, and 52.1% had diabetic ketoacidosis (DKA). The disease's start time

varied from 1 to 11 years, with a median of 6 years. The median illness duration was 6 years, ranging from 5 to 14 years. The frequency of hospital admissions varied from 1 to 8 admissions per year, with a mean of 4.02. The median values for hypoglycemia and DKA were 0 and 3 times per previous year, respectively. The average BMI, height, and weight were 18.73 kg/m^2, 146.19 cm, and 40.98 kg, respectively. The average systolic and diastolic blood pressure measurements were 101.09 mmHg and 58.8 mmHg, respectively (Table 1).

The mean values of HbA1C and serum creatinine were 9.38% and 0.53 mg/dl, respectively. The median serum pentosidine level was 43.15 ng/ml, and the median eGFR was 104.73 ml/kg/m^2. The range of the mean resistance index was 0.6 to 0.68. Approximately 20.8% of people have early-stage diabetic renal damage (Table 2).

The entire duration of the disease, age, hospital admissions, and frequency of DKA are all positively correlated with serum pentosidine in a statistically significant way. Serum pentosidine does not statistically significantly correlate with anthropometric measurements, blood pressure, or the frequency of hypoglycemia or onset of T1DM. Serum pentosidine and all forms of microalbuminuria, HbA1C, and serum creatinine have a statistically significant positive correlation. Serum pentosidine and eGFR had a statistically significant negative correlation. The correlation between serum pentosidine and mean, right, or left kidney RI is statistically significant (Table 3).

Among factors significantly correlated with serum pentosidine, only disease duration (unstandardized β = 3.254, p = 0.021), microalbuminuria (unstandardized β = 1.99, p <0.001), and HbA1C (unstandardized β = 3.96, p = 0.017) were significantly independently associated with it (Table 4).

An age-related statistically significant correlation exists between the occurrence of early stages of diabetic nephropathy. The incidence of early stages of diabetic nephropathy is not statistically significantly correlated with blood pressure, anthropometric measurements, sex, or place of residence. There is a statistically significant correlation between the frequency of DKA, the duration of the condition, hospital admissions, and the incidence of early stages of diabetic nephropathy. The incidence of early stages of diabetic nephropathy and renal history, presentation, or consequences (apart from the frequency of hypoglycemia) have statistically no meaningful relationship. A statistically significant correlation has been observed between the occurrence of early stages of diabetic nephropathy and all of the following: HbA1C, microalbuminuria, and serum creatinine, which are all significantly higher in diabetic nephropathy patients. The association between the occurrence of early stages of diabetic kidney disease and HbA1C is statistically significant. A statistically significant association has been observed between the mean RI and the occurrence of early stages of diabetic nephropathy. Serum pentosidine levels are significantly higher in individuals with diabetic nephropathy, and there is a statistically significant correlation between the occurrence of early diabetic kidney disease and these levels. (Table 5).

The best cutoff value of serum pentosidine in the diagnosis of early-stage diabetic nephropathy is ≥80.115 mg/ml with an area under curve of 0.964, sensitivity of 90%, specificity of 97.4%, positive predictive value of 90%, negative predictive value of 97.4%, and overall accuracy of 95.8% (p<0.001) (Table 6, figure 1S).

Table 1: Baseline data of studied patients

	Mean ± SD or number	Range or percentage
Age (year)	12.15 ± 3.04	6.5 – 17
Gender Female Male	 23 25	 47.9% 52.1%
Residence Rural Urban	 25 23	 52.1% 47.9%
Family History of Diabetes mellitus Negative Positive	 20 28	 41.7% 58.3%

	Mean ± SD or number	Range or percentage
Family History of kidney disease Negative Positive	 45 3	 93.8% 6.2%
Complications of diabetes mellitus		
Frequency of Hospital admission per last year	4.02 ± 1.74	1 – 8
DKA episodes	3(2 – 4)	1 - 6
Hypoglycemic episodes	0(0 – 1)	
Onset of diabetes mellitus	6(2.38 – 8)	1 – 11
Disease duration (year)	6(5 – 7.75)	5 – 14
Weight (kg)	40.98 ± 11.17	21 – 65
Height (cm)	146.19 ± 16.45	112 – 175
BMI (kg/m^2)	18.73 ± 1.64	14.72 – 21.79
Systolic blood pressure (mmHg)	101.09 ± 10.16	80 – 120
Diastolic blood pressure (mmHg)	58.8 ± 7.09	50 – 80

Diabetic ketoacidosis (DKA),Basal metabolic index (BMI)=body weight in kilogram /height in meters squared

Table 2: Distribution of studied patients according to laboratory and radiological data

