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M.A. Heba, H.R. Hasbelnabi, Mohammad Shafiq, Rehab M. ABD ELKAREEM, S.S. Fahmey

The associations between urinary neutrophil gelatinase-associated lipocalin, ambulatory blood pressure monitoring, echocardiography, and diabetic kidney disease in children

Beni–Suef University, Egypt

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One of the most common microvascular complications of diabetes is diabetic nephropathy, characterized by pathological alterations in the glomeruli leading to albuminuria, hypertension, and progressive loss of renal function.

This study **aimed** to determine whether type 1 diabetic nephropathy was present in children by evaluating urinary Neutrophil gelatinase-associated lipocalin (uNGAL) and ambulatory blood pressure monitoring (ABPM).

Materials and methods. A cross-sectional study was conducted from July 2023 to July 2024 and included 57 children with type 1 DM who were subdivided into two groups: Group 1 – 36 children without diabetic kidney disease (non-DKD), and Group 2 – 21 children with DKD. All participants underwent history taking, clinical examination, and laboratory investigations, including CBC, urea, creatinine, HbA1c, albumin/creatinine ratio, NGAL, echocardiography, and ABPM.

Results. The mean uNGAL level was significantly higher in Group 2 (10.43±18.71 pg/ml) compared with Group 1 (1.56±1.31 pg/ml) (P=0.006). The mean overall and daytime systolic and diastolic blood pressures were also significantly higher in Group 2 (DKD) compared with Group 1 (non-DKD) (P<0.01), as measured by ABPM. In addition, Group 2 had significantly lower LVESD (P=0.008), indicating left ventricular systolic dysfunction.

Conclusion. As NGAL is an early indicator of DKD, our findings highlight its predictive importance. In addition, the significantly higher systolic and diastolic blood pressures, along with left ventricular systolic dysfunction in the DKD group, underscore the importance of ABPM and echocardiography in the assessment and follow-up of children with type 1 DM.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institution's local ethics committee. The informed consent was obtained from patients. The authors declare no conflict of interest.

Keywords: diabetic kidney disease, diabetic nephropathy, neutrophil gelatinase-associated lipocalin, children

Зв'язок між ліпокаліном, пов'язаним з желатиназою нейтрофілів у сечі, амбулаторним моніторингом артеріального тиску, ехокардіографією та діабетичною хворобою нирок у дітей

M.A. Heba, H.R. Hasbelnabi, Mohammad Shafiq, Rehab M. ABD ELKAREEM, S.S. Fahmey

Beni-Suef University, Egypt

Одним із найпоширеніших наслідків діабету є діабетична нефропатія, яка характеризується патологічними змінами у клубочках нирок і спричиняє альбумінурію, високий артеріальний тиск і поступову втрату функції нирок.

Мета – визначити, чи присутня діабетична нефропатія 1 типу в пацієнтів, шляхом оцінки ліпокаліну, пов'язаного з желатиназою нейтрофілів у сечі (uNGAL), та амбулаторного моніторингу артеріального тиску (ABPM).

Матеріали та методи. Перехресне дослідження було проведено в період із липня 2023 року по липень 2024 року та охоплювало 57 дітей із цукровим діабетом 1 типу, яких далі розподілили на дві групи: Група 1 – 21 дитина з діабетичною хворобою нирок (ДХН) та Група 2 – 36 дітей без ДХН. Усі учасники пройшли збір анамнезу, клінічне обстеження та дослідження, зокрема загальний аналіз крові, сечовини, креатиніну, HBA1c, співвідношення альбумін/креатинін, рівень нітрогідроксисечовини (NGAL), ехокардіографію та артеріальну гіпертензію (SMAT).

Результати. Середні рівні uNGAL були значно вищими у Групі 1 (10,43±18,71 пг/мл) порівняно з Групою 2 (1,56±1,31 пг/мл) (P=0,006). Середній загальний та денний систолічний і діастолічний артеріальний тиск були значно вищими у Групі 1 порівняно з Групою 2 (P<0,01), виміряними за допомогою AMBP. Також, у Групі 1 спостерігалася значно нижча дисфункція лівого шлуночка (P=0,008), що вказує на систолічну дисфункцію лівого шлуночка.

