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Influence of hemodialysis membrane type on pentosidine plasma level, a marker of "carbonyl stress"

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Background. The accumulation of advanced glycation end products (AGEs) in uremia has been ascribed to the retention of carbonyl precursors of AGEs. Pentosidine plasma level has been identified as a surrogate marker of carbonyl precursors ("carbonyl stress"). The influence of hemodialysis (HD) membrane type and residual diuresis on carbonyl stress has not been studied.

Methods. We measured protein-linked and free plasma pentosidine (a surrogate marker of carbonyl stress) by high-performance liquid chromatography in patients on HD with low-flux cellulose ($N = 29$), high-flux polysulfone (PS; $N = 57$), polymethylmethacrylate (PMMA) ($N = 25$), and AN69 ($N = 15$).

Results. Both protein-linked and free pentosidine were similar on low-flux cellulose, high-flux PMMA, and AN69, but were lower ($P < 0.01$) on high-flux PS. Pentosidine levels were virtually identical on Fresenius and Asahi PS in Japanese and Belgian patients. By multivariate analysis, only the type of HD membrane and residual diuresis proved to be independent determinants ($P < 0.001$) of pentosidine levels. During a single HD session, the clearance of free pentosidine was similar with all membranes. In three patients who were switched from AN69 to PS, the protein-linked pentosidine level dropped to the control level after resumption of the AN69 membrane.

Conclusions. Both HD membrane type and residual diuresis are independent determinants of pentosidine plasma level, which is a marker of carbonyl stress.

Renal failure is characterized by elevated levels of advanced glycation end products (AGEs). AGEs modify proteins from both a structural and a functional point of view, and thus contribute to uremic toxicity [1, 2]. It has been recently demonstrated that enhanced AGE production resulted from the accumulation in uremic plasma of carbonyl AGE precursors, a so-called "carbonyl stress" [3, 4]. These various carbonyl intermediates are derived from carbohydrates, as well as from lipid sources [4–6]. The mechanisms influencing the level of carbonyl intermediates and thus the "carbonyl stress" in renal failure have become new targets of investigation.

The diversity of the carbonyl precursors in uremic serum limits the current investigation of this area. Fortunately, we previously discovered that pentosidine levels were highly correlated with the level of precursor carbonyls in uremic plasma [3]. Hence, we concentrated in this study on the determinants of plasma pentosidine level used as markers of carbonyl precursors in the plasma of patients treated by hemodialysis (HD).

Key words: dialysis, advanced glycation end products, uremic toxicity, low-flux cellulose, high-flux polysulfone, polymethylmethacrylate, AN69.

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METHODS

Patients

A total of 126 patients on three times per week maintenance HD (69 males and 57 females) either in Belgium ($N = 29$) or Japan ($N = 97$) were studied. Their mean age was 61.2 ± 13.0 (SD) years. Only two of them suffered from mild type II diabetes. All were on HD with the same membrane type for three months or more (or from the onset of HD in the few patients on HD for less than 3 months). Dialyzers were reused in 26 out of 29 Belgian patients but in none of the Japanese patients. Residual diuresis (ml/day), the surface of the dialyzer, and the duration of HD session in each patient were retrieved from the medical charts.

Membrane types

The membranes used included high-flux [ultrafiltration (UF) index more than 10 ml/mm Hg/hr] AN69 (AN69 group; from Hospal, Lyon, France), high-flux polysulfone (PS) from Fresenius (PS group; Bad Hom-

burg, Germany) and Asahi (APS group; Tokyo, Japan), high-flux polymethylmethacrylate from Toray (PMMA group; Tokyo, Japan), and low-flux cellulose from Asahi (cellulosic group; Tokyo, Japan).

Plasma samples

Plasma samples were obtained prior to the first weekly HD in all 126 patients and after the same session in 66 patients.

All samples were centrifuged rapidly, frozen at −20°C, and forwarded to the Tokai Laboratory for Cellular and Molecular Nephrology for analysis.

