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Journal of Nephrology

Review

J NEPHROL 2004; 17: 707-714

Effect of protein leaking BK-F PMMA-based hemodialysis on plasma pentosidine levels

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ABSTRACT: Background: Advanced glycation end-products (AGEs) are now considered to contribute to the middle molecule toxicity of uremia and, because they are not cleared by conventional low-flux hemodialysis, alternative strategies are needed to improve their removal. **Methods**: In a prospective cross-over trial involving 18 adult chronic hemodialysis subjects, we evaluated the intradialytic removal and the long-term effect on predialysis levels of Protein-bound (PBPe) and Free (FPe) pentosidine by high-pore, protein-leaking BK-F Polymethylmethacrylate-based hemodialysis (BK-F-HD), by comparing it to hemodialysis using low-flux dialyzers (LF-HD). **Results**: A single BK-F-HD session removed more PBPe, but not FPe, than LF-HD. Long-term BK-F-HD was associated with a significant decrease in pre-dialysis PBPe, FPe, and albumin (17.7 ± 20.8, 25.3 ± 17.3 and 8.0 ± 3.3%, $p<0.01$) and no change in body mass index and protein catabolic rate, compared to LF-HD. Multiple stepwise regression analysis identified C-reactive Protein (CRP) (standardized b coefficient=−0.629), pre-dialysis levels in LF-HD (b=0.452) and dialysis vintage (b=0.428) as significant determinants of BK-F-induced changes in predialysis PBPe, and predialysis FPe and PBPe levels in LF-HD as significant determinants of BK-F-induced changes in predialysis FPe (b=0.720 and 0.286, respectively). **Conclusions**: Our study shows that long-term standard diffusive hemodialysis with BK-F membrane reduces predialysis PBPe and FPe levels by comparison with LF-HD, largely due to a greater intradialytic clearance of PBPe. Serum albumin is also reduced without any associated changes in nutritional status markers. The study also suggests that the effect of BK-F-HD in lowering PBPe levels is modulated by the body burden of pentosidine and is blunted or even lost in the presence of elevated CRP levels.

Key Words. Pera, Polymethylmethacrylate dialyser, Low-flux dialyzer, C-reactive protein, Pentosidine, Hemodialysis

Introduction

Retention of high molecular weight (MW) and protein-bound solutes, broadly defined as middle molecules (1), has been held responsible for many aspects of the uremic syndrome, including arthropathy, accelerated atherosclerosis, neuropathy, immune system dysfunction, inflammation, malnutrition and anemia (2). Advanced glycation end-products (AGEs) are now considered to contribute to the middle molecule toxicity of uremia (3), being implicated in the pathogenesis of some major long-term complications, e.g. dialysis-related amyloidosis, dyslipidemia, accelerated atherosclerosis (3), inflammatory state (4), cardiomyopathy (5) and adynamic bone disease (6).

High circulating levels of AGEs in uremia are regarded as the result of reduced renal excretion, coupled with increased generation secondary to oxidative stress (7), continuous load from dietary sources (3,8-11) and negligible elimination by conventional dialysis with low-flux dialyzers (ultrafiltration coefficient <10 ml/h/mmHg) (LF-HD) (12).
Based on the assumption that reducing the burden of these solutes might be beneficial, the effect of alternative dialytic strategies, such as hemodialysis with high-flux and superflux dialyzers and totally or partially convective treatments, has been investigated to evaluate whether the removal of these substances can be improved.
High-flux and superflux membranes (ultrafiltration coefficient >20 ml/h/mmHg) enable an efficient removal of low MW AGE peptides (MW <10.000 D), but little or no clearance of high MW AGEs (MW >10.000 D) or protein-bound Pentosidine (PBPe) and carboxy-methyllysine (CML) (12,13), while hemofiltration can produce a modest, but significant reduction in PBPe (14).
On the other hand, medium/long-term treatment with high-flux and superflux polysulfone dialyzers has been associated with a significant, 10-30 % reduction in predialysis levels of low MW AGEs and PBPe (13,15-17) compared to conventional LF-HD, possibly more as a result of a lower generation than of greater removal of the solutes.
Lower AGE generation has also been held responsible for the further reduction in predialysis AGE-fluorescence and CML when high-flux hemodialysis is used with ultrapure dialysis fluid and convective treatments, such as hemodiafiltration and hemofiltration, compared to high-flux hemodialysis using standard dialysate (18).
An alternative strategy of potential benefit is hemo-dialysis with high-flux, large-pore, protein-leaking polymethylmethacrylate (PMMA) dialyzers, BK-F series (nominal cut off >70000 D) (BK-F), which can remove a wide range of high MW and protein-bound solutes. Indeed, several studies have shown that these membranes can effectively remove b2M (19,20), AGE peptides (20) and protein-bound solutes such as furancarboxylic acid (FCA) (21), arboxy-methyl-propyl-furanpropionic acid (CMPF) (21), homocysteine (22) and also (in preliminary observations) PBPe (23). The purpose of our study was to evaluate: a) the intradialytic removal and b) the long-term effect on predialysis levels of the protein-bound AGE molecule Pentosidine, a direct marker of glycoxidation process on plasma and tissue proteins and carbonyl stress (13), by standard diffusive hemodialysis with BK-F membrane (BK-F-HD), as opposed to conventional hemodialysis with low-flux membranes (LF-HD).

