New resting energy expenditure prediction equations for patients with rheumatoid arthritis

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Objectives. Resting energy expenditure (REE), one of the main components of total energy expenditure, can be measured via indirect calorimetry and/or predicted from equations. The latter may be misleading in RA, as they do not take into account the metabolic alterations occurring in RA. The objectives of this study are to evaluate the accuracy of widely used REE-predictive equations in RA patients against measured REE and to develop RA-specific equations.

Methods. We assessed REE (via indirect calorimetry and several predictive equations), fat-free mass (FFM; via bioelectrical impedance) and disease activity (CRP) in RA patients and healthy controls. Data from 60 RA patients (experimental group) were used to assess the accuracy of existing REE equations and to develop new equations. The new equations were validated in an independent cross-validation group of 22 RA patients. These two groups were merged and two final equations were developed.

Results. All equations significantly under-predicted measured REE (from 15% to 18.2%, all at P < 0.001) in the RA experimental group, but not in the control group. Both equations demonstrated a high validity in the cross-validation group, the new final REE prediction equations developed from the total RA sample (n = 82) were: Model 1: REE (kcal/day) = 126.1 × FFM0.638 × CRP0.045 (R² = 0.70) and Model 2: REE (kcal/day) = 598.8 × weight0.47 × age-0.29 × CRP0.066 (R² = 0.62).

Conclusion. The new equations provide an accurate prediction of REE in RA patients and could be used for clinical monitoring of resting metabolism of these patients without the requirement for specialized personnel.

KEY WORDS: Resting energy expenditure, Metabolism, Equation, Prediction.

Introduction

The assessment of energy expenditure is important for clinical practice and research, as imbalances between energy intake and expenditure may have significant health implications [1]. In healthy individuals, total energy expenditure is composed of three major components: resting energy expenditure (REE, accounting for ~70%), thermogenic effect of food and physical activity (accounting for ~15% each) [2]; however, the contribution of these components to total energy expenditure may significantly change with chronic diseases [3]. REE can be significantly altered by smoking [4], infection and chronic inflammatory disease [5–7], such as RA. This is the most common type of inflammatory arthritis in adults, with an estimated prevalence of ~1% in Europe and North America [8].

RA is accompanied by a metabolic abnormality, referred to as rheumatoid cachexia. This manifests with excessive production of pro-inflammatory cytokines, particularly TNFα. Overproduction of TNFα enhances protein catabolism [7, 9] leading to involuntary loss of fat-free mass (FFM) and increased REE [10, 11]; this may be accompanied by accumulation of fat mass, and can have detrimental health effects [12].

Indirect calorimetry, the most accurate method of measuring REE, is time consuming, involves expensive equipment and requires trained personnel [13]. Hence, several prediction equations have been developed to estimate REE from easily accessible variables (i.e. age, gender, height, weight) or FFM, the body’s metabolically active tissue [14]. In general, such equations are developed based on regression analysis using REE as the dependent variable and factors that may influence REE as independent variables. The result of such analysis highlights the most influential factors, indicating which would be the best to incorporate in the prediction equations. The existing REE formulae are easy to use, inexpensive and universally available, but they have been developed based on data deriving from healthy individuals. Therefore, they may be misleading in RA as they do not take into account the hypermetabolic processes associated with this disease [15–17], thus underpredicting actual REE in RA patients. However, accurate prediction of REE would be important in several circumstances, such as the prescription of diets that aim to counterbalance the enhanced protein breakdown seen in RA flares [18].

We hypothesized that the currently available REE-predictive equations are inaccurate in patients with RA. The aims of the present study were: (i) to evaluate the accuracy of widely used REE-predictive equations in RA patients against measured REE and (ii) to develop more accurate, RA-specific, equations.

