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The Association of Syndecan-1, Hypercoagulable State and Thrombosis and in Patients With Nephrotic Syndrome

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Abstract

The aim of this study is to investigate whether Syndecan-1 (SDC-1), an indicator of endothelial glycocalyx injury, would increase the risk of hypercoagulable state and thrombosis in patients with nephrotic syndrome (NS). The prospective study was conducted among patients undergoing renal biopsy in the Department of Nephrology in our hospital from May to September 2018. We enrolled in patients with NS as the experimental group and patients with normal serum creatinine and proteinuria less than 1 g as the control group. Patients' characteristics including age, sex, laboratory test results and blood samples were collected for each patient. The blood samples were taken before the renal biopsy. The samples were immediately processed and frozen at –80°C for later measurement of Syndecan-1. One hundred and thirty-six patients were enrolled in the study. Patients with NS and hypercoagulability had a higher level of SDC-1 compared with control group. Patients with membranous nephropathy occupied the highest SDC-1 level ($P = 0.012$). Logistic regression showed that highly increased level of SDC-1 (>53.18 ng/ml) was an independent predicator for predicting hypercoagulable state. The elevated level of SDC-1 indicated that endothelial injury, combined with its role of accelerating hypercoagulable state, might be considered of vital importance in the pathophysiological progress of thrombosis formation in patients with NS.

Keywords

nephrotic syndrome, thrombosis, hypercoagulation, Syndecan-1, endothelial injury

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Background

Thrombosis is considered as one of the most life-threatening complications in patients with nephrotic syndrome (NS). In adults, the prevalence of venous thromboembolism was eight-fold greater in patients with NS than in the general population.[1] The annual incidences of venous thrombus embolism (VTE) and arterial thrombus embolism (ATE) were 1.02% and 1.48%.[1] In the first 6 months of following up, it rose to 9.85% and 5.52%. Once thrombotic events occurred, it would aggravate proteinuria, deteriorate renal function and worsen the outcome of patients. The annual mortality of thrombotic events was about 10%.[2]

Virchow's classical theory about thrombosis was the combination of hypercoagulability, vascular endothelial injury and reduced blood flow velocity. Any single factor among Virchow's triad was not sufficient to cause thrombosis. Previous studies focused mainly on hypercoagulability and increased blood viscosity.[3,4] The decreased serum albumin, increased coagulation factor VIII, D-dimer and fibrinogen have been considered as important markers of hypercoagulation.[5,6] However, the level of albumin is greatly affected by nutritional level, liver function, infection and so on. D-dimer is also an acute-phase reactant, which may increase during inflammation. The role of endothelial integrity hasn't been fully discussed in

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most studies, which also plays an important part in thrombosis event. Syndecan-1 (SDC-1), a major component of the endothelial glycocalyx, maintains vascular barrier function and might be released into the blood due to endothelial injury.[7] It has been reported that there was an increased level of SDC-1 in patients with NS.[8] However, its possible role in thrombotic incidences remains unknown. Our study will investigate SDC-1 and its correlation with hypercoagulability and thrombosis in patients with NS.

Methods

Patients

From May to September 2018, this prospective study was conducted among patients undergoing renal biopsy in the Department of Nephrology in Zhongshan Hospital. We enrolled in patients with NS as an experimental group and patients with normal serum creatinine and proteinuria less than 1 g as a control group. Exclusion criteria included age less than 18 years, previous kidney transplantation, end-stage renal disease, severe blood coagulation dysfunction, isolated kidney, multiple organ dysfunction and other contraindications of renal biopsy. All procedures and the use of laboratory examination results were performed according to national ethical guidelines and approved by the Standing Committee for Clinical Studies of Zhongshan Hospital, Fudan University, in adherence to the Declaration of Helsinki. Informed consent was obtained from patients.

