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The Effect of Membrane Biocompatibility on Plasma β_2-microglobulin Levels in Chronic Hemodialysis Patients[1]

Raymond M. Hakim,[2] Rebecca L. Wingard, Leigh Husni, Robert A. Parker, and Tom F. Parker III

R.M. Hakim, R.L. Wingard, Department of Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN

L. Husni, T.F. Parker III, Dallas Nephrology Associates, Dallas, TX

R.A. Parker, Department of Preventive Medicine, Division of Biostatistics, Vanderbilt University Medical Center, Nashville, TN

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ABSTRACT

Several studies have shown that patients who have been dialyzed with high-flux biocompatible membranes have a lower plasma level of β_2-microglobulin and a lower incidence of amyloid disease compared with patients who have been dialyzed with low-flux bioincompatible membranes. However, because high-flux membranes are associated with significant dialytic removal of β_2-microglobulin, the specific role of membrane biocompatibility in influencing the rate of increase of β_2-microglobulin has not been previously determined. This study investigated the effect of biocompatibility on the rate of increase of plasma levels of β_2-microglobulin in 159 new hemodialysis patients from 13 dialysis centers (ten centers affiliated with Dallas Nephrology Associates and three with Vanderbilt University Medical Center) by using two low-flux membranes with widely different biocompatibilities. These patients were prospectively randomized to be dialyzed with either a low-flux biocompatible membrane or a low-flux bioincompatible membrane. Plasma β_2-microglobulin levels were measured at 0, 3, 6, 9, 12, and 18 months. Sixty-six patients completed the 18-month study. Plasma β_2-microglobulin increased in all patients; however, the increase was not significantly different from baseline at any time point in the group that used the biocompatible membrane. In this group, β_2-microglobulin increased from (mean ± SD) 27.8 ± 14.8 mg/L to 34.0 ± 10.0 mg/L at 18 months (P = not significant), and the mean increase at 18 months was 2.6 ± 14.7 mg/L. In contrast, the increase in plasma β_2-microglobulin level in the bioincompatible membrane group became significant in Month 6 when the levels had increased from a baseline of 24.8 ± 9.6 mg/L to 29.5 ± 12.2 mg/L ($P < 0.001$); these increases continued to be significant until Month 18, when serum β_2-microglobulin reached 36.8 ± 13.9 mg/L with an average increase of 11.8 ± 11.2 mg/L ($P < 0.0001$). The higher rate of plasma β_2-microglobulin increase in the group that had been dialyzed with the bioincompatible membrane was also evident when only patients who had completed the study were analyzed. There were no significant differences in the actual level of β_2-microglobulin or in residual renal function between the two groups during the 18 months of the study. It was concluded that over a period of 18 months, the use of biocompatible membranes, even in the low-flux configuration, is associated with a significantly slower increase in plasma β_2-microglobulin, independent of the influence of residual renal function.

Key Words: *β_2-microglobulin synthesis, carpal tunnel syndrome, β_2-microglobulin polymerization, reactive oxygen species, dialysis*

β_2-microglobulin (β_2m) is a protein (11,800 d) that is present on the surface of all nucleated cells, and approximately 30% of which is associated with the polypeptide chain of Class I HLA antigens (1,2). Normal turnover of nucleated cells results in the shedding of β_2m into the plasma and is subsequently excreted by normally functioning kidneys at a rate of 150 to 200 mg/day, resulting in a steady-state plasma level of approximately 1 to 2 mg/L (3–5). In patients with no residual renal function, plasma levels reach up to approximately 50 mg/L (5–7).

Amyloid-related bone disease is a complication that is frequently diagnosed in long-term hemodialysis patients, and which has clearly been shown to result from deposits of β_2m (8–12). Several studies have shown a substantial difference in the incidence of amyloid disease in long-term dialysis patients, depending on the type of dialysis membrane used (13–17). In one well-controlled multicenter study, patients dialyzed with cellulosic membranes had a statistically significant higher rate of developing bone amyloidosis. For patients starting dialysis at 60 years of age with cellulosic membranes, the relative risk of developing amyloid bone disease was more than five times greater than that found in the same patient dialyzed with a high-flux biocompatible membrane, such as the polyacrylonitrile membrane (14). Similarly, Miura *et al.* (16) found that in a group of 30 patients on chronic hemodialysis for more than 10 yr, patients with radi-

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[2] Correspondence to Dr. R.M. Hakim, Division of Nephrology, Vanderbilt University Medical Center, S-3307 MCN, 1161 21st Ave. S. & Garland, Nashville, TN 37232-2372.