Subjects and methods

Study population

The clinical and demographic characteristics of the 18 chronic hemodialysis patients included in the study are shown in Table I.

Subjects' characteristics

TABLE I

	Group 1	Group 2
Number of subjects	9	9
Females/males	4 / 5	6 / 3
Number of diabetics	2	2
Age (years)	63.3 ± 15.9	63.5 ± 16.0
Dialysis vintage (years)	7.6 ± 3.5	8.2 ± 5.8

Two groups of subjects were considered: Group 1 and Group 2 included subjects who had been on long-term LF-HD or BK-F-HD, respectively.
All subjects gave their informed consent to the study protocol, which was approved by the local Ethical Committee.
Subjects with chronic inflammatory disease, cirrhosis and neoplasia were excluded from the study. All subjects were dialyzed through a native arteriovenous fistula, except for two who had a PTFE graft and a Tesio catheter for vascular access. None of the subjects had residual diuresis and all were treated by thrice weekly hemodialysis against standard, not ultrapure, bicarbonate dialysate. Standard hemodialysis fluid was prepared from purified water obtained by reverse osmosis. Microbial contamination of dialysate was determined monthly with a prolonged incubation time of at least 5 days at 22°C and 36°C and bacterial

counts were always less than 1000 colony forming units (CFU)/mL throughout the study period. The endotoxin level in the dialysate was measured quarterly by the limulus amoebocyte lysate (LAL) assay and was always below the limit of 0.50 endotoxin units/mL. Dialyzers were not reused.

Study design

The primary purpose of our study was to compare prospectively the effects of long-term treatment with BK-F-HD and LF-HD on circulating levels of pentosidine. To avoid any potential bias introduced by differences between subjects in dietary intake of AGEs, which might affected circulating levels of pentosidine irrespective of the dialysis membranes under study (8-11), a cross-over design was planned, based on the assumption that chronic hemodialysis subjects would not change their dietary habits significantly during the observation period.
Group 1 included 9 subjects who had been on LF-HD for at least 7 months (13.3 ± 4.2 months), 4 on polysulfone 1.8 sqm dialyzer (Fresenius Medical Care, Germany) and 5 on cellulose diacetate 1.7sqm dialyzer (Nipro Corporation, Japan), who were shifted to BK-F dialyzer,1.6 sqm (Toray Industries, Japan) and followed for 7 months. Group 2 included 9 subjects who had been on BK-F-HD for at least 7 months (11.0 ± 5. 7 months) and were shifted to LF-HD (4 to polysulfone and 5 to cellulose diacetate dialyzers) and followed for 7 months.
Blood samples were drawn at the start of the first hemodialysis session of the week immediately before changing the membranes (baseline) and then after 3 and 7 months of follow-up.
At the end of the follow-up, 3 subjects from Group 1 and 2 from Group 2 returned to their initial membrane and were followed up for a further 5 months. Blood samples were then collected at the start of the first hemodialysis session of the week at the end of this additional period of observation. One patient was lost to follow-up due to a kidney transplant after 4 months.
Predialysis samples were analyzed for Free Pentosidine (FPe), PBPe, C-reactive Protein (CRP), total protein (TP), albumin, BUN and hemoglobin (Hb) concentrations.
Time on dialysis (238 ± 10 minutes), dialysis pump blood flow rate (Qb 310 ± 12 ml/min) and dialysate flow rate (Qd 500 ml/min) were kept constant throughout the study. All dialysis treatments used unfractionated heparin for anticoagulation.
The intradialytic effect of LF and BK-F membranes on solutes removal was evaluated by calculating the reduction ratio (RR) as follows :
RR = (Cpre – Cpost/Cpre) x 100, where Cpre is the concentration at the start of dialysis and Cpost the corrected or uncorrected concentration at the end of dialysis. Post-dialysis blood samples were collected from the arterial blood line of the dialyzer after 20 seconds of "slow flow" (Qb 50 - 80 ml/min). The post-dialysis concentration of PBPe was corrected for ultrafiltration during dialysis by multiplying Cpost for a correction factor (CF) based on Hb concentration at the start and end of dialysis as follows: CF = Hb pre/Hb post. Kt/V was calculated from the pre-dialyisis and post-dialysis BUN measurements according to Daugirdas (24).
Nutritional status was evaluated by the body mass index (BMI), defined as dry weight divided by height squared (Kg/sqm), and the normalized protein catabolic rate (PCRn). PCRn was calculated from the predialysis BUN level and Kt/V, according to Depner and Daugirdas (25).