Definitions

NS was defined as proteinuria (>3.5 g/d), hypoalbuminemia (less than 30 g/L) edema and severe hyperlipidemia. The diagnose of hypercoagulability was performed when patients had the partial prothrombin time (PT) 3 s shorter than normal (11-14 s), activated partial thromboplastin time (APTT) 10 s shorter than normal (35-45 s), Antithrombin III (AT-III) activity less than 0.70% and D-dimer (D-D) concentration of more than 0.5 mg/L according to the previous study.[9]

Laboratory Analysis

Blood sampling was drawn before renal biopsy. Serum albumin (Alb), platelet (PLT), platelet distribution width (PDW), blood urea nitrogen (BUN), serum creatinine (sCr), serum uric acid (UA), D-dimer, PT, APTT, AT-III, fibrinogen degradation products (FDP), total cholesterol (Tch) and triglycerides (TG) were measured using standard methods in the routine clinical laboratory. 24 h urine was collected to test the amount of 24 h urinary protein excretion. Ethylenediaminetetraacetic acid (EDTA) tubes were used to collect blood samples for each patient undergoing renal biopsy. The samples were immediately processed and frozen at −80°C for later measurement of SDC-1. SDC-1 was measured as a biomarker of endothelial glycocalyx injury using Human SDC-1 ELISA kit (CD138) and tested twice to avoid experimental error.

Table 1. Basic Characteristics of Nephrotic Syndrome (NS) Group and Control Group.

	NS group, n = 70	Control group, n = 66	*P* value
Male [n (%)]	41 (58.6%)	36 (54.5%)	0.6359[a]
Age (years)	51.96 ± 1.91	39.55 ± 1.75	<0.0001[b]
HBP [n (%)]	31 (44.3%)	23 (34.8%)	0.261[a]
DM [n (%)]	12 (17.1%)	4 (6.1%)	0.045[a]
PLT (*10^9/L)	234.43 ± 8.96	245.55 ± 7.66	0.347[b]
PDW (%)	12.66 ± 0.26	12.75 ± 0.19	0.785[b]
Alb (g/L)	23.7 ± 0.63	45.14 ± 2.98	<0.0001[b]
24h-UPRO (g/1.73 m^2)	6.41 ± 0.40	0.61 ± 0.03	<0.0001[b]
D-Dimer (g/mL)	1.25 ± 0.14	0.44 ± 0.09	<0.0001[b]
FDP (g/ml)	3.56 ± 0.47	1.17 ± 0.15	<0.0001[b]
sCr (mol/L)	122.96 ± 15.42	81.70 ± 5.11	0.013[b]
eGFR (ml/(min·1.73 m^2)	69.43 ± 4.01	89.98 ± 2.78	<0.0001[b]
sUA (mol/L)	384.97 ± 11.54	359.46 ± 10.22	0.1[b]
Tch (mmol/L)	7.31 ± 0.36	4.33 ± 0.12	<0.0001[b]
TG (mmol/L)	2.84 ± 0.20	1.52 ± 0.12	0.001[b]
SDC-1 (ng/ml)	82.83 ± 10.88	42.07 ± 4.91	0.001[b]
Hypercoagulability [n (%)]	52 (74.3%)	12 (19.6%)	<0.0001[a]
Renal biopsy diagnosis			
MN	40 (57.1%)	2 (3%)	<0.0001[a]
IgA	9 (12.9%)	34 (51.5%)	<0.0001[a]
MCD	10 (14.3%)	11 (16.7%)	0.701[a]
FSGS	3 (4.3%)	8 (12.1%)	0.094[a]
MPGN	2 (2.9%)	3 (4.5%)	0.601[a]
ATIN	1 (1.4%)	3 (4.5%)	0.282[a]

Abbreviations: HBP, high blood pressure; DM, diabetes mellitus; PLT, platelet; PDW, platelet distribution width; Alb, albumin; 24h-UPRO, 24 h urinary protein; FDP, fibrin degradation products; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; sUA, serum uric acid; Tch, total cholesterol; TG, triglyceride; SDC-1, Syndecan-1; MN, membranous nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; ATIN, acute tubular injury.
[a]Chi-square test.
[b]t test.