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olucent bone cysts consistent with amyloid bone disease had spent significantly more time on cellulosic membranes, compared with patients without such bone cysts. Such differences in the incidence of amyloid bone disease have generally been attributed to the higher intradialytic removal (by adsorption and/or convective mechanism) of β_2m by these large pore-size high-flux membranes. Better preservation of residual renal function, an important excretory route of β_2m in patients using these biocompatible membranes (18), has also been proposed as an explanation for differences in the incidence of amyloid bone disease between these classes of membranes.

Another hypothesis to explain these observations of the incidence of amyloid disease is the possibility that cellulosic membranes increase the rate of release of β_2m from nucleated cells. Such a possibility is based on *in vitro* experiments that demonstrated an increased release of β_2m by direct contact of the mononuclear cells with cellulosic membranes, which was further increased in the presence of products of complement activation (19,20). Additionally, mononuclear cell cultures, harvested from patients dialyzed with membranes of different biocompatibilities, have shown that patients who are chronically dialyzed with bioincompatible membranes that activate the complement system have an increased release of β_2m by the mononuclear cells (21).

The pathophysiology that relates a plasma level of β_2m to the subsequent deposition of amyloid in the musculoskeletal system has not been clarified and requires long-term prospective observation. In this study, we attempted to define the potential role of biocompatibility of the dialysis membrane in the increase of plasma levels of β_2m after starting dialysis. We randomly allocated patients starting chronic hemodialysis to one of two low-flux membranes (ultrafiltration ≤6 mL/mm Hg per h) with widely different complement activation potentials (22). In a prospective study over 18 months, we monitored the plasma levels of β_2m in these patients that began chronic hemodialysis at 13 centers. The results of our study suggest that the bioincompatibility of the membrane contributes to the rise in plasma β_2m levels by mechanisms independent of its flux characteristics.

PATIENTS AND METHODS

The study design was a multicenter prospective randomized study of patients that had been newly initiated to a program of chronic hemodialysis. After randomization to either a bioincompatible (BICM) or biocompatible (BCM) membrane, each patient was dialyzed with their assigned membrane type for all outpatient treatments for a period of 18 months. During the study, the attending nephrologist determined the patient's dialysis prescription according to his or her own clinical judgment and the standards of the dialysis unit. No restrictions or guidelines for patient management were made for the purposes of the study.

All patients were recruited from Vanderbilt University Medical Center (VUMC; Nashville, TN) (42 patients in three centers) and Dallas Nephrology Associates (DNA; Dallas, TX) (117 patients in ten centers), and entered into the study after their informed consent, approved by the local Institutional Review Board, was obtained. All patients over 18 years of age and newly initiated to chronic dialysis therapy during the time period of March 1, 1991 to December 31, 1992 were eligible for study participation. No patients were excluded on the basis of etiology of renal failure or any other medical conditions.

The biocompatible treatment group was assigned to dialyze with a low-flux polymethyl methacrylate membrane (PMMA; Toray B2-1.5H Filtryzer, Toray Industries, Tokyo, Japan), a membrane known to result in only low levels of complement activation. The other group was dialyzed with a cellulosic membrane (T175; Terumo Corporation, Tokyo, Japan), a membrane known to cause high levels of complement activation. More specifically, for the PMMA membrane, complement activation as measured by *in vivo* plasma C3a levels have been shown to peak at only 10% to 20% above baseline, compared with a peak C3a level of more than five times the baseline for the cellulosic membrane (22). Similar results have been found by other investigators (23,24). Neither dialyzer used for this study was known to have any significant clearance of β_2m in their low-flux configuration (25). This was verified *in vivo* for the low-flux PMMA membrane at the VUMC center, where it was shown that these dialyzers had no β_2m clearance either during first use or sixth use. Specific dialyzer characteristics are shown in Table 1. Dialyzers at both centers were reused with bleach and formaldehyde sterilants, according to established guidelines. Such reuse procedures that incorporate bleach in the reuse process have been shown to have no significant effect on the degree of leukopenia of either membrane (a reflection of complement activation) (22).

