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Published in:
American journal of physiology-Renal physiology

DOI:
10.1152/ajprenal.00005.2020

Publication date:
2020

An acute rise of plasma sodium concentration associates with syndecan-1 shedding during hemodialysis

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Author contributions

J. Koch, N.M.A. Idzerda, J. van den Born and C.F.M. Franssen conceived and designed the study; E.M. Ettema, J. Kuipers and C.F.M. Franssen executed the clinical part of the study; N.M.A. Idzerda and W. Dam performed the laboratory measurements; J. Koch, N.M.A. Idzerda, J. van den Born and C.F.M. Franssen analyzed and interpreted the data and drafted the manuscript. All authors approved the final version of the manuscript.

Abstract

Endothelial dysfunction (ED) contributes to the high incidence of cardiovascular events in hemodialysis patients. Syndecan-1 in the endothelial glycocalyx can be shed into the circulation serving as a biomarker for ED. As sodium is a trigger for glycocalyx shedding, we now tested whether hemodialysis with higher dialysate sodium concentrations is associated with more syndecan-1 shedding compared with standard hemodialysis (SHD).

In this cross-over study in 29 patients, plasma syndecan-1 was repeatedly measured during SHD and during Hemocontrol hemodialysis (HHD) which is characterized by initially higher dialysate and plasma sodium levels. Courses of syndecan-1 were compared with linear mixed models. Syndecan-1 shedding was assessed by area under the curve analysis.

Plasma sodium increased early after the start of SHD and HHD, with higher values during HHD (30 minutes: 142.3 mmol/L versus 139.9 mmol/L; $P<0.001$). Syndecan-1 increased significantly during both conditions but the percentage change was higher (42.9% versus 19.5%) and occurred earlier (120min versus 180min during) during HHD. Syndecan-1 levels were significantly higher at 120 minutes during HHD compared to SHD ($P<0.05$). Overall syndecan-1 shedding was higher during HHD compared with SHD (means: 40.4 vs. 19.0 arbitrary units; $P=0.06$). Lower predialysis plasma sodium and osmolality were associated with greater intradialytic increases in syndecan-1 levels (both groups $P=0.001$).

The rise in plasma syndecan-1 levels was more pronounced and occurred earlier during hemodialysis with higher plasma sodium levels. Although we cannot proof that the rise in plasma syndecan-1 originates from the endothelial glycocalyx, our findings are compatible with sodium-driven endothelial glycocalyx-derived syndecan-1 shedding.

Key words: sodium; syndecan-1; hemodialysis.

Introduction

Hemodialysis (HD) patients have extremely increased cardiovascular (CV) morbidity and mortality (39) and endothelial dysfunction (ED) is believed to have a major pathophysiological role (16, 39, 45, 48). Several studies have shown that HD patients have impaired endothelial function (12, 31) and markers of ED were found to predict survival of HD patients (43). Vlahu et al. showed that dialysis patients had a loss of the endothelial glycocalyx (eGC) thickness compared with healthy controls (52).

Previous studies suggest that shedding of syndecan-1 into the circulation may reflect eGC degradation in HD patients (52). Syndecan-1, a transmembrane heparan sulfate proteoglycan (HSPG) located in the endothelium, epithelium, hepatocytes and plasma cells, is involved in regenerative growth, cellular adhesion and is an important constituent of the pericellular coat or glycocalyx [reviewed in (47)]. Syndecan-1 shedding can be induced by oxidative mechanisms (20, 21) and is stimulated under inflammatory conditions (2, 32, 54) [reviewed in (3)]. More recent insights indicate that syndecan-1 may also play a role in extrarenal non-osmotic sodium storage and that syndecan-1 shedding can occur due to osmotic changes in plasma (23, 28) [reviewed in (30)] and alterations in volume status (19, 33). It has been suggested that the glycosaminoglycan domains of HSPGs in the endothelium bind and osmotically inactivate circulating sodium ions, functioning as an intravascular buffer compartment (23, 28) [reviewed in (30)]. At the same time and seemingly in contrast to its function in sodium homeostasis, several studies have shown that the endothelial glycocalyx is damaged in the presence of a sodium overload (35), probably mediated by a reduction of heparan sulfate, impairing the endothelial buffer function and thereby enhancing fluid retention (28, 38).