	Mean ± SD	Range
Serum creatinine (mg/dl)	0.53 ± 0.17	0.2 – 0.9
HbA1c (%)	9.38 ± 1.7	7 – 12.5
Microalbuminuria(mg/24hr)	20.5 ± 8.18	9 – 40
Sonographic resistive index (RI) of the right kidney	0.63 ± 0.12	0.06 – 0.7
Sonographic resistive index (RI) of the left kidney	0.65 ± 0.04	0.59 – 0.7
Mean resistance	0.65 ± 0.03	0.6 – 0.68
	Median (IQR)	**Range**
eGFR (ml/min/1.73m2) **<90** **≥90**	104.73(92.62 – 152.81) 10 38	80.06 – 320.08 20.8% 79.2%
Serum pentosidine (ng/dl)	43.15(33.08 – 66)	22.1 – 115

Hemoglobin A1C (HbA1C), Estimated glomerular filtration rate(eGFR) is calculated using Schwartz formula for children

Table 3: Correlation between serum pentosidine and different data

	r	p
Age (year)	0.366	0.01*
Onset of diabetes mellitus (year)	-0.136	0.356
Disease duration (year)	0.488	<0.001**
Hospital admission	0.346	0.016*
DKA episodes	0.383	0.007*
Hypoglycemic episodes	-0.078	0.6
Weight (kg)	0.088	0.552
Height (cm)	0.132	0.371
BMI (kg/m^2)	-0.031	0.834

	r	p
Systolic blood pressure (mmHg)	0.017	0.913
Diastolic blood pressure (mmHg)	0.151	0.318
Microalbuminuria (mg/24hr)	0.569	<0.001**
Serum creatinine (mg/dl)	0.451	<0.001**
HbA1c (%)	0.403	0.004*
eGFR (ml/min/1.37m2)	-0.478	<0.001**
Sonographic resistive index (RI) of the right kidney	0.406	0.004*
Sonographic resistive index (RI) of the left kidney	0.317	0.028*
Mean resistance index	0.394	0.006*

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant. Diabetic ketoacidosis (DKA), Estimated glomerular filtration rate (eGFR) is calculated using the Schwartz formula for children, Resistance index (RI), and Hemoglobin A1C (HbA1C).

Table 4: Linear stepwise regression analysis of factors associated with serum pentosidine

	Unstandardized Coefficients		Standardized Coefficients	t	P	95.0% Confidence Interval	
	β	Std. Error	Beta			Lower	Upper
(Constant)	-46.788	13.358		-3.503	0.001**	-73.708	-19.868
Disease duration	3.254	1.472	0.224	2.394	0.021*	0.558	6.49
Microalbuminuria (mg/24hr)	1.99	0.353	0.562	5.632	<0.001**	1.278	2.702
HbA1c %	3.96	1.59	0.232	2.491	0.017*	0.756	7.165

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant. Hemoglobin A1C (HbA1C).

Table 5: Relation between early-stage Diabetic kidney disease and different data

	Diabetic kidney disease N=10 (%)	Normal kidney function N=38 (%)	χ^2	p
Gender Female Male	 4 (17.4%) 6 (24%)	 19 (82.6%) 19 (76%)	0.317	0.573
Residence Rural Urban	 6 (24%) 4 (17.4%)	 19 (76%) 19 (82.6%)	0.317	0.573
Age (year)				
Mean ± SD	14.6 ± 2.76	11.5 ± 2.79	3.129	0.003*
Weight (kg)				
Mean ± SD	44.1 ± 12.99	40.16 ± 10.68	0.993	0.326
Height (cm)				
Mean ± SD	150.1 ± 18.05	145.16 ± 16.11	0.843	0.404
BMI (kg/m^2)				
Mean ± SD	19.05 ± 1.84	18.65 ± 1.6	0.667	0.502
Systolic blood pressure (mmHg)				
Mean ± SD	100.5 ± 12.12	101.25 ± 9.74	-0.204	0.839
Diastolic blood pressure (mmHg)				
Mean ± SD	59.0 ± 8.43	58.75 ± 6.8	0.098	0.923

