

Role of Residual Kidney Function and Convective Volume on Change in β_2 -Microglobulin Levels in Hemodiafiltration Patients

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Background and objectives: Removal of β_2 -microglobulin (β_2 M) can be increased by adding convective transport to hemodialysis (HD). The aim of this study was to investigate the change in β_2 M levels after 6-mo treatment with hemodiafiltration (HDF) and to evaluate the role of residual kidney function (RKF) and the amount of convective volume with this change.

Design, setting, participants, & measurements: Predialysis serum β_2 M levels were evaluated in 230 patients with and 176 patients without RKF from the CONvective TRANsport STudy (CONTRAST) at baseline and 6 mo after randomization for online HDF or low-flux HD. In HDF patients, potential determinants of change in β_2 M were analyzed using multivariable linear regression models.

Results: Mean serum β_2 M levels decreased from 29.5 ± 0.8 (\pm SEM) at baseline to 24.3 ± 0.6 mg/L after 6 mo in HDF patients and increased from 31.9 ± 0.9 to 34.4 ± 1.0 mg/L in HD patients, with the difference of change between treatment groups being statistically significant (regression coefficient -7.7 mg/L, 95% confidence interval -9.5 to -5.6 , $P < 0.001$). This difference was more pronounced in patients without RKF as compared with patients with RKF. In HDF patients, β_2 M levels remained unchanged in patients with $\text{GFR} > 4.2$ ml/min/1.73 m². The β_2 M decrease was not related to convective volume.

Conclusions: This study demonstrated effective lowering of β_2 M levels by HDF, especially in patients without RKF. The role of the amount of convective volume on β_2 M decrease appears limited, possibly because of resistance to β_2 M transfer between body compartments.

Clin J Am Soc Nephrol 5: 80–86, 2010. doi: 10.2215/CJN.03340509

β_2 -microglobulin (β_2 M, 11.8 kD) accumulates in kidney failure and has been implicated in the development of dialysis-associated amyloidosis (1). In addition, β_2 M levels have been widely studied as a marker for uremic toxins within the middle molecular weight (MMW) range (≥ 500 D and $<$ approximately 60,000 D) (2). β_2 M is eliminated from the extracellular volume almost exclusively by the kidneys. Consequently, serum β_2 M levels already rise when kidney function is only mildly impaired (3). In hemodialysis (HD) patients, serum β_2 M levels may be increased by 20-fold or more as compared with the general population, the highest levels being observed in patients without residual kidney function

(RKF) (4–6). It has been shown that predialysis β_2 M levels predict all-cause and infectious-related mortality in these patients (4,7,8).

Because of its size, removal of β_2 M is negligible during low-flux HD. In contrast, significant removal of β_2 M can be established with high-flux HD, because of convective transport by internal filtration within the dialyzer. The Hemodialysis (HEMO) and the Membrane Permeability Outcome (MPO) study showed lower serum β_2 M levels in high-flux HD as compared with low-flux HD patients (4,9). In addition, it has been shown that removal of β_2 M is further increased with online hemodiafiltration (HDF) by using excess ultrafiltration to provide increased convective transport. Actually, lower predialysis β_2 M levels have been reported after 3 to 12 mo treatment with HDF, as compared with low-flux or high-flux HD (10–15). It has been proposed that the improved survival of HDF patients, as reported in few observational studies (16–18), can be partly attributed to increased removal of β_2 M and other MMW uremic toxins by convective transport.

Received May 17, 2009. Accepted October 6, 2009.

Published online ahead of print. Publication date available at www.cjasn.org.

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For optimal efficiency of HDF treatment, the use of large convective volumes has been recommended (19). Indeed, a relation between the delivered convective volume and β 2M reduction ratio has been reported during a dialysis session (14,15). In addition, in the Dialysis Outcomes and Practice Patterns Study (DOPPS) a survival benefit was observed only in HDF patients who were treated with high convective volumes (replacement of ≥ 15 L/treatment) (16). However, as of yet, a direct relationship between the amount of convective volume and decrease in β 2M levels in the short or long term has not been investigated.

