Comparison of Various Scaling Parameters and Energy Expenditure in Peritoneal Dialysis Patients

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Peritoneal dialysis (PD) dosing is determined by urea clearance scaled to total body water (TBW). However, studies delivering greater peritoneal Kt/V urea have failed to demonstrate improved survival. Body surface area (BSA) has been suggested as an alternative scaling factor. Cellular metabolism generates toxins, and thus total energy expenditure (TEE) might be a preferable scaling factor. Because TEE is cumbersome to determine, we set out to determine the association of anthropomorphic scaling factors with TEE.

The TEE was determined using the Recent Physical Activity Questionnaire combined with resting energy expenditure by validated equations that use doubly labelled isotopic water and body composition by multi-frequency bioimpedance.

In 148 adult PD patients [97 men (65.5%)], mean age was 60.6 ± 20.6 years, and median PD treatment duration was 9.1 months (range: 3.5 – 25.2 months). Mean weight in the group was 73.6 ± 16.7 kg, body mass index (BMI) was 26.0 ± 4.9 kg/m^2, and BSA was 1.86 ± 0.24 m^2. The mean TEE was 1974 ± 414 kcal daily, and it correlated with BMI (men: r = *0.48,* p < *0.001; women* r = *0.36,* p = *0.018), BSA (men:* r = *0.56; women:* r = *0.63; both* p < *0.001), and TBW (men:* r = *0.62; women:* r = *0.65; both* p < *0.001). Skeletal muscle mass correlated with BMI (men:* r = *0.48; women:* r = *0.50), BSA (men:* r = *0.72; women:* r = *0.63), and TBW (men:* r = *0.98; women:* r = *0.99), all* p < *0.001.*

Comparing scaling factors, correlations with TEE were stronger for TBW and BSA than for BMI. Skeletal muscle mass was most strongly associated with TBW. Our study did not demonstrate any advantage for BSA compared with TBW as a scaling factor to adjust the dose of PD.

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Key words
Resting energy expenditure, total energy expenditure, total body water, body surface area, Kt/V urea

Introduction

Cellular metabolism generates waste products. Patients with chronic kidney disease fail to excrete many of those compounds, leading to their accumulation. Urea is generated as a byproduct of the breakdown of proteins into amino acids and the recycling of amino acids.

Urea clearance is currently recommended as the determiner of the dose of dialysis that patients receive. In the case of peritoneal dialysis (PD), urea clearance (Kt/V urea) is the sum of the averaged 24-hour urinary urea and creatinine clearance and the daily peritoneal urea clearance adjusted to total body water (TBW) estimated from anthropomorphic measurements (1,2). However, prospective studies have failed to convincingly demonstrate that increasing the peritoneal urea clearance results in improved patient survival (3). That failure could be a result of differences in urea clearance compared with the clearances of other waste products of metabolism that might have greater biologic toxicity.

An alternative hypothesis would be that adjusting urea clearance for TBW does not adequately allow for a comparison of urea clearance in different-sized patients. Some researchers have therefore suggested that alternative scaling factors for urea clearance that will allow for inter-patient comparisons are required (4). For example, rather than TBW, body surface area (BSA) is used to scale urinary creatinine clearance and measures for some visceral organs, such as left ventricular mass.

Because urea is generated by cell metabolism, urea production in the steady state is a marker of cellular protein turnover. Energy expenditure consists

of both resting energy expenditure (REE) and active energy expenditure. The REE depends on the activity of visceral organs including muscles, liver, brain, gastrointestinal tract, heart, and kidneys. Visceral organs such as the heart are typically scaled to BSA; skeletal muscle is scaled to height squared. Patients with chronic kidney disease are more vulnerable to muscle wasting, termed sarcopenia. Body composition can therefore be altered in PD patients, potentially because of increased muscle loss on the one hand and increased body fat on the other. Thus, the standard scaling factors of BSA, TBW, and body mass index (BMI), used to adjust for differences in patient size, might vary in their applicability to chronic kidney disease patients compared with healthy subjects. We therefore set out to compare the scaling of PD urea clearance based on the various scaling factors and the REE and total energy expenditure (TEE).

