Plasma concentrations of syndecan-1 are dependent on kidney function

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Abstract

Background: Elevated plasma concentrations of syndecan-1 and heparan sulfate in studies of trauma, sepsis, and major surgery are commonly assumed to indicate acute glyocalyx degradation. We explored a possible role of the kidneys for these elevations.

Methods: Plasma and urine concentrations of syndecan-1, heparan sulfate, and biomarkers of inflammation were measured over 5 hours in 15 hospital patients treated for post-burn injury. The renal clearances of syndecan-1 and heparan sulfate (CLR) were calculated and their influence on the plasma concentration predicted by simulation.

Results: The urine/plasma concentration ratio was 0.9 (0.3-3.0) for syndecan-1 and 2.8 (2.0-4.3) for heparan sulfate. The CLR varied 250-fold for syndecan-1 and 10-fold for heparan sulfate. Multiple linear regression analysis showed that CLR for syndecan-1 was positively associated with the creatinine clearance (P < .0032) and the urine flow (P < .015). CLR for heparan sulfate increased with interleukin-6 (P < .003) and the urine flow (P < .01). Simulations suggested that a change in CLR from the mean of the highest 3 to the lowest three values would double plasma syndecan-1 within 4 hours and cause a 7-fold rise after 24 hours. A similar change in CLR for heparan sulfate would triple the plasma level within 24 hours, even if no increased shedding of the glyocalyx takes place.

Conclusions: The renal elimination of syndecan-1 and heparan sulfate varied greatly. A change in kidney function, which is common after trauma and major surgery, might alone induce several-fold changes in their plasma concentrations.

1 | INTRODUCTION

Measuring syndecan-1 and heparan sulfate concentrations in plasma is a common way of assessing the integrity of the endothelial glyocalyx layer. More than 200 studies have been published that show the frequent occurrence of threefold to fourfold elevations of the plasma concentrations of endothelial surface proteins in acute and chronic inflammation, trauma, sepsis, and major surgery.1-3 A major challenge is to find different ways to avoid these elevations, as they are interpreted to imply acute injury to the glyocalyx layer.4 However, the metabolism of these glyocalyx components is poorly understood, and events other than glyocalyx degradation might possibly explain a rise in their plasma concentrations. For example, their production could be upregulated or their elimination could become less efficient.4,5

In this study, we assessed the renal clearance (CLR) as a determinant of the plasma concentration of glyocalyx degradation...
products. The data were derived from post-burn patients with a marked inflammatory response and elevated levels of syndecan-1 and heparan sulfate.

The hypothesis was that $C_{LR}$ is a major determinant of the plasma concentration. For this purpose, the $CL_R$ of syndecan-1 and heparan sulfate were calculated (primary outcome), their variability was examined, and simulations were performed to predict how the plasma concentrations are likely to change when $CL_R$ is varied (secondary outcomes).

## METHODS

This present study is a secondary report of a prospective single-center open-label trial of the volume effects and capillary leakage of 20% albumin in 15 patients recruited from the Burns Unit of Linköping University Hospital, Sweden, between October 2016 and January 2019. The study was approved by the Regional Ethics Committee of Linköping (Dnr 2016/333-32) and the Swedish Medical Products Agency (Eu-nr 2016-00996-26) and was registered at clinicaltrials.gov (NCT02952378).

Inclusion criteria were a burned Total Body Surface Area (TBSA) of > 6% and age 18–80 years. Exclusion criteria were unconscious patients or those with severe allergies, kidney failure, or heart failure. The patients were recruited during a visit 1–2 days before the trial, which took place between 4 and 14 (mean 7) days after the burn injury. They gave their informed consent both orally and in writing.

### 2.1 Sampling and analysis

The study was performed on 14 patients in the morning and on 1 patient in the evening. All patients were hemodynamically stable. They had fasted overnight but were allowed to ingest 1 sandwich and drink 1 glass (2 dL) of liquid 90 minutes prior to the experiment. The patients were placed in the supine position for at least 30 minutes before baseline measurements were taken.

