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Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients

TOM F. PARKER III, REBECCA L. WINGARD, LEIGH HUSNI, T. ALP IKIZLER, ROBERT A. PARKER, and RAYMOND M. HAKIM

Department of Medicine, Division of Nephrology and Department of Preventive Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, and Dallas Nephrology Associates, Dallas, Texas, USA

Effect of the membrane biocompatibility on nutritional parameters in chronic hemodialysis patients. Malnutrition is highly prevalent in chronic hemodialysis patients and is an important determinant of their morbidity and mortality. Several recent studies have suggested that the inflammatory response associated with the biocompatibility of the dialysis membranes is a potential contributing factor. In a prospective study of 159 new hemodialysis patients from two centers randomized to either a low-flux biocompatible (BCM) membrane or a low-flux bioincompatible (BICM) membrane, we measured the long-term effects of biocompatibility on several nutritional parameters, including estimated dry weight, serum albumin, insulin-like growth factor-1 (IGF-1), and prealbumin over 18 months. Our results show that the BCM group had a mean (± SD) increase in their dry weight of 2.96 ± 6.88 kg at month 12 and 4.36 ± 8.57 kg at month 18 ($P < 0.05$ vs. baseline for both), whereas no change in mean weight was observed in BICM group. Following initiation of hemodialysis, a significant increase was observed in serum albumin levels in both groups of patients. However, the biocompatible group had an earlier and more marked increase in serum albumin levels compared to the BICM group. The average increase in serum albumin compared to baseline was consistently greater than 0.25 g/dl after seven months in the BCM group, but did not reach this level until 12 months after initiation of dialysis in the BICM group. The difference between the groups was statistically significant at months 7, 8, and 10 ($P < 0.05$, higher in the BCM group). Furthermore, the overall difference in serum albumin concentration between the two groups was larger in the center where the dose of dialysis was equivalent ($P < 0.001$). A consistently higher value was also observed in IGF-1 levels for BCM patients compared to BICM group (P = NS). In a further analysis, changes in IGF-1 levels, but not prealbumin, predicted the subsequent changes in serum albumin. We conclude that biocompatible hemodialysis membranes favorably impact on the nutritional status of chronic hemodialysis patients, independently of the flux characteristics of the membranes, and that IGF-1 may be an early marker of nutritional status.

Several studies have reported the high prevalence of protein-calorie malnutrition and its association with increased morbidity and mortality in chronic hemodialysis (CHD) patients [1–6]. Specifically, low concentrations of serum albumin, blood urea nitrogen (BUN), serum creatinine, as well as low relative body wt are significantly associated with increased risk of death in CHD patients [7–9].

Several factors that contribute to this high prevalence of poor nutritional status have been identified. These include anorexia and decreased nutrient intake, hormonal and metabolic derangements, and catabolic factors related to the dialysis procedure [10–14]. The structure of hemodialysis membrane is an emerging and important aspect of the dialysis procedure that may play a role in this malnutrition [15]. Several studies have highlighted the acute catabolic effects of dialysis membranes that trigger the activation of the complement system, the so-called bioincompatible membranes [16, 17]; these catabolic properties have been primarily demonstrated by the excess release of amino acids in both normal subjects and uremic patients exposed to such membranes.

The favorable effect of biocompatible hemodialysis membranes on nutritional aspects of CHD patients was further supported clinically in studies by Lindsay and colleagues in which they established the link between protein catabolic rate (PCR), a putative marker of dietary protein intake in stable CHD patients, and the modality and the dose of dialysis [18, 19]. They also showed that the type of dialysis membrane used affected the nature of the relationship between the dose of dialysis and PCR. These investigators proposed that for the same dose of dialysis, patients on a high-flux biocompatible membrane had a higher PCR than patients on low-flux bioincompatible membranes. Nevertheless, these studies did not establish clearly whether the improvement in PCR would result in improvement of commonly measured nutritional parameters, such as serum albumin concentrations, weight, or body mass index. Thus, comparative studies investigating the long-term effects of repetitive exposure to complement activating membranes (independent of their flux characteristics) on nutritional status of CHD patients are lacking.

