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ORIGINAL ARTICLE

Clinical Trials Study

Endothelial injury and inflammation in patients with hyperuricemic nephropathy at chronic kidney disease stages 1-2 and 3-4

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Abstract

BACKGROUND

Endothelial injury and inflammation are the main pathological changes in hyperuricemic nephropathy (HN); however, they have not been assessed in patients in the early, middle, and late phases of HN.

AIM

To investigate endothelial injury and inflammatory conditions between patients with HN at chronic kidney disease (CKD) stages 3-4 and CKD 1-2.

METHODS

This study enrolled 80 patients (49 and 31 with HN at CKD stage 1-2 and 3-4, respectively) from the Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine between July 2021 and January 2022. Plasma levels of heparan sulfate, endocan, oxidized low-density lipoprotein (Ox-LDL), E-selectin, soluble intercellular adhesion molecule-1 (slCAM1), interleukin (IL)-1β, and IL-6 and urine levels of lipocalin-type prostaglandin D synthase (L-PGDS), IL-1β, and IL-6 were measured using enzyme-linked immunosorbnent assay.

RESULTS

Comparison between patients with HN at CKD 1-2 and those with HN at CKD 3-4 showed that age and disease course were significant factors ($P < 0.001$ and $P < 0.010$, respectively). There were no statistical differences in sex, heart rate, body

mass index, and systolic and diastolic blood pressures. The incidence of hypertension was also significant (P = 0.03). Plasma levels of heparin sulfate (P < 0.001), endocan (P = 0.034), E-selectin (P < 0.001), slCAM1 (P < 0.001), IL-1β (P = 0.006), and IL-6 (P = 0.004) and the urine levels of L-PGDS (P < 0.001), IL-1β (P = 0.003), and IL-6 (P < 0.001) were high in patients with HN at CKD 3-4 than in those with HN at CKD 1-2. The difference in plasma Ox-LDL levels was not significant (P = 0.078).

CONCLUSION

Vascular endothelial injury and inflammation were higher in patients with HN at CKD3-4 than at CKD 1-2. Plasma heparin sulfate and slCAM1 levels are synergistic factors for CKD staging in HN.

Key Words: Endothelial injury; Inflammation; Hyperuricemic nephropathy; Chronical kidney disease; Risk factors

Core Tip: This study focused on the baseline analysis of a randomized, double-blinded, controlled trial and aimed to explore the differences in vascular endothelial injury and inflammatory state in the early and middle-late stages of hyperuricemic nephropathy and the risk factors for chronic kidney disease staging.

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INTRODUCTION

Hyperuricemia (HUA) is classically defined as an increase in serum urate concentration that exceeds the solubility threshold (6.8 mg/dL)[1]. Renal injury caused by HUA is referred to as hyperuricemic nephropathy (HN)[2]. The prevalence of gout in Chinese adults was 1.1%, and the incidence increased from 1.0% in 2000–2005 to 1.3% in 2010–2016[3]. From 2000 to 2014, the pooled prevalence of HUA in mainland China was approximately 13.3%[4]. Majority of the patients with gout show kidney damage during autopsies. With the increasing incidence of HUA and gout, the number of patients with HN is also increasing, which seriously threatens human health. Chronic kidney disease (CKD) is a progressive disease associated with end-stage renal disease, which is a main outcome of CKD.

High levels of uric acid can impair the kidneys through a variety of pathways that promote inflammation. High levels of uric acid can damage the glomerular and systemic vascular endothelium. Elevated serum uric acid (SUA) levels have been associated with endothelial dysfunction[5]. Studies have found that uric acid-lowering therapy can improve endothelial function[6]. Damaged glomerular endothelial function due to renal damage caused by different factors is an important pathological change in the development of end-stage renal disease[7]. Currently, varieties of markers are available for evaluating vascular endothelial injury and inflammatory responses. We aimed to explore the differences between the levels of endothelial injury and inflammatory biomarkers in patients with HN at CKD stages 1-2 and 3-4.

MATERIALS AND METHODS

General information

This study enrolled 80 patients with HN at CKD stages 1-4 (49 with CKD 1-2 and 31 with CKD 3-4) at the Department of Nephrology, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine between July 2021 and January 2022 (patient data were obtained from randomized double-blinded controlled trial).

