

Evaluation of Urinary Neutrophil Gelatinase Associated Lipocalin and Kidney Injury Molecule-1 as Diagnostic Markers for Early Nephropathy in Patients with Type 2 Diabetes Mellitus

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Purpose: The purpose of this study was evaluating the early diagnostic value of two specific tubular markers neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) in diabetes nephropathy.

Patients and Methods: Cross-sectional study was carried in three groups of patients from 10/2017 to 10/2018 in Military Hospital 103. Group I included 30 healthy peoples with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m² and urine albumin creatinine ratio (uACR) <30 mg/g. Group II included 30 type 2 diabetic patients having uACR <30 mg/g, eGFR >60 mL/min/1.73 m². Group III included 30 type 2 diabetic patients having uACR >30 mg/g, eGFR >60 mL/min/1.73 m².

Results: Urine KIM-1 and NGAL increased progressively from control group (57.29 ± 25.91 pg/mL; 25.71 ± 13.69 ng/mL) to the group of diabetic patients with uACR <30 mg/g (167.06 ± 44.01 pg/mL; 37.42 ± 10.89 ng/mL) and the group of diabetic patients with uACR ≥30 mg/g (p < 0.05). There were moderate correlations between KIM-1 (r = 0.48, p < 0.05) and NGAL (r = 0.45, p < 0.05) with uACR. There was a mild correlation between KIM-1 and NGAL (r = 0.29, p < 0.05). KIM-1 and NGAL are the independent tests to detect diabetic nephropathy. The sensitivity and specificity of KIM-1 with cut-off value of 174.95 pg/mL were 62.37% and 73.48%, respectively; the sensitivity and specificity of NGAL with cut-off value of 35.2 ng/mL were 60.45% and 70.37%, respectively.

Conclusion: KIM-1 and NGAL in urine are independent markers for early diagnostic diabetic nephropathy.

Keywords: diabetic kidney disease, urine albumin creatinin ratio, albumin urine

Introduction

Diabetic nephropathy (DN) is a common complication of diabetes, with a high incidence and death rate. In 2019, about 463 million people (representing 9.3% of global population) are estimated to be living with diabetes worldwide. This is predicted to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045.^{1,2} Nearly 90% of patients with diabetes will develop complications of micro and macrovascular.³ Diabetic nephropathy is considered to be one of the most serious complications, affecting 20% to 40% of diabetes patients, mostly type 2 diabetes mellitus. The Southeast Asia is on the top five regions in the world with the highest prevalence of DN in both genders and the prevalence of male has even

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been increasing since 1990.⁴ Most countries in Southeast Asia are the low- and middle-income countries where diabetes mellitus has been increasing over time.⁵

The disease progresses silently, worsens and leads to irreversible damages.^{6,7} Mechanism of disease often associates with changes in the structure and function of renal cells due to the effects of prolonged hyperglycemia, the activation of metabolic mechanisms associated with redox imbalance and inflammatory response.⁸ On the other hand, the kidney injuries have been affected partly by race, ethnicity and socioeconomic status.⁹ For these reasons, the characteristics of diabetic nephropathy are different between countries in the worldwide.

Early diagnosis and treatment play an important role in diabetic nephropathy. Currently, albuminuria is a major marker for diagnosing diabetic nephropathy with cut-off values of 30 mg/24h. However, diabetic patients with lower than cut-off value albuminuria had kidney damage. In addition, most studies have focused on glomerular mutation, but one-third of patients with normal albuminuria actually have histological glomerular disease.⁶ A growing number of studies have found that renal tubular damage plays an important role in the pathogenesis of diabetic kidney disease.^{10–13}

There are several proteins and tubular enzymes involved in tubular damage such as N-acetyl- β -D-glucosaminidase, gamma-glutamyl transferase, neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1).^{14–20} In this study, we aimed to evaluate the diagnostic value of both urinary NGAL and KIM-1 for early detection nephropathy in T2DM in Vietnam, a low-income country in Southeast Asia.