In this study, we prospectively analyzed the nutritional status of patients initiating hemodialysis randomly assigned to dialysis membranes with different complement activating properties but similar ultrafiltration capabilities. We used several commonly measured plasma proteins, such as serum albumin, prealbumin, and insulin-like growth factor 1 (IGF-1), as well as the estimated dry weight of the patients, to prospectively monitor these differences in nutritional parameters.

Methods

Patient characteristics

All patients were recruited from Vanderbilt University Medical Center (VUMC, Nashville, TN, USA) and Dallas Nephrology

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Table 1. Characteristics of patient population

	BICM	BCM
No. of patients	80	79
Age *years*	54 ± 15	51 ± 14
Sex		
Males	51%	48%
Females	49%	52%
Race		
Black	46%	48%
White	43%	43%
Other	11%	9%
Etiology of ESRD		
Diabetes	49%	43%
Hypertension	15%	24%
Glomerulonephritis	14%	5%
Other	22%	28%

Associates (DNA, Dallas, TX, USA). Informed consent was obtained according to each institution's Committee for the Protection of Human Subjects. All patients over 18 years of age and newly initiated to chronic dialysis therapy during the time period of 03/01/91 to 12/31/92 were eligible for study participation. No patient was excluded on the basis of the etiology of renal failure or any other medical conditions. The demographics of the patients on different study membranes are outlined in Table 1. There were no statistically significant differences between treatment groups regarding age, gender, primary renal disease and comorbid conditions.

Membrane characteristics

The group assigned to biocompatible membrane group were dialyzed with a low flux polymethylmethacrylate membrane (PMMA, Toray B2-1.5 Filtryzer, Toray Industries, Tokyo, Japan), a membrane known to cause low levels of complement activation. The other (bioincompatible) membrane group was dialyzed with a cellulosic membrane (T175, Terumo Corporation, Tokyo, Japan), a membrane known to have high levels of complement activation. The *in vitro* urea clearance characteristics (200 ml/min solution flow) were higher for the cellulosic membranes (192 ml/min for the cellulosic membrane and 183 ml/min for the PMMA membrane). Ultrafiltration coefficients were 5 ml/hr/mm Hg for PMMA membrane and 6.0 ml/hr/mm Hg for cellulosic membranes. Both centers reused dialyzers with bleach and formaldehyde; the average number of reuses were 10 ± 3 in both centers. There was no evidence for any loss of albumin in the dialysate with these dialyzers [14].

Study design

The study was a prospective, randomized design. The enrollment was done in the order that each patient presented for initiation of dialysis treatment, and the assignment to a BCM or BICM was done in alternating order. All patients were assigned to a treatment group within the first week of initiation of outpatient dialysis therapy. After randomization, each patient was dialyzed with their assigned membrane type for all outpatient treatments for a period of 18 months. During the 18 month study period, the attending nephrologist determined the patient's dialysis prescription and estimated dry weight according to his or her own judgement, and no restrictions or guidelines for long-term patient management were made.

Duration of study participation

A total of 159 patients were enrolled in the study: 80 in the BICM group and 79 in the BCM group. Sixty-six 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 prior to 18 months for the following reasons: 13 patients were transferred to other dialysis facilities (6 BICM, 7 BCM), 12 patients were transplanted (9 BICM, 3 BCM), 10 patients were noncompliant or requested dropout (4 BICM, 6 BCM), 29 patients did not obtain adequate Kt/V with the study dialyzer (4 BICM, 25 BCM), 8 patients changed to peritoneal dialysis (3 BICM, 5 BCM), 1 BCM patient recovered renal function in the first month, 8 patients in each group died, and 4 patients dropped out for other reasons (3 BICM, 1 BCM). The average days in the study for each group was 413 ± 171 for BICM and 337 ± 208 for the BCM group.

