Measuring The Concentration of Serum Syndecan-1 To Assess Vascular Endothelial Glycocalyx Injury During Hemodialysis

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Abstract

Glycocalyx is present on the surface of healthy endothelium, and the concentration of serum syndecan-1 can serve as an injury marker. This study aimed to evaluate the hemodialysis-associated changes in the serum syndecan-1 concentration. This was a single-center, retrospective, observational study. Between March 2017 and December 2019, 145 patients who underwent hemodialysis at the Gifu University Hospital were enrolled. The median dialysis period and dialysis time were 63 months and 3.7 hours, respectively. The serum syndecan-1 concentration increased from 124.6 ± 107.8 ng/mL before hemodialysis to 229.0 ± 138.1 ng/mL after hemolysis ($P < 0.001$). Treatment with anticoagulant nafamostat mesylate inhibited hemodialysis-induced increase in the levels of serum syndecan-1 in comparison to unfractionated heparin. Dialysis time and the change in concentration of syndecan-1 were positively correlated, whereas the amount of body fluid removed and changes in the concentration of syndecan-1 were not correlated. The reduction in amount of body fluid removed and dialysis time inhibited the change in of syndecan-1 levels before and after hemodialysis. In conclusion, quantitative assessment of the endothelial glycocalyx injury during hemodialysis can be done by measuring the concentration of serum syndecan-1 which may aid in the selection of appropriate anticoagulants, hemodialysis time, and the amount of body fluid removed.

Introduction

Malnutrition, inflammation, and atherosclerosis are strongly associated in chronic kidney disease¹. and both a malnourished state and atherosclerosis can be caused by inflammation. Moreover, chronic microinflammation is observed in patients who undergo hemodialysis². Several factors, such as uremia, activation of free radicals and adhesion molecules, and hemodialysis membrane, lead to microinflammation in patients who undergo hemodialysis^{3–5}. Uremic substances and the hemodialysis membrane promote the production of free radicals and cytokines by stimulating neutrophils, and the resulting inflammation further causes endothelial injury. However, there is no method to quantitatively assess endothelial cells injury.

The vascular endothelium is composed of a thin monolayer of endothelial cells, and this lines the entire circulatory system, particularly those parts that are exposed to the circulating blood. The healthy endothelium is covered by a sugar-protein called glycocalyx^{6–10} that plays pivotal roles in vascular homeostasis^{11,12}. The endothelial glycocalyx is degraded by several factors, such as sepsis, major surgery, trauma, ischemia/reperfusion, and prolonged hyperglycemia. Persistent and diffuse alterations in the glycocalyx are associated with widespread endothelial dysfunction, changed permeability, and impaired oxygen and nutrient delivery to the cells^{11,13,14}. Several studies have revealed the relationship between endothelial glycocalyx injury and serious diseases, such as cardiovascular disease, acute kidney injury, and chronic kidney disease^{15,16}. Moreover, the structure of the endothelial glycocalyx is degraded in chronic diseases, such as aging¹⁷, diabetes¹⁸, and hypertriglyceridemia¹⁹.

The glycocalyx comprises cell-bound proteoglycans, glycosaminoglycan side chains, and sialoproteins^{13,20}. The proteoglycans consist of a core protein, such as a member of the syndecan protein family, to which glycosaminoglycan molecules are linked²¹. Syndecan-1 is the core protein in heparan sulfate proteoglycan that is found in the glycocalyx. Syndecan-1 is released from the endothelium when the glycocalyx is injured, causing an increase in its concentration in circulation²². Moreover, serum syndecan-1 has been used as an endothelial injury marker in recent clinical studies in critically ill patients^{23–26}.

Therefore, the present study aimed to assess endothelial injury using serum syndecan-1 as a marker of endothelial glycocalyx injury in patients who underwent hemodialysis. Additionally, the present study examined the medication type and factors that influence the concentration of syndecan-1.

Results

Characteristics of patients

We finally enrolled 145 patients with a median age of 66 years (Fig. 1, Table 1). The median dialysis period and dialysis time were 63 months and 3.7 hours, respectively. The most common primary illness was diabetic nephropathy which was observed in 37 patients (25.5%).

Table 1
Patient demographics.

