

Learning from the Japanese Registry: how will we prevent long-term complications?

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Abstract. As compared to Europe and USA, the survival rate of chronic haemodialysis (HD) patients in Japan is demonstrated by the Japanese Registry to be high. However, another Japanese nationwide survey on their quality of life revealed serious osteoarticular disorders increasing with the duration of HD. Selecting plasma β_2 -microglobulin (β_2 -M) as a marker, a prospective study on the long-term clinical effect of a β_2 -M-removable membrane (PMMA BK membrane) has been performed and the changes in joint pains and plasma β_2 -M have been followed for 5 years. In addition, the incidence of carpal tunnel syndrome (CTS) and bone cysts among 225 patients maintained on HD with BK membrane was analyzed retrospectively. By continued use of BK membrane, plasma β_2 -M was maintained at a significantly lower level than that in HD with conventional cellulosic membranes. The total score of joint pain in HD patients treated with BK membrane was significantly decreased and maintained at this low value throughout 5 years. In HD patients treated with BK membrane for a long period, the occurrence of CTS and bone cyst was less and postponed, as compared to patients on HD with conventional cellulosic membranes. HD-related amyloidosis had not been observed for 5 years in patients treated with BK membrane from the introduction of haemodialysis.

Key words: Osteoarthropathy; dialysis-related amyloidosis; β_2 -microglobulin-removable membrane

Introduction

The contrasting difference of mortality in chronic hemodialysis (HD) patients in Europe, USA and Japan has been attracting concern [1] and discussed at several symposia and congresses [2,3]. However, due to the

lack of the consistent registries in these three geographical areas, detailed analyses to clarify the actual causes of these differences are substantially difficult. The Japanese Society for Dialysis Therapy has been conducting a systematic survey of dialysis treatment in Japan for the past quarter of a century and its overview has been published every year.

Table 1 shows some of the key figures picked from the latest survey [4]. Following these published data the general trends regarding HD in Japan are clarified.

In addition, the Japanese Dialysis Medical Association together with the Japanese Association of Kidney Disease Patients twice performed a nationwide survey on the quality of life among chronic HD patients in Japan. According to these surveys, especially the latest one [5], long-term complications which increase with the extension of HD duration and are typified by osteoarticular disorders are demonstrated to be still serious, as shown in Figure 1.

We identified β_2 -microglobulin (β_2 -M) as a major component of amyloid fibril harvested from a chronic HD patient with carpal tunnel syndrome (CTS) in 1985 [6]. Closely following our identification, the depositions of β_2 -M in various tissues, including bone, of HD patients has been confirmed [7,8]. Almost at the same time, an *in vitro* pathogenic effect of β_2 -M

Table 1. Current status of dialysis therapy in Japan as of December 31, 1992

Population	1.24 × 10 ⁸
Maintenance Dialysis Patients	123,296
Day Time HD	88,980
Night HD	28,719
CAPD	6,011
Home HD	111
IPD	106
Centers	2,520
Consoles	49,352
Start of RRT ^a in 1992	22,475
Death in 1992	11,628

^a Renal replacement therapy.

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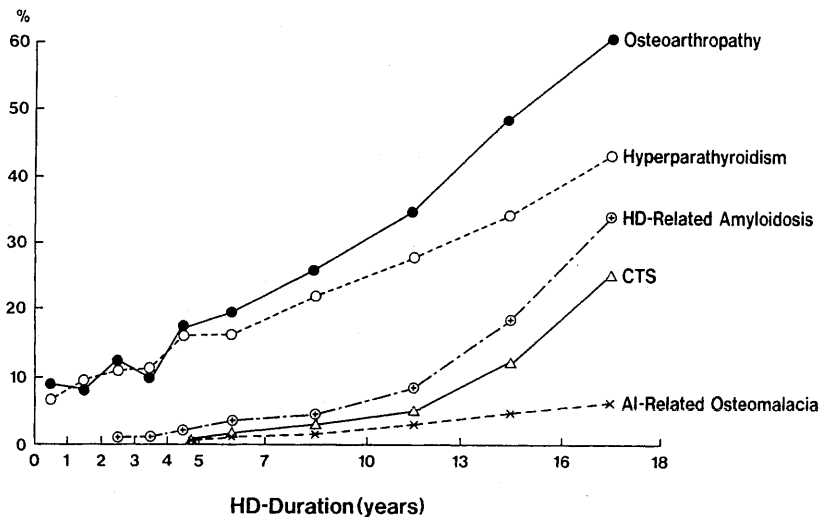


