

Is high-volume post-dilution haemodiafiltration associated with risk of fluid volume imbalance? A national multicentre cross-sectional cohort study

Charles Chazot^{1,2}, Sebastien Deleuze³, Baya Fadel⁴, Hadia Hebibi⁵, Guillaume Jean⁶, Martial Levannier⁷, Olivier Puyoo⁸, David Attaf⁹, Stefano Stuard¹⁰ and Bernard Canaud¹¹

¹NephroCare France, Nephrology & Dialysis, Fresnes, Île-de-France, France, ²F-CRIN Investigation Network Initiative and Renal Clinical Network Trialist, Nancy, France, ³Centre NephroCare, Fresenius Medical Care, Castelnaud Le Lez, France, ⁴NephroCare Belley, Nephrology & Dialysis, Belley, France, ⁵NephroCare Ile de France, Nephrology & Dialysis, Fresnes, France, ⁶NephroCare Tassin-Charcot, Sainte-Foy-Lès-Lyon, France, ⁷NephroCare Béziers, Nephrology & Dialysis, Béziers, France, ⁸NephroCare Occitanie Muret, Nephrology & Dialysis, Muret, Occitanie, France, ⁹Medical Affairs, Fresenius Medical Care, Fresnes, Île-de-France, France, ¹⁰EMEA Clinical Governance Organization, Care Value Management EMEA, Fresenius Medical Care, Bad Homburg, Germany and ¹¹Centre of Excellence Medical, Fresenius Medical Care, Bad Homburg, Germany

Correspondence and offprint requests to: Charles Chazot; E-mail: charles.chazot@fmc-ag.com

ABSTRACT

Background. Fluid overload is frequent among hemodialysis (HD) patients. Dialysis therapy itself may favor sodium imbalance from sodium dialysate prescription. As on-line hemodiafiltration (OL-HDF) requires large amounts of dialysate infusion, this technique can expose to fluid accumulation in case of a positive sodium gradient between dialysate and plasma. To evaluate this risk, we have analyzed and compared the fluid status of patients treated with HD or OL-HDF in French NephroCare centers.

Method. This is a cross-sectional and retrospective analysis of prevalent dialysis patients. Data were extracted from the EUCLID5 data base. Patients were split in 2 groups (HD and OL-HDF) and compared as whole group or matched patients for fluid status criteria including predialysis relative fluid overload (RelFO%) status from the BCM[®].

Results. 2242 patients (age 71 years; female: 39%; vintage: 38 months; Charlson index: 6) were studied. 58% of the cohort were prescribed post-dilution OL-HDF. Comparing the HD and OL-HDF groups, there was no difference between HD and OL-HDF patients regarding the predialysis systolic BP, the interdialytic weight gain, the dialysate-plasma sodium gradient, and the predialysis RelFO%. The stepwise logistic regression did not find dialysis modality (HD or OL-HDF) associated with fluid overload or high predialysis systolic blood pressure. In OL-HDF patients, monthly average convective or weekly infusion volumes per session were not related with the presence of fluid overload.

Conclusions. In this cross-sectional study we did not find association between the use of post-dilution OL-HDF and markers of fluid volume excess. Aligned dialysis fluid sodium concentrations to patient predialysis plasma sodium and regular monitoring of fluid volume status by bioimpedance spectroscopy may have been helpful to manage adequately the fluid status in both OL-HDF and HD patients.

