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ROLE OF URINARY OSTEOPONTIN IN EARLY PREDICTION OF DIABETIC NEPHROPATHY IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

Heba Mohamed El Sayed Osman[1*], Hoda Ahmed Atwa[2], Badr Eldin Mohammed Mosbah[2], Enas Fathy Elngar[3]

[1*]M.B. B.Ch. (2013), M.SC. (2019), Assistant lecturer of Pediatrics and Neonatology, Faculty of Medicine Suez Canal University (FOMSCU).
[2]Professor of Pediatrics, Suez Canal University.
[3]Assistant Professor of Pediatrics, Suez Canal University.

[*]**Corresponding author:** Heba Mohamed El Sayed Osman
[*]M.B. B.Ch. (2013), M.SC. (2019), Assistant lecturer of Pediatrics and Neonatology, Faculty of Medicine Suez Canal University (FOMSCU).

Abstract

Background: Type 1 diabetes is one of the most common endocrine diseases in pediatrics. One of the most serious micro-vascular complications is diabetic nephropathy. Osteopontin is one of the cytokine systems that is selectively regulated in the serum of Type 1 Diabetes patients, in their vascular walls, and in their kidneys.

Aim and Objectives: This study aimed to improve the quality of life of adolescents with type 1 diabetes by the main objective to measure the level of urinary osteopontin and to evaluate its role in early prediction of diabetic nephropathy in adolescents with type 1 diabetes.

Methods: This cross-sectional study included 120 adolescents. They were categorized into three groups, Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric). Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric). Group 3: Controls with ACR <30 mg/g (normo albuminuric). Data collection sheet including demographic data, diabetes duration, Clinical examination and laboratory data as serum creatinine, Urinary albumin creatinine ratio. Fasting lipid profile including cholesterol, TG, HDL and LDL, Mean of HbA1C levels, Urinary OPN, were measured.

Results: The three groups studied were age and gender matched. Urinary OPN was significantly higher among diabetics with microalbuminuria. At cut off >65 was assessed, it had a significant role in prediction of microalbuminuria from normoalbuminuria among diabetic adolescents with a sensitivity of 90%, specificity of 70%, PPV of 75%, NPV of 87.5% and area under curve was 92%. There was a high moderate positive correlation between OPN and ACR among diabetic patients (r =0.65). Also, HbA1c was moderately correlated with OPN (r =0.66) in diabetic groups. Similarly, there was a moderate positive correlation between diastolic blood pressure and OPN in diabetics. Furthermore, a weak positive correlation was revealed for both duration of diabetes and LDL with OPN. But there is no significant relation between Osteopontin and gender.

Conclusion: Urinary OPN may be used as a screening test for diabetic nephropathy in type 1 diabetes with high sensitivity and moderate specificity. This study found that poor glycemic control had a role in progression of diabetic nephropathy.

Keywords: Osteopontin, DM, nephropathy, adolescent

Introduction

According to Chiang et al. (1), type 1 diabetes is among the most prevalent endocrine disorders in children. Acute consequences of type 1 diabetes, such as ketoacidosis, hypoglycemia, microvascular and macrovascular problems, and ultimately mortality, may be directly caused by poor metabolic control (2).

Diabetic nephropathy is a severe microvascular consequence that significantly affects morbidity, mortality, and quality of life (3). The diagnostic accuracy of microalbuminuria, a commonly used biomarker for diabetic nephropathy, is restricted because kidney structural damage may occur before albumin excretion (4).

According to certain studies, microalbuminuria is not exclusive to diabetic nephropathy; it may also occur in non-diabetic individuals with progressing chronic kidney disease (5). Conversely, individuals with diabetes who have microalbuminuria could not develop end-stage renal disease. Therefore, it is necessary to have sensitive and specific indicators that can identify diabetic nephropathy (6).

