A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients

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Keywords: body composition, bioimpedance, haemodialysis, peritoneal dialysis, volume status

ABSTRACT

Background. Volume status, lean and fat tissue are gaining interest as prognostic predictors in patients on dialysis. Comparative data in peritoneal dialysis (PD) versus haemodialysis (HD) patients are lacking.

Methods. In a cohort of PD (EuroBCM) and HD (Euclid database) patients, matched for country, gender, age and dialysis vintage, body composition was assessed by bioimpedance spectroscopy (BCM, Fresenius Medical Care). Time-averaged volume overload (TAVO) was defined as the mean of pre- and post-dialysis volume overload (VO), and relative (%) (TA)VO as (TA)VO/ECV.

Results. Four hundred and ninety-one matched pairs (55.2% males, median age 60.0 years) were included. The body mass index (BMI, PD = 26.5 ± 4.7 versus HD = 25.9 ± 4.6 kg/m², P = 0.18 in males and 27.4 ± 5.8 versus 27.5 ± 6.6 kg/m², P = 0.75 in females) and fat tissue index (males: 11.5 ± 5.3 versus 11.4 ± 5.4 kg/m², P = 0.90, females: 14.8 ± 6.7 versus 15.4 ± 7.2 kg/m², P = 0.30) were not different in PD versus HD patients, whereas the lean tissue index (LTI) was higher in PD versus HD patients (males: 14.5 ± 3.4 versus 11.5 ± 3.1 kg/m², P = 0.001, females: 12.6 ± 3.3 versus 11.5 ± 2.6 kg/m², P < 0.0001). VO/extracellular water (ECW) was not different between PD versus just before the HD treatment (males: 10.8 ± 12.1 versus 9.2 ± 10.2%, P = 0.09; females: 6.5 ± 10.8 versus 7.7 ± 9.4%, P = 0.19). The relative TAVO was higher in...
INTRODUCTION

There is increasing interest in objective evaluation of volume status as an adequacy parameter in patients on renal replacement therapy (RRT) [1, 2]. Volume overload has been linked to heart failure [3], left ventricular hypertrophy [4, 5], sleep apnoea [6] and mortality [7]. It is also associated with hypoalbuminaemia [8], another negative predictor of long-term outcome. On the other hand, volume deficiency is related to decreased quality of life (cramps, dizziness, fatigue...), and is also thought to be associated with an accelerated loss of residual renal function [9]. In addition, further reducing volume status in some hypertensive RRT patients—on the basis that hypertension is generally considered as a marker of volume overload [10]—may lead to severe diastolic hypotension, decreased coronary perfusion [11] and even sudden cardiac death, particularly in those normovolaemic patients in which increased blood pressure (BP) values are mainly caused by increased vascular stiffness [1, 12]. Adequate assessment and management of volume status are critically important, and clinical parameters including blood pressure are not reliable enough to guide treatment decisions. There is thus a need for tools that evaluate volume status in the routine clinical setting, and different methods have been proposed and investigated during the last decade. Some of these methods measure the circulating volume, and its effect on cardiac pre-load (e.g. chest X-ray, inferior vena cava diameter and collapsibility, lung interstitium ultrasound [13, 14]), other methods evaluate more the capillary refill capacity during haemodialysis (HD) [15, 16], or are based on biochemical markers of atrial dilatation, difficult to interpret in anuric patients (ANP, BNP, pro-BNP, NT-proBNP) [17]. Using multi-frequency bioimpedancemetry allows us to estimate ECW and total body water, and thus indirectly also intracellular water, using mathematical modelling [18]. In this way, not only the volume status, but also lean body weight and fat mass can be derived [19], allowing in fact a bedside analysis of body composition. This is of great interest, as there is compelling evidence for an association between volume status, inflammation and nutritional status [20].