In patients on HD, ED is associated with co-morbidities such as diabetes and hypertension [reviewed in (44)], but has also been shown to be induced by the HD treatment itself (5, 26, 49). We recently found that, compared to healthy individuals, predialysis plasma syndecan-1 levels were increased three-fold in patients on conventional HD and further increased significantly during HD (22). This may be due to the HD-induced inflammatory

response and oxidative stress (42). Additionally, intradialytic changes in plasma sodium concentration may induce ED and eGC shedding as previous studies suggest (28, 38). Therefore, as constituent of the eGC (10), syndecan-1 could get shed into the circulation as well. In most dialysis centers, patients are dialyzed with a fixed dialysate sodium concentration of 139 or 140 mmol/L and, consequently, patients with a plasma sodium concentration that is lower than the dialysate concentration will experience a rise in plasma sodium concentration. In contrast to standard dialysis (SHD) with a fixed dialysate sodium concentration, the Hemocontrol biofeedback system (HHD) is characterized by the use of higher sodium levels in the first half of the HD session based on the concept that higher sodium levels enhance the osmotic pressures and increase the capillary refill rate, thus facilitating a higher ultrafiltration rate (UFR). Various studies have shown that this system improves intradialytic hemodynamic stability (4, 17, 37) which is generally explained by its effect on blood volume (4, 36).

The aim of our study was the relationship between plasma sodium and plasma syndecan-1 which we studied during HHD and during SHD. We hypothesized that the temporary rise in plasma sodium concentrations early during HHD leads to more ED. We therefore asked the question whether ED, represented by glycocalyx shedding, was higher during HHD compared to SHD, and measured plasma syndecan-1 as the principal outcome parameter (thought to originate from the endothelial glycocalyx).

Patients and Methods

Study protocol

In this post-hoc analysis of the cross-over study from Ettema et al. (15). The current work is covered under the previous IRB approval of this study (15). 29 patients on maintenance HD were studied during a single SHD and a HHD dialysis session in randomized sequence. Details of the study have been described before (15). In short, the study population consisted of clinically stable HD patients who were on a thrice weekly HD schedule. Study-related HD sessions took place in the morning or in the afternoon and lasted 4 hours. The measurements took place at the first HD treatment of the week because the UF volume and the blood volume decreases are most pronounced after the longest interdialytic interval (15). The maximum time interval between the two treatments was 2 weeks. Treatment conditions were identical during both treatments except for the dialysate sodium concentration which is the major difference between SHD and HHD (vide infra). Medication use was similar at both treatments. Patients were asked to refrain from drinking caffeine-containing beverages and not to eat starting the night before the study sessions until 1 hour intra-dialysis. Patient position during dialysis (half-supine) was standardized to exclude an effect of posture changes on the circulation. Residual renal function was defined as diuresis of >200 mL per 24 hours.

Blood samples were collected from the arterial line at 6 moments during the dialysis procedure: at the start of dialysis, after 30 minutes, after 60 minutes, after 120 minutes, after 180 minutes and after 240 minutes (end of dialysis). At these same time points, the change in blood volume and cumulative ultrafiltration (UF) volume were registered. Blood pressure and heart rate were measured every 30 minutes. Patients were treated with a single (patient-dependent) dose of intravenous nadroparin, which was given immediately after start of the dialysis procedure via the extracorporeal system before the dialyzer.

HD treatment

Both SHD and HHD were conducted on an Artis HD machine (Gambro Lundia AB, Lund, Sweden) with a low-flux polysulphon dialyzer F8 or F10 (Fresenius Medical Care, Bad Hamburg, Germany). The UF volume is the total volume of fluid that is removed during the entire dialysis session and was set to achieve dry weight at the completion of the HD session. UFR was expressed as L/h. Prescriptions regarding dry weight were made by the nephrologists during their weekly visit to the participating patients. Dry weight was evaluated clinically (peripheral edema, signs of pulmonary congestion, intradialytic and interdialytic blood pressure course) in combination with the cardiothoracic ratio on chest radiography.

