Comparison of resting energy equations and total energy expenditure in haemodialysis patients and body composition measured by multi-frequency bioimpedance

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Abstract

Background

Waste products of metabolism are retained in haemodialysis (HD) patients. Cellular metabolism generates energy, and patients with greater energy expenditure may therefore require more dialysis. To determine the amount of dialysis required, equations estimating resting and total energy expenditure (REE,TEE) are required.

Methods

We compared estimates of REE in HD patients using established equations with a novel equation recently validated in HD patients (HD equation). TEE was derived from REE (HD equation) and estimates of physical activity obtained by questionnaire. REE and TEE relationships with bioimpedance measured body composition were then determined.

Results

We studied 317 HD patients; 195 males (61.5%), 123 diabetic (38.9%), mean age 65.0±15.3 and weight 73.1±16.8 kg. REE from HD Equation was 1509±241 kcal/day, which was greater than for Mifflin St Joer 1384±259, Harris-Benedict 1437±244, Katch-McArdle 1345±232 (all $p<0.05$ vs HD Equation), but less than Cunningham 1557±236 kcal/day. Bland Altman mean bias ranged from -263 to 55 kcal/day. TEE was 1727 (1558-1976) kcal/day, and on multi-variable analysis was positively associated with skeletal muscle mass (β 23.3, $p<0.001$), employment (β 406.5, $p<0.001$), low co-morbidity (β 105.1,

p=0.006), and protein nitrogen appearance (β 2.7, p=0.015), and negatively with age (β -7.9, p<0.001), and dialysis vintage (β -121.2, p=0.002).

Conclusions

Most standard equations underestimate REE in HD patients compared to the HD Equation. TEE was greater in those with higher skeletal muscle mass and protein nitrogen appearance, lower co-morbidity, age, and dialysis vintage, and the employed. More metabolically active patients may require greater dialytic clearances.

Introduction

Although haemodialysis is an established treatment for patients with chronic kidney disease (CKD), with around 3 million patients currently treated worldwide, 5-year mortality remains higher than that for some of the more common solid organ malignancies [1]. Dialysis treatments are currently designed to achieve an adequacy target in terms of solute clearance, using the dimensionless parameter Kt/Vurea, where K is dialyser urea clearance, t the dialysis session time and V the urea distribution volume (or Watson Volume [2]) equating to total body water. Yet, when tested by a randomised prospective multicentre trial increasing dialyzer Kt/Vurea clearance failed to demonstrate greater patient survival [3], although, post-hoc analysis suggested that higher haemodialysis doses were associated with a survival advantage for women [4]. There are a number of possible explanations for this association, one of which may be the scaling of haemodialysis dose based on total body water [5].
In CKD, the products of cellular metabolism accumulate and as such an alternative suggestion has been that the amount of dialysis a patient requires would depend upon their metabolic activity [6]. Metabolic activity comprises both resting metabolic rate and that secondary to physical activity. Resting energy expenditure (REE) is relatively greater in smaller animals compared to larger animals, and rescaling the dialysis dose by body surface area (BSA) has been reported to demonstrate an association between increasing Kturea/BSA and patient survival [7]. However, this approach fails to take in to account active energy expenditure. To be able to adjust the amount haemodialysis for an

individual patient then we need to develop simple methods of estimating total energy expenditure which are valid in patients with advanced CKD.

Several equations have been developed for estimating REE [8-12], but these did not include patients with CKD. As such we have recently developed an equation to estimate REE in dialysis patients and, based on this, a method to estimate total energy expenditure (TEE), which has been validated in doubly labelled water studies [13,14].

We wished to compare the HD Equation in haemodialysis patients with other equations commonly used to estimate REE, which were developed from other patient populations. In addition, we wished to determine whether there was an association between REE and TEE and body composition as measured by bioelectrical impedance.

Patients and methods

We recruited a total of 317 adult patients under the care of a university hospital attending for outpatient thrice weekly haemodialysis. Patient demographics were obtained from computerised hospital records and comorbidity determined using a self-administered co-morbidity grading, based on medical conditions and complications, including diabetes mellitus (as defined by WHO criteria), cardiac disease, respiratory disease, liver disease, arthritis, depression and malignancy [15].