Long-term outcomes in peritoneal dialysis (PD) and HD have been reported to be equal, with a slightly better outcome for PD patients during the first years [21, 22]. This prognosis has been reported despite suggestions that PD patients are much more volume overloaded than HD patients [23] and possibly more obese (due to absorption of the intraperitoneal glucose). So far, no comparative data from large cohorts on body composition in PD versus HD are available. This observational, hypothesis generating cohort study was set up to compare body composition using bioimpedance spectroscopy in a large international cohort of PD and HD patients. We hypothesized that differences in body composition between subgroups can potentially lead to a better understanding of the differences in mortality between subgroups of patients on the two dialysis modalities.

MATERIALS AND METHODS

Patients

The data of the PD patients were collected in the EuroBCM study [1]. This was a cross-sectional, observational, multicentre trial in 28 centres in six European countries (Belgium, France, Poland, Romania, UK and Switzerland). PD patients from Belgium and Switzerland were excluded in the current analysis as no data from HD patients were available from these countries. In each selected centre, all prevalent patients on PD were assessed for eligibility for inclusion (prevalent cross-sectional cohort approach). This trial has been registered at the Cochrane Renal Group trials registry (http://www.cochrane-renal.org) under the number CRG110800153.

The HD patients used for the matching of the PD patients were extracted from a large clinical database (EuCliD—Fresenius Medical Care, NephroCare) with more than 20 000 patients with BCM measurements available. The country matched patients (5236 HD patients available) served as a pool of controls for the matching for age, gender, dialysis vintage and country. The representativeness of the final HD sample (n = 491) to the country-matched HD patients (n = 5236) was assessed by comparing age, gender distribution and dialysis vintage.

In a previous study, a Caucasian population of 1247 male and female subjects was collected, which was used as a presumed healthy reference population [18]. The subjects were equally distributed over the complete age range. They represent a ‘presumably healthy reference’ population—but no detailed clinical questionnaire or additional laboratory tests were performed. The age-dependent median of the body composition parameters of this population is used as a reference in this analysis.

BCM measurement

All body composition measurements were performed with the BCM (Body-Composition-Monitor; Fresenius Medical Care), a well-validated tool [24, 25]. The BCM measures the impedance spectroscopy at 50 different frequencies between 5 and 1 MHz. Electrodes were attached to one hand and one foot at the ipsilateral side with the patient in a recumbent position. In the PD patients, measurements were timed as described previously [1]. All HD patients were measured directly before an HD session.

Volume overload (VO) was derived from the impedance data based on a physiological tissue model [18, 19]. This model separates the patient’s body into three compartments—volume overload, normohydrated lean tissue and normohydrated fat tissue. Absolute volume overload represents the difference between the measured amount of extracellular water.
and the amount of water expected in normohydrated tissue conditions [19]. The absolute volume overload was then normated to the measured extracellular volume (VO/ECV), a parameter denoted as ‘relative volume overload’ (relative VO), expressed in percentage, to allow a more objective comparison between patients with different anthropometric features. To incorporate the change in volume overload with time between the dialysis sessions in the HD patients, we also defined a ‘time averaged volume’ (TAVO) as the mean of the pre-and post-dialytic volume overload, where the post-dialytic volume overload was calculated as the pre-dialysis volume overload minus the intradialytic ultrafiltration. Analogous to the body mass index (BMI), the lean tissue index (LTI) and fat tissue index (FTI) are calculated by dividing the measured normohydrated lean or fat tissue mass, respectively, by the squared height of the patient.

Procedure for matched pairing

For matching of cases and controls, a publicly available SAS macro (%gmatch, Biostatistics department, MAYO Clinic) was used, which was adapted to the specific conditions of our study. For each PD patient, a corresponding HD patient was identified from the same country of the same gender and with a difference in age and dialysis vintage of less than 3 years and 6 months, respectively. For 41 patients, no suitable control was available, for the other 491 patients one or more controls were identified. In case of more than one control fulfilling the matching criteria, a random selection was applied. The same procedure was applied to the subgroup of patients with confirmed diabetes (PD: n = 136, HD: n = 702). To enable a sufficient number of matches, the criteria were relaxed to age difference <5 years and vintage difference <12 months; 126 matched pairs were found for this subgroup analysis. Results of the subgroup analysis are presented in the Supplementary material.

