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## Long-Term Clinical Experience with PMMA Membrane

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### Introduction

The total number of hemodialysis (HD) patients at present in Japan has reached 167,192, and cases of HD treatment extending for more than 10 years is 22.9% [1]. According to a nationwide survey on the QOL of HD patients entitled 'Actual state of HD patients in Japan in the fiscal year of 1996', conducted by the Japanese Association of Kidney Disease Patients, osteoarticular disorders were noted in 33.7% of the total number. In cases of HD treatment extending for more than 25 years, 84.8% of them had osteoarticular disorders. Impairment of ADL and QOL by osteoarticular disorders showed a sharp increase after 15 years of HD treatment; 5.0% in patients with HD treatment for less than 15 years, 11.7% patients with HD treatment extending up to 20 years and 37.0% for cases of treatment continuing for more than 25 years. Clearly, long-term chronic dialysis-related amyloidosis (DRA) and osteoarticular disorders impair ADL and QOL in HD cases [2].

To verify osteoarticular disorder complications accompanying long-term chronic HD and the effect of HD with PMMA membrane on DRA, we have been conducting a multicenter cohort study since 1988 [3, 4]. We report the course of a prospective study of HD with PMMA membrane for 8 years which is currently still in progress and the result of a retrospective study regarding influence of HD with PMMA membrane to the development of carpal tunnel syndrome (CTS) and radiolucent bone cysts (RBC).

Table 1. Summary of HD patients in the prospective study

	Group A	Group B	Group C
Cases	46	57	32
Gender, m/f	34/12	35/22	22/10
Age at start of RRT, years	50.7±13.6	38.7±12.2	42.7±15.5
HD duration, years	<0.17	>5	>1
Joint pains	-	+	-
Underlying diseases			
CGN	27	46	23
PCKD	6	3	1
Malignant HT	1	0	1
Nephrosclerosis	4	2	2
Others	3	4	3
Unknown	5	2	2

CGN = Chronic glomerulonephritis; PCKD = polycystic kidney disease; HT = hypertension.

Table 2. Subgroup category of Group B

	Duration of conventional membrane, years	Age at switch to BK membrane, years
Subgroup I	5-9	61.1±10.3
Subgroup II	10-14	51.3±9.3
Subgroup III	15-20	48.8±8.4

## Methods

The Department of Medicine (II), Niigata University School of Medicine and 30 affiliated hospitals have been conducting a long-term clinical joint study on HD with PMMA membrane since 1988 [3, 4].

### *Prospective Study*

*Registered Cases and Their Classification.* Dialysis cases with chronic renal failure, except cases having diabetes, collagen disease or multiple myeloma as primary disease, were the subject of this study. Those registered cases from each site were classified by HD duration, HD duration with cellulosic membranes and presence or absence of joint pain (table 1).

*Study Parameters.* In group A, onset of DRA development and the time it was complicated were studied. Group B was further classified into 3 subgroups by HD duration with cellulosic membranes (table 2). Changes in joint pain after switching from HD with cellulosic

Table 3. Estimate of joint pain (apart from CTS)

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<i>Pain score grade:</i>	
4	Intolerable
3	Tolerable
2	Slight
1	Occasionally slight
0	None

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membranes to HD with PMMA membrane was evaluated using five grades shown in table 3, the degree of joint pain was evaluated for the neck, shoulders, elbows, wrists, fingers, backs, hips, coxae, knees, ankles and toes through the interview by the chief doctors. The score was summed up in each case, which was taken to be the pain score. Joint pain with clear cause such as injury, osteoarthritis, CTS and so on were excluded. We also studied successive change of serum  $\beta_2$ -microglobulin ( $\beta_2$ -M) blood concentration level before HD in each case, using the annual average of each case.

#### *Retrospective Study*

*Subjects and Classification.* To analyze valuable data accumulated for a long period regarding development of CTS and bone cysts caused by HD with PMMA membrane, a multicenter retrospective study was performed. The conventional membrane group was considered to be cases in which HD duration with PMMA accounted for less than 50% of total HD duration, and the PMMA membrane group was considered to be cases in which HD duration with PMMA accounted for 50% or more of the total HD duration. The occurrences of complications of CTS and bone cysts were compared between the conventional membrane group and PMMA membrane group every 5 years throughout the total HD duration.

