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Albumin Loss in Post-Dilution On-Line Hemodiafiltration Compared With Pre-Dilution On-Line Hemodiafiltration and Conventional Hemodialysis

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Abstract

Background: The purpose of the study was to investigate the amounts of albumin lost in the dialysate in a dialysis session using either a high-flux (on-line hemodiafiltration (HDF)) or a low-flux filter (conventional hemodialysis (HD)).

Methods: The loss of albumin was studied in 10 hemodialyzed patients, with on-line HDF (pre- and post-dilution) and with conventional HD. We determined the albumin loss in the total ultrafiltrate for four different dialysis models.

Results: No change was found in serum albumin levels when switching from conventional HD to on-line HDF. The loss of albumin in on-line HDF post-dilution, with a high-flux filter of 2.5 m^2 (group A) was marginally significantly greater than the loss with the same filter with a surface area of 2.1 m^2 (group B) ($P = 0.05$). However, there was no difference in albumin loss when comparing groups A and B with group C (conventional HD) (P = NS). Albumin loss was significantly less in group D (pre-dilution on-line HDF, with filter 2.5 m^2 surface area) compared to groups A ($P < 0.01$), B ($P < 0.01$) and C ($P < 0.03$). The urea reduction ratio in each case (groups A, B, C and D) was, on average, > 73.5%, but in group C, it was significantly lower than in groups A and B ($P < 0.05$). Transmembrane pressure in group D was clearly lower than in groups A and B.

Conclusion: The polyethersulfone filters (polynephron) used in the on-line HDF lost very little albumin in a session (more with post-dilution), but this increased when their surface area and the transmembrane pressure increased. The urea reduction ratio was above the desired target in each model of dialysis using this filter, including both surface areas.

Keywords: On-line HDF; Post-dilution; Pre-dilution; Albumin loss; Polyethersulfone; Conventional hemodialysis

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Introduction

Hemodiafiltration (HDF) has been established as the best method of dialysis for patients with end-stage renal disease. The attributed clearance it offers is the highest, both in the form of the pre- and post-dilution models. However, there are reports that the method has negative effects on patients, including loss of albumin during the session, but this has not yet been fully clarified in the literature.

The aim of our study was to determine the amount of albumin lost during a dialysis session, using a polyethersulfone filter with both pre-dilution and post-dilution HDF, and with conventional hemodialysis (HD), with filters of the same synthesis.

Materials and Methods

Patients

Ten patients were studied (seven males and three females), aged 48 - 85 years (mean ± standard deviation (SD): 65.5 ± 11, median age: 68.5 years). All had initially been on conventional HD for 10 - 450 months (145 ± 158) and subsequently on on-line HDF for at least 4 months (12.2 ± 7.08). Their primary diseases were glomerulonephritis (four), polycystic kidney disease (two), hypertensive nephrosclerosis (one), and unknown etiology (three). Six of them had a native arteriovenous anastomosis, three had a graft, and one had a double-lumen jugular vein dialysis catheter. Only three had residual renal function (24 h urine output > 400 mL/24 h in the day off dialysis), and the other seven had urine output of less than 150 mL/day (Table 1).

Patients with cancer, active infection, known cardiovascular disease, and unstable hemodynamic status during the dialysis sessions were excluded from the study.

Methods

At the mid-week session (Wednesday or Thursday), a blood sample was taken before the start of dialysis for analysis of serum urea and albumin levels. One hour after the end of the

Table 1. Age, Body Weight, Water Composition of Patient's Body, Residual Urination, Duration of Dialysis Session, Months on Conventional Dialysis, and Months on On-Line HD

Patients (a/a)	Age (years)	BW (kg)	Total body water (L)	Duration of dialysis session (h)	Residual urination/24 h (mL)	Months on dialysis	Months on HDF
1	48	74	42.5	4	500	71	24
2	69	67.5	37.2	4.15	0	258	19
3	56	73	34.8	4	100	54	10
4	57	65	31.6	4.15	150	89	24
5	68	59.5	34.6	4	0	450	10
6	70	70	36.7	4	150	61	10
7	85	84	40.3	4	100	19	9
8	77	85	41.7	4	750	10	4
9	72	69	31.7	4	500	29	8
10	53	79	40.3	4.45	0	417	4
Mean ± SD	65.5 ± 11.03 (median 68.5)	72.6 ± 7.76	37.1 ± 3.76	4.08 ± 0.14		145 ± 158	12.2 ± 7.08 (range 4 - 24)

