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ORIGINAL ARTICLE

Role of Urinary Podocalyxin in Early Diagnosis of Diabetic Kidney Disease

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Abstract

Background: **Major complications of diabetes include diabetic nephropathy (DN), the leading cause of end-stage renal disease (ESRD). When DN is diagnosed and treated early on, its progression to ESRD can be slowed. It is recommended to start screening for DN at the time of diagnosis because ~3%of newly diagnosed cases of type 2 diabetes mellitus already have overt nephropathy.**

Aim and objectives: **This study aimed to test podocalyxin in the urine for its potential as a noninvasive diagnostic for early diagnosis of diabetic kidney damage.**

Patients and methods: **Eighty patients were analyzed in this cross-sectional study that took place over 6 months in the internal medicine and nephrology units at Al-Azhar University Hospitals.**

Results: **The variations among the groups were statistically significant with regards to Duration of disease, random blood glucose (mg/dL), Alb/Cr ratio (mg/g), glycated hemoglobin (%), urinary-podocalyxin (PDX) (ng/ml) and Fundus examination. No statistically significant variations were found between the groups. Demographic characteristics, renal U/S and Pearson's correlation coefficients (r) between u-PDX and random blood glucose (mg/dL), Alb/Cr ratio (mg/g), glycated hemoglobin (%), serum total proteins (g/dL), serum albumin (g/dL), blood urea (mg/dL), serum creatinine (mg/dL) and estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) among studied groups.**

Conclusion: **These results recommend that u-PDX may play a significant role in the early diagnosis of podocyte damage and DN. There is a high prevalence of u-PDX elevation in type 2 diabetes mellitus normoalbuminuric people, and u-PDX is more useful in diagnosing DN than microalbumin.**

Keywords: Diabetic kidney disease, Early diagnosis, Urinary podocalyxin

1. Introduction

The metabolic disease class known as diabetes mellitus (DM) is represented by persistently raised blood sugar levels. Glycemic management is just one aspect of the comprehensive medical treatment that people with diabetes need daily. DM patients must be provided with the tools and support necessary to manage their condition on their own to reduce their risk of both short- and long-term problems.[1]

Proteinuria and increasing renal insufficiency characterize diabetic nephropathy (DN), a significant consequence of diabetes and the leading reason for end-stage renal disease (ESRD).[2]

When DN is diagnosed and treated early on, its progression to ESRD can be slowed. Although only about 3 % of people with newly diagnosed type 2 diabetes mellitus (T2DM) develop overt nephropathy, this does not negate the importance of beginning DN screening as soon as possible.[3]

Recent research using electron microscopic morphometric analysis of kidney biopsies has shown that podocytes separation is evident in diabetes cases with normoalbuminuria.[4]

Podocalyxin-positive element (PCX + EL) may be a viable indication of early-stage of nephropathy,

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Normoalbuminuric diabetics have been reported to contain podocytes and podocyte fragments (labeled podocalyxin) in their urine. Nephrin, synaptopodin, podocalyxin, and podocin are only a few of the podocyte damage markers that can be measured.[5]

The predominant surface antigen of human podocytes is called podocalyxin (PCX), and its expression on podocytes is unaffected by the several forms of glomerular nephritis.[6]

Assessment of urine podocalyxin as a noninvasive diagnostic for the early diagnosis of diabetic kidney disease was the focus of this study.

2. Patients and methods

In this work, researchers aimed to provide a cross-sectional analysis on 60 cases. The study was conducted through a 6 months' duration in Internal Medicine department and Nephrology units at Al-Azhar University Hospitals, in addition to 20 controlled cases.

Inclusion criteria: Age: 30–50 years, Sex: men and women and known clinically and biochemically T2DM cases.

Exclusion criteria: Age: less than 30 or greater than 50 years. Other reasons of nephropathy are: autoimmune nephropathy, obstructive nephropathy and chronic kidney disease and smokers.

2.1. Operational design

All cases were subjected to: full clinical evaluation, Fundus examination, renal ultrasound, and laboratory investigations (serum creatinine measurement, blood urea, serum albumin, glycated hemoglobin (HbA1c), urine analysis, and urinary podocalyxin) in addition to a full history taking (including personal history, any complaints, past medical and past surgical history and family history). Administrative design: the protocol was applied for approval of Research Ethics Committee. Every participant was informed about the aim of the study, its benefit to him and to the community. Written consent was taken from all participants before including them in the research and they have the right to refuse without effect on their management. All data obtained from participants was used for scientific purposes only Ensuring the confidentiality of the collected data and will not be used outside this study without personal approval. All potential channels of contact among the researchers and participants were disclosed, and all participants were made aware that they could stop taking part in the study at any time.

