Disease-specific predictive formulas for energy expenditure in the dialysis population

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Abbreviations:

REE	Resting Energy Expenditure
TEE	Total Energy Expenditure
BSA	Body Surface Area
BMR	Basal Metabolic Rate
BMI	Body Mass Index

Running Head Equations for metabolic rate in dialysis patients

ABSTRACT

Background

Metabolic rate is poorly understood in advanced kidney disease, direct measurement being expensive and time-consuming. Predictive equations for Resting Energy Expenditure (REE) are needed based on simple bedside parameters. Algorithms derived for normal individuals may not be valid in the renal population. We aimed to develop predictive equations for REE specific for the dialysis population.

Design

200 subjects on maintenance dialysis underwent a comprehensive metabolic assessment including REE from indirect calorimetry. Parameters predicting REE were identified, regression equations developed, and validated in 20 separate subjects.

Results

Mean REE was 1658±317 kCal/day (males) and 1380±287 kCal/day (females). Weight and height correlated positively with REE (r^2=0.54 and 0.31) and age negatively above 65 years (r^2=0.18). The energy cost of a unitary kg of body weight increased non-linearly for lower Body Mass Index. Existing equations derived in normal individuals underestimated REE (bias 50-114kCal/day for three equations). The novel derived equation was:

$$REE(kCal/day)=-2.497\cdot Age\cdot Factor_{age}+0.011\cdot height^{2.023}+83.573\cdot Weight^{0.6291}+68.171\cdot Factor_{sex}$$

where $Factor_{age}$=1 if ≥65 years and zero if <65, $Factor_{sex}$=1 if male, and zero if female.

This algorithm performed at least as well as those developed for normal individuals in terms of limits of agreement and reduced bias. In validation with Bland-Altman technique, bias was not significant for our algorithm (-22±96kCal/day). 95% limits of agreement were +380 to -424 kCal/day.

Conclusion

Existing equations for REE derived from normal individuals are not valid in the dialysis population. The relatively increased REE in those with low BMI implies the need for higher dialysis doses in this subgroup. This disease-specific algorithm may be useful clinically and as a research tool to predict REE.

INTRODUCTION

The primary function of the kidneys is to remove metabolic waste products and in advanced kidney disease dialysis needs to replace this function. However, methods used to assess dialysis dose in end-stage kidney disease (ESRD) do not take account of metabolic rate. Instead, the most commonly employed method adjusts urea clearance by dialysis over a single session to the subject's total body water volume – usually estimated by the Watson equation[1]. Dialysis dose is estimated using Kt/V_{urea} ,where K represents dialyser urea clearance, the duration of the session and the denominator V, body water volume[2]. This model assumes that uremic toxin production rate is a function of body water volume.

There are marked differences in survival in relation to gender and body size in patients undergoing haemodialysis (HD), in contrast to findings in the general population. Despite co-morbidities, including diabetes associated with obesity, there is a strong negative association between BMI and mortality in patients on HD[3, 4], and the survival advantage of women seen in the general population is not present in those on dialysis. DOPPS data indicate that women may benefit from a greater dialysis dose than men[5] and in a large HD dose study (HEMO), women in the higher dialysis dose intervention group (eKt/V 1.53) had a significantly lower mortality than those in the standard dose group (eKt/V 1.16)[6]. These survival differences suggest that defining minimal dialysis requirements in terms of Kt/V, may result in relative under-dialysis of women and those with lower BMI.

Morton and Singer have hypothesised that metabolic rate unidirectionally defines GFR in normal individuals, suggesting that it may be more physiological to adjust dialysis dose to a measure of metabolic rate[7, 8] rather than body water. However, little attention has been paid to the use of alternative algorithms which adjust dialysis dose to metabolic rate.