Methods

Participants

Consecutive, consenting volunteers with RA, all meeting retrospective application of the revised 1987 ACR classification criteria [19] were recruited from rheumatology outpatient clinics of the Dudley Group of Hospitals NHS Trust in the UK. Data from 60 RA patients (experimental group) and from 16 apparently healthy volunteers from hospital and laboratory personnel were used for the assessment of the agreement between measured and predicted REE (from multiple existing equations). Data from the RA experimental group were also used for the development of two new REE-prediction equations. A subgroup of the RA experimental group, consisting of 20 RA patients who had a clinical indication for treatment with anti-TNFα therapy as per guidelines currently in force in the UK [20], were assessed before (baseline) and after initiation of this treatment (2 weeks), with the re-assessment used to investigate whether the newly developed equations were accurate when disease activity changed. Another,
Resting metabolism and RA

Disease duration (yrs) 12.0 (6.0–16.0) 7.0 (3.0–16.0) 16.8 (8.0–27.0) 19.5 (8.2–33.2)
CRP (mg/l) 18.0 (9.5–29.5) 10.0 (5.2–22.7) 11.0 (6.0–28.0) –
DAS28 4.4
ESR (mm/1st h) 26.8 26.0 16.7 11.1
Height (cm) 171.0 164.1 163.8 159.0
BMI (kg/m²) 26.5 27.7 55.7 11.3
Body fat (%) 34.0 30.2 34.9 3.4
Weight (kg) 81.9 7.2 5.4 2.7
Age (yrs) 62.7 8.4 11.3 60.3

Table 1. Mean ± s.d. and median (range) for all studied variables in male and female RA patients of the model development group (experimental and cross-validation groups, n = 82)

Males (n = 26) Females (n = 56) Total (n = 82)
Age (yrs) 62.7 ± 8.0 61.7 ± 11.1 62.0 ± 10.2
Height (cm) 171.0 ± 9.7 160.8 ± 6.0** 163.9 ± 8.7
Weight (kg) 81.9 ± 15.9 66.3 ± 16.7** 71.2 ± 17.9
BMI (kg/m²) 27.7 ± 4.4 25.5 ± 5.9 26.2 ± 5.6
FFM (kg) 57.3 ± 11.6 40.7 ± 7.2** 45.5 ± 11.2
Body fat (%) 30.2 ± 5.2 34.9 ± 8.8 33.4 ± 8.1
Disease duration (yrs) 12.0 (6.0–16.0) 7.0 (3.0–16.0) 8.0 (5.0–20.0) 11.0 (6.0–28.0)
CRP (mg/l) 18.0 (9.5–29.5) 10.0 (5.2–22.7) 11.0 (6.0–28.0) –
ESR (mm/1st h) 26.0 (10.5–37.2) 16.8 (8.0–27.0) 19.5 (8.2–33.2) –
DAS28 4.4 ± 1.4 4.2 ± 1.4 4.3 ± 1.4

Significance between males and females: *P < 0.05; **P < 0.001.

Table 2. Means ± s.d. and median (range) for demographic, anthropometric and disease-related characteristics of the RA (experimental and cross-validation groups) and control groups studied

RA Controls
Experimental (n = 60) Cross-validation group (n = 22) n = 16
Gender Males 20 6 16
Females 40 16 10
Disease duration (yrs) 8.0 (2.0–16.0) 8.5 (4.2–13.2) –
Age (yrs) 62.7 ± 11.3 60.3 ± 6.1 42.1 ± 11.8**
Height (cm) 164.1 ± 9.6 164.0 ± 6.7 166.3 ± 9.8
Weight (kg) 72.3 ± 18.6 68.0 ± 15.9 70.4 ± 11.3
BMI (kg/m²) 26.5 ± 5.4 25.4 ± 6.3 24.4 ± 2.7
FFM (kg) 46.2 ± 12.2 43.6 ± 8.0 52.4 ± 10.9
Body fat (%) 34.0 ± 8.4 31.8 ± 7.3 24.3 ± 8.5**
CRP (mg/l) 11.0 (6.0–28.0) 11.0 (4.0–28.5) –
ESR (mm/1st h) 26.8 ± 23.6 – –
DAS28 4.4 ± 1.4 – –

No significant differences were found between experimental and cross-validation RA groups.

Significance between experimental RA and control groups: *P < 0.001.

