ORIGINAL ARTICLE

The effect of dialysis membrane type on plasma concentrations of pentosidine, a marker of carbonyl stress, in hemodialyzed patients

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KEY WORDS

carbonyl stress, hemodialysis, pentosidine, polysulfone membranes

ABSTRACT

INTRODUCTION Advanced glycation end products (AGEs), which accumulate in plasma of hemodialyzed patients, participate in the development of complications associated with hemodialysis (HD). Carbonyl stress plays an essential role in the formation of AGEs, including pentosidine.

OBJECTIVES The aim of the study was to assess the effect of various low-flux dialysis membranes on plasma concentrations of total (P_{tot}) and free (P_{free}) pentosidine.

PATIENTS AND METHODS We examined 56 adult patients (aged 50 ±13 years) on chronic HD. Plasma pentosidine concentrations were measured with high-performance liquid chromatography with fluorescence detection. Plasma proteins were subjected to acid hydrolysis or precipitation with trichloroacetic acid before measurement of P_{tot} and P_{free}, respectively.

RESULTS Significantly lower concentrations of P_{tot} were observed in patients dialyzed with polysulfone than non-polysulfone membranes before the HD session (22.0 ±11.9 vs 34.4 ±12.5 pmol/mg protein, respectively, $p = 0.0008$) and after the HD session (22.5 ±12.9 vs 32.9 ±12.0 pmol/mg protein, $p = 0.004$). Moreover, there was a strong inverse correlation between the percentage of HD sessions performed with polysulfone membranes during the last 3 months and P_{tot} concentration before HD ($Rs = –0.44$, $p = 0.0011$) and after HD ($Rs = –0.45$, $p = 0.00073$).

CONCLUSIONS The results suggest that polysulfone membranes reduce carbonyl stress more effectively than modified or unmodified cellulose membranes in patients on chronic HD. Determination of plasma pentosidine in hemodialyzed patients may help in comparing the physicochemical and biological properties of dialysis membranes. It may also contribute to the development of optimal strategies for renal replacement therapy.

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INTRODUCTION Pentosidine is one of the advanced glycation end products (AGEs).[1] Nonenzymatic glycation occurs in every species. It marks ageing structures and takes part in tissue remodeling. These processes are enhanced in diabetes mellitus[2,3], and particularly high concentrations of AGEs are noted in patients with chronic renal failure undergoing dialysis[4,5]. Structural and functional consequences of AGE production result from cross-linking of lysine and/or arginine, and include altered protein conformation and/or charge, lower susceptibility to protease activity, and higher resistance to denaturation.[6,7] Plasma lipoproteins modified by AGEs are less avidly bound to cellular receptors, while uptake of modified compounds by scavenger receptors localized on macrophages and monocytes leads to foam cell formation. The interaction of AGEs with their receptors initiates a cascade of reactions which cause an increased production and

release of cytokines, growth factors, and reactive oxygen species.[8-10] Thus, AGEs contribute to such complications as enhanced atherosclerosis in patients with chronic renal failure, loss of semi-permeable properties of peritoneal membrane in patients on peritoneal dialysis, and hemodialysis (HD)-related amyloidosis.[11-14] Plasma pentosidine is mostly bound to proteins and is not excreted through kidneys, therefore severe impairment of renal function is not a major contributor to significantly higher pentosidine concentrations in patients with chronic renal failure. It is rather a consequence of oxidative stress in dialyzed patients, or more specifically carbonyl stress which leads to accumulation of reactive carbonyl compounds (RCOs), being substrates to pentosidine formation.[15,16]

The previously reported data[17] demonstrated that the type of dialysis membrane is associated with intensity of carbonyl stress. We aimed to evaluate the effect of various types of dialysis membranes used in chronic HD therapy on plasma concentrations of total (P_{tot}) and free (P_{free}) pentosidine, a marker of carbonyl stress.