Blood flow and dialysate flow rates were 300 to 400 mL/min and 500 to 700 mL/min, respectively and dialysate temperature was 36.0 or 36.5 °C. These settings were identical for the individual patient at both treatments. Dialysate composition for SHD was sodium 139 mmol/L, magnesium 0.5 mmol/L, chloride 109 mmol/L, bicarbonate 34 mmol/L, acetate 3.0 mmol/L and glucose 1.0 g/dL. Dialysate potassium concentration varied between 1 and 3 mmol/L and calcium varied between 1.25 and 1.50 mmol/L depending on the prevailing plasma potassium and calcium concentration. Treatment conditions were identical for the individual patient during both treatments, except for the dialysate sodium concentration. During SHD, the dialysate conductivity was 13.9 mS/cm throughout the dialysis session. During HHD, the equivalent conductivity was set at 13.9 mS/cm, indicating an identical net sodium removal compared with SHD, with lower- and upper tolerance limits for dialysate sodium of 13.3 and 16.0 mS/cm, respectively. With HHD, large and sudden decreases in blood volume are prevented in order to improve intradialytic hemodynamic stability. To this end the patients' blood volume is guided along a predefined ideal relative blood volume trajectory by continuously adjusting UF volume and dialysate conductivity. The pre-set ideal blood volume curve has a marked decrease in the beginning of the dialysis session, whereas it is more stable during the second half of the treatment (37). Hallmark of HHD is the combination of a higher UFR and higher dialysate conductivity during the first half of the dialysis session. This results in higher plasma sodium levels during the first half of the dialysis session and a more pronounced initial decrease in blood volume. Since HHD uses

159 higher UFRs during the first half of treatment, lower UFRs can be used during the second
160 half of the dialysis session, which hemodynamically is considered to be the most critical part
161 of the treatment.
162
163 *Laboratory procedures*
164 Blood samples for sodium, potassium, urea and osmolality were collected in heparin-coated
165 tubes. Plasma sodium and potassium were measured with the indirect method of ion-
166 selective electrode on a Roche Modular (Hitachi, Tokyo, Japan). Urea was measured with
167 the colorimetric method on a Roche Modular analyzer. Plasma osmolality was measured by
168 freezing-point depression on the Osmostat Osmometer (Arkray, Kyoto, Japan). Blood
169 samples for the determination of syndecan-1 were collected in EDTA tubes and immediately
170 put on ice. Next, the samples were centrifuged and stored at −20°C, thawed once and then
171 stored at −80°C until procession. Syndecan-1 concentrations were measured in EDTA
172 plasma samples, using sCD138 sandwich ELISA kits (Diaclone, Besancon, France)
173 according to manufacturer's instructions with standard line on each plate.
174
175 *Correction for hemoconcentration*
176 Considering the Sieving characteristics of low-flux polysulphone artificial dialyzer and
177 according to the criteria proposed by the Uremic Toxin Work Group, molecules with a
178 molecular weight between 500 and 6000 Da are presumably only partially or not at all
179 removed with HD (34, 53). Since syndecan-1 has a molecular weight of ≈77.000 Da it is
180 unlikely that it is removed by dialysis. Indeed, we did not detect measurable syndecan-1 in
181 the dialysate of the first 10 patients in this study (the lower detection range of our analysis
182 was 8 ng/mL). Therefore, we concluded that syndecan-1 is not removed by HD and,
183 consequently plasma levels of syndecan-1 were corrected for hemoconcentration according
184 to reference (40).
185
186 *Statistical analysis*

Analyses were performed with SPSS version 20.0, GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA, USA) and R version 3.3.1 (R Foundation for Statistical computing). Results are expressed as mean ± SD, median [IQR] or mean (95% CI) when appropriate. Normality was tested with the Shapiro-Wilk test. A (non-parametric) Levene's test was used to verify the equality of variances in the data ($P>0.05$). Comparisons were made with a Wilcoxon Signed Rank Test, a paired T-test or Fisher's exact test when appropriate. Relationships of sodium and osmolality with syndecan-1 levels over time were assessed with a repeated measures mixed effects model. Here, the primary outcome measure was plasma syndecan-1. The models were adjusted for age, sex, systolic and diastolic blood pressure, body weight and duration of dialysis. Patient number was added as random effect. Cumulative intradialytic shedding of syndecan-1 was assessed by area under the curve analysis. Correlations between interval variables were calculated using the Pearson's correlation coefficient. Relationships of sodium with syndecan-1 shedding, as well as syndecan-1 shedding and total UF volume were assessed by univariate analysis.

Results

Patients

The patient characteristics are summarized in **Table 1**. The study population included 21 men and 8 women, the mean age was 63.4 (± 17.0) years and the dialysis vintage was 33.9 (± 27.0) months. As much as 52% of patients had a history of a previous CV event and 52% had residual renal function. There was a small but significant difference in predialysis plasma syndecan-1 levels between SHD (59.5 ng/mL; IQR 33.5 to 88.0) and HHD (51.0 ng/mL; IQR 26.0 to 87.0). Other baseline laboratory parameters, predialysis and postdialysis weight and blood pressure were comparable for the two treatments **(Table 2)**.