Completely separate group of 22 different RA patients (independent cross-validation group), who had not been included in the aforementioned RA experimental group, was also used as an independent sample for further validation of the new equations. After the development and validation of the new REE equations, we combined the experimental and cross-validation groups to develop our two final REE equations. Demographic and anthropometric data of the RA experimental and cross-validation groups and the healthy control group appear in Tables 1 and 2. RA patients had to be on stable medication for at least 3 months prior to assessment. In the RA experimental group, medications (used alone or in combination) were: 29/60 sulfasalazine, 18/60 hydroxychloroquine, 45/60 methotrexate, 2/60 azathioprine, 4/60 cyclosporin, 6/60 leflunomide, 13/60 steroids and 20/60 biological anti-TNF therapy. Exclusion criteria for both experimental and cross-validation groups were: previous/current thyroid disorders, malabsorption, pregnancy, diarrhea, proteinuria, abnormal liver function, obstructive or restrictive lung disease, congestive heart failure and current infection. Information was given to all participants in written format, and, for the special follow-up visit was arranged in the rheumatology research unit for final consent and assessment. The study had prior approval by the local research ethics committee and the Dudley Group of Hospitals Research and Development Directorate and all volunteers provided informed consent according to the Declaration of Helsinki.

Procedures

After visiting the data collection site early in the morning (8–9 a.m.) following a 12-h overnight fast, participants attended a single 2-h laboratory session. Only the patients who were treated with anti-TNFα were assessed twice, at baseline and 2 weeks after initiation of treatment, with identical procedures being followed at all visits. Demographic and anthropometric characteristics were assessed first, followed by the REE measurement. A blood sample together with assessment of the disease activity score (DAS28; [21]) were performed last.

Standing height was measured with a Seca Stadiometer 208. Body mass and body composition were evaluated via bioelectrical impedance (Tanita BC418-MA). We chose to use bioelectrical impedance as it is an accurate and valid method in healthy individuals [22, 23] and also has the advantage of reproducibility in the routine clinical setting; moreover, RA patients are willing to undergo such a measurement due to its simplicity and similarity to normal weighing [24]. Although a different bioelectrical impedance device/equation has been validated in RA patients [25], the accuracy of the current apparatus (Tanita BC418-MA) in this population is currently unknown.

Actual REE was measured via indirect calorimetry—adhering to well-described methodological standards [26] —following a 12-h overnight fast and after patients refrained from strenuous exercise for 72 h prior to assessments. Participants rested for a 20-min period prior to measurement in a semi-darkened, quiet and thermoregulated (22°C) room. An automated gas analyser (Metalyzer, Cortex Biophysik, Borsdorf, Germany), calibrated before each test using standard gases of known concentration, was used to record respiratory parameters every 20 s, while subjects inspired room air through a free-breathing face mask. Data were collected over a period of 40 min with the participants being instructed to refrain from sleeping or hyperventilating. Mean values of REE for that period were calculated using the Weir equation [27] after excluding the first and the last 5 min.

Sixteen different equations (Table 3) used in clinical practice were also utilized to predict REE in the RA experimental and healthy normal control groups. Most of them incorporated in their prediction model easily measurable values (e.g. age, weight, height) while others were based on FFM. Contemporary RA disease activity was measured via ESR and CRP (both measured in the routine laboratories of the Dudley Group of Hospitals); and clinically using the DAS28 [21], with the relevant joint counts performed by a single specialistometry nurse.

Data analyses

Routine pre-analyses were conducted using the Kolmogorov–Smirnov normality tests to detect if variables were normally distributed. Comparisons for variables that were not normally distributed were conducted using non-parametric tests (Mann–Whitney or Wilcoxon) and results are reported as median (range). Correlation coefficients (Pearson’s or Spearman’s) were utilized to investigate associations between the studied variables. Paired samples t-test, intra-class correlation coefficients and the Bland and Altman method [28] were utilized to assess agreement between all prediction equations and actual REE measured via indirect calorimetry, and to assess the validity of the new equations in the anti-TNFα-treated RA group, as well as in the independent cross-validation group. This analysis allows the calculation of bias (mean of the individual differences between estimates) via the 95% limits of agreement (i.e. ± 2 s.d. from the mean bias) and the percent coefficients of variation (percentage of error prediction calculated as s.d. of the difference between measured and predicted REE divided by the mean of the measured and predicted REE and then multiplied by 100 [28]). Assessment of linearity of relationships between REE and the predictor variables was performed first, and variables were transformed, if necessary, to obtain a linear relationship. Analysis of covariance (ANCOVA) was used to determine which of the measured demographic/anthropometric (e.g. gender, FFM) data and the disease activity assessments (CRP, ESR, DAS28) affected REE in the experimental RA group. Linear regression analysis was used for the
The development of the REE prediction equations in the experimental RA group. Following the validation of the new equations in the anti-TNFα-treated and independent cross-validation groups, we merged the experimental and the independent cross-validation groups to develop our final prediction equations via linear regression analysis. Statistical analysis was performed with SPSS software (version 11.0, SPSS Inc, Chicago, IL, USA). Statistical significance for all analyses was set at \( P < 0.05 \).

