Original Paper

Urinary RBP and NGAL Levels are Associated with Nephropathy in Patients with Type 2 Diabetes

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Key Words

Type 2 diabetic nephropathy • NGAL • RBP • TNF- α • IL-18

Abstract

Background/Aims: The diagnosis of type 2 diabetic nephropathy (T2DN) patients is important to prevent the long-term damaging effects of kidney loss in patients with diabetes and is decisive for patient outcomes. The aim of this study was to explore urine retinol binding protein (RBP) and neutrophil gelatinase-associated lipocalin (NGAL) in T2DN patients with and without albuminuria. **Methods:** A total of 293 T2DN patients were divided into three groups according to their urine albumin/urine creatinine ratio (UACR): normoalbuminuria group (UACR<30 mg/g, n=100), microalbuminuria group (UACR 30–300 mg/g, n=100) and macroalbuminuria group (UACR>300 mg/g, n=93); 50 non-diabetic subjects were recruited as the control group. The levels of urine RBP, NGAL, TNF- α and IL-18 in T2DN patients and non-diabetic subjects were measured using ELISA assays. **Results:** We first analyzed the clinical characteristics of the control and T2DN groups and found that urine NGAL, RBP, TNF- α and IL-18 levels were significantly increased and significantly correlated with the degree of albuminuria. In addition, univariate linear regression analysis showed that urine RBP was associated with UACR, BMI, Scr, BUN, TG, disease duration, SBP, NGAL, TNF- α and IL-18 levels, and urine NGAL was positively correlated with UACR, Scr, BUN, RBP, TNF- α and IL-18 levels. **Conclusion:** The results indicate that urine levels of NGAL and RBP may be independently associated with albuminuria in T2DN and may serve as novel biomarkers for the identification of T2DN.

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Introduction

As type 2 diabetes mellitus (T2DM) progresses, various complications will emerge in patients with this disease, including nephropathy [1]. Diabetic nephropathy (DN) occurs in

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20%–40% of all patients with diabetes mellitus, impacting the morbidity and mortality of diabetic patients [2, 3]. Proteinuria is the main form of DN, and approximately 40% of 32,208 diabetes patients from 33 countries present with microalbuminuria [4]. Microalbuminuria has been used as a predictor for the progression of DN [5], however, it is not very sensitive and specific marker of DN. Therefore, it is necessary to find more sensitive and specific markers other than albuminuria to predict nephropathy progression in diabetic patients.

Retinolbindingprotein (RBP), a low molecular weight protein (21 kDa) which belongs to the lipocalin super family, is freely filtered at the glomerulus and then almost completely reabsorbed in the proximal tubule [6, 7]. Urinary RBP has been identified as abiomarker of proximal tubular dysfunction and is important for the diagnosis of Dent's disease, cystinosis and cast nephropathy. Previous studies have shown that the levels of both serum and urine RBP were increased in patients with diabetes [8, 9]. Urinary RBP is also independently related to the risk of chronic kidney disease progression in patients with macroalbuminuric DN, but whether it has a role in the occurrence of normoalbuminuria and microalbuminuria in type 2 diabetic nephropathy (T2DN) requires further investigation [10].

Neutrophil gelatinase-associated lipocalin (NGAL) is released from neutrophils and epithelial cell types including kidney tubular cells [11]. Bennett et al. and Mori et al. have reported that NGAL was one of the most highly elevated proteins in kidney tubules following ischemic injury, suggesting that NGAL was a specific marker for acute kidney injury [11, 12]. Urinary NGAL levels were showed to be significantly increased in patients with diabetes when compared with nondiabetic control subjects [13, 14]. Our previous study showed that NGAL was markedly increased and correlated with the severity of albuminuria in diabetes patients [15]; however, the data was limited by the number of participants and larger studies are needed to establish NGAL as a biomarker in clinical practice.

In the current study, we evaluated the role of urinary RBP and NGAL as potential biomarkers in conjunction with albuminuria for the detection of T2DN patients, and analyzed the clinical implications of using RBP and NGAL as biomarkers of T2DN.