Course of plasma sodium concentration

As expected, plasma sodium levels were significantly higher during the first half of HHD compared with SHD and the difference was already present at 30 minutes into the dialysis procedure (139.9 mmol/L [95%CI 138.9 to 140.8] during SHD versus 142.3 mmol/L [95%CI 141.2 to 143.3] during HHD; P<0.001) and remained significant until at least 120 minutes after the start of HD (139.3 mmol/L [95% CI 138.7 to 139.9] versus 140.1 mmol/L [95% CI 139.4 to 140.9; P<0.05]). At the end of the HD session, plasma sodium was significantly lower with HHD compared with SHD (139.9 mmol/L [95%CI 139.2 to 140.6] during SHD versus 138.5 mmol/L [95%CI 137.7 to 139.2] during HHD; P<0.01) **(Table 3)**. The UFR in HHD was significantly higher at 60 minutes (0.75 vs. 0.62 L/h; P<0.001) and lower at 240 minutes (0.54 vs. 0.67 L/h; P<0.001) compared to SHD (data not shown).

Course of plasma syndecan-1 levels

Plasma syndecan-1 levels increased significantly during both SHD and HHD (**Table 3 and Figure 1**). However, the rise in syndecan-1 levels during HHD was more pronounced (peak concentration compared with baseline: +42.9% [95%CI 21.1 to 64.6] versus +19.5% [95%CI 17.3 to 31.6]; P=0.08) and occurred earlier (120 minutes versus 180 minutes). The increase in plasma syndecan-1 levels was significantly higher at 120 minutes during HHD compared

to SHD (P<0.05) (**Table 3 and Figure 1**). Cumulative shed syndecan-1 as estimated with area under the curve analysis was higher during HHD (40.4 [95%CI 15.8 to 65.1]) compared with SHD (19.0 [95%CI 2.9 to 35.1]), albeit at borderline significance (P=0.06).

Lower predialysis sodium and osmolality predict the intradialytic change in syndecan-1 levels

Plasma sodium level and osmolality before dialysis were independent predictors of syndecan-1 levels during dialysis. Lower sodium levels at baseline were associated with a larger intradialytic increase of syndecan-1: one unit (mmol/L) lower predialytic sodium level was associated with an additional increase in syndecan-1 during dialysis of 4.4% [95%CI 0.9 to 7.9; P=0.02] at 30 minutes into the dialysis session. Similarly, lower predialytic osmolality was associated with a more pronounced increase in syndecan-1 during dialysis: one unit (mosmol/kg) lower osmolality was associated with an additional increase in syndecan-1 during dialysis of 2.6% [95%CI 0.8 to 4.4; P<0.01]) at 30 minutes of HD. Additional analyses, adding potassium or urea to the mixed effect model did not change these results.

Cumulative ultrafiltration volume predicts total intradialytic syndecan-1 shedding in HHD but not in SHD

In univariate analysis, a higher total UF volume tended to be associated with a higher degree of intradialytic syndecan-1 shedding (R^2=0.085; P=0.04). When SHD and HHD were analyzed separately, a similar correlation was observed in HHD (R^2=0.135; P=0.05), but not in SHD (R^2=0.005; P=0.70) (**Figure 2**).

Multivariate analysis showed that total UF volume independently predicted total intradialytic syndecan-1 shedding during dialysis. Patients with higher total UF volume during dialysis had higher AUC values for syndecan-1 (AUC increase of 3.5 [95%CI 0.8 to 6.2]; P=0.03, per 0.1 L increase in total UF volume). Total UF volume predicted syndecan-1 AUC in HHD (AUC increase of 6.2 [95%CI 2.1 to 10.3]; P=0.01) but not in SHD (AUC increase of 1.5 [95%CI -2.4 to 5.4]; P=0.48). In the mixed effects model, the association between total

257 ultrafiltration volume and syndecan-1 was not influenced by the presence of residual renal
258 function (P=0.255).
259

Discussion

The main finding of this study was that the rise in plasma syndecan-1 levels was more pronounced and occurred earlier during HD with higher plasma sodium levels. Cumulative syndecan-1 shedding tended to be higher during HHD. Our study is the first to show this effect of higher plasma sodium levels on plasma syndecan-1 in HD patients. Although we cannot prove that the rise in plasma syndecan-1 originates from the endothelial glycocalyx, our findings are compatible with sodium-driven endothelial glycocalyx-derived syndecan-1 shedding.