Methods

Adult patients with chronic kidney disease treated with PD under the care of the Royal Free Hospital were recruited when attending for outpatient assessments of PD adequacy. Their spent dialysate effluent and serum samples were analyzed by standard methods, and the weekly dialysis dose was calculated as Kt/V urea (1,2). The protein nitrogen accumulation (PNA) rate in grams per day was estimated using the Bergström equation (2).

Multi-frequency bioimpedance (InBody 720: InBody, Seoul, South Korea) was performed in a standardized manner. Patients were asked to empty their bladder; their dialysate was subsequently drained (5,6). Skeletal muscle mass and fat mass were determined by bioimpedance.

Physical activity data were obtained using the validated Recent Physical Activity Questionnaire (7), which collects information about activities performed at home, at work, and during leisure time and also about the time spent on each activity in the preceding 4 weeks. The Recent Physical Activity Questionnaire has been shown to be a reliable tool for the estimation of energy expenditure in patients with chronic kidney disease (8). Physical activity data were determined by assigning each reported activity a metabolic equivalent of task value according to the Compendium of Physical Activities (9).

Ethics approval was granted by the U.K. National Research Ethics Committee–Essex, and the study was registered in the U.K. Clinical Research Network Portfolio (no. 14018). All patients provided written informed consent in keeping with the Declaration of Helsinki.

Statistical analysis

The statistical analysis used paired analysis, Student *t*-tests, or Wilcoxon pair analysis with appropriate correction for multiple testing, and Pearson or Spearman correlation tests (GraphPad Prism, version 7.0: GraphPad Software, San Diego, CA, U.S.A.). Data are presented as means with standard deviation, medians with interquartile range, means with 95% confidence limits, or percentages.

Results

Data were collected from 148 patients [97 men (65.5%); mean age: 60.6 ± 20.6 years; median duration of PD: 9.1 months (range: 3.5 – 25.2 months)]. Mean weight in the study group was 73.6 ± 16.7 kg, with a mean BMI of 26.0 ± 4.9 kg/m^2 and a mean BSA of 1.86 ± 0.24 m^2. The mean REE was 1534 ± 241 kcal daily, and the mean TEE was 1974 ± 414 kcal daily.

As expected, highly significant univariate correlations were observed for BMI, BSA, and TBW with body composition (Table I). However, although fat mass and BMI were highly significantly correlated, fat mass was not associated with TBW. When we compared those scaling factors with the TEE, the univariate correlations ranged from $r^2 = 0.13$ for men and $r^2 = 0.23$ for women with BMI, to $r^2 = 0.38$ for men and $r^2 = 0.42$ for women with TBW (Figure 1).

The TEE and PNA were correlated in men ($r = 0.65$, $p < 0.001$), but not in women ($r = 0.28$, $p = 0.058$). The strongest univariate association for PNA was with TBW, and the weakest was with BMI (Table I). Similarly, positive correlations between TEE and skeletal muscle mass were observed for both men and women ($r = 0.63$ and $r = 0.66$ respectively, $p < 0.001$).

Discussion and conclusions

Clinical guidelines recommend that PD patients receive a target amount of dialysis based on urea clearance adjusted for TBW (1,2). However, given that prospective studies have failed to demonstrate a survival advantage for greater peritoneal urea clearance (3), some authors have questioned the paradigm of Kt/V urea, and whether the dose of dialysis should

TABLE 1 Univariate analyses

	Men		*Women*	
Variable and comparators	r	p *Value*	r	p *Value*
Body mass index				
Weight	0.89	<0.001	0.90	<0.001
Body surface area	0.82	<0.001	0.85	<0.001
Total body water	0.46	<0.001	0.51	<0.001
Fat mass	0.78	<0.001	0.92	<0.001
Skeletal muscle mass	0.45	<0.001	0.50	<0.001
Protein nitrogen appearance	0.37	0.001	0.22	>0.05
Total energy expenditure	0.48	<0.001	0.36	0.018
Body surface area				
Weight	0.99	<0.001	0.90	<0.001
Body mass index	0.82	<0.001	0.85	<0.001
Total body water	0.75	<0.001	0.84	<0.001
Fat mass	0.63	<0.001	0.71	<0.001
Skeletal muscle mass	0.72	<0.001	0.83	<0.001
Protein nitrogen appearance	0.46	<0.001	0.40	0.008
Total energy expenditure	0.56	<0.001	0.63	<0.001
Total body water				
Weight	0.70	<0.001	0.78	<0.001
Body surface area	0.75	<0.001	0.84	<0.001
Body mass index	0.46	<0.001	0.52	<0.001
Fat mass	0.07	>0.05	0.25	>0.05
Skeletal muscle mass	0.98	<0.001	0.99	<0.001
Protein nitrogen appearance	0.62	<0.001	0.40	0.008
Total energy expenditure	0.62	<0.001	0.65	<0.001