Diagnostic criteria

Diagnostic criteria for HN: According to the standard of "Diagnosis, Syndrome Differentiation, and Efficacy Evaluation of HN (Trial Scheme)" (Nephropathy Branch of the Chinese Association of Traditional Chinese Medicine), the following criteria was referred: (1) History of gouty arthritis, gouty nodules, uric acid urinary calculi, *etc*., are common in middle-aged and elderly men or menopausal

women; (2) Chronic interstitial nephritis is symptomatic. In the early stages, only a small amount of proteinuria, abnormal urine concentration function, and normal estimated glomerular filtration rate (eGFR) values are detected. In the late stages, hypertension and azotemia may occur; (3) Diagnostic values: Male: SUA > 420 μmol/L, female: SUA > 360 μmol/L; (4) Uric acid crystals, gross or microscopic hematuria, and pyuria are detected in routine urine analysis; (5) A puncture-like translucent defect (joint damage) is observed in imaging examinations. Urinary tract stones are absent in X-ray examinations; and (6) Kidney histology: Renal tubule-interstitial lesions and urate crystals are observed in the renal interstitium and tubules.

If (3) and either of (1)–(2) and (4)–(6) are met, the diagnosis can be made.

CKD staging standards: eGFR should be calculated according to the CKD-EPI cr-cys values[8].

Inclusion criteria

(1) Diagnostic criteria for HN; (2) eGFR of CKD-EPI cr-cys ≥ 15 (mL/min/1.73 m^2); (3) Age 18–75 years, with independent behavioral ability, no gender limitation; and (4) Signed informed consent for involvement in clinical research.

Exclusion criteria

(1) Drug allergies (including all drugs in the test) or allergic conditions; (2) Pregnancy or lactation; (3) Patients undergoing or underwent renal replacement therapy (dialysis or kidney transplantation); (4) Patients with combined cardiovascular, digestive, neurological, urinary, and mental illnesses; and (5) Patients with hereditary kidney disease and chronic nephritis.

Observation indicators

Blood samples: After fasting (> 10 h), cubital venous blood samples [5 mL × 2; one biochemical and one ethylene diamine tetraacetic acid (EDTA) tube each] were collected by the laboratory department of Shuguang Hospital. The EDTA tubes were sent to the Institute of Nephrology for SUA, serum creatinine, blood urea nitrogen, and eGFR determination.

Urine samples: After fasting (> 10 h), the morning urine samples were collected (10 mL × 2). One tube was sent to the laboratory to detect urine levels of N-acetyl-β-D-glucosidase, retinol-blinding protein, β 2-Microglobulin, and albumin/Cr. Another tube was sent to the Institute of Nephrology to detect plasma levels of heparan sulfate, endocan, oxidized low-density lipoprotein (Ox-LDL), E-selectin, soluble intercellular adhesion molecule-1(slCAM1), interleukin (IL)-1β, and IL-6 and urine levels of lipocalin-type prostaglandin D synthase (L-PGDS), IL-1β, and IL-6.

The plasma and urine samples were immediately centrifuged (3000 rpm), and the supernatant was collected, aliquoted, and stored in a -80 °C ultra-low-temperature refrigerator. Enzyme-linked immunosorbnent assay (kit provided by Shanghai Wellbio Technology Co. Ltd) was used to detect the plasma levels of heparan sulfate, endocan, Ox-LDL, E-selectin, slCAM1, IL-1β, and IL-6 and urine levels of L-PGDS, IL-1β, and urine IL-6.

Statistical methods

Statistical analyses were performed using SPSS version 25.0. All statistical tests were two-sided, and statistical significance was set at $P < 0.05$. (1) Measurement data with a normal distribution were analyzed using the *t*-test, and the statistical results are expressed as ($x \pm s$); (2) The Mann-Whitney U test was used to analyze measurement data with a non-normal distribution, and the statistical results are expressed as medians and quartiles (P25–P75); and (3) The chi-square (χ^2) test was used to test the count data.

RESULTS

General information

Comparison between patients with HN at stages CKD 1-2 and CKD 3-4 showed that age and disease course were significant factors ($P < 0.001$ and $P < 0.010$, respectively). There were no statistical differences in sex, heart rate, body mass index, and systolic and diastolic blood pressures. The incidence of hypertension was also significant ($P = 0.03$) (Table 1).

