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Causes and Consequences of Interdialytic weight gain

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Key Words
Interdialytic weight gain • Haemodialysis • Nutritional status • Blood pressure

Abstract

Background/Aims: Higher interdialytic weight gain (IDWG) is associated with higher predialysis blood pressure and increased mortality. IDWG is also increasingly being recognized as an indicator of nutritional status. We studied in detail the associations of various patient factors and nutritional parameters with IDWG. Methods: We collected data during one week for IDWG and hemodynamic parameters in 138 prevalent adult haemodialysis patients on a thrice-weekly haemodialysis schedule. A multivariate linear regression analysis was employed to identify factors that are associated with IDWG. Results: The mean (±SD) age was 62.5 (±18.2) years, 36% were female, 36% had diuresis, and 23% had diabetes. Patients in the highest IDWG tertile were significantly younger, more frequently male, and had a significantly higher subjective global assessment score (SGA). A higher IDWG as a percentage of body weight (%IDWG) was associated with a younger age, greater height and weight, absence of diuresis, and lower postdialysis plasma sodium levels. The model with these five parameters explained 37% of the variance of %IDWG. Predialysis, intradialysis, and postdialysis diastolic blood pressure was significantly higher in the highest tertile of IDWG. Conclusion: The most important associations of %IDWG are age, height, weight, diuresis, and postdialysis sodium. Patients with the highest IDWG have significantly higher diastolic blood pressures.

K.J.R. Ipema and J. Kuipers contributed equally and therefore share first authorship.
Introduction

Interdialytic weight gain (IDWG) is the result of salt and water intake between two haemodialysis sessions. IDWG is used as a parameter for fluid intake while taking the daily urine output into account [1, 2]. A higher IDWG is associated with higher predialysis blood pressure [2, 3], greater intradialytic reductions in blood pressure as a result of higher ultrafiltration rates [4], and increased mortality [5-7].

At the same time, IDWG is increasingly being recognized as an indicator of nutritional status [2, 8-11]. Malnutrition is considered as a major complication among haemodialysis patients and can result in increased morbidity and mortality [12, 13]. Causes of malnutrition in dialysis patients are multi-factorial and include reduced appetite and food intake [12, 14, 15], protein-energy wasting as a result of chronic inflammation [16], and reduced physical activity [17]. Several studies demonstrated that a greater IDWG is directly associated with improved nutritional status [2, 10, 11]. Usvyat et al. recently showed that IDWG began to decline a year before death indicating that a decrease in IDWG has short-term adverse prognostic significance [18]. Thus, on the one hand, higher IDWG is associated with adverse effects such as higher blood pressure, however, on the other hand, higher IDWG may be associated with favourable effects such as better nutritional status.

The goal of this study was to identify the most important associations of a high IDWG in an effort to disentangle its ambiguous associations. To achieve this, we meticulously examined a cohort of 138 patients on a thrice-weekly haemodialysis schedule.

Patients and Methods

Participants and Study design

We retrospectively collected data from 138 haemodialysis patients scheduled for thrice weekly haemodialysis who were older than 18 years and had been undergoing haemodialysis treatment for at least three months. Since IDWG tends to fall before death [18] and this may confound the relationship between IDWG and nutritional status in patients with a short life expectancy, we excluded patients who died within 6 months after collection of the data. We used data of IDWG, various nutritional parameters, and hemodynamic measurements during one week from the patients’ records in November 2012. The study was performed in accordance with the principals of the Declaration of Helsinki and guidelines for Good Clinical Practice.

Dialysis regimens and Dietary consultation

Dialysis treatment consisted of conventional haemodialysis or home haemodialysis thrice weekly for four to five hours with blood flows and dialysate flows of 250-350 ml/min and 500-700 ml/min, respectively. All patients were dialyzed with low-flux polysulphone dialyzers and a constant dialysate conductivity of 13.9 mS/cm. The dialysate composition was as follows: sodium 139 mmol/l, potassium 1.0 or 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3 mmol/l, glucose 1.0 g/l. Low-molecular-weight heparin was used as an anticoagulant.