Висновки. Оскільки NGAL є раннім показником DKD, наша робота підкреслює його прогностичну важливість. Крім того, значно вищий систолічний та діастолічний артеріальний тиск, а також систолічна дисфункція лівого шлуночка у групі хворих на ДХН підкреслює важливість вимірювання артеріального тиску, пов'язаного з діабетом 1 типу, та ехокардіографії в оцінці та подальшому спостереженні за хворими на діабет 1 типу.

Дослідження проведено відповідно до принципів Гельсінської декларації. Протокол дослідження схвалено місцевим етичним комітетом установи. Від пацієнтів було отримано інформовану згоду.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діабетична хвороба нирок, діабетична нефропатія, ліпокалін, пов'язаний з нейтрофільною желатиназою, діти.

Diabetic kidney disease (DKD) is one of the most significant microvascular complications of type 1 diabetes. Although the overall incidence of DKD has declined in recent decades, its occurrence continues to be more frequent among children and adolescents compared with individuals who develop type 1 diabetes later in life [36]. Early recognition of DKD is critically important, as renal involvement is associated with increased morbidity and mortality among affected pediatric patients.

The progression of DKD is commonly monitored through the urine albumin-to-creatinine ratio (UACR) and the estimated glomerular filtration rate (eGFR). However, these measures have limited sensitivity for detecting early renal injury, do not directly assess histopathological changes, and may fail to identify subtle glomerular or tubular dysfunction. Although renal biopsy remains the diagnostic gold standard, it is invasive and unsuitable for routine clinical use, highlighting the need for more sensitive, non-invasive biomarkers [14].

Emerging evidence suggests that renal tubular injury plays a central role in the early pathophysiology of DKD. Among the proposed biomarkers, neutrophil gelatinase-associated lipocalin (NGAL) has shown strong potential. Elevated NGAL concentrations have been associated with acute kidney injury (AKI), chronic kidney disease (CKD), sepsis, and malignant diseases, supporting its value as an early indicator of renal impairment. Despite this, research on NGAL in children with type 1 diabetes remains limited, and only a few studies have evaluated NGAL as a biomarker for early DKD in childhood-onset diabetes [16].

Hypertension is another critical factor contributing to cardiovascular and microvascular complications in children with type 1 diabetes. High blood pressure can accelerate both nephropathy and retinopathy, making early assessment essential [28]. Given the documented value of ambulatory blood pressure monitoring (ABPM) in identifying subtle abnormalities in blood pressure patterns, its role in evaluating cardiovascular risk in pediatric diabetes has gained increasing emphasis.

Therefore, the present study ***aims*** to assess early diabetic nephropathy in children with type 1 diabetes by measuring urinary NGAL (uNGAL) and evaluating cardiovascular risk through ambulatory blood pressure monitoring (ABPM) and echocardiographic assessment.

Materials and methods of the study

This cross-sectional comparative study was performed from July 2023 to July 2024 on 57 children with type 1 diabetes mellitus (DM) aged 2 to 18 years. According to the urine albumin-to-creatinine ratio (UACR), patients were subdivided into two groups: Group 1 (non-DKD), which included 36 children without diabetic kidney disease, and Group 2 (DKD), which included 21 children with diabetic kidney disease.

Furthermore, to study the value of ABPM in detecting early DKD, we divided Group 2 into two subgroups: Subgroup 2A – the non-dipping group (loss of blood pressure dipping) and Subgroup 2B – the dipping group. Patients with acute infections, type 2 DM, acute kidney injury, eGFR<60 ML/M2/min/1.7, immunosuppression, or using immunosuppressive drugs were all excluded from the study.

All patients were subjected to full assessment, including an entire history taking with a special focus on the history of the first attack, history of DKA, family history of diabetes, type of insulin used, recurrent urinary tract infections, hematuria, urine output, and hospital admissions, family history of renal disease, and an autoimmune disease. Complete clinical examinations included weight percentile, height percentile, body mass index (BMI), abdominal examination, and cardiac examination. Laboratory investigations were applied to all the participants. They included a complete blood count (CBC) with differential conducted using the Cell-DYN 1800 (USA), with manual differential count performed when required. Creatinine and urea tests were evaluated using a semi-automated photometer ELIT Tech. group vital Diere Netherlands. HBA1C and urinary albumin/creatinine ratio were assessed using Mispa-I2 AGAPPE kits applied to the protein analyzer AGAPPE Switzerland GMBH. According to the user's manual, urinary NGAL was analyzed using QuicKey Human NGAL (Neutrophil Gelatinase Associated Lipocalin) ELISA Kit (E-TSEL-H0003). Echocardiographic studies were conducted using a Vivid S5 G.E. Healthcare machine with a 6 MHZ transducer. Echocardiograms were obtained at rest with patients in the left lateral position using standard parasternal and apical views. Shortening fraction (SF) is obtained by measuring left ventricular systolic diameter (LVSD) and left ventricular end-diastolic diameter (LVEDD) using M-mode echocardiography from a parasternal long-axis perspective. To get the SF, follow these steps: The usual

