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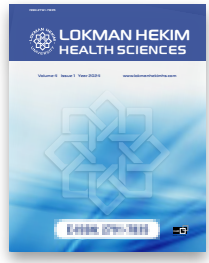

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ORIGINAL ARTICLE

Urinary Neutrophil Gelatinase-Associated Lipocalin Levels as an Indicator of Early Kidney Injury in Patients with Type 2 Diabetes Mellitus

Tip 2 Diyabetik Hastalarda Erken Böbrek Hasarı Belirteci Olarak Üriner Neutrophil Gelatinase Associated Lipocalin Düzeyleri

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Abstract

Introduction: Diabetic nephropathy is one of the major complications of diabetes mellitus. It is the most common cause of end-stage renal disease. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker that increases before serum creatinine in early acute kidney injury. We examined in this study the hypothesis that urinary NGAL levels may be elevated as an indicator of early diabetic nephropathy in patients with type 2 diabetes mellitus.

Methods: This study included a total of 78 patients (51 females and 27 males, mean age 57.74±8.97 years). The patient group consisted of 38 patients (24 females and 14 males, mean age 58.68±8.36 years) and the control group consisted of 40 healthy subjects (27 females and 13 males, mean age 56.85±9.53 years). The groups were compared in terms of anthropometric, demographic, biochemical data, and urinary NGAL levels. Urinary NGAL levels were measured using enzyme-linked immunosorbent assay.

Results: No significant difference was found in urinary NGAL levels between the patient and control groups (7.53±8.49, 9.04±9.98, p>0.05, respectively). Albumin/creatinine ratios were significantly higher in the patient group than in the control group (0.14±0.09, 0.08±0.02, p<0.05, respectively). No significant correlation was found between urinary NGAL levels and disease duration, body mass index, glomerular filtration rate, waist circumference, albumin/creatinine ratio, and HbA1c (p>0.05 for all).

Discussion and Conclusion: The results of our study show that urinary NGAL levels do not have sufficient predictive value to identify early diabetic nephropathy.

Keywords: Diabetes Mellitus; Diabetic Nephropathy; Neutrophil Gelatinase-Associated Lipocalin

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Diabetic nephropathy (DN) is one of the most common complications of type 2 diabetes mellitus (DM). It is associated with adverse outcomes and is one of the leading causes of end-stage renal disease (ESRD).[1] Microalbuminuria is an important indicator of glomerular damage[2]). However, in patients with diabetes, microalbuminuria has a low predictive value. Most of these patients are elderly and may have comorbidities such as arterial hypertension or heart failure that may lead to microalbuminuria. The fact that patients with diabetes remain normoalbuminuric despite the development of nephropathy in some cases and that some patients with diabetes with microalbuminuria later return to normoalbuminuria shows that this parameter is not very adequate in monitoring the evolution of the disease. Furthermore, albumin/creatinine ratios may vary even during the day in healthy individuals. Therefore, it has become necessary in recent years to find parameters that are more specific and sensitive than the albumin/creatinine ratio for the early detection and diagnosis of DN.[3]

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein molecule that is covalently bound to neutrophil gelatinase.[4,5] Human NGAL is mainly found in activated neutrophils. Besides neutrophils, NGAL expression has been found in other immune cells and in human adipose, lymphatic, respiratory, digestive, genitourinary, endocrine, and muscle tissues.[6] NGAL levels are known to elevate in systemic infection, inflammation, anemia, chronic hypertension, hypoxia, and malignancies.[4,7] High serum NGAL levels have been observed in cardiac hypertrophy, coronary artery disease, and some forms of acute heart failure.[8] It has also been shown to increase in psoriasis, inflammatory bowel diseases, alcoholic or nonalcoholic steatohepatitis, acute kidney injury, and malignancies.[9–12] Previous studies show that NGAL levels are a highly specific and sensitive marker of acute kidney injury.[13] Although it has been found to originate mainly from the proximal tubule in the kidney, subsequent studies showed that the Henle and collecting ducts are the main production sites for NGAL.[4] It can be readily filtered from glomeruli and reabsorbed from the proximal tubule via endocytosis. Urinary NGAL is caused by impaired reabsorption due to proximal tubule damage and synthesis of new NGAL from the tubules. It has also been shown that NGAL is a marker of early renal injury in patients with type 2 DN.[14,15]

This study compared the urinary NGAL levels in patients with type 2 diabetes with those in healthy controls to test the hypothesis that urinary NGAL levels may be an indicator of DN.

