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Analysis of Urine Podocalyxin in Type 2 Diabetes Mellitus Subjects With and Without Diabetic Nephropathy

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Abstract

Type 2 diabetes mellitus is the most common cause of diabetes, consist from about 85% of cases. Diabetic nephropathy is a complication of diabetes mellitus in the kidneys which can end up as kidney failure. Podocalyxin (PDX) is a protein expressed in kidney podocytes that is involved in various cancers, and is also essential for kidney development. The research design was carried out using observational and cross-sectional analytic methods with total participants of 25 DM with diabetic nephropathy and 25 DM without diabetic nephropathy with a purposive probability sampling technique. This research conducted at the Endocrine Polyclinic, Clinical Pathology Laboratory, Hasanuddin University Medical Research Center (HUM-RC) Laboratory, Hasanuddin University Hospital, Makassar. The results showed that the urinary PDX level in DM subjects with nephropathy were 1.160 ng/mL and DM without nephropathy were 0.167 ng/mL ($p<0.001$), the urine albumin/creatinine ratio (ACR) of DM subjects with nephropathy were 644.74 mg/ g and DM without nephropathy of 10.071 mg/g ($p<0.001$) and the correlation test results of urine PDX and urine ACR in DM subjects with nephropathy ($r=0.510$; $p=0.001$). This study concluded that there was a significant difference between urinary PDX in DM with and without diabetic nephropathy, there was a significant difference between urine ACR levels in DM with and without diabetic nephropathy, and there was a relationship between urinary PDX levels and urine ACR in DM subjects with diabetic nephropathy.

Keywords
Albumin-Creatinine Ratio, Diabetic Nephropathy, Urine Podocalyxin.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing global health problem related to the obesity epidemic. Individuals with Type 2 DM are at risk of experiencing microvascular complications such as retinopathy, nephropathy and neuropathy and macrovascular complications like cardiovascular comorbidities due to hyperglycemia and the individual components of the (metabolic) insulin resistance syndrome (1).

Diabetic nephropathy (DN) caused by diabetes mellitus is one of the major causes of end-stage kidney failure worldwide (2). Clinically, it is characterized by the development of proteinuria with decreased glomerular filtration rate, which lasts for a long time, often more than 10-20 years. If it is untreated, the resulting uremia is morbidity (3). Diabetic nephropathy is a complication of diabetes mellitus in the kidneys which can end up as kidney failure. Nephropathy is the leading cause of death and disability in people with DM (3,4).

Podocalyxin (PDX) is an anionic transmembrane sialoglycoprotein from podocytes, a member of the CD34 family (Cluster of Differentiation 34). Podocytes are visceral epithelial cells that play a role in the glomerular filtration barrier (GFB) formation. The destruction of podocytes and their release in the urine results in the detection of PDX in urine (u-PDX), making it a marker that may be useful in the early diagnosis of diabetic nephropathy (5). Podocyte injury plays an essential role in the pathological mechanisms of DN. Typical signs of podositopathy are podocyte hypertrophy, foot process effect, epithelial-mesenchymal transdifferentiation (EMT), release from the glomerular basement membrane and apoptosis (6,7).The early stages of DN are characterized by a progressive decrease in the number of podocytes, loss of their foot processes, release of podocytes through urine, and damage of the diaphragmatic filtration slits, which causes proteinuria (8). The existence of podocytes and their specific proteins in the urine can be considered as potential markers in the early detection of DN. Currently new markers for early detection of DN are being evaluated when most of the research focus on podocyte-specific proteins such as podocalyxin, nephrin, synaptopodin, podocin, mindin, etc (9).

The research results of Sun, D., Zhao, X., & Meng, L (10) defined a new role for podocalyxin in constructing cell morphology. When ectopicly expressed in kidney epithelial cells, podocalyxin dramatically enhances microvillus formation. In addition, podocalyxin is essential for foot processes (FP) elongation in kidney podocytes. Podocalyxin was originally identified in the glomeruli of the kidney, where it is not only abundant but also essential for kidney development (10). This study aims to

determine and compare urine podocalyxin levels in subjects with type 2 diabetes mellitus with and without diabetic nephropathy.