PATIENTS AND METHODS The study was conducted in 56 patients with chronic renal failure (28 women and 28 men), aged 50 ±13 years. The patients were hemodialyzed (bicarbonate dialysis) 2–3 times a week for a period of 40 ±49 months in three HD stations of north-western Poland (public hospitals in Drawsko Pomorskie and Szczecin, and the Department of Nephrology, Transplantology and Internal Medicine at the Pomeranian Medical University). Eight patients (14%) had diabetes mellitus. A mean time of dialysis session was 4.2 ±0.4 h. Blood flow through the dialyzer was 240 ±28 ml/min. Urea reduction ratio and Kt/V were 61.5 ±10.7% and 1.0 ±0.3, respectively.

TABLE 1 shows the comparison of membrane types used in the last HD session (during which the blood samples were obtained for pentosidine measurement). The ultrafiltration coefficients ranged from 4.0 to 9.4 ml/h/mmHg. The study was observational. The choice of dialyzer used in individual patients was at the discretion of the attending physician. During 3 months prior to the study, 13 patients were dialyzed using polysulfone membranes (PS), 25 using non-polysulfone (NPS) membranes, and 18 subjects were dialyzed with both types of membranes.

Blood samples were obtained before and after an HD session from peripheral venous puncture or dialysis catheter into standard test tubes containing EDTA as anticoagulant (Sarstedt Monovette). The blood was centrifuged for 15 min at 185 × g and plasma was immediately frozen at –80°C.

Plasma P_{tot} concentration (a sum of P_{free} and protein-bound pentosidine) was measured in a two-step process with high-performance liquid chromatography (HPLC) and fluorescence detection. Before the analysis, plasma was hydrolyzed with 6 M HCl at 110°C for 16 h. The inter- and intraassay coefficients of variation (CV%) were 6.4%. The procedure has been described in detail elsewhere.[18] The results are expressed per mg of plasma protein assayed with Bradford reagent[19], which helps to avoid the effect of hemoconcentration on post-HD pentosidine levels. To quantitate P_{free}, the sample was subjected to protein precipitation with 10% trichloroacetic acid. The separation procedure with HPLC has been previously described.[20] The CV% for P_{free} was 5.4%.

We also analyzed the following parameters: the mean value of pre- and postdialysis P_{tot} concentrations and the relative change of P_{tot} and P_{free} concentrations during dialysis expressed as a percentage. We evaluated the type of dialysis membrane used on the day of pentosidine measurement and the proportion of dialyses using PS membranes during 3 months prior to the study.

Statistical analysis Statistical analysis was performed using Statistica PL 7.1 software. The Kruskal-Wallis ANOVA and Mann-Whitney U tests were used to evaluate the significance of differences between parameters in the compared groups. The strength of correlation was expressed as Spearman's rank correlation coefficient (Rs). Data were presented as a mean value ± standard deviation and a median (lower quartile – upper quartile).

RESULTS **Association between pentosidine concentrations and a membrane type used in the last hemodialysis session** TABLE 1 shows concentrations of P_{tot} and P_{free} determined in plasma during the HD session using various membrane types.

No significant differences were observed in the analysis of P_{free} concentrations. A reduction of pentosidine concentrations during the HD session did not correlate with the type of membrane and the mean value was 2.9 ±10.1% for P_{tot} and 94.7 ±9.4% for P_{free}.

We observed significant differences in concentrations of P_{tot} before and after HD and mean of these values between patients dialyzed with four different types of membrane. After exclusion of PS membranes from the analysis, no significant differences were observed between patients dialyzed with three types of NPS membranes. Thus, during further analysis all patients dialyzed with NPS membranes were considered as a single group. Patients who were dialyzed with PS membranes had significantly lower P_{tot} concentrations compared with other patients (TABLE 2, FIGURE 1).