Patients and Methods

Subjects

This research included 60 diabetic patients and 30 healthy peoples enrolled in Military Hospital 103 until October 2017 to November 2018. All the diabetic patients were diagnosed according to International Diabetes Federation (IDF) criteria 2004 and fulfilled the following inclusion criteria: age \geq 18 years, estimated glomerular filtration rate (eGFR) $>$ 60 mL/min/1.73 m² and stable renal function status without increasing serum creatinine in 3 months continuous, structural normal in ultrasound imaging, no urine sediments, no history of kidney disease and transplantation before, no complications of diabetes. Patients with plasma creatinine $>$ 130 mmol/l; eGFR $<$ 60 mL/min/1.73 m², urinary albumin

creatinine ratio $>$ 300 mg/g, background with renal diseases, hypertension, other complications of diabetes, pregnancy, inflammatory disorders were excluded. The diabetic patients were divided into 2 groups II and III according to urine albumin creatinine ratio (uACR) based on KDIGO 2013.²¹ Group II contained 30 patients with normoalbuminuria (uACR $<$ 30 mg/g), group III contained 30 patients with microalbuminuria (30 $<$ uACR $<$ 300 mg/g).

Healthy peoples were selected into group I from their medical check-up visit with following inclusion criteria: fasting plasma glucose \leq 5.6 mmol/l based on 2003 ADA statement, the similar ages and socioeconomic status, no history of kidney damages, normal of kidney structure and function, eGFR $>$ 60 mL/min/1.73 m².

Sample Collection

The spot urine sample and blood samples were collected from subjects in 3 groups in the morning at their clinic visits. All the clinical characteristics were recorded at the same day.

Spot urine were used to measure: albumin, creatinine, NGAL and KIM-1. Urine albumin was quantitative determined by immuno-turbidimetric method (mg/l) in AU680 system (Beckman Coulter). Urine creatinine was determined by Jaffe method B (g/l) in AU680 system (Beckman Coulter). The eGFR were calculated using Cockcroft – Gault formula (1973): $eGFR = \{((140 - \text{age}) \times \text{weight}) / (72 \times S_{Cr})\} \times 0.85$ (if female); S_{Cr} : serum creatinine. The uACR was calculated by formula: uACR = Albumin/Creatinine (mg/g). KIM-1 was determined in spot urine by double antibody sandwich enzyme-linked immunosorbent assay (ELISA). The kit was human Kim-1 ELISA kit (My BioSource, USA). The formula to calculate urine KIM-1 and creatinine ratio were: uKIM-1/Cre = KIM-1/Creatinine (pg/g). NGAL was measured in spot urine Architect i2000 by chemiluminescent microparticle immunoassay (CMIA) (Abbott Diagnostic kit, USA). The formula to calculate urine NGAL and creatinine ratio were: uNGAL/Cre = NGAL/Creatinine (ng/g).

Glucose, cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol were determined in plasma in AU 680 system (Beckman Coulter). Plasma glucose level was accessed by hexokinase method. Plasma cholesterol level was accessed by enzyme colorimetric. HbA1c was measured in blood by high-performance liquid chromatography (HPLC) in Premiere 9201 (Trinity Biotec, USA). BMI was calculated as the ratio of the weight to the height (kg/m²).

Ethical Consideration

All participants were dispensed with written informed consents, and the protocol was approved by the Ethical Review Committee of Vietnam Military Medical University (Reference No.70/2017/VMMU-IRB). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Statistical Analysis

The data were analyzed in Microsoft Excel 2013 and Spss 20.0. Data were present as numbers of patients, mean \pm standard deviation or median, maximum, minimum for quantitative variables with normal and abnormal distribution. Difference between groups was tested with *t*-test and Mann–Whitney’s test, according to distribution. The correlation between variables was tested Pearson correlation. The results were considered to be significant at $p < 0.05$. The diagnostic accuracy was determined by using receiver operating characteristic (ROC) curves. Cut-off values were chosen by maximizing the Youden index. Based on cut-off values, the sensitivity and specificity were calculated.