Statistical analysis

For all continuous variables, mean and standard deviation are given unless otherwise noted (e.g. median and min/max for skewed distributions). Statistical comparisons between PD and HD patients are based on paired t-tests using pairs as resulted from matching, for all tests where pairing was not feasible, two-sample t-tests were used. For correlations analysis, Pearson’s r was calculated. In a multiple linear regression, the simultaneous influence of several variables on VO was examined. All analyses were done with SAS V 9.2

RESULTS

Demographic and clinical data are presented in Table 1, separately for the PD and HD cohorts. As expected, because of the matching procedure, no differences in age or dialysis vintage were observed between the PD and HD cohorts. There was no difference in systolic BP between PD and HD patients, but diastolic BP was higher in PD patients. The majority of PD patients were treated by continuous ambulatory peritoneal dialysis (CAPD) (75.9%), whereas the majority of HD patients were treated by standard HD (84.1%) and only a minority by online haemodiafiltration.

When comparing HD patients from the matched cohort (n = 491) with the HD patients from the database who were not used for matching, it became evident that the patients used for the matching have comparable age (59.2 ± 13.7 versus 58.1 ± 15.0 years), a comparable intradialytic weight loss (2.10 ± 1.05 versus 2.07 ± 1.06 kg) and a comparable BMI

<table>
<thead>
<tr>
<th>Table 1. Description of the matched PD and HD population</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (n = 491)</td>
</tr>
<tr>
<td>Gender male (%)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Vintage (months) (min–max)</td>
</tr>
<tr>
<td>France (patients/centres)</td>
</tr>
<tr>
<td>UK (patients/centres)</td>
</tr>
<tr>
<td>Poland (patients/centres)</td>
</tr>
<tr>
<td>Romania (patients/centres)</td>
</tr>
<tr>
<td>Confirmed Diabetes</td>
</tr>
<tr>
<td>Treatment Information</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
</tr>
<tr>
<td>HD (g/dL)</td>
</tr>
</tbody>
</table>

Where applicable the mean and the standard deviation are shown.
(26.7 ± 5.6 versus 26.1 ± 5.3 kg/m²), but a lower dialysis vintage (24.2 (0.5–183.2) versus 38.4 (0.0–467.3) months, respectively.

**Volume**

The relative volume overload was not different between PD versus HD patients. In the male cohort (relative), TAVO was higher in PD versus HD patients. In the subgroup with confirmed diabetes, male PD patients presented a lower relative VO as HD patients—otherwise all other results were confirmed, see Supplementary material.

VO was in a multivariate model independently predicted by male gender, PD as dialysis modality and confirmed diabetes (p of the model < 0.0001), but still a lot of variability in VO remains unexplained by our model (R² = 0.10) and may thus be attributed to other causes.

The absolute (l) and relative (% of ECW) volume overload for PD patients, HD patients before dialysis and time-averaged fluid overload in HD patients are represented in Figure 1, separately for males and females. As can be observed, the lower mean VO in HD patients was achieved by creating a severe dehydration in a substantial (62.5% < 0 L and even 37.5% <−1 L) part of patients after the dialysis session, resulting in a negative TAVO. In contrast, in the PD patients, a negative VO was only rarely observed (20.8% < 0 L and 7.5% <−1 L).

**Body composition**

Table 2 represents the body composition parameters, separately for the PD and HD population, and also segregated by gender. There was no difference in BMI or FTI between PD and HD patients. The LTI was higher in PD versus HD patients, both in males and in females, and all results were similar in the subgroup with confirmed diabetes (see Supplementary material).