Association between pentosidine concentrations and a membrane type during 3 months preceding the study After analyzing the percentage of PS membranes used in individual patients during 3 months preceding the study, a strong inverse correlation was observed between this parameter and P_{tot} concentrations before HD (Rs = –0.44,

TABLE 1 Types of dialysis membranes and dialyzers used in hemodialysis, and concentrations of total and free pentosidine assessed in plasma of dialyzed patients

Membrane type	Polysulfone n = 20		Acetate or diacetate n = 9		Cuprammonium n = 13		Hemophan n = 14		
brand name	F_5 F_6		Nipro FB 130T Nipro FB 170T Altra Nova 140		GFE 09 Diacap CE 1400 T175		GFS Plus 12 GFS Plus 16		
parameters	mean ±SD	median Q25–Q75	mean ±SD	median Q25–Q75	mean ±SD	median Q25–Q75	mean ±SD	median Q25–Q75	p
total pentosidine concentrations (pmol/mg protein)									
pre-HD	22.0 ±11.9	22.2 12.2–28.9	37.7 ±18.1	33.1 24.8–43.7	30.3 ±9.74	31.2 24.1–35.4	36.2 ±10.0	38.5 28.7–42.2	0.0062[a] 0.39[b]
post-HD	22.5 ±12.9	19.3 12.0–29.0	37.5 ±17.5	35.7 24.9–47.9	29.5 ±9.6	29.2 24.1–36.6	32.8 ±9.3	31.7 25.8–41.3	0.030[a] 0.60[b]
mean value of pre- and post-HD	22.7 ±12.4	21.3 12.3–28.2	37.6 ±17.7	34.4 25.9–45.8	29.7 ±9.3	29.7 24.1–34.2	34.1 ±9.6	33.5 27.2–41.8	0.013[a] 0.48[b]
difference between pre and post-HD (%)	–1.6 ±8.8%	–3.4 from –9.5 to +3.5%	+0.7 ±10.9%	+6.1 from –1.3 to +7.7%	–3.1 ±11.3%	–2.0 from –7.4 to +2.5%	–6.8 ±9.9%	–5.7 from –10.4 to –2.0%	0.29[a]
free pentosidine concentrations (pmol/ml)									
pre-HD	42.1 ±27.9	38.0 24.1–57.6	45.2 ±26.1	45.7 28.4–66.9	45.0 ±16.3	49.5 29.4–54.2	52.3 ±24.5	60.4 33.0–73.0	0.49[a]
post-HD	4.9 ±7.9	1.8 0–5.1	3.1 ±7.9	0 0–1.0	5.3 ±7.8	1.5 0–9.8	7.1 ±13.0	0.6 0–3.1	0.50[a]
difference between pre and post-HD (%)	–95.1 ±7.9%	–98.3 from –94.9 to –100%	–96.9 ±7.9%	–100 from –99 to –100%	–94.7 ±7.8%	–98.5 from –90.3 to –100%	–92.9 ±13.0%	–99.5 from –97.0 to –100%	0.61[a]

a Kruskal-Wallis ANOVA for the difference between four membrane types
b Kruskal-Wallis ANOVA for the difference between three non-polysulfone membrane types

Abbreviations: HD – hemodialysis, Q25 – lower quartile, Q75 – upper quartile, SD – standard deviation

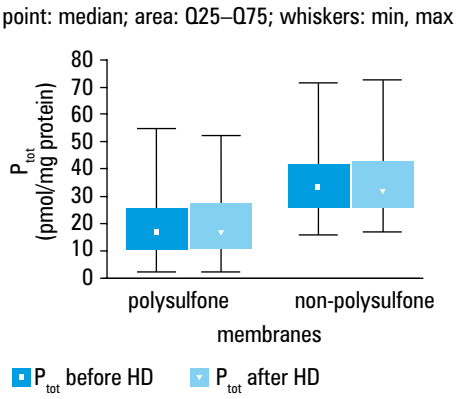

FIGURE 1 Plasma total pentosidine concentrations before and after hemodialysis with polysulfone and non-polysulfone membranes
Abbreviations: P_{tot} – total pentosidine, others – see TABLE 1