Materials and Methods

Subjects

The research was performed on 293 patients with T2DN who had been referred to the Department of Endocrinology of the Shanghai Traditional Chinese Medicine-Integrated Hospital (Shanghai, China) were enrolled. All patients involved in this study fulfilled the following inclusion criteria: age >18 years; initial diagnosis of diabetes at >30 years of age; no sign of renal disease other than DN; no history of cardiovascular disease, including stroke, heart disease and arteriosclerosis and no symptoms of acute inflammatory disease [15]. Subjects were divided into three groups according to their urine albumin/urine creatinine (UACR) ratio: normoalbuminuria group (UACR <30 mg/g, n=100), microalbuminuria group (UACR 30–300 mg/g, n=100) and macroalbuminuria group (UACR>300 mg/g, n=93) [16]. 50 healthy subjects were recruited as the control group. Control group subjects were randomly selected Age- and gender-matched non-diabetic controls were randomly selected from the Shanghai TCM-Integrated Hospital for a comprehensive medical check-up, who had no prior history of diabetes, renal disease or cardiovascular diseases including hypertension and dyslipidemia. The study was approved by the ethics committee of the Shanghai Traditional Chinese Medicine-Integrated Hospital. Informed consent was obtained from all participants before participating in the study.

Examination

After 12 h of overnight fasting, all urine and blood samples were obtained from the subjects at their clinical visits when the anthropometric measurements were performed and medical histories were obtained. Urine samples were stored at -80°C and used for examination of urinary markers. A 8 ml of venous blood samples were obtained after overnight fasting into evacuated serum separator tubes with K2EDTA (Vacuette, Greiner BioOne, Kremsmünster, Austria) and tubes without any anticoagulants (Vacuette, Greiner BioOne) by antecubital venipuncture. Blood samples in tubes with K2EDTA were used for HbA1c analysis.

Sera were separated, aliquoted and used for routine chemical tests. FBG (fasting blood glucose) and TG (triglyceride) were examined using oxidase method; TC (total cholesterol), ALT (alanine transaminase), AST (aspartate aminotransferase), BUN (blood urea nitrogen) and UA (blood uric acid) were determined using cholesterol oxidase method, enzyme colorimetry, rate method, dynamic uv method, uric acid enzymatic and immune turbidimetry respectively; HDL (high-density lipoprotein) and LDL (low-density lipoprotein) were measured by clearance assay. All above biochemical determinations using Automatic biochemical analyzer test (HITACHI7600-020). HbA1C (glycated haemoglobin) were analyzed by high performance liquid chromatography using automatic glycosylated hemoglobin analyzer (Bole D10); Insulin was measured by chemiluminescence method using chemical luminescence immunity analyzer (Beckman DXI800); C-peptide was measured by an enzyme immunoassay using gamma counting meter (SN65). Urinary albumin was measured by scattering turbidimetry using specific proteins (BNProSpec). The concentration of urine TNF- α was determined using a human TNF- α quantikine enzyme-linked immunosorbent assay (ELISA; DTA00C, R&D Systems, Minneapolis, MN, USA) [15]. A human NGAL ELISA kit (ab119600; Abcam, Cambridge, MA, USA) was used to quantify urine NGAL levels [15]. The concentration of urinary IL-18 was measured with a human IL-18 ELISA Kit (ab215539, Abcam) and the concentration of urinary RBP was measured using a human RBP ELISA Kit (ab137991, Abcam, Cambridge, MA, USA). All assays were performed according to the manufacturers' instructions. The inter-assay coefficients of variation of NGAL were between 5.2% and 7.4%, and intra-assay coefficients of variation were from 3.3% to 4.6%; The inter-assay coefficients of variation of RBP were between 5.0% and 7.9%, and intra-assay coefficients of variation were from 2.8% to 4.2%; The inter-assay coefficients of variation of IL-18 were between 4.5% and 8.2%, and intra-assay coefficients of variation were from 4.1% to 7.6%; The inter-assay coefficients of variation of TNF- α were between 5.1% and 8.9%, and intra-assay coefficients of variation were from 4.1% to 5.8%. The detection limits of the assays were: 4 pg/mL for NGAL, 0.2 μ g/mL for RBP, 62.5 pg/mL for IL-18 and 15.6 pg/mL for TNF- α .

Statistical analysis

SPSS version 13.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. All data were expressed as means $\pm$ standard deviation for normally distributed values and median (interquartile range) for nonparametric values. Distributions of continuous variables were examined for skewness and kurtosis, and logarithm-transformed values of variables with non-Gaussian distribution were used for analyses. Significant between-group differences were estimated using analysis of variance (ANOVA), followed by Bonferroni's test for normally distributed values or the Kruskal-Wallis test for nonparametric values. Skewed variables were log transformed and Spearman's correlation coefficients and partial correlation coefficients were calculated. Multiple linear regression was used to analyze the relationship between clinical parameters and urine RBP and NGAL, and also the relationship between urine RBP, NGAL and albuminuria. $P < 0.05$ was considered statistically significant, while $p < 0.001$ was regarded as highly significant, and all tests performed were two-tailed.