We analysed whether body composition or the difference in body composition between PD and HD was associated with either age or dialysis vintage (Table 3), but no firm associations were observed. Most noteworthy is the absence of an association between dialysis vintage and the difference between PD and HD in FTI and VO, see Table 3. The body composition in terms of BMI, LTI and FTI in the PD and HD cohorts is represented in Figure 2, separately for males and females. The comparison between the PD and HD patients and the healthy reference population is shown in Figure 3.

**DISCUSSION**

In this international multi-centric matched pair cohort study, we found that fluid overload (VO/ECW) was equally present...
in PD and in HD patients just before dialysis. The TAVO was, however, significantly lower in the HD patients. Irrespective of dialysis modality, male gender and confirmed diabetes were independently associated with fluid overload. In contrast to general belief, BMI and fat tissue mass were comparable between PD and HD patients, while the lean tissue mass was higher in the PD patients (independent of the diabetic state). Lean tissue mass seems to be impaired, while fat tissue is increased in dialysis patients when compared with the general population.

For a long time, the emphasis of ‘adequate dialysis’ [26] was placed on small solute clearance, mostly expressed as昆/v. Evidence is compiling that increasing small solute clearance does not lead to improved outcomes [27, 28]. In HD, it appears that increasing ‘t’ leads to improved solute removal even when昆/v remains equal [29]. It is well conceivable that

### Table 2. Body composition in the HD and PD patients

<table>
<thead>
<tr>
<th></th>
<th>Male PD (n = 271)</th>
<th>Female PD (n = 220)</th>
<th>P</th>
<th>Male HD (n = 271)</th>
<th>Female HD (n = 220)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (pre) (kg)</td>
<td>77.5 ± 15.2</td>
<td>69.1 ± 15.1</td>
<td>0.06</td>
<td>75.2 ± 15.9</td>
<td>69.0 ± 16.9</td>
<td>0.92</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 4.7</td>
<td>27.4 ± 5.8</td>
<td>0.18</td>
<td>26.0 ± 4.6</td>
<td>27.5 ± 6.6</td>
<td>0.75</td>
</tr>
<tr>
<td>FTI (kg/m²)</td>
<td>11.5 ± 5.3</td>
<td>14.8 ± 6.7</td>
<td>0.90</td>
<td>11.4 ± 5.4</td>
<td>15.4 ± 7.2</td>
<td>0.30</td>
</tr>
<tr>
<td>LTI (kg/m²)</td>
<td>14.5 ± 3.4</td>
<td>12.6 ± 3.3</td>
<td>0.001</td>
<td>13.7 ± 3.1</td>
<td>11.5 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VO (L)</td>
<td>2.3 ± 2.7</td>
<td>1.1 ± 1.9</td>
<td>0.005</td>
<td>1.7 ± 1.9</td>
<td>1.2 ± 1.5</td>
<td>0.71</td>
</tr>
<tr>
<td>TAVO (L)</td>
<td>2.3 ± 2.7</td>
<td>1.1 ± 1.9</td>
<td>&lt;0.0001</td>
<td>0.6 ± 1.9</td>
<td>0.2 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rel. VO (%) (VO/ECV)</td>
<td>10.8 ± 12.1</td>
<td>6.5 ± 10.8</td>
<td>0.09</td>
<td>9.2 ± 10.2</td>
<td>7.7 ± 9.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Rel. TAVO (%) (TAVO/ECV)</td>
<td>10.8 ± 12.1</td>
<td>6.5 ± 10.8</td>
<td>&lt;0.0001</td>
<td>3.2 ± 11.2</td>
<td>1.3 ± 10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECV (L)</td>
<td>19.3 ± 3.6</td>
<td>15.6 ± 3.0</td>
<td>&lt;0.0001</td>
<td>17.8 ± 3.1</td>
<td>14.9 ± 2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>ECV/height (L/cm)</td>
<td>0.11 ± 0.02</td>
<td>0.10 ± 0.02</td>
<td>&lt;0.0001</td>
<td>0.10 ± 0.02</td>
<td>0.09 ± 0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Weight (pre), predialysis weight for the HD patients; BMI, body mass index; FTI, fat tissue index; LTI, lean tissue index; VO, volume overload; TAVO, Time-averaged volume overload; ECV, extracellular volume. For all parameters, the mean and the standard deviation are shown.

