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ASSOCIATION OF NEPHRIN LEVELS WITH CHRONIC KIDNEY DISEASE IN PATIENTS WITH HYPERTENSION

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Abstract

Chronic Kidney Disease (CKD), a progressive condition often triggered by poorly managed hypertension, can lead to end-stage renal disease (ESRD) if not identified and treated early. This study aims to explore the role of nephrin as a parameter for detecting and predicting the development of CKD in hypertensive people. The cross-sectional study evaluated nephrin levels in hypertensive adults across different stages of CKD. A minimum of 100 participants were included. The demographic analysis showed a higher percentage of males (67%) in comparison to females. Among males, the majority (37.31%) were in the 36-45 age group. In terms of BMI, 42% of patients were classified as normal weight, 30% as overweight, 20% as obese, and 8% as underweight. Half of the patients had hypertension, 20% had diabetes, 15% had cardiovascular disease, and 15% had no significant medical history. Nephrin levels were elevated with CKD progression, increasing from 15.2 ng/mL in patients with eGFR > 90 mL/min/1.73 m² to 80.1 ng/mL in those with eGFR < 30 mL/min/1.73 m² ($p \leq 0.05$). A strong positive correlation was observed between nephrin and ACR ($R^2 = 0.99$), serum creatinine ($R^2 = 0.95$), and BUN ($R^2 = 0.96$). It is concluded that Nephrin emerges as a promising early biomarker for identifying and predicting CKD progression in hypertensive individuals, showing a significant correlation with declining kidney function markers such as ACR, serum creatinine, and BUN. Monitoring nephrin levels may enhance early detection and timely intervention, potentially slowing CKD progression and decreasing the risk of ESRD.

Keywords: *Biomarkers, Blood Urea Nitrogen, early detection, End-Stage Renal Disease, kidney function, serum creatinine.*

Introduction

Hypertension is a significant risk factor for Chronic Kidney Disease (CKD), as consistently high blood pressure damages the blood vessels in the kidneys, impairing their filtration ability over time. Bakker et al. noted that elevated intraglomerular pressure can harm podocytes, leading to nephrin detachment, which indicates damage to the glomerular filtration membrane [1]. CKD involves the gradual loss of kidney function, potentially progressing to end-stage renal disease (ESRD) if untreated [2]. This damage may result in progressive nephropathies, causing excess proteins to be filtered and deposited in tubule cells, triggering an interstitial inflammatory response [3]. Insulin has been identified as an early biomarker in hypertensive patients, alongside other biomarkers that may aid in early diagnosis. Timely intervention in CKD could potentially slow its progression to ESRD.

Podocytes are specialized cells that form the kidney's glomerular filtration barrier and are rich in nephrin, a critical protein that prevents blood proteins from leaking into urine [4]. Nephrin maintains the integrity of the slit diaphragm between podocytes and plays a vital role in filtration barrier function [5]. When this barrier is compromised, it leads to proteinuria, an early marker of glomerular impairment characteristic of CKD [6]. Chronic proteinuria resulting from nephrin dysfunction increases the kidneys' susceptibility to damage and heightens the risk of progressing to ESRD. Abnormalities in nephrin levels in hypertensive patients may serve as an initial biomarker for early glomerular injury, appearing before advanced CKD markers like reduced eGFR or increased serum creatinine [7]. Thus, studying nephrin levels in relation to CKD progression could enhance early detection and improve therapeutic targets, ultimately aiding in interventions that slow disease progression and delay the onset of ESRD.

Despite major advancements in the managing hypertension, a substantial proportion of hypertensive patients continue to develop CKD [8]. Early detection of CKD in this population remains a challenge, as current diagnostic tools often fail to identify the disease in its initial stages. There is a critical need for reliable early biomarkers that can predict CKD progression in hypertensive individuals, allowing for timely intervention and better patient outcomes. Nephrin, a protein involved in maintaining the glomerular filtration barrier, has emerged as a probable biomarker [9]. However, limited scientific trails have explored the specific role of nephrin levels in the development and progression of CKD among hypertensive patients. Addressing this gap could lead to improved strategies for early diagnosis and treatment. Existing studies have primarily examined the broader connections between CKD and hypertension; however, the specific relationship between nephrin levels and CKD in hypertensive patients remains largely underexplored. The clinical implications of fluctuations in nephrin levels as early indicators of CKD progression in this population have not been fully understood highlighting a significant gap in the literature.