Results

Clinical Characteristic of the Subjects

The results showed that there were no significant differences within 3 groups in BMI, age and gender. There were no significant differences between 2 diabetes patient’s groups in duration of disease, FPG, HbA1c, lipid disorder status. Especially, the plasma urea, creatinine concentration and eGFR were not significantly different between 2 diabetic patient’s groups (Table 1).

The results in Table 2 showed the difference in urine albumin, creatinine and uACR. The urine albumin concentration in 2 diabetic patient’s groups was higher than control group ($p < 0.05$). The urine creatinine concentration in 2 diabetic patient’s groups was lower than control group (p significantly). And the uACR were decreased from group III to II and I (p significantly) (Table 2).

The Level of Two Markers in Urine and Their Diagnostic Values in Diabetic Nephropathy

The concentration of NGAL and KIM-1 in both 2 diabetes groups was higher than control group (p significantly).

Table 1 Characteristic of the Population

	Group I (Healthy Control) (1)	Group II T2D with uARC < 30 mg/g (2)	Group III T2D with uACR \geq 30 mg/g (3)	p
n	30	30	30	
Age	61.67 \pm 10.07	63.03 \pm 10.88	64.73 \pm 6.13	$p_{1-2} > 0.05$ $p_{2-3} > 0.05$ $p_{1-3} > 0.05$
Duration of disease	–	30 (100%)	30 (100%)	
1–<5 years		12 (40%)	11 (36.7%)	
5–<10 years		16 (53.3%)	13 (43.3%)	
\geq 10 years		2 (6.7%)	6 (20%)	
Plasma glucose (mmol/l)	5.26 \pm 0.78	9.71 \pm 5.24*	8.19 \pm 2.66*	$p < 0.05$
HbA1c (%)	5.67 \pm 0.26	7.38 \pm 1.44*	7.34 \pm 1.51*	$p < 0.05$
Plasma urea (mmol/L)	5.45 \pm 1.17	6.35 \pm 1.26*	6.37 \pm 0.82*	$p < 0.05$
Plasma creatinine (μ mol/L)	77.30 \pm 12.89	86.29 \pm 19.24	84.26 \pm 21.49	$p_{1-2} > 0.05$ $p_{2-3} > 0.05$ $p_{1-3} > 0.05$
eGFR (mL/min/1.73m ²)	88.73 \pm 14.93	73.07 \pm 12.35*	75.10 \pm 14.79*	$p < 0.05$

Notes: Values were represented as mean \pm SD, *Significantly different from group I (healthy control) ($p < 0.05$).

Abbreviations: uACR, urine albumin creatinin ratio; T2D, type 2 diabetes; eGFR, estimated glomerular filtration.

Table 2 Urine Albumin, Urine Creatinine, Urine Albumin Creatinine Ratio of the Subjects

	Group II uACR < 30 mg/g (n=30) (3)	Group III uACR ≥ 30 mg/g (n=30) (2)	Group I (n= 30) (1)	p
Albuminurin (mg/l)	15.08 ± 3.23	73.73 ± 68.62	4.12 ± 3.86	P ₁₋₂ < 0.05* P ₂₋₃ < 0.05* P ₁₋₃ < 0.05*
Urinary creatinine (g/l)	0.96 ± 0.29	0.89 ± 0.29	1.35 ± 0.59	P ₁₋₂ > 0.05 P ₂₋₃ < 0.05* P ₁₋₃ < 0.05*
uACR (mg/g)	16.65 ± 4.87	84.67 ± 58.63	3.49 ± 3.14	P ₁₋₂ < 0.05* P ₂₋₃ < 0.05* P ₁₋₃ < 0.05*

Note: *Statistically significant difference between the groups.