Among the cytokine systems is osteopontin (OPN). Osteoblasts, macrophages, endothelial cells, and epithelial cells excrete this glycosylated phosphoprotein, which is normally expressed in the loop of Henle and distal nephron and is up regulated in renal tubular cells and glomeruli in glomerulonephritis, hypertension, and ischemic acute renal failure. It functions by promoting cell adhesion and migration (7).

Patients with Type 1 diabetes have preferentially elevated levels of OPN in their kidneys, vascular walls, and serum. An elevated level of serum OPN is linked to vasculopathy and subclinical atherosclerosis in children and adolescents with type 1 diabetes, according to a study that evaluated the role of osteopontin in the early prediction of diabetic nephropathy. This finding may aid in the early identification of patients who may later develop vascular complications and may enable the development of novel therapeutic agents that target the biology of vasculopathy (8).

Urinary OPN monitoring may be utilized to more accurately diagnose and track prognosis and can serve as a non-invasive, sensitive, accurate, and specific marker of glomerular damage. It may thus be used as an early indicator for diabetic nephropathy (9).

Aim of the Work

This study aimed to improve the quality of life of adolescents with type 1 diabetes by assessing the level of urinary osteopontin and to evaluate its role in early prediction of diabetic nephropathy in adolescents with type 1 diabetes.

Patients and methods

This cross-sectional study was conducted in the outpatient clinic and inpatient wards of the pediatrics department at Suez Canal University teaching hospital. The study included 120 participants who were divided into 3 groups:

Group 1: included 40 adolescents with type 1 diabetes mellitus and their albumin/creatinine ratio (ACR) <30 mg/g (normo-albuminuric group).

Group 2: included 40 adolescents with type 1 diabetes mellitus and their albumin/creatinine ratio (ACR) is 30-300 mg/g (micro-albuminuric group).

Group 3: included 40 apparently healthy controls, matched the patients in age, gender and socioeconomic level who were visiting the general pediatric outpatient clinic.

Adolescents whose age was between 10 to 19 years old (WHO/ definition of key terms, 2020) with type 1 diabetes for at least 10 years' duration on insulin therapy, both sexes and participants in group 1 and 2 should have their onset of diabetes before reaching six years old were included in the study. While patients with chronic infection, symptomatic heart disease or cardiovascular disease not related to diabetes or hypertension, familial hypercholesterolemia, rheumatoid arthritis, history of allergies,

recent trauma, liver dysfunction, connective tissue or bone disease, or other autoimmune disorders, receiving lipid lowering medication and already have chronic complications of diabetes (nephropathy, peripheral neuropathy, retinopathy or cardiovascular ischemic events) were excluded from the study.

All patients attended the diabetes clinic and the inpatient ward of pediatrics department of Suez Canal university hospital during the period from June 2021 to October 2022 and fulfilled the inclusion and exclusion criteria were included and later were allocated in either normo-albuminuric or micro-albuminuric group according to their albumin/creatinine ratio until number required for sample size is reached. While the apparently healthy control group participants were submitted from adolescents attending the general pediatrics clinic.

Each participant was subjected to history taking, clinical examinations and laboratory investigations included serum creatinine, lipid profile, Estimated Glomerular Filtration Rate (eGFR), HbA1C levels, and urinary OPN.

Statistical analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data was described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data was described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. Differences in sociodemographic and clinical characteristics was tested by T test for normally distributed continuous variables while Mann-whitney test was used for not-normally distributed data. Chi-square test was used for categorical data. Pearson coefficient to correlate between two normally distributed quantitative variables. Receiver operating characteristic curve (ROC). A two-sided P value <0.05 was considered statistically significant.

Results

This study included 120 adolescents. They were categorized into three groups, Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric). Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric). Group 3: Controls with ACR <30 mg/g (normo albuminuric). There were 50%, 50% and 27.5% males among group 1, 2, and 3 respectively. Mean age was 16.20 ± 1.54, 16.68 ± 1.75, and 16.05 ± 1.36 among the three groups respectively. The three included groups were age and gender matched. Microalbuminuria was not associated with the duration of diabetes (p=0.270) as shown in table 1.

