Original Article

The Serum YKL-40 Level is Associated with Vascular Injury and Predicts Proteinuria in Nephrotic Syndrome Patients

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***Aim*: Nephrotic syndrome (NS) is associated with an increased rate of cardiovascular events. The YKL-40 level is associated with atherosclerosis, endothelial dysfunction and proteinuria in renal and non-renal populations. The aim of this study was to investigate the relationships between the YKL-40 level and both vascular injury and proteinuria in NS patients.**

***Methods*: Sixty-nine NS patients and 20 healthy subjects were enrolled in the present study. The endothelial function was assessed according to the flow mediated dilatation (FMD) and the degree of arterial stiffness was determined based on the pulse wave velocity (PWV). The serum YKL-40 levels were measured using ELISA.**

***Results*: The YKL-40 levels and PWV values were higher and the FMD values were lower in the NS patients than in the healthy controls. However, the CA-IMT and LVEF levels were not statistically different between the two groups. The patients were divided into three groups with respect to the extent of proteinuria: the normoproteinuria group (n:18), non-nephrotic proteinuria group (n:33) and nephrotic proteinuria group (n:18). Consequently, the YKL-40 levels and PWV values were significantly increased and the FMD values were decreased in the nephrotic proteinuria group compared to that observed in both the non-nephrotic proteinuria and normoproteinuria groups. Furthermore, the YKL-40 level correlated with the FMD and PWV values in the NS patients. In addition, proteinuria correlated with the YKL-40, FMD, PWV, eGFR and fasting LDL cholesterol values in this patient group. Multivariate linear regression analyses showed that the YKL-40 and eGFR values were effective in predicting proteinuria in the NS patients.**

***Conclusions*: The serum YKL-40 level is associated with endothelial dysfunction and increased arterial stiffness in NS patients and may be an indicator of the level of proteinuria in this patient population.**

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Key words: Nephrotic syndrome, YKL-40, Vascular injury, Proteinuria

Introduction

Nephrotic syndrome (NS) is characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. This syndrome is known to be associated with endothelial dysfunction, as well as increased arterial stiffness and progressive atherosclerosis, thus resulting in an increased rate of cardiovascular events[1-3]. It has also been argued that increased oxidative stress, hypervolemia, hyperlipidemia and proteinuria intensify the vascular injury observed in patients with the syndrome[2, 3].

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YKL-40 (also named chitinase-3-like-1 and human cartilage glycoprotein-39) is an emerging novel biomarker of vascular injury. YKL-40 is a member of the family of mammalian chitinase-like proteins and a highly conserved protein[4]. It is usually generated by neutrophils, macrophages and cancerous cells and has been shown to play a role in cell proliferation and differentiation, angiogenesis, inflammation and extracellular matrix remodeling[5]. Recent studies have shown that a high YKL-40 level is associated with an increased disease activity and poor prognosis in patients with cancer, ischemic cardiovascular disease, rheumatoid arthritis, diabetes, asthma, inflammatory bowel disease and hepatic fibrosis[6-10]. Moreover, a strong relationship between the YKL-40 level and endothelial dysfunction has recently been demonstrated, particularly in diabetic populations and individuals with a history of renal transplantation[11-13]. However, the relationships between the YKL-40 level and proteinuria or vascular injury remain unknown in patients with NS.

We therefore aimed to investigate the effects of the serum YKL-40 level on the degree of proteinuria and various parameters of vascular injury (arterial stiffness and flow-mediated dilatation) in a group of patients with NS. To the best of our knowledge, this is the first such report to be published in the current literature.

Subjects and Methods

Study Population

We conducted a cross-sectional study of NS between April 2013 and December 2013. The patient population was derived from a single academic medical center and state hospital, the Erciyes University School of Medicine in Kayseri and Kahramanmaras Education and Training Hospital in Kahramanmaras, Turkey. The study protocol was approved by the University Ethics Committee, and all participants provided their written informed consent prior to participation. The following subjects were excluded from the analysis: patients under 17 or above 70 years of age and those with a history of myocardial infarction, diabetes, thrombotic events, inflammatory disease (such as rheumatoid arthritis), local or systemic infection and/or stroke. Finally, a total of 69 patients and 20 healthy subjects were enrolled in this study.