2.2. Statistical analysis

SPSS version 23 was used for data entry, validation, and analysis. In this study, quantitative data were given as mean ± standard deviation (SD), whereas qualitative data were recorded as number and percentage.

3. Results

Table 1.

Demographic data for the various categories under consideration were summarized in the table below. Sexual behavior did not differ significantly ($P = 0.624$) between the groups. There was no discernible age difference between the groups ($P = 0.944$) Table 2, Fig. 1.

Blood glucose levels (mg/dl) were compared between the different groups. There was a huge disparity in blood sugar levels between the four groups that were analyzed ($P = <0.001$) Table 3.

This table showed Alb/Cr ratio (mg/g) among the studied groups. Regarding Alb/Cr ratio, The differences among the four groups were statistically significant. ($P = <0.001$) Table 4.

This table showed HbA1c (%) among the groups. Concerning HbA1c, There was a highly significant variance amongst the four groups ($P = <0.001$) Table 5.

U-PDX levels (ng/ml) were compared between the different groups here. Among the four groups, there

Table 1. Comparison of demographics among the groups.

	Normo-albuminuria group ($n = 20$) n (%)	Micro-albuminuria group ($n = 20$) n (%)	Macro-albuminuria group ($n = 20$) n (%)	Control group ($n = 20$) n (%)	Test of Significance	P
Sex						
Male n (%)	**11 (55 %)**	**13 (65 %)**	**10 (50 %)**	**9 (45 %)**	$X^2 = 0.241$	**0.624**
Female n (%)	**9 (45 %)**	**7 (35 %)**	**10 (50 %)**	**11 (55 %)**		
Age (y)						
Mean ± SD.	**41.25 ± 4.4**	**40.45 ± 3.61**	**40.7 ± 4.03**	**40.8 ± 4.65**		
Median (IQR)	**41 (38.5–43.5)**	**41 (37.75–43)**	**41 (37.75–44.25)**	**40.5 (39–44)**	**F = 0.127**	**0.944**
Range (minimum–maximum)	**16 (35–51)**	**13 (34–47)**	**13 (33–46)**	**18 (32–50)**		

Table 2. Random Blood Glucose (mg/dl) between the studied groups.

	Normo-albuminuria group ($n = 20$)	Micro-albuminuria group ($n = 20$)	Macro-albuminuria group ($n = 20$)	Control group ($n = 20$)	Test of Significance	*P*
Random Blood Glucose (mg/dl)						
Mean ± SD.	**122.76 ± 21.99**	**146.34 ± 25.66**	**177.57 ± 33.23**	**75.78 ± 9.40**	**F = 63.053**	**<0.001**
Median (IQR)	**128.7 (107.55–137.70)**	**146.7 (124.6–167.4)**	**177.3 (156.6–205.6)**	**76.5 (69.30–83.70)**		
Range (minimum–maximum)	**82.8 (81–163.8)**	**88.2 (99–187.2)**	**124.2 (109.8–234)**	**34.2 (57.6–91.8)**		