In table 2, weight and height were not significantly differed between the three studied groups. BMI showed no difference between the three studied groups. Diabetic patients with microalbuminuria showed the highest level of blood pressure. Systolic pressure was not significantly different between diabetics with normoalbuminuria and diabetic with microalbuminuria. While diastolic blood pressure was significantly higher among diabetic with microalbuminuria group than normoalbuminuria. Systolic blood pressure was significantly higher among diabetic groups compared to controls.

In table 3, ACR showed the highest levels among microalbuminuria group and the least levels among control. Serum creatinine was significantly higher among diabetes groups than control. eGFR showed significantly lower levels among diabetic groups than control. Cholesterol was significantly higher among diabetic groups with normoalbuminuria compared to control. Triglyceride was significantly higher among diabetic groups when compared to controls. HDL and LDL did not show any significance between the three studied groups. HbA1C was significantly different between the three studied groups. The highest level was among diabetic groups with microalbuminuria then diabetic with normoalbuminuria and the lowest level among controls.

Urinary Osteopontin was significantly higher among diabetics with microalbuminuria than diabetics with normoalbuminuria and controls as in table 4 and figure 1.

In table 5 and figure 2, at cut off >65, urinary Osteopontin had a significant role in prediction of

microalbuminuria from normoalbuminuria among diabetic adolescent with a sensitivity of 90%, specificity of 70%, PPV of 75%, NPV of 87.5% and area under curve was 92%.
A positive moderate correlation between urinary Osteopontin and diastolic blood pressure. Urinary Osteopontin showed positive weak correlation with duration of diabetes and LDL. HbA1C and ACR had significantly strong correlation with urinary Osteopontin in table 6.

Tables and Figures

Table 1. Comparison between the three studied groups according to demographic data

	Group 1 (n = 40)		Group 2 (n = 40)		Group 3 (n = 40)		Test of Sig.	p
	No.	**%**	**No.**	**%**	**No.**	**%**		
Gender								
Male	20	50.0	20	50.0	11	27.5	χ^2= 5.524	0.063
Female	20	50.0	20	50.0	29	72.5		
Age								
Mean ± SD.	16.20 ± 1.54		16.68 ± 1.75		16.05 ± 1.36		F=1.760	0.177
Duration of diabetes								
Mean ± SD.	11.83 ± 1.71		12.28 ± 1.77		---		687.50	0.270

IQR: Inter quartile range SD: Standard deviation χ2: Chi square test
F: F for One way ANOVA test, pairwise comparison bet. Each 2 groups were done using Post Hoc Test (Tukey)
p: p value for comparing between the studied groups
p1: p value for comparing between Group 1 and Group 2
p2: p value for comparing between Group 1 and Group 3
p3: p value for comparing between Group 2 and Group 3
**: Statistically significant at p ≤ 0.05*
Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric).
Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric).
Group 3: Controls with ACR <30 mg/g (normo albuminuric).

Table 2. Comparison between the three studied groups according to measurements

Anthropometric measurement	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	F	p
Weight (kg)					
Mean ± SD.	54.60 ± 8.79	54.95 ± 8.90	55.35 ± 10.52	0.063	0.939
Height (cm)					
Mean ± SD.	158.8 ± 3.80	158.68 ± 4.79	158.9 ± 3.25	0.033	0.968
BMI					
Mean ± SD.	21.59 ± 2.96	21.77 ± 3.11	21.91 ± 3.55	0.101	0.904
Systolic					
Mean ± SD.	115.20 ± 5.13	117.23 ± 6.16	110.50 ± 6.77	12.962*	**<0.001***
Sig. bet. grps.	p_1=0.297,p_2=0.002*, p_3<0.001*				
Diastolic					
Mean ± SD.	72.70 ± 5.07	78.22 ± 3.94	70.60 ± 6.41	22.624*	**<0.001***
Sig. bet. grps.	p_1<0.001*,p_2=0.176, p_3<0.001*				

IQR: Inter quartile range SD: Standard deviation
p: p value for comparing between the studied groups
p1: p value for comparing between Group 1 and Group 2
p2: p value for comparing between Group 1 and Group 3
p3: p value for comparing between Group 2 and Group 3

**: Statistically significant at p ≤ 0.05*
Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric).
Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric).
Group 3: Controls with ACR <30 mg/g (normo albuminuric).