Outcome measurements

At initiation into the study, and subsequently once a month for the first year, and then at termination of the study at 18 months, the estimated dry weight prescribed by the physician was recorded and serum samples were obtained for analysis of commonly measured biochemical parameters as well as serum albumin, serum prealbumin and serum insulin-like growth factor-1 (IGF-1) levels.

Urea kinetics

Urea kinetic modeling was done for each patient every one to four months, according to each institution's protocol, to obtain Kt/V as a measure of dialysis adequacy and protein catabolic rate as a reflection of dietary protein intake. The measurements were done using commercially available personal computer software programs. The single pool model was used to measure the Kt/V at DNA, while double pool kinetics (with samples drawn 20 min following termination of dialysis) was performed at VUMC.

Blood chemistries

Common blood chemistries (BUN, creatinine, glucose, sodium, potassium, chloride, and total CO_2) were performed using standard laboratory techniques. Serum albumin was measured by bromcresol green method using Olympus 800 analyzer (Olympus Corporation, Lake Success, NY, USA). Serum prealbumin was measured by nephelometric assay (Behring BN 100 Nephelometer), and serum insulin-like growth factor-1 levels were measured by radioimmunoassay technique following extraction by acid-ethanol method (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

Statistical methods

Average values in a population over time was calculated by, first, calculating the average value for an individual subject, using all available data for the subject, and then averaging these single values per subject across subjects. Comparisons within a group between baseline and subsequent times were assessed using a paired *t*-test. Assessment of overall patterns was done using several different techniques. Comparisons between groups at specific times used the Wilcoxon Rank Sum test. Individual linear regression over time was calculated from each subject's data to assess whether adjusted levels (the intercept) or the pattern over

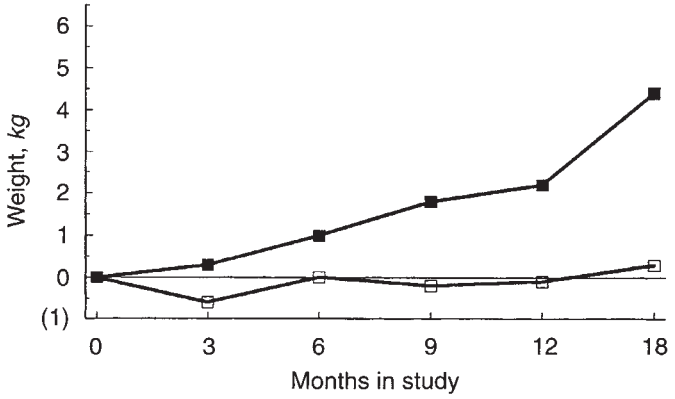

Fig. 1. *Average changes in estimated dry weights at months 1, 3, 6, 9, 12, and 18 of study patients randomized to different dialyzers: biocompatible (■) and bioincompatible (□); P < 0.05 at months 12 and 18 for biocompatible group.*

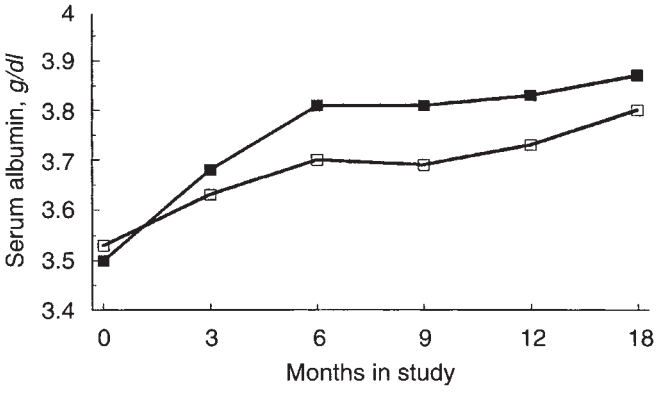

Fig. 2. *Average serum albumin levels at months 1, 3, 6, 9, 12, and 18 of study patients randomized to different dialyzers: biocompatible (■) and bioincompatible (□).*

time (the slope) were different between the two study groups. Finally, mixed model analysis of variance [20] was used to analyze the data in a repeated measures type framework without the requirement for complete data for each subject. The correlation was assessed for each individual alone, and then averaged appropriately over all subjects. The model specifically incorporates the repeated measurements in a subject, allowing for one measurement to impact on the next measurement, but with the impact decreasing over time. Thus, if the correlation for a measurement from one month to the next was ρ, then the correlation over two months would be ρ^2, the correlation over three months would be ρ^3, and so forth. Since ρ is inclusive between -1 and $+1$, the correlation decreases with increasing time.