In order to study this, it is necessary to have validated algorithms for Basal Metabolic Rate specific to the dialysis population. Developing such algorithms would permit retrospective and prospective studies investigating potential use of Kt/Metabolic Rate as an alternative to Kt/V_{urea}. Furthermore, they would also find clinical utility in the estimation of dietary requirements in dialysed patients. Equations derived historically in normal populations[9],[10],[11]

may not be applicable to subjects with renal failure given their metabolic disturbance and their burden of co-morbidities.

The principal aim of this study was to devise bedside algorithms specific to the dialysis population predicting Resting Energy Expenditure (REE), a close marker of Basal Metabolic Rate (BMR). Emphasis was placed on ensuring simplicity in the algorithm suitable for bedside use. A secondary aim was to determine the relationship of metabolic rate to gender and body size parameters including BMI which are important determinants of survival in dialysis patients. This would help to define groups that might benefit from a dialysis algorithm that adjusts dialysis requirements to REE.

METHODS

Study design

After Research Ethics Committee approval, a prospective cross-sectional study was performed on 200 patients established on dialysis. Subjects underwent a single comprehensive metabolic analysis including measurement of REE using indirect calorimetry, Fat-Free Mass (FFM) estimation using bioimpedance, and body-size parameters. This permitted development of an equation to predict REE. This equation was then validated in further cohort of 20 HD patients.

Study population

Subjects age>18 on hospital or home HD or peritoneal dialysis (PD) were included. Exclusion criteria were hospital admission in previous month, active or recent acute infection, chronic infection such as tuberculosis in the previous 12 months, blood-borne virus infection and untreated thyroid dysfunction.

Metabolic analysis

Body size parameters and nutritional investigations

Height and body weight were measured using calibrated scales. Blood nutrition parameters including blood haemoglobin, serum albumin and thyroid function were measured on the day of the metabolic study.

Indirect Calorimetery

Subjects were requested to refrain from eating and physical activity for 2 hours prior to the study. For those on HD, measurements were taken pre-dialysis. Analyses were performed in a room at 21-25^{0}C. Subjects were asked to lie supine and still for 15 minutes prior to and throughout indirect calorimetry. Measurements were taken in a quiet room ensuring no disturbance.

A VMax 29n metabolic cart (CardinalHealth/Sensormedics) was used, employing an overhead canopy to collect expired air and perform indirect calorimetry. The mass-flow sensor and gas-analyser were calibrated for each subject. Calorimetry was performed until steady-state was achieved, defined as 5 minutes of <5% variation in oxygen and carbon dioxide production rates (VO_2,VCO_2) and respiratory quotient(RQ). This was almost invariably achieved within 20 minutes, and usually in <15 minutes. In the small proportion of patients (<5%) where steady state could not be achieved in 20 minutes due to $V0_2$ or VCO_2 variability, steady state was considered as the first 5 minute period of <10% variation in above parameters. $V0_2$, VCO_2 and RQ for each patient permitted calculation of REE using the Weir equation:

REE(kCal/day)=1.44·[3.9·VO_2(ml/min)+1.1·VCO_2(ml/min)]

Bioimpedance Analysis

FFM was estimated by whole body bioimpedance using a Xitron Hydra 4200 device with wrist/ankle electrode measurements according to manufacturer guidelines. Bioimpedance analysis was performed in supine position during the period of rest prior to indirect calorimetry.

Physical activity assessment and estimation of Total Energy Expenditure

Physical activity was estimated from the Stanford 7-day recall questionnaire[12]. For each patient, time-averaged metabolic equivalent of task (MET) was calculated from questionnaire data. Time sleeping was considered to have a unitary MET value of 1. Total Energy Expenditure (TEE) was estimated by multiplying time-averaged MET by REE.

Derivation of Predictive Equation

Biometric or blood nutrition markers predicting REE were identified using Pearson's correlation. The relationships of biometric parameters with REE were determined by linear or non-linear regression. Where linear regression was appropriate, linearity was tested using runs tests. Where linearity was not demonstrated, non-linear regression was used to mathematically describe the relationship of parameters with REE. General forms of non-linear regressions used were $y=a*x^b$ or $y=a*x^b+c$.