Table 3. Comparison between the three groups studied according to laboratory investigations data.

	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	H	p
Albumin creatinine ratio in urine					
Mean ± SD.	23.48 ± 4.11	102.4 ± 73.35	19.27 ± 5.17	H= 85.145*	**<0.001***
Sig. bet. grps.	$p_1<0.001^*$,$p_2=0.016^*$,$p_3<0.001^*$				
Serum creatinine					
Mean ± SD.	0.64 ± 0.15	0.59 ± 0.15	0.49 ± 0.09	F= 13.659*	**<0.001***
Sig. bet. grps.	$p_1=0.253$,$p_2<0.001^*$,$p_3=0.002^*$				
eGFR					
Mean ± SD.	108.9 ± 28.42	119.6 ± 37.76	140.36 ± 30.60	F= 9.671*	**<0.001***
Sig. bet. grps.	p1=0.306,p2<0.001*,p3=0.014*				
Cholesterol					
Mean ± SD.	181.5 ± 28.94	173.9 ± 22.26	164.7 ± 15.80	5.382*	**0.006***
Sig. bet. grps.	$p_1=0.307$,$p_2=0.004^*$,$p_3=0.174$				
Triglycerides					
Mean ± SD.	103.8 ± 29.61	94.56. ± 22.62	80.77 ± 11.58	10.587*	**<0.001***
Sig. bet. grps.	$p_1=0.163$,$p_2<0.001^*$,$p_3=0.019^*$				
HDL					
Mean ± SD.	62.33 ± 17.61	56.08 ± 15.25	60.37 ± 7.64	2.042	0.134
LDL					
Mean ± SD.	90.05 ± 28.03	97.53 ± 22.06	86.28 ± 11.43	2.804	0.065
HbA1c					
Mean ± SD.	8.68 ± 0.72	9.89 ± 1.02	4.59 ± 0.44	529.659*	**<0.001***
Sig. bet. grps.	$p_1<0.001^*$,$p_2<0.001^*$,$p_3<0.001^*$				

IQR: Inter quartile range SD: Standard deviation
F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
p: p value for comparing between the studied groups
p1: p value for comparing between Group 1 and Group 2
p2: p value for comparing between Group 1 and Group 3
p3: p value for comparing between Group 2 and Group 3
**: Statistically significant at p ≤ 0.05*
Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric).
Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric).
Group 3: Controls with ACR <30 mg/g (normo albuminuric).

Table 4. Comparison between the three studied groups according to urinary Osteopontin.

Urinary osteopontin	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	F	P
Mean ± SD.	59.03 ± 9.74	88.77 ± 17.42	55.06 ± 9.51	83.268*	**<0.001***
Sig. bet. grps.	$p_1<0.001^*$,$p_2=0.350$,$p_3<0.001^*$				

IQR: Inter quartile range SD: Standard deviation
F: F for One way ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)
p: p value for comparing between the studied groups
p1: p value for comparing between Group 1 and Group 2
p2: p value for comparing between Group 1 and Group 3
p3: p value for comparing between Group 2 and Group 3
**: Statistically significant at p ≤ 0.05*
Group 1 Type 1 Diabetes Mellitus with ACR <30 mg/g (normo albuminuric).
Group 2: Type 1 Diabetes Mellitus with ACR is 30-300 mg/g (micro albuminuric).
Group 3: Controls with ACR <30 mg/g (normo albuminuric).