be alternatively scaled (9). Because uremic toxins are generated by cellular metabolism, it has been suggested that the amount of dialysis a patient receives should be tailored according to metabolic rate (10). However, the basal metabolic rate includes only REE (11) and does not take into account active energy expenditure (12).

We looked at the relationship between TEE and the three most commonly used scaling factors; BMI, BSA, and TBW. On univariate analysis, the weakest association was with BMI, and the strongest, with TBW (which was only marginally greater than the association with BSA). However, as shown in Figure 1, the relationship between TEE and TBW was $r^2 = 0.38$ for men and $r^2 = 0.42$ for women. Thus, approximately 40% of the variation in the TEE could

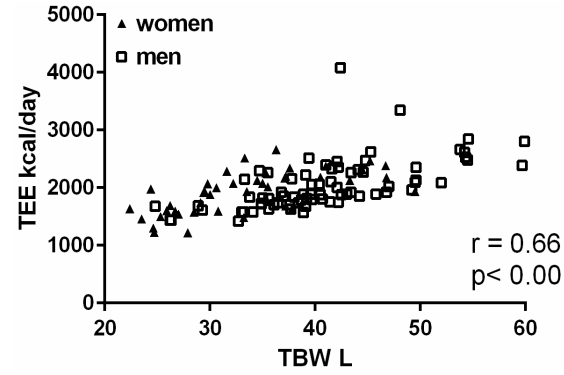

FIGURE 1 Univariate association between total energy expenditure (TEE) and anthropomorphic estimated total body water (TBW), for male and female peritoneal dialysis patients (Spearman correlation for all patients).

be explained by changes in TBW—or, conversely, 60% of the variation in the TEE cannot be explained by differences in TBW.

Because the scaling factors BMI, BSA, and TBW have parameters in common, there is mathematical coupling between them. We used a validated method to determine body composition (5,13) and noted that, compared with BSA and TBW, BMI has a greater association with body fat. As with the TEE, the univariate association was strongest between skeletal muscle mass and TBW, followed by BSA; the association with BMI was the weakest. Previous reports have suggested that skeletal muscle mass regulates metabolism because of inter-organ crosstalk (14). We found positive correlations between TEE and skeletal muscle mass that were similar in magnitude to those between TBW and skeletal muscle mass. It would therefore appear that the value of TBW as a scaling factor is linked to the underlying association between TBW and skeletal muscle mass.

This analysis comparing the three most common scaling factors suggests that, for PD patients, TBW and BSA are preferable to BMI, which has greater linkage to body fat mass. In this cohort of patients, TBW and BSA have greater linkage to skeletal muscle mass. The analysis demonstrates little difference between TBW and BSA as scaling factors. Previous reports have suggested that scaling using BSA is superior to scaling using TBW for hemodialysis (HD) patients (9,10). The difference described for HD patients might be attributable to patient selection, in that much heavier patients

(>120 kg) are generally offered HD rather than PD. Relatively more HD patients might have a larger BMI (15), and the relatively greater proportional increase in fat mass compared with the increase in body weight might account for the differences observed.

Although TBW remains the current scaling factor used in clinical practice, the TEE shows considerable variation that cannot be readily explained by changes in TBW. That variation might help to explain why studies examining the effects of delivering greater urea peritoneal clearance (based on TBW scaling of dose) have failed to demonstrate a survival advantage.

Disclosures

I understand that *Advances in Peritoneal Dialysis* requires disclosure of any conflicts of interest, and I declare that I have no conflicts to disclose.

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