Biochemical analyses

Plasma samples for PBPe assay were precipited on ice with an equal volume of 10% trichloracetic acid. The pellets were washed twice with 5% cold thricloracetic acid and hydrolized in 6 N HCl at 110 °C for 18 hrs. Acid was removed by vacuum centrifugation. The hydrolized pellet was dissolved in water/0.01 M heptafluorobutyric acid and then filtered with 0.45mm membrane filters.
Serum samples for Fpe assay were subjected to precipitation with an equal volume of 10% trichloracetic acid on ice followed by centrifugation at 5000 rpm for 15 min. The super bate was separated from residue and analyzed.
Samples were analyzed by Perkin Elmer HPLC system. The column used was a 3.9 x 300 mm C-18 m-bondpack (Waters, USA). The HPLC was programmed with a linear gradient from 0 to 39 mins of 10 to 17% acetonitrile in HPLC water and 0.1% heptafluorobutyric acid (Sigma-Aldrich, Italy) as a counter ion. Pentosidine and Fpe were detected by fluorescence excitation at 335 nm and emission at 385 nm (26). Synthetic pentosidine used for calculation was kindly provided by Prof. Vincent M. Monnier, Cleveland, USA.
BUN, total protein, albumin and Hb were measured using standard automated clinical chemistry and hematology techniques (Bayer Diagnostics, Italy). High-sensitivity C-reactive Protein (CRP) levels were measured by a commercially available automated
particle-enhanced immunonephelometric (PENIA) assay (Dade Behring, Germany). The reference range was <6 mg/L.
After collection, blood samples for pentosidine assay were immediately placed on ice, centrifuged and stored at – 70 °C until required for testing. All samples were tested at the same time.