Each patient received an intravenous infusion of 3 mL/kg 20% albumin over 30 minutes. Blood was collected in lithium-heparin plasma gel tubes and used for the measurement of the plasma albumin, creatinine, interleukin-6 (IL-6), and C-reactive protein (CRP) concentrations at 0, 60, and 300 minutes. The analyses were performed on a Cobas® 8000 system (Roche Diagnostics, Basel, Schweiz) at the certified clinical chemistry laboratory at Linköping University Hospital.

The plasma concentrations of 2 endothelial shedding products, syndecan-1 and heparan sulfate, were analyzed at the research laboratory of Södertälje Hospital at Biovation Park, Södertälje, using commercially available ELISA kits (from Diaclone, France, and Amsbio, Abingdon, UK) with coefficients of variation (CV) of 6.2% and < 10%, respectively.

The syndecan-1 assay uses an antibody that is highly specific for the syndecan-1 (CD-138) molecule. The heparan sulfate kit is based on an antibody that reacts with the 10E4 epitope, which is present in many types of heparan sulfates. Samples with high concentrations of syndecan-1 were re-analyzed after dilution to 1:3 and to 1:10, and heparan sulfate was re-analyzed with a dilution of 1:3.

Urine samples were collected from a catheter bag or through voluntarily voiding at 0 and 300 minutes. The first urine collection was made just before the infusion of 20% albumin was initiated. Urine was analyzed for creatinine, syndecan-1, heparan sulfate, albumin, and $\alpha$-microglobulin by the same technical methods used for the plasma samples.

Urine was also collected to assess the risk of acute kidney injury by Nephrocheck® (Astute Medical, San Diego, CA), which uses the product of 2 cell-cycle arrest biomarkers, insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2), to calculate an index called AKIRisk™. Risk values > 0.3 increase and > 2.0 greatly increase the risk of developing acute kidney injury within the subsequent 24 hours.

### 2.2 Calculations

The renal clearance ($CL_R$) of syndecan-1, heparan sulfate, and creatinine during the 5 hours experiment was calculated as the product of their urinary concentration and the excreted urine volume divided by the average plasma concentration at 0 and 300 minutes. The $CL_R$ is the body volume that is completely cleared from the measured molecule by renal excretion per minute. The $CL_R$ for syndecan-1 between 0 and 5 hours was given by:

$$CL_R = \frac{\text{Urine syndecan} \times \text{urine flow (mL/min)}}{\text{Plasma syndecan}}$$

The fractional excretion (FE) of syndecan-1 was calculated as follows at 0 and 5 hours:

$$\text{FE}_{syndecan} = 100 \times \frac{\text{Urine syndecan}}{\text{Plasma syndecan}} \times \frac{\text{Plasma creatinine}}{\text{Urine creatinine}}$$

The FE of heparan sulfate was calculated in the same way. The FE is the renal clearance of the studied molecule relative to the creatinine clearance.

### Editorial Comment

Measurements of syndecan-1 and heparan sulfate are commonly used to assess degree of glycocalyx degradation, a marker for the endothelial response to inflammation. In this study, concentrations of both syndecan-1 and heparan sulfate in both plasma and urine were serially measured in a cohort of burn patients, to assess the renal clearance of both proteins. Renal clearance was highly variable among patients, and this variability can potentially explain multi-fold differences in measurements not accounting for differential clearance. The results demonstrate an important limitation in using syndecan-1 and heparan sulfate measurements to assess glycocalyx degradation.
Worked-through examples of the influence of $CL_R$ changes on the plasma concentration were constructed based on a one-compartment kinetic model using 3 L as an arbitrary volume of distribution ($V_d$).

The plasma concentration at steady state ($C_{ss}$) was given by the rate of infusion ($R_i$) divided by $CL_R$.