Both NGAL and KIM-1 in group III were higher than group II ($p < 0.05$) (Figures 1 and 2).

ROC curves were carried out to access the nephropathy diagnostic values of urinary NGAL, KIM-1 in type 2 diabetes patients (Figure 3A–D). The cut-off values of urinary NGAL, KIM-1, NGAL/Creatinine, KIM-1/Creatinine were 35.3 ng/mL; 174.95 pg/mL; 44.39 ng/g; 182.06 pg/g, respectively.

Table 3 shows the sensitivity (Se), specificity (Sp) at the cut-off value of uNGAL, uKIM-1, uNGAL/Cr, uKIM-1/Cr. With the cut off value of uNGAL > 35.3 ng/mL, the sensitivity and specificity were 60.45% and 70.31%, respectively. With the cut off value of NGAL/Cr > 44.39 ng/g, the Se and Sp were 57.29% and 69.75%, respectively. The Se, Sp of

NGAL/Cr were lower than NGAL. With the cut off value of KIM-1/Cr > 174.95 pg/mL, the Se and Sp were 62.37% and 73.48%, respectively. With the cut off value of KIM-1/Cr > 182.06 pg/g, the Se and Sp were 59.46% and 75.69%, respectively. KIM-1/Cr increased the Sp in prediction the nephropathy in diabetes patients (Table 3).

The Correlations Between Two Markers and Some Clinical Characteristics

The correlations of studied markers to age, duration of disease, eGFR, albuminuria, plasma glucose, cholesterol, HDL

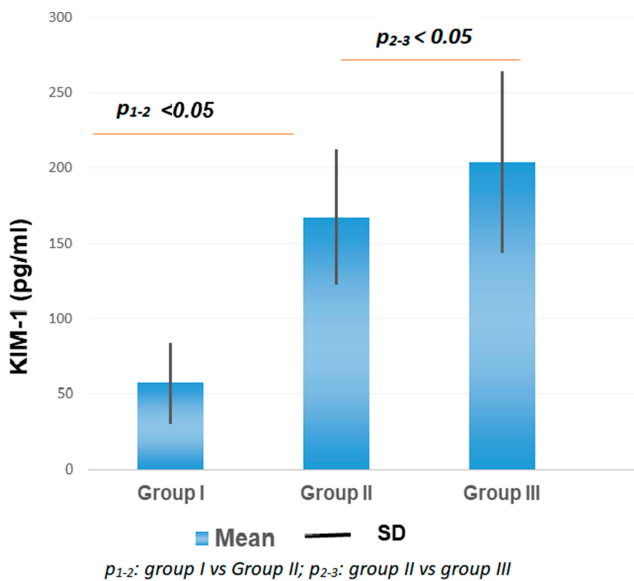


Figure 1 Concentration of urine KIM-1.

Notes: The concentration of KIM-1 in urine increased from healthy control to diabetes groups. The group II was significantly higher than group I and group III had the highest concentration. P-values in Mann–Whitney test were showed in figure.

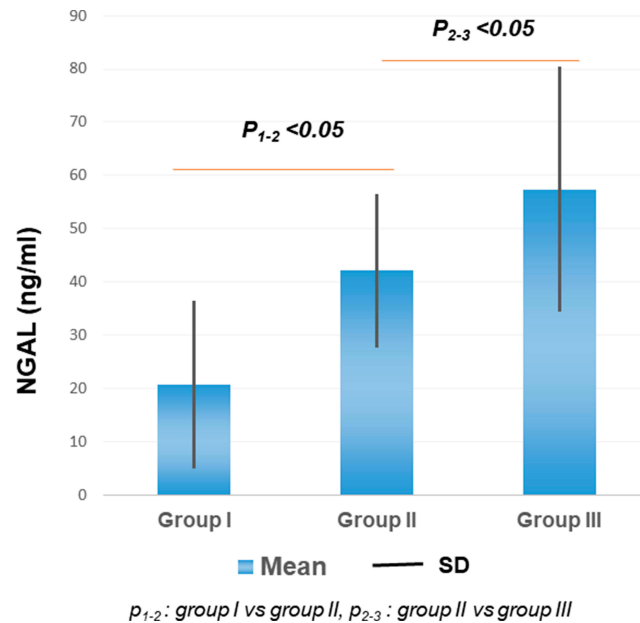


Figure 2 Concentration of urine NGAL.