#### *Statistical Analysis*

The Wilcoxon test for pain score, Cox's proportional hazards model for the influence of age at the time of introduction to renal replacement therapy, use of PMMA membrane, gender (female/male) and Kaplan-Meier method for gender difference on complication of CTS were applied to the study. T-test was applied for other items. SAS (Statistical Analysis System) was used in Cox's proportional hazards model and Kaplan-Meier method.

## **Results**

### *Prospective Study of 8 Years*

*Effect on Joint Pain.* Our results of follow-up on pain score after switching to PMMA membrane are shown in figure 1. In subgroup 1, which has the shortest duration of HD with cellulosic membranes, average pain score at the start of HD with PMMA membrane was 2.2, which was lower than that of the other two subgroups (6.3 in subgroup II and 5.5 in subgroup III). Significant

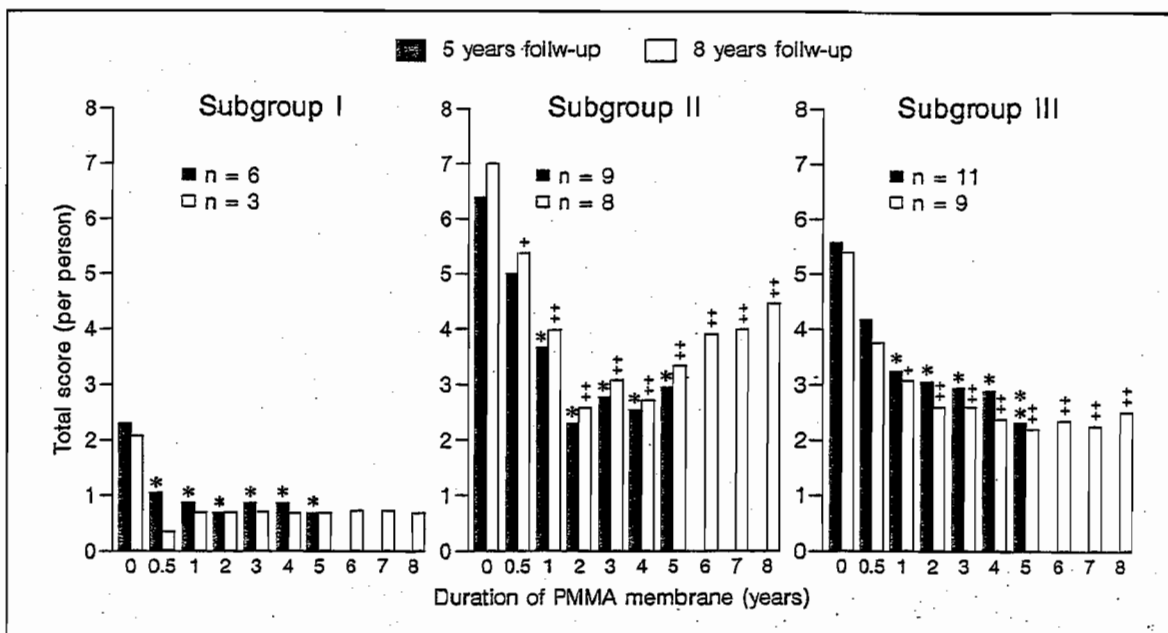


Fig. 1. Changes in the total score of joint pain in the patients of group B. Wilcoxon's test: \*+ p < 0.05; \*\*+++ p < 0.001.

improvement in the pain score was noted after 6 months from change of membrane. Subgroup II and subgroup III also showed a decrease in the pain score in 6 months after change of membrane and significant improvement was noted after 1 year. In subsequent observations, improvement in the pain score was maintained. Follow-up cases after 8 years also showed similar improvement in the pain score which was maintained.

*Change of Serum  $\beta_2$ -M Blood Concentration before HD.* As shown in figure 2, serum  $\beta_2$ -M concentration level at pre-HD increased from the beginning of HD up to 3 years in group A, and then it reached a plateau level. In group B having joint pain, the serum  $\beta_2$ -M concentration immediately went down after changing membrane, and that was maintained. Ten cases introduced to conventional membrane (control study) showed higher increase of serum concentration of  $\beta_2$ -M.

*The Clinical Course of the Group Introduced to PMMA (Group A).* During 8 years follow-up, no development of CTS, RBC or joint pain was observed.