The time required to reach $C_{ss}$ was set to equal four half-times ($T_{1/2}$), each of which is given by $\ln 2 (=0.693) \ V_d/CL_R$. The plasma concentration $C$ after any time $t$ was $^{10}$.

$$C = \left( \frac{R_i}{CL_R} \right) \left( 1 - e^{-t/\frac{CL_R}{V_d}} \right)$$

### 2.3 Statistics

Data were presented as the median and interquartile range. Relationships between variables were evaluated by simple and multiple linear regression analysis, where $r$ = correlation coefficient. Stepwise linear regression was used to identify predictors for the multiple regression analyses. Univariate analysis was used except where noted. $P < .05$ was considered statistically significant.

### 3 RESULTS

### 3.1 Plasma and urine concentrations

Demographic and basic biochemical data are shown in Table 1.

There was a reciprocal correlation between the plasma concentration and the urinary excretion of syndecan-1, both at baseline and during the experiment (Figure 1A). By contrast, the excretion of heparan sulfate increased directly with its plasma concentration (Figure 1B).

The inflammatory markers IL-6 and C-reactive protein correlated only vaguely with the plasma concentrations of syndecan-1 and heparan sulfate. However, the urinary excretion of heparan sulfate increased with the mean IL-6 concentration ($r = 0.66, P < .01$).

The albuminuria was unchanged during the study (from 0.8 [0.6-2.8] to 1.2 [0.5-2.2] mg/mmol creatinine; $P = .92$) but increased with the plasma IL-6 concentration (Figure 1C).

The urine/plasma ratio of syndecan-1 at 5 hours correlated positively with the creatinine clearance ($r = 0.71; P < .008$, one extreme outlier deleted) while the urine/plasma concentration ratio of heparan sulfate correlated positively with the TBSA ($r = 0.65; P < .01$), the mean plasma IL-6 concentration ($r = 0.70; P < .005$) and with the urine albumin concentration ($r = 0.70; P < .01$, one outlier deleted).

When the study started, the urine/plasma concentration ratio was 0.9 (0.3-3.0) for syndecan-1 and 2.8 (2.0-4.3) for heparan sulfate. At the end of the study these ratios were 1.3 (0.7-3.2) and 3.4 (2.6-4.2), respectively. The increased ratio for heparan sulfate was due to a decrease of its plasma concentration during the study ($P < .003$) while no similar change was apparent with syndecan-1.

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### 3.2 Urine/plasma ratio

### 3.3 Renal clearance

The $CL_R$ of syndecan-1 during the 5 hours experiment was 2.26 (0.66-4.00) mL/min, and it varied 250-fold. The $CL_R$ of heparan sulfate was set to equal four half-times ($T_{1/2}$). Each of which is given by $\ln 2 (=0.693) \ V_d/CL_R$. The plasma concentration at steady state ($C_{ss}$) was given by the rate of infusion ($R_i$) divided by $CL_R$.

$$C = \left( \frac{R_i}{CL_R} \right) \left( 1 - e^{-t/\frac{CL_R}{V_d}} \right)$$

### Table 1 Basic data for the 15 patients. Data are the median and 25th-75th quartile range for the value obtained just before initiation of the infusion of 20% albumin except where noted.

| Variable                  | Unit  | Baseline concentration | Reference value |
|---------------------------|-------|------------------------|-----------------|
| Age                       | y     | 42 (36-50)             | —               |
| Males/females             |       | 15 / 3                 | —               |
| Body mass index           | kg/m² | 27.8 (26.4-32.5)       | < 25            |
| Burned body area % of total |       | 15 (range 7-48)       | —               |
| Time after burn           | days  | 7 (range 4-14)        | —               |

| PLASMA                    |       |                        |                 |
|---------------------------|-------|------------------------|-----------------|
| Hb                        | g/L   | 136 (132-140)          | 115-160         |
| Albumin                   | g/L   | 39.2 (36.6-40.2)       | 35-46           |
| CRP                       | µg/L  | 86 (50-155)            | 1               |
| IL-6                      | ng/L  | 41 (19-66)             | 2               |
| Syndecan-1                | µg/L  | 71 (42-181)            | 30              |
| Syndecan-1 1 h            |       | 71 (36-169)            |                 |
| Syndecan-1 5 h            |       | 83 (42-179)            |                 |
| Heparan sulfate           | µg/L  | 1496 (627-2332)        | 200             |
| Heparan sulfate 1 h       |       | 914 (746-1355)         |                 |
| Heparan sulfate 5 h       |       | 897 (658-1171)         |                 |
| Creatinine                | µmol/L| 79 (67-89)             | < 120           |