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In patients with glomerulonephritis, the clinical course was classified as follows: normoproteinuria (24-h proteinuria <0.3 g/day), non-nephrotic proteinuria (24-h proteinuria ≥ 0.3 g/ and <3.0 g/day) or nephrotic proteinuria (24-h proteinuria ≥ 3.0 g/ day).

Biochemical Measurements

Blood samples were collected from the vein of the antecubital fossa, with the subject in a seated position after 20 minutes of rest following 12 hours of fasting. The glucose and creatinine levels and lipid profiles were determined using standard methods. The high-sensitivity C-reactive protein (CRP) level was measured using a BN2 model nephelometer (Dade-Behring, Germany). Tri-potassium EDTA-based anticoagulated blood samples were drawn to measure the complete blood count (Sysmex K-1000 autoanalyzer, Block Scientific, USA) within 30 minutes of sampling. Plasma samples were collected and handled according to standard operating procedures.

YKL-40 Measurement

The YKL-40 concentration in the EDTA plasma was determined in duplicate using samples stored at minus 80℃ according to the commercial quantitative 'sandwich' enzyme-linked immunosorbent assay technique (Omnikine, Assay Biotech). The kit allows for the detection and quantification of the endogenous levels of YKL-40 proteins within a range of 32-2,000 pg/mL.

Echocardiography

All participants were examined at inclusion using a Vivid 7 instrument (GE Medical Systems, Milwaukee, WI, USA) with a 2.5-MHz transducer and harmonic imaging. The echocardiography procedures were performed in the echocardiography laboratory at baseline by a cardiology specialist according to the recommendations of the American Society of Echocardiography. The echocardiographic examinations were conducted in the left lateral decubitus position using the parasternal long-short axis and apical views. At least three consecutive beats in sinus rhythm were recorded, and the average values were taken. The left ventricular end-diastolic and end-systolic dimensions (LVEDD and LVESD) and interventricular septal and posterior wall thicknesses (IVSd and LPWd) were measured on M-mode images of the left ventricle generated in the long-axis view with the cursor at the tip of the mitral valve leaflet. The LV ejection fraction was calculated using the formula: LVEF % = (LVEDV − LVESV)/LVEDV × 100.

Endothelial Function Test

Endothelial dysfunction was assessed according

to the method described by Celermajer *et al.*[14]. The measurements were obtained by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA, USA) with a 12-Mhz probe. The subject remained at rest in the supine position for at least 15 minutes before the start of the examination. Each subject's right arm was comfortably immobilized in the extended position to allow for consistent recording of the brachial artery 2-4 cm above the antecubital fossa. Three adjacent measurements of the end-diastolic brachial artery diameter were acquired from single 2D frames. All ultrasound images were recorded on a Super Video Home System (SVHS) videotape for the subsequent blinded analysis. The maximum flow-mediated vasodilation (FMD) diameter was calculated as the average of the three consecutive maximum diameter measurements obtained under conditions of hyperemia and nitroglycerin administration, respectively. The FMD was then calculated as the percentage change in diameter compared with the baseline resting diameter.

Pulse Wave Velocity (PWV)

The vascular studies were performed in a quiet, temperature-controlled room with the subject resting in the supine position. The systolic and diastolic blood pressures were each measured in duplicate using a semi-automated, non-invasive oscillometric sphygmomanometer following a 10-minute rest period. A pulse wave analysis of the carotid and femoral arteries was performed using a pulse wave velocity (PWV) machine (Micro Medical Pulse Trace, Rochester, UK) in accordance with the manufacturer's recommendations. Briefly, the transducers were positioned over the carotid and femoral arteries, always on the right side of the body. The PWV was automatically calculated by measuring the time for the pulse wave to travel between the carotid and femoral arteries. All measurements were obtained over 15 heart beats by a single operator blinded to the patient's group assignment.