#### Retrospective Study

*Selection of Cases for Analysis.* Factors which influence development of CTS and RBC were studied on 261 subjects having a history of HD with PMMA membrane, using Cox's proportional hazards model. Age at the time

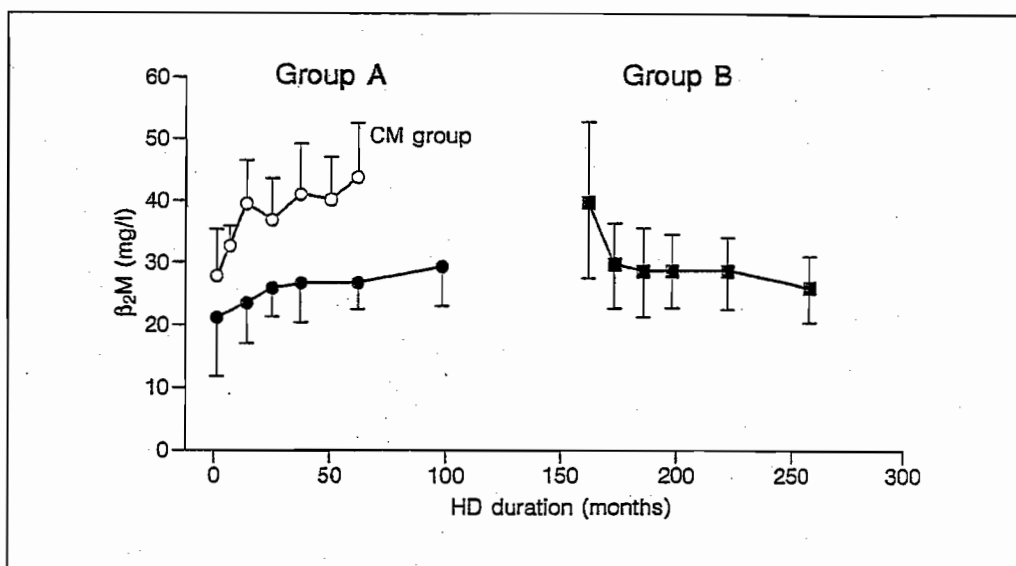


Fig. 2. Changes in predialysis serum levels of  $\beta_2$ -M. Conventional membrane (CM) group is the control for group A.

Table 4. Result of Cox's regression

Variable	Parameter estimate	$\chi^2$	Risk ratio
<i>CTS (n=222)</i>			
Age	0.02777	0.0472	1.028
PMMA (BK)	-0.42753	0.2188	0.652
Gender, f/m	0.77191	0.0091	2.164
<i>Radiolucent bone cyst (n=221)</i>			
Age	0.03907	0.0031	1.04
PMMA (BK)	-0.17003	0.6213	0.844
Gender, f/m	0.28215	0.3487	1.326

of introducing HD and gender difference (female) were significant risk factors for CTS, as well as age at the time of introducing HD for RBC. HD with PMMA membrane tended to decrease risks of those developments (table 4) [4]. Difference in development of CTS between male and female is also significantly noted by the Kaplan-Meier method [4]. To exclude any influence of coexistence of idiopathic CTS in females [5], only male cases (174 cases) were evaluated for dialysis-related CTS. For RBC, analysis was performed on all cases of subject.

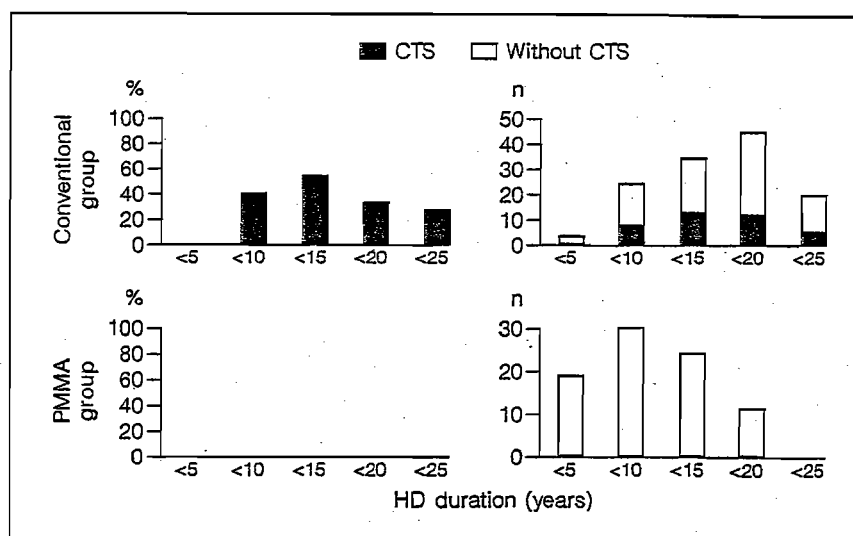


Fig. 3. Incidence of CTS.