Results

Patient baseline characteristics

The clinical characteristics of the 50 non-diabetic control subjects (control group) and T2DN patients with different degrees of albuminuria (normoalbuminuria group, microalbuminuria group and macroalbuminuria group) are shown in Table 1. At baseline, the age, gender, body weight (BW), body mass index (BMI), TG, HbA_{1c}, Insuline, C-peptide, ALT and estimated glomerular filtration rate (eGFR) were showed that there was no statistically significant differences between the studied groups, and there is a longer duration of diabetes in macroalbuminuria group than normoalbuminuria and microalbuminuria groups. The levels of FBG and diastolic blood pressure (DBP) were significantly increased in T2DN groups compared with the control group, whereas the levels of LDL and HDL were obviously decreased. Microalbuminuria group has higher systolic blood pressure (SBP) and AST than control and normoalbuminuria group, and the greater level of BUN in macroalbuminuria group than in all others group.

Table 1. Clinical characteristics of controls and T2DN patients, stratified according to albuminuria status. †p<0.05 vs. Control group; ‡p<0.001 vs. Control group; §p<0.05 vs. Normoalbuminuria group; ||p<0.001 vs. Normoalbuminuria group; ¶p<0.05 vs. Microalbuminuria group; #p<0.001 vs. Microalbuminuria group

-	Control	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	p-value
Number	50	100	100	93	-
Age (years)	63.6 ± 8.62	62.93 ± 10.54	65.22 ± 21.79	67.01 ± 17.12	0.052
Gender(male/female)	24 / 26	60 / 40	50 / 50	56 / 37	0.26
BW (kg)	65.18 ± 8.94	67.37 ± 11.9	66.49 ± 11.95	70.24 ± 13.45	0.061
BMI (kg/m ²)	23.84 ± 2.62	24.47 ± 3.8	24.37 ± 3.67	25.31 ± 4.15	0.114
Duration(years)	-	8.92 ± 7.69	9.83 ± 9.12	13.43 ± 8.1 ¶	< 0.001
SBP (mmHg)	130.66 ± 14.2	131.22 ± 15.04	135.05 ± 15.74	140.73 ± 18.04 †	< 0.001
DBP (mmHg)	73.88 ± 8.1	78.67 ± 8.83 †	77.2 ± 9.23	79.13 ± 10.14 †	0.007
FBG (mmol/L)	4.92 ± 0.59	7.99 ± 3.05 ‡	8.12 ± 2.87 ‡	8.08 ± 3.15 ‡	< 0.001
HbA1c (%)	-	9.21 ± 2.84	9.59 ± 2.71	9.12 ± 2.36	0.433
insulin	-	94.98 ± 79.26	111.61 ± 138.83	92.44 ± 69.97	0.358
C-peptide (ng/ml)	-	1.47 ± 0.89	1.4 ± 0.86	1.54 ± 1.33	0.552
Scr (umol/L)	72.36 ± 14.03	58.56 ± 14.24 †	59.56 ± 14.48	88.76 ± 49.46 † #	< 0.001
TC (mg/dL)	209.5 ± 38.08	185.54 ± 57.2 †	177.84 ± 42.4 †	187.43 ± 50.95	0.003
TG (mg/dL)	111.95 (61.28 - 218.23)	108.85 (49.51 - 282.35)	97.79 (50.27 - 368.14)	133.63 (57.52 - 410.44)	0.042
LDL (mg/dL)	126.66 ± 31.55	108.26 ± 44.1 †	100.12 ± 33.41 ‡	105.53 ± 41.4 †	0.001
HDL (mg/dL)	67.12 ± 37.3	50.91 ± 12.15 ‡	55.2 ± 17.53 †	54.62 ± 19.55 †	< 0.001
ALT (U/L)	23.3 ± 14.58	22.35 ± 8.88	19.48 ± 8	21.62 ± 15.26	0.194
AST (U/L)	23.8 ± 7.27	22.48 ± 9.59	18.41 ± 6.81 ‡ §	21.6 ± 12.2	0.002
UA (umol/L)	319.32 ± 57.64	287.75 ± 72.61	265.38 ± 64.08 ‡	352.58 ± 98.81 #	< 0.001
BUN (mmol/L)	5.29 ± 1.01	5.62 ± 1.65	5.75 ± 1.88	7.6 ± 3.5 ‡ #	< 0.001
eGFR (ml/min/1.73 m ²)	98.84 ± 22.9	149.46 ± 163.71	130.35 ± 40.58	117.03 ± 215.06	0.19
u-ACR (ng/mg)	-	14.4 (5.25 - 28.4)	72.33 (31.14 - 237.53)	671.4 (312.04 - 4208) #	< 0.001