Statistical analyses

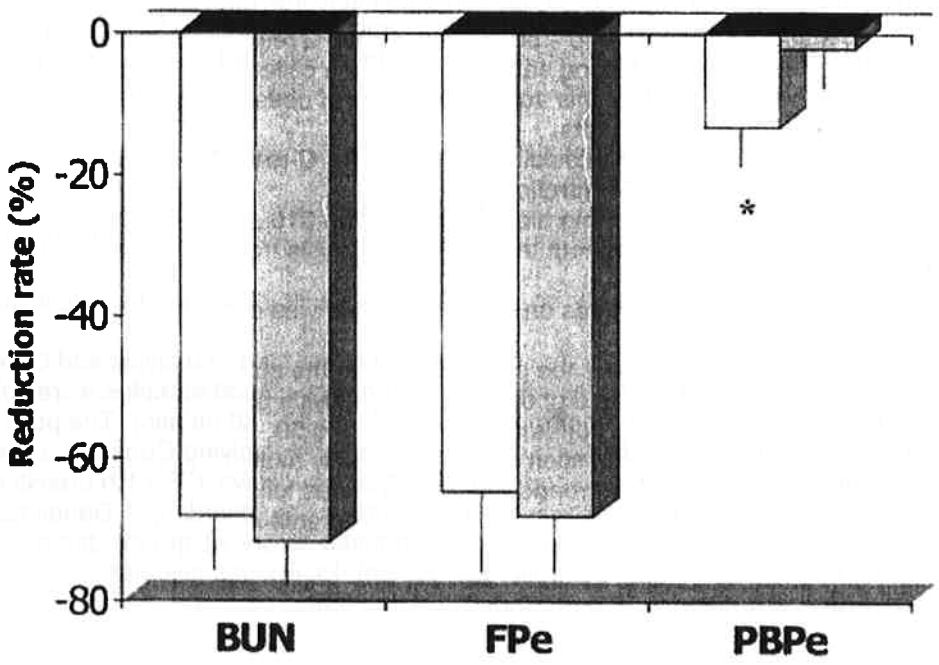
Data are presented as mean ± standard deviation, unless specified otherwise. Differences between treatment periods were evaluated by means of the general linear model for repeated measures of analysis of variance. Relationships between variables were analyzed by the Pearson correlation coefficient and multiple linear stepwise regression.
A p value of less than 0.05 was considered significant.
All statistical analyses were performed using the SPSS version 10.0 (SPSS Inc.,USA).

Results

The effects of a single hemodialysis session with LF and BK-F membranes on circulating levels of urea, PBPe and FPe are shown in Figure 1.

Reduction rate of circulating levels of the different solutes during a single hemodialysis session with BK-F dialyser (open bars) and LF dialysers (shaded bars) (n=18). * = p < 0.01 vs LF dialyser.

Fig.1



BK-F-HD provided a significantly higher reduction of PBPe than LF-HD, while urea and FPe were equally removed by the two membranes.
Raw data on the effect of swapping the membranes on the levels of predialysis solutes are presented in Tables II and III. {Table I }

Reduction rate of circulating levels of the different solutes during a single hemodialysis sess dialyser (open bars) and LF dialysers (shaded bars) (n=18). * = p < 0.01 vs LF dialyser.

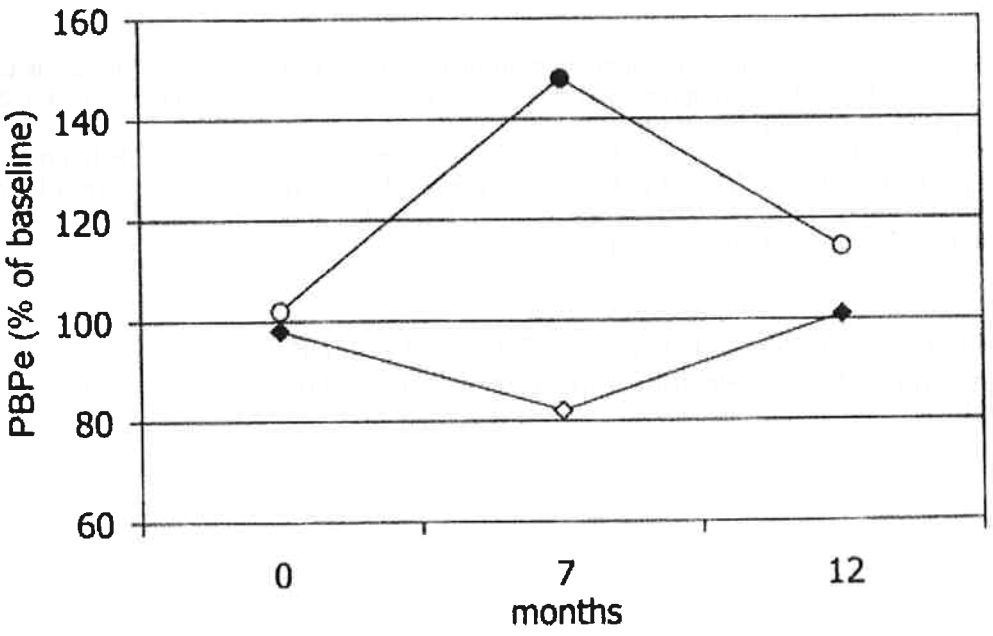
	Baseline	3 months
Membrane	BK-F	LF
Free pentosidine (pmol/mL)	40.3 ± 8.6	57.2 ± 17.5 *
Protein-bound pentosidine (pmol/mL)	1194 ± 423	1691 ± 462**
PB pentosidine /TP (pmol/mg protein)	17.4 ± 4.6	23.4 ± 7.1 **
C-reactive protein (mg/L)	3.3 ± 1.2	3.5 ± 0.8
Albumin (g/L)	35.3 ± 1.6	38.9 ± 2.7 **
Protein catabolic rate (g/kg/day)	0.96 ± 0.23	0.97 ± 0.25
Body mass index (Kg/sqm)	25.3 ± 3.8	24.9 ± 4.00
Kt / V	1.38 ± 0.13	1.34 ± 0.25