We compared estimates of REE using the HD Equation [13,14], with those calculated using the modified Harris-Benedict equation [8,9], the Mifflin St.

Joer [10], Katch McArdle [11] and Cunningham equations [12]. Physical activity data was obtained through the validated Recent Physical Activity Questionnaire (RPAQ) [16]. The RPAQ collects information about activities performed at home, work and leisure time and also the time spent on each activity in the preceding 4 weeks [13]. Physical activity data was determined by each reported activity being assigned a Metabolic Equivalent of Task (MET) value according to the Compendium of Physical Activities [16]. This was then combined with REE estimated using the HD equation to provide an estimate of TEE (see appendix)

Measurements of body composition were made using multi-frequency bioelectrical impedance assessments (MFBIA) (InBody 720, InBody, Seoul, South Korea). Bioimpedance measurements are routinely collected as part of determining HD patient target weight. Patients with pacemakers, and other implantable cardiac devices, and those unable to stand to measure bioimpedance were excluded from study. Measurements were performed in a standardised manner, post the mid-week haemodialysis session [17,18], allowing appropriate time for redistribution of fluid between body compartments post-dialysis [19,20]. Previous studies have validated this device against dual electron X ray absorptiometry [21]. Lean body mass index (LBMI) and fat mass index (FMI) were calculated by lean body mass (LBM) and fat mass (FM) divided by height squared, respectively. Skeletal muscle mass (SMM) was derived from measurement of limb muscle mass (appendicular muscle mass). Body surface area was calculated using the Gehan and George equation as recommended by the European Best Clinical Practice guidelines [22].

The Cunningham and Katch McArdle equations use an estimate of lean body mass [11,12], with lean body mass estimated by subtracting percentage body fat from patient weight. We calculated REE using both percentage body fat and also lean body mass measured by MFBIA.

Patients dialysed using Fresenius 4008H (Fresenius Bad Homberg, Germany) or Dialogue R+ (BBraun, Melsungen, Germany) with high flux polysulfone dialyzers (Elisio, Nipro Corporation, Osaka, Japan) [23] and anticoagulated with single bolus low molecular weight heparin (Tinzaparin, Leo Laboratories, Hurley, Berkshire, UK) [24]. Haemoglobin and serum urea, creatinine and electrolytes were measured by standard laboratory analyzers (Sysmex XE5000, Sysmex Corporation, Kobe, Japan and Roche Cobra, Roche Instruments Ltd, Basingstoke, UK), and serum β2 microglobulin was measured by rate nephelometry (www.Dako.com, Image 800 analyser, Beckman Coulter, High Wycombe, UK) [25].

Dialysis machines were regularly serviced and dialysate conductivity checked [26,27]. Haemodialysis adequacy was calculated as an equilibrated Kt/Vurea, and protein nitrogen appearance from pre- and post-dialysis measurements [28] and the inter-dialytic interval and bioimpedance total body water. Interdialytic urine collections were not available.

Ethical approval for determining energy expenditure was granted by the UK National Research Ethics Committee – North Wales and the study was registered in UK Clinical Research Network (CRN) Portfolio number 12023. All

patients provided written informed consent in keeping with the declaration of Helsinki.

Statistical analysis

Data variables were checked for normality (D'Agostino and Pearson), and statistical analysis was by t test, Man Whitney U test, paired t test and Wilcoxon rank sum pair test, ANOVA or Kruskal-Wallis analysis, with appropriate post hoc correction for multiple testing, Pearson or Spearman's correlation (GraphPad Prism version 7.0, San Diego, USA), and Bland Altman comparison (Analyse-It version 3.0, Leeds, UK). Variables associated with REE and TEE, $p<0.1$ and those thought to be clinically relevant were entered into a multivariable analysis and then eliminated in a step back manner if variables were not significant, unless they improved model fit (SPSS 22.0, SPSS University Chicago, USA). Multivariable models were checked for collinearity. Data are presented as mean ± standard deviation, median (inter quartile range), or mean and 95% limits of agreement (LoA), or as a percentage.