Table 2. The levels of u-RCR, u-NCR, u-TCR, u-ICR in control groups and T2DN patients with different albuminuria status. u-RCR: urine RBP/urine creatinine; u-NCR: urine NGAL/urine creatinine; u-TCR: urine TNF-α/urine creatinine; u-ICR: urine IL-18/urine creatinine. †p<0.05 vs. Control group; ‡p<0.001 vs. Control group; §p<0.05 vs. Normoalbuminuria group; ||p<0.001 vs. Normoalbuminuria group; ¶p<0.05 vs. Microalbuminuria group; #p<0.001 vs. Microalbuminuria group

-	Control	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	p-value
u-RCR (ug/mg)	9.67 (7.17 - 17.36)	11.31 (7.4 - 25.56)	17.27 (11.93 - 44.63) ‡	26.46 (15.82 - 83.83) ‡ #	< 0.001
u-NCR (ng/mg)	10.21 (4.27 - 28.82)	13.77 (5.68 - 45.37)	15.35 (5.27 - 58.91) †	33.77 (10.08 - 117.89) ‡ #	< 0.001
u-TCR (pg/mg)	8.25 (1.16 - 42.32)	6.15 (1.13 - 34.58)	16.53 (2.66 - 111.71) †	40.1 (4.92 - 238.46) ‡ #	< 0.001
u-ICR (pg/mg)	147.58 (20.42 - 1197.32)	150.92 (18.92 - 1748.83)	326.88 (21.57 - 9579.54) † §	995.32 (31.54 - 13590.18) ‡ ¶ #	< 0.001

Differences in urinary markers with respect to albuminuria

The ratios of urine RBP: urine creatinine (u-RCR), urine NGAL: urine creatinine (u-NCR), urine TNF-α: urine creatinine (u-TCR) and urine IL-18: urine creatinine (u-ICR) in the control, normoalbuminuria, microalbuminuria and macroalbuminuria groups were measured and showed significant differences between groups (Fig. 1 and Table 2). The levels of u-RCR, u-TCR and u-ICR were markedly increased in the microalbuminuria and macroalbuminuria groups, with no significant difference in levels between the control and normoalbuminuria groups. The u-NCR level was significantly higher in T2DN patients with microalbuminuria than in control subjects, but did not significantly differ from patients with normoalbuminuria.

Fig. 1. Levels of u-RCR, u-NCR, u-TCR and u-ICR in control and T2DN patients stratified according to albuminuria status. (A) u-RCR, urine RBP: urine creatinine ratio; (B) u-NCR, urine NGAL: urine creatinine ratio; (C) u-TCR, urine TNF- α : urine creatinine ratio; (D) u-ICR, urine IL-18: urine creatinine ratio. †p<0.05 vs. control group; ‡p<0.001 vs. control group; §p<0.05 vs. normoalbuminuria group; ¶p<0.001 vs. normoalbuminuria group; ¶¶p<0.05 vs. microalbuminuria group; #p<0.001 vs. microalbuminuria group.

Notably, the levels of u-NCR, u-RCR, u-TCR and u-ICR were sharply enhanced in the macroalbuminuria group compared with the other groups.

Clinical parameters related to the levels of urinary NGAL and RBP in T2DN patients

Univariate linear regression analysis was used to analyze the relationships between urine NGAL, RBP levels and clinical parameters in T2DN patients. We found a significant positive correlation between urine RBP and UACR, BMI, Scr, BUN, TG, disease duration and SBP; urine NGAL was positively correlated with UACR, Scr and BUN (Table 3).