### Table 3. Correlation table between the mean value of the pair, the difference between the pair and the mean age and the mean dialysis vintage of the pair (diff and mean refer to within the PD/HD pair)

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficient with mean pair age (years)</th>
<th>Correlation coefficient with mean pair dialysis vintage (log scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pair BMI (kg/m²)</td>
<td>0.16</td>
<td>−0.006</td>
</tr>
<tr>
<td>Mean pair FTI (kg/m²)</td>
<td>0.31</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean pair LTI (kg/m²)</td>
<td>−0.39</td>
<td>−0.09</td>
</tr>
<tr>
<td>Mean pair TAVO (L)</td>
<td>−0.01</td>
<td>−0.03</td>
</tr>
<tr>
<td>Mean pair TAVO/ECW (%)</td>
<td>0.02</td>
<td>−0.02</td>
</tr>
<tr>
<td>Mean pair albumin (n = 401) (g/L)</td>
<td>−0.16</td>
<td>0.12</td>
</tr>
<tr>
<td>Difference pair FTI (kg/m²)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Difference pair LTI (kg/m²)</td>
<td>−0.05</td>
<td>−0.06</td>
</tr>
<tr>
<td>Difference pair TAVO (L)</td>
<td>−0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Difference pair TAVO/ECW (%)</td>
<td>−0.004</td>
<td>0.07</td>
</tr>
<tr>
<td>Difference pair albumin (n = 401) (g/L)</td>
<td>−0.07</td>
<td>0.06</td>
</tr>
</tbody>
</table>
increasing ‘t’ also allows better maintenance of volume status, as it allows slower ultrafiltration, itself being associated with improved outcomes [5]. In the field of PD, better volume removal [30], not improved small solute clearance [27], was associated with improved outcomes. Head-to-head comparisons of PD versus HD with regard to volume status are scanty [23, 31]. All recent publications which aim at comparing the volume status have limitations with respect to the analysed patient numbers (n < 100), and significant differences in the age and dialysis vintage of compared patient populations. The current paper is the first to present a matched pair analysis of a large PD and HD population.

In the matched pair analysis of this large cohort, VO in PD patients was comparable with that of HD patients just before the dialysis session, but was higher when the TAVO was considered. However, this came at the expense of dehydration of a substantial part of HD patients. This observation might well explain why residual renal function is less well preserved in HD when compared with PD patients. Irrespective of treatment modality, male patients and diabetics were more volume overloaded. For diabetics, this was attributed to their increased thirst due to residual hyperglycaemia, leading to increased volume intake. Also in other PD cohorts, diabetes has been associated with VO [32]. In HD cohorts, diabetic patients tend to gain more weight in between dialysis sessions, and this is independent of their salt intake, leading to hyponatraemia in the pre-dialysis setting [33]. Although the finding of higher VO in males is consistent in most cohorts [1, 32], the underlying reasons remain unclear. As VO is associated with increased mortality, the higher volume overload in males versus females might explain to some extent the reported higher mortality in male dialysis patients, irrespective of their treatment modality [21]. Most authors attribute this higher VO in males to a lesser compliance of male patients to the dietary restrictions, although formal analysis fails to corroborate this hypothesis [34].

Despite the higher VO in PD patients, there were no differences in systolic BP. However, it has been demonstrated before that, although there is a statistically significant association between fluid overload and systolic BP, this association does not hold true for an important percentage of patients, due to confounding by vascular stiffness and congestive heart failure [1], as can also be seen in Figures 1 and 2 in the Supplementary material.

Of note, PD patients tended to have a higher diastolic BP, and thus a lower pulse pressure, when compared with HD patients. This might be a representation of the lower degree of
vascular stiffness that has been observed in PD versus HD patients [35].