Results

We studied 317 adult haemodialysis patients; 195 males (61.5%), 123 diabetic (38.9%), mean age 65.0±15.3 years, with a median dialysis vintage 3.3 (1.4-6.2) years. 138 (43.5%) were Caucasoid, 101 (31.9%) African/Afro-Caribbean, 65 (20.5%), South Asian, 9 (2.8%) East Asian, and the remainder of indeterminate ethnicity. The mean weight was 73.1±16.8 kg with a body mass

index of 26.2±5.8 kg/m^2, with a median co-morbidity grade of 2 (0-4). 41 patients (13%) were in employment. The mean equilibrated dialysis sessional Kt/Vurea was 1.40 ±0.27, with a mean dialysis session time of 236 ±26 minutes, median ultrafiltration volume 1.8 (1.0-2.2) L, and daily protein nitrogen appearance rate based solely on change in serum urea during the inter-dialytic interval, 42.1 (30.8-53.5) g/day. Pre-dialysis haemoglobin was 110.5±11.9 g/L, serum albumin 40.3±4.2 g/L, cholesterol 3.9 ±1.1 mmol/L, C reactive protein (CRP) 4.0 (2-9) mg/L, urea 18.0±5.2 mmol/L, serum creatinine 710 (572-863) umol/L, cholesterol 4.0 ±1.0 and glucose 7.1 ±2.6 mmol/L, serum β2 microglobulin 28.6 ±9.4 mg/L and post-dialysis serum urea 4.6 ±1.8 mmol/L. The median weekly erythropoietin dosage was 5000 (2000-8000) Iu/week.

The mean REE using the HD Equation was 1532±237 kcal/day, with a TEE of 1727 (1558 – 1976) kcal/day. The REE determined by the HD Equation was significantly greater than that for the modified Harris-Benedict, Mifflin St. Joer equations, and the Katch McArdle equation using lean body mass (Figure 1). REE was also calculated by estimating lean body mass from percentage body fat using the Katch McArdle and Cunningham equations, which over estimated REE compared to other equations (table 1).

Resting and total energy expenditure was less for female patients, who had less muscle mass, but greater body fat (table 1). Bland Altman plots showed that the majority of REE equations under estimated REE compared to the HD Equation, however using percentage body fat to estimate lean body mass, led to an over estimation of REE (Figures 2-5 and supplementary figures 6-7).

A number of demographic and dialysis associated variables and body composition measurements were associated with both REE and TEE (table 2). REE was greater in African-Afro-Caribbean patients compared to white or south Asians (1563±245 vs 1492±246 and 1434±210 kcal/day respectively), $p<0.05$, but TEE did not differ between ethnic groups. Patients in employment had greater REE (1613±247 vs 1493±237 kcal/day, $p<0.01$) and TEE (2268±453 vs 1731±307 kcal/day, $p<0.001$). There was no difference in REE or TEE between those with low and high co-morbidity (REE 1507±233 vs 1515±262 and TEE 1813±383 vs 1769±352 kcal/day).

Multivariable models showed that REE was independently associated with skeletal muscle mass, and negatively with age and duration of treatment with haemodialysis. TEE was also associated with skeletal muscle mass, and negatively with age and duration of treatment with haemodialysis, but was also associated with employment status, low co-morbidity and inter-dialytic protein nitrogen appearance rate determined by the increase in serum urea (table 3).

Discussion

The kidney plays a key role in the excretion of the waste products of cellular metabolism. As serum urea has the highest serum concentration of any of these retention products of cell metabolism, then dialyzer urea clearance has been used to assess dialysis adequacy. However prospective clinical studies designed to investigate the effects of increasing dialyzer urea clearance targets failed to demonstrate any survival advantage [3]. Re-analysis of this

data, and other reports have suggested that the delivered amount of dialysis was affected by body size and gender [4,5,29]. Body size and gender are key determinants of energy expenditure [8], and it has been suggested that the amount of dialysis clearance required by patients should be adjusted for metabolic rate [6].