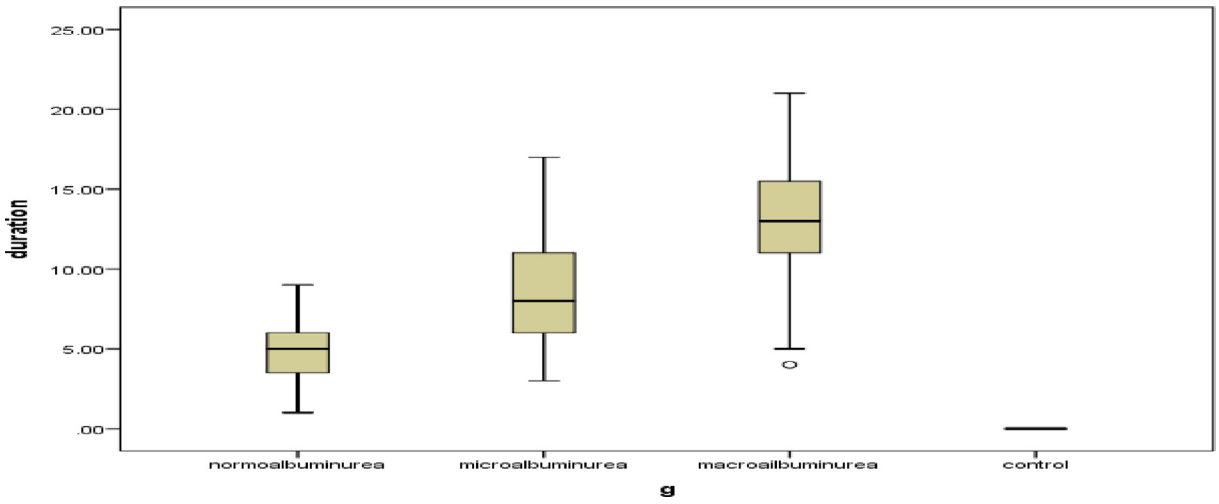

Fig. 1. Differential disease persistence was analyzed between the groups using a box plot.

Table 3. Albumin/creatinine (Alb/Cr) ratio (mg/g) among the studied groups.

	Normo-albuminuria group ($n = 20$)	Micro-albuminuria group ($n = 20$)	Macro-albuminuria group ($n = 20$)	Control group ($n = 20$)	Test of Significance	*P*
Alb/Cr ratio (mg/g)						
Mean ± SD.	**12.05 ± 3.33**	**89.8 ± 27.16**	**435.95 ± 80.09**	**15.05 ± 6.43**	**F = 451.874**	**<0.001**
Median (IQR)	**11.5 (9–14.5)**	**91 (69.75–102.25)**	**429 (367.75–492.75)**	**15 (9.75–20.25)**		
Range (Min-Max)	**12 (6–18)**	**108 (35–143)**	**252 (326–578)**	**21 (4–25)**		

Table 4. Glycated hemoglobin (%) among the studied groups.

	Normo-albuminuria group ($n = 20$)	Micro-albuminuria group ($n = 20$)	Macro-albuminuria group ($n = 20$)	Control group ($n = 20$)	Test of Significance	*P*
HbA1c (%)						
Mean ± SD.	**6.87 ± 0.61**	**7.38 ± 0.82**	**7.85 ± 0.52**	**4.69 ± 0.21**	**F = 114.747**	**<0.001**
Median (IQR)	**6.9 (6.6–7.1)**	**7.35 (6.78–7.95)**	**7.9 (7.38–8.15)**	**4.7 (4.5–4.82)**		
Range (minimum–maximum)	**2.5 (5.8–8.3)**	**3.3 (5.5–8.8)**	**1.8 (7.1–8.9)**	**0.7 (4.4–5.1)**		

Table 5. Urinary-PDX (ng/ml) between the studied groups.

	Normo-albuminuria group ($n = 20$)	Micro-albuminuria group ($n = 20$)	Macro-albuminuria group ($n = 20$)	Control group ($n = 20$)	Test of Significance	*P*
Urinary-PDX (ng/ml)						
Mean ± SD.	**51.1 ± 27.95**	**58.74 ± 18.46**	**67.75 ± 8.48**	**26.99 ± 6.35**	**F = 19.802**	**<0.001**
Median (IQR)	**48.35 (29.33–74.28)**	**59.3 (51.62–72.58)**	**68 (61.3–71.75)**	**26.75 (23.3–30.88)**		
Range (minimum–maximum)	**98.1 (3.1–101.2)**	**71.9 (13.2–85.1)**	**33.7 (52.3–86)**	**25.9 (13.1–39)**		

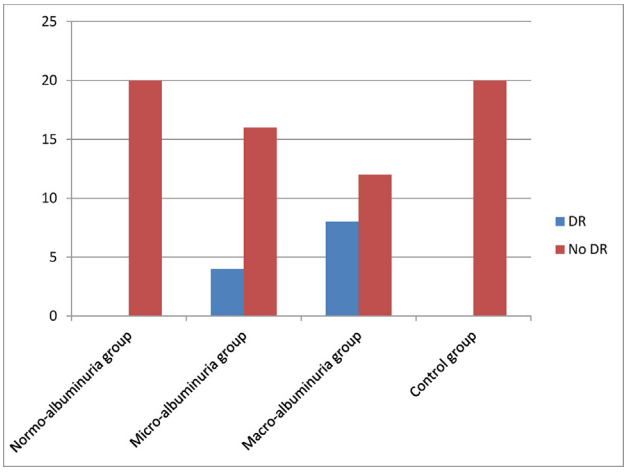

Fig. 2. The results of the Fundus examination were compared between the different groups on a bar chart.

was a significantly different distinction in u-PDX (P= <0.001) Figs. 2 and 3.