| URINE                     |       |                        |                 |
|---------------------------|-------|------------------------|-----------------|
| Syndecan-1                | µg/L  | 101 (49-129)           | …               |
| Syndecan-1 5 h            |       | 95 (76-143)            |                 |
| Heparan sulfate           | µg/L  | 2662 (1580-8158)       | …               |
| Heparan sulfate 5 h       |       | 2859 (1978-4487)       |                 |
| IGFBP7                    | ng/mL | 76 (51-148)            | …               |
| IGFBP7 5 h                |       | 62 (53-86)             |                 |
| TIMP-2                    | ng/mL | 3.0 (2.5-6.0)          | …               |
| TIMP-2 5 h                |       | 2.5 (2.2-3.4)          |                 |
| Creatinine                | mmol/L| 11.5 (7.9-14.0)        | …               |
| Creatinine 5 h            |       | 8.8 (6.1-11.0)         |                 |
| α-microglobulin           | mg/L  | 20 (7-38)              |                 |
| α-microglobulin 5 h       |       | 16 (9-33)              |                 |

*Dependent on urine flow.

$^aP = .95$ compared to 1 h.

$^bP < .003$ vs. 0 h.

$^cP < .015$ vs. 0 h.
sulfate was 4.32 (2.48-6.26) mL/min (Wilcoxon’s test $P = .074$) and varied 10-fold.

Using multiple linear regression, the $CL_R$ of syndecan-1 was positively associated with creatinine clearance ($P < .0032$; Figure 1D) and with the urine flow ($P < .015$). The latter amounted to 1.4 (1.3-3.3) mL/min.

Similarly, the $CL_R$ of heparan sulfate was independently and positively associated with the plasma concentration of IL-6 ($P < .003$; Figure 1E) and the urine flow ($P < .01$).

By contrast, the creatinine clearance was on the high side, 198 (158-239) mL/min.
Fractional excretion

The fractional excretion (FE) is the $C_{\text{N}}$ divided by the creatinine clearance.

The FE of syndecan-1 was 0.9 (0.1-2.4)% at baseline and 1.6 (0.5-2.8) at 300 minutes ($P = .20$). The corresponding data for heparan sulfate was 3.0 (1.3-4.1)% and 2.9 (1.7-5.8)%, respectively.

The FE of syndecan-1 increased with the urine flow ($r = 0.63$, $P < .016$). The FE of heparan sulfate correlated, both at 0 and 5 hours, with IL-6 ($r = 0.68$ and 0.70, respectively; $P < .01$; Figure 2A) and also with the excreted amount of α-microglobulin (Figure 2B).

Cell-cycle arrest biomarkers

Urinary concentrations of IGFBP7 and TIMP2 correlated strongly with each other ($r = 0.86$, $P < .0001$). Their relative changes during the experiments agreed well with the dilution of the urine, but not with IL-6 levels or with the creatinine clearance.

The product of these biomarkers, the AKIRisk score, decreased from 0.23 (0.15-0.82) to 0.15 (0.14-0.25) during the study. Six patients before infusion and 3 patients at the end of the study scored > 0.3, which is the cut-off indicating a risk for the development of acute kidney injury.

No statistically significant correlation with other biomarkers was found.

The change in AKIRisk during the study correlated closely with the dilution of the urine ($r = 0.83$; $P < .001$), and the numerical ratios agreed even better when AKIRisk was compared with the squared dilution ($r = 0.86$; $P < .001$, Figure 1F). We tested the latter because the 2 components of the AKIRisk (IGFBP7 and TIMP2) should both be corrected for urine dilution.