A number of equations estimating REE have been proposed over the last hundred years or so, which have been based on studies from various populations, generally including healthy subjects of varying body mass index and ages [8-12]. However body composition can be affected by CKD, particularly in terms of muscle wasting [30,31], as well as the potential effects of co-morbidities such as diabetes [32]. More recently an REE equation based on studies of UK patients on haemodialysis has been developed [13,14,33]. To determine how this HD REE equation compared with standard equations estimating REE, we studied a cohort of HD outpatients. We used multi-frequency bioelectrical impedance to measure body composition [34]. Although this is an accepted technique, bioimpedance measurements are affected by volume status, so we used bioimpedance measurements taken post-dialysis when patients were closest to their target weight, to minimise the effect of over hydration [35].

We found that the mean bias for both the modified Harris-Benedict [8,9] and Mifflin St.Joer [10] equations under estimated REE compared to the HD Equation, for both male and female HD patients. Both the Katch McArdle [11] and Cunningham [12] equations can be calculated either by using directly estimated lean body mass or lean body mass obtained by subtracting percentage

body fat from body weight. We used both methods entering lean body mass and percentage body fat measured by bioimpedance. Using lean body mass, mean bias for the Katch-McArdle equation under estimated REE, whilst the Cunningham equation over estimated REE. In contrast using percentage body fat both over estimated REE compared to the HD Equation.

Although the mean bias between the HD and the Harris-Benedict equation was modest at 73 kcal/day, the 95% LoA of this and the other equations were very large for both genders. REE depends upon the metabolic activity of high energy internal organs; including the brain, liver, kidneys, and heart [36]. Increased REE in HD patients compared to healthy subjects would be supported by previous reports of impaired mitochondrial energy transfer and increased muscle breakdown in patients with kidney failure [30,31], and the effect of the dialysis treatment itself.

Using percentage body fat, REE calculated from the Katch-McArdle and Cunningham equations was significantly greater compared to that using lean body mass. Changes in body composition, in particular changes in muscle mass, alter the relationship between percentage body fat and muscle mass in CKD [29,30]. Hence assumptions made based on body composition in healthy subjects may not hold for CKD patients.

All REE equations use anthropomorphic measurements. We noted that in addition to patient age and gender, REE was associated with anthropomorphic measurements, but also with ethnicity which has been reported to alter body composition [37], dialysis session time, dialyzer surface area, pre-dialysis serum

urea, creatinine, albumin and haemoglobin, and the inter-dialytic interval protein generation based on the increase in serum urea, along with body composition, and employment status. REE was inversely associated with haemodialysis vintage and dialysis dose (equilibrated Kt/V) on univariate analysis. Although greater energy expenditure was associated with serum albumin and lower erythropoietin requirements, suggesting that energy expenditure may be affected by inflammation, we found no association with C reactive protein. Lower energy expenditure was associated with longer dialysis vintage, which may be due to loss of residual renal function, although there was no association with β2 microglobulin concentrations. Previous studies have reported that the determination of dialysis dosing using Kt/V overestimates delivered dose in small patients and those with a lower pre-dialysis serum urea [4,5].

A multivariable model noted that REE derived by the HD Equation was independently associated with skeletal muscle mass, and negatively with both age and years of haemodialysis treatment. Both the Katch McArdle and Cunningham equations estimate REE based on lean body mass [11,12]. Muscle mass can influence energy and protein metabolism throughout the body, as muscle plays a key role in glucose uptake and storage, and is also a large potential reservoir of amino acids stored as protein, which can be released when supplies are needed elsewhere in the body [38]. Muscle mass declines with age [39], and previous reports have commented on reduced muscle glycogen stores in muscle biopsies from haemodialysis patients [40].

We also calculated TEE, by including energy expenditure due to physical activity [16]. Compared to REE, on univariate analysis TEE was positively associated with haemoglobin, and negatively with erythropoietin dose, and erythropoietin resistance. Higher haemoglobins may improve performance in endurance athletes, such as cyclists, whereas the negative association with erythropoietin dose could be due to a number of confounders including erythropoietin resistance associated with inflammation and muscle wasting [41]. On multivariable analysis, we found that TEE was also associated with protein nitrogen appearance assessed by the inter-dialysis increase in serum urea. This is in keeping with reports of energy intake being associated with skeletal muscle mass [42], and also with the relationship of TEE and urea generation rate [33]. In addition, TEE was associated with employment status and low co-morbidity. It would be expected that patients with greater co-morbidity would be less physically active as would those who were not in employment.

