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OAK.uz **Supreme Attestation Commission at the Cabinet Ministers of the Republic of Uzbekistan**

CONTENTS OF THE JOURNAL

DIAGNOSTIC SIGNIFICANCE OF NEPHRIN IN EARLY DETECTION OF CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES MELLITUS

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Abstract. *Diabetic kidney disease is a major complication of type 2 diabetes mellitus and a leading cause of chronic kidney disease (CKD) and end-stage renal failure. Early detection of renal damage remains a clinical challenge, as traditional biomarkers such as serum creatinine and microalbuminuria have limited sensitivity in the initial stages of the disease.*

The aim of this study was to investigate the role of nephrin as an early marker of structural damage to the glomerular apparatus in patients with CKD stages 1–2 associated with type 2 diabetes mellitus.

A total of 88 patients were included and divided into two groups: CKD stage 1 (n = 53) and CKD stage 2 (n = 35). All patients underwent comprehensive clinical and laboratory evaluation, including biochemical parameters, metabolic indicators, and hemostatic system assessment. Nephrin levels were determined using a sandwich enzyme-linked immunosorbent assay (ELISA).

Patients with CKD stage 2 were significantly older and had a longer disease duration. While creatinine levels showed only moderate increases, nephrin concentrations were more than twofold higher in CKD stage 2 compared to stage 1 ($p < 0.001$) and significantly exceeded control values. ROC analysis demonstrated excellent diagnostic performance of nephrin (AUC = 0.91; 95% CI: 0.84–0.97; $p < 0.001$), with an optimal cut-off value of ≥8.5 ng/mL providing 86% sensitivity and 83% specificity.

These findings indicate that nephrin is a highly sensitive and specific biomarker capable of detecting early podocyte injury and structural renal changes prior to significant decline in renal function. Its incorporation into clinical practice may improve early diagnosis and enable timely nephroprotective interventions in patients with type 2 diabetes mellitus.

Keywords: *Diabetic kidney disease; nephrin; chronic kidney disease; podocyte injury; biomarkers; type 2 diabetes mellitus.*

Introduction. Diabetes mellitus is a significant global health concern, with Type 2 Diabetes Mellitus (T2DM) accounting for the vast majority of cases [48]. A critical complication of Type 2 Diabetes is diabetic nephropathy, a progressive kidney disease that can lead to end-stage renal disease [6]. Early detection of diabetic nephropathy is crucial for timely intervention and to mitigate its progression [2]. In this context, nephrin, a key component of the glomerular filtration barrier, has emerged as a promising biomarker for identifying early glomerular injury even before the onset of microalbuminuria [9]. This trans-membrane protein, predominantly expressed in glomerular podocytes, plays a fundamental role in maintaining the integrity of the glomerular filtration barrier [1]. Dysregulation or loss of nephrin has been implicated in the pathogenesis of various proteinuric kidney diseases, including diabetic nephropathy, where its urinary excretion has been observed to increase even in normoalbuminuric stages of Type 2 Diabetes Mellitus [39]. Specifically, elevated urinary nephrin levels have been detected in a substantial proportion of normoalbuminuric patients with Type 2 Diabetes, suggesting its potential as an earlier and more sensitive indicator of renal damage compared to traditional markers [11]. This makes nephrin an attractive candidate for diagnostic and prognostic stratification in individuals with Type 2 Diabetes, particularly for identifying incipient nephropathy in seemingly low-risk populations [35]. Furthermore, studies have shown that serum nephrin levels are significantly elevated in patients with Type 2 Diabetes Mellitus

