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 (β2M) can be increased by adding convective transport to hemodialysis (HD). The aim of this study was to investigate the change in β2M 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 β2M 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 β2M were analyzed using multivariable linear regression models.

Results: Mean serum β2M levels decreased from 29.5 ± 0.8 (±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, β2M levels remained unchanged in patients with GFR >4.2 ml/min/1.73 m^2. The β2M decrease was not related to convective volume.

Conclusions: This study demonstrated effective lowering of β2M levels by HDF, especially in patients without RKF. The role of the amount of convective volume on β2M decrease appears limited, possibly because of resistance to β2M transfer between body compartments.

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β_2-microglobulin (β2M, 11.8 kD) accumulates in kidney failure and has been implicated in the development of dialysis-associated amyloidosis (1). In addition, β2M 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). β2M is eliminated from the extracellular volume almost exclusively by the kidneys. Consequently, serum β2M levels already rise when kidney function is only mildly impaired (3). In hemodialysis (HD) patients, serum β2M 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 β2M levels predict all-cause and infectious-related mortality in these patients (4,7,8).

Because of its size, removal of β2M is negligible during low-flux HD. In contrast, significant removal of β2M 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 β2M levels in high-flux HD as compared with low-flux HD patients (4,9). In addition, it has been shown that removal of β2M is further increased with online hemodiafiltration (HDF) by using excess ultrafiltration to provide increased convective transport. Actually, lower predialysis β2M 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 β2M and other MMW uremic toxins by convective transport.

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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 β2M 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 β2M 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 β2M levels were measured to evaluate short-term treatment effects. The aim of the study presented here was to investigate the change in β2M levels from baseline to 6 mo in patients randomized to HDF and HD. Because β2M strongly relates to RKF, the change in β2M 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 β2M 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 β2M 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 incompliance 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 (μmol/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 β2M (mg/L) was assessed at baseline and after 6 mo. All laboratory samples were analyzed in the local hospitals by standard laboratory techniques. Serum β2M concentrations were detected by a nephelometric method in 53% (Dade Behring BNII, Siemens, Munich, Germany), an automated immunoassay in 35% (Immunolite 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 (ml/min/1.73 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 β2M and treatment modality, a multiplicative interaction term (RKF × 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 β2M was reported separately for patients with and without RKF.

In the HDF patients, determinants of change in β2M 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 β2M. 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 β2M 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 (±SD) per treatment (interquartile range 16.4 to 22.0 L).

During follow-up, Kt/V increased from 1.39 ± 0.02 (±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 β2M levels from Baseline to 6 mo in HDF and HD Patients

Mean serum β2M levels decreased from 29.5 ± 0.8 mg/L (±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 β2M 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 β2M 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 β2M 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 β2M Levels in HDF Patients

In HDF patients, β2M 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 β2M (P for trend <0.001, Figure 2). In HDF patients with a GFR >4.22 ml/min/1.73 m^2, β2M levels did not change from baseline.

In a multivariable model, GFR was the only significant determinant of the change in β2M (Table 2). The regression coefficient was 0.9 mg/L per ml/min/1.73 m^2 (95% CI 0.4 to 1.5, $P < 0.001$), indicating that the decrease in β2M levels after 6 mo of treatment with HDF was smaller in patients with higher GFR. Change in β2M 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
β2M (mg/L)	29.5 ± 12	31.9 ± 13

[a]Values represent mean ± 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.
[b]Defined as the proportion of patients with diuresis >100 ml/24 h.
[c]In selection of patients with RKF.
[d]Mean of urea and creatinine clearance.