Fig. 1. Incidence of long-term complications among chronic HD patients as a function of HD duration observed in a nationwide survey on their quality of life which was performed in 1991 in Japan. These data were obtained from the analysis on 4857 chronic HD patients based upon the replies from the patients and those from their physicians-in-charge.

on the calcification of osteoblastic cells derived from mouse calvaria was demonstrated [9]. While strong concern had thus been raised to the removal of β_2 -M from chronic HD patients, poly(methyl methacrylate) (PMMA) BK membrane was developed by Toray Industries, Inc. in 1986 as a HD membrane which can remove β_2 -M [10–12].

To clarify the role of HD membranes in the prevention of the osteoarticular disorders in chronic HD patients, which increase definitely with the extension of HD duration and surely disturb their daily activities, we have performed a multicentre prospective study since 1987 on PMMA BK membrane monitoring plasma β_2 -M as a marker. In this study, where a group of patients were switched from HD with conventional cellulosic membranes to HD with BK membrane while the other group of patients were treated with BK membrane from the introduction of HD we have aimed to give an insight into the relationship between the performances and biological responses in each treatment and the occurrence of long-term complications. The first report of this study has been published [13]. In the present paper, we describe further data and results accumulated and analysed in this prospective study as well as those in the retrospective study additionally performed.

Methods and subjects

Basic study frame

Table 2 summarizes the outline of HD patients in this prospective study, who had been maintained on HD at 31 hospitals and were classified into 3 groups according to their HD duration with conventional cellulosic membranes and presence or absence of joint pains. This Table contains their baseline diseases as well as HD duration with cellulosic membranes before the switch to HD with BK membrane

Table 2. Summary of HD patients in the prospective study

Group	A	B	C
Cases	46	57	32
Sex (M/F)	34/12	35/22	22/10
Age at start of RRT (yrs)	50.7 ± 13.6	38.7 ± 12.2	42.7 ± 15.5
HD duration ^a (yrs)	<0.17	>5	>1
BK-HD duration (yrs)	4.1 ± 1.5	4.9 ± 1.3	3.8 ± 1.7
Joint pain	(-)	(+)	(-)
Baseline disease			
CGN ^b	27	46	23
PCKD ^c	6	3	1
Malignant HT ^d	1	0	1
Nephrosclerosis	4	2	2
Others	3	4	3
Unknown	5	2	2

^a HD using conventional cellulosic membrane.

^b Chronic glomerulonephritis.

^c Polycystic kidney disease.

^d Hypertension.

and HD duration with BK membrane after the switch. Fifty-seven patients of Group B who had been treated with cellulosic membranes for more than 5 years before the switch to HD with BK membrane and complained of joint pains, apart from CTS, at that switch were the subjects for the follow-up study on their pains. The regions including neck, shoulder, elbow, wrist, finger, back, hip, coxa, knee, ankle and toe were targeted for the observation. Estimate of joint pains, apart from CTS, was scored by patients' complaints and doctors' evaluation as follows;

- Score grade 4: Intolerable
 3: Tolerable
 2: Slight
 1: Occasionally slight
 0: None

Score grade of each joint was added and the total score grade was initially analyzed as absolute value.

For the comparison with the subjects of Group A who were introduced into HD with BK membrane from the beginning, eight patients who started HD with cellulosic membranes from the first were studied retrospectively.

Data collection and analysis regarding the occurrence of CTS and bone cyst, to which attention has been paid as long-term complications among chronic HD patients in addition to the above joint pains, was retrospectively carried out on 225 patients (including 135 patients listed in Table 2) maintained on HD with BK membrane at 31 hospitals where the above prospective study has been performed. The outlines of those 225 subjects are summarized in Table 3.

In the above prospective and retrospective studies, patients with diabetic mellitus, primary and secondary amyloidosis were excluded.

Statistical analysis

For the analysis on the total score of pain, Wilcoxon's signed rank sum test was applied. As to the occurrence of CTS and bone cyst, Kaplan-Meier method [14] was employed and log-rank test was used to analyze the effect of sexual difference on their occurrence. Cox's proportional hazards model [15] was applied to assess the influence of sex, use of BK membrane and age at the start of renal replacement therapy. For those statistical analyses except Wilcoxon's test, SAS (Statistical Analysis System) [16] was used where LIFETEST and PHREG were employed as procedures. Unless otherwise stated, Student's *t*-test was employed.