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics for Windows (ver. 22, IBM Corp.). Continuous variables were expressed as mean ± SD or median and interquartile range as appropriate. Categorical data were expressed as proportions. One-way ANOVA was used to compare means of more than 2 groups. Baseline statistics was conducted according to the level of SDC-1. Those variables with $P < 0.2$ or clinical significance were involved in univariate logistic analysis. Those with $P < 0.05$ were considered of statistical significance and were included in multivariate logistic regression analysis. ROC curve and logistic regression were performed to investigate the risk factors for hypercoagulability. The 2-tailed test was used, and $P < 0.05$ was considered statistically significant.

Results

Population and Baseline Characteristics

Finally, 136 patients were enrolled in the study (Table 1). Seventy patients were diagnosed as NS, accounting for

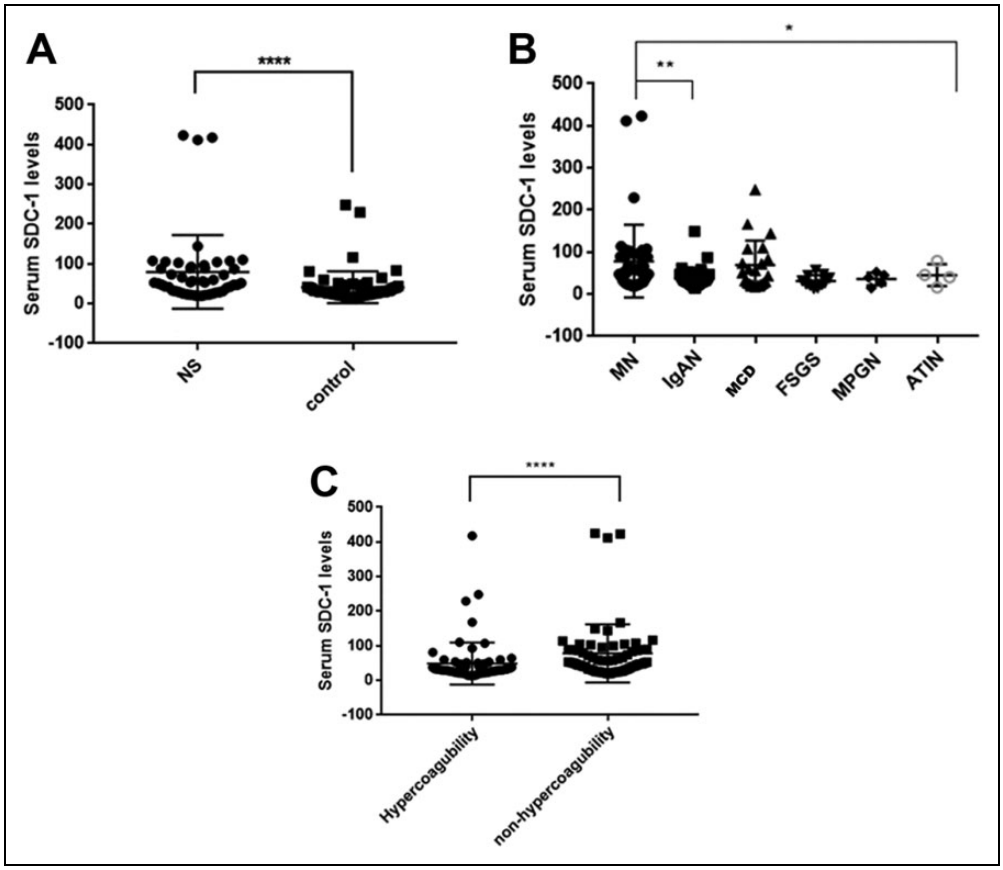

Figure 1. (A) Comparison of SDC-1 between NS and control group ($P < 0.001$); (B) comparison of SDC-1 among different renal biopsy types ($P = 0.0119$; MN vs IgA $P = 0.0017$); (C) comparison of SDC-1 between hypercoagulable and non-hypercoagulable group ($P < 0.0001$). *SDC-1, Syndecan-1; NS, nephrotic syndrome; MN, membranous nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; ATIN, acute tubular injury.