The objective is to investigate the association of nephrin levels with development of CKD in patients with hypertension, and to assess whether nephrin levels can serve as a predictive biomarker for CKD in hypertensive individuals. Moreover, the study aimed to contribute to the early detection and management of CKD within the hypertensive population, which may ultimately reduce the progression to ESRD.

Methodology

This study utilized a cross-sectional observational model to inspect the association between CKD in patients diagnosed with hypertension. This methodology permits accessing nephrin levels in selected population at a single point in time, facilitating the documentation of possible correlations between various stages of CKD and nephrin levels. This study included patients diagnosed with hypertension with age 18 years or older. It involved individuals at various stages of CKD, demonstrated by their estimated kidney function

(eGFR) and urine albumin-to-creatinine ratio (ACR). Functional exclusionary criteria served to protect the reliability of study conclusions. All the patients with Acute Kidney Injury (AKI) or any relevant kidney diseases not due to Hypertension were excluded from this trail in order to eliminate confounding elements. Subjects receiving prescriptions which may have affected nephrin expression (eg, immunosuppressives) were also excluded. The sample size for this study was calculated based on a CKD prevalence of 10-15% in the general population, using a 95% confidence level and a 5% margin of error. This ensured adequate representation across CKD stages. Hundred patients were set as the target to confirm the output would be reliable and valid.

Data were collected on patient demographics i.e. age, gender, body mass index (BMI), medical history, how long they had hypertension, and whether there was a family background of kidney disease or not. Blood samples were taken from all individuals selected for study and serum nephrin levels were analyzed with the help of enzyme-linked immunosorbent assay (Catalog Number: SEA937Hu) [10]. Further, kidney function was assessed by determining blood urea nitrogen (BUN), serum creatinine and estimating the glomerular filtration rate (eGFR) to evaluate overall kidney condition. Urine samples were collected to demonstrate the urine albumin-to-creatinine ratio (ACR), which is a an indicator of proteinuria and kidney dysfuction.

Patients were categorized into various groups according to glomerular filtration rate (eGFR) to help analyze nephrin levels in relation to the severity of CKD. The classification was as follows:

Group 1: Hypertensive individuals without CKD, categorized by an eGFR greater than 90 mL/min/1.73 m²

Group 2: Hypertensive individuals with mild CKD, categorized by eGFR values ranging from 60 to 89 mL/min/1.73 m²

Group 3: Hypertensive individuals with moderate CKD, categorized by eGFR values between 30 and 59 mL/min/1.73 m²

Group 4: Hypertensive patients with severe CKD, categorized by an eGFR of less than 30 mL/min/1.73 m²

Percentages and frequencies were calculated for gender and CKD stages. For continuous variables, such as nephrin levels, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (ACR), the mean and standard deviation were determined. Analysis of variance was used to compare nephrin levels among the four groups of patients categorized by their eGFR. Simple linear regression and Pearson's correlation analysis were applied to assess the relationships between nephrin levels and eGFR, ACR, and blood pressure.

The study established ethical approval from the Institutional Review Board (IRB) (Ref: 2186) was obtained from the office of superintendent district headquarters hospital AJK Neelum, certifying that all research obeyed mentioned ethical guidelines. Before gathering the samples, participants were fully informed about the study, and their consent was obtained. To protect their privacy, individual's confidentiality was strictly upheld, and all data were kept secure to safeguard personal information. This study lasted for six months

Results

Distribution of patients based on gender and age

The demographic analysis of the patients revealed a varied distribution across different age groups and genders who were suffering CKD. Among males, the highest proportion (37.31%) was in the 36-45 age group, followed by 29.85% in the 26-35 age group, 17.91% in the 18-25 age group, 11.94% in the 46-55 age group, and 2.99% aged above 55 years. In contrast, females were more evenly distributed, with 24.24% in both the 18-25 and above 55 age groups, 21.22% in the 46-55 age group, and 15.15% in both the 26-35

and 36-45 age groups. The total population comprised 67 males and 33 females, representing 100% of each gender.