Notes: The concentration of urine NGAL increased from group I to III. The differences between groups were significant. Mann–Whitney test was used to compare two groups and calculate p value.

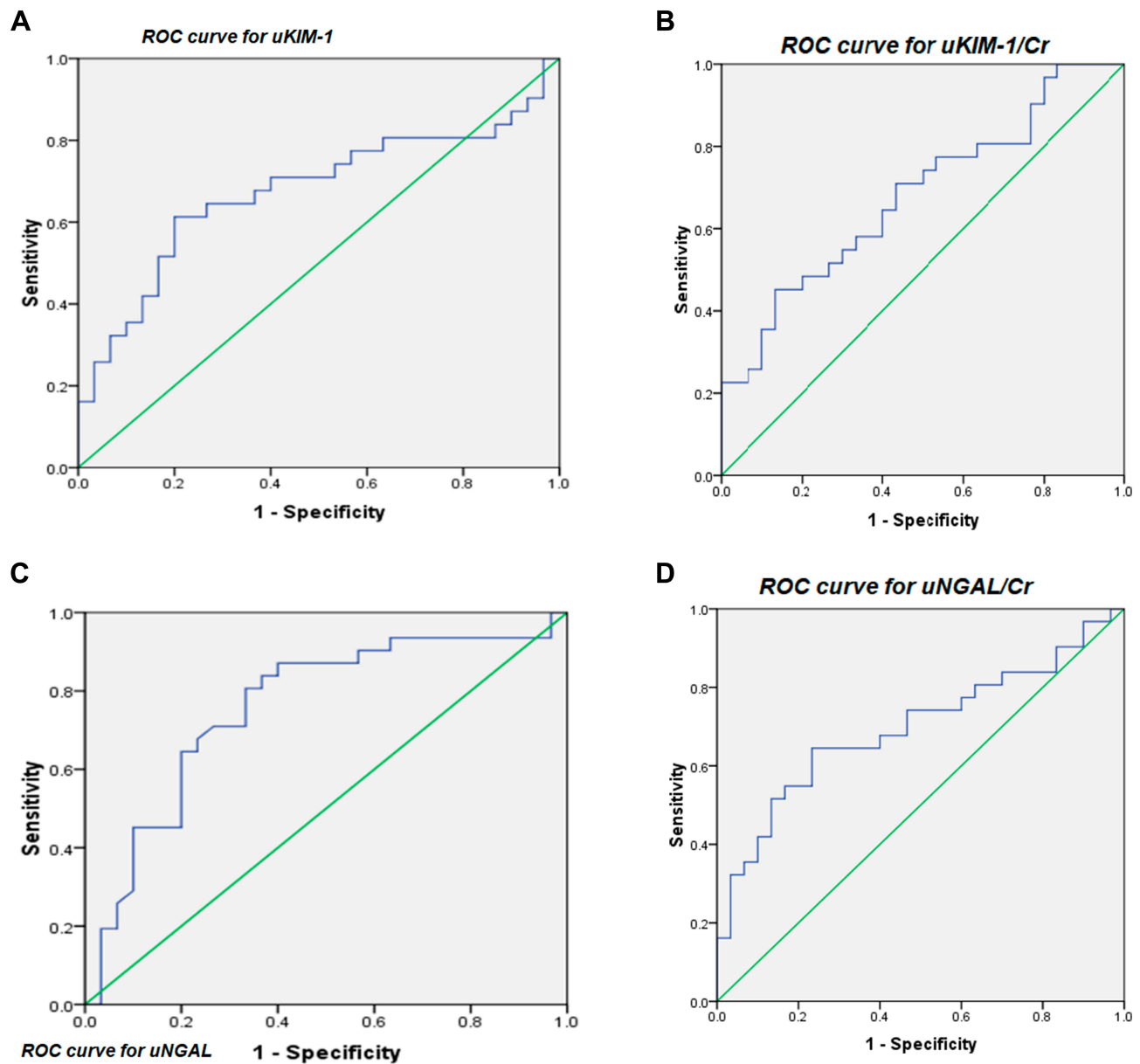


Figure 3 ROC curves analysis of NGAL, KIM-1, NGAL/Cr, KIM-1/Cr in diabetes patients with nephropathy group versus diabetes patients without nephropathy group. **Notes:** Receiver operating characteristic curves for urine markers for diagnosing nephropathy in T2D: **(A)** Urinary KIM-1 with AUC=0.576; **(B)** Urinary KIM-1/creatinine (uKIM-1/Cr) with AUC= 0.68; **(C)** Urinary NGAL with AUC = 0.692; **(D)** Urinary NGAL/creatinine (uNGAL/Cr) with AUC = 0.697.

Abbreviations: uKIM-1, urinary KIM-1; uKIM-1/Cr, urinary KIM-1/Creatinin; uNGAL, urinary NGAL; uNGAL/Cr, urinary NGAL/Creatinin.

– cholesterol, LDL – cholesterol, triglyceride, HbA1c are showed in Table 4. There was no significant correction between uNGAL and u KIM-1 to them except uACR.

Figure 4 shows the positive light correlation between uNGAL and u KIM-1 ($r=0.29$; p significantly) (Figure 4).

Discussion

KIM-1, kidney injury molecule 1, is a transmembrane protein type 1, with an immunoglobulin and mucin domain. NGAL, neutrophil gelatinase-associated lipocalin, is secreted by