The ongoing CONvective TRANsport STudy (CONTRAST) has been designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (20). As part of CONTRAST, predialysis serum β 2M levels were measured to evaluate short-term treatment effects. The aim of the study presented here was to investigate the change in β 2M levels from baseline to 6 mo in patients randomized to HDF and HD. Because β 2M strongly relates to RKF, the change in β 2M during the study period was analyzed separately for patients with and without RKF. In addition, the relationships of the extent of RKF and the amount of convective volume with the change in β 2M levels were evaluated in HDF patients.

Materials and Methods

Patients and Study Design

For these analyses, the first 406 consecutive patients participating in the CONTRAST study (NCT00205556) were included who all had completed 6 mo of follow-up by January 2009 and had serum β 2M assessments at baseline and after 6 mo. Patients were recruited from 26 dialysis centers in The Netherlands ($n = 24$), Canada ($n = 1$), and Norway ($n = 1$). Primary diagnoses of kidney disease were: vascular disease (30%), diabetes mellitus (17%), primary glomerulopathy (12%), interstitial nephropathy (8%), cystic kidney disease (8%), multisystem disease (5%), other (13%), or unknown (7%). The study design of CONTRAST has been described previously (20). In short, all patients were randomized centrally into a 1:1 ratio for treatment with online HDF or continuation of low-flux HD, stratified per participating center. Upon randomization, patients were stable with a minimum dialysis single-pool Kt/V for urea of 1.2 or higher. Patients were eligible for inclusion if they were treated 2 or 3 times per week with chronic HD for at least 2 mo. Exclusion criteria were age below 18 yr, treatment with HDF or high-flux HD in the 6 mo preceding randomization, a life expectancy less than 3 mo because of another cause than kidney disease, participation in another clinical intervention trial evaluating cardiovascular outcomes, and severe noncompliance regarding frequency and duration of dialysis treatment. The study was conducted in accordance with the Declaration of Helsinki and was approved by a central and local medical ethics review board. Written informed consent was obtained from all patients before randomization.

Dialysis Procedures

Routine patient care was performed according to Quality of Care Guidelines of the Dutch Federation of Nephrology. Treatment times were fixed during follow-up in both treatment arms unless dialysis single-pool Kt/V for urea was below 1.2. Online HDF was performed in the postdilution mode. Blood flow rates could be increased in HDF

patients to improve convective volumes. HDF patients were treated with synthetic high-flux dialyzers [FX80 = 27%, FX100 = 11%, and Optiflux F200NR = 8% (Fresenius Medical Care, Bad Homburg, Germany); Polyflux 170H = 25%, and Polyflux 210H = 27% (Gambro Corporation AB, Lund, Sweden); or other dialyzers = 2%]. HD patients were treated with synthetic low-flux dialyzers [F6HPS = 5%, F8HPS = 45%, and Optiflux 18NR = 9% (Fresenius); Polyflux 14L = 2%, and Polyflux 17L = 30% (Gambro); or other dialyzers = 9%]. HD and HDF patients were treated with ultrapure dialysis fluids, defined as <0.1 CFUs/ml and <0.03 endotoxin units per ml.