Outcome Measures

At initiation into the study and at Months 3, 6, 9, 12, and 18, plasma samples were obtained before dialysis from each study subject and frozen at −70°C. All samples from each center were subsequently sent to VUMC and analyzed for β_2m by the same technical personnel by using commercially available RIA kits (Abbott Laboratories, Abbott Park, IL). For a mean level of 10 mg/L, the intra-assay coefficient of variation (CV) was 4.8%, and the interassay CV was 4.5%. Recovery of "spiked" samples up to a concentration of 30 mg/dL was a mean of 102%.

In addition to plasma β_2m levels, residual renal function was monitored to determine the influence of renal clearance of β_2m on changing plasma levels. Both study sites routinely

TABLE 1. Characteristics of dialyzer membranes[a]

Characteristic	T175	Toray B2-1.5H
Membrane Type	Cellulosic	PMMA
Surface Area (m^2)	1.7	1.5
KUF (mL/mm Hg per h)	6.0	5.0
Urea Clearance at QB of 200 mL/min	192	183
In Vivo β_2m Clearance at QB of 200 mL/min	Negligible	Negligible[b]

[a] Manufacturer's *in vitro* data, except for *in vivo* β_2m clearance measured at Vanderbilt University Medical Center. KUF, coefficient of ultrafiltration; QB, blood flow rate.
[b] All arterial-venous clearances were negative, consistent with hemoconcentration.

measured adequacy of dialysis by urea kinetics every 1 to 4 months with measurement of residual renal function by urea clearance (Kr) when urine output was greater than 200 mL in 24 h. Although dialysis dose (KT/V) was monitored, it was not controlled for study purposes because it has no known influence on β_2m levels when using low-flux membrane dialyzers, as selected for this study. However, the target level of KT/V did affect the number of patient dropouts. During the time of the study, there was increasing recognition and acceptance of the need to aim for a delivered KT/V of at least 1.4 (single pool). Because of the limitation in the surface area and *in vivo* urea clearance of the biocompatible membrane, the higher KT/V was achieved with a longer dialysis time, whereas the target KT/V could be achieved with less dialysis time when using the larger surface area cellulosic dialyzers. This resulted in a large number of dropouts (patient or physician initiated) in the group of patients that were initially randomized to the biocompatible group.

Duration of Study Participation

One hundred fifty-nine patients were enrolled in the study: 80 in the BICM group and 79 in the BCM group. A total of 66 patients (43 in the BICM group and 23 in the BCM group) completed the 18-month study period. The remaining patients dropped out of the study before 18 months for the following reasons: 13 patients were transferred to facilities not participating in the study (six BICM and seven BCM), 12 patients were transplanted (nine BICM and three BCM), ten patients were noncompliant or dropout was requested by the patient or nephrologist (four BICM and six BCM), 29 patients did not obtain adequate KT/V with the study dialyzer (four BICM and 25 BCM, of which 16 were during the first 2 wk of the study and were not used in data analysis), eight patients changed to peritoneal dialysis (three BICM and five BCM), one BCM patient recovered renal function in the first month, eight patients in each group died, and four patients dropped out for other reasons (three BICM and one BCM). The average number of days in the study for each group was 413 ± 171 for BICM and 337 ± 208 for the BCM group.

Statistical Methods

Assessment of changes in plasma β_2m levels from baseline to a specific time point was made by use of a paired *t* test. Results are reported as the current value minus the baseline value, averaged over all patients with both values. For two patients missing a value for Month 1, the Month 3 value was used as the baseline value (these two patients were not included in the paired *t* test of changes from baseline to Month 3). In addition, we calculated a linear regression of plasma β_2m levels (dependent variable) against time separately for each subject, and compared average regression coefficients between the two groups by use of a *t* test.

RESULTS

The characteristics of the study population at the start of the study are shown in Table 2. The mean age (mean ± SD) was 54 ± 15 yr in the BICM group and 51 ± 14 yr in the BCM group. There were no significant differences in age, sex, race, or etiology of renal disease. Statistical analysis of the subgroup of patients who completed the study also showed no statistical difference in age, sex, or race. There was some evidence for a difference in primary diagnosis between the two groups: the BICM group had 63% patients

TABLE 2. Characteristics of patient population[a]