Dry weight was evaluated clinically (peripheral oedema, signs of pulmonary congestion, intra- and interdialytic blood pressure course, muscle cramps) in combination with the predialysis cardiothoracic ratio on a chest X-ray as a surrogate marker of hydration status.

All patients had regular contact with the dietician every four to six weeks according to usual clinical practice. During these visits, the nutritional status was evaluated, and changes in weight, laboratory results, and appetite were monitored.

Measurements

For all of the patients, we collected demographic data including age, gender, level of education, and patient characteristics such as dialysis vintage, weight, and height. Body mass index (BMI) was calculated as: postdialysis weight (kg)/length (m)^2. Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, stroke or peripheral vascular disease, and hypertension. Residual renal
function was defined as diuresis ≥200 ml/day. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second generation logarithmic Daugirdas equation [19].

The nutritional status of the patients was assessed with various parameters: the seven-point subjective global assessment (SGA), serum albumin, dry body weight, body height, BMI, and protein catabolic rate (PCR). The SGA has been described and validated in dialysis patients in the Netherlands Cooperative Study on the Adequacy of Dialysis [20]. A score of ‘1’ indicates severe protein energy wasting, and a score of ‘7’ indicates a normal nutritional status. Blood samples were collected in heparin-coated tubes from the arterial line at the initiation and at the end of the first haemodialysis session of the study week in order to determine sodium and albumin levels. Plasma sodium was measured with the indirect method of ion-selective electrode on a Roche Modular (Hitachi, Tokyo, Japan).

IDWG was calculated as predialysis weight minus the postdialysis weight of the previous haemodialysis session. Since body weight may influence nutritional and fluid intake, the results are also shown for IDWG as a percentage of dry body weight (%IDWG) [9]. The ultrafiltration rate was calculated by dividing the ultrafiltration volume (ml) by the length of time of the dialysis session (hours) and target dry weight (kg). Blood pressure was measured with an automatic oscillometric monitor that is incorporated in the haemodialysis apparatus. The results of IDWG, ultrafiltration volume and rate, and blood pressure for the three haemodialysis sessions in the study week were averaged.

**Statistical Analyses**

Data are reported as mean±SD for continuous variables with normal distributions and numbers (percent) for categorical data. Demographic characteristics, laboratory data, and blood pressures were categorized into tertiles of IDWG and %IDWG. Differences between tertiles were analysed by ANOVA followed by Tukey’s honest post hoc test. For categorical data, the Pearson Chi-Square test and the Generalized Cochran Mantel-Haenszel Test were used.

A multivariate linear regression analysis was utilized to identify patient factors including various nutritional parameters that were associated with IDWG and/or %IDWG. IDWG or %IDWG was entered as a response variable. The following possible explanatory variables were entered into the model: age, gender, weight, height, Kt/V, dialysis vintage, diuresis, diabetes, SGA, nPCR, serum albumin, and predialysis and postdialysis plasma sodium concentration (Figure 1). Next, to identify variables significantly contributing to IDWG, the Bayesian Information Criterion (BIC) for model selection was used [21]. Statistical analyses were performed with SPSS version 20 (SPSS inc., IBM company, USA) and statistical programming language R (R Development Core Team) [22]. Two-tailed P-values <0.05 were considered statistically significant.
Results

Patient characteristics

Patient characteristics are depicted in Table 1. The mean (±SD) age was 62.5 (±18.2) years, 36% were female, 36% had diuresis, and 23% had diabetes. Patients in the highest IDWG tertile were significantly younger (P=0.004), more frequently male (P=0.001), taller (P<0.0001), heavier (P=0.009), and had a significantly higher SGA (P=0.004) compared with patients in the other tertiles (Table 1). Similar results were obtained for %IDWG (data not shown).

IDWG and possible explanatory variables.