Association of changes over time between variables were assessed using Spearman (Rank) Correlation. All data analyses was done using SAS statistical software packages (SAS Institute, Cary, NC, USA). Results are presented as mean ± SD. A P value < 0.05 was considered statistically significant.

Results

Adequacy of dialysis

Both study sites routinely measured adequacy of dialysis by measurement of Kt/V. However, Kt/V was not controlled for study purposes and final analysis showed that the mean Kt/V was higher in the BICM group compared to BCM group (1.37 ± 0.29 vs. 1.24 ± 0.27, $P < 0.01$). A subgroup analysis showed that this difference was due to a higher Kt/V in one of the sites. Specifically, the mean Kt/V values over the study period for DNA were 1.45 ± 0.27 for BICM and 1.28 ± 0.29 for BCM (single-pool; $P < 0.01$). These values for VUMC were 1.14 ± 0.23 for BICM and 1.12 ± 0.19 for BCM (double-pool; $P > 0.5$); these values correspond to single pool values of approximately 1.36 for both membranes.

Nutritional measures

Estimated dry weight. Patients dialyzed with a biocompatible membrane had a significant increase in their estimated dry weight compared to their baseline weights. The initial estimated dry weights of the patients in the BCM group and the BICM group were 72.1 kg and 73.8 kg, respectively. Figure 1 depicts the mean changes in dry weights for study months 1, 3, 6, 9, 12, and 18 for both study membranes. As can be seen, the increase in dry weight in the BCM group was observed beginning at month 6 and became statistically significant compared to baseline at month 7. The mean increase in weight was 2.24 ± 6.99 kg in month 12 and 4.36 ± 8.57 kg in month 18, which were both significantly higher than the baseline dry weight (all $P < 0.05$). In contrast, no change from baseline was observed in the mean dry weights of the patients who were dialyzed with the bioincompatible membrane. The coefficient of variation of month-to-month changes in estimated dry weight was relatively constant and was within 5% of SD.

Similar changes were observed in % ideal body wts (IBW) of the patients. At entry into the study, the patients were on average 4.5% below their IBW. The mean % ideal body wt increased by 6.5% for patients dialyzed with biocompatible membranes, whereas the mean % ideal body wts showed no change (compared to baseline) for the patients dialyzed with bioincompatible membranes.

Protein catabolic rate (PCR). PCR tended to increase significantly in both treatment groups. However, compared to baseline the absolute increase was significant only in months 4, 7, 9, 10, and 14, only for the BICM group. There was no significant difference between the groups in change from baseline.

Serum albumin concentration. Serum albumin levels increased significantly above baseline values in both membrane groups after the initiation of dialysis. This effect was continuous throughout the entire study period for both membranes. Figure 2 shows the changes in serum albumin levels for study months 1, 3, 6, 9, 12, and 18 for both study membranes. Note however, that there was an earlier and more marked increase in serum albumin levels in BCM group compared to the BICM group. In fact, the average increase in serum albumin was consistently greater than 0.25 g/dl compared to baseline after seven months in the BCM group, but did not reach this level until 12 months after initiation of dialysis in the BICM group. Indeed, at month 7, only 32% of patients on BICM group had an increase in serum albumin concentration ≥ 0.25 g/dl, whereas twice as many patients (57%) on the BCM group had an increase in serum albumin ≥ 0.25 g/dl compared to baseline. Also, the absolute levels of serum albumin was significantly higher in the BCM group versus BICM group at month 7 (3.82 ± 0.48 g/dl vs. 3.65 ± 0.39 g/dl; $P < 0.05$), month 8 (3.86 ± 0.41 g/dl vs. 3.69 ± 0.36 g/dl; $P < 0.05$) and month 10 (3.89 ± 0.34 g/dl vs. 3.73 ± 0.35 g/dl; $P < 0.05$).