	Diabetic kidney disease N=10 (%)	Normal kidney function N=38 (%)	χ^2	p
Family history of diabetes Negative Positive	 4 (20%) 6 (21.4%)	 16 (80%) 22 (78.6%)	0.014	0.904
Family history of kidney disease Negative Positive	 10 (22.2%) 0 (0%)	 35 (77.8%) 3 (100%)	Fisher	>0.999
DKA episodes Absent Once More than once	 2 (8.7%) 7 (29.2%) 1 (100%)	 21 (91.3%) 17 (70.8%) 0 (0%)	5.748¥	0.019*
Hypoglycemic episodes Absent Once More than once	 8 (25.8%) 2 (16.7%) 0 (0%)	 23 (74.2%) 10 (83.3%) 5 (100%)	1.808¥	0.179
Onset (year)				
Mean ± SD Median (IQR)	5.5(2 – 6.63)	6(388 – 8)	-1.406	0.296
Disease duration (year)				
Mean ± SD Median (IQR)	8.5(6.75 – 11.25)	6(5.5 – 7)	-3.627	<0.001**
Hospital admission				
Mean ± SD Median (IQR)	6(4.75 – 7)	3.5(2 – 5)	-3.129	<0.001**
eGFR (ml/min/1.73m2)				
Median (IQR)	82.6(82.03 – 82.6)	115.64(101.48 – 161.86)	-4.285	<0.001**
Microalbuminuria (mg/24hr)				
Mean ± SD	31.9 ± 4.93	17.05 ± 5.65	7.576	<0.001**
Serum creatinine (mg/dl)				
Mean ± SD	0.74 ± 0.1	0.48 ± 0.14	5.552	<0.001**
HbA1c (%)				
Mean ± SD	11.15 ± 1.63	8.92 ± 1.39	-3.436	<0.001**
Mean RI				
Mean ± SD	0.68 ± 0.027	0.635 ± 0.059	2.318	0.025*
Serum pentosidine (ng/dl)				
Median (IQR)	106.15(100.5 – 112.38)	39.06(31.71 – 48.44)	-4.481	<0.001**

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant. Estimated glomerular filtration rate (eGFR) is calculated using Schwartz formula for children. Hemoglobin A1C (HbA1C). Mean resistance index (RI)

Table 6: Performance of serum pentosidine in prediction of early-stage Diabetic kidney disease

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥80.115(ng/dl)	0.964	90%	97.4%	90%	97.4%	95.8%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

Table 7: Correlation between serum pentosidine and ultrasonographic data:

	r	p
Sonographic resistive index (RI) of the right kidney	0.406	0.004*
Sonographic resistive index (RI) of the left kidney	0.317	0.028*
Mean resistance index	0.394	0.006*

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

DISCUSSION

Diabetic nephropathy (DN), a common result of diabetes, is typified by increased excretion of albumin in the urine, specific diabetic glomerular lesions, and a progressive decrease in glomerular filtration rate (GFR). Globally, DN is a major contributor to end-stage renal disease (ESRD) and chronic kidney disease (CKD) [20].

A significant microvascular consequence of diabetes mellitus that affects 20%–40% of patients is diabetic nephropathy, which eventually requires renal replacement therapy [21]. Pathologically, DN is a widespread process that affects the interstitium, tubular epithelial cells, and glomerular endothelial cells. The progression of the condition involves several stages, such as glomerular hyperfiltration, silent normoalbuminuric phase, microalbuminuria (incipient nephropathy), macroalbuminuria (vert nephropathy), and established renal failure. The question of whether tubular epithelial and interstitial injury in diabetic individuals is related to albuminuria or occurs either before or after glomerular endothelial injury is still up for dispute [22].

Recent studies suggest that early identification of biomarkers like pentosidine, alongside measures of renal resistance, may provide a more accurate assessment of kidney function compared to traditional markers such as albuminuria and eGFR. Notably, DN can progress even in the absence of albuminuria, challenging the reliability of conventional diagnostic approaches [23]. Therefore, newer biomarkers, including TNFR1, VEGF, and pentosidine, offer promising insights into early detection and disease management [24].

An advanced glycation end product called pentosidine is created when proteins undergo non-enzymatic glycation. (AGE). Elevated levels of pentosidine are frequently observed in diabetic patients and contribute to both microvascular and macrovascular complications, including DN. Pentosidine has been identified as a biomarker for tissue damage resulting from chronic hyperglycemia and shows potential for predicting the progression of diabetic nephropathy [25].

This study aims to investigate the potential utility of serum pentosidine levels and Doppler ultrasonography in the early detection of pediatric nephropathy. The cross-sectional study, conducted in the pediatric outpatient clinics at Zagazig University Hospitals, included 48 participants with T1DM. The demographic analysis revealed a mean age ± SD of 12.15 ± 3.04 years (range: 6.5–17 years), with no statistically significant differences between patients concerning demographic characteristics.

This study revealed a statistically significant difference in DKA episodes between diabetic patients, though no significant differences were observed regarding BMI or blood pressure.

