Urinary Neutrophil Gelatinase Associated Lipocalin as a Marker of Nephropathy in Type 2 Diabetic Patients

Dear Editor,

Kidney failure is a major complication of diabetes mellitus (DM). The prevalence of DM is 3.7% in Nigeria.[1] Diabetic nephropathy occurs three to six times more in African-Americans than Caucasians, with a higher tendency of kidney failure. A meta-analysis showed a 28% pooled prevalence of diabetic nephropathy in Nigeria.[2]

The earliest definitions of diabetic nephropathy rely on the demonstration of albuminuria. Albuminuria is usually diagnosed only after significant glomerular damage. In the absence of albuminuria, individuals with type 1 or 2 DM show a decline in glomerular filtration rates (GFR).[3] These factors suggest the need to identify more sensitive markers for diabetic nephropathy.

Several markers of tubular injury, with variable utility in diabetic kidney disease, have been identified: kidney injury molecule 1, N-acetyl-β-D-glucosaminidase, heart and liver type fatty acid binding protein, and neutrophil gelatinase-associated lipocalin (NGAL), with the last being the most promising in assessing severity and progression of renal disease.[4] We evaluated if NGAL was a better option for type 2 DM in 59 patients Ibadan, Nigeria including 29 controls. The participants were age and gender-matched. Ethical approval for the study was obtained from the University of Ibadan/University College Hospital Ibadan Health Research Ethics.

Baseline characteristics were obtained for each participant, and the HbA1c, serum creatinine, uNGAL concentrations; urine albumin: creatinine ratio (uACR); and estimated glomerular filtration rate (eGFR) were compared between groups. The DM participants were classified A1, A2, and A3 based on albuminuria categories for chronic kidney diseases (CKD). Biochemical assays were conducted using standard laboratory methods. GFR was estimated using Chronic Kidney Disease Epidemiology Collaboration Creatinine 2009 Equation (mL/min/1.73m^2).

The urinary NGAL values significantly increased from A1 to A3, when patients were grouped according to their ACRs [Table 1]. Similar findings on type 1 and 2 diabetes were reported by Megallaa *et al*.[5] When stratified into A1, A2, and A3 categories according to their ACRs, there was a significant difference between the median urinary NGAL between groups.

There was no significant association between urine NGAL and HbA1c [Table 2]. This is an unexpected finding considering the pre-established relationship between glycemic control and the development and progression of nephropathy. A probable explanation is that HbA1c reflects glycemic control over the 12 weeks before measurement, while diabetic nephropathy develops and progresses over 5 to 20 years. An accurate reflection of glycemic control over the course of the disease would require serial measurement. Thus, demonstrating an association with NGAL requires long-term prospective studies.

Multivariate regression analysis showed that eGFR had a strong negative association with NGAL [Table 2]. Romejko *et al*.[6] confirmed this association. This may represent an important advantage over the urinary albumin excretion marker. Urinary albumin excretion, though important, does not always increase with a decline in GFR, especially in the case of normoalbuminuric diabetic nephropathy.[7] In a large-scale study, 30% of patients with diabetes with GFR $<$ 60 mL/min/1.73m^2 had normal urinary albumin excretion.[8] NGAL may, therefore, play a role in identifying renal dysfunction due to DM.

Table 1: Characteristics of study participants based on urine albumin/creatinine ratio

Parameters	Controls	Diabetic patients (cases)			p
		A1	A2	A3	
	n=29	n=20	n=30	n=9	
Age (years)	60.1 ± 6.8	59.9 ± 7.2	61.4 ± 7.2	59.7 ± 5.2	0.836
HbA1c (%)	5.0 ± 0.6	6.9 ± 1.2	7.30 ± 2.1	7.27 ± 1.0	<0.001*
Serum creatinine (µmol/L)	67.2 ± 21.2	76.9 ± 29.2	104.3 ± 48.6	152.9 ± 4.4	<0.001*
eGFR (mL/min/1.73 m^2)	119.6 ± 25.5	102.5 ± 30.6	75.8 ± 24.9	46.4 ± 17.9	<0.001*
Urine albumin (g/L)	0.009 (0.006-0.016)	0.01 (0.007-0.014)	0.029 (0.015-0.061)	0.148 (0.084-0.201)	<0.001*
Urine creatinine (µmol/L)	6188 ± 2387	884 ± 1680	4420 ± 2652	1768 ± 884	0.090
Urine ACR (mg/mmol)	1.5 (1.0-2.3)	2.3 (1.6-2.8)	7.8 (4.5-12.6)	69.7 (65.1-149.9)	<0.001*
Urine NGAL (ng/mL)	15 (10-30)	60 (16.2-272.3)	221 (126.5-467.3)	625 (448-922.5)	<0.001*

*p < 0.050, A1: normal to mildly increased albuminuria group (uACR <3mg/mmol), A2: moderately increased albuminuria group (uACR 3-30mg/mmol), A3: severely increased albuminuria group (uACR >30mg/mmol), HbA1c: glycated hemoglobin, eGFR: Estimated glomerular filtration rate, ACR: Albumin:Creatinine ratio, NGAL: Neutrophil gelatinase-associated lipocalin, uACR: urine albumin: creatinine ratio

Table 2: Multivariate regression analysis of some parameters with urine NGAL in the diabetic participants

Correlating pair	β	p
NGAL vs HbA1c	0.064	0.631
NGAL vs Serum creatinine	0.568	<0.001*
NGAL vs Urine albumin	0.551	<0.001*
NGAL vs Urine ACR	0.626	<0.001*
NGAL vs eGFR	-0.860	<0.001*

*p < 0.050, HbA1c: glycated hemoglobin, eGFR: estimated glomerular filtration rate, ACR: Albumin:Creatinine ratio, NGAL: Neutrophil gelatinase-associated lipocalin, β: Regression coefficient

This study demonstrated the elevation of urinary NGAL in normoalbuminuric DM patients with normal eGFR. This protein may be a potentially sensitive marker for early diabetic kidney damage, even in the Sub-Saharan African population.

The study population was small. A larger sample size may have ensured more representation from different subgroups. As in all cross-sectional studies, all variables were measured simultaneously; this limits the ability to define the temporal relationship between the variables.

Conflicts of interest: There are no conflicts of interest.

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