51.5% of the participants. NS group had higher percentage of hypercoagulability compared to control group (52 (74.3%) vs 12 (19.7%), $P < 0.001$). Patients in NS group were older (51.96 ± 1.91 vs 39.55 ± 1.75 yrs, $P < 0.0001$) and more likely to have diabetes mellitus (DM) (17.1% vs 6.1%, $P = 0.045$). NS group had lower blood albumin level (Alb) (23.7 ± 0.63 vs 45.14 ± 2.98 g/L, $P < 0.0001$), higher D-dimer level (1.25 ± 0.14 vs 0.44 ± 0.09 μg/mL, $P < 0.0001$) and higher FDP (3.56 ± 0.47 vs 1.17 ± 0.15 μg/mL, $P < 0.0001$). The kidney function appeared to be much better in control group with lower sCr level of (81.70 ± 5.11 vs 122.96 ± 15.42 μmol/L, $P < 0.05$) and higher estimated glomerular filtration rate (eGFR) of (89.98 ± 2.78 vs 69.43 ± 4.01 ml/(min·1.73 m^2). NS group were more likely to suffer from hyperlipemia compared to control group with higher Tch (7.31 ± 0.36 vs 4.33 ± 0.12 mmol/L, $P < 0.0001$) and TG (2.84 ± 0.20 vs 1.52 ± 0.12, $P = 0.001$). SDC-1 level was much more significantly increased in NS group (82.83 ± 10.88 vs 42.07 ± 4.91 ng/ml, $P = 0.001$) (Figure 1A). After renal biopsy, the majority of people in NS group were diagnosed as membranous nephropathy (57.1% vs 3%, $P < 0.0001$), while those in control group were mostly diagnosed as IgA nephropathy (51.5% vs 12.9%, $P < 0.0001$).

SDC-1 Level and Thrombosis Relevant Characteristics

SDC-1 level was equally divided into 3 categories, containing Level 1 (<29.74 ng/ml), Level 2 (29.80 to 52.58 ng/ml) and Level 3 (>53.18 ng/ml) (Table 2). Based on clinical experience and former researches, variables relevant to thrombosis were included to test their association with SDC-1. The baseline characteristics such as sex, age, HBP and DM, as well as the laboratory results such as PLT, sCr, eGFR and UA showed no significant difference among the 3 groups. Significantly high level of SDC-1 was observed in patients with hypercoagulation state and NS ($P < 0.001$).

Level 3 had the highest level of 24 h proteinuria (4.28-6.66 g), D-dimer (0.87-1.44 μg/mL), FDP (2.45-4.98 μg/mL) and lowest level of Alb (23.92-29.13 g/L) ($P < 0.001$). The Tch level was also highest in Level 3 (5.85-7.87 mmol/L, $P = 0.015$), while TG level was of no statistical significance ($P = 0.061$). Compared with Level 1, Level 3 showed a significant increase in 24 h proteinuria, D-dimer and FDP level and decreased in Alb level ($P < 0.001$). Compared with Level 2, the above 4 factors in Level 3 showed statistical difference ($P < 0.05$) except for D-dimer.

Table 2. Baseline Characteristics of SDC-1 Level Equally Divided into 3 Categories.