range for the shortening fraction (SF) is 25–45%, and the SF was calculated using the formula:

SF = [(LVEDD – LVESD) / LVEDD] × 100 (I.Z. Ben-Dov et al., 2007).

Ambulatory blood pressure monitoring. Everyone was put through a 24-hour AMBP using validated Oscillo metric equipment (CONTEC ABP50. CONTEC MEDICAL SYSTEMS CO., LTD. CHINA). The patients were told to go about their daily lives as usual, but not to strain themselves too much and to maintain their non-dominant arms calm and steady while the measures were being taken. At night (from 23:00 to 07:00 hours) and every 30 minutes throughout the day (from 07:00 to 23:00), the gadget was programmed to take blood pressure readings. Participants were instructed to document their daily routines and the time they slept. After sorting the blood pressure readings into «awake» and «asleep» periods based on the diary entries, the next step was to analyze the data.

Evaluation of the dipping profile of the patients. The dipper profile of the patients was defined as the percent of nocturnal blood pressure (BP) drop, as recommended by the American Heart Association:

Dip = 1 – (nSBP / dSBP) × 100%,

where nSBP – night systolic BP (SBP), dSBP – day SBP [18].

Average BP during the day divided by average BP during the night is the night-to-day BP ratio. Most people's BP drops, or «dips», when they sleep. We will accept as an artificial cutoff to classify participants as «dippers» the discovery of a nocturnal BP decline of more than 10% of daytime values (night-day BP ratio <0.9). There are several more types of dippers, such as non-dippers (BP range 0 to 10%), severe dippers (BP range >20%), and reverse dippers (BP range <0%).

Statistical methods. For the qualitative variables, percentages and frequencies were used. Quantitative variables were described using mean and standard deviation, expressed as mean ± S.D. We used the chi-square (χ^2) test to compare qualitative variables. The Student's T-test with two independent samples was used when comparing quantitative variables. We use correlation analyses as needed. Additional statistical analysis will be conducted using appropriate significance tests. The results are considered statistically significant if the p-value is less than 0.05. All tests were done using the Statistical Package for the Social Sciences (SPSS version 20) for Windows 10.

The study was approved by the local Ethics committee (FMBSUREC/05072022/HasbElnaby) and was conducted in agreement with the Declaration of Helsinki.

Results of the study

DKD was reported in 21 (36.8%) of the patients. Macroalbuminuria was reported in 2 (3.5%) patients, non-dipping BP was reported in 13 (22.8%) patients; 10 (47.6%) of them in the Group 2 (P=0.01).

Table 1

Comparison between patients with and without DKD regarding demographic, clinical, and laboratory data

Parameters	Group 1 (N=36)	Group 2 (N=21)	P-value
Age, years	11.14±1.29	11.10±1.81	0.916
Age at presentation	6.78±1.31	5.05±1.53	<0.001
Attacks of diabetic ketoacidosis (DKA)	1.03±0.16	2.00±0.63	<0.001
Weight, kg	27.14±4.599	26.71±5.34	0.753
Weight percentiles	5.94±9.14	8.47±11.54	0.365
Height, cm	144.78±8.377	142.38±10.09	0.339
Height percentiles	43.33±13.36	41.66±14.43	0.661
BMI, kg/m^2	12.87±1.28	13.07±1.47	0.584
HbA1c	8.40±0.47	11.26±2.15	<0.001
Urea, mg/dl	13.64±3.20	22.33±7.35	<0.001
Creatinine, mg/dl	0.94±0.23	1.00±0.1	0.280
eGFR, ml/ min/1.73 m^2	99.92±17.21	84.06±8.2	0.000
Albumin/Create Ratio, mg/g creatinine	14.56±7.584	211.62±95.19	0.020
NGAL, pg/ml	1.56±1.31	10.43±18.71	0.006
NGAL/create, pg/mg	4.40±4.30	27.62±7.22	0.010

A comparison between Groups 1 and 2 in terms of demographic, clinical, and laboratory data is shown in Table 1.