Endothelial injury and inflammation level marker analysis

The plasma levels of heparan sulfate ($P < 0.001$), endocan ($P = 0.034$), E-selectin ($P < 0.001$), slCAM1 ($P < 0.001$), IL-1β ($P = 0.006$), and IL-6 ($P = 0.004$) and urine levels of L-PGDS ($P < 0.001$), IL-1β ($P = 0.003$), and IL-6 ($P < 0.001$) were high in patients with HN at stages 1-2 than that at 1-4. Additionally, the difference in plasma Ox-LDL level was not significant ($P = 0.078$) (Table 2).

Table 1 General data of patients in stages chronic kidney disease 1-2 and chronic kidney 3-4

Items		CKD 1-2 (*n* = 49)	CKD 3-4 (*n* = 31)	t/Z/χ^2	*P* value
Age (yr)		42 (35-52)	66 (61-69)	6.514	< 0.001[c]
Sex	Male	48 (98.0%)	29 (93.5%)	1.023	0.312
	Female	1 (2.0%)	2 (6.5%)		
Course of gout (mo)		45.7 (14.8-80.55)	81.3 (39.3-173.63)	2.583	0.010[a]
Heart rate (beats/min)		75.04 ± 9.836	74.87 ± 8.62	0.079	0.937
BMI		25.95 (24.54-27.66)	24.77 (24.00-27.28)	-1.487	0.137
Systolic pressure (mmHg)		129.18 ± 10.55	130.61 ± 10.70	-0.587	0.559
Diastolic pressure (mmHg)		83.94 ± 8.59	82.97 ± 6.44	0.540	0.591
Incidence of hypertension %		39 (79.6%)	30 (96.8%)	4.727	0.030[a]
SUA (umol/L)		474.41 ± 102.34	483.90 ± 107.97	-0.396	0.693
Scr (mmol/L)		92.78 ± 12.55	145.87 ± 48.14	-7.360	< 0.001[c]
BUN (mmol/L)		5.20 ± 1.06	9.35 ± 3.46	-7.857	< 0.001[c]
eGFR (ml/min/1.73 m^2)		91.73 ± 14.82	40.91 ± 11.84	16.111	< 0.001[c]
Urine NAG (U/L)		0.70 (0.10-5.08)	0.70 (2.05-14.82)	3.402	0.001[b]
Urine RBP (mg/L)		0.20 (0.10-0.30)	0.58 (0.20-1.95)	3.059	0.002[b]
Urine β2-MG (mg/L)		0.20 (0.10-0.30)	0.30 (0.12-1.91)	2.615	0.009[b]
Urine Alb/Cr (mg/g)		4.79 (2.07-9.04)	45.76 (8.22-316.75)	4.504	< 0.001[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
CKD: Chronic kidney disease; BMI: Body mass index; SUA: Serum uric acid; Scr: Serum creatinine; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; NAG: N-acetyl-beta-D-glucosidase; RBP: Retinol binding protein; β2-MG: β2-Microglobulin; Alb/Cr: Albumin-to-creatinine.

Analysis of CKD staging and markers based on binary multivariate logistic regression analysis

Using CKD 1-2 (early stage) and CKD 3-4 (middle and late stages) as the response variables and plasma levels of heparan sulfate, Endocan, Ox-LDL, E-selectin, slCAM1, IL-1β, and IL-6 and urine levels of L-PGDS, IL-1β, and IL-6 as the independent parameters, plasma heparan sulfate [odds ratio (OR) = 1.004, $P = 0.016$] and slCAM1 (OR = 8.831, $P = 0.008$) levels were identified as HN co-risk factors for CKD staging (Table 3).

DISCUSSION

Endothelial cells of the microvasculature regulate the blood flow in local tissue beds, thereby regulating coagulation, inflammation, and vascular permeability. The diverse functions of endothelial cells make them key drivers and targets of inflammatory and thrombotic processes, which ultimately damage the kidneys.