epithelial and neutrophil. KIM-1 and NGAL had found to appear early in acute renal tubular injury.^{22–26} Many researches had improved them as markers for injury in chronic kidney disease.^{15,22,27,28} Urinary NGAL was a noninvasive biomarker of normoalbuminuria renal in type 2 diabetes.^{29,30} Serum KIM-1 had performed as a marker for rapid decline renal functions in type 2 diabetes.^{16,31}

Histopathological types of T2DM nephropathy include disproportionate tubulo-interstitial, glomerulosclerotic and vascular changes. Due to the reabsorption a large amounts

Table 3 Diagnostic Values of All Markers

Variables	Cut-Off Value	Sensitivity	Specificity
KIM-1 (pg/mL)	>174.95	62.37	73.48
NGAL (ng/mL)	>35.30	60.45	70.37
KIM-1/Creatinine (pg/g)	>182.06	59.46	75.69
NGAL/Creatinine (ng/g)	>44.39	57.29	69.75

Note: The sensitivity and specificity were calculated based on the cut-off values.

Table 4 The Correlations Between Some Characteristic to KIM-1 and NGAL

	KIM-1		NGAL	
	P	r	P	r
Age	>0.05	0.05	<0.05	0.26
BMI	>0.05	-0.16	>0.05	-0.12
Glucose	>0.05	-0.05	>0.05	-0.05
Urea	>0.05	-0.09	>0.05	-0.20
Creatinine	> 0.05	-0.15	>0.05	-0.07
HbA1c	>0.05	-0.07	>0.05	-0.24
Cholesterol	>0.05	-0.04	>0.05	-0.18
HDL-C	>0.05	0.07	>0.05	-0.05
LDL-C	>0.05	0.05	>0.05	-0.11
Triglyceride	>0.05	0.16	>0.05	-0.28
uACR	<0.05	0.48	<0.05	0.45

Notes: The bold value showed the variables had correlation to markers with $p < 0.05$. NGAL had correlation to ages and uACR. KIM-1 only had correlation to uACR. r, Pearson correlation coefficient; P-value: correlation is significant at 0.05.