Body water was determined by Watson formula. BW: body weight; HDF: hemodiafiltration; SD: standard deviation.

session (to allow for urea redistribution in the body), a blood sample was taken to determine the same parameters. All procedures were in accordance with the ethical standards of the Scientific Council of our Hospital.

Low molecular weight heparin (bemiparin) was used in all patients in doses of 2,500 - 3,500 IU/session, depending on their body weight. For all patients, the blood supply to the filter was 400 mL/min, with arterial aspiration pressure < 200 mm Hg [1] and the dialysate flow rate was 500 mL/min, as previously specified by others [2] (all HD machines used were the Nikkiso DBB EXA). The duration of the sessions for seven patients was 4 h, for two patients, it was 4 h and 15 min, and for one patient, it was 4 h and 45 min (Table 1).

Polyethersulfone-polynephron filters (Elisio 2.1 m^2 and 2.5 m^2 high-flux and 2.1 m^2 low-flux) were used. All patients underwent one post-dilution on-line HDF session with a filter surface area of 2.5 m^2 (group A) and a second session with a 2.1 m^2 surface area (group B), one pre-dilution HDF session with a 2.5 m^2 high-flux filter (group D) and one session of conventional HD with a low-flux filter of 2.1 m^2 (group C). The substitution volume used in the post-dilution was 25% of the blood pump (i.e., > 24 L/session), while in the pre-dilution, it was 50% of the blood pump (i.e., > 48 L), which was considerably greater than the body water of each of our patients. In our analysis of the results, the median value of transmembrane pressure (TMP) during the session was used (Table 1).

The entire ultrafiltrate was collected in a specially made volumetric barrel. At the end of the session, and after mixing the ultrafiltrate with an electric stirrer for 10 min, a sample was taken for the determination of urea and albumin levels.

The Abbott Alinity C analyser was used to determine the parameters studied. Urea was determined by an enzymatic method, while albumin was determined by a colorimetric method.

For the statistical analysis, the Student's *t*-test and the paired *t*-test were used. Differences were considered significant when the significance level was $P < 0.05$.

Results

Previously, as mentioned, all patients had been in a conventional HD program for 10 - 450 months (mean ± SD: 145 ± 158 months). Then, for another 4 - 24 months, they had been on on-line post-dilution HDF (mean ± SD: 12.2 ± 7.08 months). Before the start of the on-line HDF, their serum albumin levels were, on average, 42.1 ± 2.6 g/L (in nine > 40 g/L and in one 39 g/L). After 4 - 24 months on the new method (post-dilution on-line HDF), this had essentially not changed, since it was now on average 41.4 ± 2.8 g/L (in eight > 40 g/L, in one 37 g/L and in another one 39 g/L), a difference that was not statistically significant (P = NS) (Table 2).

Albumin loss in group A was marginally significantly greater compared to albumin loss in group B (2.82 ± 1.19 vs. 1.94 ± 0.97 g/dialysis session, P = 0.05), but there was no difference in albumin loss between group A and group C (2.82 ± 1.19 vs. 2.36 ± 0.87 g/dialysis session, P = NS). However, the loss in group D was statistically significantly lower than that in all the other groups (A, B, C) ((A-D) 2.82 ± 1.19 vs. 1.75 ± 0.097 g/dialysis session, $P < 0.01$; (B-D) 1.94 ± 0.97 vs. 1.75 ± 0.097 g/dialysis session, $P < 0.01$; (C-D) 2.36 ± 0.87 vs. 1.75 ± 0.097 g/dialysis session, $P < 0.03$) (Table 2). TMP was significantly lower in group D compared to groups A ($P < 0.0001$) and B ($P < 0.0001$).