Endothelium plays an important role in the regulation of renal function[9]. Renal capillaries deliver oxygen and nutrients to the renal tubules, regulate vasoactivity, maintain a local balance between pro- and anti-angiogenic factors, and are essential for normal renal function. Mechanical damage, hypoxia, or uric acid leads to glycocalyx shedding, resulting in endothelial dysfunction[10,11]. Microvascular damage, which is observed in various kidney diseases, eventually progresses into CKD.

The prevalence of hypertension was high in patients with CKD 1-4; however, the prevalence was significantly higher in CKD 3-4 than that in the early stages (1-2), suggesting that vascular endothelial damage is very common. Moreover, as CKD progresses, vascular endothelial damage becomes more severe.

Microvascular injury can lead to vasoconstriction, increased vascular permeability, inflammation, oxidative stress, endothelial cell apoptosis, and necrosis and is closely related to the progression of CKD to end-stage renal disease[12].

Currently, according to the existing literature on CKD, the markers used to evaluate vascular endothelial injury include glycocalyx injury, cell adhesion molecules, endothelial inflammation, and

Table 2 Differences in levels of biomarkers between chronic kidney disease 1-2 and chronic kidney 3-4

Markers (plasm or urine)	CKD 1-2 (*n* = 49)	CKD 3-4 (*n* = 31)	t/Z	*P* value
Plasm heparan sulfate (pg/mL)	410.37 (174.13-608.45)	853.59 (646.14-1032.49)	4.763	< 0.001[c]
Plasm endocan (pg/mL)	81.78 (48.23-120.75)	131.33 (60.02-199.01)	2.115	0.034[a]
Plasm Ox-LDL (ng/mL)	2.65 (1.58-3.67)	3.58 (1.94-5.03)	1.760	0.078
Plasm E-selectin (pg/mL)	396.33 (274.44-548.49)	558.75 (488.06-733.80)	3.672	< 0.001[c]
Plasm slCAM1 (ng/mL)	662.03 ± 32.28	991.55 ± 64.83	-4.906	< 0.001[c]
Urine L-PGDS (ng/mL)	0.10 (0.08-0.39)	0.63 (0.19-1.28)	3.580	< 0.001[c]
Plasm IL-1β (pg/mL)	33.42 (31.63-36.38)	36.60 (33.20-39.74)	2.732	0.006[b]
Plasm IL-6 (pg/mL)	12.12 (10.04-15.17)	18.16 (11.43-20.86)	2.899	0.004[b]
Urine IL-1β (pg/mL)	7.16 (5.46-12.16)	12.00 (7.84-18.24)	2.928	0.003[b]
Urine IL-6 (pg/mL)	2.18 (01.39-3.83)	7.42 (3.57-14.16)	4.370	< 0.001[c]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
CKD: chronic kidney disease; Ox-LDL: Oxidized low density lipoprotein; slCAM1: Soluble intercellular adhesion molecule-1; L-PGDS: Lipocalin-type prostaglandin D synthase; IL: Interleukin.

Table 3 Chronic kidney disease multivariate logistic regression analysis of staging and markers of endothelial injury and inflammation levels

Makers (plasm or urine)	B	Wald	Exp(B)	95%CI	Sig
Plasm heparan sulfate (pg/mL)	0.004	5.845	1.004	1.001-1.008	0.016[a]
Plasm endocan (pg/mL)	< 0.001	< 0.001	1.000	0.987-1.014	0.987
Plasm Ox-LDL (ng/mL)	-0.214	0.606	0.807	0.471-1.384	0.436
Plasm E-selectin (pg/mL)	0.002	0.644	1.002	0.997-1.007	0.422
Plasm slCAM1 (ng/mL)	2.178	6.952	8.831	1.749-44.588	0.008[b]
Plasm L-PGDS (ng/mL)	0.033	0.002	1.034	0.195-5.490	0.969
Plasm IL-1β (pg/mL)	-0.046	0.952	0.955	0.870-1.048	0.329
Plasm IL-6 (pg/mL)	-0.041	0.421	0.960	0.848-1.087	0.516
Urine IL-1β (pg/mL)	-0.010	0.016	0.990	0.847-1.157	0.901
Urine IL-6 (pg/mL)	0.046	0.126	1.047	0.813-1.348	0.723

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
CKD: Chronic kidney disease; Ox-LDL: Oxidized low density lipoprotein; slCAM1: Soluble intercellular adhesion molecule-1; L-PGDS: Lipocalin-type prostaglandin D synthase; IL: Interleukin; B: Partial regression coefficient; Wald: χ^2 value; Exp(B): Odds ratio; CI: Confidence interval; Sig: Significance.

glomerular endothelial injury markers.