Characteristic	BICM	BCM
No. of Patients	80	79
Age (yr)	54 ± 15	51 ± 14
Sex		
Males	(51%)	(48%)
Females	(49%)	(52%)
Race		
Black	(46%)	(48%)
White	(43%)	(42%)
Other	(11%)	(10%)
Etiology of ESRD		
Diabetes	(49%)	(43%)
Hypertension	(15%)	(24%)
Glomerulonephritis	(14%)	(5%)
Other	(22%)	(29%)

[a] BICM, bioincompatible membrane; BCM, biocompatible membrane.

primarily diagnosed as diabetic, whereas the BCM group had only 40%; this difference was statistically significant ($P = 0.02$). However, we found no association of initial diagnosis with change over 18 months in either membrane separately or combined, suggesting that this difference would not account for the difference in the rate of change in β_2m observed between the two membrane groups.

In both groups of patients, there was a steady increase in the average plasma level of β_2m. However, in the cellulosic dialyzer group, these increases became statistically significant beginning in the sixth month of study, when the mean plasma β_2m had reached 29.5 ± 12.2 mg/L, compared with a baseline of 24.8 ± 9.6 mg/L ($P < 0.001$); this increase continued to be statistically significant through the 18th month, when plasma β_2m had increased to 36.8 ± 13.9 mg/L ($P < 0.001$, see Table 3 and Figure 1). In contrast, in the BCM group, there was no statistically significant increase from baseline in plasma β_2m at any time point during the 18-month period of study. Baseline β_2m in this group was 27.8 ± 14.8 mg/L and increased to 34.0 ± 10.0 mg/L at 18 months (P = not significant (NS)). The same trend was observed when the data for the subset of 66 patients who completed the 18-month study were analyzed. These data are shown in Table 4, where it is seen that at 18 months, the average change of β_2m from baseline was 12.3 ± 10.8 mg/L ($P < 0.001$) for the BICM group and 2.6 ± 15.1 in the BCM group ($P > 0.1$). However, the absolute level of β_2m was not statistically different between the two groups of patients.

When linear regression analysis was used, there was a significant time trend in β_2m in the cellulosic group (0.91 ± 1.95 mg/L per month, $P < 0.0001$), but only a marginal increase (approximately half as large) was seen in the BCM group (0.49 ± 2.13 mg/L per month, $P = 0.98$) when all patients were analyzed. There was also a significant difference in the slope

TABLE 3. Absolute values and change from baseline in serum β_2-microglobulin (mg/L) in all patients in the study at the time of sampling

Time Point	BICM			BCM		
	N	Concentration (mg/L)	Change from Baseline	*N*	Concentration (mg/L)	Change from Baseline
Baseline	79	24.8 ± 9.6		59	27.8 ± 14.8	
3 months	74	26.1 ± 10.3	1.19 ± 7.67	49	29.4 ± 12.7	1.07 ± 9.55
6 months	68	29.5 ± 12.2	4.38 ± 9.13[a]	40	30.4 ± 12.1	0.43 ± 11.62
9 months	62	33.2 ± 14.7	8.13 ± 10.98[a]	35	33.1 ± 13.9	3.59 ± 13.47
12 months	51	35.8 ± 14.6	10.30 ± 12.21[a]	31	33.5 ± 14.1	3.55 ± 13.96
18 months	43	36.8 ± 13.9	11.77 ± 11.20[a]	23	34.0 ± 10.0	2.63 ± 14.71

[a] $P < 0.001$ compared with baseline.

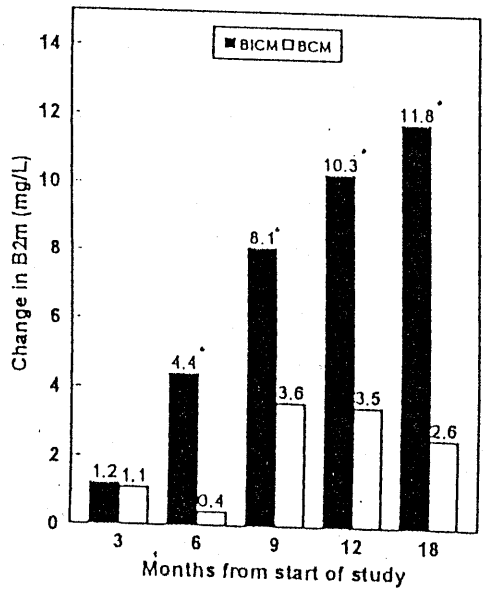

Figure 1. Mean change in β_2-microglobulin levels from baseline for biocompatible (□, BCM) and bioincompatible (■, BICM) membranes. * $P < 0.001$ compared with baseline.

with time between the two groups ($P = 0.01$). In the subgroup of 66 patients who completed the 18-month study, the time trend was again statistically significant in the BICM group (0.73 ± 0.55 mg/L per month, $P < 0.0001$), with no significant increase in the BCM group (0.21 ± 0.72 mg/L per month, $P > 0.1$). The difference in the slope with time between the two groups was also significant ($P = 0.002$).