In the multivariate linear regression model with optimizing BIC, the response variable IDWG was significantly associated with the explanatory variables height, age, the presence of residual diuresis, and postdialysis sodium levels. The model incorporating these four variables explained 35% of the variance of absolute IDWG (Table 2). The response variable %IDWG was significantly associated with the presence of residual diuresis, age, weight, height, and post-dialysis sodium levels. The model with these five variables explained 37% of the variance of the %IDWG (Table 3). Height was positively associated with absolute IDWG and %IDWG. Weight was positively associated with %IDWG. Age had a negative effect on IDWG whereby one year of older age resulted in a decrease of 0.016 kg and 0.023% in absolute IDWG and %IDWG, respectively. The presence of residual diuresis was associated with a significantly lower IDWG and %IDWG. Postdialysis sodium levels had a negative association with both IDWG and %IDWG: higher postdialysis sodium levels were associated with lower
IDWG and %IDWG. Since this was an unexpected finding, we analysed the course of pre- to postdialysis plasma sodium concentration per tertile (Figure 2). Patients in the middle and highest IDWG tertiles had a lower plasma sodium concentration, both pre- and postdialysis, compared with patients in the lowest IDWG tertile (Table 1). However, differences between the IDWG tertiles were only significant for postdialysis sodium concentration (Table 1). The other tested dependent variables (Kt/V, dialysis vintage, diabetes, SGA, serum albumin, and predialysis plasma sodium level) did not significantly contribute to explaining the variance of absolute IDWG or %IDWG.

**Effect of gender and age**

Table 1 shows that patients with the highest IDWG (tertile 3) were younger and more frequently male. As demonstrated in Figure 3a, younger males (median age ≤ 65 years (yr))
indeed had a significantly higher IDWG compared with younger females (median age ≤ 69.5 yr, P=0.002), older females (median age > 69.5 yr, P=0.000), and older males (median age > 65 yr, P=0.008). For %IDWG, there was only a significant difference between younger males (median age ≤ 65 yr) and older females (median age > 69.5 yr, P=0.030) (figure 3b).
Table 4. Differences in blood pressures between tertiles of absolute IDWG

<table>
<thead>
<tr>
<th>Tertile 1 IDWG</th>
<th>Tertile 2 IDWG</th>
<th>Tertile 3 IDWG</th>
<th>p*</th>
<th>95% CI for differences between tertiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.48 L (N=46)</td>
<td>1.48 – 2.09 L (N = 46)</td>
<td>≥2.09 L (N = 46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm/Hg) predialysis</td>
<td>143.3±22.3</td>
<td>143.4±25.4</td>
<td>149.5±24.6</td>
<td>0.367</td>
</tr>
<tr>
<td>DBP (mm/Hg) predialysis</td>
<td>67.4±12.6</td>
<td>65.6±12.0</td>
<td>74.9±15.5</td>
<td>0.003*</td>
</tr>
<tr>
<td>SBP (mm/Hg) intradialysis</td>
<td>133.1±21.3</td>
<td>132.0±26.3</td>
<td>135.6±23.4</td>
<td>0.766</td>
</tr>
<tr>
<td>DBP (mm/Hg) intradialysis</td>
<td>64.1±12.4</td>
<td>61.9±12.8</td>
<td>72.6±16.1</td>
<td>0.001*</td>
</tr>
<tr>
<td>SBP (mm/Hg) postdialysis</td>
<td>142.7±24.4</td>
<td>135.7±27.0</td>
<td>134.3±26.2</td>
<td>0.250</td>
</tr>
<tr>
<td>DBP (mm/Hg) postdialysis</td>
<td>66.4±12.6</td>
<td>62.0±10.3</td>
<td>70.5±14.4</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Table 5. Differences in blood pressures within tertiles of %IDWG

