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Diabetic Nephropathy in Children With Normoalbuminuria, The Detection of An Earlier Tubulopathy.

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Abstract

Introduction: Diabetic nephropathy (DN) is a major cause of morbidity and mortality among young adults with type 1 diabetes (T1DM). Albuminuria measurement is used as gold standard to diagnose early DN. Early diabetic kidney disease, however, is not detected by this test in some cases. We aimed at evaluating the level of urinary neutrophil gelatinase-associated lipocalin (uNGAL) in urine as a marker of tubulointerstitial damage in children and adolescents with (T1DM) in relation to the level of albuminuria and other parameters.

Subjects and methods: 50 children and adolescent patients with T1DM > 5yrs were included in this study (16 males and 34 females), with a mean age of 13.84±4.0 yrs while 18 matched healthy children served as controls. Patients with overt albuminuria (>300mg/g creatinine) or inflammatory states were excluded. uNGAL and microalbuminuria and uAlbumin/creatinine ratio were measured in patients and controls as well as other parameters.

Results: uNGAL was significantly higher in microalbuminuric in comparison to normoalbuminuric patients and controls, and correlated positively with Alb/Cr ratio. Positive uNGAL was observed in 12/38 of normoalbuminuric patients (31.6%) compared to 9/12 in microalbuminuric patients (75%). A positive correlation was reported between uNGAL and both HbA1c and duration of diabetes (p=0.001 and p=0.007 respectively), but not with eGFR or hypertension.

Conclusion: Diabetic patients showed increased uNGAL, even in some normoalbuminuric candidates. This finding may support the hypothesis of a “tubular phase” of diabetic disease preceding overt DN and hence the use of uNGAL measurement for early evaluation of renal involvement.

Keywords: Urinary NGAL, Microalbuminuria, Type 1 diabetes mellitus, Diabetic nephropathy, Hb A1c,

Introduction

Diabetes is a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism. It may be classified as autoimmune mediated type 1 diabetes, or as insulin resistance associated type 2 diabetes, or a combination of these factors. Type 1 diabetes mellitus (T1DM) commonly occurs in childhood or adolescence, although the rising prevalence of type 2 diabetes mellitus (T2DM) in these age groups is now being seen worldwide . [1]

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus, greatly affecting the life quality and survival of the patients. In adults, DN is one of the leading causes of end stage renal disease (ESRD) [2] **.** The prevention of the disease or at least the postponement of its progression has emerged as a key issue. Adverse outcomes of renal failure can be prevented or delayed through early detection and treatment**.** [3]

At present, albuminuria measurement is used as a standardized, noninvasive test to diagnose early DN. Diabetic kidney disease, however, is not detected by this test in some cases**.**[4]

Pathological albuminuria and proteinuria constitute the consequence of diffuse diabetes induced glomerular damage. However, renal tubulointerstitium also seems to play an equally important role in the genesis of DN, as the consequence of a persistent exposure to a variety of metabolic and hemodynamic injuring factors associated with sustained diabetic disease**.** [5]

Neutrophil gelatinase associated lipocalin (NGAL) is an acute phase protein that is rapidly released not only from neutrophils, but also a variety of cell types upon inflammation and tissue injury. Its small molecular size and protease resistance could render it an excellent biomarker of renal injury [6] **.**Circulating NGAL is filtered by the glomerulus and captured by the proximal tubule and only a minimal amount is excreted in urine [7]**.**

In contrast, urinary NGAL (uNGAL) derives mostly from the thick limbs of Henle and collecting ducts in both the postischemic and postseptic kidney. Its values in children and adults are markedly elevated with acute kidney injury, anticipating the rise of creatinine by 24-48 hrs .[7]

NGAL might play an important role in the pathophysiology of renal adaptation to diabetes, probably as a defensive mechanism aiming to mitigate tubular suffering. Furthermore, uNGAL measurement might become a useful and noninvasive tool for evaluation of renal involvement in diabetic patients in its incipient phase, even earlier than the established phase of DN assessed classically by microalbuminuria (MA) [5] **.**

Subjects and methods

Subjects:

This study included 50 children and adolescents with T1DM for more than 5 years duration. Patients were recruited from regular attendance of Diabetic Endocrine Metabolic Unit DEMPU, Children Hospital, Cairo University, Egypt .Their mean age ± (SD) was 13.84±4.0 years. Microalbuminuria was measured in the 50 patients included in the study group who were further subdivided to group 1 : normoalbuminuric patients (< 30 mg/g) (n=38 patients) and group 2: microalbuminuric patients (30-300 mg/g) (n=12 patients) .Patients enrolled in the study were not on ACEI or angiotensin receptor blockers (ARBs) at the time of sampling .Those who were on ACEI or ARBs had them stopped one week before the study and, in case of hypertension,were shifted to amlodipine or beta blocker. Exclusion criteria included those with overt albuminuria (>300mg/g creatinine) or inflammatory states. Eighteen healthy age and sex matched children served as controls, with mean age ± (SD) 12.17 ± 4.32 years.

Methods:

In a cross-section study all patients were subjected to a detailed history including onset of the disease, frequency of DKA or hypoglycemia as well as insulin therapy (type, basal to bolus ratio, dose of insulin IU/kg/day, frequency). Any history suggestive of complications was recruited

from patients' files including ocular, cardiac, neurological, dermatological, or other associated diseases such as autoimmune thyroiditis, Addison's disease, celiac disease etc.

Special focus on renal complications including hypertension , MA was noted.

A thorough physical examination was done to all patients and controls

To all patients, the following investigations were done: 1) In Blood:

- Serum creatinine and estimated Creatinine (eGFR) calculated by Schwartz formula: eGFR = K x Height in(cm)/sCr in(mg/dL). K was equal to 0.55 in children aged 5 to 13 years , 0.7 in adolescent males and 0.55 for adolescent females. [4],[8]
- Lipid profile including: Total Cholesterol (TC) , serum High density lipoprotein- cholesterol (HDL-c), and Triglycerides (TG) concentrations were determined enzymatically using commercially available kits on autoanalyzer (Olympus AU 400, USA) . Low density lipoprotein-cholesterol (LDL-c) was estimated using Friedewald's Formula. [9]
- Thyroid profile including: Free T4 measured with RIA (Radioimunonoassay) methods, serum TSH with IRMA (Immunoradiometric assay) method by commercial kits for DPC (Diagnostic products corporation) (Los Angeles, USA).
- Mean values of last 3 HbA1c (glycosylated hemoglobin HbA1c) in the last 9 months prior to the study with Quantitative Colorimetric Determination of Glycohemoglobin in whole blood with cation-exchange resin, Stanbio Laboratory.1261 North Main Street. Texas . [10]

2) In urine:

- Complete urine analysis .
- Albumin/ Creatinine ratio in first morning urine sample.
- Persistent Microalbuminuria (first morning sample) confirmed by three successful Alb/Cr ratio more than 30 mg/g (on 3 separate occasions). Assessment of MA was done in absence of confounders namely urinary tract infections, exercise and menstrual bleeding. Microalbuminuria was measured by immunonephelometric method on Prospec Siemens, Siemens Healthcare Diagnostic Inc. Newark, DE 19714 U.S.A . [11]
- Measurement of uNGAL in urine.(which was done for controls as well as for patients)

A written informed consent was taken from patients' care providers prior to the study. The current study agrees with the Declaration of Helsinki and its revisions and it was approved by the committee on human experimentation in the Center of Pediatric Nephrology and Transplantation (CPNT), and the department of Pediatric Endocrinology , Cairo University Children Hospital, and received as well, the approval of the research and scientific committee of the general pediatric department, Cairo University

Statistical Methods:

Statistical Package of social science (SPSS) version 15.0 was used for analysis of data. Data was summarized as mean and SD. Non Parametric test (Mann Whitney –U) was used for analysis of two quantitative data. Chi Square test was used for analysis of qualitative data. One way ANOVA test was used for analysis of more than 2 quantitative data followed by post HOCC test for detection of significance. Spearman rank's correlation was also done. r was considered weak if < 0.25, mild if > 0.25 - < 0.5, moderate if > 0.5 - < 0.75 and strong if > 0.75. Cut off of uNGAL is calculated as mean ± SD of the controls. P-value was considered significant if < 0.05.

Results

The present cross sectional study included 50 patients with T1DM with mean age ± (SD) was 13.84±4.0 years , all patients included had a duration of diabetes more than 5 years with a mean duration of diabetes of 8.57±0.53 years, their sex distribution was 32% males (16 patients) and 68% females (34 patients). A sample of 18 healthy children and adolescents with a mean age of 12.17±4.32 years were included in the study as controls , 38.89% of them were males (7 patients) and 61.11% were females (11 patients).

