Differences in prescribed $K_t/V$ and delivered haemodialysis dose—why obesity makes a difference to survival for haemodialysis patients when using a ‘one size fits all’ $K_t/V$ target

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ABSTRACT

Background. Morbid obesity is reported to be a survival factor for haemodialysis patients compared with those with a normal body mass index (BMI), yet morbid obesity (BMI >35) is a mortality risk factor for obese patients in the general population. Traditionally, haemodialysis dosing is prescribed to achieve a target $K_t/V$ corrected for total body water (TBW). As obese patients typically have increased body fat, which contains less water than muscle, then obese patients may have lower levels of body water than their slimmer counterparts, and as such delivered $K_t/V$ could be greater than that estimated using standard anthropomorphic equations, and so increased dialysis dose may help explain the increased survival reported for obese patients.

Methods. We compared multi-frequency bioelectrical impedance analysis (MF-BIA) measurements of TBW in healthy haemodialysis outpatients, and compared TBW with that calculated from the Watson equation derived from anthropomorphic measurements.
INTRODUCTION

Mortality risk progressively increases with chronic kidney disease staging [1], and intuitively treatment with a greater amount of dialysis might be expected to improve patient survival. The National Cooperative Dialysis Study (NCDS) showed that those patients treated by thrice weekly haemodialysis with higher time-averaged urea concentrations were more likely to become unwell, and defined a threshold adequacy, based on urea clearance [2]. Urea clearance was expressed as $\text{Kt}/\text{V}$, where $K$ is the dialysance urea clearance, $t$ is the duration of the dialysis session and $V$ is the volume of urea distribution [3]. Later studies showed a relationship between carbamylated haemoglobin [4] and $\text{Kt}/\text{V}$ [5]. Subsequent observational studies reported improved patient survival rates with $\text{Kt}/\text{V} > 1.0$ [6, 7], and by consensus dialysis sessional $\text{Kt}/\text{V}$ targets were increased to 1.2 [8]. The Haemodialysis study (HEMO study) [9], the second randomized controlled trial to investigate the effect of $\text{Kt}/\text{V}$ on patient outcomes, reported that higher doses did not improve overall patient survival. However, on subgroup analysis, women who had been established on haemodialysis for more than 3 years did benefit from higher $\text{Kt}/\text{V}$ targets. This led to suggestions that using an estimate of body water in underdosing of some patient groups on one hand and potentially delivering greater doses to others [10]. Whereas for the general population, morbid obesity is associated with increased mortality [11], several observational studies have reported that survival is increased for the morbidly obese haemodialysis patients [12, 13]. This apparent paradox may be due to changes in body composition, as fat contains less water than muscle, and the standard equations used to calculate body water may not reflect these differences.

RESULTS

We studied 363 adult patients, mean age 58.1 ± 16.7 years, 60.9% male and 29.9% diabetic were studied. MF-BIA-measured body composition showed that as BMI increased from <20 to >35, the percentage skeletal muscle mass fell from 42.8 ± 4.9 to 29.2 ± 5.5% (P < 0.01) whereas the % fat mass increased from 24.5 ± 11.6 to 46.7 ± 6.8% (P < 0.01). As such, TBW measured by MF-BIA was significantly lower from that predicted by the Watson equation at higher BMIs (BMI > 35; 38.9 ± 6.8 versus 44.7 ± 6.9 L, P < 0.01 and BMI = 30–35; 37.2 ± 7.5 versus 41.9 ± 7.3 L, P < 0.01), and as such the delivered $\text{Kt}/\text{V}$ using MF-BIA was much greater than that using the Watson-based urea volume of distribution for the obese patients (BMI > 35; sp$\text{Kt}/\text{V}$ 1.63 ± 0.48 versus 1.41 ± 0.35 and BMI 30–35; 1.65 ± 0.3 versus 1.46 ± 0.26, both P < 0.01).

Conclusions. Prescribing dialysis or quantifying on-line clearance based on the anthropomorphically derived Watson equation leads to underestimation of the delivered dose to obese patients, due to changes in underlying body composition. As such, when using a ‘one size fits all’ target $\text{Kt}/\text{V}$, obese patients have an advantage over patients with normal BMI, in that they will receive a greater delivered dose of dialysis, and this may potentially explain the paradoxical survival advantage of the morbidly obese haemodialysis patient.

MATERIALS AND METHODS

Multi-frequency bioimpedance measurements were made post dialysis in 361 healthy haemodialysis outpatients attending their mid-week dialysis session (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea) [17], using direct segmental MF-BIA with tetrapol 8-point tactile electrodes [18], in a standardized manner [19]. Patients with cardiac pacemakers, implantable defibrillators, amputees and those unable to stand on the bioimpedance machine were excluded from study. Fresenius F4000H or 5000H dialysis machines (Fresenius Bad Homburg, Germany) were used with polysulfone high-flux dialysers (Nipro Corporation, Osaka, Japan) [20], with ultrapure quality dialysis water and low-molar-ecular-weight heparin (Tinzaparin, Leo Laboratories, Princes Risborough, UK) [21]. Pre- and post-dialysis dialysis blood samples were taken in a standardized fashion measured with a standard laboratory auto-analyser (Roche Integra, Roche diagnostics, Lewes, UK) and haemoglobin (XE-2100 Sysmex Corporation, Kobe, Japan).