Keywords: bioimpedance, fluid overload, post-dilution haemodiafiltration, sodium balance, sodium gradient

INTRODUCTION

End-stage kidney disease patients present with higher risk of mortality from cardiovascular (CV) disease than several chronic diseases, including malignant ones [1]. Chronic fluid overload (FO) plays a critical role in this increased CV risk in haemodialysis (HD) patients [2]. Many factors enhance the risk of sodium and fluid imbalance, including kidney disease deterioration as well as poor adhesion to a low salt diet [3], limited accuracy of fluid status assessment by clinical examination [4], disruption of fluid removal due to hypovolaemia and intradialytic hypotensive (IDH) episodes [5]. Furthermore, this risk may be aggravated by intradialytic positive sodium balance from sodium profiling or high dialysate sodium content [6]. High-volume post-dilution online haemodiafiltration (OL-HDF) has been shown to reduce all-cause and CV mortality in patients pooled from four randomized controlled trials (RCTs)

[7]. Clinical benefits of OL-HDF on patient outcomes are dose-dependent with a threshold value for the substitution volume set at 21 L/1.73 m²/session [8]. However, its use is far from universal. In France, in 2016, OL-HDF represented 30% of renal replacement therapy [9]. Because of the large amount of online substitution fluid used and because of the dialysate–plasma sodium gradient potentially not being adequately adjusted (e.g. relative hypotonicity of ultrafiltrate due to Gibbs–Donnan effect), there is a risk of positive sodium mass balance. In a prospective study, Locatelli *et al.* [10] found that patients assigned to pre-dilution haemofiltration or pre-dilution HDF had fewer IDH episodes. The hypotheses were a possible thermal effect or a positive sodium balance; this last hypothesis is supported by the fact that pre-dialysis blood pressure (BP) increased significantly from baseline in patients under pre-dilution OL-HDF. Also, in the Turkish study comparing prospectively HD and post-dilution OL-HDF [11], at the end of the follow-up the pre-dialysis systolic BP was significantly higher in the OL-HDF group, whereas the difference was not significant at baseline. In the three other prospective trials comparing post-dilution OL-HDF with HD, no such difference in BP was reported between the two modalities. We report here a cohort of HD patients treated either by HD or OL-HDF in which markers of fluid excess have been compared.

MATERIALS AND METHODS

This is a national multicentre cross-sectional retrospective cohort study including all HD patients treated in 35 NephroCare French centres during the month of November 2017. Incident patients with <3 months from HD start and patients with prolonged hospitalizations (>2 weeks) were excluded. Patients with <3 weekly sessions were also excluded. All data regarding the patients (demographics, vascular access and Charlson index), the dialysis prescription and sessions parameters [effective treatment time, processed blood volume, effective blood flow, dialysis modality, substitution volume, sodium dialysate, pre- and post-dialysis body weight (BW), interdialytic weight gain and the delta between achieved and prescribed post-dialysis BW], the labs (pre-dialysis natraemia, haemoglobin, serum albumin) and fluid status [pre-dialysis systolic BP, pre-dialysis relative FO (RelFO%) from Body Compositor Monitor (BCM[®])] were extracted from the EuCliD 5 (European Clinical database version 5) software common to all the NephroCare dialysis units in France. EuCliD 5 integrates all this information in real time from the dialysis machine 5008[®], the lab, the BCM and the scale [12]. All the data were averaged for the month of November 2017. The included BCM data were the last recorded in the last 3 months. Plasma sodium was assessed by indirect potentiometry in all centres except two (direct potentiometry). The dialysate sodium was estimated from the dialysate conductivity continuously monitored by the dialysis machine during the session. Preventive maintenance including conductivity calibration is done once a year. For the analysis, graft as vascular access was grouped with native arteriovenous fistula because of the low number (36 among the overall cohort).

Patients were split into two groups according to the dialysis modality (HD or post-dilution OL-HDF). Fluid status was

assessed from several parameters including monthly average of pre-dialysis systolic BP, interdialytic weight gain, ultrafiltration rate (mL/h/kg), sodium dialysate prescription and dialysate–plasma sodium gradient. Pre-dialysis RelFO% status was assessed from the BCM[®] in the last 3 months as described in previous studies [2, 13]. This value for one patient is the ratio in percentage of extracellular fluid excess (in litres) and her/his total extracellular fluid (in litres). The extracellular fluid excess is estimated from the database of healthy normohydrated subjects comparable according to age, gender, height and weight. A significant risk of increased mortality is associated with RelFO% when >15% in males and 13% in females.