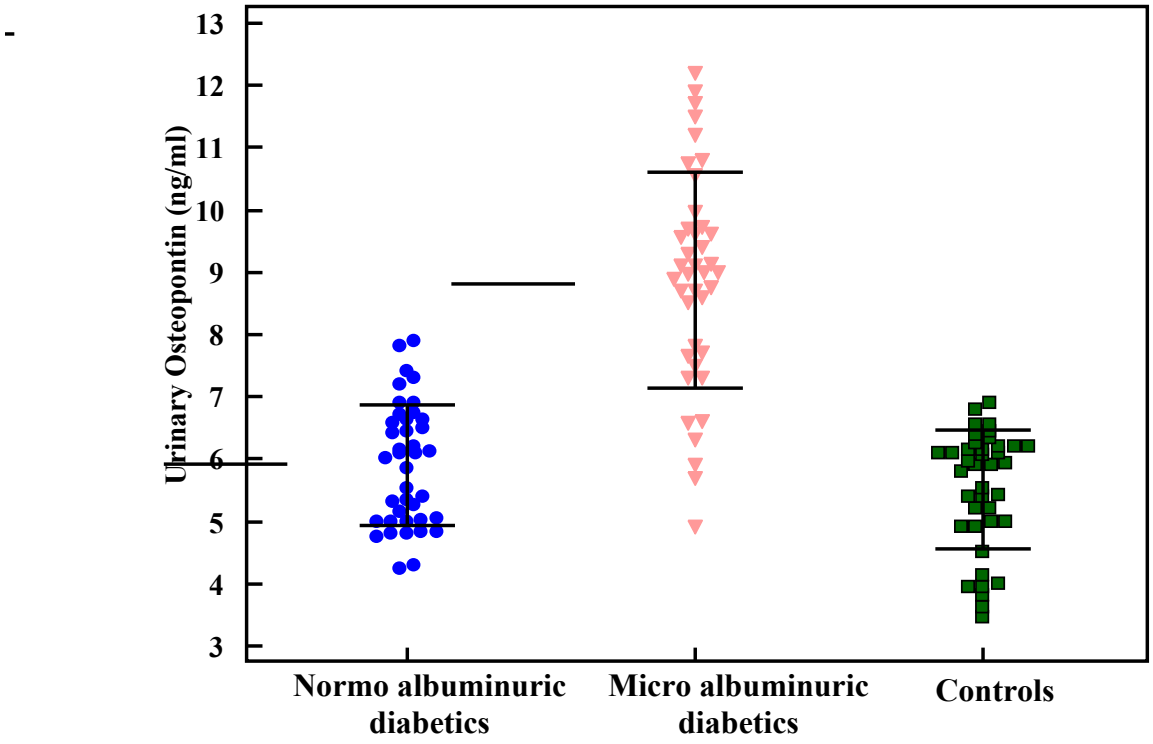

Figure 1. Comparison between the three studied groups according to urinary Osteopontin.

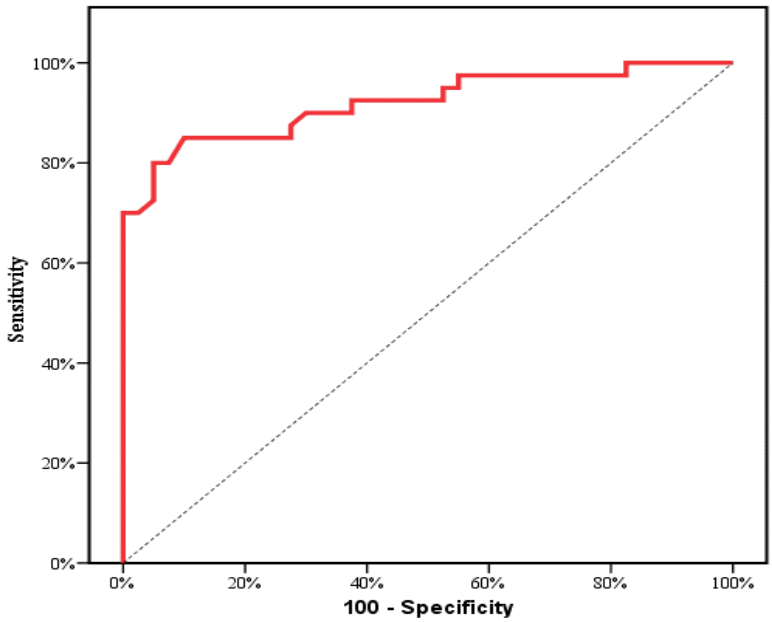

Figure 2. ROC curve for urinary osteopontin to discriminate micro albuminuric (n = 40) from normo albuminuric (n = 40).