Descriptive statistics of demographic, anthropometric, clinical and laboratory data of patients with type 1 diabetes are shown in table 1.

Mean uNGAL level of controls was 5.66 ng/mL ± 5.08 (median = 4.6 ng/mL , ranging from 0.25 to 15.8 ng/mL.) which was significantly lower when compared with the studied 50 patients (p = 0.02). Further subdivision of patients yielded 2 groups : normoalbuminuric group (n=38) with mean uNGAL= 15.69 ng/ml ±23.25 (median = 5.7ng/ml , ranging from 0.4-100) and microalbuminuric group (n=12) with mean = 39.14 ng/ml ± 33.98 (median= 31.25 ng/ml, ranging from 2.7-100)

Comparison of levels of uNGAL after further subdivision to normo and microalbuminuric groups with controls is illustrated in table 2.

Urinary NGAL level, was significantly higher in microalbuminuric patients compared to both normoalbuminuric patients and controls (P=0.001), and though its level was higher in normoalbuminuric patients compared to controls this difference was not statistically significant.

A receiver operating characteristic (ROC) curve analysis for uNGAL in normo and microalbuminric groups was done and is illustrated in figure 1 with area under the curve (AUC) of 0.821 .The cutoff level for NGAL with the best sensitivity and specificity was measured to be at 11.75 ng/mL with sensitivity 82% and specificity 67%.

Discussion

In the current study, as well as in other studies [4],[12] , uNGAL was significantly higher in all diabetic patients in comparison to the controls. Bolignano and colleagues reported that the mean uNGAL values in microalbuminuric group were significantly high compared with controls and normoalbuminuric patients ($p<0.05$) [5] . Also, Fu and coworkers observed that the median of uNGAL in microalbuminuric patients was higher than normoalbuminuric patients and controls ($p<0.05$). [13]

In our work , though the mean uNGAL level was higher in normoalbuminuric patients compared to controls, this difference was not statistically significant, meanwhile, microalbuminuric group showed significantly higher levels . Therefore, uNGAL seems to increase in parallel with the severity of renal disease, reaching higher levels in patients with

manifest DN. Nielsen and colleagues reported that u-NGAL increases significantly with increasing albuminuria, as this tubular protein increased significantly from the normo- to the micro- and further to the macroalbuminuric group ($p<0.05$) and they also reported that uNGAL was higher in normoalbuminuric vs. control subjects ($p<0.01$) [14]. In our work uNGAL was positively correlated to Alb/Cr in microalbuminuric patients denoting that the more severe the kidney affection, the higher the values of uNGAL.

Interestingly, increased uNGAL levels were found in 12 of 38 patients (31.6%) without early signs of glomerular damage i.e. in normoalbuminuric patients, that is to say tubular suffering as measured by uNGAL might precede early signs of glomerular damage (MA). These results are in accordance with recent studies that reported similar tendencies for uNGAL in patients without appearance of pathological MA, the early classic measurable sign of DN.[15] This attractive finding supports the growing hypothesis of a "tubular phase" of diabetic disease that precedes the manifestation of typical glomerular lesions. Thus, the increase in uNGAL values may express the degree of subclinical tubular impairment, representing an earlier measurable index of renal distress compared with classic glomerular signs .[4],[5],[14,15]

After studying the level of serum and uNGAL and their relations to albumin excretion rate (AER) in children with normal-range albuminuria (assumingly don't have DN), Zachwieja and colleagues concluded that normal-range albuminuria does not exclude DN and that NGAL measurement can be more sensitive than MA.[4]

On the other hand, 3 microalbuminuric patients in the present study had low uNGAL (2.7, 7.6 and 4.2 ng/ml respectively). It is not clear why these 3 patients showed low uNGAL, but other factors than MA alone were shown in our work to impact uNGAL level, such as disease duration, Hb A1c and glycemic control (discussed below). These 3 patients had the least duration of the disease in MA group (6, 5 and 6 years respectively) compared to much longer duration in other MA patients. Moreover they showed a rather good glycemic control (Hb A1c 7.5, 7.4 and 6.2 respectively). Although ACEI were stopped adequately prior to sampling (1 week), we could not surely cancel any extended effect on uNGAL as no prior basal levels of uNGAL were obtained. Nevertheless, it's worth mentioning that these patients were on higher doses of ACEI prior to their stopping. The effect of using ACEI on decreasing uNGAL was previously reported