There is a widespread belief that the glucose absorbed during the PD dwell leads to an increase in weight and fat mass. BMI was not higher in PD when compared with HD patients in this cohort of age, gender and dialysis vintage matched patients. We also did not observe an association between BMI or FTI and dialysis vintage which is another important fact to note against intuitive expectations. Our data demonstrates that fat mass is increased both in PD and in HD patients when compared with a healthy reference population not on dialysis, but that there is no difference in PD versus HD patients. On the other hand, it is clear from our data that patients on dialysis have a reduced lean tissue mass when compared with the general population not on dialysis, an effect that is much more mitigated, however, in patients on PD. It can be speculated that the presence of an additional caloric load because of the absorbed glucose protects the PD patients from using muscle protein as an energy source. Our data support the idea that HD patients are severely protein and calorie malnourished, whereas PD patients seem to be relatively protected from catabolism through their more appropriate caloric load associated with the continuous glucose absorption. Also, PD patients have a better correction of their metabolic acidosis when compared with HD patients, due the continuous infusion of buffer, and growing evidence suggests that correction of acidosis leads to improvement of muscle mass and nutritional status [36, 37]. The data in Table 3 reveals that PD patients do not accumulate more VO and fat mass in the time they are on the PD therapy when compared with the HD patients. In this respect, there is no difference between the dialysis modalities.

The data indicate that male patients are more susceptible to VO and additionally to the loss in lean tissue mass when compared with the healthy reference population. These differences in the development of body composition between male and female subjects open a wide field of future research to analyse if genetic, hormonal or psychological effects are explanations for these observations.

**Limitations**

No detailed clinical questionnaire or additional laboratory tests were available from the healthy reference population. If anything, deviation between the results of the cohorts on RRT and the truly healthy population is thus underestimated in this approach. Only limited information was available on the comorbid conditions of the patients. No information on the clinical presence of oedema was collected during this study. This is mainly due to the origin of the HD patients data, with only limited availability of detailed background patient information in this cohort. We performed a subgroup analysis in the patients with confirmed diabetes—all major findings were confirmed. In the future, it would be important to take into account also the presence of cardiac failure and residual renal function, although both these parameters cannot be considered mere ‘confounders’ as they can both result or cause VO and malnutrition. This hypothesis generating matched pair analysis of PD and HD patients opens the field for future studies, as uncertainty remains about the causal relations between the observed results.
Conclusion

Volume overload is a frequent problem in PD and HD patients. It seems that PD patients have a higher TAVO when compared with HD patients. However, VO immediately before the HD session was equal to PD, and the lower TAVO is thus obtained at the expense of a certain period of underhydration immediately after the HD session in a substantial part of the HD patients. Both PD and HD patients have increased fat mass and decreased lean tissue mass when compared with a healthy reference population. These changes in body composition seem to be triggered by the underlying uremic state, and not by the treatment modality itself. Most importantly PD patients do not present an increased BMI or fat mass when compared with HD patients, despite the glucose overload in PD patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

P.W. and V.S. are employees of Fresenius Medical Care, Germany. Adrian Covic and Monika Lichodziejewska-Niemierko are employed at dialysis units of Fresenius Medical Care. W.V., K.C., S.F. and C.V. received travel grants from Fresenius Medical Care, Baxter and Gambro on different occasions.

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Received for publication: 16.3.2013; Accepted in revised form: 26.5.2013

Longer interdialytic interval and cause-specific hospitalization in children receiving chronic dialysis

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Keywords: admission, end-stage renal disease

ABSTRACT

Background. Previous studies have demonstrated a relationship between longer interdialytic intervals and hospitalization for cardiovascular causes in adults maintained on hemodialysis (HD). This association has not been previously demonstrated in children. We hypothesized that the risk of hospitalization for hypertension (HTN), fluid overload or electrolyte abnormalities would be increased on the days following a longer interdialytic interval in children.