Design of an equation to predict REE

The relationships of body-size parameters such as height and weight with REE were non-linear, and initially non-linear regressions for REE of the general form below were including height, weight and age as variables of the general form:

$$REE = H * Height^h + W * Weight^w + A*Age^a \qquad \text{Equation1}$$

These multiple non-linear regressions had multiple solutions (multiple global minima), so multiple linear regression was employed after linearising the relationship of weight and height with REE using power function transformations. The relationship of these variables with REE was found to be of the form $REE=a*variable^b$. The optimum power function transformation for each variable was determined separately, by plotting log(variable) against log REE. The slope was used to estimate "b" using a linear regression in the form:

$\ln(REE) = b * \ln(variable) + c$ Equation2

where variable represents height or weight and the slope b represents the linearising power transformation that can be applied to the variable to linearise its relationship with REE. Linearity of the transformed function was confirmed using the runs test.

In multiple linear regression for REE, gender was treated as a binary variable. Age was considered to have a linear relationship with REE for subjects ≥65 years (see results).

A multiple linear regression equation was constucted for REE by including age, height^{b1}, weight^{b2} and gender as factors in the model where b1 and b2 represent the linearising power transformations from equation 2. Multiple linear regression was performed with SPSS v 16 software. The resulting regression equation represented the novel equation for REE based on the parameters above.

Validation of an equation to predict REE

The novel equation for REE was validated by two methods. First, by comparison in the study population, by the Bland-Altman technique[13], of measured REE and REE predicted by the novel equation and existing equations derived in the normal population (Schofield[10], Harris-Benedict[9] and Mifflin-St Jeor[11]). Secondly, the novel equation for REE was applied to a validation cohort (n=20) and predicted REE compared to measured REE using the Bland-Altman technique.

RESULTS

Population demographics

96.5% of subjects were on HD and 3.5% PD (Table 1). 15.6% of patients were on low-dose prednisolone (5-7.5mg/daily), for reasons including previous transplantation, vasculitis and polymyalgia rheumatica.

Resting Energy Expenditure, physical activity and Total Energy Expenditure in the study population

REE from indirect calorimetry and physical activity level (time-averaged METs) derived from the Stanford questionnaire, are shown in Table 2 along with estimated TEE. Physical activity did not significantly differ between males and females but REE was significantly higher in males as was estimated TEE (Figure 1). REE correlated weakly with physical activity level (time-averaged MET) (r^2=0.03, p<0.009). The least physically active tertile had lower REE than the most active tertile (1483 v 1636 kCal/day, p=0.02).

Relationship of biometric parameters with REE

Variables correlating with REE are shown in Table 3. Age and blood hemoglobin concentrations had inverse correlations with REE. Height, weight, pulse rate, body temperature, mean daily MET, serum creatinine, FFM (bioimpedance) and residual renal urea clearance correlated positively with REE. Age, height and weight had highest correlation coefficients with other parameters explaining only a small proportion of the variance. Serum CRP and parathyroid hormone did not correlate with REE. There were no ethnic differences although our population was predominantly white with the non-white group constituting a relatively small proportion of the study population (see Table 1).

Height had a non-linear relationship with REE. The optimum linearising power transformation derived from the regression ln(REE)=b*ln(height)+c for height was 2.023 (95% C.I. 1.618-2.428) such that REE could be described as a function of height:

$REE=fn(height^{2.023})$ Equation 3

This is shown in Figure 2. Linearity of the transformed data was confirmed using the runs test (p=0.53).

The relationship of weight with REE could be similarly described. The optimal power transformation for weight to linearize its relationship with REE was 0.629 (95% CI 0.548-0.710). Linearity of the transformed data was confirmed using the runs test (p=0.74). Consequently, REE could be described as a function of weight (Figure 3) as:

$REE=fn(weight^{0.6291})$ Equation 4

The relationship of age with REE was more complex, REE reducing as age increased. The relationship could be explained using a power function, but confidence intervals were very wide. It was therefore decided to describe the relationship using linear regression. A cut-off age above which age correlated best with REE was calculated and determined to be ≥65. For those with age≥65 the relationship of REE with age could be considered linear (runs test p=0.99), with REE reducing as age increased (r=-0.428, p=0.009, Figure 4). For those aged <65 there was no significant relationship of age with REE (r=0.064, p=0.55).