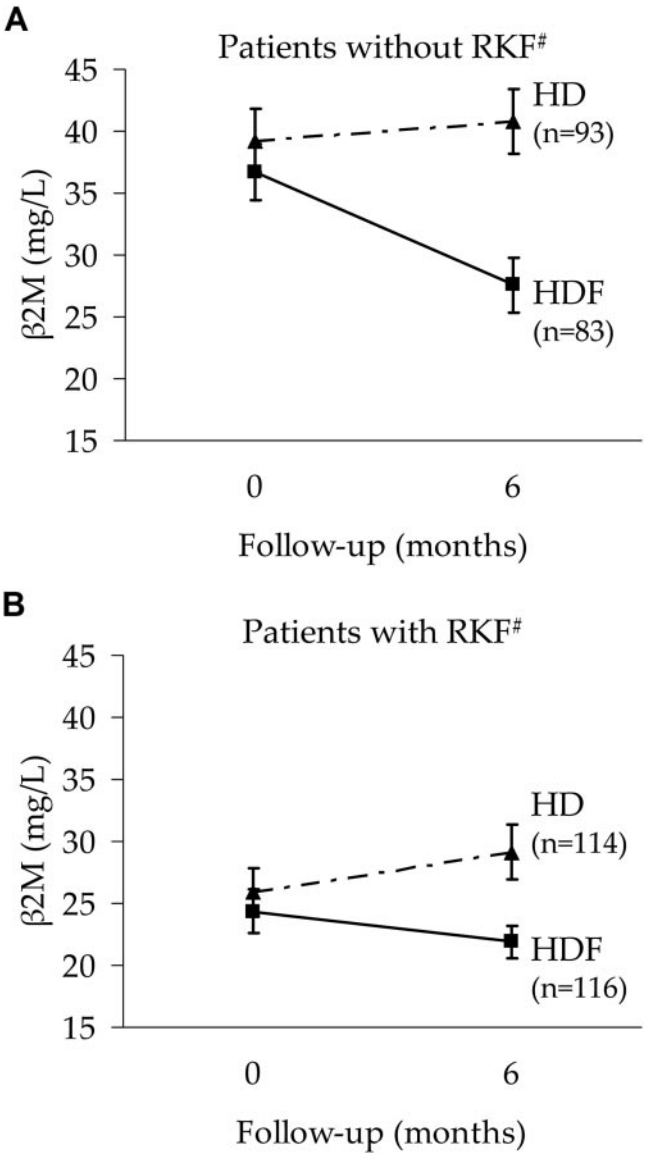

Figure 1. Changes in predialysis serum β2M levels by dialysis modality in patients (A) without and (B) with RKF. Bars represent 95% CI. $^{\#}P < 0.001$ (for difference between HDF and HD).

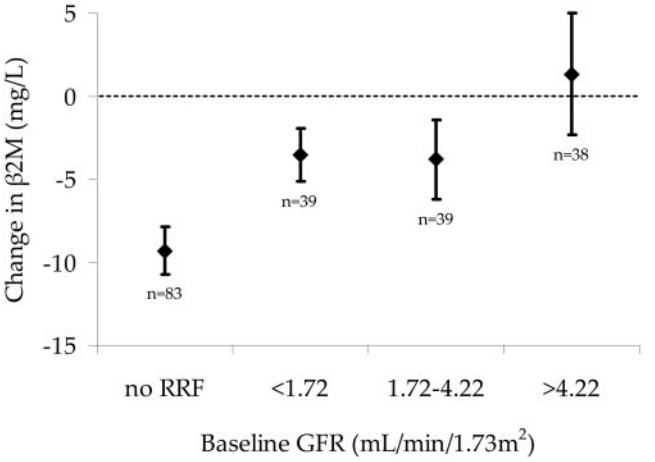

Figure 2. Relationship between baseline GFR and change in β2M level from baseline to 6 mo in HDF patients adjusted for participating center. Baseline GFR is subdivided in tertiles. Bars represent 95% CI. *P* value for trend <0.001.

tive volume during HDF, or any other of the evaluated variables (Table 2). In a subgroup analysis of patients without RKF, change in β2M was also not related to the delivered convective volume (data not shown).

Discussion

This study demonstrated that serum β2M levels decreased after 6 mo of treatment with online HDF, whereas β2M levels slightly increased in HD patients. To our knowledge, the study presented here is the first showing that the effect of HDF on β2M 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 β2M, whereas the amount of delivered convective volume was not.

Previous studies in HDF patients have shown a decrease in predialysis β2M 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 β2M 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 β2M 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 β2M 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), β2M 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, β2M levels decreased by 25% in anuric patients, which is well within the range, as previously reported.

An inverse relation between β2M levels and RKF in dialysis patients has been shown previously (5,22). In agreement, we found much higher β2M levels in anuric patients as compared with patients with RKF. Yet, we are the first to report that the decrease in β2M 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 m^2 may outweigh the effects of convective clearance by HDF for clearance of β2M 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 β2M 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		

[a]Adjusted for participating center.
[b]The regression coefficient (B) reflects the change in β2M levels between baseline and 6 mo. Positive values of B indicate smaller decreases in β2M during the study period.
[c]$P < 0.001$.