**Results**

**Measured REE in RA and controls**

A total of 103 RA patients were asked to participate, of whom 82 agreed. Demographic and anthropometric data for the RA and control groups are shown in Tables 1 and 2. Compared with the RA experimental group, controls had similar height, weight, BMI and FFM (all at \( P > 0.05 \)) but were significantly younger (\( P < 0.001 \)). Unadjusted, measured REE did not differ significantly between RA patients and controls (1638.3 ± 359.5 vs. 1576.5 ± 203.8 kcal/day, \( P > 0.05 \), respectively) but the difference was highly significant after adjustment (using ANCOVA for age, gender and FFM). It is well known that REE increases proportionally with FFM [14], weight [29] and disease activity [11]. Indeed our results from ANCOVA revealed that FFM and weight had the highest prediction power in the total RA sample (both at \( R^2 = 0.50, P < 0.001 \)) while gender did not significantly influence the prediction of REE (\( P > 0.05 \)) when CRP was incorporated in the models. Using linear regression analyses, the best prediction models of REE (dependent variable) were achieved after incorporating as independent variables (i) FFM (\( F_{1.57} = 95.3, P < 0.001 \)) and CRP (\( F_{1.57} = 38.9, P < 0.001 \) with a prediction power of \( R^2 = 0.73 \) (adjusted \( R^2 = 0.72 \)) and (ii) weight (\( F_{1,59} = 61.3, P < 0.001 \), age (\( F_{1,59} = 9.3, P = 0.004 \)) and CRP (\( F_{1,59} = 15.9, P < 0.001 \) with an \( R^2 = 0.67 \) (adjusted \( R^2 = 0.66 \)). As such, by adopting a previously used similar model structure [30], we have developed two prediction models for REE:

- **Model 1**: REE = 127.74 + FFM\(^{0.62}\) × CRP\(^{0.068}\)
- **Model 2**: REE = 421.57 + weight\(^{0.51}\) × age\(^{-0.25}\) × CRP\(^{0.75}\)

**Validation**

**Experimental—anti-TNFα group**. These new equations were applied in the 20 RA patients of the experimental group, who were evaluated twice, i.e. before (baseline) and after initiating anti-TNFα treatment (2 weeks). Disease activity in this subgroup decreased significantly after anti-TNFα treatment [baseline vs. 2 weeks: CRP = 22.0 (7.0–41.7) vs. 12.0 (7.0–22.5) mg/l, \( P = 0.026; ESR = 31.0 (27.0–43.0) \) vs. 14.5 (9.7–31.0) mm/1st h, \( P = 0.001; DAS28 = 5.7 ± 0.7 vs. 4.6 ± 0.6, P < 0.001 \)]

At baseline, the predicted REE from Model 1 (prediction of REE from FFM and CRP) was not significantly different from that measured in the laboratory (1811.2 ± 279.8 vs. 1810.5 ± 299.7 kcal/day, \( P > 0.05 \)) and the correlation between them was strong (\( r = 0.84, P < 0.001 \)). Moreover, for the same variables the bias ± 95% limits of agreement and prediction error were 0.7 ± 419.5 kcal/day and 11.8%, respectively. At 2 weeks, predicted and measured REE were again not significantly different (1734.3 ± 302.2 vs. 1691.5 ± 307.9 kcal/day, \( P > 0.05 \)) and had a similarly strong correlation (\( r = 0.89, P < 0.001 \)). The bias ± 95% limits of agreement and percent coefficient of variation were 42.8 ± 362.4 kcal/day and 10.7%, respectively.

