Author’s response to reviews

Title: Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status

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Author’s response to reviews: see over
October 30th, 2013

Hayley Henderson, PhD
Senior Executive Editor, BMC Nephrology

Dear Doctor Henderson,

Thank you for the opportunity to resubmit our revised review manuscript entitled "Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status".

We found the reviewer's comments very interesting and helpful, and have addressed his concerns in the present manuscript, as described in our point-by-point response below. Because the principal message of our manuscript has been reinforced, we would like to ask you to reassess our revised manuscript for publication in "BMC Nephrology". Further, stimulated by the reviewer's remarks and suggestions, we have now expanded the included figures and changed their order, as the evident difference in fluid overload between overweight and underweight patients does not confer to interdialytic weight gain; a finding which certainly deserves attention.

Additionally, you will find our response to the editorial comments regarding patient participation and trial registration below as requested.

Best regards,

Marcus D. Säemann Medical University of Vienna
Marlies Antlanger Medical University of Vienna
Editorial Comments

1. Consent
Informed consent must be documented in all studies involving human participants. Did you obtain patient consent to participate in this study? Did the ethical committee agree to waive the requirement of consent to participate? If so, can you please forward documentary evidence from the ethical committees to hayley.henderson@biomedcentral.com

As the bioimpedance spectroscopy-based BCM measurements at all three participating centers as well as the analyzed blood collections from the University hospital were carried out per the centers' clinical routine, providing written informed consent was waived for the presented analysis. Concerning this matter, the protocol which was approved by two independent ethical committees explicitly states that the BCM measurement was carried out as part of the routine patient assessment at the three participating centers.

Word-for-word translation of the protocol approved by the ethical committees: '…we are planning on a clinical study on patients with a fluid overload above 15% ECW determined by the bioimpedance measurements with the body composition monitor (BCM) which are carried out as part of the dialysis routine…'

2. Trial Registration Number
The trial registration number included in the Methods section (NCT01416753) does not actually correlate to this cross-sectional study. Could you please provide further information in the methods section to make it clear what that trial showed and how this study follows on from this. Can you please remove this information from the Abstract. Apologies for any confusion caused.

The present study is presenting information on a cross-section of hemodialysis patients at 3 dialysis centers, some of whom constituted the study population of our prospective BVM-Reg trial. The bioimpedance spectroscopy-based BCM measurements were carried out as routine examinations in all centers. The results of these measurements were used as a prerequisite for the BVM-Reg trial where those patients that were detected to be fluid overloaded were randomized to one of three study arms (conventional dry weight reduction, dry weight reduction with ultrafiltration and temperature regulation and dry weight reduction with ultrafiltration and conductivity regulation) in order to remove the excessive fluid ([1] and Abstract 4062, TH-PO588, presented at the ASN 2012, San Diego, CA / USA [Hecking et al., “Blood
Volume-Monitored Regulation of Ultrafiltration in Fluid Overloaded Hemodialysis Patients”). As you requested, we removed the registration number from the Abstract.
Point-by-point response

Reviewer's report
Title: Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status
Version: 2
Date: 30 July 2013
Reviewer: Paul Chamney

Reviewer's report:
MAJOR COMPULSORY REVISIONS
None.

MINOR ESSENTIAL REVISIONS
1) Page 2, ABSTRACT, Background. The sentence “We hypothesized that a relationship exists between fluid overload and [i] cardiovascular and [ii] inflammatory laboratory parameters” Could this sentence be re-worded? Does this mean that cardiovascular parameters may linked to fluid overload AND inflammatory parameters?

Thank you for this comment; we changed this sentence, as follows; “We hypothesized that a relationship exists between fluid overload and [i] cardiovascular parameters as well as between fluid overload and [ii] inflammatory laboratory parameters” The relationship between fluid overload and cardiovascular parameters is thus to be described independently of the relationship between fluid overload and inflammatory markers.

2) Page 2, ABSTRACT, Results. Some minor punctuation to sort out (spaces, full stops to be omitted/added). Acronyms such as FO need only be written in full once in abstract, i.e. ‘Fluid overload’ repeated several times in abstract and use of FO might help with word/character count if close to limit.

Thank you, your remarks. We now corrected the punctuation and avoided the use of acronyms in the abstract.