Complications

One patient suffered complications during the subsequent hospital care. This was a male patient with the largest burn wound (48%) and highest CRP (300 µg/L) in the series. He developed chills and fever 5 days and 8 days after the experiment. Plasma creatinine transiently increased from 90 µmol/L to 112 and 155 µmol/L, respectively. This patient had AKIRisk of 1.0 but an immediately high value after correction for the squared dilution.

Worked-through examples

Mathematical examples were used to illustrate the consequence of the variability in $C_{\text{N}}$ the plasma concentration $C$.

A sudden change in the $C_{\text{N}}$ for syndecan-1 from the average of the 3 highest values in the case series (14.5 mL/min) to the 3 lowest (0.11 mL/min) would raise the plasma concentration in these patients from 43 µg/L to 5700 µg/L with a half-time of 13 days. The plasma concentration would be doubled after 4 h (Figure 2C) and would have risen by 292 µg/L within 24 hours.

For heparan sulfate, $C_{\text{N}}$ from the average of the 3 highest (10.4 mL/min) to the 3 lowest (2.0 mL/min) would raise the plasma concentration from 1445 µg/L to 7514 µg/L. By 24 hours, the plasma concentration would have increased by 4637 µg/L, which is 3.2-fold, even if no increased release of heparan sulfate from the glycosaminoglycans occurred.

4 | DISCUSSION

Elevated plasma concentrations of syndecan-1 and heparan sulfate are frequently used as evidence for degradation of the endothelial glycosaminoglycan layer, and alternative explanations are rarely considered. The present study suggests that abrupt changes in renal function may contribute to elevated plasma levels in acute clinical settings.

The basis for this view is that urine concentrations of syndecan-1 and heparan sulfate are usually the same or slightly higher than the plasma concentrations, while the renal handling of them vary considerably. The $C_{\text{N}}$ for syndecan-1 and heparan sulfate varied 10-fold or more in this small cohort of post-burn patients, showing that patients with normal plasma creatinine levels can display marked differences in renal handling of glycosaminoglycan degradation products.

The plasma concentrations of syndecan-1 and heparan sulfate were elevated at a virtual steady state throughout this study, making it unlikely that the hypervolemia induced by infusing 20% albumin would degrade the glycosaminoglycans. Their plasma concentrations did not correlate significantly with indices of inflammation, but we still assume that the inflammatory state of these post-burn patients is the key factor explaining the elevation of the plasma levels of the 2 studied biomarkers.

The highest plasma concentrations of syndecan-1 were invariably associated with poor renal excretion and varied with the creatinine clearance. By contrast, the excretion of heparan sulfate increased with its plasma concentration and was further accelerated by inflammation. The renal elimination of both biomarkers also increased with the urine flow, which was most apparent for syndecan-1. These variables are key factors involved in the development of acute kidney injury and often abruptly changed in trauma, sepsis, and major surgery.

Syndecan-1 is a proteoglycan with a molecular weight of 32 kD that is coded by the sdc-1 gene. This molecule serves as a membrane protein but has an extracellular part at which heparan sulfate and chondroitin sulfate chains can be attached. There are several types of heparan sulfates, and the antibody in the analysis kit we use reacts with most of them. The basic molecular structure contains 2 saccharides, an amino sugar, and uronic acid. The molecular weight of the heparan sulfates range between 10 and 70 kD. During a shedding process these glycosaminoglycans are easily detached from the syndecan-1 molecule, although the proteoglycan can also be enzymatically shed with the attached glycosaminoglycans intact.

Little is known about the turnover of endothelial glycoproteins and glycosaminoglycans, but the renal elimination route should be
important because the $CL_R$ suggests that the entire plasma pool becomes eliminated by renal excretion within 24 hours. Without a feedback mechanism that controls the plasma concentration, our simulations show that marked elevations of plasma syndecan-1 and heparan sulfate are likely to occur if a patient experiences a decrease in $CL_R$ secondary to an acute reduction in the urine flow and/or the creatinine clearance. The changes are powerful enough to suggest that elevations of syndecan-1 and heparan sulfate should be evaluated with consideration taken of the potential influence of recent changes in kidney function.