Table 1 Distribution of patients with respect to gender and age

Age group	Males (%)	Female (%)
18-25	12 (17.91 %)	8 (24.24%)
26-35	20 (29.85 %)	5 (15.15%)
36-45	25 (37.31 %)	5 (15.15%)
46-55	8 (11.94 %)	7 (21.22%)
Above	2 (2.99 %)	8 (24.24%)
Total	**67 (100 %)**	**33 (100%)**

Values in parenthesis are percentages

Patient's Clinical Characteristics

The analysis of clinical and demographic variables revealed a diverse profile among the patients as presented in Table 2. In terms of body mass index (BMI), 42% of individuals were categorized within the normal weight range (18.5 - 24.9), while 30% were classified as overweight (25 - 29.9), and 20% as obese (≥ 30). A small proportion of participants (8%) were underweight (BMI < 18.5). Hypertension was the most prevalent condition, affecting 50% of the population, followed by diabetes (20%) and a history of cardiovascular disease (15%). Notably, 15% reported no significant medical conditions. Among hypertensive patients, 40% had been hypertensive for 6-10 years, 30% for 0-5 years, 20% for 11-15 years, and 10% for over 16 years. Furthermore, a family history of kidney disease was reported by 35% of participants, while the remaining 65% had no family history of the condition.

Table 2 Clinical characteristics of hypertensive patients included (n=100)

Variable	Category	Percentage (%)
Body Mass Index (BMI)	underweight (< 18.5)	8
	optimum weight (18.5 - 24.9)	42
	Over weight (25 - 29.9)	30
	Obese (≥ 30)	20
Total		100
Medical History	Hypertension	50
	Diabetes	20
	Cardiovascular Disease	15
	None	15

Total		100
Duration of Hypertension	0-5 years	30
	6-10 years	40
	11-15 years	20
	16 and above	10
Total		100
Family History of Kidney Disease	Yes	35
	No	65
Total		100

Grouping of patients based on estimated Glomerular Filtration Rate (eGFR)

Patients in the study were categorized based on their estimated glomerular filtration rate (eGFR) to assess kidney function (Table 3). Group 1 included individuals with an eGFR over 90 mL/min/1.73 m², representing 30% of participants. Group 2, with eGFR values between 60 and 89 mL/min/1.73 m², accounted for 40%. Group 3, characterized by eGFR levels between 30 and 59 mL/min/1.73 m², comprised 20%. Lastly, Group 4, consisting of individuals with severe kidney impairment (eGFR below 30 mL/min/1.73 m²), represented 10% of the cohort.

Table 3 Distribution of individuals on the basis of estimated Glomerular Filtration Rate

Group	eGFR Range (mL/min/1.73 m²)	Percentage (%)
Group 1	> 90	30
Group 2	60 – 89	40
Group 3	30 – 59	20
Group 4	< 30	10
Total		100

Biochemical parameters among four eGFR based group of patients

The biochemical analysis revealed distinct variations ($p \leq 0.05$) in nephrin levels, serum creatinine, blood urea nitrogen (BUN), and urine albumin-to-creatinine ratio (ACR) across the four patient groups based on their estimated glomerular filtration rate (eGFR) ranges (Table 4). Group 1, with an eGFR > 90 mL/min/1.73 m², exhibited a mean nephrin level of 15.2 ± 3.5 ng/mL, serum creatinine of 0.9 ± 0.1 mg/dL, BUN of 10.5 ± 2.0 mg/dL, and ACR of 5.1 ± 1.2 mg/g. Group 2, with eGFR ranges between 60-89 mL/min/1.73 m², had a nephrin level of 35.8 ± 5.1 ng/mL, serum creatinine of 1.2 ± 0.2 mg/dL, BUN of 15.0 ± 3.0 mg/dL, and ACR of 15.3 ± 2.5 mg/g. In Group 3, characterized by eGFR ranges between 30-59 mL/min/1.73 m², the nephrin level increased to 50.3 ± 6.8 ng/mL, serum creatinine rose to 2.0 ± 0.3 mg/dL, BUN reached 25.0 ± 4.0 mg/dL, and ACR was 25.7 ± 3.6 mg/g. Lastly, Group 4, with the severe kidney damage (eGFR < 30 mL/min/1.73 m²), showed the highest nephrin level at 80.1 ± 7.4 ng/mL, serum creatinine at 3.5 ± 0.4 mg/dL, BUN at 45.0 ± 5.0 mg/dL, and ACR at 45.9 ± 4.2 mg/g.