The urea reduction ratio (URR) in every case (groups A, B, C, D) was, on average, > 73.5% but, in fact, it was significantly lower in group C compared to groups A and B (Table 2).

Discussion

The serum albumin concentration is the net result of its synthesis by the liver (about 12 g/24 h), its catabolism (about 4%/24 h) (which increases in inflammatory diseases) [3], its volume

Table 2. Serum Albumin (Before and After Starting On-Line HDF), Dialysate Albumin During On-Line HDF and Conventional Hemodialysis and URR of Patients in Every Group

Patients (a/a)	Serum albumin (g/L)		Dialysate albumin (g/session)				URR (%)				TMP (median)		
	Serum albumin during HD	Serum albumin during HDF	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D	Group A	Group B	Group D
1	40	44	2.93	1.46	2.43	1.68	70.4	70	66.2	69.2	173	197	74
2	43	41	4.55	4.55	3.77	1.77	76.5	76.1	75.2	74.7	69	198	63
3	48	42	2.93	1.45	2.51	1.70	76.5	79.2	74.5	76.4	164	108	58
4	40	42	3.08	1.52	1.28	1.79	77.2	77.9	73.5	77.1	171	196	54
5	41	40	4.35	1.45	3.68	1.68	77.6	80	76.5	78.1	77	193	105
6	44	39	4.30	1.46	2.47	1.75	74	73.4	71.4	72.7	176	175	72
7	44	48	1.49	1.43	2.43	1.73	75.6	76.1	75.2	76.2	165	187	71
8	39	41	1.43	2.90	1.22	1.70	74.3	73.2	70.8	70.7	166	167	82
9	42	40	1.46	1.45	1.23	1.65	78	78.6	77.1	79.4	164	112	70
10	40	37	1.72	1.71	2.60	2.01	80.1	78.8	75.8	73.4	122	121	79
Mean ± SD	42.1 ± 2.6	41.4 ± 2.8	2.82 ± 1.19	1.94 ± 0.97	2.36 ± 0.87	1.75 ± 0.097	76.0 ± 2.5	76.3 ± 3.1	73.33 ± 3.3	74.8 ± 3.1			
P	Paired *t*-test (P = NS)		*t*-test: P(A-B) = 0.05; P(A-C) = NS; P(B-C) = NS; P(A-D) < 0.01; P(B-D) < 0.01; P(C-D) < 0.03				*t*-test: P(A-C) < 0.05; P(B-C) < 0.05; P = NS for all other correlations				*t*-test: P(A-B) = NS; P(A-D) < 0.0001; P(B-D) < 0.0001		

Group A patients on post-dilution on-line HDF with filter 2.5 m^2, group B on post-dilution on-line HDF with filter 2.1 m^2, group C on conventional hemodialysis with filter 2.1 m^2 and group D on pre-dilution on-line HDF with filter 2.5 m^2. HD: hemodialysis; HDF: hemodiafiltration; SD: standard deviation; TMP: transmembrane pressure; URR: urea reduction ratio.

of distribution, its exchange between the intra- and extra-vascular space (70% of albumin is normally in the vascular space, which also applies to hemodialyzed patients), and losses from the body (via the digestive system, the kidneys or due to the dialysis filter). In our patients, the clearance was excellent, since the URR was > 73.5% in every model of dialysis used. Of course, in cases where there are reduced serum albumin levels, the most important role is played by its reduced synthesis. This is due to the inhibitory effect on the synthesis of albumin from acute phase response, which usually happens in infections, but also in other conditions (cancers, immune diseases, etc.).