Data Collection

At baseline, data on demography, history of cardiovascular disease, diabetes mellitus, type of vascular access, and the duration of dialysis (dialysis vintage) were collected. In addition, treatment time, blood flow rate, intradialytic weight loss, infusion volume, and (predialysis) blood pressure was assessed at baseline and each visit thereafter (*i.e.*, each 3 months). Convective volumes (L/treatment) were defined as the sum of the intradialytic weight loss and the infusion volume. At each visit, samples were drawn before dialysis for assessment of urea (mmol/L), creatinine (μ mol/L), phosphate (mmol/L), albumin (g/L), and hemoglobin (mmol/L). In addition, samples for determination of urea and creatinine were also drawn after this dialysis session. Serum β 2M (mg/L) was assessed at baseline and after 6 mo. All laboratory samples were analyzed in the local hospitals by standard laboratory techniques. Serum β 2M concentrations were detected by a nephelometric method in 53% (Dade Behring BNII, Siemens, Munich, Germany), an automated immunoassay in 35% (Immunitest 2000 or 2500, Siemens, Munich, Germany), an immunoturbidimetric method in 6% (Roche C6000/C501, Basel, Switzerland), or other methods in 6% of the patients. Interdialytic urinary samples were collected each visit in patients with a urinary production of ≥ 100 ml/d. RKF was expressed as GFR, which was calculated by the mean of creatinine and urea clearance and adjusted for body surface area ($\text{ml}/\text{min}/1.73 \text{ m}^2$). GFR was considered zero in patients with a urinary production <100 ml/d. The second generation Daugirdas formula was used to calculate single-pool Kt/V for urea (21).

Statistical Methods

All variables were reported as proportions or as means with SD or standard error (SEM) when appropriate. Paired *t* tests were used to evaluate changes from baseline to 6 mo in the HDF and HD groups. Moreover, differences in change during follow-up between the two treatment modalities were evaluated with linear regression models. To explore whether RKF modified the relation between change in β 2M and treatment modality, a multiplicative interaction term (RKF \times treatment modality) was added to the regression model. This interaction term was statistically significant ($P = 0.006$), indicating modification (*i.e.*, interaction). Hence, the effect of treatment modality on β 2M was reported separately for patients with and without RKF.

In the HDF patients, determinants of change in β 2M were studied using multivariable linear regression. Sex, age, history of cardiovascular disease, diabetes mellitus, dialysis vintage, body mass index, type of vascular access, dialysis frequency, and serum albumin level were selected for the multivariable model if they showed a univariable relation ($P < 0.15$) with the change in β 2M. In addition, GFR and convective volume were added beforehand to the multivariable model. All models were adjusted for participating center to adjust for possible differences in β 2M assays. A *P* value <0.05 was considered statistically significant. SPSS software was used for all statistical analyses (version 15.0.0; SPSS, Inc., Chicago, IL).

Results

Patient and Dialysis Characteristics

The median age of the patients ($n = 406$) was 66 yr (interquartile range 54 to 74) and 64% were men. Patient characteristics were balanced between the treatment groups (Table 1). Patients were predominantly dialyzing 3 times/wk (93%). In the HDF patients, the mean convective volume was 19.1 ± 5.0 L (\pm SD) per treatment (interquartile range 16.4 to 22.0 L).

During follow-up, Kt/V increased from 1.39 ± 0.02 (\pm SEM) at baseline to 1.61 ± 0.03 after 6 mo in HDF patients and from 1.36 ± 0.01 to 1.39 ± 0.02 in HD patients. The change in Kt/V between the two treatment modalities reached statistical significance ($P < 0.001$). The dialyzer blood flow rate increased from 302 ± 3.4 to 325 ± 4.5 ml/min in the HDF patients and remained stable in the HD patients (299 ± 3.8 and 300 ± 4.0 ml/min, respectively), with a statistically significant difference between the two treatment groups ($P < 0.001$). Treatment time was stable during follow-up in both groups.

Change in Serum β 2M levels from Baseline to 6 mo in HDF and HD Patients

Mean serum β 2M levels decreased from 29.5 ± 0.8 mg/L (\pm SEM) at baseline to 24.3 ± 0.6 mg/L (*i.e.*, an 18% decrease, $P < 0.001$) after 6 mo in HDF patients and increased from 31.9 ± 0.9 mg/L to 34.4 ± 1.0 mg/L (*i.e.*, an 8% increase, $P < 0.001$) in HD patients. The regression coefficient (B), indicating the difference of change in β 2M from baseline to 6 mo between

the treatment groups was -7.7 mg/L [95% confidence interval (CI) -9.5 to -5.6 , $P < 0.001$].