For Model 2 (prediction of REE from weight, age and CRP), baseline-predicted REE was not significantly different to that

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**Table 3. Mean ± s.d., differences, bias (95% limits of agreement) and percent coefficient of variation (prediction error) between measured and predicted REE from known formulae [indicated by author or organization name (reference)] in the experimental RA and healthy control groups**

<table>
<thead>
<tr>
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<th>Experimental RA group (n = 60)</th>
<th>Controls (n = 15)</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± s.d.</td>
<td>Bias (LIM&lt;sub&gt;MAQ&lt;/sub&gt;)</td>
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<tr>
<td>Measured REE</td>
<td>1638.3 ± 359.5</td>
<td>–</td>
</tr>
<tr>
<td>Harris–Bennectid [29]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1414.5 ± 277.2&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–230.8 (472.2)</td>
</tr>
<tr>
<td>FAO/WHO/UNU [35]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1459.6 ± 163.3&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–185.8 (523.9)</td>
</tr>
<tr>
<td>Owen et al. [33, 34]</td>
<td>1428.1 ± 292.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–217.3 (637.8)</td>
</tr>
<tr>
<td>Mifflin et al. [36]</td>
<td>1330.5 ± 289.9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–314.9 (453.9)</td>
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<tr>
<td>20 kcal/kg ratio [37]</td>
<td>1449.7 ± 375.4&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–195.7 (526.0)</td>
</tr>
<tr>
<td>Cunningham [38]</td>
<td>1500.2 ± 264.1&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–146.3 (461.1)</td>
</tr>
<tr>
<td>Riff predicted from B</td>
<td>1344.4 ± 340.2&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–309.2 (530.4)</td>
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<tr>
<td>Luke and Schoeller [41]</td>
<td>1509.6 ± 244.5&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–136.9 (464.8)</td>
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<tr>
<td>Ravussin et al. [43]</td>
<td>1433.6 ± 254.6&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–212.9 (462.5)</td>
</tr>
<tr>
<td>Ravussin et al. [44]</td>
<td>1446.4 ± 255.9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–200.2 (462.3)</td>
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<tr>
<td>Elia [53]</td>
<td>1425.9 ± 254.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–220.6 (461.9)</td>
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<tr>
<td>McNell et al. [42]</td>
<td>1323.0 ± 262.8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–323.5 (461.3)</td>
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<tr>
<td>Heymsfield et al. [39]</td>
<td>1300.6 ± 264.1&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–345.9 (461.1)</td>
</tr>
<tr>
<td>Kashwazachi et al. [40]</td>
<td>1436.7 ± 299.8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>–209.8 (462.6)</td>
</tr>
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</table>

<sup>a</sup>Most widely used equations.

<sup>**</sup>Level of significance between measured and predicted REE: \( P < 0.05 \); \( * P < 0.001 \).

<sup>LIM<sub>MAQ</sub></sup>: 95% limits of agreement; CV<sub>%</sub>: percent coefficient of variation; BI: bioelectrical impedance.
measured in the laboratory (1788.4 ± 219.3 vs 1810.5 ± 299.7 kcal/day, P > 0.05), correlated at r = 0.60 (P = 0.01) while the bias ±95% limits of agreement and prediction error were −22.0 ± 473.5 kcal/day and 13.4%. After 2 weeks, predicted REE was again not found to be different from measured REE (1715.3 ± 196.0 vs 1691.5 ± 307.9 kcal/day, P > 0.05). The correlation between the variables was r = 0.74 (P = 0.001) and the bias ±95% limits of agreement and prediction error were 23.7 ± 408.3 kcal/day and 12.2%.