Urinary marker levels (urine NGAL and RBP) and clinical parameters (age, BW, duration of diabetes, BMI, HbA1c, SBP, DBP, FBG, Scr, Insulin, C-peptide, BUN, TC, TG, LDL, HDL, AST and UA) were analyzed in T2DN patients using multivariate linear regression analysis. The results indicated that urinary NGAL was associated with UACR and RBP as independent factors (regression equation: $Y_{\text{NGAL}} = 11.337 + 0.008 \text{ UACR} + 0.558 \text{ RBP}$), and urinary RBP was associated with UACR and NGAL as independent factors (regression equation: $Y_{\text{RBP}} = 10.932 + 0.006 \text{ UACR} + 0.319 \text{ NGAL}$).

Relationship between urinary markers and UACR in T2DN patients

To determine if urinary markers were related to albuminuria, multiple linear regression analysis was employed. Multivariate models for UACR were adjusted for age, BW, duration of diabetes, BMI, HbA1c, SBP, DBP, FBG, Scr, Insulin, C-peptide, BUN, TC, TG, LDL, HDL, AST, UA,

Table 3. Spearman's rank correlation coefficient between levels of urine NGAL, urine RBP and clinical parameters in T2DN patients

	RBP		NGAL	
	r	p	r	p
UACR	0.713	<0.001	0.409	<0.001
BMI	0.144	=0.013	-0.07	=0.235
HbA1c	0	=0.999	-0.042	=0.469
Scr	0.213	<0.001	0.187	<0.001
BUN	0.155	=0.008	0.189	<0.001
TG	0.122	=0.037	0.066	=0.262
Duration	0.142	=0.015	0.114	=0.051
LDL	0.004	=0.94	0.027	=0.203
HDL	0.77	=0.191	0.041	=0.487
SBP	0.213	<0.001	0.062	=0.293
DBP	0.067	=0.056	0.009	=0.876

Fig. 2. Single regression analysis of the relationship between urinary NGAL and RBP levels and other urine markers in T2DN patients. (A) The correlation of RBP and NGAL levels. (B) The correlation of NGAL and TNF- α levels. (C) The correlation of NGAL and IL-18 levels. (D) The correlation of RBP and TNF- α levels. (E) The correlation of RBP and IL-18 levels.

NGAL, RBP, TNF- α and IL-18. Our analysis revealed that the independent variables associated with UACR including Scr, BW, HDL, SBP, C-peptide, NGAL, RBP and TNF- α (regression equation: $Y_{UACR} = -2419.288 + 11.82\text{Scr} + 137.768\text{HDL} + 5.192\text{SBP} - 98.0\text{C-peptide} + 7.336\text{BW} + 9.435\text{NGAL} + 12.528\text{RBP} + 2.476\text{TNF-}\alpha$).

Relationship between urine NGAL, RBP, TNF- α and IL-18 levels in T2DN patients

We performed single linear regression analysis on the relationship in T2DN patients between urine NGAL and RBP, between NGAL and TNF- α and IL-18 levels, and between RBP and TNF- α and IL-18 levels. As shown in Fig. 2, positive associations were found between NGAL and RBP ($r = 0.514$, $p < 0.001$), NGAL and TNF- α ($r = 0.215$, $p < 0.001$), NGAL and IL-18 ($r = 0.119$, $p < 0.05$), RBP and TNF- α ($r = 0.297$, $p < 0.001$) and RBP and IL-18 ($r = 0.211$, $p < 0.001$).

Discussion

DN is one of the most significant long-term complications in terms of morbidity and mortality for diabetic patients [17,18]. Diagnosis at an advanced stage and the high rate of recurrence results in a poor prognosis for DN [19]. Thus, the diagnosis and treatment of DN has critical clinical significance in DN patients. In our study, we showed that urinary RBP, NGAL, TNF- α and IL-18 were significantly elevated in the microalbuminuria and macroalbuminuria groups compared with those in the normoalbuminuria and control groups and that these

urinary biomarkers were independently associated with albuminuria in T2DN patients. In addition, urinary RBP levels were significantly correlated with UACR, BMI, Scr, BUN, TG, disease duration, SBP, NGAL, TNF- α and IL-18, and urinary NGAL was positively correlated with UACR, Scr, BUN, RBP, TNF- α and IL-18. Our results suggest that urinary levels of NGAL and RBP may serve as novel biomarkers for the identification of T2DN.