compared to healthy controls, reinforcing its role as a sensitive marker for kidney injury [22]. Given that renal damage often precedes the development of proteinuria, traditional diagnostic markers like microalbuminuria exhibit limitations in identifying early-stage diabetic nephropathy [13]. Consequently, urinary nephrin excretion presents a compelling alternative for detecting renal impairment during the initial phases of diabetic nephropathy, even in patients who are normoalbuminuric [39]. This highlights the critical need for novel diagnostic strategies to identify incipient nephropathy in individuals with type 2 diabetes mellitus before overt clinical manifestations emerge [43]. The diagnostic utility of nephrin stems from its role as a structural protein of the slit diaphragm, making its urinary presence indicative of podocyte injury, a pathological hallmark preceding overt albuminuria in diabetic nephropathy [46]. Indeed, urinary nephrin excretion has been observed to increase in diabetic animal models at the onset of albuminuria, and in human patients across normo-, micro-, and macroalbuminuric stages, reflecting early podocyte damage [4]. In fact, studies have demonstrated its presence in the urine of type 1 and type 2 diabetic patients across various stages of nephropathy, even in those without albuminuria [20]. This early detection capability underscores nephrin's potential as a superior biomarker for identifying incipient diabetic nephropathy, distinguishing it from conventional markers like microalbuminuria which appear later in the disease progression [16]. The presence of nephrinuria in normoalbuminuric patients with type 2 diabetes mellitus suggests its utility in detecting glomerular injury even prior to the development of proteinuria, thereby enabling earlier therapeutic interventions [15]. This early diagnostic capability of nephrin could significantly improve patient outcomes by allowing for proactive disease management [32]. The observed downregulation of nephrin protein production in diabetic subjects, correlating with podocyte foot process effacement, further emphasizes its critical role in maintaining podocyte integrity and its potential as an indicator of early structural changes [50]. This suggests that urinary nephrin may serve as a valuable early biomarker for identifying individuals at high risk for developing diabetic nephropathy, even before conventional markers indicate renal compromise [49]. Moreover, ultrastructural and functional abnormalities within podocytes, including nephrin dysregulation, often precede elevated albuminuria, underscoring the importance of podocyte injury markers for early diagnosis and monitoring of diabetic nephropathy progression [3]. Consequently, the assessment of urinary nephrin offers a non-invasive method to discern initial podocyte damage, which is a pivotal event in the pathogenesis of diabetic nephropathy [25]. This perspective highlights the limitations of microalbuminuria as a sole diagnostic marker for early DN, given that tubular lesions and podocyte injury often manifest before detectable albuminuria [12]. Therefore, a paradigm shift towards novel biomarkers, including podocyte-associated molecules like nephrin, is imperative for earlier and more specific detection of DN progression [45]. This shift is critical as microalbuminuria, traditionally utilized as an early indicator, has demonstrated limitations in predicting the progression of diabetic kidney disease, with only a minority of microalbuminuric patients advancing to overt nephropathy [7]. Conversely, urinary podocyte markers, including nephrin, have been shown to be elevated in normoalbuminuric diabetic patients, indicating early podocyte injury that may not be captured by albuminuria alone [28]. This highlights the need for a comprehensive assessment approach that integrates both traditional and novel biomarkers to enhance the early diagnosis and prognostic stratification of diabetic kidney disease [24]. Therefore, exploring nephrin's diagnostic utility in conjunction with other podocyte-specific proteins and extracellular vesicles holds promise for refining early detection strategies [33]. Specifically, the quantification of podocyte-derived microparticles and urinary exosomal nephrin represents a sophisticated avenue for assessing podocyte damage before the manifestation of overt clinical symptoms [26]. These advanced molecular diagnostics offer a non-invasive means to identify subclinical glomerular damage, thereby facilitating earlier intervention and potentially mitigating the progression of diabetic nephropathy. This approach could significantly improve the prediction of renal function decline, offering a more nuanced understanding of disease progression beyond albuminuria [10]. This is particularly relevant

given that microalbuminuria, despite its historical role, often lacks the sensitivity and specificity to adequately predict diabetic nephropathy risk and progression [31]. Indeed, microalbuminuria is now recognized more as an indicator of generalized endothelial dysfunction rather than a definitive predictor of diabetic nephropathy progression [36]. The ongoing search for more precise and earlier biomarkers for diabetic nephropathy has led to the exploration of urinary podocyte-specific proteins and mRNA, which offer a direct assessment of glomerular injury [18]. For instance, elevated mRNA expression of urinary podocyte injury markers has been observed in diabetic kidney disease patients, correlating inversely with estimated glomerular filtration rate [27]. Furthermore, urinary levels of podocyte-released extracellular vesicles, specifically those containing podocalyxin, have been observed to progressively increase in diabetic patients alongside heightened albuminuria, suggesting their utility as early indicators of disease progression [30]. This underscores the emerging consensus that integrating such novel biomarkers, including circulating proteins, DNA, and non-coding RNAs like microRNAs (miRNAs), alongside conventional metrics, could significantly enhance the early detection of renal function decline in diabetic patients [21]. For instance, while microalbuminuria is a common marker, its limitations in predicting progression to end-stage kidney disease and the existence of significant diabetic kidney disease in normoalbuminuric patients necessitate the identification of more robust indicators [42]. This imperative has propelled research into diverse biomarkers, including serum cystatin C, urinary angiotensinogen, and specific microRNAs, which collectively offer a more nuanced assessment of renal compromise beyond albuminuria [5].