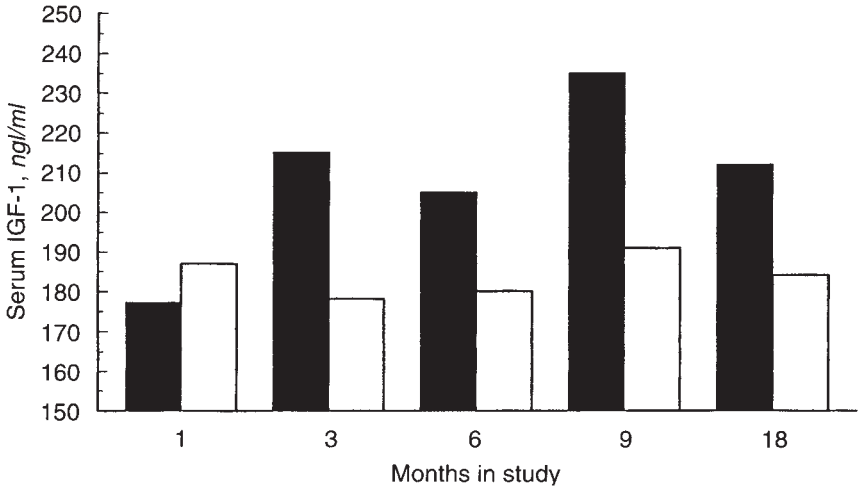

Fig. 3. *Average serum insulin-like growth factor-1 levels at months 1, 3, 6, 9, and 18 of study patients randomized to different dialyzers: biocompatible (■) and bioincompatible (□).*

We also used the mixed model analysis of variance to analyze the data for overall differences due to the membrane. There were significant differences overall between the two membrane groups for serum albumin ($P < 0.001$) levels in patients dialyzed at the center where the Kt/V was the same in both membrane groups, with the group on BCM having higher serum albumin level. These results were not found when the centers were combined.

Serum IGF-1 and prealbumin. The changes in serum IGF-1 levels are shown in Figure 3 for both study membranes. Although a consistently higher value was observed in IGF-1 levels for BCM patients, this trend was not statistically significant compared to either baseline or BICM patients, probably due to large SDS in the measurements of this assay between study patients. Of note, the changes from baseline for months 3 and 9 were marginally significant ($P = 0.06$ and 0.07, respectively) only for BCM patients. There was also a marginal difference in IGF-1 levels between BCM and BICM at month 9 (236 ± 119 ng/ml for BCM vs. 191 ± 100 ng/ml for BICM; $P = 0.09$). On the other hand, no significant trend was observed in prealbumin levels in either BCM or BICM patients.

We again used the mixed model analysis of variance to analyze the data for overall differences for IGF-1 and prealbumin levels between the two membrane groups. There were significant differences overall between the two membrane groups for IGF-1 ($P < 0.05$) and prealbumin ($P < 0.025$) levels in patients dialyzed at the center where the Kt/V was the same in both membrane groups, with the group on BCM having higher serum IGF-1 and prealbumin levels. These results were not found when the centers were combined.

Correlation analysis of serum albumin with IGF-1 and Prealbumin. In an attempt to define an association between the changes in serum albumin and IGF-1 or prealbumin (separately), we performed correlation analysis as described in statistical methods section. The analysis shows that the early changes in IGF-1 levels from months 1 to 6 were significantly associated with changes in serum albumin from baseline to subsequent time points (Table 2). This relationship was not observed between serum albumin and prealbumin levels.