In this group, we have also performed an additional analysis to see whether individual changes in REE could be accurately tracked by the newly developed prediction equations. Results revealed that the changes in measured REE between baseline and 2 weeks (92.7 ± 208.4 kcal/day) were not significantly different from the changes (baseline vs 2 weeks) of either predicted REE from Model 1 (57.8 ± 115.4 kcal/day) or Model 2 (68.1 ± 114.9 kcal/day) (both at P > 0.05). The bias ±95% limits of agreement and percent coefficient of variation between measured and predicted REE were −10.3 ± 385.0 kcal/day and 12.1%, respectively. In addition, Equation (2) was also not significantly different from laboratory measured REE (1591.3 ± 258.6 vs 1618.2 ± 342.0 kcal/day, P > 0.05); the correlation was significant (r = 0.78, P < 0.001); the bias ±95% limits of agreement and percent coefficient of variation were −26.9 ± 420.2 and 13.3%, respectively.

Independent cross-validation RA group. In this group (n = 22), REE predicted by Model 1 was not significantly different to measured REE (1566.2 ± 278.2 vs 1552.5 ± 277.1 kcal/day, P > 0.05) and correlated strongly with it (r = 0.75, P < 0.001). The bias ±95% limits of agreement and percent coefficient of variation were 13.6 ± 385.0 kcal/day and 12.5%, respectively. Moreover, no significant differences were detected for Model 2 (predicted: 1551.7 ± 251.8 vs measured: 1552.5 ± 277.1 kcal/day, P > 0.05). The two variables correlated significantly (r = 0.57, P = 0.007) and the bias ±95% limits of agreement and percent coefficient of variation were −0.7 ± 481.0 kcal/day and 15.8%.

Final REE equations

Given that the REE equations developed using the experimental RA group were valid, we combined the experimental (n = 60) and cross-validation (n = 22) RA groups, and developed the following final two equations that revealed a prediction accuracy of $R^2 = 0.70$ (adjusted $R^2 = 0.69$) and $R^2 = 0.62$ (adjusted $R^2 = 0.61$), respectively.

$$REE \text{ (kcal/day)} = 126.1 \times \text{FFM}^{0.638} \times \text{CRP}^{0.045}$$  \hspace{1cm} (1)

$$REE \text{ (kcal/day)} = 598.8 \times \text{weight}^{0.47} \times \text{age}^{-0.29} \times \text{CRP}^{0.066}$$  \hspace{1cm} (2)

Figures 1–3 depict the association of FFM, weight and CRP with REE before and after log transformation; their curvilinear relationship diminished after log transformation. REE values obtained by Equation (1) and indirect calorimetry were not significantly different (1610.9 ± 285.4 vs 1621.2 ± 342.9 kcal/day, P > 0.05) and correlated significantly (r = 0.89, P < 0.001). The bias ±95% limits of agreement and percent coefficient of variation of measured and predicted REE were −10.3 ± 385.0 kcal/day and 12.1%, respectively. In addition, Equation (2) was also not significantly different from laboratory measured REE (1591.3 ± 258.6 vs 1618.2 ± 342.0 kcal/day, P > 0.05); the correlation was significant (r = 0.78, P < 0.001); the bias ±95% limits of agreement and percent coefficient of variation were −26.9 ± 420.2 and 13.3%, respectively.

Discussion

The findings of this study confirm our hypothesis that existing REE equations were inaccurate, all under-predicting REE in RA patients, possibly due to RA-induced hypermetabolism. This made necessary the development of new, RA-specific equations. The REE equations developed have better prediction power and accuracy than any of the multiple equations evaluated in this study.

REE in the experimental RA sample was slightly—but not significantly—higher compared with the healthy control group. Previous studies have clearly established that REE is increased in patients with RA compared with age- and gender-matched controls due to the excessive production of pro-inflammatory cytokines, particularly TNFα [11, 32]. This is evident when the reduction of FFM typical of rheumatoid cachexia is taken into account [11]. The present study was not aimed at confirming this, so accurate matching of patients and controls was not employed, and this may be a limitation. However, it is worth noting that REE elevation of >10% above normal levels [11], has serious...
health implications, particularly when this extra energy derives from enhanced muscle catabolism [7, 9].