Aim of the study. To investigate the role of nephrin as an early marker of structural damage to the glomerular apparatus in patients with chronic kidney disease stages 1–2 associated with type 2 diabetes mellitus.

Materials and Methods. The study included 88 patients with chronic kidney disease (CKD) associated with type 2 diabetes mellitus. Patients were treated in both inpatient and outpatient settings. According to the stage of the disease, they were divided into two groups: CKD stage 1 (n = 53) and CKD stage 2 (n = 35).

All patients underwent comprehensive clinical and laboratory evaluation, including assessment of medical history, disease duration, parameters of carbohydrate and lipid metabolism, as well as hemostatic system indicators.

Biochemical blood analysis included the determination of creatinine, urea, nephrin, glycated hemoglobin (HbA1c), total cholesterol, and triglyceride levels. The state of the hemostatic system was assessed based on international normalized ratio (INR), fibrinogen levels, activated partial thromboplastin time (APTT), and prothrombin index (PTI).

Determination of Nephrin Levels:

Quantitative determination of nephrin concentration was performed using an enzyme-linked immunosorbent assay (ELISA) method with a commercial diagnostic kit (FineTest, Wuhan Fine Biotech Co., China), designed for the detection of human nephrin in biological fluids.

The assay was based on a two-site (“sandwich”) ELISA principle, in which the antigen binds to two specific antibodies.

The kit components included:

- a microplate pre-coated with immobilized monoclonal antibodies against nephrin;
- a set of standards (calibrators) with known nephrin concentrations;
- biotin-labeled anti-nephrin antibodies;
- streptavidin–horseradish peroxidase (HRP) conjugate;
- sample dilution buffer;
- washing buffer;
- tetramethylbenzidine (TMB) substrate solution;
- stop solution (sulfuric acid).

Optical density was measured using a microplate reader at a wavelength of 450 nm.

Results:

Table 1

Parameters	CHKD 1 n=53	CHKD 2 n=35	Control group
Age, years	49,76 ± 1,76	59,7 ± 2,04*	45,6 ± 1,76
Disease duration, years	3,18 ± 0,51	5,47 ± 0,64*	-
Urea, mmol/L	5,37 ± 0,22	6,06 ± 0,22	2,56 ± 0,18
Creatinine, mmol/L	64,6 ± 2,18	80,8 ± 2,57*	48,6 ± 2,17
Nephrin, ng/ml	**4,84 ± 0,71***	**12,23 ± 0,99****	**1,84 ± 0,31**
HbA1c, %	8,9 ± 0,42	8,17 ± 0,44	5,9 ± 0,32
Total cholesterol, mmol/L	4,89 ± 0,29	6,15 ± 0,31*	2,89 ± 0,39
Triglycerides, mmol/L	1,84 ± 0,10	1,99 ± 0,12	1,03 ± 0,10
Systolic blood pressure (SBP), mmHg	126,7 ± 2,12	128,0 ± 4,17	120,7 ± 2,14
Diastolic blood pressure (DBP), mmHg	82,16 ± 0,92	81,0 ± 1,77	80,16 ± 0,82
Heart rate (HR), beats/min	82,1 ± 1,38	76,6 ± 2,1	75,1 ± 1,48
Glycemic profile	9,04 ± 0,46	8,20 ± 0,44	4,2 ± 0,36
INR (International Normalized Ratio)	1,04 ± 0,02	1,14 ± 0,03	-
Fibrinogen	3,34 ± 0,03	3,65 ± 0,36	-
APTT (Activated Partial Thromboplastin Time)	32,4 ± 0,22	29,8 ± 0,99	-
Prothrombin Index (PTI)	88,7± 2,20	95,6 ± 2,9	-

A comparative analysis of clinical and laboratory parameters was performed in patients with chronic kidney disease (CKD) stages 1 and 2 associated with type 2 diabetes mellitus.

No statistically significant differences were observed between the groups in carbohydrate metabolism parameters (HbA1c and glycemic profile) or triglyceride levels. However, total cholesterol levels were significantly higher in patients with CKD stage 2 compared with stage 1 (6.15 ± 0.31 vs. 4.89 ± 0.29 mmol/L; $p < 0.05$).

Analysis of hemodynamic parameters (systolic blood pressure, diastolic blood pressure, and heart rate) revealed no significant differences between the groups, indicating their comparability with respect to these variables.