<table>
<thead>
<tr>
<th>Tertile 1 IDWG</th>
<th>Tertile 2 IDWG</th>
<th>Tertile 3 IDWG</th>
<th>p*</th>
<th>95% CI for differences between tertiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.00% (N=46)</td>
<td>2.00 – 2.97% (N = 46)</td>
<td>≥2.97% (N = 46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm/Hg) predialysis</td>
<td>143.9±21.3</td>
<td>124.2±25.2</td>
<td>149.9±25.5</td>
<td>0.294</td>
</tr>
<tr>
<td>DBP (mm/Hg) predialysis</td>
<td>66.6±12.4</td>
<td>66.7±12.5</td>
<td>74.7±15.4</td>
<td>0.005*</td>
</tr>
<tr>
<td>SBP (mm/Hg) intradialysis</td>
<td>133.3±20.9</td>
<td>131.7±24.7</td>
<td>135.7±25.6</td>
<td>0.732</td>
</tr>
<tr>
<td>DBP (mm/Hg) intradialysis</td>
<td>63.3±12.4</td>
<td>63.4±13.8</td>
<td>71.7±15.7</td>
<td>0.008*</td>
</tr>
<tr>
<td>SBP (mm/Hg) postdialysis</td>
<td>142.3±23.6</td>
<td>136.1±26.9</td>
<td>134.3±27.1</td>
<td>0.305</td>
</tr>
<tr>
<td>DBP (mm/Hg) postdialysis</td>
<td>65.6±11.7</td>
<td>63.6±12.4</td>
<td>69.7±14.1</td>
<td>0.071</td>
</tr>
</tbody>
</table>

IDWG and blood pressure
Pre-, intra- and postdialysis systolic blood pressure did not vary significantly between tertiles of IDWG. Predialysis, intradialysis, and postdialysis diastolic blood pressure (DBP) was significantly higher in the highest IDWG tertile compared with the lowest tertile (Table 4, Figure 4a and 4b). For %IDWG, predialysis and intradialysis DBP was significantly higher in the highest %IDWG tertile compared with the lowest tertile (Table 5, Figure 4c and 4d).
In this study, we found that a higher IDWG was notably evident for those of a younger age, greater height and weight, presence of residual diuresis, and lower postdialysis sodium levels. In a combined analysis of age and gender, younger men had the highest IDWG, and patients with a higher IDWG had significantly higher diastolic blood pressures. Although gender was not associated with IDWG in multivariate analysis, body height and weight were important determinants of IDWG. Our results indicate that dietary advice including fluid restriction should be individualized based on age, body height and weight, and residual diuresis.

Our finding that age is an important factor in IDWG is in accordance with previous studies [23, 24]. Residual diuresis is an obvious determinant of IDWG and reveals that it is important to maintain residual diuresis.

SGA was significantly higher in the highest IDWG tertile, however, in multivariate analysis, SGA did not significantly contribute to IDWG. Other nutritional indicators such as serum albumin and nPCR also did not have significant associations with IDWG. In this study, in contrast with other studies, we did not find a strong association between IDWG and nutritional status [2, 8, 10, 11]. PCR was higher in the highest IDWG tertile, but when PCR was normalised by weight (nPCR) there was no significant difference between IDWG tertiles. In multivariate analysis, nPCR was not significantly associated with IDWG. Taller and heavier dialysis patients generally consume more protein and, thus, have a higher PCR. A higher PCR may contribute to a higher IDWG. When in a steady state, PCR mirrors protein anabolism/protein intake. A higher protein intake could reflect a higher overall metabolic rate with more substantial amounts of proteins, carbohydrates, and fats used for energy production and the subsequent generation of carbon dioxide and water. The carbohydrate is eliminated from the body by pulmonary ventilation whereas the water will result in higher IDWG. However, the contribution of this effect to the total IDWG has not yet been quantified. Additionally, it is conceivable that patients who consume more protein have a higher salt intake resulting in thirst. Thirst is prevalent in dialysis patients and is associated with higher IDWG and lower quality of life [25].

Salt intake is a major factor in IDWG [26]. Haemodialysis patients primarily have osmometric thirst of which salt intake is the primary cause [9, 26], however, during haemodialysis, there may also be diffusive sodium transfer to the patient. Immediately following a dialysis session, patients may also experience volumetric thirst caused by hypovolemia as a result of the ultrafiltration of fluid [26]. Several studies found that diffusive sodium transfer to the patient during haemodialysis contributed to incomplete sodium removal which could be prevented by individualizing the dialysate sodium prescription [27-30]. Combined dietary and dialytic sodium restriction can possibly prevent volume overload in haemodialysis patients [28, 31].