Measurements of total and free pentosidine

For quantitation of total pentosidine, the sample (50 μl) was lyophilized and hydrolyzed by 100 μl of 6 N HCl for 16 hours at 110°C under nitrogen, followed by neutralization with 100 μl of 5 N NaOH and 200 μl of 0.5 M phosphate buffer (pH 7.4), and then the sample was filtered through a 0.5 μm-pore filter and diluted 20 times with phosphate-buffered saline (PBS). For quantitation of free-form pentosidine, the sample (50 μl) was mixed with an equal volume of 10% trichloroacetic acid (TCA) and centrifuged at 5000 × *g* for 10 minutes. The supernatant was filtered through a 0.5 μm filter and diluted four times with distilled water. Pentosidine in these specimens was analyzed by reverse-phase high-performance liquid chromatography (HPLC) [7]. Briefly, a 50 μl solution of acid hydrolysate of plasma (corresponding to 25 μg of proteins) or diluted protein-free plasma (corresponding to 6.25 μl of plasma) was injected into an HPLC system and separated on a C18 reverse-phase column (Waters, Tokyo, Japan). The effluent was monitored using a fluorescence detector (RF-10A; Shimadzu) and an excitation-emission wavelength of 335/385 nm. Synthetic pentosidine was used to obtain a standard curve.

Protein-linked pentosidine (pentosidine/prot; pmol/mg protein) was calculated as follows:

$$\frac{\text{Total plasma pentosidine} - \text{Free pentosidine (pmol/ml)}}{\text{Plasma protein concentration (mg/ml)}}$$

Statistical analysis

Results are presented as means ± SD or as percentages. Residual diuresis data were log transformed before statistical analysis. The individual characteristics and pentosidine levels were compared between groups of patients on HD with different membranes by one-way analysis of variance (with F tests). Further analyses were performed to compare membrane groups two by two, using a Bonferroni criterion. The frequency of the persistence of residual diuresis was compared between the various groups by a chi-square test. The relationship between the pentosidine/prot and free pentosidine level on the one hand and residual diuresis on the other was analyzed by generalized linear regression analysis. The independent effect of each explanatory variable on the dependent variables (pentosidine/prot and free pentosidine) was assessed using forward stepwise multiple regression analysis with four dummy variables as indicators of the type of membrane; the fifth membrane corresponded to all four dummy variables equal to zero. Those dummy variables were forced into the regression equation before testing other variables and could not be removed thereafter. First-order interactions between dummy variables and explanatory variables were also considered as potential covariates for regression. Such an analysis is a more general approach to compare the different membranes than a two-way analysis of variance, because it allows one to control for the effects of dummy covariates as well as continuous covariates; the two-way analysis of variance is a special linear regression in which only dummy variables (main effects and interactions) are considered. An explanatory variable was considered as having an independent effect on the dependent variable if it led to a significant reduction in likelihood ratio statistics, and the effect was reported as partial correlation coefficient *r*. All analyses were performed using the BMDP statistical software [8]. *P* values of less than 0.05 were considered significant.

RESULTS

The characteristics of the five groups of patients of the cross-sectional study are listed in Table 1.

The groups do not differ significantly from each other for age. Plasma protein level was higher in the AN69 and cellulosic groups; dialyzer surface, duration of HD prior to the study, and duration of HD session were larger or longer in the APS group, whereas residual diuresis was higher in the PS group.

Predialysis plasma levels of protein-bound and free pentosidine were similar in the AN69, PMMA, and cellulosic groups and were significantly lower in the PS and APS groups. There was no significant difference between the two latter groups (Table 2).

Univariate analysis of the various factors that might influence predialysis plasma pentosidine levels disclosed a significant influence of residual diuresis on protein-bound and free pentosidine: the higher the diuresis, the lower the pentosidine levels. Neither plasma protein nor albumin levels, nor age nor duration of prior dialysis was correlated with pentosidine levels (Table 3). In the PS groups (PS–APS), predialysis pentosidine levels were similar in Belgian and in Japanese subjects whether given Fresenius or Asahi PS dialysis (Table 4).