In a study by Kamaleldeen et al. [26], when microvascular problems were examined in children and teenagers with T1DM, it was discovered that patients with microvascular problems experienced DKA at a significantly higher frequency (39.2% vs. 10.6%, p = 0.000) and hypoglycemic episodes at a frequency that was noticeably higher than that of individuals without microvascular problems (47.1% vs. 29.5%, p = 0.001).

Our study demonstrates a statistically significant relationship between the incidence of diabetic renal illness in its early stages and the total eGFR (significantly lower among those with diabetic kidney disease), HbA1C, microalbuminuria, and serum creatinine (significantly higher among those with diabetic kidney disease).

Traditionally, microalbuminuria has been considered the earliest clinical indicator of DN [27]. However, research indicates that certain histopathological changes related to DN can occur even before microalbuminuria becomes detectable [28].

Efforts to identify noninvasive methods for early DN diagnosis have focused on potential biomarkers, particularly serum pentosidine. Pentosidine, an advanced glycation end product (AGE), accumulates in renal tissues and is associated with prolonged hyperglycemia and subsequent tissue damage. Elevated pentosidine levels are frequently observed in DN patients, suggesting its involvement in disease

pathogenesis [29]. Studies have demonstrated that increased pentosidine levels correlate with the progression of renal dysfunction in pediatric T1DM patients [30]. Importantly, elevated serum pentosidine levels can precede microalbuminuria, indicating that pentosidine might serve as an earlier marker for DN [31].

Serum pentosidine levels and variables such as age, disease onset, disease duration, hospital admissions, and frequency of diabetic ketoacidosis (DKA) showed a statistically significant positive association, according to our study. However, no significant correlation was found between serum pentosidine and anthropometric measures, blood pressure, or frequency of hypoglycemia. These findings are consistent with Yürük Yıldırım et al. [32]. They found that diabetes patients' mean serum pentosidine levels were considerably greater than those of controls (100.16 ± 108.28 ng/mL vs. 21.46 ± 18.59 ng/mL; p = 0.0001).

Additionally, our investigation revealed a strong relationship between microalbuminuria and serum pentosidine, and the length of the disease (unstandardized β=3.254, p=0.021) (unstandardized β=1.99, p<0.001) and HbA1C (unstandardized β=3.96, p=0.017) significantly independently associated with it. The incidence of childhood-onset type 1 diabetes has significantly increased, especially in children under five years old. DN has a significant role in the development of end-stage renal disease (ESRD), yet only a tiny percentage of T1DM patients reach this severe state [33]. Evaluating vascular resistivity within the renal parenchyma can provide diagnostic and prognostic insights [34]. Doppler ultrasonography, used to assess renal disease, detects both macroscopic vascular abnormalities and microvascular blood flow changes [35]. It is a non-invasive, cost-effective tool for predicting the course of DN [36].

In our study, doppler sonography revealed a mean resistive index (RI) of 0.68, indicating a statistically significant relationship between early-stage diabetic kidney disease and the mean RI. However, inconsistent results have been reported regarding the associations between RI and factors such as urinary albumin excretion, kidney function, age, diabetes duration, HbA1c, and blood pressure [37]. For example, Kliewer et al. [38] found variations in peak systolic velocity (PSV) among renal Doppler parameters, but these were deemed clinically insignificant. Similarly, Nektaria et al. [39] suggested that pentosidine levels were unaffected by puberty.

Our study identified the best cutoff value for serum pentosidine in diagnosing early-stage diabetic kidney disease as ≥80.115 ng/mL, 0.964 for the area under the curve (AUC). The diagnostic performance was notable, with a sensitivity of 90%, specificity of 97.4%, positive predictive value of 90%, negative predictive value of 97.4%, and overall accuracy of 95.8% ($p < 0.001$). Likewise, Tang et al. [40] reported high diagnostic accuracy for serum pentosidine, with an AUC of 0.88 in cross-sectional studies and 0.98 in cohort studies.

In contrast, Ribitsch et al. [41] reported a sensitivity of just 1.72% (95% CI: 0.044–9.2%) for serum pentosidine in diagnosing contrast-induced acute kidney injury (AKI). Variations in diagnostic accuracy for serum pentosidine in AKI have been observed, with AUC values ranging from 0.54 to 0.96 [42]. These differences could be the result of different clinical circumstances or short sample sizes. However, serum pentosidine had an AUC of 0.815 and diagnostic odds ratio (DOR) of 18.6 in predicting AKI, according to a comprehensive meta-analysis of 19 investigations involving 2,538 patients.