Baseline data of the studied participants. The two groups were matched for age (P=0.916). Age at presentation was significantly lower in Group 2 (P<0.001), and the frequency of DKA was significantly higher in Group 2 (P<0.001).

Anthropometric measurements of the studied participants. There were no significant differences between the two groups regarding weight (P=0.753), weight percentiles (P=0.365), Height (P=0.339), height percentiles (P=0.661), and BMI (P=0.584).

Laboratory data results of the studied participants. Patients of Group 2 showed significantly higher levels of HbA1c (P<0.001), urea (P<0.001), and albumin/creatinine ratio (P=0.020). The eGFR levels were significantly lower in Group 2 (P<0.001).

Creatinine levels were comparable in the two groups (P=0.280).

Urinary NGAL results among studied patients. The mean urinary NGAL levels were signifi-

Table 2

Correlations between NGAL/create and Albumin/Create and other variables

Parameters		uNGAL/creatinine	Albumin/Creatinine Ratio
Age, years	Pearson Correlation	0.297	0.105
	Sig. (2-tailed)	0.025	0.436
Age at presentation	Pearson Correlation	0.125	0.168
	Sig. (2-tailed)	0.355	0.211
Attacks of DKA	Pearson Correlation	0.567	0.486
	Sig. (2-tailed)	0.000	0.000
HbA1c	Pearson Correlation	0.335*	0.427**
	Sig. (2-tailed)	0.011	0.001
Urea	Pearson Correlation	0.441	0.357
	Sig. (2-tailed)	0.001	0.006
Creatinine	Pearson Correlation	0.055	0.042
	Sig. (2-tailed)	0.683	0.757
eGFR	Pearson Correlation	0.170	0.157
	Sig. (2-tailed)	0.206	0.244
Albumin/Creatinine Ratio	Pearson Correlation	0.484	1.0
	Sig. (2-tailed)	0.000	–
LV end diastolic, cm	Pearson Correlation	0.239	0.170
	Sig. (2-tailed)	0.074	0.206
LV end systolic, cm	Pearson Correlation	0.154	0.237
	Sig. (2-tailed)	0.253	0.076
Ejection Fraction (EF)	Pearson Correlation	0.150	0.136
	Sig. (2-tailed)	0.265	0.312
Mean overall SBP, %	Pearson Correlation	0.327*	0.218
	Sig. (2-tailed)	0.013	0.103
Mean overall DBP, %	Pearson Correlation	0.002	0.071
	Sig. (2-tailed)	0.989	0.599
Mean day SBP, %	Pearson Correlation	0.349**	0.243
	Sig. (2-tailed)	0.008	0.069
Mean day DBP, %	Pearson Correlation	0.066	0.123
	Sig. (2-tailed)	0.624	0.363
Mean night SBP, %	Pearson Correlation	0.212	0.230
	Sig. (2-tailed)	0.113	0.085
Mean night DBP, %	Pearson Correlation	0.133	-0.063-
	Sig. (2-tailed)	0.324	0.641

Notes: Pearson correlation coefficients are shown; P<0.05 is statistically significant;* – significant at P<0.05; ** – significant at P<0.01.

Table 3

Comparison between patients with and without DKD regarding systolic and diastolic blood pressure, M±SD

Parameters	Group 1 (N=36)	Group 2 (N=21)	P-value
Mean overall SBP	101.36±6.634	109.33±6.102	<0.001
Mean overall SBP, percentiles	53.89±8.028	67.38±12.002	<0.001
Mean-day SBP	103.89±5.859	112.62±5.792	<0.001
Mean-day SBP, percentiles	55.56±9.085	75.71±10.552	<0.001
Mean night SBP	95.47±5.146	99.52±3.907	0.003
Mean night SBP, percentiles	50.00±0.000	52.86±9.562	0.077
Mean overall DBP	62.44±7.157	67.71±6.908	0.009
Mean overall DBP, percentiles	61.92±11.819	70.00±16.279	0.035
Mean-day DBP	64.06±7.123	72.14±7.337	<0.001
Mean-day DBP, percentiles	64.94±10.746	76.57±14.959	0.001
Mean night DBP	56.61±6.271	60.29±7.623	0.054
Mean night DBP, percentiles	51.67±5.606	58.05±11.664	0.007
Dipping BP	11.39 ±.5.83	8.02±3.41	0.008