MATERIALS AND METHODS

Study Design and Patients

This research was an observational study with a cross-sectional research design. This research received ethical approval from the Health Research Ethics Commission (KEPK) Hasanuddin University Faculty of Medical-UNHAS (RSPTN UH) with ethical number 596/UN4.6.4.5.31/PP36/2022.

Collection of Clinical Data

Sampling locations were carried out at the Endocrine Polyclinic at Hasanuddin University Hospital, the Clinical Pathology Laboratory at Hospital of Hasanuddin and the Clinical Pathology Laboratory at RSUP. Wahidin Sudirohusodo Makassar. Furthermore, the research carried out at the Hasanuddin University Medical Research Center (HUM-RC) Laboratory, Hasanuddin University Makassar State University Hospital and the Parahita Makassar Clinical Laboratory. A total of 50 participants were grouped into the 25 participants of T2DM with DN and 25 participants of T2DM without DN using a non-probability sampling technique.

Pathological Data

The inclusion criteria in this study were participants who were willing to take part in a series of studies, participants T2DM with or without DN, and excluded pregnant women, preeclampsia, lupus nephritis, cancer, hypertension, and coronary heart disease. The diagnosis of T2DM participants was based on the results of laboratory tests, namely fasting blood glucose levels of 126 mg/dL or HbA1c values of 6.5%. Participants diagnosis with and without DN by examining the urine albumin creatinine ratio (ACR) with an interpretation of the results of <30 mg/g means not diagnosed with diabetic nephropathy and if ≥ 30 mg/g means diagnosed with diabetic nephropathy.

Measurement of Urine Podocalyxin

The measurement of urine podocalyxin levels used the Enzyme-linked Immunosorbent Assay (ELISA) method with Assay PharmaGenie® (SBRS1004) at a wavelength of 450 nm and reported in ng/mL. Urine albumin and creatinine levels were examined by the Cobas 311 instrument with the immunoturbidimetric method and stated in mg/g.

Statistical Analysis

Data processing was performed using the Windows computer program SPSS (statistical product and science service) version 23. The data analysis used was bivariate analysis using the Mann-Whitney test to compare urine podocalyxin levels in

subjects of T2DM with and without DN, compared ACR in T2DM subjects with and without DN, followed by a correlation test using the Spearman test. The test results are significant if p*<0.05.

RESULTS

The research results are presented in a table accompanied by an explanation. Participant characteristics (Table 1) such as gender, age, diagnosis of T2DM participant based on measurement results of HbA1c and diagnosis of T2DM with DN based on ACR ≥ 30 mg/g. Table 2 and Table 3 present a comparison test of urine podocalyxin levels and ACR levels in T2DM participant with and without DN, then Table 4 presents a correlation test of urine podocalyxin levels with ACR in T2DM with DN.

Table 1. Participant Characteristics

Characteristics	n	%
Sex		
Male	24	43.6
Female	31	56.4
Ages (years old)		
30 – 40	3	5.5
41 – 50	8	14.5
51 – 60	23	41.8
61 – 70	18	32.7
> 70	3	5.5
HbA1c		
<6.5 %	5	9.1
≥6.5 %	50	90.9
Urine Albumin/Creatinine Ratio		
< 30 mg/g (T2DM with DN)	27	49.1
≥ 30 mg/g (T2DM without DN)	28	50.9

Table 1 shows the characteristics of research participant based on gender showing female participant (56.4%) were dominant compared to male participant (43.6%). Based on age category, most of the participant was aged between 51–60 years (41.8%). HbA1c level as an indicator of glycemic control in the category ≥6.5% for 50 participants (90.9%) and <6.5% for 5 participants (9.1%). ACR as a biomarker in the ≥30 mg/g category were 28 paticipants (50.9%), the average urine podocalyxin value in nephropathy participant was 1.160 ng/mL, while the average urine podocalyxin in participant without nephropathy including, diabetics was 0.167 ng/mL.

