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Evaluation of β_2-Microglobulin Removal with High-Performance Hemodiafiltration

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Abstract: Several lines of evidence suggest that β_2-microglobulin (β_2M) accumulation in long-term hemodialysis (HD) patients results in so-called dialysis-associated amyloidosis (DAA), which is clinically manifested by carpal tunnel syndrome, osteoarthropathy, and the other organ involvements. For the purpose of preventing the β_2M accumulation, the efficiency of β_2M removal during hemodiafiltration (HDF) with high-performance membranes (HPM), hemofiltration (HF), HD, and charcoal hemoperfusion was evaluated. Among 27 patients treated with these methods, significant β_2M removal was noted in HDF with HPM and HD with polyacrylonitril (PAN) membrane. However, treatment of HDF with HPM for more than 6 months caused no remarkable improvement in clinical symptoms of patients, and serum β_2M levels decreased in only two out of 15 patients. These results imply that β_2M might be most effectively removed by HDF with HPM and HD with PAN membrane, but further long-term studies will be necessary to conclude whether these procedures could become successful therapeutic regimen for DAA. Key Words: β_2-microglobulin—Dialysis-associated amyloidosis—High-performance membrane—Hemodiafiltration—Hemofiltration—Hemodialysis.

There are growing incidences of dialysis-associated amyloidosis (DAA) among long-term hemodialysis patients, which are manifested by carpal tunnel syndrome, osteoarthropathy, and the other organ dysfunctions. Though it has been noted that patients with renal failure showed extraordinary high serum levels of β_2-microglobulin (β_2M), the pathogenetic property of this low-molecular-weight protein (MW, 11,800) was unclear until Gejyo et al. identified that the amyloid protein of DAA mainly consisted of β_2M (1).

Since β_2M is hardly eliminated with the conventional dialysis membrane, an alternative, more effective removal procedure should be considered for prevention of β_2M accumulation.

In this study, we examined the elimination of β_2M during hemodiafiltration (HDF) with different types of high-performance hemodiafilters, of which molecular cutoff points were estimated to be from 4.8×10^4 to 10×10^4 dalton, and compared them with other blood purification methods, including conventional hemofiltration (HF), hemodialysis (HD), and charcoal hemoperfusion (HP). Additionally, short-term effects of β_2M removal on clinical symptoms were evaluated.

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MATERIALS AND METHODS

Patients

Twenty-seven anuric patients receiving regular HD longer than 5 years (11 male and 16 female patients; mean age, 46.2 ± 7.8 years old; mean duration of hemodialysis, 8.7 ± 2.4 years) were randomly divided into nine groups, each of which consisted of three patients. These patients were treated thrice a week for more than 6 months according to the following procedures.

Blood purification methods

Patients were treated with the following five types of hemodiafilters (Table 1): (a) BK-1.0H (polymethylmethacrylate [PMMA] 1.0 m^2; Toray Medical Co. Ltd., Tokyo, Japan) with simultaneous infusion of 5 L of substitution fluid; (b) Duo-flux HP (cellulose acetate [CA], 1.6 m^2; C-D Medical, Inc., Miami, FL, U.S.A.) with 9 L of substitution fluid; (c) TAF-120S (cuprammonium rayon [Cu], 1.2 m^2; Terumo Japan Co., Ltd., Tokyo, Japan)

TABLE 1. *Hemodiafilters with high performance membrane*

	Industry	Membrane area (m^2)	Membrane material	UFR (ml/hr · mmHg)	Cut-off point ($\times 10^4$ dalton)	S.C. of B_2-microglobulin
BK-1.0H	Toray	1.0	PMMA	76	10	0.13 ± 0.05
Duo-flux HP	C-D Medical	1.6	CA	15	6	0.31 ± 0.17
TAF-120S	Terumo	1.2	Cu	12	4.8	0.17 ± 0.05
TF-E15PH	Teijin	1.5	CA	24	7	0.54 ± 0.22
KF-101	Kuraray	1.5	EVA	5	7–8	N.D.