Characteristics	Median (range) or number
Number of cases, n	145
Age (years), mean (IQR)	68 (60–77)
Sex (female/male), n (%)	44 (30.3) / 101 (69.7)
Dialysis period (months), median (IQR)	20.0 (1.0, 87.0)
Dialysis time (hours), median (IQR)	4.0 (3.0, 4.0)
Primary illness, n (%)	
Chronic glomerulonephritis	29 (20.0)
Rapidly progressive glomerulonephritis	4 (2.8)
Polycystic kidney disease	8 (5.5)
Nephrosclerosis	8 (5.5)
Diabetic nephropathy	37 (25.5)
Nephritis with autoimmune disease	6 (4.1)
Renal/urological tumor	5 (3.4)
Obstructive urinary tract/urination disorders	1 (0.7)
Paraproteinemia (myeloma)	1 (0.7)
Acute kidney injury	10 (6.9)
Congenital anomalies of the kidney and urinary tract	1 (0.7)
Unknown	33 (22.8)
Others	2 (1.4)
Hemodialysis type, n (%)	
HD	133 (91.7)
HDF	12 (8.3)
Dialysis efficiency	
Kt/V	1.20 (0.06–1.86)
Medication, n (%)	
Unfractionated heparin	101 (69.7)
<i>HD</i> hemodialysis, <i>HDF</i> hemodiafiltration, <i>IQR</i> interquartile range.	

Characteristics	Median (range) or number
Low-molecular-weight heparin	24 (16.6)
Nafamostat mesylate	20 (13.8)
Dialysis membrane, n (%)	
Polyethersulfone	110 (75.9)
Polysulfone	34 (23.4)
Asymmetric triacetate	1 (0.7)
<i>HD</i> hemodialysis, <i>HDF</i> hemodiafiltration, <i>IQR</i> interquartile range.	

The number of patients who underwent hemodialysis and hemodiafiltration was 133 (91.7%) and 12 (8.3%), respectively. Anticoagulation agents, such as unfractionated heparin, low-molecular-weight heparin, and nafamostat mesylate, were administered to 101, 24, and 20 patients, respectively. Median Kt/V, an index of dialysis efficiency, was 1.20.

Concentration Of Serum Syndecan-1 And Hemodialysis

The concentration of serum syndecan-1 before and after hemodialysis was 124.6 ± 107.8 ng/mL and 229.0 ± 138.1 ng/mL, respectively; this indicates that the concentration of serum syndecan-1 had significantly increased ($P < 0.001$) after hemodialysis (Table 2).

Table 2
Serum SDC-1 concentration before and after hemodialysis.

Status	SDC-1 concentration (ng/mL)	<i>P</i> -value
Before HD	124.6 ± 107.8	< 0.001
After HD	229.0 ± 138.1	
<i>SDC-1</i> syndecan-1, <i>HD</i> hemodialysis.		
<i>P</i> -values were obtained from a mixed-effects model.		

The concentration of serum syndecan-1 significantly increased after hemodialysis in patients who received unfractionated heparin and low-molecular-weight heparin; however, the concentration of syndecan-1 was not significantly different before and after hemodialysis in those who received nafamostat mesylate (Table 3).

Table 3
Serum SDC-1 concentration and anticoagulants.

Anticoagulants	Before HD (ng/mL)	After HD (ng/mL)	P-value
Unfractionated heparin	112.0 ± 79.8	235.4 ± 126.8*	< 0.001
Low-molecular-weight heparin	144.1 ± 135.8	248.5 ± 174.1*	< 0.001
Nafamostat mesylate	164.2 ± 171.1	173.3 ± 141.3	0.459
<i>SDC-1</i> syndecan-1, <i>HD</i> hemodialysis.			

Additionally, according to the multivariable regression analysis after adjusting for age, sex, dry weight, and dialysis period, treatment with nafamostat mesylate inhibited the increase in the concentration of serum syndecan-1 during hemodialysis compared to treatment with unfractionated heparin and low-molecular-weight heparin (Table 4).

Table 4
Results of multivariable regression analysis between anticoagulants.

Anticoagulants	Coefficient*	95% LCL	95% UCL	P-value
Low-molecular-weight heparin vs. unfractionated heparin	-18.07	-56.776	20.637	0.358
Nafamostat mesylate vs. unfractionated heparin	-116.473	-158.442	-74.504	< 0.001
Nafamostat mesylate vs. low-molecular-weight heparin	-98.403	-150.482	-45.324	< 0.001
*Coefficients from the multivariable linear regression model adjusted for age, sex, dry weight, and dialysis period, shown as differences in serum syndecan-1 concentration for low-molecular-weight heparin vs. unfractionated heparin, nafamostat mesylate vs. unfractionated heparin, and nafamostat mesylate vs. low-molecular-weight heparin, respectively.				
<i>LCL</i> lower confidence limit, <i>UCL</i> upper confidence limit.				

Association of concentration of serum syndecan-1 with dialysis time and body fluid removal

The relationship between the concentration variability of syndecan-1 and the dialysis condition, including the dialysis time and the amount of body fluid removed, was confirmed. The amount of body fluid removal was corrected by dry weight. The dialysis time and change in concentration of syndecan-1 showed positive correlation ($P = 0.033$), but there was no significant association ($P = 0.111$) between the amount of body fluid removed and changes in the concentration of syndecan-1 (Table 5).