Baseline β 2M levels were higher in 176 patients without RKF (38.0 ± 0.9 mg/L) as compared with 230 patients with RKF (25.1 ± 0.7 mg/L, $P < 0.001$). The difference in change of β 2M from baseline to 6 mo between the treatment groups was more pronounced in patients without RKF than in patients with RKF (B = -10.7 mg/L, 95% CI -13.9 to -7.5 , $P < 0.001$ and B = -5.6 mg/L, 95% CI -7.7 to -3.6 , $P < 0.001$, respectively, Figure 1).

Determinants of Change in β 2M Levels in HDF Patients

In HDF patients, β 2M levels decreased from 36.7 ± 1.2 mg/L to 27.6 ± 1.1 mg/L in the absence of RKF (25% decrease, $P < 0.001$, Figure 1A) and from 24.3 ± 0.9 mg/L to 21.9 ± 0.7 mg/L in the presence of RKF (10% decrease, $P = 0.001$, Figure 1B). Baseline GFR in HDF patients was related to the decrease in β 2M (P for trend < 0.001 , Figure 2). In HDF patients with a GFR > 4.22 ml/min/1.73 m², β 2M levels did not change from baseline.

In a multivariable model, GFR was the only significant determinant of the change in β 2M (Table 2). The regression coefficient was 0.9 mg/L per ml/min/1.73 m² (95% CI 0.4 to 1.5, $P < 0.001$), indicating that the decrease in β 2M levels after 6 mo of treatment with HDF was smaller in patients with higher GFR. Change in β 2M was not related to the delivered convec-

Table 1. Patient characteristics at baseline^a

	HDF ($n = 199$)	HD ($n = 207$)
Gender (% male)	62	65
Age (yr)	66 (53 to 74)	66 (55 to 75)
History of cardiovascular disease (%)	45	44
Diabetes mellitus (%)	25	20
Dialysis vintage (yr)	1.7 (0.8 to 3.4)	2.2 (1.1 to 4.1)
Body mass index (kg/m ²)	24.9 ± 4.7	25.0 ± 4.2
Systolic blood pressure (mmHg)	147 ± 21	150 ± 21
Diastolic blood pressure (mmHg)	76 ± 13	77 ± 11
Vascular access (% arteriovenous fistula)	76	80
Treatment time (min)	240 (210 to 240)	240 (210 to 240)
Blood flow (ml/min)	302 ± 37	299 ± 43
Dialysis Kt/V _{urea}	1.39 ± 0.22	1.36 ± 0.17
RKF (%) ^b	58	55
Urinary volume (ml/24 h) ^c	700 (288 to 1150)	750 (350 to 1210)
GFR (ml/min/1.73 m ²) ^{c,d}	3.1 (1.3 to 5.6)	3.3 (1.1 to 5.4)
Hemoglobin (mmol/L)	7.4 ± 0.8	7.4 ± 0.7
Phosphorus (mmol/L)	1.69 ± 0.52	1.63 ± 0.49
Albumin (g/L)	36.5 ± 4.6	36.7 ± 4.5
β 2M (mg/L)	29.5 ± 12	31.9 ± 13

^aValues represent mean \pm SD, median (interquartile range), or proportion (%). To convert hemoglobin in mmol/L to g/dl, divide by 0.62; phosphate in mmol/L to mg/dl, divide by 0.323; and albumin in g/L to g/dl, divide by 10.

^bDefined as the proportion of patients with diuresis > 100 ml/24 h.

^cIn selection of patients with RKF.

^dMean of urea and creatinine clearance.