Forward stepwise multiple regression analysis confirmed the result of the previous analyses. Membrane type and residual diuresis were the two sole, independent

Table 1. Characteristics of the five groups of patients dialyzed with different membranes

	APS $N = 29$	PS $N = 28$	AN69 $N = 15$	PMMA $N = 25$	Cellulosic $N = 29$	ANOVA P value
Age *years*	58 ± 12	61 ± 13	64 ± 7	61 ± 13	64 ± 16	NS
Time on HD *years*	13.7 ± 7.5[g]	5.4 ± 6.8	7.8 ± 6.7	9.2 ± 6.5	5.5 ± 4.4	<0.001
Protein plasma level *g/dl*	6.7 ± 0.5[b]	6.3 ± 0.7	6.8 ± 0.6	6.2 ± 0.3[c]	7.0 ± 0.4[a]	<0.001
Albumin plasma level *g/dl*	3.9 ± 0.3[e]	3.6 ± 0.4[d]	3.9 ± 0.4[f]	3.6 ± 0.3	4.2 ± 0.3[a]	<0.001
Duration of HD session *hours*	4.5 ± 0.23[h]	3.98 ± 0.40	4.13 ± 0.23	4.04 ± 0.48	4.00 ± 0.00	<0.001
Surface of hemodialyzer m^2	1.8	1.28 ± 0.36	1.42 ± 0.34	1.31 ± 0.32	1.32 ± 0.24	ND[j]
Residual diuresis *ml/day*						
Geometric mean (SD)	47 (10)	213 (250)[i]	34 (13)	47 (8)	26 (8)	<0.001
(Range)	(0–800)	(0–3050)	(0–500)	(0–400)	(0–400)	
						χ^2 P value
Prevalence of residual diuresis %	33%	50%[i]	20%	28%	17%	<0.001

Abbreviations are: APS, high-flux polysulfone membrane manufacturered by Asahi (Japan); PS, polysulfone membrane from Fresenius (Germany); AN69, high-flux membrane from Hospal (France); PMMA, high-flux polymethacrylate from Toray (Japan); cellulose, low-flux cellulose from Asahi; HD, hemodialysis.

[a] $P<0.001$ vs. PS and PMMA groups
[b] $P<0.001$ vs. PMMA group
[c] $P<0.05$ vs. AN69 group
[d] $P<0.05$ vs. APS group
[e] $P<0.01$ vs. PMMA and cellulosic group
[f] $P<0.05$ vs. cellulosic group
[g] $P<0.01$ vs. all other groups
[h] $P<0.001$ vs. all other groups
[i] $P<0.05$ vs. cellulosic group
[j] The surface of the hemodialyzer cannot be considered as a random variable as it is fixed by the physician; therefore, it cannot be compared by a statistical test

Table 2. Pre-dialysis pentosidine levels in the five membrane groups

	APS $N = 29$	PS $N = 28$	AN69 $N = 15$	PMMA $N = 25$	Cellulosic $N = 29$	ANOVA P value
Pentosidine/prot *pmol/mg prot*	16.2 ± 4.8	15 ± 6.1	25.4 ± 8.4[a]	23.2 ± 9.3[a]	21.7 ± 6.3[a]	<0.001
Free pentosidine *pmol/ml*	32.4 ± 11.3	41.4 ± 22.9	76.4 ± 28.5[a]	68.8 ± 26.7[a]	53.7 ± 18.2[a]	<0.001

Abbreviations are in Table 1.

[a] $P<0.01$ vs. PS and APS groups

Table 3. Univariate analysis of the relationship between pentosidine level and potentially explanatory continuous variables: r values

	logDIU	Total protein	Albumin	Age	Duration
Pentosidine/protein	-0.28[a]	-0.08	0	0.14	0.03
Free pentosidine	-0.36[b]	0.01	-0.12	0.15	0.02

[a] $P<0.01$
[b] $P<0.001$

determinants of predialysis protein-bound and free pentosidine (Table 5). None of the interactions were significant; thus, the influence of residual diuresis on pentosidine level was not affected by membrane type.

To further evaluate the mechanism of the membrane effect on predialysis pentosidine levels, the predialysis and postdialysis levels of pentosidine were evaluated in four groups of patients given either high-flux PS (Fresenius), AN69, PMMA, or low-flux cellulosic dialysis (Table 6). As anticipated from previous studies, protein-bound pentosidine changed very little, irrespective of membrane type. Only free pentosidine decreased markedly, but the percentage decrease was similar in all groups, ranging from 76% with AN69 to 67% with PMMA (not significant). Thus, an improved clearing ability of the membrane could not account for the lower predialysis pentosidine levels observed in PS-treated patients.