Results

Changes in plasma levels of β_2 -M

Figure 2 depicts changes in plasma β_2 -M, where the follow-up data on 135 patients in the prospective study and 8 patients treated throughout with conventional cellulosic membranes in the retrospective study are demonstrated. It is noted that significantly decreased plasma β_2 -M in Groups B and C by the switch to HD with BK membrane were maintained during 5 years. We previously presumed that the earlier introduction of BK membrane can reduce plasma β_2 -M more than in the case of its later introduction [13]. However, the mean plasma β_2 -M in Group A gradually increased while it maintained a significant difference from that

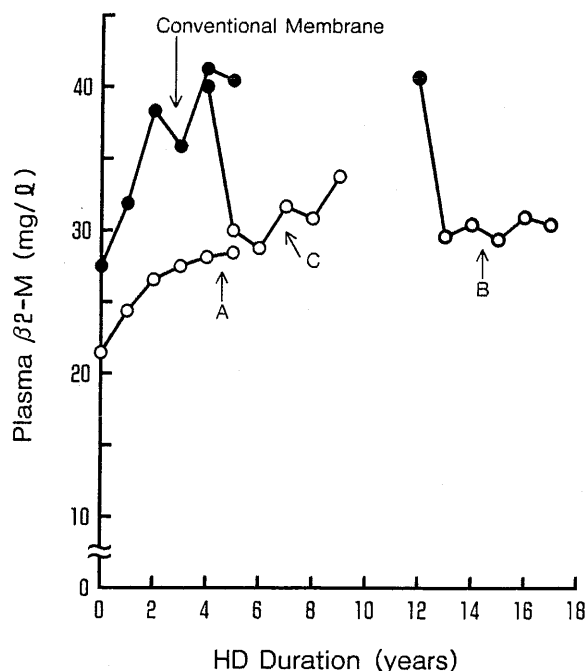


Fig. 2. Changes in plasma β_2 -M observed in the prospective study (Groups A, B and C: see Table 2). Only the data on the group who were introduced into HD with conventional cellulosic membranes were analyzed retrospectively. Open and closed circles designate data for BK and cellulosic membranes, respectively.

in the patients who were introduced into HD with cellulosic membranes from the first.

In order to give an insight into the change in plasma β_2 -M during the introduction phase, the changes of the preserved urine volume in Group A and the corresponding group were compared, although it is generally not an accurate parameter due to its high patient-patient variation. The half-life period, during which the volume is decreased to the half of that at the introduction into HD, was 22.1 months in Group A while it was 8.1 months in the corresponding group. As the increase in plasma β_2 -M in the early phase of HD treatment is partially due to the decline of residual renal function, slower decrease of the urine volume in Group A than that in the corresponding group may be interpreted to exert a significant effect on the above lesser increase in plasma β_2 -M in Group A than Group B.

Changes of joint pains in the prospective study

Changes of joint pains in patients studied as Group B are shown in Figures 3 and 4 demonstrating the absolute and relative scores, respectively. Thirty-five among 57 patients in Group B had been observed for whole 5 years and were classified into three subgroups according to their duration of HD with cellulosic membranes before the switch to BK membrane, that is, Subgroup I; 5-9; II; 10-14 and III; 15-19 years. In the Subgroup I (10 patients, mean age at the switch to HD with BK membrane; 61.1 ± 10.3 years), the mean joint pain score at the switch to BK membrane

Table 3. Summary of HD patients in study on CTS and bone cyst

Cases	225
Sex (M/F)	152/73
Age at start of RRT (yrs)	43.5 ± 13.4
Baseline disease	
CGN ^a	180
PCKD ^a	12
Malignant HT ^a	2
Nephrosclerosis	11
Others	11
Unknown	9
Total	225

^a See footnote to Table 2.