Table 2. Comparison Test of Urine Podocalyxin Levels in Participant with Diabetic Nephropathy and Without Diabetic Nephropathy

Parameter	Characteristics	Mean	SD	p*
Urine Podocalyxin (ng/mL)	T2DM with DN	1.160	2.066	<0.001
	T2DM without DN	0.167	0.047	

*Mann Whitney test

Table 2 shows that the average urine podocalyxin value in diabetic nephropathy participants is 1.160 ng/mL with a standard deviation of 2.066 ng/mL, while the average urine podocalyxin value in participants without diabetic nephropathy is 0.167 ng/mL with a standard deviation of 0.047 ng/mL. This result indicates that the average urinary podocalyxin in diabetic nephropathy is bigger than participant without diabetic nephropathy ($p < 0.05$). This result showed a significant difference between urine podocalyxin levels in diabetic nephropathy participants and participants without diabetic nephropathy.

Table 3. Comparison Test of Albumin/Creatinine Ratio Levels in Participants with Diabetic Nephropathy and Without Diabetic Nephropathy

Parameter	Characteristics	Mean	SD	p*
Albumin/Creatinine Ratio Levels (mg/g)	T2DM with DN	633.74	1546.11	<0.001
	T2DM without DN	10.071	7.883	

*Mann-Whitney test

The average albumin creatinine ratio in diabetic nephropathy subjects were 633.74 mg/g with a standard deviation of 1546.11 mg/g, while the average value of albumin creatinine ratio in conditions without diabetic nephropathy was 10.071 with a standard deviation of 7.883 (Table 3). This result showed that the average albumin creatinine ratio in diabetic nephropathy is higher than the albumin creatinine ratio in conditions without nephropathy ($p < 0.05$). This showed a significant difference between the albumin creatinine ratio in participants with diabetic nephropathy and those without diabetic nephropathy.

Table 4. Correlation Test of Urine Podocalyxin Levels With Albumin/Creatinine Ratio in Diabetic Nephropathy Participant

		Albumin/Creatinine Ratio
Urine Podocalyxin	R	0.510
	P	< 0.001
	N	55

*Spearman-rho test, R=correlation, P=level of significance, N=number of samples

Table 4 showed the correlation test results between urine podocalyxin and albumin creatinine ratio in participant with diabetic nephropathy. There is a correlation between urinary podocalyxin and albumin creatinine ratio in diabetic nephropathy participants ($p<0.001$).

DISCUSSION

This study determined and compared urine podocalyxin levels in DM participants with and without diabetic nephropathy (11). Podocalyxin is a main component of the charge barrier of the glomerular basement membrane (GBM) and plays an important role in regulating the permeability of the glomerular filtration barrier (12).

Based on Table 2, the urine podocalyxin comparison test in nephropathy and non-nephropathy participants showed a significant difference between urine podocalyxin in participants with nephropathy and urine podocalyxin without nephropathy. Kostovska I, et al (13) reported an increase in urine podocalyxin levels in 48.2% of patients with normoalbuminuria, 64% of patients with microalbuminuria and 100% of patients with macroalbuminuria (13). Similar result research by Hara M, et al. (2012) demonstrated that podocalyxin is found in urine in the early stages of diabetic nephropathy, before the apperance of microalbuminuria (14).