Statistical Analysis

Continuous variables were tested for a normal distribution using the Kolmogorov-Smirnov test, and the results are presented as the mean value ± SD for parametric variables (normal data distribution) or median (minimum, maximum) for non-parametric variables (not a normal data distribution). The statistical analysis of differences in non-parametric variables between the three groups was performed using the Kruskal -Wallis test and Mann-Whitney *U* test with the Bonferroni correction. Pearson correlation coefficients were calculated to examine the degree of association between the variables. Variables for which the unadjusted univariate p value was <0.10 in a linear regression analysis were included in the multivariate analysis. Variables were considered to be significant at a p value of <0.10 in the univariate analysis and subsequently included in the model. We reduced the model by using backward elimination at a $p<0.10$ stringency level in the multivariate linear regression analysis. A p value of <0.05 was considered to be significant, and the confidence interval (CI) was set to 95%. All statistical analyses were performed using the SPSS version 15 software program (SPSS, Inc., Chicago, IL, USA).

Results

The demographic, clinical and laboratory characteristics of the study population are shown in **Table 1**. There were significant differences between the two groups in terms of the serum lipid parameters and uric acid, albumin, proteinuria, hs-CRP, eGFR, FMD and PWV values. Additionally, the YKL-40 levels were higher than in NS patients than in the healthy controls (95 (33-189) vs. 43 (29-56) $p<0.001$). However, the CA-IMT and LVEF levels were not statistically different between the two groups (**Table 1**).

The patients were divided into three groups based on the level of proteinuria: the normoproteinuria group (n:18), non-nephrotic proteinuria group (n:33) and nephrotic proteinuria group (n:18) (**Table 2**). Consequently, the uric acid, YKL-40, FMD and PWV values were significantly different between the three groups, whereas the hs-CRP levels were not. In addition, the uric acid and PWV levels were significantly lower and the FMD values were significantly higher in the normoproteinuria group than in either the non-nephrotic proteinuria or nephrotic proteinuria group. However there were no significant differences between the non-nephrotic proteinuria group and the nephrotic proteinuria group in terms of the uric acid, PWV and FMD values. Meanwhile, the YKL-40 levels were significantly increased in the nephrotic proteinuria group compared to that observed in both the non-nephrotic proteinuria and normoproteinuria groups.

The univariate correlations among the selected markers in the patients with NS are listed in **Table 3**. In the NS group, proteinuria correlated with the YKL-40 (r: 0.62, $p<0.001$), PWV (r: 0.52, $p<0.001$), fasting LDL cholesterol (r: 0.33, $p=0.021$) values and inversely correlated with the FMD (r: −0.39, $p=0.001$) and eGFR (r: −0.67, $p<0.001$) values (**Fig. 1**), but not the hs-CRP level (r: 0.23, $p=0.059$) or age (r:

Table 1. Demographic data, biochemical parameters, causes of nephrotic syndrome (NS) and the cardiovascular function in the study patients