$\text{Kt}/\text{V}$ was calculated using the Daugirdas equation [22]. Body composition was derived from multi-frequency bioelectrical impedance assessments (MF-BIA) [15, 23]. Using TBW measured post dialysis by MF-BIA, $\text{Kt}/\text{V}$ was recalculated [24] assuming the Watson formula for TBW [25]. Ethical approval was granted by the local ethical committee as part of UK National Health Service audit and clinical service development.

Statistical analysis

Results are expressed as mean ± standard deviation, or median and inter-quartile range, or percentage. Statistical analysis was by $\chi^2$ analysis, corrected for small numbers by Yates’ correction, students’ $t$-test for parametric and the Mann–Whitney $U$-test for nonparametric data, Student’s pair $t$-test and Wilcoxon rank-sum pair test for paired values with Bonferroni correction for multiple analyses where appropriate and by ANOVA with Tukey post-hoc correction. Statistical analysis used Graph Pad Prism version 6.0 (Graph Pad, San Diego, CA, USA) and SPSS version 17 (University Chicago, USA). Statistical significance was taken at or below the 5% level.
25.8 ± 5.4 kg/m², dialysis session time 3.94 ± 0.5 h with pre- and post-dialysis serum urea 19.8 ± 6.0 and 5.3 ± 2.3 mmol/L, respectively, with a urea reduction ratio 73.3 ± 7.1%. Pre-dialysis haemoglobin 11.4 ± 1.5 g/L, albumin 40.9 ± 3.9 g/L, median C-reactive protein 4 (2–11) mg/L and glucose 5.9 (4.8–8.4) mmol/L. TBW, measured by MF-BIA post-dialysis was 35.2 ± 7.5 L and did not differ from that estimated from Watson (36.6 ± 7.0 L), but single-pool \( Kt/V \) was statistically different for that using MF-BIA 1.65 ± 0.41 compared with that using the Watson equation, 1.56 ± 0.32, \( P < 0.001 \). MF-BIA skeletal muscle mass was 26.3 ± 6.2 kg, fat mass 23.0 ± 12.0 kg, giving a percentage body skeletal muscle content of 37.6 ± 6.9% and fat content of 31.4 ± 13.0%.

Patients were divided according to BMI into five groups, those with a BMI 19 or lower, 20–25, 25–30, 30–35 and >35.0. There was no difference in ethnic distribution between the groups, although there were differences in sex distribution and diabetes with BMI (Table 1). TBW was significantly greater when calculated by the Watson equation compared with that measured by MF-BIA for those patients with the greater BMIs (Figure 1).

The pre-dialysis serum urea was lower in those patients with the smallest BMI compared with the highest quintile, whereas the urea reduction ratio was higher for the lowest quintile BMI compared with the highest (Table 1). Comparing single-pool \( Kt/V \) measured by the Daugirdas equation [23], and that recalculated using MF-BIA, then \( Kt/V \) was greater with the Daugirdas equation for those patients with the lowest BMIs, and lower for those with the highest BMIs (Figure 2). The percentage ultrafiltration to MF-BIA measured TBW was greater for the highest BMI groups (Table 1). Although there was a trend for patients with a lower BMI having shorter dialysis sessions, this was not significant when correcting for multiple analyses (Table 1).

Body composition, in terms of muscle and fat differed between the BMI quintiles, with reducing muscle mass and increasing fat as BMI increased (Figure 3).

### Discussion

Although the NCDS study helped to define a lower limit for dialysis dosing, based on urea clearance [2, 3], subsequent prospective studies failed to show that increasing the delivered dialysis dose based on \( Kt/V \) prescription increased patient survival [9]. This could be due to many confounders, including

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**Table 1. Patients divided according to body mass index (kg/m²)**