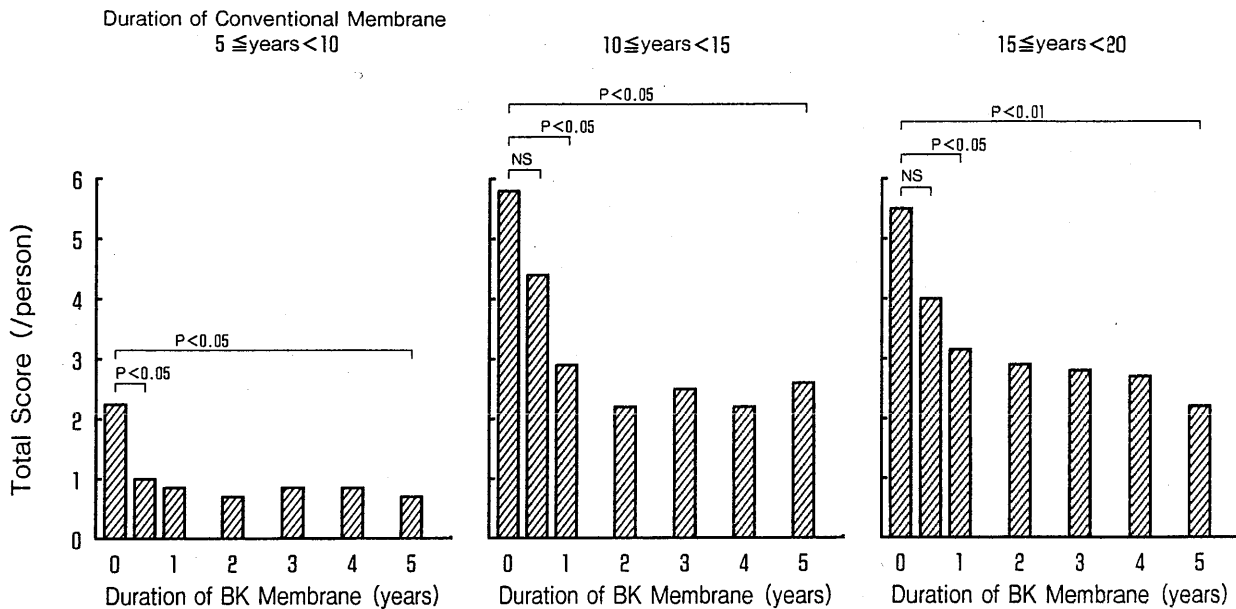


Fig. 3. Changes in the total score of joint pains in the patients of Group B (see text).

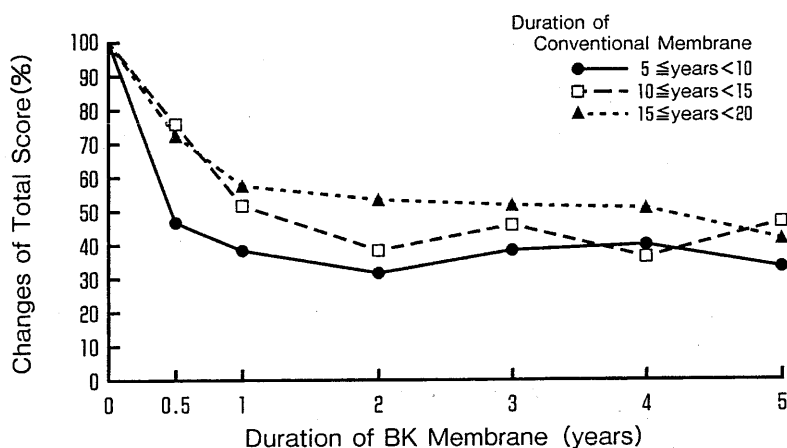


Fig. 4. Relative changes in the joint pain score in the patients of Group B (see text).

was 2.2 which was significantly lower than those in the other two subgroups. After the continued use of BK membrane for 6 months, the mean joint pain score of this subgroup was significantly decreased to 1.0 (Wilcoxon's test; $P < 0.05$). For Subgroup II (20 patients, mean age at the switch to BK membrane; 51.3 ± 9.3), the corresponding value was significantly improved from 5.8 to 3.0 through the continued use of BK membrane for 1 year ($P < 0.05$). In Subgroup III (15 patients, mean age at the switch to BK membrane; 48.8 ± 8.4), where the duration of HD with cellulosic membranes before the switch to BK membrane was longer than in the other two subgroups, the value was also significantly decreased from 5.5 to 3.2 after 1 year's use of BK membrane ($P < 0.05$). The mean joint pain scores after the continued use of BK membrane for 5 years were improved to 0.7*, 2.7* and 2.3** for Subgroups I, II and III, respectively (*: $P < 0.05$, **: $P < 0.01$). Joint pains thoroughly disappeared

during these 5 years in 7 (70%), 6 (30%) and 5 (33%) cases for Subgroups I, II and III, respectively.

As described below, age was demonstrated to be a high risk factor in the incidence of CTS and bone cyst. In the above analysis on joint pains, the mean age at the initiation of HD with BK membrane was decreasing in the order of Subgroups I, II and III as shown above (I to II; $P < 0.05$, I to III; $P < 0.01$, II to III; NS) and, therefore, the results did not seem to be biased by age.