Research by Rongzhen Wang, et al (15) reported that PCX excretion through urine increased along with decreased PCX expression in the kidneys, which would be consistent with the release of PCX protein from the kidney into the urine (15). Previous investigations determined that elevated urinary levels of PCX could be used as a biomarker to predict early kidney damage and the development and progression of complications in patients with early-stage diabetic nephropathy, anaphylactic purpuric nephritis, lupus nephritis, or IgA nephropathy (16,17). Moreover, measuring PCX in urine is a non-invasive method that can be applied soon in clinical settings. Although previous studies focused on patients with early-stage diabetic nephropathy, this study included patients with diabetic nephropathy and clinical albuminuria. The present study's finding that urinary PCX levels are increased in nephropathy patients and are significantly associated with reduced kidney function suggests the potential clinical utility of this parameter as a biomarker in patients with early-stage DN (17).

Based on Table 2, the results of comparison test of albumin creatinine ratio for DM with and without nephropathy showed a significant difference between the albumin creatinine ratio in nephropathy participant and participant without nephropathy. Shoji M, et al (18) in their research reported a significant positive

correlation between the urinary microalbumin creatinine ratio and podocalyxin (18). This finding is different from that obtained from the results of a study by Kostovska I, et al (13) which detected a weak positive correlation between urine podocalyxin levels and albumin creatinine ratio.

Furthermore, a previous study conducted by Kostovska I, et al (13) reported that urine podocalyxin levels were higher in type 2 diabetes mellitus patients compared to control subjects with a p-value <0.05 (13). The urinary podocalyxin level increased gradually with the degree of diabetic nephropathy (p<0.029). Urinary podocalyxin levels positively correlated with urinary microalbumin/creatinine ratio (UM/CR) (r=0.227; p=0.002). Measurement of podocyte molecules in urine samples can serve as a specific marker of kidney podocyte cell damage (19). Further research is needed on urinary podocyte cytology as a non-invasive test to assess the level of glomerular damage (20). Research conducted by Asao R, et al (20) revealed a significant correlation between urinary podocalyxin levels and the degree of acute extra capillary damage (r=0.72; p<0.001), but the level of protein excretion did not correlate with acute glomerular disorders (20).

Hypertension in T2DM patients is one of the factors that affect podocalyxin levels because it is directly related to kidney function. Research conducted by Abe, H, et al (21) explains that exposure to AGEs can interfere with the RII-Smad3 signal, giving rise to the Elf3 protein, which indicates irreversible podocyte injury (r=0.73; p <0.05) (21). Akankwasa, G, et al (22) in his research on the comparison of podocalyxin and nephrin as a marker of impaired kidney function (22) which was updated through the research of Watanabe, K, et al (23), which explained that increased urine albumin leakage is closely related to glycocalyx injury in glomeruli and renal podocytes (23). A cross-sectional study conducted by Ikuma, D, et al (24) concerning the correlation of urine podocyte count and urinary podocalyxin levels to lupus nephritis histology showed significant results (r=0.50; p=0.0012) (24).

Apart from pathological factors, several technical factors play a role in measuring podocalyxin levels. Research conducted by Kimura, M, et al (25) regarding the detection of podocyte cells in urine samples of DN patients using the cytocentrifugal method can detect positive WT-1 cells in DN (25).

This study may have limitations such as the research method used cross-sectional which only looks at one event at a time, in addition to the small sample size of the study. We recommend further prospective studies with a larger sample size to compare of urine podocalyxin levels and microalbuminuria (MAU) as a marker for early detection of DN.

CONCLUSIONS

The study concluded there was a differences in urine podocalyxin levels in T2DM with and without DN, found differences of ACR in T2DM with and without DN, and a significant correlation between urine podocalyxin and ACR in T2DM with DN.

AUTHOR CONTRIBUTIONS

Jusni Ekasari Pelu: conceptualization, methodology, writing-original draft, formal analysis, and funding acquisition. Liong Boy Kurniawan & Yuyun Widaningsih: supervision, data curation, writing-original draft preparation. Alfian Zainuddin, Husaini Umar & Nurahmi: writing-original draft, writing-reviewing. Theosobia Grace Orno: project administration, writing-original draft, visualization.

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CONFLICT OF INTEREST

There is no conflict interest.

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