Urinary RBP has been classically used as a marker of proximal tubular damage [8]. Previous studies reported that the urinary excretion of RBP was enhanced in diabetic subjects compared with healthy controls, and found that RBP was associated with microalbuminuria and other complications of diabetes mellitus, suggesting that RBP might act as a renal biomarker for predicting diabetic complications [8, 20]. Urinary RBP was also independently related to the risk for macroalbuminuric DN in diabetic patients, suggesting that RBP could be used as a marker for follow-up clinical monitoring of diabetics with DN; however, its role in normoalbuminuria and microalbuminuria in DN should be further explored [10]. Mohamed et al. evaluated the diagnostic value of serum RBP for detection of nephropathy in type 2 diabetic patients and showed that it may be useful as a tool for clinical monitoring the development and progression of DN [21]. However, other studies have indicated that elevated RBP4 serum concentrations are not necessarily corrected by a decrease in urinary RBP4 excretion [20, 22]. Thus, whether serum RBP4 could be a predictor for the progress of DN will require more investigation and additional data. In this study, we examined changes in urinary RBP level and its correlation with urinary albuminuria in T2DN patients. We found that the level of RBP in urine was significantly higher in the microalbuminuria and macroalbuminuria patient groups compared with the normoalbuminuria and control groups. In addition, urine RBP levels were significantly and positively correlated with UACR, BMI, Scr, BUN, TG, disease duration, SBP, NGAL, TNF- α and IL-18 levels, indicating that urinary RBP may be a biomarker for detection of DN in T2DN patients.

Urinary NGAL excretion has been shown to be increased in many pathological conditions including ischemia, inflammation, cardiac surgery and renal injury [23, 24]. Wu et al. reported that serum NGAL level may serve as a new biomarker for the diagnosis of diabetic kidney disease (DKD) in T2DM [25]. De Carvalho et al. showed that NGAL was enhanced in T2DM patients with normal or mildly increased albuminuria, which indicated that tubular and glomerular injuries may be occurring even at the earliest stage of DKD [26]. Nielsen et al. found that urinary NGAL was elevated in type1diabetic (T1DM) patients with or without albuminuria, demonstrating tubular damage at an early stage [27]. Thus, the level of urinary NGAL appears to increase in the very early phase of T1DM before microalbuminuria develops. Patients with T1DM should be considered to have diabetic kidney injury from the time of diagnosis and preventive interventions should be initiated at an early stage to preclude the progression to end-stage renal disease [28]. Here, we found that the level of urine NGAL was significantly higher in the normoalbuminuria, microalbuminuria and macroalbuminuria groups compared with the control group, and found that urine NGAL was independently associated with albuminuria in T2DN. Moreover, we analyzed the relationship between NGAL level, clinical characteristics and inflammatory cytokines and showed that urine NGAL was significantly correlated with UACR, Scr, BUN, RBP, TNF- α and IL-18. The results suggest that urine NGAL may serve as a biomarker for diagnosis of T2DN.

Cytokine is one of the major mediators composing the immune system, and change of immunological function is one of the leading causes of DN occurrence [29, 30]. TNF- α is essential in the regulation of inflammation in the kidney, and is correlated with renal injury and a disruption of the glomerular permeability barrier in patients with diabetes [15, 31]. Navarro et al. showed that TNF- α level in patients with type 2 diabetes at an early stage of nephropathy was independently linked with urinary albumin excretion [32]. In addition, our previous study have reported that TNF- α was able to provide additional prognostic information with regard to the progression of DN at the early stage [15]. IL-18 has been shown as a pro-inflammatory cytokine that is released in response to ischemia-reperfusion injury of the renal proximal tubules [33]. IL-18 was also reported that it is increased in human tubular epithelial cells in diabetic nephropathy [34]. In this study, we also investigated the

correlation of urinary inflammatory marker TNF- α and IL-18 with albuminuria in T2DN. We found that urinary TNF- α and IL-18 enhanced with the degree of albuminuria and showed a relationship with NGAL and RBP levels, and clinical characteristics. The results suggest that urinary TNF- α and IL-18 could serve as a biomarker for diagnosis of T2DN.

In conclusion, our study determined that urinary RBP, NGAL, TNF- α and IL-18 were independently associated with albuminuria in T2DN patients. These results suggest that levels of RBP, NGAL, TNF- α and IL-18 in urine may be useful as novel biomarkers for diagnosis of T2DN, and may also help in follow-up clinical monitoring tracking the development and progression of T2DN.

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Disclosure Statement

No potential conflicts of interest were disclosed.

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