Energy cost of body weight and its relationship to Body Mass Index

The energy "cost", of a unitary kg of body weight was determined for each patient from the ratio of REE to body weight ($kCal.day^{-1}kg^{-1}$). The relationship with BMI is shown in Figure 5. The relationship was non-linear - for lower BMI, REE/kg increased,.

Predictive equation for REE in dialysis patients

Multiple linear regression to generate a predictive equation for REE

The multiple linear regression for REE included parameters $height^{2.023}$, $weight^{0.6291}$, age (if ≥65) and gender in the form:

$REE=A\cdot Age\cdot Factor_{age}+H\cdot height^{2.023}+W\cdot Weight^{0.6291}+S\cdot Factor_{sex}$ Equation5

where A, H, W and S are constants in the linear regression, units are height (cm), weight (kg), age (years). $Factor_{age}$ is 0 if age <65 of 1 if ≥65 and $Factor_{sex}$=0 if female or 1 if male.

Parameter estimates for A, H, W and S are shown in Table 4 with confidence intervals. All were significant predictors of REE in the model. The regression explained 66.3% of the variance in REE (r^2=0.663), therefore the final predictive equation for REE was:

$REE=-2.497\cdot Age\cdot Factor_{age}+0.011\cdot height^{2.023}+83.573\cdot Weight^{0.6291}+68.171\cdot Factor_{sex}$ Equation6

Addition of a constant did not improve variance in REE explained by the model. When other variables correlating with REE (Table 3) were added to this regression model they were not

found to be significant predictors of REE except for addition of pulse rate which improved the model marginally (r^2=0.674). However, we did not include this parameter in the final model as its measurement may be difficult to standardise. Exclusion of patients on peritoneal dialysis from the regression model did not significantly improve the variance in REE explained by the model (r^2=0.664).

*Validation of the novel predicted equation for REE and performance of existing equations developed in normal individuals***.**

The performance of equation 6 and existing equations for REE in the study population (n=200) are shown in Table 5 compared to measured REE using Bland-Altman analyses. Existing equations had a tendency to under-estimate REE in this population (Table 6). Performance of equation 6 against measured REE is also shown graphically in Figure 6.

Performance of Equation 6 in the validation study (n=20) is shown in Figure 7. Bias was -22kCal/day (95% CI of bias +74 to -118kCal/day) which was not significantly non-zero. The upper 95% limit of agreement was 380kCal/day (95% CI of upper 95% limit of agreement 214-546) and lower 95% limit of agreement was -424kCal/day (95% CI of 95% lower limit of agreement -258 to -591). Bias was not significantly correlated with the average of measured and predicted REE (r=0.30, p=0.2). The correlation r^2 coefficient of predicted REE to measured REE was 0.64 in the validation group.

DISCUSSION

We set out to derive an algorithm specific to the dialysis population to predict metabolic rate using biometric parameters. The parameters best predicting REE were weight and height. These parameters were not linearly related with REE. It is known that weight and FFM closely predict REE in normal individuals[14]. However, FFM estimation is not easily obtainable without use of bioimpedance, and therefore it is unlikely to be useful in developing bedside predictive equations for REE or for algorithms that may be applied to population or registry-based studies.

We found a complex relationship of REE with age. Below the age of 65, there was no significant relationship of REE with age but above this there was an inverse correlation. Equations developed in normal individuals, such as the Schofield equation[10], have attempted to address this by developing different equations for REE for different age groups. However, in our dataset there were limited numbers of younger individuals, which is typical of dialysis populations, making this approach more difficult. The decision to exclude age as a factor when <65 was pragmatic.