Using the RA experimental cohort, we evaluated the predictive accuracy of several existing REE formulae. Some of them incorporate easily obtained anthropometric data such as weight, height and age [29, 33–36], while others are based on FFM [37–44]. Estimation of FFM in the present study was different to some of the other studies; this may have resulted in a wider bias in the prediction of REE. None of these REE equations widely used in the clinical setting were accurate in RA, although some were accurate in our normal healthy controls. The most likely reason for this is that all formulae have been developed to predict resting metabolism in healthy individuals, thus not taking into account the metabolic changes occurring in RA. These findings reinforced the need for the development of RA-specific predictive equations. It is possible that similar disease-specific equations are required for other conditions with a significant systemic inflammatory component, such as inflammatory bowel disease.

In the course of developing such equations, we found that the best prediction power was achieved by incorporating in the model FFM and CRP. FFM reflects the biologically active metabolic component of the human body [14], and is therefore, the major determinant of REE prediction [45]. CRP, due to its relatively short half-life of ~19 h [46], is an accurate measurement of current systemic inflammatory load, more so than ESR, which has a much more prolonged ‘half-life’. We also found a strong association between REE and weight; hence, despite that it may not precisely reflect the metabolically active tissue of the body of RA patients (at the same weight, RA patients have significantly less FFM and more fat compared with healthy individuals [24]), we have developed a second equation based on weight, age and

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**Fig. 2.** Relationship between REE and CRP prior to and after log transformation.

**Fig. 3.** Relationship between REE and weight prior to and after log transformation.
CRP. The reason for developing this formula is that we wanted to produce an equation from variables that can be easily assessed (weight and CRP measured routinely in the clinics) and can be widely used in the clinical settings in the absence of FFM estimation. Our results showed that this equation achieved a higher prediction accuracy compared with all existing studied prediction formulae, and thus—based on its validity—it can be used for the prediction of REE in RA. Studies that have incorporated the same anthropometrical data in such formulae in the general population have revealed similar prediction power [29, 35, 36].

The new equations can facilitate continuous monitoring of REE in the RA population, without a requirement for sophisticated equipment (indirect calorimetry), specialized staff and prolonged time for assessment. This may help improve the management of these patients with nutritional support particularly in prolonged disease flares, during which increased protein intake may counterbalance protein catabolism [18], restore the equilibrium between energy intake and expenditure and possibly reduce the chances of increased fat deposition, which may be important in the context of the high cardiovascular morbidity and mortality associated with RA [47, 48]. Interestingly, in this sample of RA patients, gender did not have a significant impact on REE, so development of gender-specific equations, such as the Harris–Benedict, did not appear to be necessary. For the equation incorporating FFM, it is probable that by the inclusion of FFM in the new equation we have accounted for the differences between the genders; this is because dissimilarities in the resting metabolism between genders are mainly due to the differences in FFM [2] whereas after standardizing for FFM, REE difference between genders appears to be non-significant [49]. The lack of association between REE and gender in the equation incorporating weight and age is interesting: our analyses suggest that although gender was a significant predictor of REE, this significant influence diminished when CRP was incorporated in REE prediction. Hence, compared with gender, current inflammatory load has a more powerful influence on REE of RA patients suggesting that this acute inflammatory marker was necessary in our equations. The new REE equations need to be tested in larger and more diverse populations of males and females with RA, to include a wider age range, degrees of functional disability and disease activity.

Strengths of this study include the validation of the new REE equations in an independent patient group, as well as in a sub-group in whom disease activity, but not anthropometric characteristics, was changed within 2 weeks of treatment with anti-TNFα therapy. Moreover, the resulting total RA population in this study has age and gender characteristics similar to the total RA population followed up in our department (>1700 patients); as such, generalizability of our results in the general RA population may be appropriate. Weaknesses include the moderate sample size of the group used to develop the final REE formula: although several studies introduced REE equations deriving from smaller samples [33, 50, 51], there are studies utilizing data from a larger number of participants [36, 45, 52]. The use of more accurate apparatus for the estimation of FFM, such as dual energy X-ray absorptiometry, may also have added more credence to the present findings, since the estimation of FFM from the current apparatus has not yet been validated. Within these limitations, we conclude that existing prediction equations underestimate levels of REE in RA patients, most probably because the systemic inflammatory load associated with the disease is not taken into account. The RA-specific equations developed in the present study are accurate and valid (even when disease activity changes) and display a much improved REE prediction power.