both in animal and human studies. Kuwabara and colleagues demonstrated that the angiotensin receptor blocker candesartan dramatically decreased urinary NGAL excretion in lipoatrophic- and streptozotocin-induced mouse models of DN [16]. In addition, Nielsen and co-workers measured uNGAL in a randomized cross-over study of 56 T1DM patients with DN treated with lisinopril 20, 40 and 60 mg daily. The study reported that uNGAL was reduced by approximately 15% during 2 months of 20mg lisinopril treatment, although the difference did not elicit statistical significance (p=0.216) [14].

Thrailkill and colleagues report, as well as the current work, a positive correlation between uNGAL and duration of the disease (p=0.006) (r=0.25) [12] . Other authors, however, report the absence of this correlation in their results.[4],[5]

In the present study, a strong correlation is reported between values of uNGAL and HbA1c as a measure of glycemic control of diabetes. The previous conclusion matches with the reports of Diabetes Control and Complications Trial Research Group (DCCT research group) that has shown that there is a strong association between poor metabolic control and development of diabetic complications (DN included) [17], and also matches with the study of Rewers et al**,** who recommended HbA1c target range for all groups of <7.5% and as teens approach adulthood, lower targets similar to those of adult population were suggested <7% [18]. This correlation was not shown in other previous studies. [4],[5],[14],[19]

Dyslipidemia is reported as a risk factor for the development of DN [20]. In the current study we found positive significant correlation between uNGAL and cholesterol of all patients and positive correlation between uNGAL and cholesterol in normoalbuminuric patients though some authors, could not elicit this correlation [5],[19] .

Conclusion

Urinary NGAL had a positive correlation with Alb/Cr ratio, duration of diabetes, HbA1c and dyslipidemia, also positive uNGAL results were found even in normoalbuminuric patients. We therefore can suggest that uNGAL can be used as an early biomarker for DN in

normoalbuminuric patients especially those with long standing diabetes, uncontrolled diabetes and dyslipidemia, however, larger studies are still needed .

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Table (1): Descriptive statistics of all patients included in the study (n=50)

Variables	Minimum	Maximum	Mean±Std.Deviation
Demographic data			
• Age (yrs)	6.10	18.0	13.84 ± 4.00
• Duration of disease (yrs)	5.00	17.5	8.57 ± 0.53
• Insulin dose IU / kg/day	0.40	2.30	1.16 ± 0.44
Anthropometric data			
• Weight (kg)	15.50	97.00	47.88 ± 18.08
• Weight (SDS)	-2.44	3.89	0.28 ± 1.49
• Height (cm)	112	161.50	56.18 ± 71.21
• Height (SDS)	-3.47	2.60	-1.05 ± 1.38
• BMI (Kg/m^2)	14.17	40.10	22.19±5.79
• BMI (SDS)	-3.67	3.10	0.75±1.39
Clinical data			
• Systolic blood pressure (mmHg)	85.00	150.00	112.70± 15.0
• Diastolic blood pressure(mmHg)	50.00	110.00	72.90± 12.21
Laboratory data			
• Urinary Alb/Cr (mg/g)	4.00	280.00	34.75±51.71
• Creatinine(mg/dl) (Normal range≤1)	0.30	1.20	0.67±0.16
• eGFR (ml/mim/m²) (Normal range=90-120)	67.80	278.60	133.53± 38.90
• HbA1c(%) (Normal range<7)	5.90	10.80	8.29± 1.29
• HDL-C (mg/dl) (Normal range=30-70)	14.00	86.00	51.96± 15.60
• LDL-C (mg/dl) (Normal range<130)	49.00	217.00	116.61± 33.81
• Total Cholesterol (mg/dl) (Normal range=100-200)	96.00	327.00	174.18± 40.77
• Triglycerides (mg/dl) (Normal range=35-160)	21.00	244.00	66.19± 37.57
• uNGAL(ng/ml)	0.4	100.00	21.32± 27.80*

SDS: standard deviation score. BMI: body mass index. Alb/Cr ratio: albumin creatinine ratio. eGFR: estimated glomerular filtration rate. HbA1c: glycosylated hemoglobin. HDL-C: high density lipoprotein cholesterol. LDL-C: low density lipoprotein cholesterol. FT4: free T4. TSH: thyroxin stimulating hormone. uNGAL: urinary neutrophils gelatinase associated lipocalin.
*Median of uNGAL was 10.15 ng/ml

Table (2): Comparison between normoalbuminuric, microalbuminuric patients and controls.