Table 5. Validity (AUC, sensitivity, specificity) for urinary osteopontin to discriminate micro albuminuric (n = 40) from normo albuminuric (n = 40).

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Urinary osteopontin	0.920	<0.001*	0.858 – 0.982	>65	90.0	70.0	75.0	87.5

AUC: Area Under a Curve *p value: Probability value*
CI: Confidence Intervals
NPV: Negative predictive value *PPV: Positive predictive value*
**: Statistically significant at p ≤ 0.05*

Table 6. Correlation between Urinary osteopontin and different parameters in total patient (n= 80).

	Urinary osteopontin	
	r	**P**
Age	0.210	0.062
BMI	0.162	0.151
Duration of diabetes	0.260	0.020*
Serum creatinine	-0.096	0.397
eGFR	0.088	0.440
Systolic	0.208	0.064
Diastolic	0.412	<0.001*
Cholesterol	0.082	0.470
Triglycerides	-0.097	0.393
HDL	-0.136	0.231
LDL	0.271	0.015*
HbA1c (Mean over 1 year)	0.668	<0.001*
Albumin creatinine ratio in urine	0.656	<0.001*

r: Pearson coefficient
**: Statistically significant at p ≤ 0.05*

Discussion

According to Wang et al. (10), albuminuria, often known as ACR, has been the gold standard diagnostic and prognostic biomarker for the beginning and progression of diabetic nephropathy for the last thirty years. Numerous clinical and physiological processes, including insulin resistance, glomerulonephritis, atherosclerosis, cancer, chronic inflammatory illness, and inflammation of adipose tissue, are actively influenced by osteopontin (11).

Therefore, the purpose of this cross-sectional research was to assess urine osteopontin levels and their potential for early diabetic nephropathy prediction in adolescents with type 1 diabetes. In this research, 120 teenagers participated. They were divided into three groups based on matching gender and age. In the present investigation, diabetics with microalbuminuria had considerably greater urine OPN than both controls and diabetics with normo-albuminuria.

These results can be explained by the fact that osteopontin has been demonstrated to be constitutively expressed in the human kidney and to be locally upregulated during fibrosis and inflammation, which strengthens osteopontin expression and inflammatory function in the renal compartments (12).

According to a number of published research, children and adolescents with type 1 diabetes who have microalbuminuria had greater levels of osteopontin. Abo El-Asrar et al. (8), El Dayem et al. (13), Talat et al. (14), and Gordin et al. (15). Additionally, it was shown by Talat et al. (14) that juvenile T1DM patients with microalbuminuria and normo-albuminuria had substantially higher blood OPN levels than healthy individuals ($p < 0.001$). Furthermore, Osteopontin was shown to be greater in T1DM patients with positive microalbuminuria ($p = 0.001$), according to El Dayem et al. (13).

Furthermore, all T1DM patients had substantially higher blood OPN concentrations than the control group (median [IQR], 90 [50 – 120] ng/mL vs 50 [40 – 65] ng/mL; $p=0.002$), according to Abo El-Asrar et al. 2018. Additionally, OPN was considerably greater ($p<0.001$) in individuals with microvascular problems than in those without.

Additionally, Yamaguchi et al. (16), Yan et al. (17), Assy et al. (18), and Nawaz et al. (19) revealed a correlation between kidney disease and microalbuminuria. Serum OPN (ng/ml) varied significantly across all groups in a prior research by Assy et al. (18), with the control group having lower levels and the adults with DN group having higher levels than the other groups.