The Mifflin-St Jeor, Harris-Benedict and Schofield equations assumed the relationships of weight and height with REE to be linear, though we have shown these to be non-linear. Hence their approach risks systematic bias as is demonstrated in our Bland-Altman analyses. We attempted to use multiple non-linear regression to predict REE using functions including weight and height as power functions. However there were wide confidence intervals for iterated parameters. We therefore used linear regression after applying linearizing transformations to height and weight. This may be criticised as there is co-linearity between height and weight. This limitation should be considered but is not easily resolved given the constraints of subject numbers that can be recruited in such studies for regression models.

The final equation developed for REE from multiple linear regression (equation 6) included height, weight, gender and age. Addition of further parameters (Table 3) to the model was possible, but without substantial improvement in the variance explained by the model with the exception of pulse rate which improved the model very marginally. Pulse rate was excluded from the final model as its measurement requires careful standardisation and its inclusion in the model would have limited the usefulness of the equation in registry datasets. Residual renal urea clearance correlated significantly with REE was not included in the final regression as its inclusion did not improve the model.

Performance of Equation 6 in the original study population compared to existing equations developed in normal individuals showed no significant bias and improved limits of agreement. However, this should be interpreted with caution as this validation procedure was performed in the same study population as that from which the formula had been derived. Consequently, a second validation was performed in 20 separate subjects using the Bland-Altman technique[13]. Again, REE predicted from Equation 6 showed similar limits of agreement and no significant bias as in the first Bland-Altman plot, although confidence intervals are wider due to the smaller number of subjects in this validation study. We therefore conclude that the novel equation for REE performs at least as well as existing equations for REE in terms of limit of agreement, and reduces bias when compared to the Schofield, Mifflin-St Jeor and Harris-Benedict equations.

There is only one other study in the literature which describes a predictive equation for REE in the dialysis population. This is a recent pilot study with low numbers (N = 67). The best

model included age, REE, serum albumin and CRP. The predictive power of this model at R^2 = 0.489 was less than that of the three generic equations described here[15].

Equations for REE derived in normal populations tended to underestimate REE in the dialysis population. We caution, however, against a potentially false conclusion that REE is relatively raised in patients on dialysis compared to the general population. This may not be correct as these equations were derived in historic populations of normal individuals which bear little resemblance to a modern dialysis population. Without a control group of normal individuals in this study it is not possible to draw conclusions about the effect of renal failure and the uraemic state on REE. Our own results differ somewhat from those reported by Kamimura *et al* of REE in patients with kidney disease in Brazil where they demonstrated that the Harris-Benedict and Schofield equations tended to over-estimate REE[16]. However, this study population was very different from ours in that gender mix was reversed, ages were considerably lower, ethnicity different, and the study included subjects with non-dialysed chronic kidney disease. Limited available data from small studies suggest that REE may be increased in those on HD compared to normal controls[17, 18] but reduced in those with chronic kidney disease[16, 19, 20]. Reduction in REE in CKD compared to normal controls may be due to lower level of physical activity[21]. This demonstrates the need to validate equations for REE in the population in which they are to be used.

Equation 6 is likely to be both useful clinically particularly when used in combination with an estimate of mean MET to allow estimation of total daily energy expenditure. In keeping with previous data[22] we found low levels of physical activity in this group. The contribution of estimated physical-activity-related energy expenditure to total energy expenditure was approximately one third in men and women. Due to the small degree of inter-individual variation in physical activity level, it is possible to estimate that TEE is therefore REE*1.44 for men and 1.42 for women (Table 2) and therefore it is possible to obtain a rapid bedside estimate of TEE in patients on dialysis. In the normal population, physical activity is more variable so this estimation is much less likely to be accurate[12]. Low physical activity level in patients with ESKF has also been previously demonstrated in studies assessing physical activity using questionnaire-based techniques and accelerometers[23]. Similar findings have

been found with even early CKD[24]. The relationship (though weak) between REE and physical activity level may be related higher FFM in more physically active individuals.