<table>
<thead>
<tr>
<th>BMI</th>
<th>≤20</th>
<th>20–25</th>
<th>25–30</th>
<th>30–35</th>
<th>&gt;35.0</th>
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<tbody>
<tr>
<td>n</td>
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<td>14</td>
<td>12</td>
</tr>
<tr>
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<td>38</td>
<td>31</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Not diabetic</td>
<td>36</td>
<td>103</td>
<td>89</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Caucasian</td>
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<td>51</td>
<td>50</td>
<td>19</td>
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<td>10</td>
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<td>8</td>
</tr>
<tr>
<td>Asian</td>
<td>16</td>
<td>49</td>
<td>33</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Pre urea (mmol/L)</td>
<td>17.2 ± 5.5</td>
<td>20.0 ± 6.7</td>
<td>19.8 ± 5.0</td>
<td>20.4 ± 5.8</td>
<td>21.7 ± 5.7*</td>
</tr>
<tr>
<td>URR (%)</td>
<td>75.2 ± 8.6</td>
<td>74.5 ± 6.3</td>
<td>73.0 ± 6.6</td>
<td>71.1 ± 6.5</td>
<td>78.7 ± 9.8*</td>
</tr>
<tr>
<td>UF/TBW%</td>
<td>2.4 (1.4–3.2)</td>
<td>3.1 (1.9–4.0)</td>
<td>3.4 (2.3–5.0)</td>
<td>4.9 (2.8–6.5)</td>
<td>4.6 (3.5–7.7)*</td>
</tr>
<tr>
<td>Session time (h)</td>
<td>3.8 ± 0.62</td>
<td>3.89 ± 0.46</td>
<td>4.0 ± 0.46</td>
<td>3.97 ± 0.55</td>
<td>4.12 ± 0.57</td>
</tr>
</tbody>
</table>

Comparison of sex, diabetes and racial origin, Sub Sahara African-AfroCaribbean (African), \( \chi^2 \) analysis. Pre-dialysis serum urea (Pre-urea), URR, urea reduction ratio. Dialysis session time in hours. Males versus females \( P = 0.035 \), diabetes versus no diabetes \( P < 0.001 \). Ultrafiltration volume (UF) to total body water (TBW). Results expressed as mean ± SD or median (inter-quartile range).

* \( P < 0.05 \) BMI < 20 versus BMI > 35.
residual renal function, the time to accumulate uraemic toxins to cause morbidity and mortality [26], and the effects of intradialytic weight gains and extracellular volume control [27]. In addition, the mean Kt/V values in the HEMO study were not too dissimilar between the groups at 1.16 versus 1.32, so another potential confounder could have been that patients with higher BMIs had an underestimate of the actual dose delivered, and those with lower BMIs an overestimate, so that the groups were not as separated as initially thought.

When dialysis is prescribed according to Kt/V, or measured by on-line clearance using the Watson equation to estimate the volume of urea distribution, then V will be overestimated in the morbidly obese patient due to the relative increase in fat mass and reduction in muscle, due to the lower water content of adipose tissue. In addition, to achieve a pre-determined target, it is most likely that dialysis session time will be increased for the obese patient, so they additionally benefit both from increased clearance of time-dependent solutes, such as phosphate [28], and also control of sodium balance and overhydration. This is supported by our study with both a trend to increased dialysis session time and an increasing proportion of ultrafiltration to TBW with increasing BMI. As such, this improved delivery of a higher dose of dialysis for the obese patient could potentially explain the apparent paradox of an apparent survival advantage for the morbidly obese (BMI > 35) haemodialysis patient compared with those with normal BMI, whereas the morbidly obese patient in the general population has increased risk of mortality.

The Watson equation, which is advocated as the standard for calculating TBW, and recommended by many clinical guideline committees [29], was derived from studies in the 1950s and 1960s. Since then, body composition has changed in many economically developed countries, with a trend to increased obesity. Our data support earlier smaller anthropomorphic studies [30] and the more recent analysis from the HEMO study [31], which reported that the Watson equation overestimates TBW in haemodialysis patients, and these differences in expected and delivered dialysis dose would help to explain the reports of increased survival reported in overweight patients [32].

More recently, some groups have used alternative scales, such as body surface area rather than urea volume distribution to adjust dialysis dose for body size [33]. Normalizing Kt/V to body surface area rather than Watson-derived TBW, lowered the dose of dialysis delivered to women compared with men in the HEMO study [33]. Subsequent re-analysis of the HEMO study group using dialysis dose corrected for body surface area (BSA) recently reporting different dose–mortality relationships, which were substantially different from those using the original volume-based dosing regimen, reporting an increased survival for haemodialysis patients up to a Kt/V of 1.6 [34]. Morbidly obese patients were however excluded from the HEMO study, and our data would suggest that although correction for BSA may well be an improvement on the Watson-derived urea volume, any adjustment for BSA assumes a fixed relationship with body composition [35], which may well no longer hold given the current epidemic of obesity in the developed world.

Our data show that when prescribing or delivering haemodialysis to a pre-determined target or on-line Kt/V, the actual dose of dialysis delivered to the obese patient will be greater than that predicted by using anthropomorphically derived equations of TBW, and conversely reducing the dose of dialysis to the patient with a low BMI. Thus, to achieve current, one size fits all, Kt/V targets the morbidly obese patient potentially benefitting from not only greater small solute clearances, but also from longer session times, with improved clearance of time-dependent solutes and reduced risk of overhydration. As such obesity with increased body fat content, by containing less water than muscle, paradoxically has become a survival advantage for haemodialysis patients using current treatment target paradigms.

CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest. The data contained in this paper have not been previously published in whole or part form, or by abstract.

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