In addition to Nawaz et al. (19), OPN levels were considerably greater ($p < 0.05$) in adult patients with microvascular problems than in those without. Aside from diabetes, osteopontin was also linked to renal disorders. According to Feldreich et al. (12), there was a strong correlation between incident chronic kidney disease and higher levels of serum and urine osteopontin. Azoz et al. (20) discovered that patients with stage V CKD had considerably greater levels of OPN compared to other groups.

With a sensitivity of 90%, specificity of 70%, PPV of 75%, NPV of 87.5%, and area under the curve of 92%, the validity of urine OPN at cutoff >65 was evaluated in this research and demonstrated a significant role in predicting microalbuminuria from normoalbuminuria among adolescents with diabetes.

According to Al-Malki (21), the urine level of osteopontin consistently detected microalbuminuria with an AUC of 0.73, sensitivity of 92.3%, and specificity of 89.9%.

Abo. El-Asrar et al. (8) found that serum OPN at a cutoff value of 90 ng/mL had a sensitivity of 81.7%, a specificity of 95.8%, and an area under the curve (AUC) of 0.815 ($p<0.001$) that allowed for the differentiation of patients with and without microvascular problems. According to Assy et al.

(18), the optimal cutoff point for blood OPN levels between the DN and control groups was >137.3 ng/ml. This level had an 82.05% sensitivity for identifying diabetic patients with nephropathy and an 85% specificity for excluding diabetic patients without nephropathy.

According to Al-Rubeaan et al. (22), serum OPN may also identify microalbuminuria in type 2 DM with 88.8% sensitivity, 54.7% specificity, 63.7% PPV, and 84.6% NPV.

Both serum and urine osteopontin levels varied significantly between investigations.
Another research by Icer et al. (23) reported that the urine osteopontin level in the healthy control group was between 1 and 11 ng/ml, while Askenazi et al. (24) found that it was between 1.3 and 4.2 ng/ml. It was between 34.50 and 69.0 ng/ml in the healthy control group of this research.

Urinary osteopontin and diastolic blood pressure have a somewhat favorable association, according to these findings. The correlation between elevated OPN concentrations and atherosclerosis and arterial stiffness may help to explain this (25).

According to Talat et al. (14), there was a modest correlation (r = 0.48), between high diastolic blood pressure and OPN levels. In contrast, OPN and blood pressure were shown to have a weakly positive connection (r = 0.2; r = 0.06) by Al-Rubeaan et al. (22) and Nawaz et al. (19). The various research participants, all of whom were adults with type 2 diabetes, may be the cause of this diversity. On the other hand, the shorter duration of diabetes may be the cause of the weak positive correlation in El Dayem et al., (r = 0.01) (13).

Furthermore, OPN levels and LDL had a modest correlation (r = o.2), according to this research. Just as Talat et al. (14), and El Dayem et al. (13) reported. In contrast, the research by Gordin et al. (2014) found a substantial correlation between the length of diabetes and OPN levels. However, this might be explained by the fact that the study sample consisted of individuals with longer durations of diabetes.

According to the present research, there is no meaningful correlation between gender and osteopontin. Male and female OPN did not vary considerably, according to Abo El-Asrar et al. (8). Furthermore, there was no discernible gender difference in T1DM patients' OPN levels. Talat and associates (14).

One of the study's limitations was that it was cross-sectional, which meant that there was no long-term follow-up to track the association between osteopontin levels and the development of diabetic nephropathy.

Conclusion

In conclusion, urinary OPN may be used as a screening test for diabetic nephropathy in type 1 diabetes with high sensitivity and moderate specificity. This study found that poor glycemic control had a role in progression of diabetic nephropathy. Also, further large follow-up studies on the same study groups to confirm the role of Osteopontin in diabetic nephropathy and its predictive value in detecting progression of diabetic nephropathy. Moreover, further studies should be directed to compare between urinary OPN levels and gold standard renal biopsy histopathology on animal models to conclude its sensitivity and specificity in diabetic nephropathy.

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