Plasma syndecan-1 levels not only increased during HHD but also during SHD confirming our previous findings in SHD patients (22). Acute rises in plasma syndecan-1 levels can be elicited by inflammatory and oxidative stimuli. Both stimuli are inherent to the HD procedure due to the bioincompatibility reaction that results from the contact between blood and the extracorporeal system. The present study shows that the intradialytic course of plasma sodium levels is an additional and modifiable factor.

Syndecan-1 shedding after an acute inflammatory insult (such as the HD procedure) is considered to originate from the endothelium (47) among other cells/tissues and to reflect glycocalyx damage by being cleaved and shed into the circulation (2, 7, 13, 52). Although syndecan-1 is present in the glycocalyx of multiple different cell types, its location and shedding from the endothelial glycocalyx is a possibility that has been shown by previous researchers (38). We conclude that higher plasma sodium concentrations in HD patients are associated with an earlier and more pronounced intradialytic rise in plasma syndecan-1 levels. Referring to the literature, it is likely that (among other tissues) this syndecan-1 shedding takes place from the endothelial glycocalyx. This is in accordance with *in vitro* data using endothelial cells in culture. These in-vitro studies have shown that the stability of the eGC can be influenced by sodium. Here, incubation of human endothelial cells (EA.hy926) with human plasma containing high sodium levels (147 mM or + 2–5 mM) led to the collapse of the eGC resulting in endothelial stiffening as measured with atomic force microscopy (28). In fact, next to a reduction in the glycocalyx component heparan sulfate in

immunofluorescence stainings, syndecan-1 was also found to be increased in the supernatant upon sodium overload (38). This indicates that sodium is a factor in glycocalyx breakdown and cleavage of syndecan-1. Moreover, research has shown that high sodium levels cause a down-regulation of nitric oxide formation in endothelial cells, again indicating ED (6, 8, 29). Also human studies in normotensive men have shown that intravenous sodium loading has a direct damaging effect of the endothelial surface layer (35).

In our study, lower predialytic plasma sodium concentrations and osmolality were associated with greater intradialytic increases in syndecan-1 levels. This could indicate that lower predialytic plasma sodium levels provide a stronger stimulus for syndecan-1 shedding and thus ED. Alternatively, lower predialytic plasma sodium concentrations could reflect diluted plasma sodium levels due to higher intravascular fluid volume as a result of overhydration. Volume overload could be responsible for syndecan-1 shedding which is in line with previous research findings (9). Dekkers et al. reported an association between moderate and severe fluid overload and lower survival in HD patients which was linked to inflammation (11). Further studies explored that volume overload can lead to ED next to inflammation, which has also been reported in HD-dependent patients with CKD (27). This is in accordance with our finding that higher total UF volume tended to be associated with a higher degree of intradialytic syndecan-1 shedding in the HHD modality. Again, we think this association is only found in the HHD group because of the higher initial sodium load that potentiates syndecan-1 shedding.

Several studies have shown the detrimental effects of excessive sodium intake which has been linked to the expansion of extracellular volume and hypertension. Various studies showed evidence that low sodium intake reduces blood pressure in both normotensive individuals and hypertensive patients. (1, 18) Interestingly, subjects with a long term stable sodium diet showed changes in total body sodium that were not related to changes in extracellular volume or body weight (52). This advocates the presence of a buffer where sodium can be stored in a non-osmotic way. Studies on marine invertebrates versus vertebrates have shown that the more a subject is exposed to sodium, the more sulfated

316 GAGs would be required (14, 50). In humans, such highly sulfated heparan sulfated GAGs
317 are especially found in tissues that serve as a barrier, such as the skin, the lungs and the
318 endothelium. In the skin, the inactivation of sodium by binding to GAGs in an non-osmotic
319 way has already been shown by Titze et al. (46) The highly sulfated negatively charged
320 GAGs in the endothelial glycocalyx may have similar sodium-binding properties. In contrast
321 to the skin interstitium, the endothelial glycocalyx is in direct contact with circulating sodium
322 and could therefore serve as a buffer before it enters the interstitium. In vitro experiments
323 using sodium nuclear magnetic resonance have shown that sodium binds reversibly to GAGs
324 in the endothelial glycocalyx under flow (41). The negatively charged GAGs may attract
325 positively charged sodium ions which form the most abundant group of cations in the blood
326 (41). Vlahu et al. have shown that elevated levels of plasma syndecan-1, reflecting
327 glycocalyx breakdown, has been associated with increased need for ultrafiltration (51).
328 According to these data, GAGs in the endothelial glycocalyx seem to play a role in sodium
329 homeostasis. Next to that, there seems to be a detrimental effect of sodium on the
330 endothelial glycocalyx as well, which has been shown by Oberleithner et al. (28) and other
331 research groups (35, 38). So far, no study has investigated yet how this seemingly paradox
332 is related. We speculate that one underlying mechanism could simply be an overload of
333 sodium in the endothelial glycocalyx which possibly results in a breakdown or collapse.