PMMA; polymethylmethacrylate, CA; cellulose acetate, Cu; cuprammonium rayon, EVA; ethylene vinylalcohol, UFR; ultrafiltration rate, S.C.; sieving coefficient. Sieving coefficients of each hemodiafilter were clinically evaluated in this study (N.D.; not evaluated).

with 5 L of substitution fluid; (d) TF-E15PH (CA; 1.5 m^2; Teijin Co. Ltd., Osaka, Japan) with 5 L of substitution fluid; and (e) KF-101 (ethylene vinylalcohol [EVA], 1.5 m^2; Kuraray Co. Ltd., Osaka, Japan) with 9 L of substitution fluid.

Other patients were treated with the Sartorius hemofilter (cellulose triacetate, 0.6 m^2; Sartorius Gmbh, Göttingen, F.R.G.) with 18 L of substitution fluid.

Other patients were treated with 5 h of hemodialysis with three different types of hemodialyzers: (a) TF-1200 (regenerated cellulose [RC], 1.2 m^2; Teijin Co. Ltd.); (b) B_2-1.3H (PMMA, 1.3 m^2; Toray Medical Co. Ltd.), and (c) Biospal-2400S (polyacrylonitril [PAN], Hospal Industrie, Meyzieu, France).

An additional five patients were treated with cellulose-coated activated charcoal (Hemocels TC-200, 200 g of activated charcoal; Teijin Co. Ltd.) for 3 h.

The mean blood flow rate during each treatment was corrected about 200 ml/min, and the mean dialysate flow rate during HDF and HD was adjusted to 500 ml/min. Each HDF and HF treatment was performed for 5 h.

Measurement

Serum β_2M, biochemical data, and peripheral blood counts were evaluated before and after the treatment twice a month. β_2M was assayed by RIA (Eiken Chemical Co. Ltd., Tokyo, Japan), and the posttreatment value of β_2M was corrected by the changes in hematocrit in order to exclude the influences of hemoconcentration or hemodilution.

RESULTS

Changes in serum β_2M concentration with various treatments

Serum β_2M concentration significantly decreased during HDF with all types of membranes (Fig. 1); the most remarkable reduction was noted in BK-1.0H and TF-E15PH. Serum β_2M concentration decreased to 57.8 ± 7.1% of prevalue in BK-1.0H, 58.7 ± 1.9% in TFE-15PH, 71.1 ± 6.6% in Duo-flux HP, 76.1 ± 10.3% in TAF-120S, and 77.3 ± 6.6% in KF-101 (Fig. 2).

After hemofiltration with 18 L of substitution fluid, serum β_2M concentration decreased to the level of 89.0 ± 9.7% (Fig. 2).

After HD with RC and PMMA membrane, the serum β_2M level increased to 107.5 ± 21.6%, 112.2 ± 17.7% of prevalue although these value were not significant compared with prevalue (Figs. 3 and 4). On the other hand, a marked reduction in β_2M concentration was observed during HD with PAN, to 61.0 ± 27.0% of prevalue (Figs. 3 and 4).

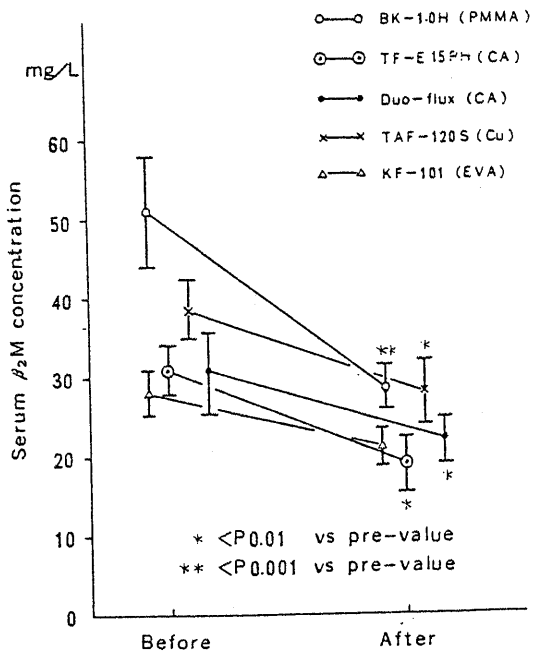

FIG. 1. Changes in serum β_2-microglobulin (β_2M) concentration during hemodiafiltration with high-performance hemodiafilters. The serum β_2M concentration after treatment was corrected by a hematocrit change.