Our study also included measurements of the urinary concentrations of 2 renal cell-cycle arrest biomarkers, IGFBP7 and TIMP2. Their product yields an index, AKIRisk, for which high values predict an increased risk for the development of acute kidney injury. The only finding was that the AKIRisk value correlated closely with the urine dilution (Figure 1F). We and others have suggested that AKIRisk should routinely be corrected for dilution, as is the common practice for most other biochemical measurements performed on sampled urine.\textsuperscript{13,14} The manufacturer and experts on kidney injury claim that the results stand out even when corrected for dilution. An insight relevant to this debate might be that the AKIRisk value shown in Figure 1F should be corrected by the square of the urine dilution (Figure 1F). We and others have suggested that AKIRisk should routinely be corrected for dilution. An insight relevant to this debate might be that the AKIRisk value shown in Figure 1F should be corrected by the square of the urine dilution (Figure 1F). We and others have suggested that AKIRisk should routinely be corrected for dilution, as is the common practice for most other biochemical measurements performed on sampled urine.\textsuperscript{13,14} The manufacturer and experts on kidney injury claim that the results stand out even when corrected for dilution. An insight relevant to this debate might be that the AKIRisk value shown in Figure 1F should be corrected by the square of the urine dilution (Figure 1F). We and others have suggested that AKIRisk should routinely be corrected for dilution, as is the common practice for most other biochemical measurements performed on sampled urine.\textsuperscript{13,14} The manufacturer and experts on kidney injury claim that the results stand out even when corrected for dilution. An insight relevant to this debate might be that the AKIRisk value shown in Figure 1F should be corrected by the square of the urine dilution (Figure 1F). We and others have suggested that AKIRisk should routinely be corrected for dilution, as is the common practice for most other biochemical measurements performed on sampled urine.\textsuperscript{13,14} The manufacturer and experts on kidney injury claim that the results stand out even when corrected for dilution.

The limitations of this study include that the excreted syndecan-1 and heparan sulfate is assumed to stem from the bloodstream, although syndecan-1 is expressed in the renal tubules as well. The predictions of changes in plasma concentrations resulting from a reduction of $CL_R$ assume that the studied glycoproteins follow one-compartment kinetics, that their release to the circulation is unchanged, and that the plasma volume is 3 L. Moreover the data represent a secondary publication to a study of the clinical efficacy of 20% albumin in burn injury.\textsuperscript{6,7} The patients had overcome the acute stage of burn injury and were studied approximately 1 week after the burn incident. 1 patient had suffered from inhalation injury along with skin burns. At the time of the study, their clinical challenges were inflammation and wound infection. The small size of the study group should be noted, and the relatively high BMI is probably a remnant of the early volume loading performed during the acute phase of the burn injury.

Our testing of how glycocalyx shedding products survive storage of plasma samples until analysis also shows that syndecan-1 is quite stable, whereas heparan sulfate levels decrease over time. This fact might explain why the heparan sulfate concentrations reported here are lower than those reported in earlier work by our group.\textsuperscript{18}

5 | CONCLUSIONS

Urinary excretion is an important route for elimination of syndecan-1 and heparan sulfate. Their $CL_R$ values vary greatly and are associated with kidney function variables, such as creatinine clearance and urine flow. Excretion of heparan sulfate seems to be facilitated by inflammation. The simulations illustrate that sudden reductions in the $CL_R$ values for syndecan-1 and heparan sulfate are likely to cause several-fold elevations in the plasma concentrations of these substances even without an assumption of increased glycocalyx degradation.

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CONFLICT OF INTEREST

RGH holds a grant from Grifols for the study of 20% albumin as infusion fluid. MZ and JZ declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available as a File S1.xls and the calibration curves for the ELISA kits as File S2.docx.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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