3) Page 2, ABSTRACT, Conclusions, first sentence. “Fluid overload in hemodialysis patients correlated inversely with body mass index and serum albumin, indicating that dry weight was inadequately prescribed and/or difficult to achieve in overweight patients.” Several points to clarify and possibly the main finding/message of the manuscript: Both NT-proBNP and Rel OH show the same relationship with BMI which is a consistent result. The inference is that high BMI subjects have a relatively lower dry weight (possibly in the direction of dehydration). Associated with the lower Relative fluid overload is the lower TnT in the high BMI group. Is it a problem of inadequate dry weight prescription or a consequence of other factors? If the weight of patients is reduced to the lowest
tolerated weight then it may be that the high BMI patients tolerate a relatively lower hydration status. Possibly there is a tendency to dry high BMI subjects further because it may be more difficult to differentiate body fat and free fluid as you have suggested in the discussion. Possibly the subjects in low to normal BMI range are either insufficiently dry (dry weight set too high) or the tolerance to fluid removal is poorer (as highlighted in your feedback) compared with high BMI subjects. The relationship between albumin and FO is as expected (presumably a dilution effect as you mention later) but possibly not sufficiently important to justify inclusion here in the abstract conclusion. Suggest the first sentence is replaced with something like: “Fluid overload in HD patients by different methods was found to be lower in patients with high body mass index, indicating a tendency to achieve lower dry weight.”

We agree with you that both NT-proBNP and FO (and also, but to a lesser extent troponin T) show a correlation with BMI, in that they are all higher in patients with lower body weight. We speculate that this is indeed partly due to inadequate dry weight prescription in these patients. In line with this hypothesis, the presence of pre-existing coronary artery disease does not correlate with higher troponin T levels, as has been suggested previously by Velasco et al [2]. Overweight patients naturally appear more fluid overloaded even though they might not be, while slim patients are often misjudged due their cachectic physique, while they still have pretibial edema or pulmonary congestion which are often overlooked.

The second factor potentially contributing to our finding is - as you suggested - that patients with low BMI do not tolerate fluid removal as well as high BMI patients, possibly in consequence of a poorer general state of health.

We thank you for the proposed rewording and now state: ‘Fluid overload in HD patients was found to be lower in patients with high body mass index, indicating that dry weight was inadequately prescribed and/or difficult to achieve in overweight patients.’ This statement should allow to account for the 2 distinct mechanisms thought responsible, i. e. false clinical assessment and clinical inability to reach the prescribed weight.

4) Page 10, Results. It would be useful to expand Table 1 with some additional information on comorbidity distribution in each centre, particularly % of diabetic patients and a measure such as Charlson Comorbidity Index. This would help support the statement in the discussion later: “The highest rate of fluid overload was detected in the University-based dialysis unit, possibly because patients from this center comprised a collective with more comorbidities and were therefore more prone to chronic fluid overload” Furthermore, was there a higher prevalence of comorbid conditions in those patients in the fluid overloaded
We agree with your remark that comorbidity can constitute an important factor in such an analysis. We have calculated the Charlson comorbidity index for the 126 patients from the University-based hospital. This score, which predicts a patient's 10-year mortality incorporates several important morbidities which are highly prevalent in maintenance hemodialysis patients, including congestive heart failure, diabetes mellitus, peripheral vascular disease and chronic lung disease.

On page 11, the second paragraph includes the following statement: 'Similarly, patient comorbidities represented by the Charlson comorbidity index (CCI) [31], showed a significant association with fluid overload, as the CCI was significantly lower in patients exhibiting normohydration (mean 4.06 ± 2.04) compared to those with percental fluid overload (mean 4.96 ± 2.27 (p=0.024)).' This finding has now also been incorporated into Table 2. Further, a multiple regression analysis was run to predict NT-proBNP from percental fluid overload and comorbidities represented by the Charlson Comorbidity Index. These variables statistically significantly predicted NT-proBNP ($F(2,115)=13.665$, $p<0.001$, $r=0.438$) but, interestingly, only fluid overload added statistically significantly to the prediction with a $p<0.001$ ($p=0.059$ for CCI).

Unfortunately, it was not possible to access the data necessary to calculate the Charlson Comorbidity Index from the two smaller dialysis centers due to documentation incompatibilities.

5) Page 12, Results. If available, relative inter-dialytic weight gain (IDWG) would be interesting to report in terms of BMI groupings. (Relative IDWG would be the absolute weight gain normalised to body weight) If relative IDWG in high BMI group is similar to low & mid BMI groups, it could be argued that better hydration status is achieved in the high BMI group. On the other hand, if relative IDWG is higher in the high BMI group, this may indicate a tendency for dehydration to be encountered. Either way this may shed further light regarding how dry weight is set/should be set, what is tolerated and how patient specific requests play out in the clinical setting.

Thank you for this very important and interesting comment! We have now calculated relative IDWG for all patients and found that no difference exists between the various BMI groups whereas fluid overload is significantly lower in this group (especially in patients with a BMI > 30 kg/m²), which undermines the hypothesis that this specific patient group of heavier patients does indeed have a better hydration status. Again,
the reason for this finding can only be speculated about, given that several factors such as patient assessment, patients’ own preference regarding dry weight setting and ultrafiltration tolerance influence the dry weight determination.