Table 5
Relationship between syndecan-1 concentration variability and dialysis conditions.

Factors	Coefficient*	95% LCL	95% UCL	<i>P</i> value
Body fluid removed/dry weight (per 0.01 L/Kg increase)	9.107	0.144	18.07	0.111
Dialysis time (per 1 minute increase)	23.349	-8.836	55.533	0.033
*Coefficients from the multivariable linear regression model adjusted for age, sex, and dialysis period, shown as increment in serum syndecan-1 concentration for a unit change in factors.				
<i>LCL</i> lower confidence limit, <i>UCL</i> upper confidence limit.				

Next, we examined the association between changes in the concentration of syndecan-1 and dialysis parameters, including dialysis time and the amount of body fluid removed. The change in the concentration of syndecan-1 before and after hemodialysis increased with respect to enhanced removal of body fluids and prolonged dialysis time (*P* for interaction = 0.063, Fig. 2). However, the amount of change in the concentration of syndecan-1 before and after hemodialysis decreased with respect to a decrease in the amount of body fluid removed and shortened dialysis time.

Discussion

The present study revealed that a) the endothelial glycocalyx is injured during hemodialysis; b) endothelial glycocalyx injury is attenuated by administering nafamostat mesylate as an anticoagulant; and c) endothelial glycocalyx injury is aggravated by an increase in the amount of body fluid removed and prolonged dialysis time.

The endothelial glycocalyx is injured in patients with chronic kidney disease and by plasma volume expansion²⁷. Therefore, we hypothesized that the serum syndecan-1 levels would increase in patients who undergo hemodialysis. A previous study indicated that the concentration of serum syndecan-1 was approximately 20 ng/mL in healthy people¹⁹; in contrast, in the present study, it was 124.6 ± 107.8 ng/mL in patients who underwent hemodialysis. This result confirmed that the endothelial glycocalyx sustained injuries in patients who undergo hemodialysis.

Endothelial glycocalyx injury may be attenuated by a decrease in fluid volume after hemodialysis. However, the levels of serum syndecan-1 increased after hemodialysis than those before hemodialysis. This finding suggests that the endothelial glycocalyx is injured during hemodialysis due to neutrophils and inflammation via the production of free radicals and cytokines.

During hemodialysis, unfractionated heparin, low-molecular-weight heparin, and nafamostat mesylate were used as anticoagulating agents. Low-molecular-weight heparin and nafamostat were administered

in patients that had any disease which was associated with bleeding tendencies. The results of the present study suggest that an increase in the concentration of syndecan-1 is attenuated in patients who receive nafamostat mesylate.

Nafamostat mesylate, a synthetic serine protease inhibitor, is a short-acting anticoagulant²⁸, and is also used during hemodialysis to prevent proteolysis of fibrinogen into fibrin²⁹. It is a slow, tight-binding substrate that traps the target protein in the acyl-enzyme intermediate form, and inhibits enzyme activity^{30,31}. Nafamostat has been recently identified as a potential therapy against COVID-19³². Infection with SARS-CoV-2 induces endotheliitis due to viral involvement and inflammatory response of the host, and thus, it is associated with endothelial glycocalyx injury²¹. Therefore, nafamostat mesylate may have a beneficial effect on the endothelial glycocalyx, although it is supported by only circumstantial evidence.

Extension of dialysis time is a strategy to improve prognosis³³; however, it remains controversial^{33,34}. The present study identified that changes in the levels of serum syndecan-1 are small in patients who have prolonged dialysis time and slow removal of body fluid. Therefore, these two strategies could prevent endothelial glycocalyx injury. Several reports have also revealed that prolonged hemodialysis was associated with improved blood pressure and fluid management^{35–37}. Additionally, rapid removal of body fluid is associated with a greater risk of mortality and cardiovascular events³⁸. Moreover, hypotension during hemodialysis is also associated with higher mortality³⁹.

These mechanisms may explain how lower ultrafiltration rates with prolonged hemodialysis and slow removal of body fluids may ameliorate endothelial vascular permeability via attenuation of endothelial glycocalyx injury. Therefore, we propose that slow removal of body fluids with prolonged hemodialysis can reduce hypotension during hemodialysis.

This study has some limitations. First, the hemodialysis time in most patients was less than 4 h. Therefore, an accurate examination of prolonged hemodialysis could not be performed. Second, less type of dialyzer was used in the present study. Although further studies are required, measuring the concentration of serum syndecan-1 may help in the assessment of endothelial injury under low blood flow (e.g., chronic hemodiafiltration), and of membrane compatibility by using a different type of dialyzer. Moreover, serum syndecan-1 is proposed to be a useful biomarker for daily monitoring of organ dysfunction, and may be an important risk factor for mortality in critically ill patients²⁵.