Table 4 Biochemical variation among four eGFR based group of patients

Groups	Nephrin Level (ng/mL)	Serum creatinine (mg/dL)	BUN (mg/dL)	ACR (mg/g)
Group 1	15.2±3.5d	0.9±0.1cd	10.5±2.0d	5.1±1.2d
Group 2	35.8± 5.1c	1.2±0.2c	15.0±3.0c	15.3±2.5c
Group 3	50.3±6.8b	2.0±0.3b	25.0±4.0b	25.7±3.6b
Group 4	80.1±7.4a	3.5±0.4a	45.0±5.0a	45.9±4.2a
Least significant difference ($p \leq 0.05$)	5.8	0.3	3.5	3.2

Means followed by different latters are significantly different. ± shows the standard deviation between samples taken.

Association between Nephrine levels among four eGFR based group of patients

The scatter plot presents the observed nephrin levels across four groups of patients, with error bars representing the standard deviation of each group's mean nephrin level (Figure 1). A linear regression analysis revealed a strong positive correlation between the different patient groups and nephrin levels, with an impressive R^2 value of 0.96. Nephrin levels increased steadily across the groups, starting at 15.2 ng/mL for Group 1 (those with eGFR > 90 mL/min/1.73 m^2) and reaching 80.1 ng/mL for Group 4 (those with eGFR < 30 mL/min/1.73 m^2). This trend suggests that nephrin levels are higher in patients with severe CKD.

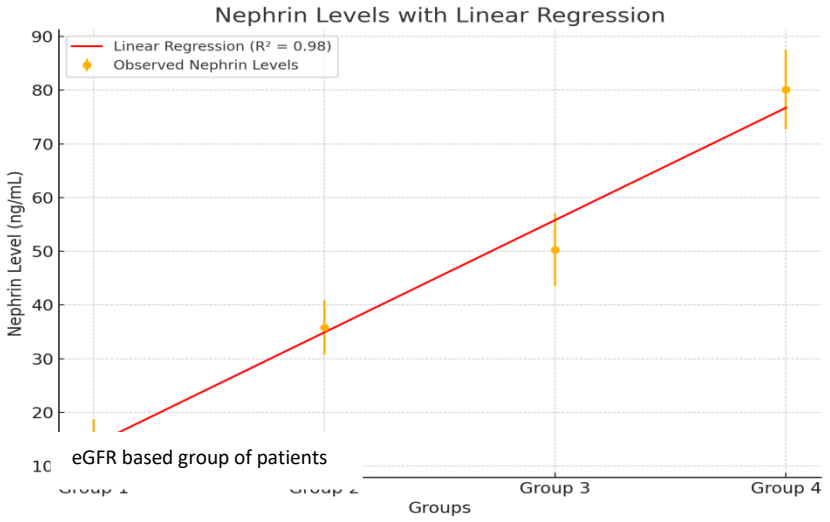

Figure 1 Association between naphrin levels and four eGFR based group of patients.

Group 1: hypertensive patients without CKD (eGFR > 90 mL/min/1.73 m²); Group 2: mild CKD (eGFR 60-89 mL/min/1.73 m²); Group 3: moderate CKD (eGFR 30-59 mL/min/1.73 m²); Group 4: high CKD (eGFR < 30 mL/min/1.73 m²).

Pearson's correlation among biochemical parameters

The heatmap analysis (Figure 2) showed significant relationships between nephrin levels, serum creatinine, blood urea nitrogen (BUN), and the urine albumin-to-creatinine ratio (ACR). A strong positive correlation was observed between nephrin and ACR (R^2 = 0.99), suggesting a link between higher nephrin levels and worsening albuminuria, an indicator of kidney damage. Nephrin also correlated moderately with serum creatinine (R^2 = 0.95) and strongly with BUN (R^2 = 0.96), reinforcing its potential as a marker for impaired renal function. Furthermore, ACR was highly associated with both serum creatinine and BUN (R^2 = 0.98), reflecting declining kidney function.