Materials and Methods

A total of 78 subjects were enrolled in this study. The type 2 diabetes group was composed of 38 patients, and the control group comprised 40 healthy subjects. Both the patients and the healthy subjects provided informed consent. This study was approved following the tenets of the Declaration of Helsinki by the Ethics Committee of the Goztepe Training and Research Hospital by decision dated 28-08-2012 and numbered 25/M.

The inclusion criteria for the diabetes group were as follows: 20 years or older, type 2 DM diagnosed for at least 5 years, and consenting to study participation. The inclusion criteria for the control group were as follows: those who applied for a health checkup and did not have any acute or chronic disease. Exclusion criteria for the diabetes group were as follows: acute and chronic infectious disease, acute or chronic inflammatory disease, malignancy, pregnancy, disease-causing chronic kidney disease other than diabetic nephropathy, acute renal failure, type 1 DM, use of nephrotoxic drugs, kidney transplantation, and not consenting to participate in the study.

Criteria of the American Diabetes Association were used for type 2 diabetes mellitus diagnosis. In all patients, systolic and diastolic blood pressure was measured using a suitable sphygmomanometer in both arms after at least 10 min of rest and in a sitting position. Body weight, waist circumference, and height were measured by the same person using standardized measuring instruments. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2).

Following 12-h fasting glucose, HbA1c, fasting glucose (FPG), creatinine, alanine aminotransferase (ALT), total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured from venous blood samples. FPG levels were measured via the hexokinase method; creatinine, total-C, HDL-C, LDL-C, and TG were measured via the enzymatic colorimetric method with Olympus AU2700 analyzer (Olympus Inc, USA). HbA1c measure was carried out using the Primus Ultra 2 (Trinity Biotech, Jamestown, New York, USA) device with the boronate affinity HPLC method. Albuminuria was defined as normoalbuminuria <30 mg/g, microalbuminuria 30–300 mg/g, macroalbuminuria mg/g according to albumin/creatinine ratio and was calculated according to albumin (mg/dl)/creatinine (mg/dl) ratio in spot urine. Glomerular filtration rate was calculated according to the Cockcroft–Gault formula [Estimated creatinine clearance (ml/min) = (140-age × body weight, kg)/72×SCr [mg/dl]).

Table 1. Evaluation of demographic characteristics by groups

	Groups				p
	Patient (n=38) Mean±SD		Control (n=40) Mean±SD		
	n	%	n	%	
Age (year)	58.68±8.36		56.85±9.53		**0.370**
Height (cm)	163.47±6.76		163.30±7.42		**0.914**
Weight (kg)	76.34±11.75		71.78±10.84		**0.078**
BMI (kg/m^2)	28.58±4.14		26.87±3.35		**0.048**
Waist circumference (cm)	95.61±7.20		82.73±7.82		**0.001**
Systolic blood pressure (mmHg)	114.21±10.30		112.50±10.31		**0.466**
Diastolic blood pressure (mmHg)	66.05±5.94		65.50±5.52		**0.236**
Sex					
Male	24	63.2	27	67.5	**0.869**
Female	14	36.8	13	32.5	
Smoking					
Yes	6	15.8	7	17.5	**1.000**
No	32	84.2	33	82.5	

SD: Standard deviation; n: Number; BMI: Body mass index.

For NGAL analysis the patient's first morning urine sample (preferably midstream) was taken and placed in a sterile urine container. Urine samples were centrifuged at 4,000 rpm for 4 min within 30 min and stored at −80°C until the study day. Urine NGAL measurement was performed at Biochemistry Clinic, using the NGAL enzyme-linked immunosorbent assay (ELISA) kit of Aviscera Bioscience Inc, USA. Urinary NGAL level was measured with the ELISA method according to the manufacturer's instructions. The urine samples were diluted 10-fold. Urinary NGAL concentrations were given as "ng/ml." Nevertheless, NGAL levels measured in spot urine were expressed as "ng/mg creatinine" units by proportioning creatinine due to daily urine volume changes. In urine samples, intra-measurement differences were 4%–6% and inter-measurement differences were 8%–10%. Analytical sensitivity was 10 pg/ml.

Statistical Analyses

Statistical analysis was carried out using NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 statistical software (Utah, USA). Student's t-test was employed to compare normally distributed parameters when comparing quantitative data, as well as descriptive statistical methods (standard deviation, median, mean, frequency, and ratio). To compare the two groups of parameters that were not normally distributed, the Mann–Whitney U test was utilized. The Yates continuity correction test was employed to compare qualitative data. Spearman correlation analysis was also employed to assess relationships between parameters. Significance was considered at the level of $p<0.05$.