Markers of glycocalyx damage

Plasma heparan sulfate is currently used to detect systemic endothelial glycocalyx damage[13]. Glycosaminoglycans, including heparan sulfate, chondroitin sulfate, and non-sulfated hyaluronan, are the main negatively charged polysaccharides that constitute the glycocalyx[14]. One of the earliest changes after endothelial cell activation is an alteration in the glycocalyx composition[9]. The properties of the endothelial glycocalyx are significantly altered under inflammatory conditions[15], which are favorable for rolling and tight adhesion of leukocytes[9].

Plasma adhesion molecules

Plasma slCAM1 and soluble E-selectin can be used as markers of endothelial adhesion molecules[13].

Cell adhesion molecules mediate the interaction between leukocytes and platelets with endothelial cells. This interaction occurs in all microvasculatures under certain physiological and pathological conditions, such as hemostasis and inflammation. Adhesion molecules regulate the rolling of leukocytes on the endothelium, and leukocyte recruitment processes regulated by adhesion molecules often lead to endothelial cell dysfunction[9]. Selectin is a lectin-like molecule that can be divided into various types according to its differential expression in different blood cells. L-selectin is expressed in leukocytes, whereas E-selectin and P-selectin are expressed in endothelial cells. P-selectin is also expressed in platelets[16]. Soluble circulating selectins can be detected in plasma, and selectin levels are elevated in the serum of patients and animals with inflammatory diseases[17]. Cytokines, bacterial toxins, and oxidants can promote the synthesis of E-selectin and P-selectin in endothelial cells[18]. The interaction between leukocytes and endothelial cells is achieved through selectin and cell adhesion molecules, and this effect may be related to shedding of these adhesion molecules[9]. Endothelially released E-selectin is a biomarker for endothelial activation[19,20]. E-selectin expression is restricted to endothelial cells and induced by inflammation. Soluble E-selectin reflects the late stage of endothelial cell activation[21].

Endothelial inflammation

The markers used to evaluate endothelial inflammation include plasma cytokines (such as IL-6 and IL-1 β), plasma endothelial cell-specific molecules (endocan), and Ox-LDL, which along with its active lipid components induces inflammation[9].

Recent data have confirmed the importance of endocan in inflammation, vascular proliferation, and neogenesis[22]. In human umbilical vein endothelial cells under intermittent hypoxia, endocan promotes the expression of the cell adhesion molecule slCAM1. This plays a key role in enhancing adhesion between monocytes and endothelial cells, potentially leading to endothelial cell dysfunction [23]. In addition, endocan elicits severe vascular inflammatory responses in cellular and animal experimental models of sepsis[24].

Urate crystals can activate the NLRP3 inflammasome in different kidney cells and trigger the secretion of pro-inflammatory cytokines. NLRP3 activation can lead to glomerular and tubulointerstitial damage and renal fibrosis. After inflammasome activation, the secretion of IL-1β increases, leading to severe renal damage. IL-1β induces foaming of renal vascular endothelial cells, aggregation of inflammatory cells in the vessel wall, smooth muscle cell proliferation, and vasodilation. In contrast, IL-1β recruits neutrophils and releases additional proinflammatory cytokines such as IL-6, which aggravates the inflammatory response[25,26].

Urine L-PGDS

L-PGDS synthesizes prostaglandin D2, a secreted protein of the lipocalin superfamily. It is synthesized in the choroid plexus or pia mater of the brain and is stably secreted into circulating blood by the cerebrospinal fluid. The chemical properties of L-PGDS are related to serum similar to those of albumin and its molecular weight is much smaller than that of serum albumin[27,28]. Therefore, L-PGDS is more likely to pass through the glomerular capillary wall than serum albumin and reflects early glomerular capillary damage than albumin[29].