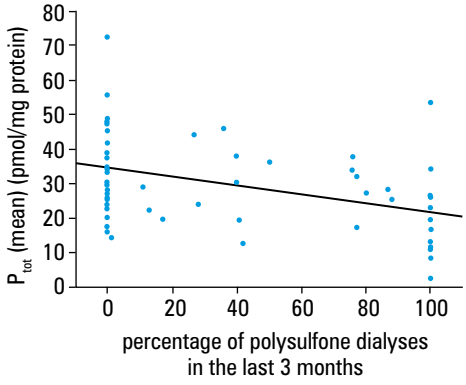

FIGURE 2 Association between plasma total pentosidine concentrations (mean before and after hemodialysis) and the percentage of polysulfone membranes used during the 3 months preceding the study
Abbreviations: see TABLE 1, FIGURE 1

p = 0.0011), after HD (Rs = –0.45, p = 0.00073) and a mean value from both measurements (Rs = –0.45, p = 0.00054). FIGURE 2 illustrates the relationship between mean P_{tot} concentration and a percentage of PS membranes.

The proportion of PS membranes did not affect P_{free} concentrations before HD (Rs = –0.13, p = 0.37) or after HD (Rs = –0.03, p = 0.81).

DISCUSSION

Dialysis membrane is the major determinant of the effectiveness of chronic HD therapy. Depending on the material, there are four different types of membranes:

1 cellulose membranes (cuprammonium cellulose)
2 cellulose membranes modified with acetate groups (cellulose acetate, diacetate, triacetate)
3 cellulose membranes modified with other groups (Hemophan with tertiary amines)
4 synthetic membranes (polyacrylnitrile, polysulfone, polycarbonate).[21]

Our study, which involved an analysis of the last HD session, demonstrated that only P_{tot} concentrations were affected by the type of membrane in low-flux dialyzers. The concentrations of P_{tot} before HD, after HD, and the mean value from the two measurements were significantly lower in patients dialyzed with PS membranes compared with patients dialyzed with NPS, but no significant differences were observed when various types of NPS membranes were compared.

The mean value of P_{tot} concentrations before HD in patients dialyzed with NPS membranes (34.4 ±12.5 pmol/mg protein) was more than 20-fold higher compared with healthy subjects.[18] Our results were similar to those of Stein et al. whose patients were dialyzed with low-flux membranes (polycarbonate and cellulose: 28 ±13.4 pmol/mg protein)[22], and insignificantly higher than those published by Miyata et al. whose patients underwent dialysis using cellulose membranes (21.7 ±9.5 pmol/mg protein[4], 17.15 ±5.64 pmol/mg protein[23]).

In the current study, concentrations of P_{free} measured before the HD session were similar in patients dialyzed with both NPS and PS membranes. For NPS membranes the mean value of the above parameter was 48.0 ±22.0 pmol/ml, which was consistent with the results of Miyata et al. (53.7 ±19.3 pmol/ml[4], 54.0 ±13.1 pmol/ml[23]).

The analysis, which considered the proportion of dialyses with PS membrane in each patient during 3 months preceding the study, showed that subjects dialyzed only with PS membranes had approximately 44% lower P_{tot} concentrations than those dialyzed only with NPS. The more frequently PS membranes were used, the lower P_{tot} concentrations were noted (FIGURE 2). Similar results, indicating lower plasma concentrations of P_{tot} in patients dialyzed with PS membranes, were published by Jadoul et al.[24], although these investigators used high-flux membranes. The differences between patients dialyzed exclusively with low-flux PS or NPS membranes were more distinct in our study (mean concentrations of P_{tot} before HD: 20.0 and 35.7 pmol/mg protein, respectively) than in the study of Jadoul et al. (15–16 and 22–25 pmol/mg protein, respectively). A similar analysis of P_{free} concentrations did not reveal significant differences (mean P_{free} concentrations before HD for patients dialyzed only with PS and NPS membranes were 37.7 and 47.8 pmol/ml, respectively). A beneficial effect of PS membranes on P_{tot} and P_{free} concentrations has been reported by Stein et al.[25] However, their results should be interpreted with caution because PS membranes they compared were high-flux while NPS membranes were low-flux. Yet, another study proves that using high-flux rather than low-flux dialyzers (both with PS membranes) does not significantly affect plasma P_{tot} or P_{free} concentrations.[26] The results of our and other cited studies suggest that the use of PS membranes is associated with lower plasma P_{tot} concentrations independently of dialyzer permeability.