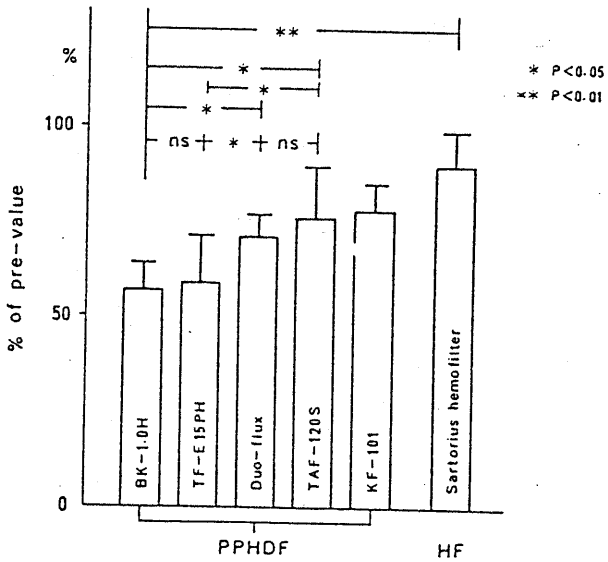

FIG. 2. Changes in β_2-microglobulin concentration during hemodiafiltration with five types of hemodiafilters and hemofiltration.

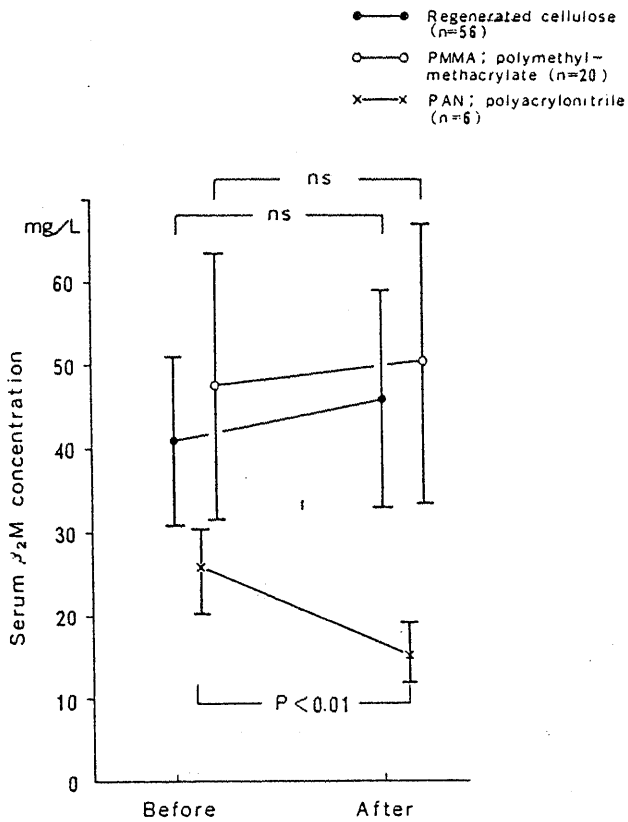

FIG. 3. Changes in serum β_2-microglobulin concentration during hemodialysis with three types of hemodialyzer.

There were no significant changes in serum β_2M concentration during 3 h of HP (97.2 ± 9.3% of prevalue) (Fig. 4).

Six months' effect of HDF with high-performance hemodiafilters

Figure 5 illustrates serial changes in serum β_2M levels in five patients under HDF. All of these patients suffered from either persistent osteoarthropathy or carpal tunnel syndrome, which had been pathologically demonstrated by β_2M deposition. There were no remarkable changes in serum β_2M concentrations in the 6-months observation period, except for two patients treated with BK-1.0H, whose clinical symptoms never altered.

DISCUSSION

It is believed that DAA will become one of the most serious complications among long-term hemodialysis patients; however, there is no effective treatment to prevent the development or symptomatic relief of DAA at present. As it is clear that β_2M (MW, 11,800), which has recently been confirmed to be a main constituent of amyloid protein (1), cannot be eliminated by standard hemodialysis technique (2), and that the number of the patients suffering from DAA will increase steadily, the development of therapeutic methods for DAA should be an urgent problem. Among these methods, the removal of accumulated β_2M from HD patients appears to be a meaningful procedure.