Parameters	Healthy Subjects ($n=20$)	NS group ($n=69$)	p
Age (years)	38.3 ± 10.0	41.9 ± 12.5	0.23
Gender (F/M)	9/11	35/34	0.65
Hemoglobin (g/dL)	13.1 ± 0.7	13.5 ± 2.1	0.44
White blood cell count (10^3/uL)	6.6 ± 1.4	7.6 ± 2.9	0.13
Weight (kg)	68.2 ± 9.3	70.4 ± 11.5	0.15
Height (cm)	165 ± 12	167 ± 16	0.23
Smoking (patients)	5	13	0.42
Plasma fasting glucose (mg/dL)	87.3 ± 14.1	96.7 ± 25.5	0.12
Fasting total cholesterol (mg/dL)	169 ± 30	210 ± 49	0.001
Fasting LDL cholesterol (mg/dL)	112 ± 19	128 ± 33	0.039
Fasting triglyceride (mg/dL)	121 (51-201)	161 (50-796)	< 0.001
Uric acid (mg/dL)	3.8 ± 1.0	6.5 ± 1.8	< 0.001
Albumin (g/L)	4.01 ± 0.59	3.56 ± 0.54	< 0.001
Proteinuria (mg/day)	130 (70-330)	600 (100-11000)	< 0.001
hs-CRP (mg/L)	2.3 (1.0-4.1)	3.6 (1.4-12.3)	< 0.001
YKL-40 (ng/mL)	43 (29-56)	95 (33-189)	< 0.001
eGFR (mL/min/1.73 m^2)	105 (93-146)	78 (35-134)	< 0.001
FMD (%)	7.56 ± 1.4	6.64 ± 1.0	0.002
LVEF (%)	64.3 ± 4.9	62.7 ± 5.5	0.24
PWV (m/sec)	6.0 ± 0.8	7.47 ± 1.0	< 0.001
Cause of glomerulonephritis			
Lupus Nephritis		9	
Membranous GN		27	
Membranoproliferative GN		13	
Mesangial GN		2	
Minimal Change Disease		6	
IgA nephropathy		5	
FSGS		7	
Using of Immunosuppressive Drugs			
None		7	
Only steroid		15	
Steroid + Calcineurin inhibitors		12	
Steroid + Cyclophosphamide		10	
Steroid + Azathioprine		17	
Steroid + Mycophenolatemofetil		8	

NS: nephrotic syndrome, eGFR: estimated glomerular filtration rate, Hs-CRP: high-sensitivity C-reactive protein, YKL-40 (chitinase-3-like-1 and human cartilage glycoprotein-39), LVEF: leftventricular ejection fraction, FMD: flow-mediated vasodilation, PWV: pulse wave velocity, FSGS: focal segmental glomerulosclerosis

0.18, $p=0.09$). Additionally, the YKL-40 levels correlated with the PWV values (r: 0.29, p: 0.017) and inversely correlated with the FMD (r: −0.25, $p=0.04$) and eGFR (r: −0.40, p: 0.01) values, but not age (r: 0.10, $p=0.39$) or the hs-CRP (r: 0.12, $p=0.28$), uric acid (r: 0.09, $p=0.46$), fasting LDL cholesterol (r: 0.19, $p=0.12$) and CA-IMT (r: 0.17, $p=0.18$) values.

The independence of multiple correlations was analyzed using multivariate linear regression analyses. The original model included age, YKL-40, eGFR, PWV and FMD. In the NS subjects, proteinuria was independently predicted by the YKL-40 (β: −0.39, $p<0.001$) and eGFR (β: −0.40, $p<0.001$) values, but not age, PWV or FMD (**Table 4**). Furthermore, in the NS subjects, the PWV was independently predicted by the YKL-40 (β: 0.080, p: 0.017), hs-CRP (β:

Table 2. Comparison of clinical and cardiovascular parameters between the three groups

Parameters	Normoproteinuria Proteinuria < 0.3 n = 18	Non-nephrotic proteinuria 0.3 ≤ Proteinuria < 3.0 n = 33	Nephrotic proteinuria Proteinuria ≥ 3.0 n = 18	p	p1	p2	p3
Uric acid (mg/dL)	5.2 ± 1.5	6.8 ± 1.9	7.4 ± 1.4	0.001	0.007	0.001	0.370
hs- CRP (mg/L)	3.3 (2.4-7.7)	3.5 (1.4-12.3)	4.7 (2.1-8.4)	0.160			
YKL-40 (ng/mL)	64 (33-112)	95 (54-137)	130 (74-189)	< 0.001	< 0.001	< 0.001	0.001
FMD (%)	7.2 ± 1.0	6.5 ± 1.0	6.2 ± 0.7	0.010	0.049	0.009	0.530
PWV (m/sec)	6.64 ± 0.64	7.54 ± 1.0	8.1 ± 0.76	< 0.001	0.005	< 0.001	0.080