** – $p < 0.05$ vs baseline ; ** – $p < 0.01$ vs baseline.*

Switching from LFHD to BK-F-HD was associated with a significant reduction of predialysis FPe, PBPe and albumin levels, with no change in CRP levels, PCRn, BMI and Kt/V.
Switching from BK-F-HD to LF-HD was associated with a significant increase in predialysis FPe, PBPe and albumin levels, with no change in CRP levels, PCRn, BMI and Kt/V.
To confirm the specific effect of BK-F-HD on PBPe levels, 5 subjects (3 of them swapped from LF-HD to BK-F-HD and 2 from BK-F-HD to LF-HD) were returned to the initial membranes and followed up for a further 5 mths (Fig. 2).

Effects of hemodialysis membrane shifts on predialysis PBPe levels. Results are expressed as % of the initial plasma levels, which were 28.2, 17.8 and 27.6 pmol/mg protein in the subjects who were on LF-HD at time 0 (closed diamonds) and 13.6 and 14.5 pmol/mg protein in those who were on BK-F-HD at baseline (open circles). Closed symbols indicate LF-HD and open symbols BK-F-HD.

Fig.2

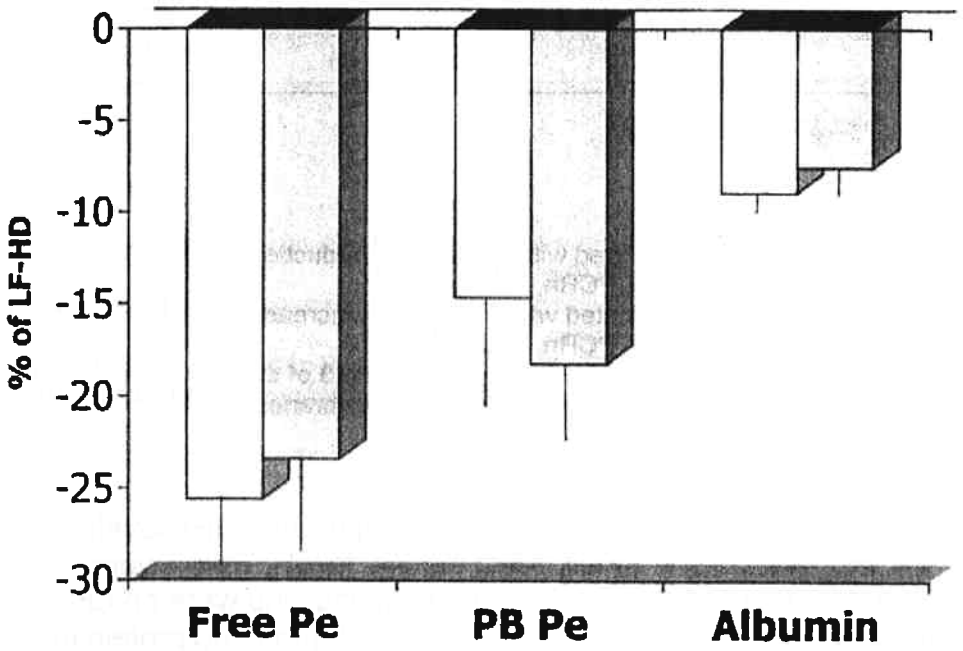


After switching from LF-HD to BK-F-HD, PBPe levels dropped and returned to control levels after resuming LF-HD, while they rose after changing from BK-F-HD to LF-HD and returned to the baseline after resuming the BK-F membrane.