The 1999 - 2010 NHANES study showed that 53% of patients with an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 had serum albumin levels < 42 g/L [4]. The percentage will clearly be even lower in hemodialyzed patients compared to the general population. Indeed, the KDOQI guidelines recommend that serum albumin levels in hemodialyzed patients be maintained above 40 g/L [5]; however, the DOPPS data show that over 60% of hemodialyzed patients have serum albumin levels < 40 g/L [6]. Lowrie and Lew also reported mean serum albumin levels of 38 g/L in 12,000 cases [7]. Eriguchi et al (n = 36,757) found mean serum albumin levels of 35.7 ± 4.6 g/L [8]. Ye et al (n = 110,794) found mean serum albumin levels of 35 ± 5 g/L [9], while Kalantar-Zadeh et al (n = 58,058) reported mean serum albumin levels < 40 g/L in 72% of their patients, with 52% of them having serum albumin levels < 38 g/L [10]. Compared to the figures reported in these studies, almost all our patients had higher serum albumin levels and were within the desired level.

Basically, in hemodialyzed patients, the synthesis of albumin is related to its level in the plasma [11], which means that, in the absence of malnutrition or inflammation, patients maintain albumin levels within normal limits through an increase in its synthesis [12]. This is confirmed by data showing that in nephrotic patients, relative to the degree of albuminuria, the absolute rate of albumin synthesis increases by 7.7 g/1.73 m^2/24 h (a 73% increase), compared to controls (i.e., patients: 18.2 ± 2 vs. controls: 10.5 ± 1 g/1.73 m^2/24 h) [12].

Based on data in the literature, the question remains whether the reduction in serum albumin levels due to filter loss is harmful. It is not known whether the loss with on-line HDF has an impact on serum albumin levels or on patient survival [13]. This is because the main cause of hypoalbuminemia in hemodialyzed patients is the reduction in the rate of albumin synthesis and an increase in its catabolism due to the stimulation of the acute phase response [14] and not due to its loss. This may explain why we did not find a decrease in serum albumin levels in our patients after 4 - 24 months of HDF.

Albumin, on the other hand, is a protein binder for uremic toxins, so it could play a positive role in ameliorating the toxicity of uremia [15, 16]. Obviously, as more of it is removed with on-line HDF, the higher the molecular weight of the uremic toxins removed with dialysis. In other words, its loss may be beneficial, due to the significant removal of associated toxins, and also due to the loss of its oxidized form (that is, the form that has lost its antioxidant activity), as well as the end glycosylation products [17]. It is noted that this loss can promote the synthesis of new albumin that does have antioxidant properties [18].

There is a loss of albumin during the replacement of renal

function, and as we found, the amount that is lost varies with the model of dialysis. High-flux membranes achieve better removal of medium- and high-molecular weight toxins [19], and several studies show that albumin loss during on-line HDF with high-flux membranes ranges from 1 to 3 g per session [20-22], consistent with our findings. Other researchers have argued that a weekly loss of < 12 g of albumin during dialysis sessions, due to the use of filters, appears to be of little risk [23]. This finding agrees with those of others who suggest that a "desirable loss of albumin in one session should be less than 4 g" [24]. At this level of loss, serum albumin levels are stable in patients on long-term on-line HDF [25], as our results confirmed. However, using these membranes, some researchers have found an initial increase in serum albumin levels [26]. After 6 months of dialysis with these filters, others have found an increase in serum albumin of 0.5 - 1.1 g/L [27].

As is to be expected, albumin loss by the convection treatment is greater, especially when using post-dilution on-line HDF (range 0.08 - 7.0 g/4 h of treatment) [23, 28-31]. In the literature, albumin loss in pre-dilution on-line HDF is generally less (range: 3.0 - 4.8 g/4 h session), due to the diluted albumin available for transport [29, 32-34], as we also noted.

Since HDF relies on convection, which is the driving force for the removal of small molecular weight proteins, the loss of albumin and larger uremic toxins is dependent on the TMP, and the greater the TMP, the greater the loss, particularly in comparison with conventional HD [17]. This difference can be seen in pre- and post-dilution: in post-dilution, the TMP is higher and therefore, the albumin loss is greater, as we also found in our study.

Convection treatments significantly increase the removal of middle molecular weight toxins, compared to diffusion treatments, especially when high TMPs are applied [28, 35, 36]. In fact, it was found that the loss of albumin was greater during the first 30 - 60 min of the session, due to the high TMP applied to the intact membrane [34, 37]. This loss is then limited by the creation of a secondary protein layer on the dialysis membrane, due to deposition of proteins such as fibrinogen.