The HD session only slightly affected plasma concentrations of P_{tot}. A mean decrease of 2.9% in pentosidine concentrations was observed but no significant differences were noted with reference to the membrane type. It is consistent with the reports of most investigators and results from the fact that protein-bound pentosidine is not filtered through the dialysis membrane. A slight decrease might be caused by the clearance of P_{free} or pentosidine bound to low-molecular-weight peptides.[22,23,25,27,28] Henle et al.[29], who used high-flux dialysis membranes, showed

TABLE 2 Total pentosidine concentrations in patients dialyzed with polysulfone and non-polysulfone membranes

Variables	Polysulfone n = 20		Non-polysulfone n = 36		p[a]
	mean ±SD	median Q25–Q75	mean ±SD	median Q25–Q75	
total pentosidine concentrations (pmol/mg protein)					
pre-HD	22.0 ±11.9	22.2 12.2–28.9	34.4 ±12.5	33.2 24.9–40.0	0.0008
post-HD	22.5 ±12.9	19.3 12.0–29.1	32.9 ±12.0	31.2 24.9–40.4	0.004
mean value of pre- and post-HD measurements	22.7 ±12.4	21.3 12.3–28.1	33.4 ±12.0	32.8 24.9–38.4	0.0018

a Mann-Whitney U test

Abbreviations: see TABLE 1

in their study a slightly greater (7%) reduction of P_{tot} concentrations after HD session.

On the other hand, the HD session eliminated most of P_{free} (the mean value was 94.7% and median 98.9% for all patients) but again no association between the elimination and the membrane type was observed. In approximately half of patients P_{free} after HD was not detected. Miyata et al., who evaluated P_{free} during cuprammonium low-flux HD session, showed a reduction in pentosidine concentrations by approximately 82%[23], while in a study of Stein et al.[25] the proportion of elimination for low-flux NPS, high-flux PS, and super-flux membranes was 76.1%, 76.6%, and 82.4%, respectively. High effectiveness of all membrane types in eliminating P_{free} is probably associated with its low molecular weight of 379 Da.

Many investigators evaluate the effectiveness of different types of dialysis membranes in eliminating P_{free} and P_{tot}.[22,24,25] Yet, no data are available to evaluate the influence of different types of low-flux membranes on plasma P_{free} and P_{tot} concentrations. We can only provide a hypothetical explanation for the lower P_{tot} concentrations in patients dialyzed with PS compared with NPS membranes, which we observed in our study. The interpretation of our results is confounded by the fact that the dialyzers had not only different membranes but also other parameters including surface area and blood volume. Probably, dialysis with PS membranes more efficiently removes RCOs, which are involved in pentosidine production[12,16] and have relatively low molecular weight (below 5000 Da)[16]. Because their excessive accumulation induces protein modification and AGE production, the condition is known as carbonyl stress, and plasma concentrations of protein-bound pentosidine are a marker of that condition.[30] The presence of carbonyl stress in chronically hemodialyzed patients was proved by Miyata et al.[16] They incubated the plasma of hemodialyzed patients, which was free from particles with molecular weight of more than 5000 Da. After 4 weeks they demonstrated an increase in pentosidine concentrations, particularly in the samples obtained before HD. Adding inhibitors of advanced glycation reactions, whose mechanism of action is to block reactive carbonyl compounds, suppressed the rise in pentosidine concentrations.