Statistical analysis

The two groups of patients (HD and OL-HDF) were compared using non-parametric tests and analyses because of the non-normal distribution of the data. Median is given with 95% confidence interval (CI) unless specified differently. A case–control matching using the nearest neighbour matching algorithm without replacement was applied on four main confounding parameters (age, gender, Charlson index and vascular access) of the two groups, HD and OL-HDF, to evaluate the role of convective therapy on FO status. The calipers were set, respectively, at 3 years for age, 1 point for the Charlson index and an exact match for the two dichotomous variables (gender and vascular access). Parameters associated with RelFO% were searched with Spearman's rank correlation test from the entire cohort and for each treatment modality group. A P-value was found significant when ≤ 0.05 .

To look for an association with dialysis modality and FO, we applied a stepwise logistic regression with RelFO% above the thresholds of 15% in males and 13% in females as a dependent variable in the overall cohort and after removing the self-care patients, and in the overall matched cohorts. The selected variables for the model were age, vintage, body mass index (BMI), serum albumin, Charlson index and dialysis modality (HD or OL-HDF). Variables were included if $P < 0.05$, removed if $P > 0.1$, with a classification table cut-off value at 0.5. We applied the same logistic regression analysis to investigate the association of the dialysis modality and high pre-dialysis systolic BP (>160 mmHg) adding to the variables the pre-dialysis RelFO%. We also investigated the same way the association between the convective volume and FO and high BP in OL-HDF patients. To address the possible bias by indication beyond the case–control matching, we selected a subgroup of patients excluding the self-care units not allowed by regulation to implement OL-HDF and two units not meeting the requirements to perform OL-HDF because of the water treatment system.

The MedCalc[®] software (Ostend, Belgium) was used for the analysis.

RESULTS

In November 2017, 2674 patients were treated with HD in the 35 French NephroCare centres. One hundred and fifty-eight patients were excluded because of having started HD therapy for <3 months (incident patients). Among the 2516 prevalent patients, 1153 were prescribed HD and 1353 OL-HDF. Two

Table 1. Patients characteristics (overall cohort)

	Before matching		After matching	
	HD	OL-HDF	HD	OL-HDF
No. of patients	873	1169	694	694
Age ^a , years	68 (58–80) ^a	74 (64–82)*	70 (60–81)	70 (61–81)
Gender (% female)	41	37	39	39
Vintage average (months)	41 (20–81)	36 (18–69)**	42 (21–86)	37 (18–71)**
Vintage 3–6 months (%)	2.3	3.9***	3.0	2.3
BMI (kg/m ²)	25.3 (22.3–29.3)	26.0 (22.8–29.9)**	25.3 (22.3–29.2)	26.1 (22.4–30.2)***
Catheters (%)	16	20***	30.1	30.1
Diabetes (%)	20	29**	19.5	22.5
Charlson index	5 (4–7)	6 (5–7)*	5 (4–7)	5 (4–7)
Weekly treatment time (min)	720 (706–731)	713 (700–726)*	719 (706–732)	714 (702–727)*
Dialysate [Na ⁺] (mmol/L)	140 (140–140)	140 (140–140)	140 (138–140)	140 (139–140)*
Serum sodium (mmol/L)	138 (138–138)	138 (138–139)	138 (136–140)	138 (137–140)
Ionic KT/V	1.64 (1.45–1.87)	1.79 (1.53–2.03)*	1.65 (1.45–1.88)	1.80 (1.57–2.05)*
OL-HDF (%)	0	100	0	100
Convective volume (L/session) ^b	0	26.1 (23.7–28.6)	0	26.1 (23.8–28.6)
Haemoglobin (g/dL)	11.5 (10.7–12.2)	11.2 (10.6–12.0)*	11.5 (10.7–12.2)	11.2 (10.6–11.9)*

^aMedian (25–75th percentiles).