Variables	Normoalbuminuric patients(n=38)		Microalbuminuric patients(n=12)		Controls (n=18)		P-value
	Mean	±Std. Deviation	Mean	±Std. Deviation	Mean	±Std. Deviation	
Systolic blood pressure (mmHg)	110.00[a]	13.0	121.25[b]	18.11	111.39[a]	7.63	0.04*
Diastolic blood pressure (mmHg)	70.79[a]	11.18	79.58[b]	13.39	74.17[a,b]	8.09	0.05*
uNGAL(ng/ml)	15.69[a]	23.35	39.14[b]	33.98	5.66[a]	5.08	0.001*

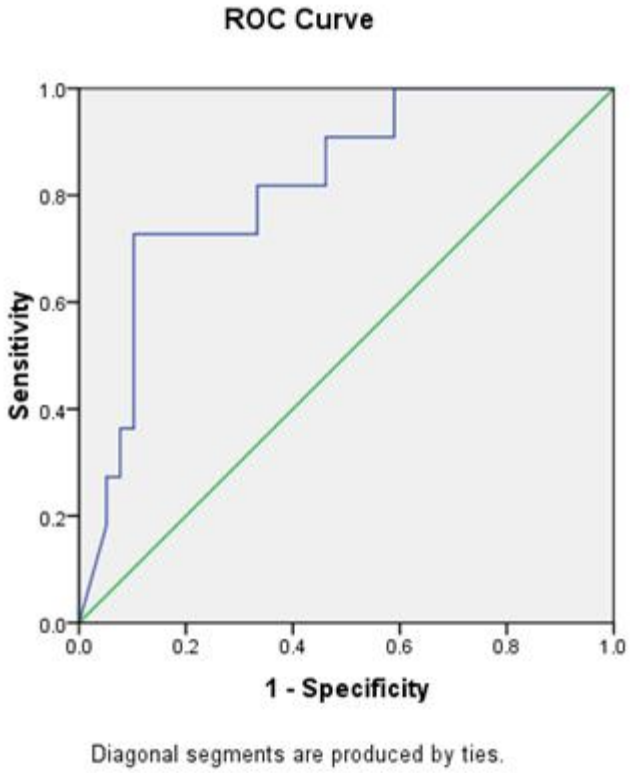
Different symbol indicate significant. P-value is significant if <0.05*

Table (3): Correlation between uNGAL (ng/ml) of normoalbuminuric and microalbuminuric patients (n=38) with other parameters.

	All Patients N=50		Normoalbumiuric N=38		Microalbuminuric N=12	
Variables	**R**	**P-value**	**r**	**P-value**	**r**	**P-value**
Age (yrs)	0.2	0.1	0.1	0.7	0.2	0.5
Duration of disease (yrs)	0.4	0.007*	0.3	0.09	0.3	0.3
BMI (Kg/m^2)	0.2	0.2	0.03	0.9	0.1	0.7
BMI (SDS)	0.1	0.5	- 0.1	0.7	0.2	0.5
Systolic blood pressure (mmHg)	0.1	0.4	- 0.03	0.9	0.1	0.9
Diastolic blood pressure (mmHg)	0.04	0.8	- 0.03	0.9	- 0.2	0.6
Albumin creatinine ratio(mg/day)	0.5	0.001*	- 0.02	0.9	0.6	0.05*
eGFR(ml/mim/m²)	- 0.2	0.2	- 0.1	0.5	- 0.4	0.2
HbA1c(%)	0.5	0.001*	0.4	0.02*	0.8	0.001*
HDL-C (mg/dl)	0.3	0.07	0.1	0.7	0.7	0.007*
LDL-C (mg/dl)	- 0.1	0.6	-0.01	0.9	- 0.4	0.3
Total Cholesterol (mg/dl)	0.3	0.03*	0.4	0.01*	0.1	0.7
Triglycerides (mg/dl)	0.1	0.1	0.1	0.6	- 0.01	0.9

* P-value is significant if <0.05

Figure (1): Receiver operating characteristic (ROC) plot analysis of uNGAL in normo and microalbumuinuric patients



AUC= 0.821, sensitivity = 82% and Specificity = 67%