Data from the two groups were then pooled and the effect of BK-F-HD was expressed as percentage of predialysis levels on LF-HD at different follow-up times (Fig. 3).

Effect of BK-F-HD on predialysis solute levels expressed as % of the values during LF-HD at 3 month (open bar) and 7 month (shaded bars) follow-up. Data are expressed as mean ± standard error. All changes are significantly different from baseline at the level of $p < 0.01$.

Fig.3



BK-F-HD was associated with a significant reduction in predialysis FPe, PBPe and albumin levels by 27.2 ± 20.1%, 14.6 ± 21.8% and 9.3 ± 4.3%, respectively, at 3-month follow-up and 24.3 ± 17.3%, 17.7 ± 20.8% and 8.0 ± 3.3%, respectively, at 7-month follow-up
($p < 0.01$). A significant positive correlation was found between the predialysis levels on LF-HD and the BK-F-HD induced changes for both PBPe/TP ($r=0.751$, $p < 0.001$) and FPe ($r=0.769$, $p < 0.001$), while there was a significant negative correlation between CRP levels on BK-F-HD and changes induced by BK-F-HD in predialysis PBPe/TP ($r=0.715$, $p < 0.001$) (Fig. 4).

Relationship between CRP levels on BK-F-HD and BK-F induced changes in predialysis Protein Bound Pentosidine levels. $r = 0.715$, $p < 0.001$.