In this study, the removal efficiency of β_2M in various blood purification methods was examined and significant β_2M elimination during HDF with high-performance hemodiafilters, HF and HD, with PAN membrane was found.

Among five types of hemodiafilters, the β_2M removal rate was mainly dependent on the membrane cutoff point; BK-1.0H and TF-E15PH, which had higher cutoff points than the other hemodiafilters, showed the highest β_2M elimination. However, as to BK-1.0H, which consisted of PMMA, β_2M would be removed by adsorption onto membrane as well as filtration, because the sieving coefficient of β_2M with BK-1.0H was unexpectedly low compared with other hemodiafilters (Table 1).

As to HF, a lesser extent of β_2M removal than with HDF was observed. Although it was calculated that about 90 mg of β_2M was discarded into about 20 L of ultrafiltrated fluid by each HF, only 10% of serum β_2M reduction was noted after HF.

After HD using RC or PMMA membrane, serum β_2M levels increased slightly although the changes were not statistically significant in our study. However, there are several reports that β_2M showed significant increases after HD with cellulosic membrane (3,4), and some investigators suggest the en-

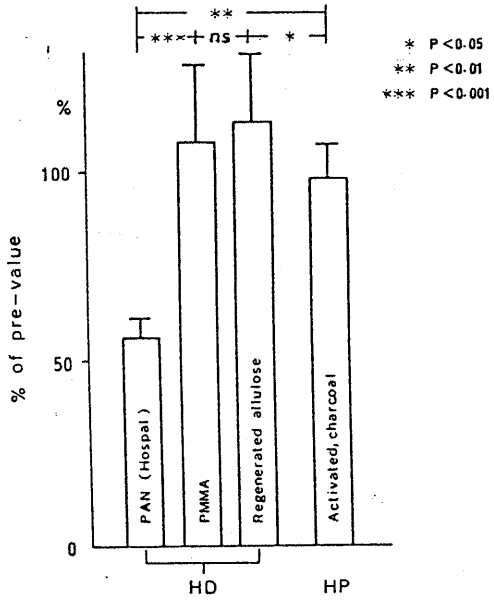

FIG. 4. Changes in β_2-microglobulin concentration during hemodialysis with three types of hemodialyzer and charcoal hemoperfusion.

hanced production of β_2M during HD using these membranes, as well as the participation of inflammatory-activating factors, especially interleukin-1, in this phenomenon (5,6). Further study will clarify the problem of cellulosic membrane–induced β_2M production. In regard to PMMA membrane, different results were noted in β_2M behavior between HD and HDF. This would be due to the difference of membrane characteristics, such as the pore size distribution between dialyzer for ordinary HD and for HDF with a high cutoff point and ultrafiltration rate.

The most striking result among HD procedures was observed in the use of PAN membrane. Serum β_2M was remarkably reduced after HD with PAN, and its reduction rate was comparable with that of HDF with BK-1.0H or TF-E15PH, which showed the highest β_2M elimination efficiency among the five types of hemodiafilter. As it is unlikely that dialysis itself could have the ability to remove β_2M, other mechanism(s) should be considered. It has been reported that the PAN membrane could adsorb or fix relatively specific proteins, such as activated complements (C3a, C5a) (7), which has never occurred in other membrane materials. So, the most probable explanation of β_2M removal with PAN may be adsorption although a precise mechanism by which β_2M would fix or adsorb is not known.

HP with commercially available activated charcoal (AC) could not adsorb β_2M at all. As the adsorptive affinity of AC is thought to depend mainly