A repeated measure analysis of variance on the level of β_2m and the amount of change of β_2m from baseline for the subgroup of patients who completed the study showed that there was an overall time × membrane interaction for β_2m ($P < 0.01$) and a significant membrane effect for the change from baseline ($P < 0.01$). These results are consistent, suggesting that the pattern of β_2m is not the same over time for the two membrane groups, with one group (BICM) substantially increasing although the other group (BCM) remained basically unchanged.

Finally, we analyzed the data starting at Month 3, to adjust for the possibility that differences in the rate of increase of β_2m primarily reflected differences in baseline β_2m level. When using changes starting at Month 3, there is still a statistically significant difference between membranes ($P < 0.01$), again suggesting that the membrane effects the rate of change even if we analyze the data starting at Month 3 and beyond.

Residual renal urea clearance (Kr) levels were also followed serially in both groups, with monthly data recorded (see Figure 2). Although the mean level of Kr was higher at baseline in the BICM group than in the BCM group (1.07 ± 2.61 mL/min *versus* 0.67 ± 1.26 mL/min), this difference was not statistically significant ($P > 0.5$). Differences in the mean levels of residual renal function between the two groups of patients were not significant at any of the trimonthly measurements taken during the study.

DISCUSSION

The results of this study, using only low-flux dialysis membranes with no measurable clearance of β_2m, suggest that the biocompatibility of the dialysis membrane, as judged by the extent of complement activation, influences the long-term rate of increase of plasma levels of β_2m. This result is in agreement with previous studies that suggested that complement activation is associated with a statistically significant increase in the release of β_2m from nucleated cells (21,26,27).

The pathophysiology that links the biocompatibility or complement-activating potential of the dialysis membrane to increased plasma β_2m levels has been elucidated in a number of studies. Studies by Schoels *et al.* (19) have shown that contact of the mononuclear cells with cellulosic membranes leads to increased transcription of the β_2m mRNA. This increase is more marked in the presence of complement products such as C5a and C5b-9. In a crossover study, Zaoui *et al.* (21) demonstrated that mononuclear cells that had been harvested from patients on a low-flux biocompatible membrane had a significantly lower rate of β_2m release than patients dialyzed with cellulosic-type dialyzers. Finally, Memoli *et al.* (26) also showed

TABLE 4. Absolute values and change from baseline in serum β_2-microglobulin (mg/L) in patients who completed 18 months of study

Time Point	BICM			BCM		
	N	Concentration (mg/L)	Change from baseline	*N*	Concentration (mg/L)	Change from Baseline
Baseline	43	25.1 ± 9.5		23	30.8 ± 14.1	
3 months	43	26.9 ± 10.4	1.81 ± 6.87	23	28.9 ± 13.2	−1.84 ± 11.68
6 months	43	29.9 ± 12.5	4.80 ± 8.0[a]	23	30.5 ± 13.0	−0.30 ± 12.03
9 months	43	31.8 ± 12.3	6.67 ± 7.93[b]	23	31.7 ± 15.5	0.93 ± 13.10
12 months	43	34.6 ± 13.3	9.51 ± 9.70[b]	23	32.2 ± 15.5	1.39 ± 14.24
18 months	43	37.4 ± 13.4	12.28 ± 10.85[b]	23	33.4 ± 9.9	2.60 ± 15.10

[a] $P < 0.01$ compared with baseline.
[b] $P < 0.001$ compared with baseline.