^bMonthly average.

*P<0.05; **P<0.01; ***P <0.001 from Mann–Whitney or Chi-squared tests.

Table 2. Fluid status criteria in the two groups of patients (HD and OL-HDF) in the overall cohort and pair-matched patients^a

	Overall cohort		Pair-matched cohort	
	HD	OL-HDF	HD	OL-HDF
No. of patients	873	1169	694	694
Pre-dialysis systolic BP (mmHg)	140 (126–154)	143 (127–155)	142 (127–155)	139 (127–154)
Interdialytic weight gain (kg)	2.9 (2.1–3.9)	2.9 (2.1–3.9)	3.0 (2.1–3.9)	2.9 (2.1–3.9)
Achieved–prescribed post-dialysis BW (kg)	−0.1 (−1.1 to 1.0)	−0.1 (−1.2 to 1.1)	−0.1 (−1.2 to 1.1)	0.0 (−1.1 to 1.1)
[Na] _{dialysis}	140 (138–140)	139 (139–140)	140 (138–140)	140 (139–140)
Dialysate–plasma Na gradient (mEq)	−1 (−4 to 1)	−2 (−4 to 1)	−2 (−3 to 0)	−1 (−4 to 1)
Fluid removal rate (mL/h/kg)	8.8 (7.0–10.4)	8.8 (7.0–10.7)	8.9 (7.0–10.9)	8.7 (7.0–10.3)
Pre-dialysis RelFO (%)	6.1 (0.8–12.3)	6.7 (1.0–12.3)	6.4 (0.5–11.9)	6.3 (0.7–12.5)

^aData are presented as median (25–75th percentiles).

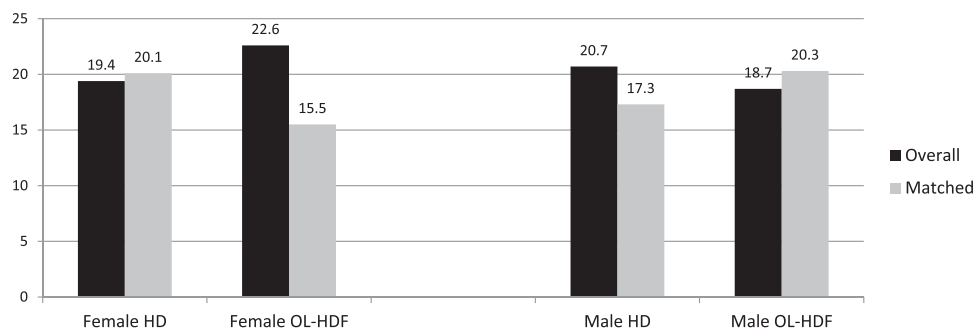


FIGURE 2: Overhydration distribution (%) among male and female patients in HD and OL-HDF in both the overall cohort and in the pair-matched patients. Overhydration is defined from the pre-dialysis BCM[®] measurement when RelFO% is $\geq 13\%$ in females and $\geq 15\%$ in male patients.

infusion volume were not related to the presence of FO and to pre-dialysis high BP (>160 mmHg; data not shown).

As self-care HD units were part of the overall cohort, while it is not permitted to implement OL-HDF for regulatory reasons, we ran the same analysis excluding 18 exclusively self-care units, leaving 1711 patients for analysis in 17 units in which both modalities were available. The same analyses were run as in the overall cohort. In this new cohort and opposite to the

overall one, HD and OL-HDF patients did not significantly differ for age, vintage, the percentage of catheters as vascular access and for Charlson index (Supplementary data, Table S1B). After matching, BMI remained significantly higher in OL-HDF patients, as well as ionic clearance KT/V, and haemoglobin. After matching, dialysate sodium became significantly different for OL-HDF due to narrower distribution (Supplementary data, Table S1B). In Supplementary data, Figure S2B, there is no