This table showed that there was a low + ve relationship among u-PDX and random blood glucose among studied groups. There was a low positive relationship among u-PDX and Alb/Cr ratio among studied groups. There was a low + ve relationship among u-PDX and HbA1c among studied groups. There was a low positive correlation among u-PDX and serum total proteins among studied groups. There was a low positive relationship among u-PDX and serum albumin among studied groups. There was a low negative relationship among u-PDX and blood urea among studied groups. There was a low positive relationship among u-PDX and serum creatinine among studied groups. There was a low negative correlation among u-PDX and eGFR among studied groups.

4. Discussion

Among the many complications of T2DM, DN is the most prevalent and most severe. Forty percent or more of people with T2DM acquire DN. Proteinuria, high blood pressure, and declining kidney function are all hallmarks of DN. With DN being the most common cause of ESRD, the rising need for renal replacement therapy (dialysis and transplantation) has become a major public health concern.[7]

The progression of DN to ESRD can be slowed by early identification and early management in DN. Since about 3 % of individuals with new-onset T2DM have obvious kidney damage, screening for DN should begin at diagnosis.[8]

The main results were as follows:

Our current study showed that demographic characteristics among the studied population. Regarding sex, there was not a significant variance among the four groups (P = 0.624). Regarding age, there was not a significant variance among the four groups (P = 0.944).

Shoji and colleagues who studied many individuals with diabetes to determine the correlation between urine podocalyxin and several clinical indicators, corroborate our findings. 204 participants were split into three categories according to their albuminuria levels: Normo-albuminuria, Micro-albuminuria, and Macro-albuminuria. The average age across all demographics is 61.8 (10.5).[9]

Our results are in agreement with those of Wang and colleagues who investigated the relationship among PCX expression in renal tissues and PCX levels in urine and the progression of proteinuria and renal dysfunction in patients with DN to ascertain whether renal or urinary PCX could serve

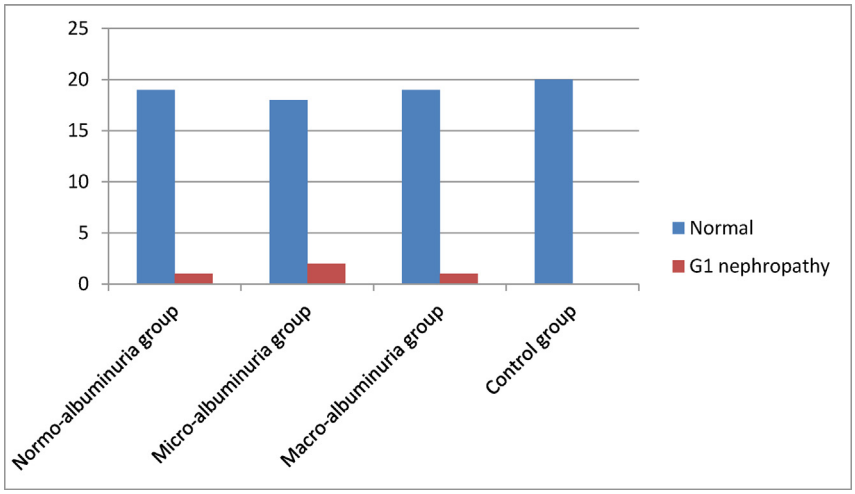

Fig. 3. The results of Renal U/S were compared between the different groups in a bar chart.

as a reliable marker for predicting the progression of DN. Thirty-two patients T2DM and DN took part in the research. There was no statistically significant difference in age or sex between the groups ($P > 0.05$).[10]

In our current study showed that regarding duration of disease, there was a highly significant variance among the four studied groups (P= <0.001).

Our outcomes are confirmed by Kostovska and colleagues who reported that there was a statistically important variance in disease duration among the four groups (P= <0.05).[11]

In our current study presented that regarding Alb/CR ratio, significant differences were found across the four groups (P= <0.001).

Our results are supported by Kostovska and colleagues who reported that concerning Alb/CR ratio, there was a significant difference among the four studied groups (P= <0.05).[11]

In our current research found that regarding HbA1c, there was a highly significant difference between the four studied groups (P= <0.001).

Consistent with our findings, Wang and colleagues found a statistically significant difference in HbA1c levels among the four groups they compared.[10]

In our current study showed that regarding Fundus examination findings, there was a significant variance among the four studied groups ($P = 0.001$). Regarding U/S, there was not a significant variance among the studied groups ($P = 0.5$).

In our current study regarding Pearson's Correlation Coefficient (r) among u-PDX and random blood glucose was 0.207. There was a low positive Correlation between u-PDX and random blood glucose.