In conclusion, the study presented a method for the quantitative assessment of endothelial glycocalyx injury by measuring the concentration of serum syndecan-1 during hemodialysis. Although hemodialysis causes endothelial glycocalyx injury, it may be mitigated by maintenance of hemodialysis duration and by modulation of the amount of body fluid removed via the quantitative assessment of the serum syndecan-1.

Methods

Patients

This was a single-center, retrospective, observational study conducted at the Gifu University Hospital, affiliated to Gifu University, Gifu, Japan. Patients who underwent hemodialysis at the Gifu University Hospital between March 2017 and December 2019 were enrolled in the study. Patients aged <20 years, who underwent plasma apheresis, plasma exchange, and double filtration plasma therapy, and who had not maintained their dry weight were excluded from the analysis. Finally, data from 145 patients were used for the final analyses in this study (Fig. 1).

Ethics approval and consent to participate

The study conformed to the principles outlined in the Declaration of Helsinki⁴⁰. Ethics approval was obtained from the Medical Ethics Committee of the Gifu University Graduate School of Medicine, Gifu, Japan (record no.: 2021-A005). The need for informed consent from participants was waived by the medical ethics committee due to the retrospective nature of the study. Before initiation, the study was registered in the UMIN Clinical Trials Registry (registry number: UMIN000051415).

Data collection and study design

Blood was routinely sampled before and after hemodialysis from eligible patients at the time of last hemodialysis before being discharged from Gifu University Hospital, and data from these blood samples were used in the present study. All laboratory data (except serum syndecan-1), dry weight, and other patient demographics were extracted from the hospital's electronic medical records. The concentration of serum syndecan-1 was measured using an enzyme-linked immunosorbent assay (950.640.192; Diaclone, Besancon, Cedex, France). The data were retrospectively analyzed. As an index of the efficiency of dialysis, Kt/V was calculated as described previously⁴¹.

Statistical analysis

Patients' baseline characteristics are presented as median and interquartile range (IQR) for continuous variables, and frequency and proportion for categorical variables. For the primary analysis, a mixed effect model was used to assess the change in syndecan-1 levels with hemodialysis. The difference in syndecan-1 levels before and after hemodialysis in the anticoagulant subgroup was confirmed using paired *t*-test. A multivariable linear regression analysis was performed to compare the change in syndecan-1 levels before/after hemodialysis and treatment with anticoagulants. The covariates in the regression model were age, sex, dry weight, and dialysis period⁴². These variables were selected a priori on the basis of previous studies. In another model, dry weight and dialysis period were simultaneously incorporated into the linear regression model to evaluate the effect of factors during dialysis on the levels of syndecan-1. An interaction term was included in the model to confirm the effect of modification of dry weight and dialysis period on changes in the levels of syndecan-1. If the interaction term was statistically significant, the effect of the dialysis period (or dry weight) on syndecan-1 was determined to be modified by dry weight (or the dialysis period). There were no missing values in the data used in the analyses. A

two-sided $P < 0.05$ was considered to be statistically significant. The study is exploratory and there were concerns about low statistical power; therefore, the interaction was evaluated with a two-sided $P < 0.1$. R version 4.1.0 was used for statistical analyses (www.r-project.org).

Data availability

The data that support the findings of this study are available from the corresponding author (HO) upon reasonable request.

Declarations

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Author contributions

K.K. and H. Okada wrote the manuscript. K.K., Kodai S., S.N., H. Okamoto, G.Y., R.K., and T. Miura collected the blood samples. Y. Keiko S., C.T., Y. Kawasaki, T. Minamiyama., A.N., H.F., T.S., Y.T., Tomoki Y., and Y.N. measured the syndecan-1 concentration using ELISA. Keiko S. and R.Y. created a database. T.I. performed statistical analysis. Y.M., T. Miyake, Y. Kitagawa, T.F., T.D., and Takahiro Y. treated the patients. H.T., S.Y., and S.O. supervised the study. H. Okada and A.S. revised and edited the manuscript. The final manuscript was reviewed and approved by all authors.

Competing interests

All authors declare no competing interests.

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Figures

Figure 1

Figure 1

Flow diagram for the selection of study participants for data analysis.

Figure 2

Figure 2

Effect of dialysis time and the amount of body fluid removed on the change in the serum syndecan-1 concentration. The change in the concentration of syndecan-1 before and after hemodialysis increased with respect to the enhanced body fluid removal and prolonged dialysis time. However, the change in the concentration of syndecan-1 before and after hemodialysis decreased with respect to the decreased amount of body fluid removal and the shortened dialysis time.