As for your request, we have now given this issue more attention and have replaced the original Figure 1 with Suppl. Fig. 1 and included rel. IDWG and compared it between the respective BMI groups; no statistically significant differences could be found, while strong differences between the respective BMI groups were seen regarding fluid overload.

6) Page 14, Discussion. “This interesting phenomenon might be explained...” It is not clear to which effect this sentence refers (as the previous paragraph refers to low weight malnourished patients). If I understand the meaning correctly, it might be better to start with “The observation of lower fluid overload in high weight/ high BMI subjects might be explained....”

Thank you for the remark; we reworded this sentence and now state on page 15, first paragraph: ‘This observation might be explained by clinical misclassification - patients appear fluid overloaded due to their physique, when they are in fact normo- or even dehydrated - and/or deliberately insist on dry weight reduction despite normohydration. Clearly, further studies are necessary to delineate the underlying mechanisms of these observations.’

7) Page 17, Discussion, Conclusion, last paragraph. Break the sentence into two sentences, i.e. “Fluid overload has emerged as a parameter that strongly correlates with cardiovascular biomarkers but seems to be independent of inflammation as well as elevated blood pressure in hemodialysis patients. Therefore we propose that fluid overload could be defined as an independent single entity - equivalent to a biomarker - with the potential to be introduced for intervention guidance.”

We implemented your suggested change, thank you.

8) Arguably, the most interesting results are in supplementary Figure 1 and these to a large extent are different representations of the original Figure 1. Thus there is some duplication, so the suggestion would be to substitute the relevant x-y plots with the BMI box plots. There is no reference in the main text to the supplementary figures.
We agree that the findings from Suppl. Fig. 1 deserve more attention in the manuscript as they have gained importance throughout the development and revision process of this article. We have therefore opted for a substitution of the original Fig. 1 with Suppl. Fig. 1 and have changed the respective references in the manuscript.

**DISCRETIONARY REVISIONS**

1) **Page 14, Discussion.** “These findings are in accordance with our results enforcing the view that underweight patients are more susceptible for fluid overload, whereas adipose patients tend to be in an underhydrated condition.” Any suggestions why underweight (presumably malnourished) are more susceptible for fluid overload? Is this additional fluid ‘normal’ for malnourished patients, does the dry weight tend to be set too high in these patients or is there a problem with tolerance (CV instability) when attempts are made to normalise the fluid status?

It appears likely that underweight patients are simply in a worse state of health. As you state, these patients are presumed to be malnourished, most likely as a consequence of systemic illness such as cardiovascular morbidity (heart failure, ischemic cardiac disease), any oncologic disease or recurring infections. One important, potentially contributing factor might be systolic dysfunction in terms of cardiomyopathy with decreased ejection fraction predisposing this set of patients to severe intradialytic hypotensive episodes which, in turn, lead to an artificial dry weight increase as patients - and doctors - aim at avoiding these potentially dangerous incidents. It can therefore be suspected that psychological effects play an important role regarding the dry weight setting, both in terms of patient preference as well as the doctor’s clinical assessment.

2) **Page 14 Discussion.** The order of the two paragraphs starting “This interesting phenomenon might be explained...” and “The so-called reverse epidemiology in the hemodialysis population” respectively might be better swapped. i.e. first discuss the observations of fluid, low weight, high weight and the findings of others etc., then offer your explanation of why these effects may be the consequence of clinical practice.

We changed the order of the two paragraphs as you suggested!

3) **Page 16, Discussion.** Can you speculate why D-Dimer might be increased in fluid overloaded subjects?
Many factors have shown to significantly associate with an increase of D-dimer levels. Among these, many represent systemic illness and/or severe morbidity such as immobility, active malignancy, prior venous thromboembolism or recent surgery [3].

Approximately two thirds of hemodialysis patients have been shown to test positive for D-dimer; this finding could be reproduced by our study: 69.2% of our analyzed patients had positive D-dimer values. As reviewed in the Discussion section (p. 16, second abstract), D-Dimer tends to be elevated more often in patients with a central venous catheter, which itself is generally regarded a state of increased risk for thrombosis and pulmonary embolism, potentially also due to the anatomical proximity to the pulmonary vasculature. As our fluid overloaded patients had higher levels but not a higher rate of central catheters, it can be speculated that these patients have higher rate of subclinical thrombosis and fibrinolysis, irrespective of the presence of a catheter. This might again be due to their aforementioned worse state of health: patients with a Charlson comorbidity index above the mean (i.e. a CCI of 5 or higher) had significantly higher D-Dimer levels (2.18±3.19 vs. 0.99±0.12, p=0.005, µg/ml).