Table 2. Correlation analysis between the changes in insulin-like growth factor 1 (IGF-1) levels from month 1 to month 3 (MI-M3) and to month 6 (M1-M6), and subsequent changes in serum albumin levels

	S_{Alb}	M1-M3	M1-M6	M1-M9	M1-M12	M1-M18
IGF M1-M3	Corr. coef	0.218	0.126	0.150	0.143	0.076
	P value	< 0.05	> 0.1	> 0.1	> 0.1	> 0.1
IGF M1-M6	Corr. coef.	N/A	0.288	0.231	0.257	0.238
	P value	N/A	< 0.01	< 0.05	< 0.05	0.07

Discussion

The results of our study demonstrate that the biocompatibility of hemodialysis membranes, assessed by their complement activating properties, improves the long-term results of several nutritional indices in chronic hemodialysis patients. The beneficial effects of biocompatibility on nutritional indices is suggested by an early and more pronounced increase in serum albumin level, a significantly higher weight gain, an increase in % ideal body wt and substantially higher serum IGF-1 levels. These improvements were seen in the group of patients on biocompatible dialyzers using membranes that had lower ultrafiltration and sieving coefficients for middle molecules, and which, because of their limited surface area, resulted in a lower dose of dialysis.

The adverse effect of complement activating membranes on amino acid and protein metabolism was previously suggested by experimental data by Gutierrez and colleagues, in both normal volunteers and CHD patients [16, 17]. Specifically, they showed that membranes that resulted in higher complement activation were associated with increased amino acid release from peripheral muscle tissue, consistent with increased protein catabolism; this adverse effect was not observed during dialysis with biocompatible membranes.

The mechanism by which activation of complement pathway results in increased protein catabolism is not clear. Production of cytokines, such as interleukin-1 and tumor necrosis factor-alpha (TNF-α) may induce muscle protein degradation and excess amino acid release [21–23]. In these studies, the release of amino acids during dialysis with bioincompatible membranes was most prominent at six hours after the initiation of hemodialysis [16], a time period consistent with activation of monocytes, and subsequent release of cytokines and their action on muscle cells [15]. Complement activation has been shown to result in increased transcription of TNF-α, and in a recent study by Canivet and

co-workers increased serum TNF-α levels were reported in CHD patients dialyzed with a complement activating membrane [24].

These observations are further supported by the studies by Lindsay and co-workers who suggested that at a given dialysis dose patients dialyzed with a biocompatible dialysis membrane had a higher PCR compared to patients dialyzed with a bioincompatible membrane [25]. The results of our study thus confirm that CHD patients may benefit nutritionally from long-term treatment with biocompatible membranes. This may well be part of the explanation for differences in the relative risk of mortality by membranes with different biocompatibilities [26].

A notable finding of our study is the earlier and more marked increase in serum albumin levels in BCM patients. Serum albumin is the most well documented predictor of mortality in CHD patients [3, 9, 27]. In an analysis of more than 12,000 CHD patients, Lowrie and Lew reported that the risk of death increased exponentially as the concentration of serum albumin decreased [7]. Specifically, when compared to a serum albumin of greater than 4.0 g/dl, serum albumin values of 3.5 to 4.0 g/dl resulted in a twofold increase in the relative risk of death. It is important to note that this latter value of albumin is in the range of "normal" for many laboratories. Therefore, a small difference in serum albumin levels, even in the normal ranges, may affect the relative mortality risk in CHD patients. This is relevant to our study patients in that, although small, the increase in serum albumin concentrations in the patients dialyzed with BCM membrane was earlier and consistently higher throughout the entire study period. Furthermore, in one of the centers where the dose of dialysis was equivalent between two membrane groups, the difference in this parameter was even more marked. This difference is probably related to the inflammatory response induced by the bioincompatible membranes which can elicit an acute phase protein response. Such an acute phase reaction has been shown to result in a reduction in albumin synthesis [28, 29].