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

The decline in β2M 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 β2M 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 β2M reduction ratio by approximately 10% (*i.e.*, an increase in β2M reduction ratio from approximately 70 to 80%). The data presented here suggest that such small increases in β2M removal during HDF do apparently not result in lower predialysis β2M levels after 6 mo of treatment. This remarkable finding may be explained by the multicompartmental distribution of β2M. Because the removal rate of β2M by HDF is almost similar to the transfer rate from the extravascular to the vascular compartment, efforts to increase β2M 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 β2M 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 β2M 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 β2M in dialysis patients, such as biocompatibility of treatment and inflammatory state of patients. Patients treated with cellulose membranes were shown to have higher β2M levels (22). Adsorption to the dialyzer membrane partly contributes to β2M 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 β2M concentrations, possibly because of a decreased inflammatory response and subsequent decreased β2M 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 β2M 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 β2M levels were already reached after 6 mo of treatment. However, in a preliminary analysis of CONTRAST data, β2M 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 β2M levels were measured, so β2M 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 β2M 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 β2M 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 β2M (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 m^2. Furthermore, this study showed that when high convective volumes are applied (replacement ≥15 L/treatment) the amount of convective volume is not related to the decrease in predialysis β2M levels, possibly because of resistance to β2M transfer between extracellular and

intracellular body compartments. More intensified treatment regimes in terms of duration and frequency can possibly further decrease β2M levels. Whether this leads to improved outcomes remains to be established.

Appendix

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Disclosures

None.

References

1. Miyata T, Jadoul M, Kurokawa K, van Ypersele de SC: Beta-2 microglobulin in renal disease. *J Am Soc Nephrol* 9: 1723-1735, 1998
2. Vanholder R, De SR, Glorieux G, Argiles A, Baurmeister U, Brunet P, Clark W, Cohen G, De Deyn PP, Deppisch R, scamps-Latscha B, Henle T, Jorres A, Lemke HD, Massy ZA, Passlick-Deetjen J, Rodriguez M, Stegmayr B, Stenvinkel P, Tetta C, Wanner C, Zidek W: Review on uremic toxins: Classification, concentration, and interindividual variability. *Kidney Int* 63: 1934-1943, 2003
3. Viberti GC, Bilous RW, Mackintosh D, Keen H: Monitoring glomerular function in diabetic nephropathy. A prospective study. *Am J Med* 74: 256-264, 1983
4. Cheung AK, Rocco MV, Yan G, Leypoldt JK, Levin NW, Greene T, Agodoa L, Bailey J, Beck GJ, Clark W, Levey AS, Ornt DB, Schulman G, Schwab S, Teehan B, Eknoyan G: Serum beta-2 microglobulin levels predict mortality in dialysis patients: Results of the HEMO study. *J Am Soc Nephrol* 17: 546-555, 2006
5. Fry AC, Singh DK, Chandna SM, Farrington K: Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. *Blood Purif* 25: 295-302, 2007
6. Kabanda A, Jadoul M, Pochet JM, Lauwerys R, van Ypersele de SC, Bernard A: Determinants of the serum concentrations of low-molecular-weight proteins in patients on maintenance hemodialysis. *Kidney Int* 45: 1689-1696, 1994
7. Cheung AK, Greene T, Leypoldt JK, Yan G, Allon M, Delmez J, Levey AS, Levin NW, Rocco MV, Schulman G, Eknoyan G: Association between serum beta-2 microglobulin level and infectious mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 3: 69-77, 2008
8. Okuno S, Ishimura E, Kohno K, Fujino-Katoh Y, Maeno Y, Yamakawa T, Inaba M, Nishizawa Y: Serum beta2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. *Nephrol Dial Transplant* 24: 571-577, 2009
9. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R: Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol* 20: 645-654, 2009
10. Wizemann V, Lotz C, Techert F, Uthoff S: On-line haemodiafiltration *versus* low-flux haemodialysis. A prospective randomized study. *Nephrol Dial Transplant* 15: 43-48, 2000
11. Schiffl H: Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. *Eur J Med Res* 12: 26-33, 2007
12. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlandini G: Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. *Kidney Int* 50: 1293-1302, 1996
13. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W: A comparison of on-line hemodiafiltration and high-flux hemodialysis: A prospective clinical study. *J Am Soc Nephrol* 11: 2344-2350, 2000
14. Lin CL, Yang CW, Chiang CC, Chang CT, Huang CC:

Long-term on-line hemodiafiltration reduces predialysis beta-2-microglobulin levels in chronic hemodialysis patients. *Blood Purif* 19: 301-307, 2001
15. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van Malderen P, D'Haenens P: On-line haemodiafiltration. Remarkable removal of beta2-microglobulin. Long-term clinical observations. *Nephrol Dial Transplant* 15: 49-54, 2000
16. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK: Mortality risk for patients receiving hemodiafiltration *versus* hemodialysis: European results from the DOPPS. *Kidney Int* 69: 2087-2093, 2006
17. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R: Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol Dial Transplant* 23: 2337-2343, 2008
18. Jirka T, Cesare S, Di BA, Perera CM, Ponce P, Richards N, Tetta C, Vaslaky L: Mortality risk for patients receiving hemodiafiltration *versus* hemodialysis. *Kidney Int* 70: 1524-1525, 2006
19. Tattersall J, Martin-Malo A, Pedrini L, Basci A, Canaud B, Fouque D, Haage P, Konner K, Kooman J, Pizzarelli F, Tordoir J, Vennegoor M, Wanner C, ter Wee P, Vanholder R: EBPG guideline on dialysis strategies. *Nephrol Dial Transplant* 22: ii5–21, 2007
20. Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, Nube MJ, van der Tweel, I, ter Wee PM; the CONTRAST study group: Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis patients - the Dutch CONvective TRAnsport STudy (CONTRAST): Rationale and design of a randomised controlled trial [ISRCTN38365125]. *Curr Control Trials Cardiovasc Med* 6: 8, 2005
21. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4: 1205-1213, 1993
22. McCarthy JT, Williams AW, Johnson WJ: Serum beta 2-microglobulin concentration in dialysis patients: importance of intrinsic renal function. *J Lab Clin Med* 123: 495-505, 1994
23. Ward RA, Greene T, Hartmann B, Samtleben W: Resistance to intercompartmental mass transfer limits beta2-microglobulin removal by post-dilution hemodiafiltration. *Kidney Int* 69: 1431-1437, 2006
24. Maduell F, Navarro V, Torregrosa E, Rius A, Dicenta F, Cruz MC, Ferrero JA: Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. *Kidney Int* 64: 305-313, 2003
25. Raj DS, Ouwendyk M, Francoeur R, Pierratos A: Beta(2)-microglobulin kinetics in nocturnal haemodialysis. *Nephrol Dial Transplant* 15: 58-64, 2000
26. Padrini R, Canova C, Conz P, Mancini E, Rizzioli E, Santoro A: Convective and adsorptive removal of beta2-microglobulin during predilutional and postdilutional hemofiltration. *Kidney Int* 68: 2331-2337, 2005
27. Klinke B, Rockel A, Abdelhamid S, Fiegel P, Walb D: Transmembranous transport and adsorption of beta-2-microglobulin during hemodialysis using polysulfone, polyacrylonitrile, polymethylmethacrylate and cuprammonium rayon membranes. *Int J Artif Organs* 12: 697-702, 1989
28. Arizono K, Nomura K, Motoyama T, Matsushita Y, Matsuoka K, Miyazu R, Takeshita H, Fukui H: Use of ultrapure dialysate in reduction of chronic inflammation during hemodialysis. *Blood Purif* 22: 26-29, 2004
29. Furuya R, Kumagai H, Takahashi M, Sano K, Hishida A: Ultrapure dialysate reduces plasma levels of beta2-microglobulin and pentosidine in hemodialysis patients. *Blood Purif* 23: 311-316, 2005
30. Ouseph R, Jones S, Dhananjaya N, Ward RA: Use of ultrafiltered dialysate is associated with improvements in haemodialysis-associated morbidity in patients treated with reused dialysers. *Nephrol Dial Transplant* 22: 2269-2275, 2007
31. Van der Weerd NC, Penne EL, Blankestijn PJ, Bots ML, Van den Dorpel MA, Grooteman MP, Nube MJ, Ter Wee PM: No increase in erythropoietin (epo) sensitivity despite increased middle molecular weight (MMW) clearance in patients treated with online hemodiafiltration (HDF) in the Dutch CONvective TRAnsport STudy (CONTRAST) [Abstract]. *J Am Soc Nephol* 19: 270A, 2008