	Level 1 (<29.74 ng/ml), n = 45	Level 2 (29.80-52.58 ng/ml), n = 45	Level 3 (>53.18 ng/ml), n = 46	*P* value
Male [n (%)]	21 (46.7%)	26 (57.8%)	30 (65.2%)	0.2[a]
Age (years)	42.09 ± 2.36	45.2 ± 2.29	50.41 ± 2.5[b,c]	0.045[d]
HBP [n (%)]	4 (8.9%)	4 (8.9%)	8 (17.4%)	0.346[a]
DM [n (%)]	17 (36.8%)	20 (44.4%)	17 (37%)	0.727[a]
PLT (*10^9/L)	236.91 ± 9.24	251.11 ± 10.91	231.63 ± 10.53	0.448[d]
Alb (g/L)	42 (32.86-38.8)	39 (32.84-38.49)	25 (23.92-29.13)[b,c]	<0.001[d]
24h-UPRO (g/1.73 m^2)	0.74 (1.75-4.06)	0.86 (1.57-3.18)	5.54 (4.28-6.66)[b,c]	<0.001[d]
D-Dimer (g/mL)	0.3 (0.33-0.70)	0.45 (0.48-1.33)	0.98 (0.87-1.44)[b,c]	<0.001[d]
FDP (g/ml)	0.94 (0.91-1.64)	1.12 (1.29-3.05)	2.84 (2.45-4.98)[b,c]	<0.001[d]
sCr (mol/L)	82.46 ± 5.63	86.8 ± 5.01	138.74 ± 23.22	0.112[d]
eGFR (ml/(min·1.73 m^2)	83.91 ± 4.39	85.02 ± 3.24	68.6 ± 5.5	0.127[d]
UA (mol/L)	350.33 ± 11.83	383.68 ± 12.94	383.48 ± 15.04	0.162[d]
Tch	4.88 (4.66-5.97)	4.97 (4.83-6.17)	5.77 (5.85-7.87)[b,c]	0.015[d]
TG	1.61 (1.60-2.48)	1.56 (1.56-2.46)	2.04 (2.05-3.03)	0.061[d]
Hypercoagulability	17 (37.8%)	16 (35.6%)	37 (80.4%)	<0.001[a]
NS	13 (38.9%)	19 (42.2%)	32 (72.1%)	<0.001[a]
Renal biopsy diagnosis				<0.001[a]
IgA	15 (33.3%)	23 (51.1%)	5 (11.1%)	
MN	12 (26.7%)	8 (17.8%)	22 (48.9%)	
MCD	7 (15.7%)	4 (8.9%)	10 (22.2%)	

Abbreviations: HBP, high blood pressure; DM, diabetes mellitus; PLT, platelet; PDW, platelet distribution width; Alb, albumin; 24h-UPRO, 24 h urinary protein; FDP, fibrin degradation products; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; sUA, serum uric acid; Tch, total cholesterol; TG, triglyceride; SDC-1, Syndecan-1; NS, nephrotic syndrome; MN, membranous nephropathy; MCD, minimal change disease.
[a]Chi-square test.
[b]1 vs 3 (age $P = 0.044$; Alb $P < 0.0001$; 24h-UPRO $P < 0.0001$; D-Dimer $P < 0.0001$; FDP $P < 0.0001$; Tch $P < 0.0001$).
[c]2 vs 3 (age $P = 0.318$; Alb $P < 0.0001$; 24h-UPRO $P = 0.0001$; D-Dimer $P = 0.10$; FDP $P = 0.03$; Tch $P = 0.059$).
[d]One-way ANOVA/nonparametric test.

Table 3. Univariate Regression for Predicting Hypercoagulable State.

	OR	95% CI	*P*
Age	1.039	1.016-1.063	0.001
Alb	0.861	0.820-0.903	<0.001
24h-UPRO	1.537	1.318-1.792	<0.001
sCr	1.007	1.000-1.014	0.036
Tch	1.470	1.191-1.813	<0.001
TG	1.395	1.053-1.849	0.02
SDC-1 Level 2	1.799	0.075-4.315	0.188
SDC-1 Level 3	6.059	2.435-15.078	<0.001

Abbreviations: Alb, albumin; 24h-UPRO, 24 h urinary protein; sCr, serum creatinine; Tch, total cholesterol; TG, triglyceride; SDC-1, Syndecan-1.