Table 3. Spearman rank correlations of patient and dialysis parameters with the pre-dialysis RelOH% (overall cohort)

	HD		OL-HDF	
	<i>r</i>	P-value	<i>r</i>	P-value
Age	0.14	0.0002	0.08	0.01
Vintage	0.12	0.0008	0.20	<0.0001
BMI	-0.27	<0.0001	-0.32	<0.0001
Weekly processed blood volume	-0.09	0.014	-0.04	0.90
Fluid removal rate	0.19	<0.0001	0.24	<0.0001
Charlson index	0.15	<0.0001	0.11	0.0003
Serum albumin	-0.16	<0.0001	-0.12	0.0001
Dialysate-plasma Na gradient	-0.03	0.45	0.025	0.43
Pre-dialysis systolic BP	0.094	0.009	0.12	0.0001
Convective volume ^a	-	-	0.12	0.0028

^aMonthly average per session.

Table 4. Logistic regression analysis exploring the parameters associated with gender-defined RelOH% threshold for significant fluid overload (RelOH% >13% in females; RelOH% >15% in males) in the overall cohort

	Overall cohort	
	Female Odds ratio (95% CI)	Male Odds ratio (95% CI)
Age	Not included	Not included
Vintage	1.00* (1.00-1.01)	1.01* (1.00-1.01)
Charlson index	1.10** (1.00-1.20)	Not included
BMI	0.92* (0.89-0.96)	0.91* (0.87-0.94)
Serum albumin	0.63** (0.42-0.94)	0.45* (0.31-0.65)
HD/OL-HDF	Not included	Not included

The selected variables for the analysis were: age, vintage, serum albumin, BMI, Charlson index, dialysis modality (HD or OL-HDF).

*P < 0.05; **P < 0.01.

difference between HD and OL-HDF for patients over the bioimpedance thresholds of FO according to the gender before and after matching. Regarding the parameters reflecting FO before matching (Supplementary data, Table S2B), there was no difference between HD and OL-HDF except for pre-dialysis systolic BP (138 versus 143 mmHg). This difference was not confirmed after matching. Dialysate sodium was significantly different between groups before and after matching related to narrower distribution. Supplementary data, Table S3B presents the Spearman correlations between pre-dialysis RelFO% and number of parameters. As in the overall cohort, the convective volume was associated with RelFO% ($r = 0.12$, $P = 0.0001$) but not with the dialysate-plasma sodium gradient. Supplementary data, Tables S4B and S5B show the stepwise logistic regression analyses for RelFO% thresholds of FO according to gender and for high pre-dialysis systolic BP. The dialysis modality was not associated with these markers of fluid accumulation. Also, the monthly average convective volume or the weekly infusion volume was not associated with FO nor with high pre-dialysis systolic BP (data not shown).

DISCUSSION

This multicentre cross-sectional study involving a large cohort of HD patients delivers several important findings. First, HD and OL-HDF patients did not show difference in the usual

Table 5. Stepwise logistic regression analysis exploring the parameters associated with high pre-dialysis systolic BP (>160 mmHg) in the overall cohort

	Overall cohort Odds ratio (95% CI)
Age	Not included
Vintage	Not included
Charlson index	Not included
BMI	Not included
Serum albumin	1.69* (1.22-2.34)
RelFO% ^a	1.03** (1.02-1.05)
HD/OL-HDF	Not included

The selected variables for the analysis were: age, vintage, serum albumin, BMI, Charlson index, RelFO% and dialysis modality (HD or OL-HDF).

^aPre-dialysis relative fluid overload.

*P < 0.05; **P < 0.01.

clinical parameters evaluating FO (pre-dialysis systolic BP, interdialytic weight, delta between prescribed and achieved post-dialysis BW). Secondly, FO assessed with multi-frequency bioimpedance was not different between HD and OL-HDF. To our knowledge, this study is the first one to compare this objective assessment of fluid balance between standard and convective therapies. Thirdly, from different statistical analyses, we did not find a significant association between the dialysis modality (standard or convective) and objectively assessed FO or pre-dialysis high BP. This is in line with the results of the European pooling project agglomerating the four main RCTs that have identified a significant reduction of CV mortality with post-dilution OL-HDF [7].