The following are suggested from these results;

(i) Although it was not so high when HD duration with cellulosic membranes was less than 10 years, the pain score strikingly increased in excess of 10 years.

(ii) In the cases of the early switch to BK membrane demonstrated in Subgroup I (HD duration with cellulosic membranes; 5 to 9 years), the pain score rapidly decreased and was maintained at a low level as compared to the other two subgroups.

(iii) Even in the case of the later switch to BK

membrane after HD with cellulosic membranes for more than 10 years, the pain score decreased to about a half by the continued use of BK membrane and did not rebound during 5 years, although the level reached was not so low as compared to that in the case of the early switch.

Any incidence of joint pain or dialysis-related amyloidosis such as CTS has not been observed in Group A these 5 years since the introduction into HD with BK membrane.

Analysis on the occurrence of CTS and bone cyst in the retrospective study

In addition to joint pains, CTS and bone cyst have been of increasing concern as long-term complications among chronic HD patients. By enlarging the scope of subjects to 225 patients, who had been maintained on HD with BK membrane from the beginning or after a certain period of HD with cellulosic membranes, the occurrence of CTS and bone cyst was retrospectively investigated. For those 225 patients, Figure 5 shows the duration of HD with cellulosic membranes, that with BK membrane and the occurrence of CTS.

The relationship of age at HD introduction, use of BK membrane and gender difference with the occurrence of CTS and bone cyst was first analyzed by using Cox's regression analysis. The results are summarized in Table 4. The age at HD introduction and gender (female to male) were demonstrated to be significantly effective factors to increase the risk of CTS. One year elevation of age at HD introduction increased the risk of CTS by the ratio of 1.028. Female/male showed highly significant ratio of 2.164, which means that CTS was more incident to female than male. As for bone cyst, one year elevation of age at HD introduction

Table 4. Cox's regression

	Variable	Parameter estimate	Pr> chi-square	Risk ratio
CTS	Age	0.02777	0.0472	1.028
	BK	-0.42753	0.2188	0.652
	Sex	0.77191	0.0091	2.164
Bone cyst	Age	0.03907	0.0031	1.04
	BK	-0.17003	0.6213	0.844
	Sex	0.28215	0.3487	1.326