Serum pentosidine has shown promising prognostic accuracy, particularly in pediatric populations. Its diagnostic odds ratio (DOR) in children is 25.4, and its area under the curve (AUC) is 0.93, compared to 10.6 and 0.782 in adults, indicating its effectiveness as a predictor. [43]. The predictive accuracy of serum pentosidine levels is further supported by a more recent meta-analysis.

Despite highlighting the potential of serum pentosidine as a diagnostic tool for diabetic nephropathy, this study has limitations (DN). Because it was a cross-sectional study with a small sample size and was done at one center, it was unable to record the evolution of pentosidine levels over time. Longitudinal follow-up of these patients is crucial for understanding how pentosidine levels change as the disease progresses. Future research should involve prospective, multi-center studies with larger and more diverse patient populations to enhance our understanding of serum pentosidine's role in DN. Such research could pave the way for new interventions to prevent the severe consequences of DN in children.

According to our research, serum pentosidine levels rise in the early stages of type 1 diabetes mellitus (T1DM) even before microalbuminuria develops. Consequently, starting at the time of diagnosis, children with type 1 diabetes should be watched for diabetic kidney damage, and early intervention is needed to stop or slow the development of end-stage renal disease (ESRD). Type 1 Diabetes Mellitus (T1DM) represents a growing public health concern with significant implications. The annual increase in T1DM incidence is approximately 3%. In the Delta region of Egypt, T1DM prevalence is around 26.8 per 100,000, with an annual incidence of

3.1 per 100,000. The age range where disease onset is most common is 10 to 14 years old. In 20–30% of people with both type 1 and type 2 diabetes, diabetic nephropathy (DN), a serious consequence, results in end-stage renal disease (ESRD).

Early detection of DN is critical, as interventions such as optimal glycemic control, lifestyle modifications, renin-angiotensin system (RAS) inhibitors, and cholesterol-lowering medications can slow or halt DN progression. Identifying accurate biomarkers for early DN detection remains a significant challenge.

CONCLUSION

Early T1DM is associated with elevated serum pentosidine levels and renal resistance index, which may be early indicators of diabetic kidney damage. To stop the progression of at-risk youngsters to ESRD, early identification and the application of preventative measures are essential. It is advised that future research with bigger sample numbers and more widespread geographical coverage support these conclusions and confirm the value of serum pentosidine and renal resistance index as biomarkers for early-stage DN.

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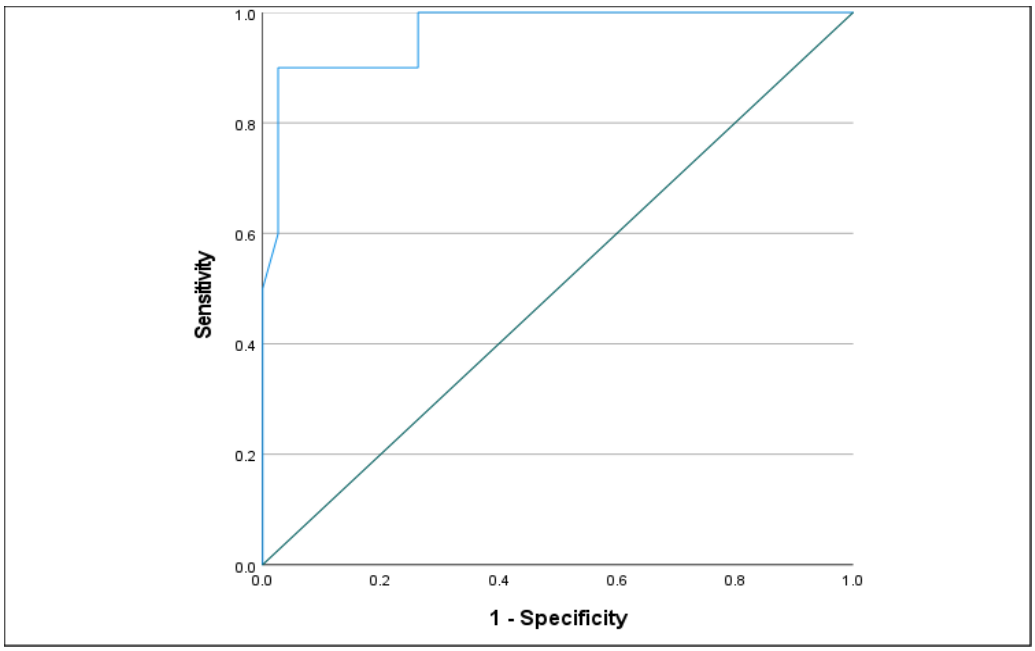

Figure 1S: ROC curve showing Performance of serum pentosidine in prediction of early stage Diabetic kidney disease

Citation

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