Another parameter that plays a role in the removal of albumin through the filter is the surface area [38]. An increase in its area, as well as an increase in blood supply to the filter, has been associated with an increased loss of amino acids [39, 40], as we also found to be true for albumin when using blood flow to the filter of 400 mL/min with a filter surface area of either 2.5 or 2.1 m^2 (group A vs. group B, $P = 0.05$).

Inadequate dialysis clearance can lead to anorexia, with consequent malnutrition and hypoalbuminemia. That is, the synthesis of albumin depends on the severity of the uremia and therefore on the dialysis dose. This association has been confirmed by studies showing an improvement in serum albumin levels after increasing the dialysis dose [41]. We also found our on-line HDF patients had a mean URR > 73.5% (range 70.4-80.1%) with serum albumin in the normal range, although some others do not agree with these results [42].

Albumin loss during convection with high-flux membranes is generally reported to range from 0 to 2 g per 4 h dialysis session, depending on membrane synthesis and filter surface area [3, 39, 43-46]. Our results confirm these findings.

Regarding serum albumin levels, studies have shown that when switching from high permeability HD membranes to a corresponding permeability (high-flux) for post-dilution on-line HDF, there is a decrease in serum albumin [47, 48]. It is important to note, however, that although albumin loss increases in patients who are on on-line HDF, no deterioration in nutritional status was noted. Although albumin loss increases with this model of dialysis, when patients who had serum levels of 39.2 ± 3.3 g/L on conventional HD, changed to post-dilution on-line HDF, after 1 year their serum levels were 39.1 ± 2.98, after 2 years they were 39.5 ± 3.03, after 3 years they were 39.4 ± 2.97, and after 4 years they were 41.4 ± 2.55 g/L, thus showing no statistically significant difference. Thus, a small decrease in serum levels was found, compared to conventional HD [47], indicating that albumin levels on conventional HD correspond to those of patients on on-line HDF, results with which do not agree with those of other researchers [49].

Finally, a study that investigated the efficacy and safety of 19 filters concluded that thermal sterilization increased the permeability of the membrane pores to albumin, compared to sterilization with γ-radiation [50]. The polynephron filters are sterilized by γ-radiation and this may have played a role in the small amount of albumin removed during the session.

Comparing the two types of membrane (polynephron and polyethersulfone), researchers found that polynephron showed less albumin loss in post-dilution on-line HDF [33]. In fact, it was found that the average loss of albumin in the dialysate ranged from 1.8 ± 0.6 to 5.7 ± 2.1 g per session. In post-dilution, polynephron is associated with a lower loss of albumin, compared to polysulfone, while in general, albumin loss is greater in post-dilution with both membranes, as we also found [33].

The polynephron membrane has a thin capillary wall (30 μm) and a relatively large pore size (78 Å), aiming overall at better elimination of large molecules, without higher loss of albumin. Of course, not all large pore membranes can be considered the same, even when their size or the polymers from which they are made, are identical [51, 52]. However, others investigating the polynephron membrane found no loss of albumin in the dialysate (considering the possible hemoconcentration at the end of the dialysis session with post-dilution) [53].

Finally, elixone and polyethersulfone membranes have been compared for albumin loss in on-line HDF. It was found that the latter lost more albumin than elixone, and that when the substitution volume was greater, more albumin was lost [36].

Conclusion

The conclusion is that polynephron filters in on-line HDF lose more albumin in the post-dilution model, which increases further if their surface area increases, and also with an increase of TMP, but the serum albumin levels do not drop below the recommended levels. The URR achieved with these filters was very good in every model of treatment investigated in our study.

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Conflict of Interest

The authors have no conflict of interest relevant to this article to disclose.

Informed Consent

Written informed consent was obtained from the patient before the study.

Author Contributions

KSM designed the study, read the literature, and wrote the manuscript. IMK and PSP found the literature, selected the patients, and helped run the study. All authors reviewed and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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