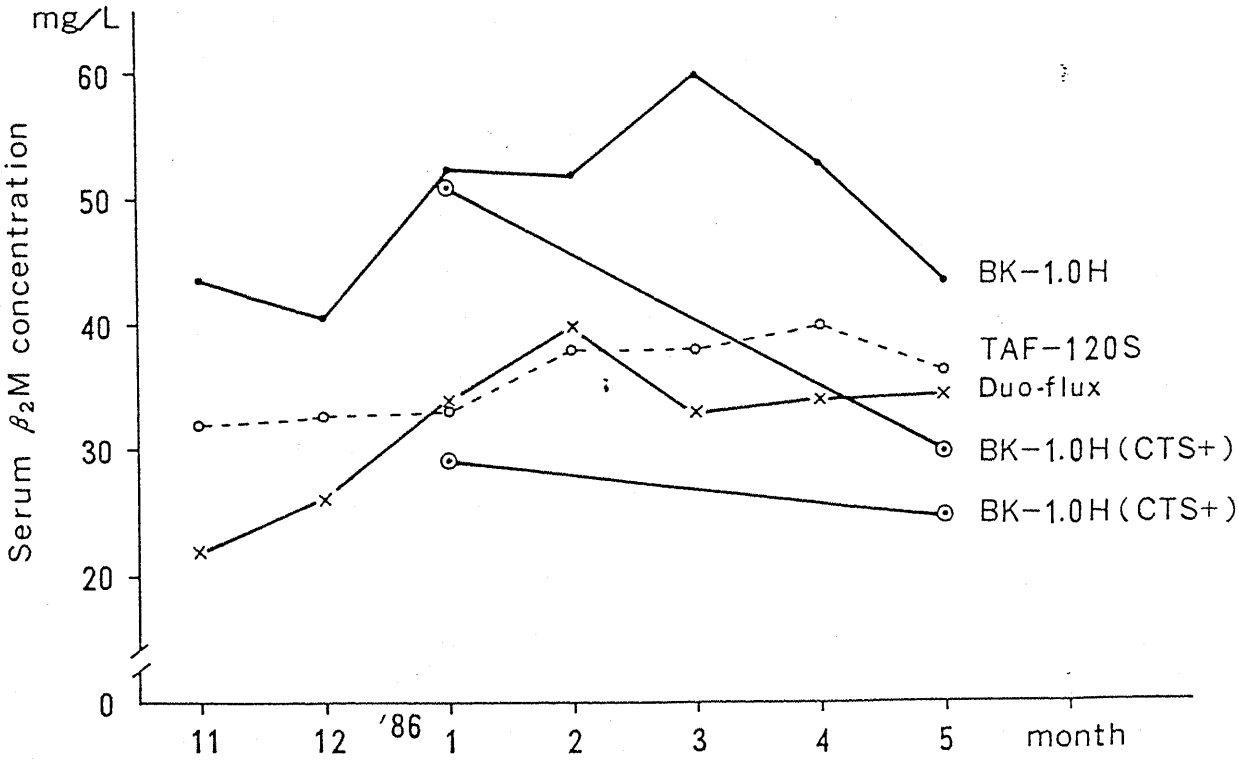

FIG. 5. Serial changes in serum β_2-microglobulin concentration among five patients under hemodiafiltration with high-performance hemodiafilters (CTS, carpal tunnel syndrome).

on molecular weight and conformation of the solute in general, AC may be unsuitable in both regards.

These results imply that β_2M could be most effectively removed with HDF with a high-performance hemodiafilter or HD with PAN membrane. Clinically, the short-term effect (about 6 months) of HDF with a high-performance membrane resulted in no significant relief of symptoms. Also, serum β_2M levels showed no remarkable decrease, except in two patients treated with BK-1.0H. Although the observation period in this study was too short to understand totally the clinical workings of β_2M elimination therapy with HDF, HDF with a high-performance membrane provided little effect on the symptoms of DAA and maintenance of serum β_2M in low levels. It has been reported recently that long-term HD patients treated with a PAN membrane showed a lesser incidence of DAA (8). It would be possible that with HDF with a high-performance membrane applied at an earlier stage in renal failure treatment, the development of DAA might be decelerated. A long-term study with high-performance HDF is still necessary to conclude the therapeutic efficacy for DAA.

CONCLUSIONS

Significant β_2M removal was observed during HDF with high-performance hemodiafilters and HD with PAN membrane although treatment with these procedures for 6 months did not decrease baseline levels of serum β_2M concentration or improve clinical symptoms related to DAA. Long-term study will be necessary to conclude whether HDF with a high-performance membrane could become a useful treatment for DAA. More effective methods for β_2M elimination should be expected for the prevention and treatment of DAA.

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