If the amount of dialysis a patient requires is related to energy expenditure, then equations which are relatively simple to apply in routine clinical practice are required. Our study demonstrates that in this setting, estimates of REE obtained using an equation derived in HD patients are higher than those obtained using standard equations. Both REE and TEE were independently associated with skeletal muscle mass, and negatively with age and duration of treatment with haemodialysis. Understanding the relationship between body composition and energy expenditure is important for patients with kidney failure treated by dialysis, as patients with greater TEE generate more

waste products of cellular metabolism, and may potentially require greater dialytic clearance.

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Figure 1: Resting energy expenditure (REE) measured using the HD Equation [7,8], with the modified Harris-Benedict equation [11,12], the Mifflin St. Joer [13], Katch McArdle [14] and Cunningham equations [15]. * p <0.05, *** p<0.001 vs HD equation.

Figure 2: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with the modified Harris-Benedict equation (mean bias women -96 (95% limits of agreement -244 to 52), men -263 (-855 to -329).

Figure 3: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with the Mifflin St. Joer equation (mean bias women -191 (-330 to -52), men -86 (-205 to 34).

Figure 4: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with the the Katch McArdle using lean body mass (mean bias women -214 (-550 to 121) mean bias men -160 (-560 to 239)

Figure 5: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with the Cunningham equation using lean body mass; women mean bias -4.4 (-340 to 331), men 53 (-350 to 457)

Supplementary Figure 6: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with Katch McArdle equation calculated from % body fat with a mean bias for women 357 (-124 to 840) mean bias men 299 (-270 to 869

Supplementary Figure 7: Bland Altman plots of resting energy expenditure (REE) kcal/day measured using the HD Equation compared with Cunningham equation calculated from % body fat with a mean bias for women mean bias 577 (83 to 1072), men 521 (-58 to 1101) respectively.

Table 1: Table comparing male and female patients, in terms of body composition and resting energy expenditure (REE) estimated by five different equations, using either lean body mass or weight minus % body fat for the Katch McArdle and Cunningham equations.

	Patients	Male	Female
number	317	195	122
Age years	65.0±15.9	66.9 ±15.2	63.4 ±15.5
Body mass index kg/m^2	26.2±5.8	25.8 ±4.6	27.0 ±7.3
Pre dialysis serum urea mmol/L	18.0±5.2	18.3 ±5.1	17.6 ± 5.3
Equilibrated dialysis session Kt/Vurea	1.40±0.27	1.36 ±0.26	1.46 ±0.28**
% Body fat	31.6±11.8	29.0 ± 0.3	35.7 ±12.9***
Lean body mass kg	26.2±6.6	28.3 ±6.4	22.8 ±5.4***
Appendicular muscle mass kg	19.1±6.3	20.7 ±6.3	16.1 ±4.6***
Fat mass index kg/m^2	23.4±12.3	21.9 ±10.4	26.4 ±14.8*
Fat free mass index kg/m^2	17.4±2.7	17.9 ±2.6	16.4 ±2.6***
REE HD Equation kcal/day	1509±241	1572 ±215	1408 ±248***
REE Harris-Benedict kcal/day	1437±244	1515 ±233	1311 ±206***
REE Mifflin StJoer kcal/day	1384±259	1417 ±229	1218 ±240***
REE Katch McArdle kcal/day	1345±232	1571 ±227	1206 ±188***
REE Cunningham kcal/day	1557±236	1631 ±224	1416 ±192***
REE Katch McArdle (%body fat) kcal/day	1834±239	1873 ±387	1770 ±417**
REE Cunningham (%body fat) kcal/day	2055±391	2095 ±364	1990 ±425**
Total energy expenditure kcal/day	1801±374	1890 ±369	1657 ±338***

. Data expressed as number, mean ± standard deviation, or percentage
* p<0.05, ** p<0.01, p<0.001 vs male patients.