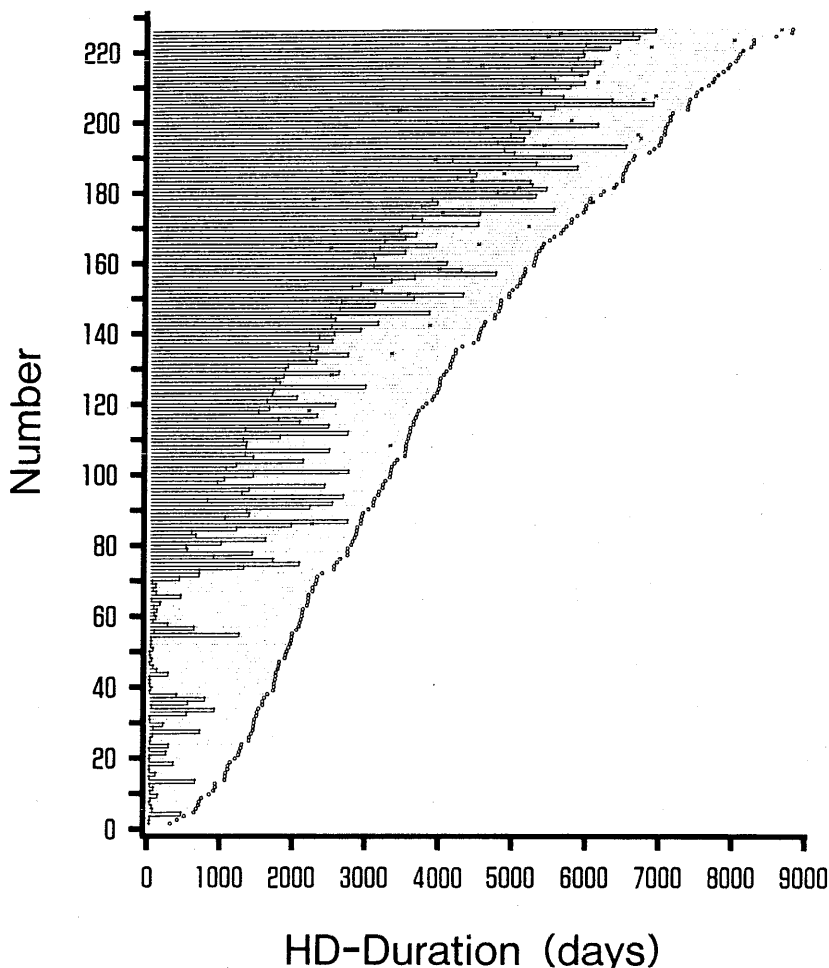


Fig. 5. HD periods of 225 patients observed in the retrospective study, where HD duration with conventional cellulosic membranes and that with BK membrane are depicted as solid and dotted lines, respectively. Onset of CTS is marked with X.

significantly incremented the risk by the ratio of 1.04. Female patients again showed a greater tendency of the incidence of bone cyst although statistically not significant. On the other hand, the use of BK membrane tended to decrease the occurrence of both CTS and bone cyst as demonstrated as their risk ratios (BK/conventional) to less than one, although statistically not significant. In the above analysis, however, the subjects who were treated with BK membrane even for a short period such as 1 year were classified into BK group. As described below (Tables 5 and 6), further detailed analysis on the effect of the membranes was carried out by grouping the subjects into BK and

conventional membrane groups according to the durations of these two types of membranes, that is, which membrane was used for a longer period than the other over total HD duration.

Figure 6 shows the effect of gender on the period until the occurrence of CTS which was separately analyzed by Kaplan-Meier method. Again the significantly frequent occurrence of CTS in female patients as compared to male was thus demonstrated (log-rank test; $P=0.0073$).

As a high incidence of CTS in the female may be interpreted to be due to coexistent idiopathic disease as discussed below, only male patients from the total

Table 5. Analysis on CTS incidence in male patients

	Group ^a	Total HD duration			
		0 ≤ yrs < 5	5 ≤ yrs < 10	10 ≤ yrs < 15	15 ≤ yrs
	Conv	2.9 ± 1.2	7.7 ± 1.5	12.5 ± 1.4	18.6 ± 2.4
	BK	4.1 ± 0.3	8.2 ± 1.3	11.0 ± 0.6	—
	χ ² -test	NS	NS	$P < 0.01$	
CTS incidence (%)	Conv	0.0(0/3)	38.9(7/18)	29.0(9/31)	34.5(10/29)
	BK	0.0(0/2)	0.0(0/18)	0.0(0/8)	—
	χ ² -test	NS	$P < 0.01$	NS	
Age at start of RRT (yrs)	Conv	49.3 ± 29.3	45.7 ± 12.7	42.0 ± 12.7	33.9 ± 10.1
	BK	44.5 ± 34.6	44.8 ± 13.2	37.3 ± 11.3	—
	χ ² -test	NS	NS	NS	
Percentage of period of BK-HD over total HD duration (%)	Conv	36.8 ± 6.1	23.4 ± 17.5	31.1 ± 18.8	21.2 ± 11.9
	BK	51.9 ± 0.4	69.4 ± 9.1	56.2 ± 2.5	—
	χ ² -test	NS	$P < 0.01$	$P < 0.01$	

^a Conv: percentage of period of BK-HD over total HD duration < 50%.
BK: percentage of period of BK-HD over total HD duration ≥ 50%.

Table 6. Analysis of bone cyst incidence

	Group ^a	Total HD duration			
		0 ≤ yrs < 5	5 ≤ yrs < 10	10 ≤ yrs < 15	15 ≤ yrs
	Conv	1.9 ± 1.9	8.1 ± 1.5	12.6 ± 1.5	18.3 ± 2.2
	BK	4.1 ± 0.2	8.3 ± 1.2	10.9 ± 0.6	—
	χ ² -test	$P < 0.01$	NS	$P < 0.01$	
Bone cyst incidence (%)	Conv	70.0(7/10)	30.0(6/20)	32.6(14/43)	35.6(16/45)
	BK	0.0(0/4)	0.0(0/30)	0.0(0/10)	—
	χ ² -test	$P < 0.05$	$P < 0.01$	$P < 0.05$	
Age at start of RRT (yrs)	Conv	49.4 ± 15.0	47.5 ± 12.4	43.0 ± 11.9	33.0 ± 10.1
	BK	42.8 ± 21.7	43.6 ± 11.7	39.1 ± 11.0	—
	χ ² -test	NS	NS	NS	
Percentage of period of BK-HD over total HD duration (%)	Conv	11.0 ± 18.0	28.1 ± 15.4	27.0 ± 18.6	19.4 ± 12.4
	BK	59.2 ± 8.4	67.6 ± 9.1	56.5 ± 2.5	—
	χ ² -test	$P < 0.01$	$P < 0.01$	$P < 0.01$	

^a Conv: percentage of period of BK-HD over total HD duration < 50%.
BK: percentage of period of BK-HD over total HD duration ≥ 50%.