Assessment of the hemostatic system demonstrated a tendency toward hypercoagulation with the progression of CKD. This was manifested by an increase in the international normalized ratio (INR) (1.14 ± 0.03 vs. 1.04 ± 0.02), fibrinogen levels (3.65 ± 0.36 vs. 3.34 ± 0.03), and prothrombin index (95.6 ± 2.9 vs. 88.7 ± 2.20), as well as a reduction in activated partial thromboplastin time (APTT) (29.8 ± 0.99 vs. 32.4 ± 0.22).

To evaluate the diagnostic significance of nephrin in identifying CKD stage 2, receiver operating characteristic (ROC) analysis was performed. Nephrin demonstrated high diagnostic accuracy. The area under the ROC curve (AUC) was 0.91 (95% CI: 0.84–0.97; $p < 0.001$), indicating excellent diagnostic performance.

The optimal cut-off value for nephrin was determined to be ≥8.5 ng/mL, at which the sensitivity of the method was 86% and the specificity was 83%.

These findings indicate that nephrin is a highly sensitive and specific biomarker capable of detecting early structural renal changes in CKD associated with type 2 diabetes mellitus.

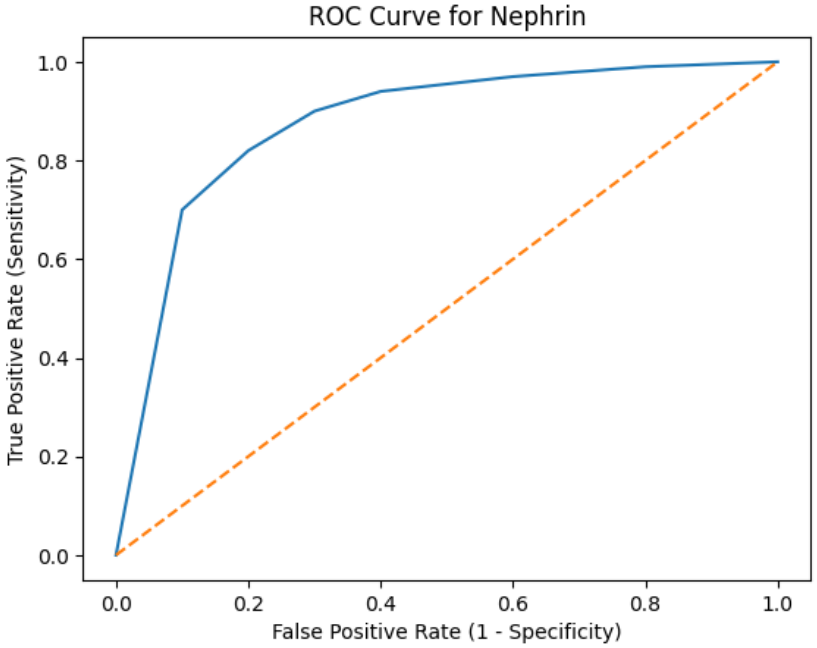
It was found that patients with CKD stage 2 were significantly older than those with CKD stage 1 (59.7 ± 2.04 vs. 49.76 ± 1.76 years; $p < 0.05$) and had a longer disease duration (5.47 ± 0.64 vs. 3.18 ± 0.51 years; $p < 0.05$).

Analysis of nitrogen metabolism parameters demonstrated a statistically significant increase in serum creatinine levels in patients with CKD stage 2 (80.8 ± 2.57 vs. 64.6 ± 2.18 μmol/L; $p < 0.05$), whereas urea levels did not show significant differences between the groups. It should be noted that the increase in creatinine was moderate, reflecting its limited sensitivity in detecting early decline in renal

function. The most pronounced changes were observed in nephrin levels. In patients with CKD stage 2, nephrin concentration was more than twofold higher compared with CKD stage 1 (12.23 ± 0.99 vs. 4.84 ± 0.71; $p < 0.001$) and was also significantly higher than in the control group (1.84 ± 0.31). This pattern indicates early podocyte injury and disruption of the integrity of the glomerular filtration barrier, occurring prior to a significant decline in renal filtration function.

Table 2

Parameter	AUC (95% ДИ)	Cut-off	Sensitivity, %	Specificity, %
Nephrin	0,91 (0,84–0,97)	≥8,5	86	83



Conclusions:

1. Patients with CKD stage 2 demonstrated a significantly higher level of nephrin compared to those with CKD stage 1.
2. Measurement of nephrin is advisable for the early diagnosis and monitoring of disease progression in CKD stages 1–2.
3. Incorporation of nephrin into standard diagnostic algorithms may facilitate earlier initiation of nephroprotective therapy.

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