Results

The ages of the subjects included in the study ranged between 40 and 84 years (mean 57.74±8.97 years). The mean disease duration was 10.6±5.4 years. 65.4% (n=51) were female and 34.6% (n=27) were male. Table 1 shows the demographic and anthropometric characteristics of the groups. Age and gender characteristics were similar between both groups ($p>0.05$ for both). Mean BMI was higher in patients than in controls ($p<0.05$).

Table 2 shows the biochemical characteristics of the groups. Albumin/creatinine ratios were higher in patients than in controls (0.14±0.09 vs. 0.08±0.02, p=0.001). Moreover, Table 3 shows urinary NGAL levels were not statistically significantly different between groups ($p>0.05$). The median value was 4.74 in the case group and 5.53 in the control group.

Fasting blood glucose (p=0.001), total cholesterol (p=0.030), triglycerides (p=0.018), creatinine (p=0.031), urea (p=0.042), and HbA1c (p=0.001) were significantly higher in patients than in controls. GFR values were not significantly different between the groups (101.01±22.87 vs. 113.14±31.46, $p>0.05$). Table 4 presents the correlation analysis evaluating the relationship between urinary NGAL

Table 2. Evaluation of biochemical parameters by groups

	Groups		p
	Patient (n=38) Mean±SD	Control (n=40) Mean±SD	
Fasting blood glucose (mg/dl); (median)	168.00±78.40 (143.50)	90.65±9.18 (90.00)	**0.001**
Total cholesterol (mg/dl)	200.58±47.30	181.78±21.69	**0.030**
HDL-C (mg/dl)	50.84±13.28	52.18±13.05	**0.656**
LDL-C (mg/dl)	122.39±41.84	114.05±21.62	**0.277**
Triglyceride (mg/dl)	137.13±64.82	108.95±29.41	**0.018**
AST (ıu/lt)	17.76±5.31	17.80±5.63	**0.976**
ALT (ıu/lt)	20.21±8.18	18.25±7.59	**0.277**
Creatinine (mg/dl)	0.79±0.14	0.72±0.14	**0.031**
Urea (mg/dl)	31.05±7.11	27.68±7.28	**0.042**
HbA1c (%)	8.07±1.93	5.51±0.19	**0.001**
Spot urine albumin/creatinine (mg/g) (median)	0.14±0.09	0.08±0.02	**0.001**
GFR (ml/min)	101.01±22.87	113.14±31.46	**0.055**

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HbA1c: Hemoglobin A1c; GFR: Glomerular filtration rate.

Table 3. Evaluation of urinary NGAL/creatinine by groups

		NGAL/creatinine (ng/mg)					
Group	n	Mean	SD	Median	Min	Max	p
Patient	38	7.53	8.49	4.74	0.17	45.02	**0.535**
Control	40	9.04	9.98	5.53	0.94	37.15	

NGAL: Neutrophil gelatinase-associated lipocalin; Min: Minimum; Max: Maximum.

Table 4. Evaluation of the relationship between urinary NGAL/creatinine and disease duration, BMI, waist circumference, HbA1c, GFR, and spot urine albumin/creatinine values

Patient group (n=38)	NGAL/creatinine	
	r	p
Disease duration	0.289	**0.070**
BMI	0.270	**0.101**
Waist circumference	-0.173	**0.298**
HbA1c	-0.179	**0.283**
GFR	-0.066	**0.694**
Spot urine albumin/creatinine	0.142	**0.395**

and disease duration, BMI, waist circumference, HbA1c, GFR, and albumin/creatinine ratios. Urinary NGAL and clinical features were not significantly correlated.

Discussion

DN develops over time in 20%–40% of patients with DM. To investigate early kidney damage in adult diabetics, albumin/creatinine ratio and calculation of GFR are employed.[2] Urine and serum NGAL levels have been reported to increase in HIV-associated nephropathy, IgA nephropathy, type 1 DM- and type 2 DM-associated nephropathy, lupus nephritis, and renal damage due to cisplatin and cyclosporine use.[4] Urinary NGAL level has been found to be more valuable than serum creatinine in the evaluation of graft function in kidney transplant patients.[16] NGAL is a sensitive biomarker for acute kidney injury compared to the routinely used renal markers. NGAL increases significantly in the urine and blood within 2 h of kidney injury.[17] Hence, high NGAL levels indicate the occurrence of acute kidney injury.[18] Elevated plasma NGAL levels were predictive of kidney injury progression and reflected renal disease severity.[19] NGAL has been present in patients without microalbuminuria or with a normal albumin/creatinine ratio, suggesting that tubular damage occurred before the onset of classic DN symptoms.[20,21]