cantly higher in Group 2 compared to Group 1 (P=0.006). Also, the mean urinary NAGL/Creatinine levels were significantly higher in the Group 2 compared to the Group 1 (P=0.010). Patients in Subgroup 2A showed a significantly higher uNAGL/Creatinine ratio (5.08± ±2.04 pg/mg) compared to patients in Subgroup 2B (2.97±1.50 pg/mg) (P=0.02).

On the other hand, the uNAGL was higher in the Subgroups 2A (1.68±0.7 pg/ml) compared to the Subgroups 2B (1.06±0.63 pg/ml) but with no significant differences (P=0.16). The NGAL/creatinine significantly correlated to the number of attacks of DKA (P=0.000), HbA1c (P=0.011), urea (P=0.001), albumin/creatinine ratio (P=0.000), mean overall SBP (P=0.013), and mean day SBP (P=0.008). The albumin/creatinine ratio significantly correlated with the number of attacks of DKA (P=0.000), HbA1c (P=0.001), and urea (P=0.006) (Table 2). To investigate the predictive role of uNAGL, uNAGL/Creatinine ratio, and Albumin/Creatinine ratio in the prediction of the progression to DKD, the ROC curve analysis showed that uNAGL had a significant role in the prediction of DKD at a cutoff value >2.5 pg/ml with sensitivity 86.96%, Specificity 97.06% and AUC (Area Under the Curve) 0.909. Also, the uNAGL/Creatinine ratio significantly predicted DKD at a cutoff value >10 pg/mg with a sensitivity of 73.91%, Specificity of 88.24%, and AUC of 0.836. The Albumin/Create ratio significantly predicted DKD at a cutoff value >29 with a sensitivity of 91.30%, Specificity of 100.0%, and AUC of 0.980.

Blood pressure measurements of the studied participants (Tables 3 and 4). The overall SBP and their percentiles were significantly higher

Table 4

Comparison between patients with and without DKD regarding different systolic blood pressure percentiles

Parameters		< 50th	50–90th	90–95th	95–99th	P-value
Overall SBP, %	Non-DKD	29 (80.6%)	7 (19.4%)	0 (0.0%)	0 (0.0%)	<0.001
	DKD	5 (23.8%)	14 (66.7%)	1 (4.8%)	1 (4.8%)	
Mean day SBP	Non-DKD	26 (72.2%)	10 (27.8%)	0 (0.0%)	0 (0.0%)	<0.001
	DKD	0 (0.0%)	16 (76.2%)	5 (23.8%)	0 (0.0%)	
Mean night SBP	Non-DKD	36 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.169
	DKD	19 (90.5%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	
Overall DBP, %	Non-DKD	16 (44.4%)	19 (52.8%)	0 (0.0%)	1 (2.8%)	0.018
	DKD	6 (28.6%)	10 (47.6%)	5 (23.8%)	0 (0.0%)	
Mean day DBP	Non-DKD	10 (27.8%)	24 (66.7%)	1 (2.8%)	1 (2.8%)	0.029
	DKD	2 (9.5%)	12 (57.1%)	5 (23.8%)	2 (9.5%)	
Mean night DBP	Non-DKD	33 (91.7%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0.016
	DKD	13 (61.9%)	6 (28.6%)	2 (9.5%)	0 (0.0%)	

Table 5

Comparison between patients with and without DKD regarding Echocardiography findings

Parameters	Group 1 (N=36)	Group 2 (N=21)	P-value
LVEDD, cm	4.69±0.577	4.57±0.598	0.447
LVSD, cm	3.33±0.756	2.76±0.768	0.008
EF, %	57.75±4.481	57.76±3.463	0.992

in the Group 2 (P<0.001). Also, the mean day SBP and its percentiles were significantly higher in Group 2 (P<0.001). In addition, the mean night SBP was significantly higher in Group 2 (P=0.003). The mean night SBP percentiles were comparable in the two groups (P=0.077).