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1 concentration; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; uACR, urine albumin creatinin ratio.

of protein of the renal tubules, inflammatory response and fibrosis are developed in renal tubular cells. Inflammatory interstitial infiltrates appeared with lymphocytes and macrophages.³² Moreover, proteinuria causes tubular cell death. Recent evidence has focused on the importance of identifying renal tubular injury and its association with kidney damage in diabetes patients.^{10,11,33,34} With the appearance of inflammatory and cell death, the amount of NGAL and KIM-1 would have appeared earlier than albumin. Because in the early stage, glomerular basement membrane is thickened only so that albuminuria would not appear. Our study researched the concentration of urinary NGAL and KIM-1 in the T2DM had normal eGRP more than 60 mL/min/1.73m². We found that both urinary NGAL and KIM-1 of microalbuminurin group had increased higher than normal albuminurin group. So that both KIM-1 and NGAL increased and appeared in the urine earlier than albumin. Although our diabetic subject had different average age, duration of disease, race

and socioeconomic status, the result had high consistency with other studies and also demonstrated that NGAL and KIM-1 appeared earlier in nephropathy.^{15,16,27,28,31,35-39}

Sensitivity and specificity of urine NGAL and KIM-1 in early diagnostic diabetic nephropathy of our study were similar to other researches.^{39,40} Kapoula et al had showed the pooled sensitivity and specificity among the different settings analyzed ranged from 0.42 (95% CI, 0.22–0.66) to 1.00 (95% CI, 0.99–1.00) and 0.72 (95% CI, 0.62–0.80) to 0.98 (95% CI, 0.50–1.00) in T2DM patients, respectively.⁴⁰ Zylka et al had found sensitivity of NGAL and KIM-1 were 80%, 79%, respectively, and specificity of NGAL, KIM –1 was 61%, 51%, respectively.³⁹ Based on these values, urinary NGAL and KIM-1 could be used as independent markers for diagnostic and prediction for diabetic nephropathy.

Our results show that KIM-1 has a moderate correlation with uACR index ($r = 0.48, p < 0.05$), NGAL was positive correlated with uACR index ($r = 0.45, p < 0.05$). KIM-1 and NGAL were not correlated with other biochemical tests such as plasma glucose, urea, creatinine, cholesterol, HDL-C, LDL-C, triglycerides, HbA1c. We found some common points in our research results with the one carried by Zylka et al in 2018, which studied on 80 type 2 diabetic patients divided into 2 groups: 61 patients with uACR <30 mg/g, 19 patients with uACR > 30 mg/g, normal eGRF. The authors found that there was no correlation between KIM-1 and NGAL with other tests and duration of diabetes but there was a moderate correlation between KIM-1 and NGAL with uACR index ($r = 0.39, p < 0.001$ and $r = 32, p = 0.005$). When the correlation between KIM-1 and NGAL was adjusted for urinary creatinine, the authors also found that NGAL/Cr and KIM-1/Cr were positively correlated with uACR ($r = 0.36, p = 0.02$ and $r = 0.45, p < 0.05$), there was no correlation between KIM-1 and NGAL with duration of diabetes.³⁹ Research made by de Carvalho et al also found that there was a positive correlation between uKIM-1 and uNGAL with uACR index ($r = 0.64, p < 0.001$; $r = 0.72, p < 0.001$).⁴¹

Although NGAL and KIM-1 had been considered as an early marker for DN since 2000 years,^{25,42} our study had some differences to earlier studies such as: the socioeconomic status, the average age and the known disease duration, the background diseases of the diabetic subjects. Vietnam is a developing country with the low income so the life and health care system for treatment and control the complications are still limited. Moreover, since 1990, the Southeast Asia region has always been one of five regions had highest DN prevalence.⁴ The geographic region, race,