Table 4. Multivariate Regression for Predicting Hypercoagulable State.

	OR	95% CI	*P*
SDC-1 Level 3	5.352	1.748-16.384	0.003
Alb < 30	10.735	4.259-27.060	<0.001

Abbreviations: SDC-1, Syndecan-1; Alb, albumin.

SDC-1 Level, Hypercoagulation and Thrombosis

No thrombosis events were observed. The hypercoagulability state was observed as high potential to develop thrombosis. Patients with hypercoagulability had a significantly higher level of SDC-1 (52.88 [57.24-99.04] vs 30.43 [34.54-63.41] ng/ml, $P < 0.001$) (Figure 1C). Univariate regression analysis was applied to address the risk factors (Table 3) and those with $P < 0.5$ were concluded in multivariate regression to predict hypercoagulable state. Highly increased level of SDC-1 (>53.18 ng/ml) and hypoproteinemia (Alb < 30) were the independent risk factors for hypercoagulable state (OR = 5.352, 95% CI: 1.748-16.384, $P = 0.003$; OR = 10.735, 95% CI: 4.259-27.060, $P < 0.001$) (Table 4). The AUC of the model was 0.830 (95% CI: 0.758-0.901) (Figure 2).

SDC-1 Level and Renal Biopsy Types

The SDC-1 level varied in the renal biopsy types (Figure 1B). Membranous nephropathy (MN) patients occupied the highest SDC-1 level ($P < 0.001$). In patients with MN, nearly half of the patients obtained SDC-1 Level 3 while over half of patients with IgA acquired SDC-1 Level 2 (Table 2).

Discussion

To explore the pathophysiological progress in developing thrombosis in patients with NS. We presumed that endothelial dysfunction played a major part. Unfortunately, due to

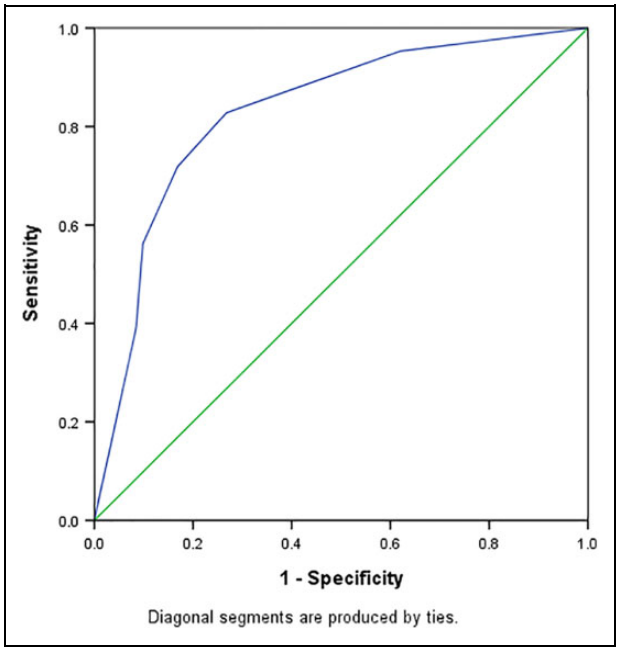

Figure 2. ROC curve containing risk factors to predict hypercoagulability state. AUC value was 0.830 (95% CI: 0.758-0.901).

cautiously anti-coagulant therapy in our study, we haven't observed thrombosis events among objects during their hospital stay and one-year following up. However, we discovered that SDC-1 was highly associated with hypercoagulable state. Particularly, the highly increased level of SDC-1 might explain more thrombosis events in MN compared to other biopsy types.