To confirm a specific pentosidine-lowering effect of PS, a longitudinal study was performed in three anuric patients given long-term (more than five years) AN69 dialysis. The patients were switched to a PS (Fresenius) dialyzer of similar surface area for 10 weeks and then returned to AN69. Predialysis samples were obtained every two weeks prior to the switch (two samples), during PS dialysis (five samples), and 14 to 16 weeks after resumption of AN69 (two samples). The protein-bound pentosidine level fell progressively in each patient after switching to PS to return to control level after resumption of AN69 dialysis (Fig. 1).

DISCUSSION

The most striking, and rather unexpected, observation of this study is that pentosidine levels are lower in pa-

Table 4. Pentosidine levels and residual diuresis in polysulfone groups, according to polysulfone brand and/or country of patients

	Fresenius Belgium	Fresenius Japan	Asahi Japan	*P* value
Pentosidine/protein *pmol/mg prot*	14.6 ± 6.2	15.3 ± 6.3	16.2 ± 4.8	NS
Free pentosidine *pmol/ml*	37.3 ± 19.6	45.4 ± 25.9	32.4 ± 11.3	NS
Residual diuresis *ml/day*	938 (23)	49 (14)	47 (10)	0.004

Table 5. Forward stepwise multiple regression analysis of determinants of pentosidine levels

	Pentosidine/protein		Free pentosidine	
	Increase in R	*P* value	Increase in R	*P* value
Membrane type	0.53	<0.001	0.59	<0.001
Log. diuresis	−0.21	<0.001	−0.36	<0.001
Total protein	−0.17	NS	0.05	NS
Albumin	−0.05	NS	−0.1	NS
Age	0.12	NS	0.16	NS
Time on HD	−0.01	NS	−0.08	NS

tients given PS dialysis than in those treated with several other membranes. The observation that pentosidine levels are lower both in Belgian and in Japanese patients treated with PS membranes produced by two different companies strengthens this observation.

The observed difference cannot be accounted for by differences in residual diuresis. Indeed, the stepwise multiple regression analysis demonstrates an independent effect of membrane and residual diuresis on pentosidine levels. Furthermore, although patients given Asahi PS dialysis are virtually anuric, their pentosidine level is equally low. In the Fresenius PS group, exclusion of patients with a residual diuresis above 300 ml/min does not modify the statistical significance of the differences of pentosidine levels. Finally, the longitudinal study discloses a membrane-related effect on pentosidine levels in all three patients switched from high-flux AN69 to high-flux PS. Still, the interpretation of these results requires confirmation.

No obvious explanation can account for these results. The effect is unrelated to the porosity of the membrane because AN69 is also a high-flux membrane. Furthermore, both high-flux AN69 and low-flux cellulosic dialysis result in similar predialysis pentosidine levels.

More specifically, pentosidine levels appear independent of the ability of the membrane to clear pentosidine. We had previously shown that HD itself does not modify total or protein-bound pentosidine [9], a finding in agreement with the fact that over 95% of pentosidine is bound to nondiffusible albumin [7]. These data confirm this finding with four different types of membranes. By contrast, free pentosidine decreases during HD, but this phenomenon is similar with all membranes, a result to be expected when the molecular weight of free pentosidine (379 Da) is considered. The similarity of the pre-HD/post-HD pentosidine levels for all membranes suggests that not only diffusive transport, but also the adsorption of pentosidine is similar during dialysis with PS and with the other membranes. *In vitro*, radiolabeled free pentosidine adsorption is minimal and virtually identical for cellulose and PS membranes (T. Miyata, unpublished observation).

Thus, improved removal of pentosidine by PS membranes does not seem to account for the lower predialysis levels. Alternatively, it is possible that PS dialysis is associated with a lower production of pentosidine.

As pointed out, pentosidine levels reflect the concentration of carbonyl precursors derived from carbohydrates. PS membranes might have a specific effect on the removal of these carbonyls and therefore on pentosidine production. Alternatively, PS membranes might decrease the oxidative stress reportedly associated with uremia [5, 6, 10–13]. A lowered oxidative stress might reduce the production of carbonyls and thus of pentosidine [6].