The overall diastolic BP (DBP) and its percentiles were significantly higher in Group 2 (P=0.009 and P=0.035, respectively). Also, the mean day DBP and its percentiles were significantly higher in Group 2 (P<0.001 and P<0.001, respectively). While the mean night DBP showed non-significant differences between the two groups (P=0.054), the mean night DBP percentiles were significantly higher in Group 2 (P=0.007).

The 50–90th overall SBP percentiles were significantly more frequent in Group 2. Regarding the mean day SBP, the 50–90th and 90–95th percentiles were more frequent in the DKD than in Group 1. The two groups had no significant differences regarding the mean night SBP percentiles. The 90–95th overall DBP percentiles were significantly more frequent in Group 2. Regarding the mean day DBP, the 50–90th and 90–95th percentiles were more frequent in Group 2 than in Group 1. Also, the 50–90th and 90–95th percentiles were more frequent in Group 2 than in Group 1 regarding the mean night DBP.

Patients in Group 2 showed a significantly lower dipping BP (8.02±3.41) compared to Group 1 (11.39±.5.83) (P-value 0.008). On the other hand, loss of BP dipping was reported.

Echocardiography findings of the studied participants (Table 5). LVSD was significantly lower in Group 2 (P=0.008). At the same time, there were no significant differences between the two groups regarding the LVEDD (P=0.447) and Echocardiography findings (EF) (P=0.992).

Discussion

This study aimed to assess early diabetic nephropathy in children with type 1 diabetes by measuring uNGAL and evaluating cardiovascular risk through ABPM and echocardiography. Our results demonstrate that HbA1c levels, urea, and albumin/creatinine ratio were significantly higher in the DKD group, whereas the eGFR was significantly lower in this group. Similarly, H. Li et al. (2022) reported that patients with DKD exhibited higher HbA1c values than those without DKD [18]. Consistent findings were also reported in more recent research showing that the coexistence of diabetes and chronic kidney disease increases HbA1c levels, which contributes to CKD progression and remains an independent risk factor for adverse renal outcomes [19]. In agreement with these observations, Y. Lin et al. (2023) also noted that patients with non-albuminuric DKD tend to have lower rates of achieving adequate HbA1c targets [19].

In contrast, S. Roy et al. (2021) found no significant difference between groups; HbA1c levels were slightly lower in individuals with DKD than in those without DKD (7.1% vs. 7.2%), although this difference did not reach statistical significance [29]. The relatively small cohort size in our study may partially explain the absence of statistical significance among some variables that otherwise reflect a greater diabetes burden.

Because not all children with diabetes who have micro- or macroalbuminuria will also have a decline in kidney function, albuminuria has limitations as a biomarker for predicting and diagnosing DKD. Fever, illness, nutrition, hydration status, hemodynamics, stress, exercise, menstruation, and hyperglycemia can all influence albuminuria, UACR, and eGFR. In addition, strict control of blood glucose and blood pressure can normalize albuminuria in many patients with microalbuminuria (up to 40%) [19].

Another study by H. Li et al. showed that patients in the DKD group had lower eGFR levels and persistently higher serum creatinine and blood urea nitrogen compared to the non-DKD group, which is consistent with our data [18]. Similarly, Y. Lin et al. found that urea levels were higher in individuals with DKD compared to those without DKD [19]. S. Roy et al. also reported that most individuals with DKD

exhibited UACR values in the microalbuminuria range (67.2%) [29].

In our study, urine ACR levels were significantly higher in children with type 1 diabetes – approximately one-third of participants – compared with controls. Supporting our findings, microalbuminuria was detected in 25% of children with type 1 diabetes, while macroalbuminuria was found in 3.5% of cases. Additionally, 3.5% (7 out of 199) of children developed microalbuminuria within two years of diabetes diagnosis, and in two cases it appeared as early as 7 months after diagnosis [38].

S. Chen et al. demonstrated that patients with DKD had a higher likelihood of experiencing a ≥50% decline in eGFR, highlighting the prognostic value of dynamic proteinuria monitoring for identifying high-risk CKD patients [5]. Our results also showed that NGAL and the NGAL/creatinine ratio were significantly higher in the DKD group and positively correlated with HbA1c, urea, albumin/creatinine ratio, mean overall systolic BP, and mean daytime systolic BP. These findings align with those of S. Duan et al., who reported markedly elevated urinary NGAL/creatinine ratios in DKD compared with non-DKD patients [9].