334 There are important limitations in our study. Although this is the largest study
335 comparing courses of syndecan-1 during different salt conditions, the study population is still
336 relatively small. Future studies with greater power have to be performed before definite
337 conclusions can be drawn. As this is a short-term study of the effects of a temporary
338 intradialytic increase in plasma sodium, we cannot extrapolate the findings to long-term
339 treatment with HHD. Therefore, the clinical implications of the more pronounced increase in
340 syndecan-1 levels during HHD are still unknown. This should be addressed in future studies
341 using robust clinical outcome parameters, for instance data on arterial stiffness (24, 25) and
342 functional ED tests, CV events and survival, as well as markers for inflammation and the
343 endothelium.

In conclusion, the rise in plasma syndecan-1 levels was more pronounced and occurred earlier during hemodialysis with higher plasma sodium levels. Although we cannot prove that the rise in plasma syndecan-1 originates from the endothelial glycocalyx, our findings are compatible with sodium-driven endothelial glycocalyx-derived syndecan-1 shedding.

Our findings also suggest that the HD procedure itself may contributes to ED in dialysis patients. Further research should explore the pathophysiology and clinical implications in further depth and in a larger cohort.

Grants

This study was supported by the Dutch Kidney Foundation (grant C08.2279) and the Graduate School of Medical Sciences of the University Medical Center Groningen.

Disclosures

None to declare.

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Figure 1. Levels of plasma sodium and plasma syndecan-1.

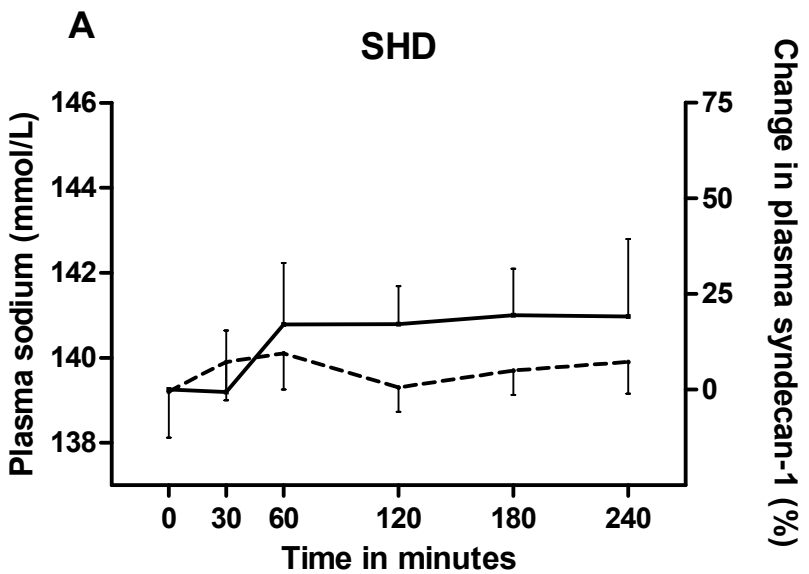
Courses of plasma sodium (dotted line) and plasma syndecan-1 (solid line) during SHD (A; left panel) and during HHD (B; right panel). Values are presented as mean for sodium and percentage change for plasma syndecan-1; error bars indicate 95%confidence intervals.