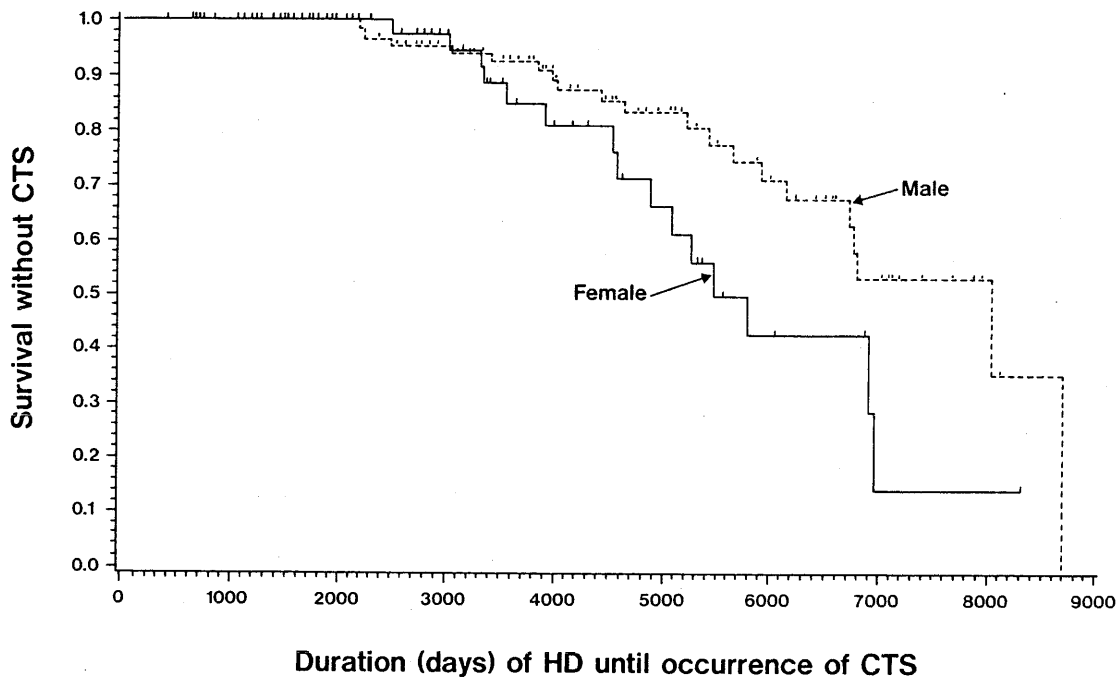


Fig. 6. Incidence of CTS in male and female patients analysed by Kaplan-Meier method (see text). Vertical bar (|) represents a censored case.

225 were analysed as follows and the results are listed in Table 5. According to the total HD duration, they were classified into four subgroups, that is, less than 5, 5 to 9, 10 to 14 and more than 15 years. Then, according to the membranes which were used for longer period than the other, they were divided into conventional membrane group (Conv) and BK membrane one (BK). Although none of BK membrane group have as yet been treated for more than 15 years, less incidence of CTS in BK group was suggested. Especially in the subgroup of total HD duration from 5 to 9 years, where no significant differences were confirmed as to total HD duration and age at start of HD, 7 out of 18 patients and none out of 18 were diagnosed as CTS in conventional and BK groups, respectively ($P < 0.01$).

Similar analysis on bone cysts was performed for both sexes because the effect of gender difference on the incidence of bone cyst was not demonstrated to be statistically significant. However, the subjects who were treated with conventional cellulosic membranes for less than 1 year were excluded for the comparison between the two membrane groups. The results are shown in Table 6. While an increased incidence in conventional membrane group was shown even in the case of the shortest total HD duration, which may suggest the coexistence of bone cyst independent from renal failure as already reported [17], none was observed in BK groups.

Although these contrasting data remain to be studied for longer with wider clinical evaluations, a lower incidence rate of dialysis-related amyloidosis is suggested in the patients who were switched to HD with BK membrane from cellulosic ones in the early phase.