Lower plasma pentosidine concentrations in patients hemodialyzed with PS membranes may result from the fact that they eliminate pentosidine precursors more effectively. On the other hand, PS membranes may be associated with lower production of RCOs.[24] The HD procedure itself contributes to increased oxidative stress.[31-33] RCOs are produced mainly during carbohydrate, lipid, and amino-acid autooxidation.[15] Pentosidine concentration correlates positively with oxidative stress markers[34] and advanced oxidation protein products in plasma[35]. Therefore, the less oxidative stress is generated, the less RCOs and pentosidine are produced. To test these hypotheses, a prospective randomized trial with allocation of patients to homogenous groups using specific types of membranes is needed.

Our results suggest that PS membranes used in chronic HD therapy are more effective in reducing carbonyl stress and its markers than modified and unmodified cellulose membranes. Pentosidine determination in plasma of chronically hemodialyzed patients may help in comparing physicochemical and biological properties of dialysis membranes and in developing optimal strategies for renal replacement therapy.

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ARTYKUŁ ORYGINALNY

Wpływ rodzaju błon dializacyjnych na osoczowe stężenia pentozydyny – wskaźnika stresu karbonylowego – u hemodializowanych pacjentów

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błony polisulfonowe, hemodializa, pentozydyna, stres karbonylowy

STRESZCZENIE

WPROWADZENIE Zaawansowane końcowe produkty glikacji (*advanced glycation end products* – AGEs), gromadzące się w osoczu pacjentów poddawanych przewlekle hemodializom (*hemodialysis* – HD), uczestniczą w patogenezie powikłań związanych z tą metodą leczenia. Stres karbonylowy odgrywa kluczową rolę w tworzeniu się AGEs, w tym pentozydyny.

CELE W tym badaniu podjęto próbę oceny wpływu różnych typów niskoprzepływowych błon dializacyjnych na osoczowe stężenia pentozydyny całkowitej (P_{tot}) i wolnej (P_{free}).

PACJENCI I METODY Badania wykonano u 56 pacjentów w wieku 50 ±13 lat poddawanych przewlekle hemodializom. Stężenia pentozydyny w osoczu oznaczano przy użyciu wysokosprawnej chromatografii cieczowej z detekcją fluorescencyjną. Oznaczając P_{tot} białka osocza poddawano hydrolizie kwaśnej, a dla oznaczenia P_{free} wytrącano je kwasem trichlorooctowym.

WYNIKI Wykazano istotnie niższe stężenia P_{tot} u pacjentów dializowanych przy użyciu błon polisulfonowych niż niepolisulfonowych. Wynosiły one odpowiednio 22,0 ±11,9 i 34,4 ±12,5 pmol/mg białka ($p = 0,0008$) przed sesją HD oraz 22,5 ±12,9 i 32,9 ±12,0 pmol/mg białka ($p = 0,004$) po sesji HD. Ponadto wykazano silną ujemną korelację pomiędzy procentowym udziałem dializ polisulfonowych w okresie trzech miesięcy poprzedzających badanie, a stężeniem P_{tot} przed HD ($Rs = –0,44$, $p = 0,0011$) i po HD ($Rs = –0,45$, $p = 0,00073$).

WNIOSKI Wyniki przeprowadzonych badań sugerują, że błony polisulfonowe stosowane w przewlekłej hemodializoterapii są skuteczniejsze w redukcji stresu karbonylowego w porównaniu z błonami wykonanymi z modyfikowanej i niemodyfikowanej celulozy. Oznaczanie pentozydyny w osoczu pacjentów przewlekle hemodializowanych może być jedną z metod służących do porównania właściwości fizykochemicznych i biologicznych błon dializacyjnych oraz opracowania optymalnych strategii leczenia nerkozastępczego.

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