YKL-40 (chitinase-3-like-1 and human cartilage glycoprotein-39), FMD: flow-mediated vasodilation
p = between all groups
p1 = compared with the normoproteinuria and non-nephrotic proteinuria groups
p2 = compared with the normoproteinuria and nephrotic proteinuria groups
p3 = compared with the non-nephrotic proteinuria and nephrotic proteinuria groups

Table 3. Univariate correlations between proteinuria and selected markers in the NS group

Parameters	Proteinuria (mg/24 h)	
	r	p
YKL-40 (ng/mL)	0.62	< 0.001
hs-CRP (mg/L)	0.23	0.059
FMD (%)	− 0.39	0.001
PWV (m/sec)	0.52	< 0.001
Age (years)	0.18	0.09
eGFR (mL/min/1.73 m^2)	− 0.67	< 0.001
Fasting LDL cholesterol (mg/dL)	0.33	0.021

eGFR: estimated glomerular filtration rate, Hs-CRP: high-sensitivity C-reactive protein,YKL-40 (chitinase-3-like-1 and human cartilage glycoprotein-39), FMD: flow-mediated vasodilation, PWV: pulse wave velocity

0.125, p: 0.039) and eGFR (β: 0.013, p: 0.002) values (**Table 5**).

Discussion

In this cross-sectional study, we compared NS patients with a healthy population and found relationships between the YKL-40 level, vascular injury parameters and proteinuria in the NS patients. In addition, we demonstrated for the first time that the YKL-40 level is a predictor of proteinuria in such patients.

We emphasize three basic conclusions based on the results of this study. First, vascular injury may be present in patients with nephrotic syndrome. In a study conducted by Hooman *et al.*, the degree of carotid atherosclerosis was increased in patients with NS compared with that observed in healthy subjects[15]. In contrast, no such differences were noted in another study[16]. Meanwhile, Sharma *et al.* suggested that the endothelial function is disrupted in pediatric NS patients[17], in association with the disease activity, and Rahul *et al.* reported that the brachial FMD values are lower pediatric patients than in healthy subjects[16]. In keeping with the findings of these studies, we found that the brachial FMD values were lower in the adult NS patients than in the healthy subjects. We also previously demonstrated that the degree of arterial stiffness is higher in adult patients with NS than in controls[2]. However, the mechanisms underlying the onset of vascular injury in patients with NS are not completely understood. A widely accepted theory involves the effects of increased oxidative stress in patients with NS[18]. In addition, increased oxidative stress has been shown to be associated with glomerular injury, which affects the clinical course and prognosis of NS patients. Hence, impaired glomerular and tubular antioxidative defense mechanisms may be linked to vascular injury in this population. Additionally, hypervolemia, proteinuria and high levels of paraoxonase activity, LDL and homocysteine, which have been reported in patients with NS, may contribute to the increased risk