This study tends to confirm that the infusion of large substitution volume produced online from dialysis fluid is not associated with sodium imbalance and risk of FO. Pre-dialysis BP in OL-HDF-treated patients did not differ from that of the HD-treated group before or after the case-control matching in the overall cohort. After removing patients treated in self-care dialysis units, pre-dialysis systolic BP was higher in OL-HDF than in HD patients. However, this difference disappeared after matching. Our data are in line with the CONTRAST, ESHOL (Estudio de Supervivencia de Hemodiafiltración On-Line) and Frenchie studies [8, 14, 15] and opposite to the Turkish [11] and the Italian study [10]. Higher BP findings of the latter two studies are not easy to explain because they were not confirmed in the more recent studies [8, 15] in which the convective volume was kept at a much higher volume. However, the Italian study included patients under pre-dilution haemofiltration and HDF with much higher convective volume compared with post-dilution technique, respectively, at 60.4 and 39.9 L (26.1 L in our study). This might have played a role in the higher pre-dialysis BP level. In the Turkish study, the pre-dialysis BP level was lower than in the other trials (126 and 129 mmHg in HD and OL-HDF, respectively). The data are issued from an area in which volume control, low salt diet and BP control have been emphasized for a long time [16]. Therefore, the clinical impact of this slight difference at such an unusual low level of pre-dialysis systolic BP is unknown. Moreover, we looked at a possible role of sodium dialysate content in these cohorts. When high tonicity is induced from a positive sodium dialysate-plasma gradient, there is a significant association with the interdialytic

weight gain [17]. In our study, interdialytic weight gain was not different between HD and OL-HDF before and after the case-control matching. The dialysate sodium concentration prescribed was not different between the two groups. Only in the pair-matched cohort excluding self-care patients was a significant difference on sodium dialysate content found, whereas the medians were comparable (140). The difference came from the fact that in one large unit OL-HDF prevalence is low and dialysate sodium is mainly prescribed at 138 mmol/L. We estimate that the impact of this finding is limited because the dialysate sodium concentration prescription remained in relatively close range of plasma sodium concentration with a low dialysate-plasma sodium gradient. This observation is important since, due to the Donnan effects on ultrafiltrate, a limited dialysate-plasma sodium gradient may play a role in the absence of positive sodium balance even under high infusion volume. Also in a recent cross-over study by La Milia *et al.* [18], in 47 HD patients, the sodium removal and the plasma tonicity during the dialysis session were equivalent between the two dialysis modalities. Also, we have been able to use the routine data of fluid assessment implemented in the NephroCare dialysis units. This is a direct and objective assessment of fluid status based on the multi-frequency bioimpedance spectroscopy. This quality control approach may also play a role in the absence of fluid excess in these patients as the nephrologists have an objective tool to quantify fluid volume excess. Few reports have used multi-frequency bioimpedance to evaluate OL-HDF patients. Recently, in a small cohort, Molina *et al.* [19] evaluated the switch from HD to OL-HDF and used BCM[®] for nutrition evaluation. During the follow-up, pre-dialysis FO remained stable all through the follow-up. However, in the Molina study, no normalization of fluid excess to total extracellular fluid was applied in our study. The switch from HD to OL-HDF did not affect significantly the absolute value of fluid excess during the 1-year follow-up from patients who had remained on standard HDF. Last but not least, we found a weak but significant correlation between the convective volume and the relative hydration status. This could suggest that the higher the convective volume, the higher the risk of FO by sodium imbalance. This was strengthened by the same association with the weekly infusion volume. However, the logistic regression analyses did not confirm the association between OL-HDF and FO, between OL-HDF and high pre-dialysis BP, neither the association of the convective volume nor infusion volume with the FO from the BCM[®] or the high pre-dialysis BP.