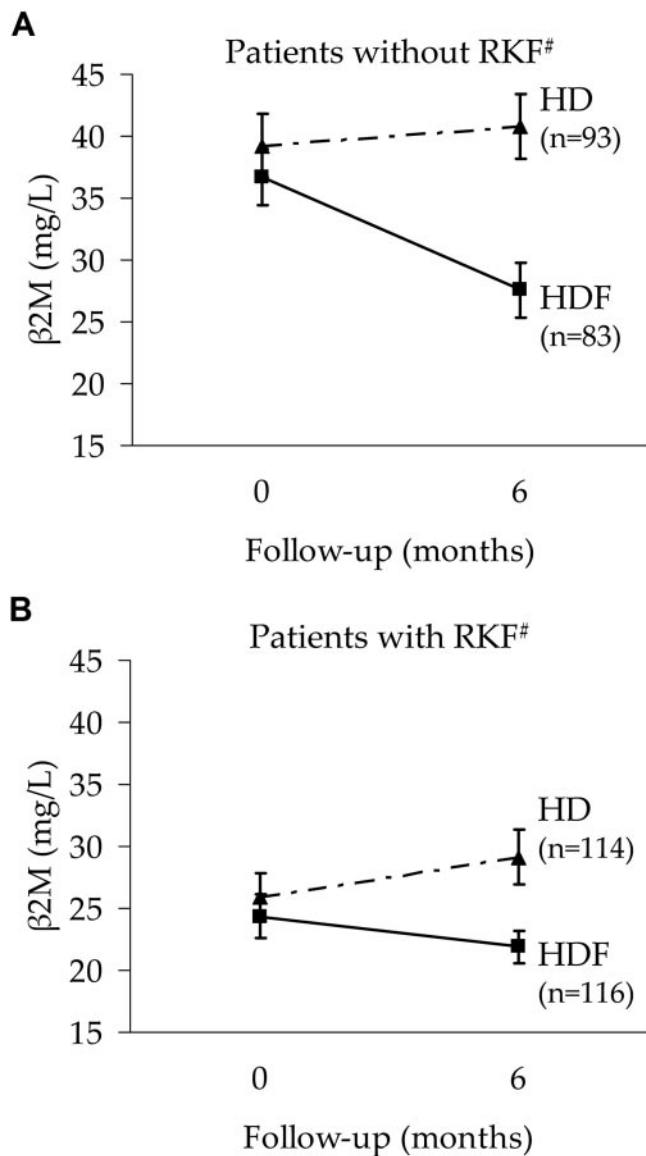


Figure 1. Changes in predialysis serum β 2M levels by dialysis modality in patients (A) without and (B) with RKF. Bars represent 95% CI. # $P < 0.001$ (for difference between HDF and HD).

tive volume during HDF, or any other of the evaluated variables (Table 2). In a subgroup analysis of patients without RKF, change in β 2M was also not related to the delivered convective volume (data not shown).

Discussion

This study demonstrated that serum β 2M levels decreased after 6 mo of treatment with online HDF, whereas β 2M levels slightly increased in HD patients. To our knowledge, the study presented here is the first showing that the effect of HDF on β 2M levels is larger in patients without RKF as compared with patients with RKF. In HDF patients, the degree of RKF was related to the decrease in β 2M, whereas the amount of delivered convective volume was not.

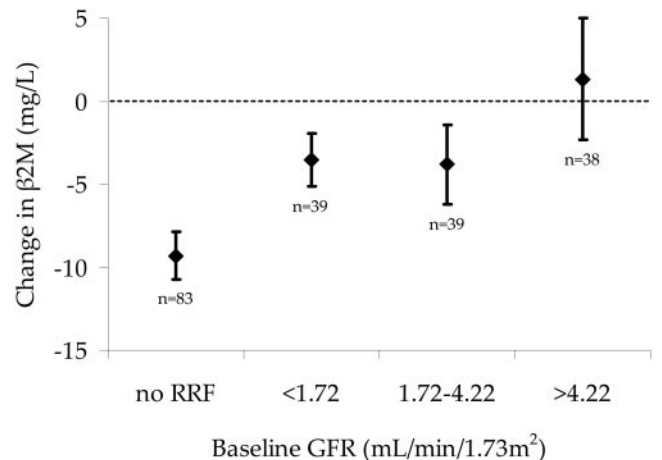


Figure 2. Relationship between baseline GFR and change in β 2M level from baseline to 6 mo in HDF patients adjusted for participating center. Baseline GFR is subdivided in tertiles. Bars represent 95% CI. P value for trend < 0.001 .