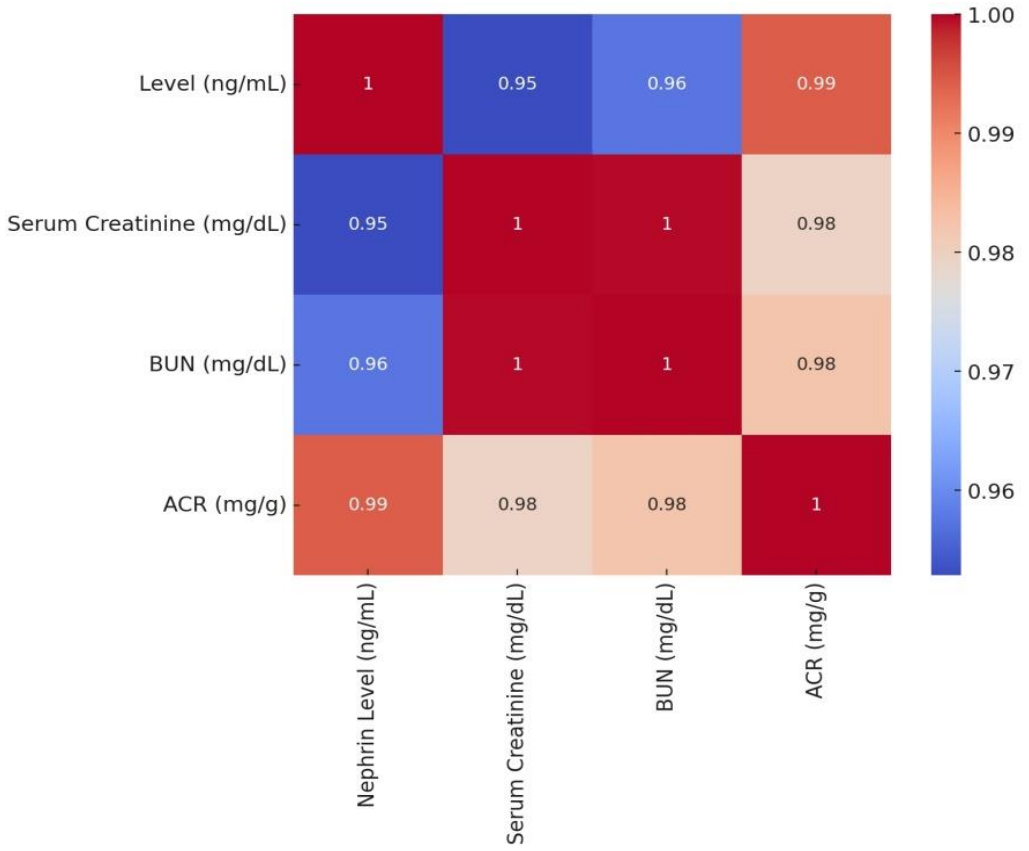

Figure 2 Heatmap showing correlation between different biochemical parameters of four eGFR based group of patients

Discussion

Men in their 30s and 40s exhibited a higher prevalence of CKD, possibly because they are more exposed to risk factors like diabetes, hypertension as well as lifestyle choices i.e. smoking. These factors are more dominant among men and can lead to kidney disease [11]. On the contrary, females exhibit a more even distribution, with increased incidence in older age groups, mainly postmenopausal women. This could be explained by hormonal changes, as estrogen has been presented to have a protective effect on kidney function in premenopausal women, decreasing the risk of CKD progression as stated by Petrica t al. [12]. The notable representation of younger individuals with CKD in this study points to the global trend of early-

onset CKD, driven by obesity and poor lifestyle choices, which increase the incidence of diabetes and hypertension in younger populations [13].

Significant impact of BMI, hypertension, and family history on chronic disease risk, particularly kidney disease was prominent. The high proportion of individuals classified as overweight (30%) and obese (20%) showed positive association with danger of CKD, primarily due to the intensified likelihood of developing conditions like hypertension, which are major precursors of CKD progression [14]. Obesity, in particular, has been shown to aggravate renal damage through mechanisms i.e. glomerular hyperfiltration, increased renal workload, and the promotion of insulin resistance and inflammation as mentioned by Hall et al. [15]. The finding that 50% of participants suffer from hypertension is particularly concerning, as hypertension remains one of the leading causes of CKD globally. The duration of hypertension among the cohort further supports the chronic nature of this condition, with 40% of patients having lived with hypertension for 6-10 years, significantly increasing their risk for CKD due to prolonged damage to the renal vasculature [16]. The diabetic percentage of patients having CKD shows that poorly controlled blood sugar levels damage the kidneys' filtering systems, leading to diabetic nephropathy, a major contributor to ESRD [17]. As per results, 35% of participants described a family history of kidney malfunctioning showing that genetic factors can possibly influence people to CKD, especially in the presence of environmental or lifestyle triggers. The 15% prevalence of cardiovascular disease (CVD) highlights the strong link between CKD and CVD. Both conditions share comparable risk factors, and CVD can both result to kidney disease [18].