Our results are supported by Kostovska and colleagues who reported that there was +ve relationship among u-PDX and random blood glucose ($r = 0.19$).[12]

In our current study showed that regarding Pearson's (r) among u-PDX and UM/CR was 0.22. There was a low + ve relationship among u-PDX and UM/CR.

Our results supported with Shoji et al. (2016) who reported that there was a low positive Correlation between u-PDX and UM/CR.

The current study demonstrated that the relationship among u-PDX and HbA1c was −0.152 (Pearson's Correlation Coefficient). The relationship among u-PDX and HbA1c was moderately positive.

Contrary to what was found by Shoji and colleagues who found no association between u-PDX and HbA1c, we find a significant positive correlation (r > 0.2 in Pearson's Correlation Coefficient). DPP4i or a-GI medication for decreasing blood sugar levels did not prevent further elevation of u-PCX levels. Although HbA1c is a reliable measure of glycemic control over the long run, the trial only ran for a very little period, from January 2011 to September 2012.[9]

In our current study showed that regarding Pearson's (r) among u-PDX and total proteins was 0.148. There was a low + ve relationship among u-PDX and Total proteins.

Our results supported with Kostovska et al. who reported that there was +ve relationship among u-PDX and total proteins. (Pearson's Correlation Coefficient (r) = 0.157).[11]

In our current study showed that regarding Pearson's (r) among u-PDX and serum albumin was 0.1. There was a low + ve relationship among u-PDX and serum albumin.

Our results are supported by Shoji and colleagues who stated that there was+ ve relationship among u-PDX and serum albumin9.

Our results are in line with Wang and colleagues who reported that there was a positive relationship among renal podocalyxin expression and serum albumin and negative relationship among u-PCX/urinary creatinine and serum albumin ($P < 0.001$).[10]

In our current study showed that regarding Pearson's (r) between u-PDX and blood Urea was −0.032. There was a low negative Relationship among u-PDX & blood Urea.

Our results are supported by Kostovska and colleagues who found that there was negative relationship among u-PDX and blood urea. (Pearson's Correlation Coefficient (r) = -0.02).[11]

Our current study showed that regarding Pearson's Correlation Coefficient (r) among u-PDX and serum Creatinine was 0.148. There was a low positive relationship among u-PDX and serum creatinine.

Our consequences were in line with Wang and colleagues who reported that there was a -ve relationship among renal podocalyxin expression and serum Creatinine and +ve relationship among u-PCX/urinary creatinine and serum creatinine ($P < 0.001$).[10]

In our current study showed that regarding Pearson's Correlation Coefficient (r) between u-PDX and eGFR was −0.057. There was a low negative Correlation between u-PDX and eGFR.

However, Shoji and colleagues found no association between u-PDX and eGFR, which contradicts our findings ($r = 0.07$, using Pearson's method of correlation). This is because eGFR and albumin creatinine ratio (ACR) are generally accepted as gold standards for diagnosing DN.[9] However, since decreased eGFR is the ultimate result of kidney

Table 6. Pearson's correlation coefficients (r) between u-PDX and random blood glucose (mg/dL), albumin/creatinine ratio (mg/g), glycated hemoglobin (%), serum total proteins (g/dL), serum albumin (g/dL), Blood Urea (mg/dL), serum creatinine (mg/dl) and eGFR (ml/min/1.73 m^2) among studied groups.

	u-PDX (ng/ml)	
ALB/Cr ratio (mg/g)		*P*
	0.220	**0.050**
Blood glucose (mg/dl)		
	0.207	**0.065**
HbA1c (%)		
	0.152	**0.179**
Serum total proteins (g/dl)		
	0.148	**0.190**
Serum albumin (g/dl)		
	0.100	**0.376**
Blood urea (mg/dl)		
	−0.032	**0.780**
Serum creatinine (mg/dl)		
	0.148	**0.190**
eGFR (ml/min/1.73 m^2)		
	−0.057	**0.615**

disease, it is crucial to identify an early biomarker of renal impairment.[3]

4.1. Conclusion

In this study, we found that u-PDX had a greater diagnostic accuracy than microalbumin in cases with DN and that a high percentage of T2DM normoalbuminuric people had raised levels of u-PDX, suggesting that u-PDX could be essential in the early diagnosis of podocyte injury and DN. We conclude that u-PDX has potential as a sensitive and specific marker for early identification of DN, much more so than microalbuminuria. Larger-scale follow-up research are required to corroborate our findings Table 6.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Conflict of interest

The authors declared that there were NO conflicts of Interest.

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