NGAL is produced by renal tubular epithelial cells in response to injury and is considered a sensitive marker of tubular damage. In diabetic nephropathy, increased tubular secretion of NGAL correlates with worsening renal function [12]. Urinary NGAL has also been shown to be useful in assessing progression and severity of renal impairment from various causes, including its utility as the NGAL/creatinine ratio [4,7,24].

Furthermore, before a decline in GFR becomes detectable, studies have demonstrated that injured renal tubular cells begin producing NGAL early in the course of acute kidney injury [23]. In addition, urinary NGAL has been shown to serve as an early biomarker of diabetic nephropathy [3]. Consistent with this, F. Piani et al. reported that NGAL is associated with tubular damage, AKI-related changes, and proximal tubular dysfunction in the early stages of DKD [27].

In our study, we identified a negative correlation between uNGAL and the uNGAL/creatinine ratio. We also observed that uNGAL and uNGAL/creatinine were higher in the non-dipping non-DKD group. Furthermore, the albumin/creatinine ratio was positively correlated with the number of DKA episodes, HbA1c, urea levels, and NGAL/creatinine ratio.

Regression of microalbuminuria over a 2-year period was significantly associated with lower baseline tubular injury markers, as reported by V.S. Vaidya et al. [35]. Additionally, mild elevations in urinary NGAL may occur due to impaired tubular reabsorption even within the normoalbuminuria range [13]. A meta-analysis in children also concluded that urinary NGAL is a useful biomarker, particularly in the normoalbuminuric stage of diabetic nephropathy, where both glomerular and tubular injury contribute to disease progression. Importantly, evidence shows that tubular dysfunction may appear earlier than glomerular injury or microalbuminuria, even when glomerular proteinuria is not yet detectable [30].

The positive association between urinary NGAL and ACR observed in our study further supports the potential of urinary NGAL as an early marker of diabetic tubulopathy in children with type 1 diabetes, even before overt glomerular damage becomes clinically evident. Our study found that the mean daytime and overall systolic and diastolic blood pressure (SBP and DBP), as well as their percentiles, were significantly higher in the DKD group. Although mean nocturnal SBP percentiles were comparable between groups, the mean nocturnal DBP percentiles were significantly higher in children with DKD. We also observed a higher frequency of loss of nocturnal BP dipping in the DKD group. These findings are consistent with a large study of 3,529 children and adolescents with type 1 diabetes, which demonstrated altered BP regulation characterized by elevated SBP, reduced systolic dipping, increased nocturnal DBP, and elevated mean arterial pressure [8].

In children with type 1 diabetes, Lurbe et al. demonstrated that nocturnal systolic blood pressure (SBP) elevation occurs before the development of microalbuminuria, highlighting the importance of early BP profiling in this population [20]. Similarly, F. Rohani et al. identified hypertension as a modifiable risk factor for the development of diabetic kidney disease (DKD) [28]. Abnormal BP dipping has been linked to both microvascular and macrovascular complications in individuals with diabetes [2,17]. Consistent with this, L. Mamilly et al. reported that abnormal nocturnal BP patterns were common among children with type 1 diabetes, even in

early stages of nephropathy [21]. Furthermore, Muntean and colleagues emphasized that BP abnormalities serve as key indicators of early diabetic nephropathy [28], and current recommendations advise measuring BP at diagnosis and annually thereafter in children with diabetes [11].

Arterial hypertension greatly increases the risk of cardiovascular disease in children and adolescents with type 1 diabetes [28]. Supporting this, N.M. Shalaby and N.M. Shalaby demonstrated abnormal SBP and DBP patterns, including significant loss of nocturnal dipping, in diabetic children [31]. Patients with type 1 diabetes who develop microalbuminuria are more likely to exhibit non-dipping BP patterns. Large clinical data involving 3,529 children and adolescents further confirmed that poor BP regulation manifested by elevated SBP, higher nocturnal DBP, increased mean arterial pressure, reduced systolic dipping, and altered diastolic dipping is a consistent marker of impaired BP control in type 1 diabetes [8].