The plasma levels of heparan sulfate, endocan, E-selectin, and slCAM1 in patients with CKD 3-4 were higher than those with CKD 1-2, indicating that vascular endothelial injury in patients at an advanced stage was more serious than those in the early stages of CKD. Urinary L-PGDS levels were also significantly different between the two groups, indicating that renal endothelial injury was more severe in the middle-late stages than in the early stages. The levels of plasma IL-1β, plasma IL-6, urinary IL-1β, and urinary IL-6 in patients with CKD 3-4 were higher than those with CKD 1-2, indicating that the level of inflammation in patients with advanced disease was more severe compared to those in the earlier stages of disease.

Endothelial injury and inflammation are the critical causes of many diseases, including CKD, cardiovascular disease, and diabetes. As mentioned above, as CKD progresses, injury to the endothelium becomes more severe under the persistent impact of factors such as uric acid, which is in accordance with the current literature. Excessive uric acid may injure the vascular endothelium, including the renal endothelium. In patients with HN, uric acid may directly impair the endothelium or initiate inflammation, both contributing to CKD progression.

This study was based on baseline data from a randomized double-blind controlled trial. However, this study had some limitations. First, patients with CKD 5 were excluded owing to the design of our study; these patients should be involved in the future studies. Second, larger samples are needed to analyze the differences between CKD 1, CKD 2, CKD 3, and CKD 4 (also CKD 5). Third, oxidative stress levels are also related to endothelial injury, and there may be a need to add markers of oxidative stress and evaluate the differences among patients at CKD stages 1-4.

CONCLUSION

Vascular endothelial injury and inflammatory state of patients with HN at CKD stages 3-4 were higher compared to those at stages 1-2. Plasma heparin sulfate and slCAM1 levels are synergistic risk factors for CKD staging in HN.

ARTICLE HIGHLIGHTS

Research background

Chronic kidney disease (CKD) has been threatening people's lives. Without any intervention, CKD can progress to end-stage renal disease. Previously, researchers focus more on diabetic nephropathy, however there are no reports about hyperuricemic nephropathy (HN) patients. It is important to figure out the pathological difference between patients with HN in early stage and middle and late stage with CKD.

Research motivation

As reported, there are currently lots of classic and new biomarkers of endothelial injury and inflammation which can be tested in the blood and urine samples of CKD patients.

Research objectives

Through testing biomarkers, we have a clear idea of the difference in endothelial injury and inflammation between patients with HN in CKD 1-2 and CKD 3-4.

Research methods

This study is a baseline data of randomized double-blinded controlled trial. During patients' first care visit, general information and urine and plasma samples were collected. Enzyme-linked immunosorbnent assay were used to detect endothelial injury and inflammation biomarkers including plasma heparan sulfate, plasma endocan, plasma oxidized low-density lipoprotein (Ox-LDL), plasma E-selectin, plasma soluble intercellular adhesion molecule-1 (slCAM1), urinary Lipocalin-type prostaglandin D synthase (L-PGDS), plasma interleukin (IL)-1β, plasma IL-6, urinary IL-1β, and urinary IL-6 levels.

Research results

Comparison between patients with HN at CKD 1-2 and those with HN at CKD 3-4 showed that age and disease course were significant factors ($P < 0.001$ and $P < 0.010$, respectively). There were no statistical differences in sex, heart rate, body mass index, and systolic and diastolic blood pressures. The incidence of hypertension was also significant ($P = 0.03$). Plasma levels of heparin sulfate ($P < 0.001$), endocan ($P = 0.034$), E-selectin ($P < 0.001$), slCAM1 ($P < 0.001$), IL-1β ($P = 0.006$), and IL-6 ($P = 0.004$) and the urine levels of L-PGDS ($P < 0.001$), IL-1β ($P = 0.003$), and IL-6 ($P < 0.001$) were high in patients with HN at CKD 3-4 than in those with HN at CKD 1-2. The difference in plasma Ox-LDL levels was not significant ($P = 0.078$).

Research conclusions

Vascular endothelial injury and inflammatory state of patients with HN in CKD 3-4 were higher than those of patients in CKD 1-2. Plasma heparin sulfate and plasma slCAM1 levels are synergistic risk factors for CKD staging in HN.

Research perspectives

We now concluded that levels of biomarkers endothelial injury and inflammation are significantly different between patients with HN in CKD 1-2 and CKD 3-4. In the future assessment, heathy subjects, and HN patients in CKD 5 should also be involved.

FOOTNOTES

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