The strengths of our study are the large number of the patients in this French cohort and the routine use of BCM[®] providing objective data of fluid status. The limitations are several such as the cross-sectional nature of this cohort analysis and the obvious bias of OL-HDF prescription as restricted to in-centre facilities in which elderly and more comorbid patients are treated. The case-control matching was our first response to this bias. Secondly, excluding the units dedicated only to self-care dialysis had no impact on the results that were comparable in pair-matched patients. Moreover, as residual renal function is not routinely assessed in French NephroCare centres, we could not adjust our result on this specific variable. It is important because patients with significant diuresis have lower interdialytic weight

gain and this may impact the fluid status. The vintage was significantly lower in OL-HDF-treated patients in the overall cohort, even after matching. This could suggest that OL-HDF patients had a more important residual diuresis and could be less prone to FO. However, the proportion of new patients with vintage between 3 and 6 months was not different, and vintage was the same after removing the patients treated in self-care dialysis units without changing the findings of the overall cohort. Also, as glycaemia was not available in the routine lab analysis, the sodium gradient data must be interpreted with caution as there were significantly more diabetic patients in the OL-HDF group. Last but not least, data on IDH episodes and nurse intervention were not available and are not reported here. However, this was out of the scope of our study as better haemodynamic tolerance with OL-HDF is now recognized from several RCTs [8, 10, 15].

CONCLUSIONS

Our findings support the absence of hazards of post-dilution OL-HDF on sodium and fluid balance. This is in line with the CV protective effect of OL-HDF reported from the European pooling project of RCTs [7]. Both prescription of dialysate sodium aligned with patient pre-dialysis plasma sodium and the availability of regular bioimpedance measurement are helpful to manage adequately both OL-HDF and HD patients.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

ACKNOWLEDGEMENTS

These data were presented at the HDF Expert meeting in Paris, France, December 2017. The results presented in this article have not been published previously in whole or part. We thank all the nephrologists of the French NephroCare units for the dedicated care they provided to the patients. C.C., D.A., S.S and B.C. are Fresenius Medical Care employees.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Nordio M, Tessitore N, Feriani M *et al.* Mortality in the Veneto population on renal replacement therapy. *J Nephrol* 2013; 26 (Suppl 20): S23–S33
2. Zoccali C, Moissl U, Chazot C *et al.* Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol* 2017; 28: 2491–2497
3. Kayikcioglu M, Tumuklu M, Ozkahya M *et al.* The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant* 2008; 24: 956–962
4. Ronco C, Verger C, Crepaldi C *et al.* Baseline hydration status in incident peritoneal dialysis patients: the initiative of patient outcomes in dialysis (IPOD-PD study). *Nephrol Dial Transplant* 2015; 30: 849–858
5. Davenport A, Cox C, Thuraisingham R. Achieving blood pressure targets during dialysis improves control but increases intradialytic hypotension. *Kidney Int* 2008; 73: 759–764
6. Moret K, Hassell D, Kooman JP *et al.* Ionic mass balance and blood volume preservation during a high, standard, and individualized dialysate sodium concentration. *Nephrol Dial Transplant* 2002; 17: 1463–1469