There was no statistically significant difference (p>0.05) in urinary NGAL levels between patients and controls in our study. A weak correlation between urinary NGAL levels and the microalbuminuric group was found by Nielsen et al.;[22] 58 normoalbuminuric, 45 microalbuminuric, and 45 macroalbuminuric patients with type 1 diabetes and 55 healthy controls were included in this study. Urinary NGAL levels were significantly higher in the normoalbuminuric group compared with controls and in the macroalbuminuric group compared with normoalbuminuric. No statistically significant difference

was found in the microalbuminuric group when compared with either the macroalbuminuric or normoalbuminuric group. Similar to our study, no relationship between urinary NGAL level and BMI could be established. There was a significant negative correlation ($p<0.01$) observed with the decrease in GFR in the macroalbuminuric group. Nonetheless, no patients progressed to macroalbuminuria in our study, and the mean GFR of our patient group was higher than in this study (48.7–70 ml/min). The patients in this study had type 1 diabetes, and the mean disease duration ranged between 34 and 37 years; conversely, this duration was shorter in our study. Most of the patient group had blood pressure values that required antihypertensive treatment. Nevertheless, our patients were selected from nonhypertensive patients with type 2 diabetes, and none of them received antihypertensive treatment.

Urinary NGAL levels showed a strong positive correlation in the macroalbuminuric group compared to the microalbuminuric, normoalbuminuric, and control groups ($p=0.001$) in another study by Kim et al.[13] This study included 118 patients with type 2 diabetes (58 normoalbuminuric, 33 microalbuminuric, and 27 macroalbuminuric) and 24 healthy controls. There was no difference observed between the control group and the normoalbuminuric group. In this study, disease duration, age, and BMI were similar to our study. However, GFR was lower (93.7–95.8 vs. 107.23 ml/min) and HbA1c level was higher (7.3%–8.9% vs. 6.7%) compared to our study. Another important difference is that in our study, no patients progressed to macroalbuminuria. The patient group in our study consisted entirely of microalbuminuric patients, and urinary NGAL levels were interestingly similar to microalbuminuric patients in this study.

Bolignano et al.[19] also showed that normoalbuminuric, microalbuminuric, and macroalbuminuric patients with type 2 diabetes had increased urinary NGAL levels compared to controls. Urinary NGAL correlated positively with albuminuria and negatively with GFR. Urinary NGAL levels were also elevated in normoalbuminuric patients with diabetes. This demonstrates the usefulness of urinary NGAL as a marker of early DN.[13] Urinary NGAL levels were significantly elevated in patients with type 2 diabetes compared to controls, as shown by Fu et al.[23] Urinary NGAL levels were strongly positively correlated with albuminuria ($p<0.05$) and negatively correlated with GFR ($p<0.05$). Urinary NGAL levels increased from the normoalbuminuric group to the macroalbuminuric group. This was consistent with the severity of albuminuria.

Based on the results of previous studies and our study, the results of urinary NGAL are affected by the duration of the disease, the severity of the disease, and the presence of comorbidities that can lead to nephropathy. Regarding all these parameters, our study consists of a more moderate group of patients. Patients were selected from the group of type 2 diabetics without hypertension. They had no known history of other diseases that could lead to nephropathy. At the same time, the entire patient group consisted of microalbuminuric patients and had more moderate levels of albumin/creatinine ratio compared to other studies. Compared to the control group, there was a significant difference in albumin/creatinine ratio. There was no statistically significant difference between disease duration, BMI, waist circumference, HbA1c, albumin/creatinine ratio, GFR, and urinary NGAL levels. No difference was found in GFR between the two groups.

The limitation of our study is the small number of patients and controls. Moreover, no patients progressed to macroalbuminuria. The strength of our study is that all patients were selected from the nonhypertensive type 2 diabetes group.

Conclusion

The results of our study showed that the albumin/creatinine ratio in the patient group was significantly higher than in the control group. No significant difference was found in GFR between the patient and control groups. There was no significant correlation between urinary NGAL levels and the duration of the disease, BMI, waist circumference, albumin/creatinine ratio, GFR, or HbA1c. Urinary NGAL levels were not significantly different between the patient and control groups. Long-term, prospective, multicenter studies that involve heterogeneous groups are needed in order to determine whether urinary NGAL levels have a role in the early diagnosis of DN.

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Ethics Committee Approval: The Goztepe Training and Research Hospital Ethics Committee granted approval for this study (date: 28.08.2012, number: 25/M).

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