A somewhat surprising difference between the two groups of patients was the significant increase in dry weights (and % ideal body wts) of BCM patients, compared to the virtual absence of change in BICM patients. This increase became statistically significant beginning at month 6, and the difference between the groups continued to increase until the completion of the study. Along with serum albumin, increases in dry weight is an important nutritional marker of CHD patients. Although dry weight is considered to be an imprecise marker of nutritional status in CHD patients, it is a valid and important index of nutrition and mortality in this patient population, as suggested by Lowrie and colleagues [8]. In an analysis of more than 12,000 CHD patients for specific variables associated with increasing risk of death, these authors reported that almost 42% of the patients had weights below their calculated ideal body wt, and further found that decreasing percentage of ideal weight was associated with increasing odds of death. Therefore, an increase in body wt (and % ideal body wt) further substantiates the beneficial effects of biocompatible membranes on nutritional status of CHD patients.

We also prospectively measured the serum concentrations of IGF-1 and prealbumin in our study patients, two other putative markers of nutritional status in CHD patients [30, 31]. Although both IGF-1 and prealbumin have a short half-life and are closely related to dietary food intake in different patient populations [32], studies relating these parameters to nutritional status of CHD patients have been cross sectional, and measurement of these indices as a continuous variable in association with overall nutritional status are lacking. In this prospective study, there was a substantial difference between IGF-1 levels of the study patients, consistent with the trends of serum albumin levels and dry weights. Specifically, patients dialyzed with biocompatible membranes had a marked increase in mean serum IGF-1 concentrations beginning at month 3, followed by consistently higher levels throughout the entire study period. In contrast, BICM group showed no change in their mean serum IGF-1 levels. However, we were unable to find a similar trend for serum prealbumin levels.

Our study further supports the predictive value of IGF-1 by defining the significant association between the early changes in serum IGF-1 levels with subsequent changes in serum albumin levels. Specifically, the changes in serum IGF-1 levels from months 1 to 3 and 6 were associated with changes in serum albumin at subsequent time points. (This relationship was not observed with serum prealbumin levels.) Since serum albumin has a long half-life (20 days) and its concentration is affected by shifts between intra- and extra-vascular spaces, it is considered an important, but late marker of nutritional status [4]. Our results suggest that a change in serum IGF-1 concentrations may be an earlier index for nutritional status of CHD patients, compared to serum albumin levels. Nevertheless, the validity and importance of IGF-1 as a predictor of clinical outcome need to be defined with further studies.

Protein catabolic rate was another nutritional parameter that we followed in our patient population. There was a significant increase over time in PCR in both study groups. However, in contrast to the above-mentioned differences in other nutritional parameters, this increase was not different between two groups. This may be related to limited number of observations of PCR, especially in BCM group, and large variations within patient groups, or to the lack of relevance of PCR to nutritional intake.

Two other proposed mechanisms that may improve the nutritional status of CHD patients are higher dose of dialysis and improved middle molecule clearance during dialysis [4, 18, 33, 34]. In our study design, we were able to separate the effects of middle molecule clearance by using low-flux dialyzers in both study groups. However, the mean dose of dialysis, measured by Kt/V, was significantly higher in BICM group. Based on previous studies, a higher dialysis dose would be expected to improve nutritional status of those patients [18, 34]. If true, this further highlights the importance of biocompatibility on the long-term nutritional parameters of the study groups, since a more favorable nutritional status was observed in BCM group, despite having a lower Kt/V in comparison to BICM group. This hypothesis is further supported by the more marked difference in nutritional parameters between the two membrane groups in the center with equivalent dose of dialysis.

In summary, our study suggests that biocompatibility of hemodialysis membranes is an important factor that affects the nutritional status of CHD patients. Hemodialysis patients dialyzed long-term with a biocompatible membrane have higher serum albumin and IGF-1 levels, and significantly increase their body wt, as compared to patients dialyzed with a bioincompatible membrane. In an additional analysis, our results show that serum IGF-1 levels are predictive of changes in serum albumin levels. The effects of these findings on subsequent mortality and morbidity of these patient groups needs to be determined with further studies.

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Reprint requests to Raymond M. Hakim, M.D., Ph.D., Vanderbilt University Medical Center, 1161 21st Ave. S. & Garland, Division of Nephrology, S-3307 MCN, Nashville, Tennessee 37232-2372, USA.

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