7. Peters SA, Bots ML, Canaud B *et al.* Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016; 31: 978–984
8. Maduell F, Moreso F, Pons M *et al.* High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013; 24: 487–497
9. REIN Registry: Rapport Annuel 2016. Saint Denis, France: Agence de la Biomédecine, 2019
10. Locatelli F, Altieri P, Andrulli S *et al.* Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. *J Am Soc Nephrol* 2010; 21: 1798–1807
11. Ok E, Asci G, Toz H *et al.* Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 2013; 28: 192–202
12. Steil H, Amato C, Carioni C *et al.* EuCliD—a medical registry. *Methods Inf Med* 2004; 43: 83–88
13. Wizemann V, Wabel P, Chamney P *et al.* The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 1574–1579
14. Grooteman MP, van den Dorpel MA, Bots ML *et al.* Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012; 23: 1087–1096
15. Morena M, Jaussent A, Chalabi L *et al.* Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. *Kidney Int* 2017; 91: 1495–1509
16. Ok E, Asci G, Chazot C *et al.* Controversies and problems of volume control and hypertension in haemodialysis. *Lancet* 2016; 388: 285–293
17. Munoz Mendoza J, Sun S, Chertow GM *et al.* Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? *Nephrol Dial Transplant* 2011; 26: 1281–1287
18. La Milia V, Ravasi C, Carfagna F *et al.* Sodium removal and plasma tonicity balance are not different in hemodialysis and hemodiafiltration using high-flux membranes. *J Nephrol* 2019; 32: 461–469
19. Molina P, Vizcaino B, Molina MD *et al.* The effect of high-volume online haemodiafiltration on nutritional status and body composition: the ProtEin Stores prEservaTion (PESET) study. *Nephrol Dial Transplant* 2018; 33: 1223–1235

Received: 11.4.2019; Editorial decision: 11.6.2019

Nephrol Dial Transplant (2019) 34: 2095–2104
doi: 10.1093/ndt/gfy289
Advance Access publication 8 October 2018

Association of thyroid status prior to transition to end-stage renal disease with early dialysis mortality

Amy S. You¹, John J. Sim², Csaba P. Kovesdy^{3,4}, Elani Streja^{1,5}, Danh V. Nguyen⁶, Gregory A. Brent^{7,8}, Kamyar Kalantar-Zadeh ^{1,5} and Connie M. Rhee¹

¹Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine School of Medicine, Orange, CA, USA, ²Kaiser Permanente Southern California, Department of Nephrology, Los Angeles, CA, USA, ³Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, USA, ⁴Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA, ⁵Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA, USA, ⁶Division of General Internal Medicine, University of California Irvine, Orange, CA, USA, ⁷Division of Endocrinology, Diabetes and Hypertension, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA and ⁸Department of Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Correspondence and offprint requests to: Connie M. Rhee; E-mail: crheel@uci.edu

ABSTRACT

Background. Advanced chronic kidney disease (CKD) patients, including those receiving dialysis, have a high prevalence of thyroid dysfunction. Although hypothyroidism is associated with higher death risk in end-stage renal disease (ESRD) patients, no studies have examined whether thyroid status in the pre-ESRD period impacts mortality after dialysis initiation.

Methods. Among US veterans with CKD identified from the national Veterans Affairs database that transitioned to dialysis over the period from October 2007 to September 2011, we examined the association of pre-ESRD serum thyrotropin (TSH) levels averaged over the 1-year pre-dialysis ('prelude') period with all-cause mortality in the first year following dialysis initiation.

Results. Among 15 335 patients in the 1-year prelude cohort, TSH levels >5.0 mIU/L were associated with higher mortality in expanded case-mix Cox models (reference: TSH 0.5–5.0 mIU/L): adjusted hazard ratio (aHR) [95% confidence interval (CI) 1.20 (1.07–1.33)]. Similar findings were observed for TSH >5.0 mIU/L and mortality in the 2- and 5-year cohorts: aHRs (95% CI) 1.11 (1.02–1.21) and 1.15 (1.07–1.24), respectively. Analyses of finer gradations of TSH in the 1-year prelude cohort demonstrated that incrementally higher levels >5.0 mIU/L were associated with increasingly higher mortality in expanded case-mix models (reference: TSH 0.5–3.0 mIU/L): aHRs (95% CI) 1.18 (1.04–1.33) and 1.28 (1.03–1.59) for TSH levels >5.0–10.0 mIU/L and >10.0 mIU/L, respectively. In the 2- and 5-year cohorts, mortality associations persisted most strongly for