Discussion

Comparing the survival rates of chronic HD patients among Europe, U.S.A. and Japan, the highest value in Japanese patients has been presented although its actual causes are not pinpointed yet. Not a few long-surviving Japanese HD patients, however, still suffer from long-term complications such as osteoarthropathy and dialysis-related amyloidosis and their daily activities are significantly impaired due to those complications.

Selecting β_2 -M as a marker, a long-term clinical evaluation has been performed prospectively for 6 years using PMMA BK membrane which can remove β_2 -M through not only permeation but also adsorption [18]. In addition, a retrospective analysis on 225 patients maintained on HD with BK membrane from the beginning or after HD treatment with cellulosic membranes for a certain period, 135 of whom were the subjects of the prospective study, was carried out employing Kaplan-Meier method and Cox's test.

In the present study, changes in plasma β_2 -M caused by the introduction of HD with BK membrane from the first or by the switch from cellulosic membranes to BK were demonstrated. By the continued use of BK membrane, plasma β_2 -M was decreased and maintained at a certain level, which was significantly less than that in HD with cellulosic membranes. To give an insight into these changes of β_2 -M, especially in the introduction phase, data on preserved urine volume were collected. As mentioned above, its decrease in BK group was observed to be slower than in the corresponding group. Gung *et al.* reported about the different influence on residual renal function between

biocompatible and bioincompatible membranes in an animal model [19]. Furthermore, Hakim proposed his hypothesis on the possible clinical significance of biocompatibility on the maintenance of renal function in clinical settings [20]. Although our data on the preserved urinary volume were still preliminary, they seemed to support the above hypothesis by Hakim.

Very few papers regarding long-term follow-up on joint pains among chronic HD patients have been published, maybe due to its difficulty. In the present study, continuous observation on joint pains over 5 years has been conducted and significant decreases in joint pains by the continued use of BK membrane was demonstrated. It is especially noted that the early introduction of BK membrane is associated with a more prompt and better improvement in joint pains and the diminished pains do not seem to rebound over 5 years.

In the retrospective analysis on the occurrence of CTS and bone cyst, age at HD induction and gender were shown to exert a significant effect in both and only CTS respectively, while the use of BK membranes was demonstrated to have a tendency to delay their occurrence although not significantly. Frequent occurrence of CTS in females observed in this study seems to be consistent with the results already reported [21,22] and is considered to be in part due to idiopathic CTS, frequently observed in females. Although the effect of sexual difference on those complications were seldom discussed in the past long-term clinical studies on HD [23,24], the results obtained in this study strongly suggest the necessity for considerations on those factors.

After grasping the outline of key factors in the incidence of CTS and bone cyst, the effect of the membranes was further evaluated. As to CTS, only male patients were analyzed due to high incidence of coexistent idiopathic CTS in female patients and, as demonstrated in Table 5, its delayed incidence in BK membrane group was strongly suggested. Therefore, further results which will be collected in the still going long-term clinical study, are expected. On the other hand, analysis on the incidence of bone cyst was performed for both sexes. While the effect of the use of BK membrane was analysed irrespective of its duration in Cox's regression test (Table 4), the analysis listed in Table 6 was carried out taking into consideration the duration of use of two types of membranes. Although the high incidence rate in the conventional membrane group, especially in the case of shorter total duration of HD, may be caused by biased selection of patients and due to coexistent bone cyst independent from renal failure and/or HD treatment [17], no incidence in BK group at all was striking. Further data collection in the still going study is also expected.

Results of retrospective analysis on the occurrence of CTS and bone cyst thus performed based upon the considerations of sex, age at HD initiation and HD duration with BK and cellulosic membranes were interesting and seemed to be consistent with those observed in the above prospective study.

In summary, the followings were suggested by the continued use of BK membrane from the HD induction or through the switch from conventional cellulosic membranes to BK membrane although further confirmation remains to be done;

(i) A decrease in plasma β_2 -M and its maintenance at a reduced level.

(ii) A decrease in joint pains and its maintenance at the improved level.

(iii) A decrease in the incidence rate of CTS and bone cyst and the elongation until their occurrence.

Combining our results obtained in the prospective and retrospective studies, continued use of BK membrane from the beginning seems to be clinically desirable from the viewpoint of prevention of the long-term complications typified by osteoarticular disorders and dialysis-related amyloidosis.

Appendix

Niigata Research Programme for β_2 -M removal membrane

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