Use of this equation will allow the design of both retrospective and prospective research studies to examine the hypothesis that dialysis dose would be better adjusted according to metabolic rate, rather than Watson Volume[8, 25, 26]. It has already been demonstrated that adjusting dialysis dose according to body surface area (BSA) rather than Watson volume would deliver greater dialysis to women and men of lower body mass index[27, 28], the groups who seem relatively under-dialysed by the current Kt/V algorithm. This may be because of a close mathematical relationship of REE to BSA.

Potential reasons for the relative under-dialysis of certain subgroups by the Kt/V_{urea} model are suggested in this study. The relationship of BMI with the unitary energy "cost" of 1kg of body weight demonstrates that the cost increases at low body mass index. At low body mass index, the relatively higher metabolic rate per unit of body mass may be reflected in increased uremic toxin generation. This important relationship requires further exploration and may underlie body size differences in survival[3]. Our data is supported by a recent study of urea generation rate in patients on dialysis which showed higher urea generation rate per unit body mass in small women[29].

A limitation of this study is that the population was largely on HD as our unit has only a small PD programme. Although these patients were included in the study, numbers were low and the validity of the novel equation for the PD population cannot be assumed. We felt it advantageous to include a mixture of patients on HD and PD to generate an algorithm for REE that is broadly applicable to the dialysis population. The small size of PD programmes in comparison to HD is likely to limit development of equations for REE specific to the PD population. The majority of our subjects were Caucasian which may limit the applicability of the equation to other groups. If TEE is also estimated from REE then it should also be considered that there may be variation in physical activity level according to ethnic group[30].

A further limitation is that the thermic effect of food was not fully excluded by our instructions that patients fast for 2 hours prior to the indirect calorimetry, potentially resulting in slight over-estimation of REE. The thermic effect of food is related to its energy content and is likely

to have been of <50kCal magnitude for patients who ingested food in the 12 hour period prior to indirect calorimetry[31]. Considering the high proportion of patients with diabetes we felt it unlikely that a more prolonged fast would be rigorously adhered to by patients.

In conclusion, this study proposes a novel equation for REE specific to patients on dialysis which may be clinically useful. Its use in registry-based datasets might help determine whether adjusting dialysis dose according to REE might expose relatively under-dialysed groups and the effect of this on their survival.

Practical Application

Resting Energy Expenditure, similar to Basal Metabolic Rate, is the amount of energy expressed in kCal/day required for one day in conditions of rest. The algorithm presented, specific to the dialysis population, provides a method of its estimation based on simple body-size measures and may be useful for nutritional assessment.

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Table 1

Demographics of 200 subjects recruited in study of metabolic rate in patients on dialysis

	Mean ± SD or proportion(%)
Dialysis modality	
Hospital HD	95.0%
Home HD	1.5%
Peritoneal dialysis	3.5%
Age (years)	62.7 ± SD 15.2
Gender	59.5% male 40.5% female
Height (cm)	168.5 ± SD 10.3
Weight (kg)	75.0 ± SD 18.6
Dry weight	73.6 ± SD18.4
Body Mass Index	26.2 ± SD5.9
Body surface area (Dubois formula, m^2)	1.84 ± SD0.25
Waist diameter (cm)	100.7 ±SD16.2
Hip diameter (cm)	89.5 ±SD12.5
Waist:hip ratio	1.13 ±SD0.16
Ethnicity	
White	82.5%
Non-white	17.5%
Comorbidities	
Diabetes	27.1%
Ischemic heart disease	30.3%
Structural heart disease	17.1%
Peripheral vascular disease	16.7%
Malignancy	9.5%
Thyroid dysfunction	9.0%
Treated hyperthyroidism	1.5%
Treated hypothyroidism	7.5%
Stroke or TIA	12.6%
Treatment with corticosteroids	15.6%
Blood haemoglobin (g/dL)	11.4± SD1.2
Serum albumin(mg/L)	35.3± SD4.7