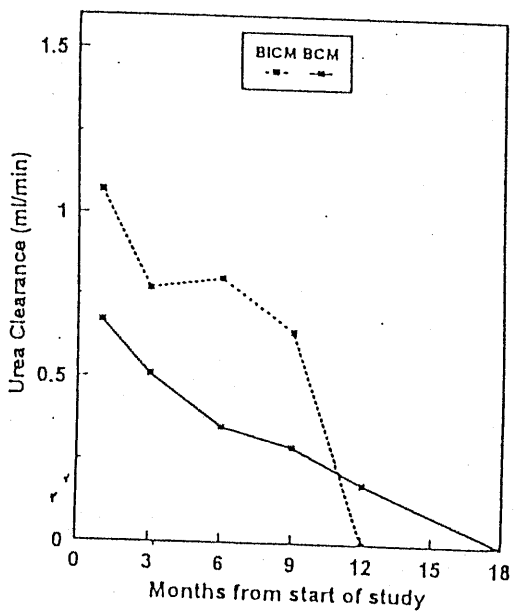

Figure 2. Residual renal function (Kr) from start to end of study for Biocompatible (—■—, BCM) and Bioincompatible (- -■- -, BICM) Membranes.

that incubation of monocytes with cellulosic membranes leads to increased production of IL-6 as well as β_2m; these authors also found a significant strong correlation between IL-6 and β_2m production. Thus, bioincompatible membranes may result in increased transcription and release of β_2m either by direct contact or via complement activation products or other cytokines, such as IL-1, TNF, or IL-6. In addition, in a small clinical study of plasma kinetics of iodine-131-labeled β_2m, the synthetic rate of β_2m was also found to be, on average, 23% higher in the patients dialyzed with the cellulosic membrane, compared with those dialyzed with polysulfone (28). Nevertheless, in this group of 10 patients (five in each group), these differences were not found to be statistically significant.

High-flux membranes have a further beneficial effect on plasma β_2m level, because β_2m is cleared by these membranes either by adsorption or convective clearance (29,30). Nevertheless, the rates of intradialytic removal by available dialyzer membranes, estimated at 400 to 1000 mg/wk (28,31–33), do not match the rates of synthesis of new β_2m of approximately 1400 to 2300 mg/wk (4,28,34). Therefore, in general, the level of β_2m is only moderately reduced in patients dialyzed with high-flux membranes, compared with the β_2m level in the patients on cellulosic low-flux membranes (3). In addition, because high-flux membranes appear to preserve residual renal function for longer periods of time, several investigators have suggested that this mechanism also contributes to a lower level of β_2m in patients on the high-flux biocompatible membranes. In agreement with this additional mechanism, our study suggests a slower decline of Kr in patients on the biocompatible membranes for the duration of the study. This was not statistically significant in our study, but was found to be so in another study (18).

The relationship between plasma β_2m and the development of amyloid bone disease has also not been clarified. In this short-term study, we did not determine differences in the development of amyloid bone disease because this process takes several years to develop. Whether the chronically lower rate of increase or level of serum β_2m achieved in patients on chronic dialysis with high-flux biocompatible membranes explains the difference in the incidence of amyloid bone disease has not been resolved. A recent study has suggested that membranes that activate complement participate in the development of amyloid bone disease not only from the increased release of β_2m but also by providing an environment in which products of complement activation, reactive oxygen species, and activated neutrophils may result in sufficient modification and polymerization of β_2m to enhance their position (35). Studies by Linke *et al.* (36) also suggested that amyloid deposits in ESRD patients require specific lysine cleavage of β_2m, which occurs in the presence of activated and degranulated polymorphonuclear cells. These studies provide addi-

tional evidence in support of the role of bioincompatibility in the development of amyloid disease.

In summary, the study presented here demonstrated that there is no significant increase in plasma β_2m levels over 18 months when low-flux biocompatible membranes are used for chronic hemodialysis. On the other hand, the use of bioincompatible membranes leads to a marked rise in plasma β_2m levels, which becomes statistically significant beginning 6 months after dialysis initiation. This effect occurs in the absence of intradialytic β_2m removal or significant differences in residual renal function. These findings are consistent with the hypothesis that membranes associated with a marked degree of complement activation result in increased synthesis or release of β_2m from the surface of nucleated cells.