Table 2:
Statistically significant univariate associations between resting energy expenditure (REE) and total energy expenditure (TEE) and patient demographics, dialysis factors and body composition.

variable	REE		TEE	
demographics	r	p	r	p
Age yr	-0.455	<0.001	-0.521	<0.001
months of haemodialysis	-0.236	<0.001	-0.201	0.003
Dialysis associated factors				
session time hour	0.498	<0.001	0.318	<0.001
dialyzer surface area m^2	0.469	<0.001	0.409	<0.001
Protein nitrogen appearance generation g/day	0.428	<0.001	0.405	<0.001
equilibrated Kt/V	-0.419	<0.001	-0.456	<0.001
Pre dialysis blood results				
creatinine umol/L	0.375	<0.001	0.395	<0.001
urea mmol/L	0.212	<0.001	0.249	<0.001
haemoglobin g/L	0.099	0.079	0.149	0.008
albumin g/L	0.146	0.011	0.221	0.001
weekly erythropoietin dose IU	-0.077	0.168	-0.120	0.031
erythropoietin resistance IU/week.kg.gHb	-0.258	<0.001	-0.268	<0.001
Body size and composition				
Weight kg	0.886	<0.001	0.743	<0.001
extracellular water L	0.719	<0.001	0.561	<0.001
intracellular water L	0.681	<0.001	0.643	<0.001
skeletal muscle mass kg	0.717	<0.001	0.640	<0.001

skeletal muscle mass index kg/m^2	0.665	<0.001	0.643	<0.001
fat free mass kg	0.658	<0.001	0.279	<0.001
height m	0.619	<0.001	0.578	<0.001
body mass index kg/m^2	0.521	<0.001	0.378	<0.001
fat free mass index kg/m^2	0.481	<0.001	0.477	<0.001
body fat mass kg	0.461	<0.001	0.290	<0.001
fat mass index kg/m^2	0.419	<0.001	0.272	<0.001
% body fat	0.125	0.029	0.036	0.534

(r values) as Pearson or Spearman univariate correlation analysis.

Table 3:

Multivariable association with resting energy expenditure (REE) and total energy expenditure (kcal/day).

	β	StE β	St β	t	95% CI	p
REE						
age	-5.3	-0.69	-0.32	-7.6	-6.7 to -3.9	<0.001
SMM	14.9	1.02	0.62	14.7	13.0 to 16.9	<0.001
vintage	-96.7	22.9	-0.17	-4.2	-141.9 to -51.5	<0.001
TEE						
age	-7.9	1.25	-0.29	-6.3	-10.4 to -5.5	<0.001
SMM	23.3	2.87	0.40	8.1	17.5 to 28.9	<0.001
employment	406.5	49.7	0.37	8.2	308 to 505	<0.001
vintage	-121.2	38.1	-0.14	-3.2	-196 to -46	0.002
Co-morbidity	105.1	3.82	0.12	-2.8	30.5 to 181	0.006
PNA	2.7	1.09	0.12	2.5	0.5 to 4.8	0.015

Age years, Skeletal muscle mass (SMM) kg, log dialysis vintage (vintage) years, co-morbidity score Low vs High (Comorbidity), employment vs no employment (employment), protein nitrogen appearance (PNA) g/day. Standard error β (StE β), standardised β (St β), 95% confidence interval (95% CI). (REE model: r^2 0.79, adjusted r^2 0.62, TEE model: r^2 =0.81, adjusted r^2 0.64).

Appendix

Resting Energy Expenditure (REE) was estimated from a newer novel predictive equation which was derived and validated in a cohort of HD patients [4].

$REE = -2.497 * Age(years) * Factor_{age} + 0.011 * Height^{2.023}(cm) + 83.573 * Weight^{0.6291}(kg) + 68.171 * Factor_{sex}$

where Factor age is 0 if age <65 and 1 if ≥65 and Factor sex is 0 if female and 1 if male

Physical activity data - Each reported activity was assigned a Metabolic Equivalent of Task (MET) value as per the Compendium of Physical Activities [16]. Sleep time per day was assumed to be 8 hours and any unreported time during the day was assumed as the time performing light activities at home. A Mean daily MET value was calculated.

Total Energy Expenditure (TEE) was estimated from the following equation.

$$TEE = REE * Mean\ Daily\ MET$$

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