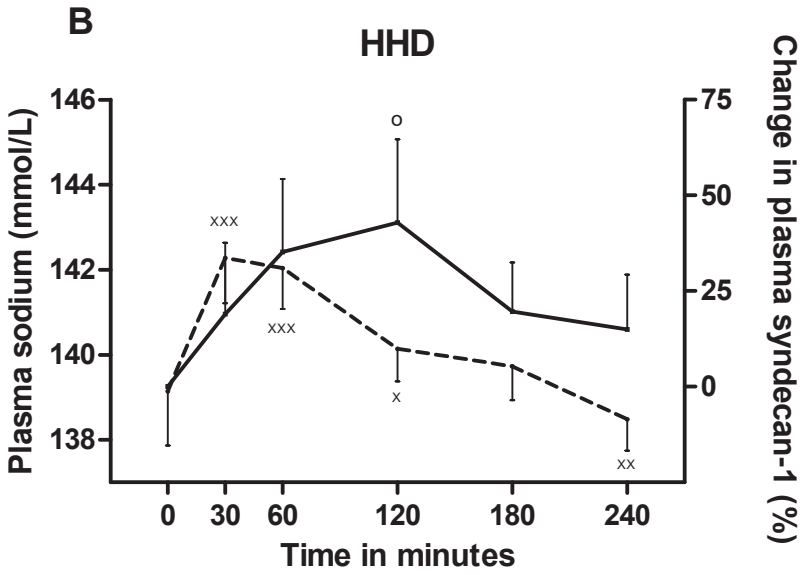
×: P-value of <0.05, **××**: P-value <0.01, **×××**: P-value<0.001 for the difference in plasma sodium between SHD and HHD. **O**: Indicates P-value of <0.05 for the difference in plasma syndecan-1 level between SHD and HHD.

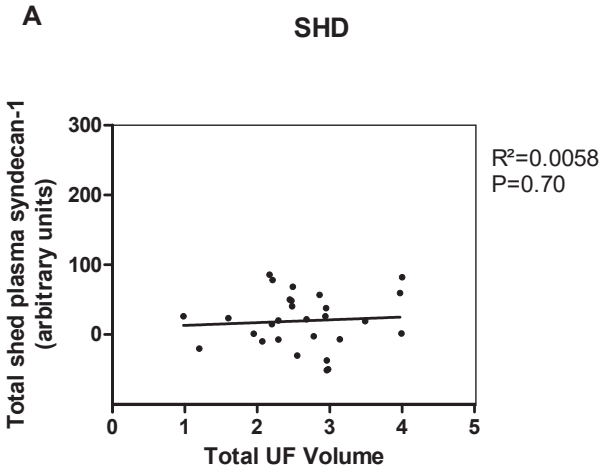
539 **Figure 2. Relationship between the total UF volume and total syndecan-1 shedding.**

540 Univariate relationship between total shed plasma syndecan-1 and total UF volume during

541 SHD (A; left panel) and HHD (B; right panel).







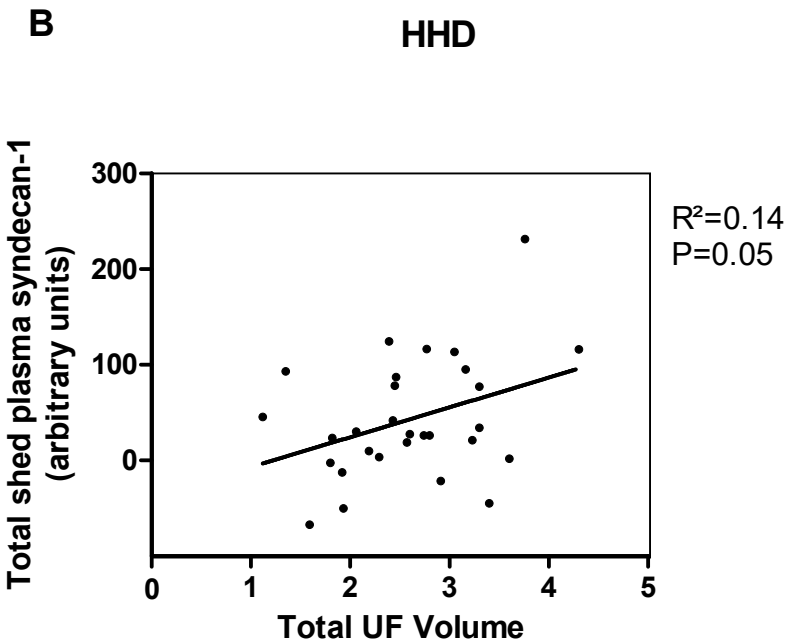


Table 1. Patient characteristics.