Remarkably, higher postdialysis sodium levels were associated with a lower IDWG. This contrasts with the general belief that higher postdialysis plasma sodium levels induce thirst and subsequent increased fluid intake. This can possibly be explained by the fact that patients with a high IDWG often begin haemodialysis with a low plasma sodium concentration resulting from dilution that does not rise to normal levels during treatment despite diffusive sodium transfer to the patient during haemodialysis. Our finding that postdialysis plasma sodium concentrations indeed differ between the IDWG tertiles may suggest that this could be the case (Figure 2). Additionally, patients with a high IDWG often do not achieve their dry weight by the end of the dialysis session and may have a decreased postdialysis plasma sodium concentration as a result of dilution. There are only a minimal number of studies that have specifically studied the association between postdialysis plasma sodium levels and IDWG. To the best of our knowledge, there is only one study that found a trend towards higher postdialysis sodium levels with higher IDWG, but this was not statistically significant [32]. A few authors measured predialysis and postdialysis plasma sodium concentration
and suggested that postdialysis sodium reflects the prescription of the dialysate sodium [33, 34]. However, in neither of these studies was the relation between postdialysis plasma sodium levels and IDWG studied. All of our patients were dialyzed with a dialysate sodium concentration of 139 mmol/l. Thus, differences in sodium dialysate concentration cannot explain the association between the higher postdialysis sodium levels and lower IDWG. Notably, predialysis sodium in our study was not associated with higher IDWG, however, in other studies, a relationship between low predialysis plasma sodium and high IDWG was found [31, 35].

In our study, patients with the highest IDWG had a significantly higher predialysis DBP. This observation is in accordance with previous studies [2-4]. Inrig et al. found that a higher %IDWG was associated with higher predialysis blood pressure [4]. Kuipers et al. found that predialysis blood pressure is highest during the first dialysis session of the week probably due to a more pronounced fluid overload [3]. Patients with the highest IDWG also had a significantly higher DBP during and after dialysis. These findings are in line with other studies and are a consequence of a higher IDWG [3, 27, 36].

According to the EBPG guidelines, diet restrictions for fluids do not need to be adjusted for weight, gender, body composition, or age. The guidelines for daily fluid intake vary from 500 to 1000 ml in addition to daily urine output, although 4.0-4.5% weight gain as a percentage of dry weight may be acceptable in patients with an optimal nutritional intake and salt restriction [9]. Our results show that various factors affect IDWG. Being both young and male is associated with a higher IDWG. Flythe et al. suggested a different approach to the fluid guidelines that focuses on the amount of time of the treatment that allow target levels of ultrafiltration to be achieved without exceeding ultrafiltration rates of 10 ml/hour/kg dry body weight while still respecting a minimum time to enable beneficial dialysis efficiency [37]. Besides fluid restriction, longer and/or more frequent dialysis sessions have been suggested to decrease the IDWG [37, 38]. However, various studies indicated an increase in daily fluid intake after the transition from conventional to frequent nocturnal haemodialysis [39-41]. Munoz Mendoza et al. demonstrated that patients undergoing thrice-weekly in-center nocturnal haemodialysis with lower sodium concentrations in the dialysate experienced a lower IDWG and predialysis systolic blood pressure compared with treatment on dialysate sodium concentrations of the standard 140 mEq/L [38]. Modification of dialysate sodium concentrations should also be considered as a tool to lower the IDWG [38].

A limitation of our study is the relatively small number of patients. However, most of our results are in accordance with previous studies. The use of predialysis serum albumin concentration as a marker for nutritional status in studies on IDWG is limited by possible dilution as a result of fluid overload [42, 43]. Another limitation is that we did not include information on antihypertensive medication. The strong points are that we created comprehensive models of factors that may be associated with IDWG including nutritional parameters and that we also focus on the relation between IDWG and blood pressure.

**Conclusion**

The major associations of the IDWG and %IDWG in our cohort are age, body height and weight, diuresis, and postdialysis sodium. Being male and of a young age are major risk factors for a significantly higher IDWG. Our findings highlight the importance of a personalized advice on fluid and sodium restriction.

**Disclosure Statement**

The authors declare that they have no conflict of interest.
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