We hypothesized that endothelial damage could promote hypercoagulable state in patients with NS, which served as a possible cause of thrombosis. The thrombosis in patients with NS has been greatly attributed to a hypercoagulable state in former studies.[10,11] An imbalance between pro-/anti-coagulant/thrombotic factors might contribute to thrombosis in deep veins or arteries. Interestingly, some scholars concluded that the form of thrombosis might be considered as an overactive protective role of the body's response to the damage on the vessel walls.[12] When the procoagulant factors are too strong, it leads to the excessive reaction of thrombosis formation. Endothelial damage caused the release a wide variety of pro-coagulant molecules, such as tissue factors (TF)[13] and Factor V (FV).[14] In recent studies, SDC-1 also served as a promising marker for identifying endothelial dysfunction in NS patients.[8] Highly increased level of SDC-1 was considered as an independent predicator for hypercoagulable state in our study. The association might indicate the synergistic effect between endothelial injury and hypercoagulability, which might accelerate the formation of thrombosis in patients with NS.

Endothelial dysfunction might also directly promote thrombosis in NS patients. An animal study suggested the aggregation of SDC-1 in the thrombi caused by infection, which indicated the prothrombotic role of SDC-1.[15] Heparin, an anticoagulant preparation structurally similar to shed SDC-1, might cause Heparin-Induced Thrombosis in clinical practice.[16] The underlying pathology between SDC-1 and thrombosis remained unclear, but fluid overload and infection in patients with NS might be involved. Edema was commonly observed and fluid overload might lead to the shedding of SDC-1 in animal studies[17] and clinical observations.[18] Besides, patients with NS are vulnerable to systemic infections due to impaired immune systems and applications of corticosteroids and immunosuppressive drugs. During acute infection, endothelial cells was exposed, leading to the release of coagulation factors (TF) and the loss of anticoagulation factors (such as antithrombin III).[19] As a result, severe endothelial damage, marked by high level of SDC-1, might increase the risk of developing thrombosis in patients with NS.

The histological pattern seems to influence the risk of thrombosis in NS patients, among which patients with MN were most likely to suffer from VTE.[20] MN is a disorder of the glomerular filtration barrier, and central to the filtration mechanism of the glomerular filtration barrier is the podocyte. Several clinical trials found that the risk of VTE was highest in patients with membranous nephropathy. After adjusting gender, proteinuria, and serum albumin, the histologic subtype remained an independent risk factor for VTE and the risk was still highest in patients with membranous nephropathy (HR = 10.8).[21] A cohort study found that 30.1% patients with MN developed VTE and 81.5% patients with VTE were at NS status after 5 years following up.[22] A recent study focused on genetic testing found the similar result and revealed the underlying inherited factors.[23] In our study, it was significant that SDC-1 level was highest in MN patients among all the renal biopsy types. The rising of SDC-1 further proved that there might be endothelial damage in MN, which led to hypercoagulable state or even thrombosis in these patients.

There are several limitations to our study. First, since we collected data from a single center, the external validity or generalizability of our results might need to be further proved in multicenter studies. In addition, this study was a cross-sectional study, so we might not draw the casual relationship. Broader studies containing more patients would be necessary to define SDC-1 level in different races and populations. What's more, our center applied prophylactic anticoagulation to high-risk patients who might develop thrombosis considering their coagulability state after renal biopsy during hospitalization, which lead to a significant reduction in the thrombotic events. Lack of sufficient imaging exams might also be the cause and should be promoted in further studies.

In conclusion, endothelial injury was observed in patients with NS, marked by high level of SDC-1. On one hand, highly increased level of SDC-1 and hypoproteinemia indicated the hypercoagulable state among these patients. On the other hand, endothelial injury might contract vascular smooth muscle and activate platelets, thus forming thrombosis. Therefore, endothelial injury might contribute to the thrombosis formation through internal and exogenous coagulation pathways. SDC-1 was very promising to be analyzed among patients with NS

in order to perform timely prophylactic anticoagulation strategy to avoid adverse events.

Authors' Note

This study was approved by the Ethical Committee of Zhongshan Hospital affiliated to Fudan University (No. B2018-175).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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