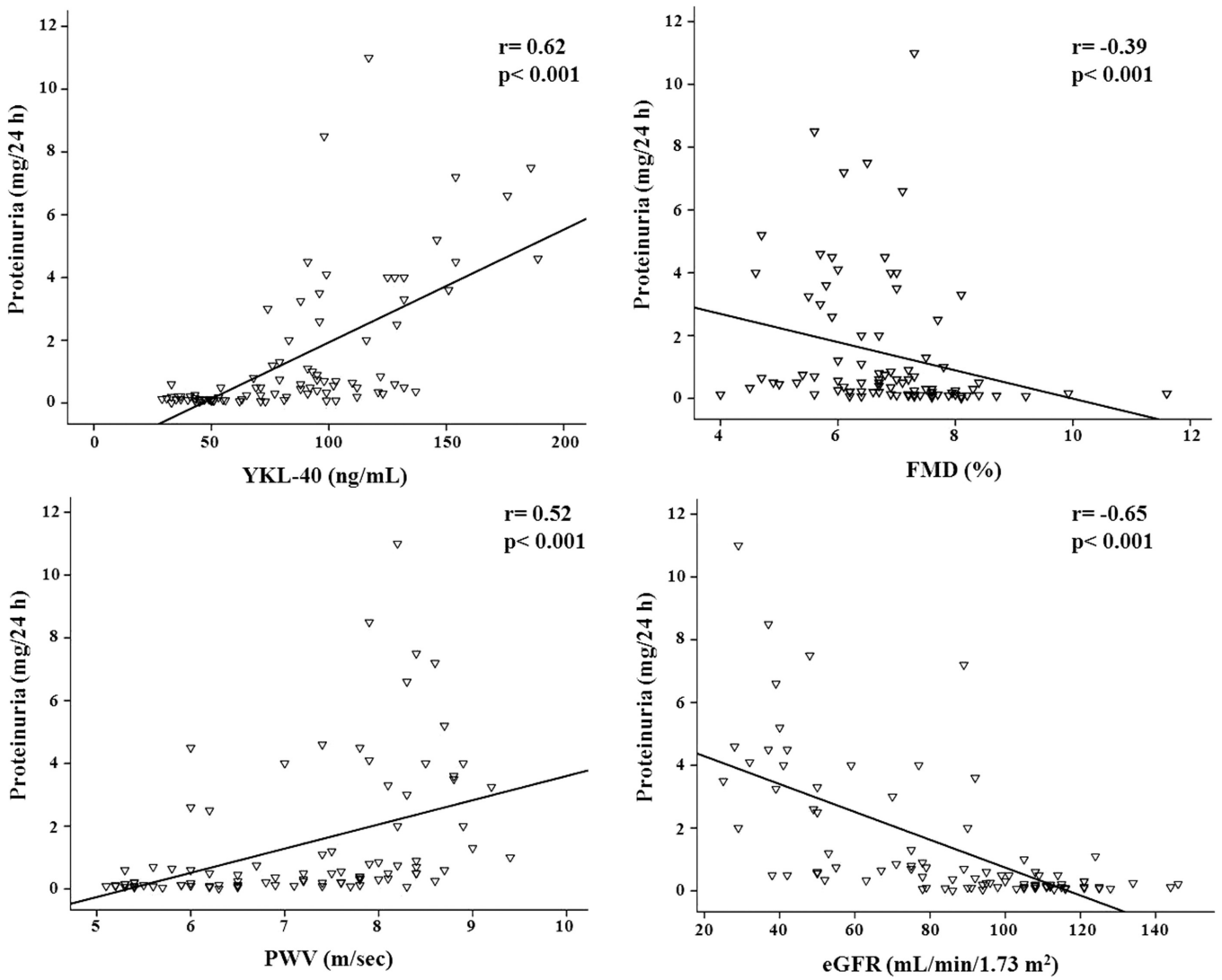

Fig. 1. Correlation between proteinuria and the YKL-40, PWV, FMD and eGFR values.

of vascular injury noted in this population[2, 18]. However, further studies are needed to clarify this issue.

Second, the YKL-40 level is associated with vascular injury parameters. In this study, a negative relationship was found between the YKL-40 level and FMD. However, there is a limited number of studies on this matter, and one report by Diao *et al.* found no correlations between the YKL-40 level and FMD[19]. In addition, we found a positive correlation between the YKL-40 and PWV in this study. Notably, Ma *et al.* reported a positive correlation between the YKL-40 level and arterial stiffness in hypertensive patients[20], and Turkyılmaz *et al.* reported the YKL-40 level to be associated with the PWV in patients with rheumatoid arthritis[21]. YKL-40 is a 40-kDa heparin- and chitin-binding glycoprotein that is also secreted by activated macrophages and neutrophils in different tissues under conditions of inflammation, as well as vascular smooth muscle cells, cancer cells and arthritic chondrocytes. Moreover, YKL-40 also plays a role as an adhesion and migration factor for vascular cells[22, 23], and it has been documented that the YKL-40 levels are elevated in patients with inflammatory diseases[24]. The participation of YKL-40 in the pathogenesis of vascular incidents and inflammation suggests that this marker may have a role in the development of endothelial dysfunction and atherosclerosis. *In vitro* studies have shown that YKL-40, following activation against exogenous stimuli, induces atheroma plaque formation by stimulating vascular endothelial cells towards chemotaxis, migration and proliferation[25-27]. Furthermore, YKL-40 has been reported to be a contributing