The assessment of patients by eGFR presents crucial perceptions in the various stages of kidney function, which is vital for understanding CKD advancement. With 30% of patients maintaining normal kidney function, the presence of risk factors like hypertension and diabetes in this group advocates an early opportunity for intervention, as these conditions are known to accelerate kidney damage as time passes. The higher proportion, 40%, displayed mild kidney damage, showing the status of early-stage CKD detection and management, which has been shown to reduce disease progress through blood pressure control and lifestyle changes [19]. As kidney function depreciates, more intensive clinical interference becomes critical. For the 20% of patients with CKD, timely administration of complications i.e. electrolyte imbalances and anemia are vital to preventing further severity. In the most severe cases, comprising 10% of the cohort, the risk of reaching ESRD and developing heart related complications is increased [20].

The biochemical differences observed among individuals underscore the progressive nature of CKD. Elevated nephrin levels in patients with lower eGFR indicate glomerular damage, as nephrin is essential for maintaining glomerular filtration barrier integrity [21]. Higher nephrin levels in advanced CKD stages suggest worsening podocyte injury with declining renal function, supporting its role as a potential early biomarker for CKD progression. This observation aligns with prior studies showing that podocyte dysfunction and loss contribute significantly to proteinuria and CKD progression [22]. Serum creatinine and BUN, widely used indicators of renal clearance, also increased progressively with declining eGFR, consistent with the buildup of metabolic waste, such as creatinine and urea, due to impaired filtration [23]. In severe CKD cases, the sharp rise in BUN and serum creatinine reflects substantial loss of renal function, showing relevance in tracking CKD progression. The urine ACR, reflects glomerular permeability and endothelial dysfunction [24]. Increasing ACR levels across CKD stages in this study indicate a declining filtration barrier, leading to higher urinary albumin excretion. Elevated ACR is linked not only to CKD progression but also to increased cardiovascular mortality, particularly in advanced CKD where endothelial dysfunction is prominent. The rise in ACR among patients with lower eGFR thus underscores the interconnected

risks associated with kidney dysfunction and cardiovascular health.

The positive association demonstrated relationship between decreasing estimated eGFR and increasing nephrin. This increase revealed the potential of nephrin as a biomarker for renal impairment, as elevated nephrin levels are indicative of podocyte injury and glomerular dysfunction [25]. The findings propose that nephrin levels reflect the severity of kidney damage, aligning with discoveries from present literature that associate higher nephrin with severe renal dysfunction and increased albuminuria. That is why; the linear regression analysis not only reinforces the diagnostic value of nephrin in monitoring CKD progression but also emphasizes its role in facilitating early intervention strategies for patients at risk of rapid renal decline. Nephrin, a key component of the kidney's filtration barrier, plays a crucial role in detecting early kidney dysfunction, especially in albuminuric patients, where elevated nephrin levels indicate podocyte malfunction and potential kidney damage [26]. In CKD progression, podocyte injury raises permeability, leading to proteinuria. Elevated serum creatinine and BUN reflect reduced renal clearance and waste buildup, highlighting nephrin as a key marker of renal impairment [27]. Monitoring nephrin alongside ACR, serum creatinine, and BUN can improve early CKD detection and management in hypertensive patients, helping to prevent further renal decline.

Conclusion

The study underlines the potential of nephrin as imperative early biomarker for predicting the progression of CKD in individuals with hypertension. The findings showed a significant correlation between elevated nephrin levels and declining kidney function, as reflected by higher ACR, serum creatinine, and BUN levels, across different stages of CKD. These results advocate that tracking nephrin levels could improve early detection of kidney damage and providing timely treatment. Timely intervention, based on nephrin levels, may help slow CKD progression and reduce the probability of reaching end-stage renal disease (ESRD) in hypertensive patients.

Conflict of interest

All the authors have stated that they have no competing interest.

Author's contributions

All the authors collaboratively worked and contributed to conducting the research and preparing the manuscript.

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