Fig.4

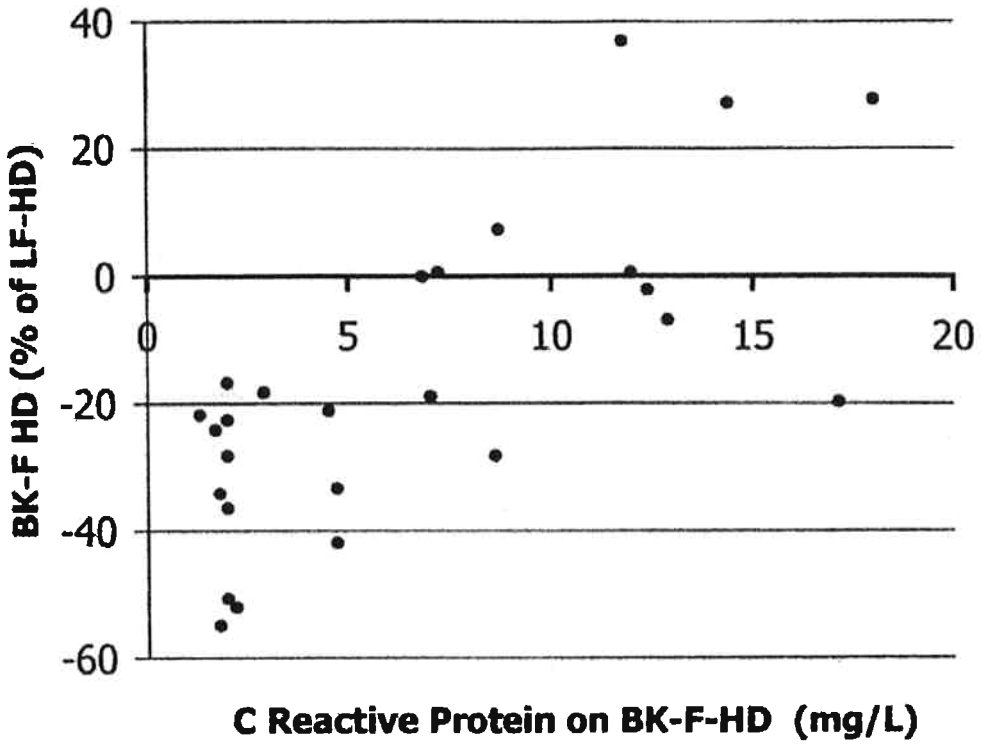


Figure 4 also shows that normal CRP levels are associated with an average 32.5 ± 9.9% decrease in predialysis PBPe levels on BK-F-HD ($p < 0.01$), while the presence of even minor increases in CRP levels is associated with no change in PBPe levels (mean increase of 3.2 ± 21.5%, p=ns).
Multiple stepwise regression analysis identified CRP, predialysis PBPe/TP on LF-HD and dialysis vintage as the only significant predictors of the changes induced by BK-F-HD in predialysis PBPe/TP levels (standardized b coefficients were respectively: −0.629, $p < 0.001$; 0.452, p=0.004 and 0.428, p=0.007). Pre-dialysis FPe and PBPe/TP on LF-HD were significant predictors of the changes induced by BK-F-HD in predialysis FPe (standardized b coefficients: 0.720, $p < 0.001$ and 0.286, p=0.046, respectively). BK-F-HD and PCRn were the only significant predictors of predialysis serum albumin levels (standardized b coefficients were respectively: −0.460, $p < 0.001$ and 0.450, $p < 0.001$).

Discussion

Retention of AGEs (which are not removed by conventional low-flux hemodialysis) has been considered responsible for several long-term uremic complications (2). Based on the assumption that decreasing the burden of these substances might be beneficial, the effect of alternative dialytic strategies has been investigated to evaluate whether their removal rates could be improved.
One of the alternatives investigated is the high-flux, large pore, protein leaking BK-F PMMA dialyzer, which is able to remove high MW and protein-bound solutes, even when it is used in a standard diffusive hemodialysis procedure.
Our study shows that a single hemodialysis session with BK-F dialyzer achieves a significantly greater reduction in circulating levels of PBPe than LF dialyzers. The intradialytic removal of PBPe is an unique feature of the BK-F dialyzer, which proves better than high-flux and superflux dialyzers (12) and similar to the convective technique hemofiltration (14). On the other hand, the intradialytic removal of FPe was much the same with BK-F and LF dialyzers, as was to be expected given the low MW of the solute.
Our study also shows that long-term hemodialysis (up to 7 mths) with the BK-F dialyzer enables a significant reduction in predialysis levels of FPe and PBPe compared to the use of LF dialyzers. These reduction rates are quantitatively similar to those reported in a cross-over study switching patients from hemodialysis with cellulosic LF membranes to hemodiafiltration with superflux polysulfone membrane and better than those observed after switching to hemodialysis with high-flux polysulfone membrane (16). The elective role of the BK-F membrane is confirmed by the finding that the effect of BK-F-HD on PBPe and FPe plasma levels is reversible.
The greater intradialytic removal is the most immediate explanation for the lowering effect of long-term BK-F-HD on PBPe levels compared to LF-HD, though multivariate regression analysis indicates that factors other than the BK-F membrane may influence PBPe levels.
The finding that both dialysis vintage and plasma levels of PBPe on LF-HD are significant positive predictors