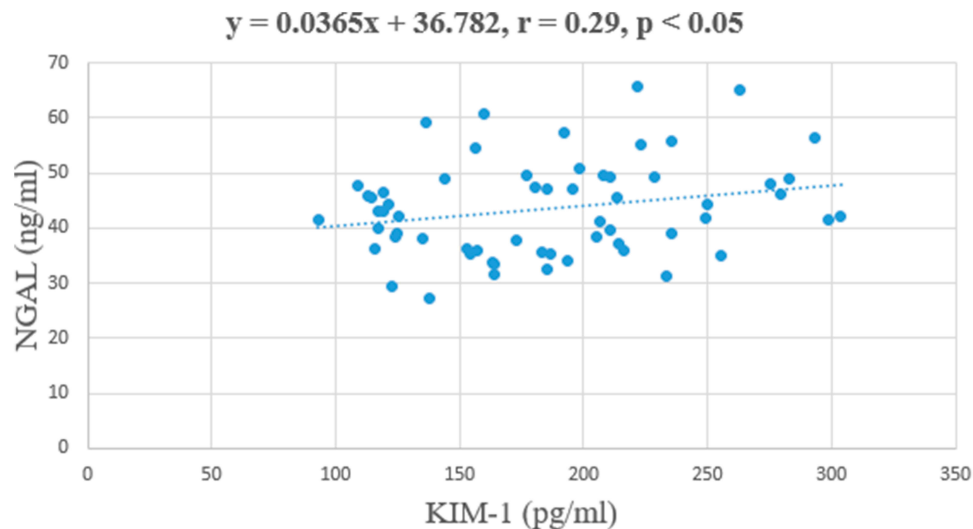


Figure 4 The correlation between NGAL and KIM-1.

Notes: r, p-value with pearson correlation between urine NGAL and urine KIM-1 were showed on the figure.

life style, the health care system and socioeconomic status may affect the diabetic kidney disease. On the other hand, our exclusion criteria for diabetic subject were the background of hypertension, other renal diseases which diseases the patients often affected together with diabetes could eliminate other causes of the kidney disease. The other studies^{39,41,42} selected the microalbuminurine patients group had the average known disease duration 5 years longer than the normoalbuminurine patients group. Our study selected these two groups had similar disease duration (average 5 years) means these complications may appear and could be detected more earlier, especially in the diabetic patients in the high-risk world region as Southeast Asia.

The first limitation of this study is the small sample size, only 30 T2DM patients with normal albuminuria and 30 T2D patients with microalbuminuria were enrolled in this study. This might be not reflected for all disease groups because the numbers of diabetic patients have been increased rapidly. If we had studied in larger number of patients, we would have divided the population into many groups with the level of albuminuria or uACR to understand exactly the correlation and changes of urine NGAL, KIM-1 and ACR. Secondly, we had to collect the spot urine of all patients to quality the markers. Some researchers had improved the diagnostic value of urine ACR.⁴³ But in some cases, that might reflect insufficient the total amount of albuminuria in 24 hours and the status of kidney damage. Thus, the main limitation of our research was the cross-sectional setting so that we could

not follow up the patients. So the assessment of kidney damage progress and increasing the markers were not carried out by the time. The indication for biopsy in diabetic nephropathy was still limited. So that the relationship between these markers to histopathonic injury has not been found. Besides, NGAL depends on many factors such as body mass index, age,³⁶ the re-absorbance itself in renal.³⁰

Conclusion

KIM-1 and NGAL in urine are independent markers for early diagnostic diabetic nephropathy in Vietnamese population. Prospective researches and studies with larger population or multicenter studies are required to clarify the value of two markers.

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This is the first study on evaluation of the diagnostic value of urinary NGAL and KIM 1 in type 2 diabetic nephropathy in Vietnam; We would like to thank Military Hospital 103 for creating favorable conditions for the research to be conducted. We also would like to send our deepest thanks to the research team members for their dedication and hard work to complete the study.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it

critically for important intellectual content; gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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