Osteopontin as an Early Urinary Marker of Diabetic Nephropathy in Adolescents with Type 1 Diabetes Mellitus

RFC-325

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Amany Ibrahim has no relevant financial or non financial relationships to disclose

INTRODUCTION AND OBJECTIVES

- Cytokine systems including and osteopontin (OPN) have been implicated in tubulointerstitial injury. OPN is a glycosylated phosphoprotein that is normally expressed the loop of Henle and distal nephron and is upregulated renal tubular cells and glomeruli in glomerulonephritis, hypertension, and ischemic acute renal failure, is produced by osteoblasts, macrophages, endothelial cells, and epithelial cells and acts by facilitating cell adhesion and migration (1). OPN protein is selectively upregulated in the serum of T1D patients, in their vascular walls, and in their kidneys (2).
- However, OPN is found in bone and mainly regulates the formation and calcification of bone tissue, it is also linked to vascular remodelling and calcification, in diabetic vessels, and is shown to associate with diabetic retinopathy and nephropathy (DN) in patients with T2D, as well as CVD events in nondiabetic subjects with a history of coronary artery disease (3).
- Marked increase of OPN-positive proximal tubular cells was detected in human diabetes mellitus kidneys and significantly correlated with cortical scarring in those patients. This finding indicates that OPN expression may play a major role in the interstitial fibrosis associated with DN (4).
- The aim of the study is to evaluate urinary OPN as an early marker for DN in children and adolescents with T1D.

CONCLUSIONS

- Longer duration of diabetes and poor glycemic control are associated with increased risk of developing DN.
- Monitoring urinary OPN may provide a non-invasive tool that is a sensitive, accurate, and specific biomarker of glomerular injury and can be used to more reliably detect and monitor prognosis. Therefore, it can be used as an early marker for DN
- Urinary OPN was significantly higher in microalbuminuric than normoalbuminuric groups. However, urinary OPN did not correlate significantly with the disease characteristics or demographic data of the patients.

METHODS

- This cross-sectional study was carried out on 60 children and adolescent with T1D diagnosed more than 5 years based on ADA (2018) (5), with age range (7-18 years), were recruited from the outpatient clinic of Diabetic Endocrine Metabolic Pediatric Unit (DEMPU) over a period of one year.
- Detailed medical history was initially taken including age, diabetes duration, insulin dose as well as complications.
- A careful physical examination including Weight, height, systolic and diastolic blood pressure (SBP, DBP (mmHg) were measured. Body mass index (BMI) (kg/m2) and SDS for weight, height and BMI were obtained.
- Recent laboratory results including serum creatinine, urine A/C ratio, estimated GFR fasting lipid profile including; TC, TG, HDL and LDL were obtained from the medical records. Mean HbA1C levels over the preceding year were calculated.
- Urinary OPN was measured by ELIZA and urinary creatinine was detected in all T1D patients.
- They were divided into two groups according to albumin creatinine ratio (ACR), normoalbuminuric: ACR < 30 mg/g (n=30); microalbuminuric: ACR 30-300 mg/g (n=30) (6).

RESULTS

- The anthropometric and clinical data among the two patient groups showed no significant difference.
- A significant negative correlation between urinary OPN/Cr ratio and Frequency of DKA in last year prior to study (r = -0.34; p =0.018).
- Urinary OPN (ng/ml) was significantly higher in microalbuminuric than normoalbuminuric patients (P<0.001). There was significant positive correlation between urinary OPN (ng/ml) and ACR (P <0.001) and between urinary OPN/Cr ratio and LDL levels.
- The ROC analysis showed that urinary OPN was a significant discriminator of DN (AUC 0.961) at cut-off value of 183.79 ng/ml. The sensitivity was 95.7% and the specificity was 83% (figure 1)

Table (1) Comparison between normo-albuminuric and micro-albuminuric T1D patients

Variables	Normo n= 30		Micro n=30		P-value
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
HbA1c (%)	9.5 ± 1.9	9.6 (6.7-15.3)	9.9 ± 1.9	9.7 (7.3 - 12.5)	0.363
Cholesterol (mg/dl)	176.3 ± 39.4	167 (121 - 269)	174.2 ± 32.4	169 (115 - 266)	0.947
TG (mg/dl)	96 ± 35.5	92.5 (69 - 149)	82.3 ± 38.3	70.5 (54 - 192)	0.076
HDL (mg/dl)	49.4 ± 13.4	46.5 (30.7 - 86)	52.3 ± 12.1	51.5 (27 - 75.6)	0.239
LDL (mg/dl)	103 ± 35.6	95.5 (48 - 175)	101.1 ± 27.6	105.5 (38 - 148)	0.988
Serum creatinine (mg/dl)	0.6 ± 0.2	0.6 (0.1 - 0.9)	0.6 ± 0.3	0.54 (0.1 - 0.85)	0.766
ACR (mg/gm creat)	16.3 ± 7.9	16.5 (2.7 - 25.7)	126.4 ± 78.8	109.5 (56 - 212)	< 0.001*
Estimated GFR	128.9±42.7	121.1 (73.2 - 225)	130.6 ± 38.9	135.5 (43 - 209.4)	0.595
Urinary creatinine (mg/dl)	30.5	(12.6 - 51.9)	53.9	(23.4 - 93.5)	0.015*
Urinary OPN (ng/ml)	149.4	111.9 -178	256.8	(218 - 344)	< 0.001*
urinary OPN (ng/mg creatinine)	591.7	(346.2 - 1280.6)	528.2	(314.8 - 1391.6)	0.852

Table (2) Correlations between the OPN and urinary OPN /Cr ratio with other parameters in all T1D studied

Variables	Urinary OPN (ng/ml)		urinary OPN /creatinine Ratio	
	R	P-value	R	P-value
HbA1c (%)	-0.043	0.778	0.056	0.713
cholesterol(mg/dl)	-0.046-	0.763	0.106	0.485
TG(mg/dl)	-0.291-	0.050	0.132	0.383
HDL(mg/dl)	0.137	0.370	-0.212	0.163
LDL (mg/dl)	0.052	0.735	0.329	0.027*
Creatinine (mg/dl)	0.057	0.713	-0.073	0.636
Estimated GFR	0.017	0.913	-0.004	0.982
ACR(mg/gm creat)	0.672	< 0.001*	-0.034	0.827

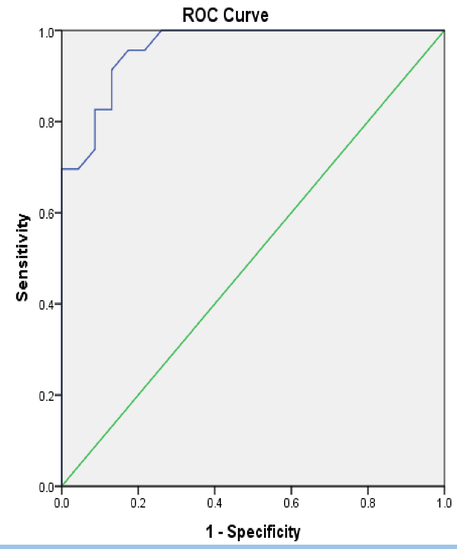

Figure 1: ROC curve showing the diagnostic accuracy of Urinary OPN (ng/ml).

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