E. Lurbe et al. also reported that rises in nocturnal SBP precede microalbuminuria, suggesting that BP dysregulation may appear before renal biochemical abnormalities [20]. The non-dipping pattern is one of the earliest BP abnormalities observed in youths with type 1 diabetes, and it represents a significant risk factor for renal morphological changes and glomerular hyperfiltration. Hypertension accelerates microvascular complications, including nephropathy [28]. Hypertension is also increasingly recognized as a risk factor for progression to DKD, and its prevalence is rising among diabetic youth, especially in type 2 diabetes, where obesity contributes to treatment-resistant hypertension [32,34].

Current clinical guidelines recommend initiating antihypertensive treatment promptly when BP exceeds the 95th percentile, along with lifestyle modification. For diabetic patients, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) are preferred, with reproductive counseling provided for adolescent girls. Target BP should remain below the 90th percentile to optimize renal and cardiovascular outcomes [11].

One of the earliest abnormalities in the blood pressure profile of children with type 1 diabetes is the loss of nocturnal systolic dipping, which L. Mamilly et al. (2021) reported to be associated with elevated urinary NGAL levels. Their findings further demonstrated that the NGAL/creatinine ratio correlates with albumin excretion even when the urine microalbumin/creatinine ratio remains within normal limits, emphasizing the value of this inflammatory biomarker for detecting diabetic nephropathy before the microalbuminuric phase [21].

In our study, the LV end-systolic diameter was significantly higher in the DKD group, while LV end-diastolic diameter and EF did not differ significantly. These findings align with X. Wang et al. (2023), who identified urine albumin as a sensitive marker for early renal impairment and cardiovascular risk in patients with diabetes and hypertension [37]. Previous evidence has linked albuminuria to LVH; however, confirmation from large multi-center prospective studies is needed, as most earlier investigations were retrospective and single-center [1]. Additional research has shown that microalbuminuria is generally associated with reduced LV diastolic function, whereas significant albuminuria is linked with impairment of both diastolic and systolic function, with LV mass index increasing as urinary albumin rises [26]. Similarly, S. Chillawar et al. (2017) demonstrated that both micro- and macroalbuminuria are associated with LVH [6].

X. Wang et al. (2023) further demonstrated that increasing proteinuria is an independent predictor of LVH in DKD [37]. Our findings suggest that subtle LV longitudinal myocardial systolic dysfunction – rather than diastolic dysfunction – may represent an early indicator of preclinical diabetic cardiomyopathy in patients with preserved EF and no clinical signs of heart failure, which is consistent with mechanistic insights described by G. Jia et al. (2018) and J. Mehta et al. (2021) [15,22]. Differences in diastolic function between DKD and non-DKD etiologies may reflect distinct underlying pathophysiological processes. J. Miyazato et al. (2005) reported that individuals with diabetic nephropathy demonstrate more pronounced impairments in LV diastolic function compared to those with chronic glomerulonephritis [25]. This may be attributed to diabetes-related mechanisms, including oxidative stress, increased pro-inflammatory and profibrotic cytokine activity, and accumulation of advanced glycation end products [10]. The early stage of DKD in our study population may explain why our findings differ from studies conducted in populations with more advanced disease.

Conclusions

Our research highlights the importance of NGAL as a predictor of diabetic nephropathy and an early indicator of the condition. In addition, the significantly higher SBP and DBP with loss of dipping, along with left ventricular systolic dysfunction in the DKD groups, highlight the importance of AMBP and echocardiography in the assessment and follow-up of DM type 1 for early detection and control of DKD.

The authors declare no conflict of interest.

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Відомості про авторів:
Heba Mostafa Ahmed – Professor of Pediatrics of Department of Pediatrics, Faculty of Medicine, Beni-Suef University, Egypt. Email: Heba_most@yahoo.com.
Hager Ramadan – Department of Pediatrics, Faculty of Medicine, Beni-Suef University, Egypt. Email: rahagar632@gmail.com.
Mohammad Shafiq – Assistant Professor of Cardiology of Department of Cardiology, Faculty of Medicine, Beni-Suef University, Egypt. Email: mohamed.awad@med.bsu.edu.eg.
Rehab M. ABD ELKAREEM – Assistant Professor of Clinical and Chemical Pathology of Department of Clinical and Chemical Pathology, Faculty of Medicine, Beni-Suef University, Egypt. Email: Drrehablashin@gmail.com.
Fahmey Sameh Samir – Professor of Pediatrics of Department of Pediatrics, Faculty of Medicine, Beni-Suef University, Egypt. Email: ssfahmey@yahoo.com.

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