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TABLE 3. Absolute values and change from baseline in serum β_2-microglobulin (mg/L) in all patients in the study at the time of sampling

Time Point	BICM			BCM		
	N	Concentration (mg/L)	Change from Baseline	*N*	Concentration (mg/L)	Change from Baseline
Baseline	79	24.8 ± 9.6		59	27.8 ± 14.8	
3 months	74	26.1 ± 10.3	1.19 ± 7.67	49	29.4 ± 12.7	1.07 ± 9.55
6 months	60	29.5 ± 12.2	4.38 ± 9.13[a]	40	30.4 ± 12.1	0.43 ± 11.62
9 months	62	33.2 ± 14.7	8.13 ± 10.98[a]	35	33.1 ± 13.9	3.59 ± 13.47
12 months	51	35.8 ± 14.6	10.30 ± 12.21[a]	31	33.5 ± 14.1	3.55 ± 13.96
18 months	43	36.8 ± 13.9	11.77 ± 11.20[a]	23	34.0 ± 10.0	2.63 ± 14.71

[a] $P < 0.001$ compared with baseline.

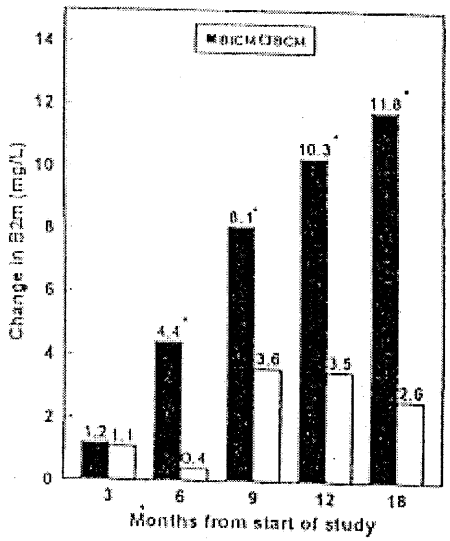

Figure 1. Mean change in β_2-microglobulin levels from baseline for biocompatible (□, BCM) and bioincompatible (■, BICM) membranes. * $P < 0.001$ compared with baseline.

with time between the two groups ($P = 0.01$). In the subgroup of 66 patients who completed the 18-month study, the time trend was again statistically significant in the BICM group (0.73 ± 0.55 mg/L per month, $P < 0.0001$), with no significant increase in the BCM group (0.21 ± 0.72 mg/L per month, $P > 0.1$). The difference in the slope with time between the two groups was also significant ($P = 0.002$).

A repeated measure analysis of variance on the level of β_2m and the amount of change of β_2m from baseline for the subgroup of patients who completed the study showed that there was an overall time × membrane interaction for β_2m ($P < 0.01$) and a significant membrane effect for the change from baseline ($P < 0.01$). These results are consistent, suggesting that the pattern of β_2m is not the same over time for the two membrane groups, with one group (BICM) substantially increasing although the other group (BCM) remained basically unchanged.

Finally, we analyzed the data starting at Month 3, to adjust for the possibility that differences in the rate of increase of β_2m primarily reflected differences in baseline β_2m level. When using changes starting at Month 3, there is still a statistically significant difference between membranes ($P < 0.01$), again suggesting that the membrane effects the rate of change even if we analyze the data starting at Month 3 and beyond.

Residual renal urea clearance (Kr) levels were also followed serially in both groups, with monthly data recorded (see Figure 2). Although the mean level of Kr was higher at baseline in the BICM group than in the BCM group (1.07 ± 2.61 mL/min *versus* 0.67 ± 1.26 mL/min), this difference was not statistically significant ($P > 0.5$). Differences in the mean levels of residual renal function between the two groups of patients were not significant at any of the trimonthly measurements taken during the study.

DISCUSSION

The results of this study, using only low-flux dialysis membranes with no measurable clearance of β_2m, suggest that the biocompatibility of the dialysis membrane, as judged by the extent of complement activation, influences the long-term rate of increase of plasma levels of β_2m. This result is in agreement with previous studies that suggested that complement activation is associated with a statistically significant increase in the release of β_2m from nucleated cells (21,26,27).

The pathophysiology that links the biocompatibility or complement-activating potential of the dialysis membrane to increased plasma β_2m levels has been elucidated in a number of studies. Studies by Schoels *et al.* (19) have shown that contact of the mononuclear cells with cellulosic membranes leads to increased transcription of the β_2m mRNA. This increase is more marked in the presence of complement products such as C5a and C5b-9. In a crossover study, Zaoui *et al.* (21) demonstrated that mononuclear cells that had been harvested from patients on a low-flux biocompatible membrane had a significantly lower rate of β_2m release than patients dialyzed with cellulosic-type dialyzers. Finally, Memoli *et al.* (26) also showed