Previous studies in HDF patients have shown a decrease in predialysis β 2M levels varying from 10% to 40%, after switch from low-flux or high-flux HD. However, most studies were small (10-13) or uncontrolled (14,15) and none of these studies specifically addressed the effect of RKF or convective volume on β 2M decrease. Relatively large effects of HDF were reported in a randomized study in 42 patients, comparing mid-dilution HDF with exchange volumes of 60 L/treatment with low-flux HD and using ultrapure dialysis fluids. Predialysis β 2M levels decreased by 40% in HDF and did not change in low-flux HD patients. The presence or absence of RKF was not reported (10). In a randomized crossover study in 76 patients (of which 68% was anuric), predialysis β 2M levels were 22% lower after 12 mo of HDF treatment (postdilution substitution volumes 17 to 21 L) as compared with high-flux HD, using ultrapure dialysis fluids in all patients (11). Finally, in two randomized studies in 50 and 20 mostly anuric HDF patients (postdilution, convective volumes 8 to 12 L and 16 to 20 L, respectively), β 2M levels decreased by 10% to 15% as compared with baseline treatment with low-flux or high-flux HD. However, this decrease was not significantly different from high-flux HD (12,13), perhaps because of the small number of subjects or low convective volumes. In the study presented here, β 2M levels decreased by 25% in anuric patients, which is well within the range, as previously reported.

An inverse relation between β 2M levels and RKF in dialysis patients has been shown previously (5,22). In agreement, we found much higher β 2M levels in anuric patients as compared with patients with RKF. Yet, we are the first to report that the decrease in β 2M in HDF patients after conversion from conventional HD strongly relates to the degree of RKF. This underscores the importance of RKF and suggests that a GFR > 4.2 ml/min/1.73 m² may outweigh the effects of convective clearance by HDF for clearance of β 2M and possibly also for other MMW uremic toxins. From this perspective, more attention to preservation of RKF may be justified. At the same time, it may

Table 2. Results from univariable and multivariable linear regression analyses^a of 6-mo change in β 2M in HDF patients

Determinant	Univariable Regression		Multivariable Regression	
	B ^b	95% CI	B	95% CI
Gender (male)	1.3	−2.0 to 4.6		
Age (per 10 yr)	0.2	−0.9 to 1.3		
History of cardiovascular disease	2.5	−0.7 to 5.7	1.9	−1.3 to 5.2
Diabetes mellitus	2.7	−1.0 to 6.3	1.7	−2.1 to 5.5
Dialysis vintage (per yr)	−0.4	−0.9 to 0.2		
Body mass index (per kg/m ²)	0.0	−0.3 to 0.3		
Arteriovenous fistula	0.2	−3.5 to 3.9		
Convective volume (per L/treatment)	0.1	−0.3 to 0.6	0.3	−0.2 to 0.7
Dialysis frequency (per session/wk)	−6.3	−12.7 to 0.1	−3.7	−10 to 3.0
GFR (per ml/min/1.73 m ²)	0.9	0.5 to 1.4 ^c	0.9	0.4 to 1.5 ^c
Serum albumin (per g/dl)	−0.2	−0.7 to 0.2		

^aAdjusted for participating center.

^bThe regression coefficient (B) reflects the change in β 2M levels between baseline and 6 mo. Positive values of B indicate smaller decreases in β 2M during the study period.

^c $P < 0.001$.

be proposed that especially anuric patients may benefit from HDF treatment.