Number of patients	29
Females, n (%)	8 (28)
Age, y	63.4 ± 17.0
Dialysis vintage, m	33.9 ± 27.0
Residual renal function (RRF),	
Proportion of patients with RRF, n (%)	15 (51.7)
RRF, ml/min	1 (0.0 to 3.1)
Cardiovascular history, n (%)	15 (52.0)
Diabetes mellitus, n (%)	8 (28.0)
Hypertension, n (%)	26 (90.0)
Cause of renal failure, n (%)	
Hypertension	8 (28.0)
Glomerulonephritis	4 (14.0)
Diabetes mellitus	3 (10.0)
Hydronephrosis	2 (7.0)
Other	6 (21.0)
Unknown	6 (21.0)
Concomitant medication, n (%)	
Statins	9 (31.0)
Antihypertensive drugs	23 (79.0)
Immunosuppressive drugs	4 (14.0)
Insulin	7 (24.0)

Data are shown as means ± SD, except for RRF which is shown as medians with interquartile ranges in parentheses. Categorical distributed variables are shown as numbers and percentages [*n* (%)]. Abbreviations: m, months; n, number; RRF, residual renal function; y, years.

Table 2. Characteristics for SHD and HHD.

	SHD	HHD	P-value*
Sodium, mmol/L Predialysis	139.0 ± 3.0	139.0 ± 3.4	0.90
Plasma syndecan-1, ng/mL Predialysis	59.0 (33 to 88)	51.0 (26.0 to 87.0)	0.023
Plasma potassium, mEq/L Predialysis	4,8 (4,6 to 5,3)	4,8 (4,5 to 5,1)	0,803
Plasma urea, mmol/L Predialysis	27,1 (20,8 to 31)	26,8 (19,7 to 30,6)	0,973
Osmolality, mosm/kg Predialysis	285.0 ± 5.7	286.0 ± 6.1	0.85
Ultrafiltration volume, L	2.6 ± 0.7	2.6 ± 0.7	0.95
Weight, kg			
Predialysis	82.1 ± 16.0	82.3 ± 16.0	0.96
Postdialysis	80.0 ± 16.0	80.1 ± 16.0	0.50
Systolic BP, mmHg			
Predialysis	136 (121 to 147)	137.0 (122 to 150)	0.62
Postdialysis	135 (114 to 147)	139 (120 to 153)	0.54
Diastolic BP, mmHg			
Predialysis	73 ± 12	74 ± 11	0.87
Postdialysis	72 ± 12	71 ± 12	0.83

Data are shown as means ± SD, except for plasma syndecan-1 and systolic BP which are shown as medians with interquartile ranges in parentheses. Abbreviations: BP, blood pressure; HHD, Hemocontrol hemodialysis; kg, kilogram; L, liter; mmHg, millimeter of mercury; mmol/L, millimol per liter; mosm/kg, milliosmol per kilogram; ng/mL, nanogram per milliliter; SHD, standard hemodialysis. * P-value for difference at baseline between SHD and HHD.

Table 3. Change in plasma sodium and percentage change in plasma syndecan-1 levels during SHD and HHD.

	SHD		HHD		SHD versus HHD
Time	**Plasma sodium, mmol/L**				
		P-value*		P-value*	P-value
0 min	139.2 [138.1, 140.4]		139.1 [137.9, 140.4]		
30 min	139.9 [138.9, 140.8]	0.0299	142.3 [141.2, 143.3]	<0.0001	<0.0001
60 min	140.1 [139.3, 140.9]	0.0130	142.0 [141.1, 142.9]	<0.0001	<0.0001
120 min	139.3 [138.7, 139.9]	0.7259	140.1 [139.4, 140.9]	0.0523	0.037
180 min	139.7 [139.1, 140,1]	0.2673	139.7 [138.9, 140.5]	0.3296	0.971
240 min	139.9 [139.2, 140.6]	0.4441	138.5 [137.7, 139.2]	0.3956	0.002
Time	**Plasma syndecan-1, percentage change**				
0 min	0	P-value*	0	P-value*	P-value
30 min	-0.6 [-16.8,15.5]	0.678	19.0 [0.3, 37.6]	0.007	0.313
60 min	17.0 [0.9, 33.1]	0.162	35.2 [16.2, 54.3]	<0.001	0.069
120 min	17.2 [7.3, 27.1]	0.003	42.9 [21.1, 64.6]	<0.001	0.029
180 min	19.5 [7.3, 31.6]	0.016	19.7 [6.8, 32.5]	0.026	0.891
240 min	19.1 [-1.1, 39.4]	0.515	14.9 [0.6, 29.3]	0.223	0.701

Results for sodium are presented as mean [95% confidence interval]. Results for plasma syndecan-1 are presented as percentage change from 0 min [95% confidence interval]. * P-value for percentage difference in syndecan-1 levels and absolute difference in sodium levels compared to baseline (0 min) within dialysis modalities. Abbreviations: HHD, Hemocontrol hemodialysis; min, minutes; mmol/L, millimol per liter; SHD, standard hemodialysis.