of response to BK-F-HD suggests that the change in PBPe levels induced by BK-F-HD is greater, the larger the plasma and tissue pool of PBPe.
On the other hand, the negative correlation between BK-F-HD dependent drop in PBPe and CRP levels suggests that the beneficial effect of BK-F-HD can be masked in the presence of biochemical evidence of inflammation.
One possible explanation of the relationship between CRP and changes in PBPe levels induced by BK-F-HD is that activation of the acute phase response per se increases the circulating levels of PBPe (thereby overriding the lowering effect of the membrane), since it has been demonstrated that high oxidative stress increases the endogenous generation of carbonyl precursors and thus of pentosidine (7).
An alternative explanation for the relationship between the effect of BK-F-HD on PBPe and PCR stems from recent findings that diets with regular (high) AGE content lead to elevated circulating AGE levels in nondiabetic uremic patients (9) and can trigger an inflammatory response in peritoneal dialysis patients (11) and diabetics (27). It may be that a higher dietary burden of pentosidine is responsible for both the rise in CRP levels and the blunted response to BK-F-HD due to an increase in PBPe plasma levels. In addition, the observation that plasma pentosidine content mirrors CRP levels in uremic patients (28) and that high AGEs stimulate CRP production in vitro (4) further support the notion that high CRP levels may be due to high pentosidine levels.
Predialysis FPe levels were significantly lower during long-term BK-F-HD compared to LF-HD, though intradialytic clearance by the two membranes was similar, suggesting that the long-term reduction in pre-dialysis FPe levels is not a direct effect of the membrane, but the consequence of a lower PBPe burden. This conclusion is supported by the multiple regression analysis that identified predialysis PBPe levels on LF-HD as a significant predictor of BK-F-HD-induced changes in FPe, and by the assumption that FPe in uremic plasma originates from the catabolism of pento-sidine linked to body proteins (29), though no correlation was found between plasma concentrations of FPe and PBPe and the changes induced in them by BK-F-HD in our study.
We are aware, however, that the reduction in pentosidine levels obtained by BK-F-HD is unlikely to influence tissue AGEs accumulation and additional, dialysis-unrelated strategies are needed to reduce AGEs burden in uremia, including dietary modifications, use of antioxidants and inhibitors of AGEs formation and function (30).
We confirm that chronic BK-F-HD leads to a significant decrease in serum albumin levels. In our study, the decrease in albuminemia was not transient and was also slightly higher than that reported elsewhere, which found either a 5% decrease after 6 mths of treatment with a BK-F dialyzer (22) (compared to the 8% decrease after 7 mths in the present study) or an average reduction in serum albumin of 2.4 g/L after 3 mths of BK-F-HD (31), compared to the 3.8 g/L decrease observed in this study. This reduction in serum albumin levels does not seem to be affected by changes in inflammatory status in our study, but it may be the result of an inadequate ability to compensate for the significant losses by an increased albumin synthesis, possibly as a consequence of our patients' sub-optimal protein (and calorie) intake.
The chronic loss of albumin resulting from BK-F-HD is reason for great concern, since hypoalbuminemia has been associated with malnutrition, greater mortality (32-33) and cardiac disease (34) in hemodialysis patients. In our population, however, the decrease in serum albumin levels did not seem to worsen the patients' nutritional status over the 7-mth follow-up, as already reported by others, who documented good nutritional status in patients on treatment with BK-F dialyzers for more than 2 yrs (22). We should bear in mind, however, that PCRn and BMI are rather insentive measures of nutritional status. On the other hand, the relationship between hypoalbuminemia and higher mortality was observed in hemodialysis patients treated mostly with low-flux dialyzers and this observation may not necessarily apply to patients treated with the high-flux protein-leaking BK-F membrane.
One possible criticism to our study is that a more appropriate comparison would have been between the BK-F membrane and high flux non-protein leaking rather than low flux dialysers. However, the only available cross-over study on the effect of dialysis membranes on plasma Pe showed no significant changes in pre-dialysis PBPe levels by shifting from low-flux to high-flux polysulfone hemodialysis (16), suggesting that that BK-F-HD would be expected to reduce PBPe levels by comparison with high flux dialysers too.
Obviously, future prospective trials are needed to address this issue.
Despite its shortcomings, such as the small sample size, short follow-up and lack of randomization, our study shows that the BK-F dialyzer has the potential to reduce plasma pentosidine levels to a greater extent than any other high-flux membrane during standard diffusive hemodialysis. Our findings also provide some preliminary information on important aspects, such as the increase in CRP levels, that may influence the effect of the dialysis membrane on plasma pentosidine levels. In conclusion, our study shows that long-term standard diffusive hemodialysis with high-flux, large pore, protein leaking BK-F-HD reduces circulating levels of PBPe, FPe and albumin, compared to LF-HD. In the case of PBPe, this reduction is largely due to a greater intradialytic removal, whereas the drop in FPe is probably secondary to the reduction in PBPe. The trade-off for the better clearance of high MW and PB solutes is a modest reduction in serum albumin levels apparently unassociated with any decline in nutritional status. Finally, our study suggests that the lowering effect of BK-F-HD on PBPe depends on the body burden of the solute and may be blunted or even lost in the presence of a subclinical inflammatory condition often observed in uremia.

Part of the work was presented at the 33rd Annual Meeting of the American Society of Nephrology, Toronto, Canada, October 10 – 16, 2000.

Acknowledgements

The Authors wish to thank the subjects who took part in the study and Mrs Frances Coburn for her assistance in editing the manuscript.

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