Table 4. Multiple regression model of variables predicting proteinuria in the GN group

Parameters	Proteinuria (mg/24 h)	
	Beta	*p*
Age (years)	−0.09	0.23
YKL-40 (ng/mL)	0.39	<0.001
eGFR (mL/min/1.73 m^2)	−0.40	<0.001
PWV (m/sec)	−0.11	0.08
FMD	−0.07	0.20

eGFR: estimated glomerular filtration rate, Hs-CRP: high-sensitivity C-reactive protein,YKL-40 (chitinase-3-like-1 and human cartilage glycoprotein-39), FMD: flow-mediated vasodilation, PWV: pulse wave velocity
Bold text indicates significant values ($p<0.05$). Adjusted $r^2=0.49$ for proteinuria.

Table 5. Multiple regression model of variables predicting vascular injury in the GN group

	PWV (m/sec)	
	Beta	*p*
YKL-40 (ng/mL)	0.080	0.017
hs-CRP (mg/L)	0.125	0.039
Uric acid (mg/dL)	0.105	0.097
SBP (mmHg)	0.171	0.090
FMD		
eGFR (mL/min/1.73 m^2)	0.013	0.002

eGFR: estimated glomerular filtration rate, Hs-CRP: high-sensitivity C-reactive protein,YKL-40 (chitinase-3-like-1 and human cartilage glycoprotein-39), FMD: flow-mediated vasodilation, PWV: pulse wave velocity, SBP: systolic blood pressure
Bold text indicates significant values ($p<0.05$). Adjusted $r^2=0.34$ for PWV and $r^2=0.15$ for FMD.

factor to the onset of arterial wall stiffness, likely via a mechanism possibly related to arterial endothelial dysfunction.

Third, the serum YKL-40 level is an indicator of proteinuria in NS patients. Proteinuria is the most significant characteristic of NS and a consequence of glomerular injury. Proteinuria is also associated with cardiovascular morbidity and mortality in both diabetic and non-diabetic patient populations[28, 29]. Although the potential mechanisms linking proteinuria and cardiovascular disease remain unclear, it has been proposed that an increased level of proteinuria is a marker of vascular damage in the kidneys, which subsequently reflects the extent of systemic endothelial dysfunction[30]. Recently, many authors have suggested that there is a relationship between the YKL-40 level and proteinuria; however, the underlying mechanism has not been clearly identified[12, 13]. Evidence suggests that proteinuria does not solely reflect renal pathology, but is also associated with a systemic increase in vascular permeability. The mechanism accounting for this increase in vascular permeability in proteinuric subjects may be associated with an abnormal endothelial function[31]. This finding is in accordance with the results of previous studies showing that both micro- and macroalbuminuria are accompanied by increased levels of a variety of markers of endothelial dysfunction[32]. Such ongoing endothelial dysfunction promotes further vascular permeability and proteinuria. The findings of a relationship between the YKL-40 level and both FMD and proteinuria in the current study support this mechanism. However, further studies should be performed to fully clarify this issue.

This study is associated with several limitations. For example, the design was cross-sectional and the serum YKL-40 levels and vascular injury markers were measured only once. Another possible limitation is the small sample size.

In conclusion, the serum YKL-40 level is associated with endothelial dysfunction and may be an indicator of proteinuria in patients with NS.

Conflict of Interest

None.

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