The decline in β 2M levels during follow-up in the HDF patients was not related to the amount of delivered convective volume in this study. Also, in the subgroup of patients without RKF such relation could not be established. In contrast, two previous studies have observed a positive relation between the convective volume and the reduction of β 2M during HDF, although the magnitude of this relation was modest. In those studies, an increase of the convective volume from 15 to 25 L was associated with an increase in the β 2M reduction ratio by approximately 10% (*i.e.*, an increase in β 2M reduction ratio from approximately 70 to 80%). The data presented here suggest that such small increases in β 2M removal during HDF do apparently not result in lower predialysis β 2M levels after 6 mo of treatment. This remarkable finding may be explained by the multicompartamental distribution of β 2M. Because the removal rate of β 2M by HDF is almost similar to the transfer rate from the extravascular to the vascular compartment, efforts to increase β 2M removal by increasing convective transport will be disappointing (23). Hence, alternative dialysis strategies, such as increased dialysis frequency or treatment time, are needed to further reduce β 2M concentrations (23). In fact, this has been suggested for short daily HDF (24) and daily nocturnal high-flux HD (25). It is possible that a relation between convective volume and change in β 2M could be found at lower volumes than applied in this study (*i.e.*, <10 to 15 L).

It should be noted that other factors may contribute to the level of β 2M in dialysis patients, such as biocompatibility of treatment and inflammatory state of patients. Patients treated with cellulose membranes were shown to have higher β 2M levels (22). Adsorption to the dialyzer membrane partly contributes to β 2M removal (26) and may also differ between various types of dialyzers (27). In addition, the use of ultrapure

dialysis fluid has been associated with lower β 2M concentrations, possibly because of a decreased inflammatory response and subsequent decreased β 2M production (28–30). In this study, HD and HDF patients were treated with synthetic biocompatible dialyzers and only ultrapure dialysis fluids were used. However, although unlikely, a decrease in generation as a cause of the lower concentrations of β 2M in the HDF arm of this study cannot be excluded.

It can not be concluded from the present data whether maximal effects of HDF on β 2M levels were already reached after 6 mo of treatment. However, in a preliminary analysis of CONTRAST data, β 2M levels at 12 mo seemed to be similar to those at 6 mo (31). Other studies indicate that a steady state is reached after 3 to 12 mo (10,12,13). Furthermore, only predialysis β 2M levels were measured, so β 2M clearance could not be calculated. Finally, it should be noted that in the CONTRAST study, high-flux dialyzers are used for online HDF whereas low-flux dialyzers are used for conventional HD. The extent of decrease in β 2M levels after 6 mo of treatment with HDF as found in this study can therefore not be generalized to patients treated with high-flux dialyzers.

In conclusion, the study presented here demonstrated that a considerable decrease in predialysis β 2M levels can be obtained after 6 mo of treatment with HDF in comparison with low-flux HD. This decrease was much more pronounced in patients without RKF, suggesting that these patients are especially most likely to benefit from HDF. In addition, kidney clearance of β 2M (and possibly also other MMW solutes) seems to be much more important than convective clearance by HDF in patients with a GFR >4.2 ml/min/1.73 m². Furthermore, this study showed that when high convective volumes are applied (replacement \geq 15 L/treatment) the amount of convective volume is not related to the decrease in predialysis β 2M levels, possibly because of resistance to β 2M transfer between extracellular and

intracellular body compartments. More intensified treatment regimes in terms of duration and frequency can possibly further decrease β 2M levels. Whether this leads to improved outcomes remains to be established.

Appendix

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Acknowledgments

CONTRAST is financially supported by a grant from the Dutch Kidney Foundation (Nierstichting Nederland, grant C02.2019) and unrestricted grants from Fresenius Medical Care (The Netherlands) and Gambro Lundia AB (Sweden). Additional support was received from the Dr. E.E. Twiss Fund, Roche Netherlands; the International Society of Nephrology/Baxter Extramural Grant Program; and the Dutch Organization for Health Research and Development (ZonMW, grant 17088.2802). The authors are grateful to all nursing staff and patients participating in this project. This work was previously presented at the Annual Meeting of the American Society of Nephrology in Philadelphia, PA (November 6 through 9, 2008).

Disclosures

None.

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