Table 2

Energy expenditure in males and females in the dialysis population

	Males (Mean ± SD)	Females (Mean ± SD)	Males v Females (T-test, p)
Time-average METs	1.44 ± 0.13	1.42 ± 0.11	p=0.26
Resting Energy Expenditure(kCal/day)	1658 ± 317	1380 ± 287	<0.001
Exercise-related Energy Expenditure (kCal/day)	743± SD303	583 ±SD195	<0.001
Calculated Total Energy Expenditure (kCal/day)	2401 ± SD565	1963 ± SD433	<0.001

Table 3

Factors correlating significantly with REE

Parameter	r	r^2	p
Age	-0.35	0.12	<0.001
Height	0.55	0.31	<0.001
Weight	0.74	0.54	<0.001
Pulse	0.25	0.06	<0.001
Body Temperature	0.14	0.02	0.05
Mean daily Metabolic Equivalent of Task	0.18	0.03	0.009
Serum hemoglobin	-0.19	0.04	0.006
Residual renal urea clearance	0.21	0.04	0.003
Fat free mass (bioimpedance)	0.68	0.46	<0.001
Creatinine (pre-dialysis in HD or plateau in PD)	0.20	0.04	0.006

Table 4
Parameter estimates in a multiple linear regression for REE based on age, height, weight and sex described in equation 5

Parameter	Parameter estimate	Standard Error	95% Confidence Interval Lower bound	95% Confidence Interval Upper bound
A	-2.497	0.363	-3.213	-1.78
H	0.011	0.003	0.004	0.018
W	83.573	6.608	70.541	96.605
S	68.171	32.198	4.673	131.67

Table 5
Bland-Altman analyses comparing measured REE with that predicted by existing equations and equation 6. Bias was significant for the Schofield, Harris-Benedict and Mifflin-St Jeor equations which indicated that they under-estimate REE. The greatest In terms of r^2, the best performing equation was the novel equation.

	Schofield equation[1]	Harris-Benedict equation	Mifflin-St Jeor equation	*Equation 6*
Upper 95% CI of upper 95% limit of agreement	503	491	560	*426*
Upper 95% limit of agreement	454	443	511	*379*
Lower 95% CI of upper 95% limit of agreement	404	396	462	*332*
Upper 95% CI of bias	78	83	142	*27*
Bias	50	55	114	*0*
Lower 95% CI of bias	21	27	85	*-27*
Upper 95% CI of lower 95% limit of agreement	-304	-286	-235	*-332*
Lower 95% limit of agreement	-354	-334	-284	*-379*
Lower 95% CI of lower 95% limit of agreement	-404	-381	-333	*-426*
Correlation with measured REE (r^2)	0.62	0.65	0.63	*0.66*

Legend of Figures

Figure 1
Total Energy Expenditure in the study population was considered to be a combination of REE and exercise-related energy expenditure. Error bars shown represent the standard error of the means.

Figure 2
Non-linear relationship of REE and height
The shallow curve shown shows a non-linear regression in the form $REE=height^{2.023}+c$ (equation 3)

Figure 3
Non-linear relationship of weight and REE
The curve shown shows a non-linear regression in the form $REE=weight^{0.629}+c$ (equation 4).

Figure 4
Relationship of age with REE
Using an age cutoff of ≥65, below this there was no significant relationship of REE with age. Above this age correlated negatively with REE, this relationship being linear. The linear regression line with 95% C.I. is shown.

Figure 5
Body Mass Index and its relationship with energy "cost" of a unitary 1kg of body weight.

Figure 6
Bland Altman plot comparing measured REE with that predicted by equation 6 in the study population (n=200).
Broken lines show bias, which was not significant, and the upper and lower 95% limits of agreement (see Table 5).

Figure 7
Bland Altman plot comparing measured REE with that predicted by equation 6 in the validation dataset (n=20 patients).
Broken lines show bias, which was not significant, and the upper and lower 95% limits of agreement.

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