The fall in pentosidine levels observed after switching patients from AN69 to PS dialysis in the longitudinal study is only one third of the difference observed between the PS and the AN69 groups in the cross-sectional study (3.6 vs. 10.4 pmol/mg protein). This discrepancy might be related to the fact that the observation period on PS lasted only 10 weeks. Such a slow fall of protein-bound pentosidine is to be expected if PS decreases the generation rate of pentosidine. Under those circumstances, the protein-bound pentosidine level will decrease only to the extent that the protein is catabolized. A similar observation was made after successful renal transplantation. The fall in protein-bound pentosidine was markedly delayed [9, 14] when compared with the fall in serum β2 microglobulin, an observation taken to illustrate the slow decay of protein-bound pentosidine.

Pentosidine is a marker of carbohydrate-derived carbonyl precursors. It has been recently demonstrated that the uremia-associated "carbonyl stress" also results from the accumulation of lipid-derived carbonyl precursors [4, 5]. It remains to be demonstrated that PS membranes have a similar effect on those precursors.

These data provide the first indication that residual renal function is a critical determinant of serum pentosidine levels and thus of its carbonyl precursors. A similar role of residual renal function has been previously dem-

Table 6. Influence of a single hemodialysis session on pentosidine level

	PS $N = 14$	AN69 $N = 15$	PMMA $N = 9$	Cellulosic $N = 28$
Pentosidine/protein *pmol/mg prot*				
Pre	14.6 ± 6.2	25.4 ± 8.4	24.3 ± 8.5	21.8 ± 6.4
Post	13.8 ± 6.6	23.4 ± 5.6	22.8 ± 8.3	22.1 ± 5.8
Free pentosidine *pmol/ml*				
Pre	37.3 ± 19.6	76.4 ± 28.5	70.3 ± 26	53.5 ± 18.5
Post	10.9 ± 6.6	17.5 ± 4.9	21.7 ± 7	14.7 ± 6.9
Reduction ratio %	(71 ± 11)	(76 ± 7)	(67 ± 9)	(73 ± 6)

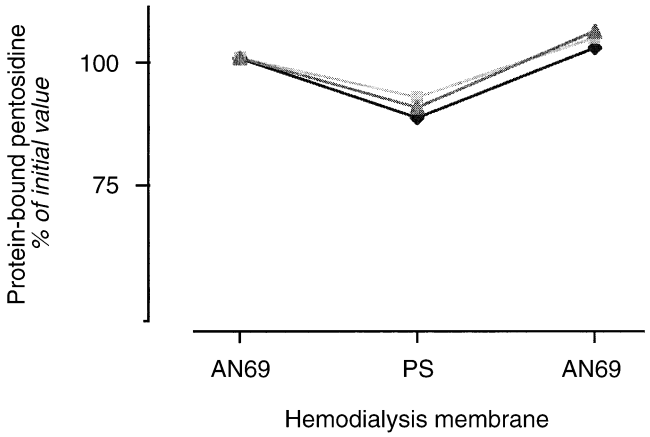

Fig. 1. Effect of hemodialysis (HD) membrane type switch on plasma pentosidine level (pmol/mg protein) in three patients. Results are expressed as the percentage of the initial value (41.8, 22.1, and 28.5 pmol/mg protein, respectively, in patients 1 (◇), 2 (□), and 3 (△). Individual values are the average of the last two samples obtained at two-week intervals at the end of each period (−2 and 0 weeks on AN69, 8 to 10 weeks after switch to PS, and 14 to 16 weeks after resumption of AN69).

onstrated for the plasma levels of a variety of low molecular weight proteins [15], the clearance of which rests largely on glomerular filtration with subsequent destruction during tubular absorption. Interestingly, experimental evidence gathered in the rat demonstrates that pentosidine or AGE peptide is largely cleared by a similar mechanism of glomerular filtration with eventual catabolism during the tubular reabsorptive process [16, 17]. Our results further underline the critical importance of residual renal function in patients with end-stage renal disease.

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