Reviewer's report

**Title:** Online-Haemodiafiltration vs. conventional haemodialysis: a cross-over study.

**Version:** 2  
**Date:** 5 November 2014

**Reviewer:** Claire H den Hoedt

**Reviewer's report:**

Major Compulsory Revisions.

1. **Abstract:** Line 14-16 ‘Patient medications…. Medication’ is unnecessary information for the abstract.

2. **Abstract:** The authors perform HDF, is this predilution/ postdilution. From the conclusion it seems to be predilution, but in the methods it is postdilution.

3. **Introduction:** Line 14-15. In the introduction quite a lot of advantages of HDF are mentioned, regarding to the authors there are only two disadvantages. The reason why this study was conducted is unclear to me, what is the gap in knowledge you want to clarify? What is new information? The aim is not specific about which clinical and biochemical parameters you are looking and why you are interested in these?

4. **Methods:** Line 2 ‘The study protocol was in accord’ no sound English. Furthermore I would like to know if it was ethical according to national standards and to the declaration of Helsinki.

5. **Statistical analysis:** Line 9- Why were only last 2 months of 6 months periods compared? You should use all the measurements you did, making it less probable that external factors other than the dialysis form are the cause for the concentrations of biochemical parameters.

6. **Statistical analysis:** ‘The differences between the 3 periods were investigated using ANOVA and a paired-t test.’ What was the input for the ANOVA? Were it the means of the 3 periods? Or were the delta’s period 1 to 2 and delta 2 to 3 the input for the ANOVA? The p values of which test are in the figures? I do not see the results of paired T-tests in the results section.

7. **Statistical analysis:** Line 34. In my opinion one way correlations do not add information in such complex patients as dialysis patients and no conclusions can follow a correlation without adjustments for confounders. The analysis should be left out.

8. **Statistical analysis:** ‘A receiver operator curve (ROC) was generated for the primary continuous data associated 3 with albumin concentration changes.’ ROC curves are mainly used in diagnostic research (therefore sensitivity and 100-specificity) and are as far is I know no tool to show a correlation/association between the mean convective volume and serum albumin decreases, how it was used in this study. This ROC analysis should be left out.
9. Results line 30-32. Which comparison does the p-value represent? What are the lines depicted in Figure 1 and 2: Confidence intervals? Standard errors or standard deviations? In figure 1 and 2 a large overlap of values is visible, with the mean always projecting over the confidence intervals (?) of the other periods, making a statistically significant difference unrealistic with these numbers.

10. The distribution plot in Figure 3 does not add much information.

11. Results page 6 Line 4-6: ‘Factors associated with lower serum albumin levels during the HDF periods included diabetes (64 vs. 23%, p= 0.04) and lower convection volumes (20.8 vs. 22.9 L, p= 0.04).’ It is not mentioned, which other factors were tested. Furthermore it is not clear what was tested against diabetes, was it the delta (than which delta), was it de albumin concentration, or was there a cut-off value for ‘lower serum albumin’, or was it a negative delta in both periods? As I wrote at point 7 in my opinion the correlation analysis is not useful without adjustments and actually the numbers are to low. The same holds true for the correlation with convection volume and b2m.

12. Figure 5 should be left out.

13. Discussion: The first paragraph with the conclusion might be different if all the measurements of the 6 months periods would be used.

14. Discussion: The part of the discussion on correlation of albumin decrease and diabetes and convection is unnecessary if this analysis is not in the results anymore.

Minor Essential Revisions.

1. Results line 26 ‘Kt/V ranged from 1.64….’ , no standard deviations are mentioned.

2. Discussion: p6 line 31- page 7 line 3: We showed in a long term RCT that no difference in rate of change of serum albumin was found between HDF and low-flux HD (den Hoedt et al., Kidney International 2014). Furthermore it is interesting to note that changes in albumin occur over time as a result of clinical events (both cardiovascular and infectious), changes in nutritional status etc. Patients with diabetes seem to have a larger decline of albumin over time. (den Hoedt, Clin J Am Soc Nephrol. 2014 Feb ). The question is: Is this an effect of time, or an effect of treatment? In our KI study we did not find dan interaction of diabetes on the effect of HDF compared to HD on changes in albumin.

3. Discussion: Line 2-3, page 7, ‘independent of’ suggests adjustments, which were not carried out.

4. Discussion Line 12-14: ‘our observation... explained’. Should be left out.

5. Page 7 Line 17: ‘negative impact of albumin’, Is albumin really causally related to mortality or a marker of worse prognosis?

6. Discussion page 7 Line: 15-28: You could shorten this paragraph by concluding the results of the RCT’s, leaving out the observational studies and not getting into detail about the limitations of these studies, since survival is not the subject of your study.
7. The same holds true for the paragraph of phosphate. (points 6). In this paragraph are also some typo’s.

8. Page 8 Line 28-30, can be left out. Does not add information to your findings. Why do some studie find better haemodynamic control and others not?

9. Page 9 ‘However, the crossover design of the study allowed for highly significant differences between the 3 periods. Besides, we plan to measure albumin loss using an appropriated device for dialysate analysis.’ A cross-over study could give a more sound comparison, but there was also drop –out and the same patients can be in very different state after 6 or 12 months. ‘ Allow for differences’ is a strange formulation.

10. Conclusion page 9. ‘The long-term clinical impact of these biochemical observations, and their association with diabetes’ these parameters have been assessed in large RCT’s.

Discretionary revisions.

1. Introduction Line 9- For your information: Mazairac et al. showed no effect of HDF on Quality of life in a long term randomized controlled trial. CJASN 2013

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.