*Complication of CTS.* Since the longest term of HD with PMMA membrane is 8 years, there are no cases which belong to the group of total HD duration from 20 to 25 years. In other groups, no patients developed complications of CTS in the PMMA group (fig. 3). In the conventional membrane group, complications of CTS were seen in 38.6% of the cases of total HD duration for 5 years and more. No significant difference between those groups in patients with different age at the time of introducing HD was noted.

*Bone Cysts.* In the conventional membrane group, complications of RBC were noted in 42.7% (27.8–75%) of the cases on average. In the PMMA group, the incidence was as low as 4.3% (0–12.5%). Unlike the complications of CTS, appearance of RBC was present in both groups at an early stage of HD (fig. 4). However, all of those cases occurred in elderly patients.

## Discussion

For alleviation of joint pain by HD with PMMA membrane, the therapeutic advantage was seen in the group with relatively shorter HD duration with conventional membrane, and diminished as the HD term using conventional membrane was prolonged. It is suggested that this might be a result of joint pain noted in long-term HD cases being caused by a variety of reasons. In group A, serum  $\beta_2$ -M level was significantly increased for several years after introducing HD. Possibly the excretion of  $\beta_2$ -M by the kidney itself

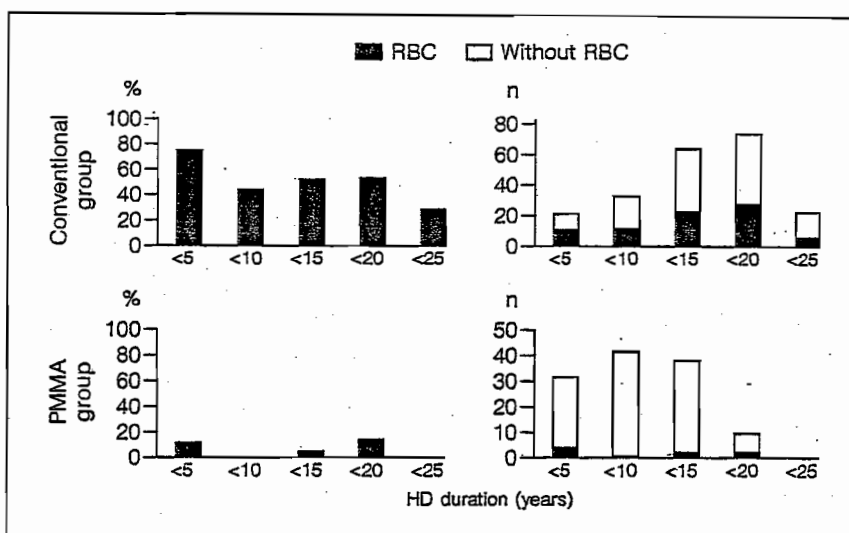


Fig. 4. Incidence of RBC.

influenced the blood concentration. Regarding complications of DRA, influence of dialysate quality should be considered. Baz et al. [6] reported that incidence of CTS was lower in cases using ultrapure dialysate. Though such ultrapure dialysate was not used in this study, Miura et al. [7] reported a low incidence of RBC in HD with PAN membrane using non-RO-treated dialysate. Thus, the character of the HD membrane could influence complications of DRA to a greater degree than purity of dialysate. It was reported that a back-diffusion or a back-filtration of endotoxin is relatively reduced when using a PMMA membrane even with dialysate made from tap water containing a high concentration of endotoxin [8]. There is a possibility that HD with PMMA membrane was performed with relatively clean dialysate.

### Conclusion

To conclude:

(1) Joint pain of HD patients is significantly decreased within 6 months to 1 year after switching from conventional membrane to PMMA membrane, and the improved state is maintained. (2) When switching from conventional membrane to PMMA membrane, the  $\beta_2$ -M serum concentration before HD decreases, and this decreased level is maintained. (3) By switching from conventional membrane to PMMA membrane, the risk of complication with CTS and RBC is decreased.

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