Resting energy expenditure in a cohort of female patients with bipolar disorder: indirect calorimetry *vs* Harris-Benedict, Mifflin-St. Jeor, LARN Equations

Dispendio energetico a riposo in un campione di pazienti di genere femminile con disturbo bipolare: calorimetria indiretta vs equazioni Harris-Benedict, Mifflin-St. Jeor, LARN

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Summary

Objectives
To compare predictive formulae commonly used to calculate resting energy expenditure (REE) with the indirect calorimetry (IC) in a sample of female outpatients with bipolar I disorder, stabilised with long-term psychopharmacological treatment.

Methods
Seventeen female patients with bipolar I disorder were evaluated with an IC instrument (VO2000). IC values were compared with the Harris-Benedict, Mifflin-St. Jeor and LARN equation methods.

Results
The measured REE was not significantly correlated with the three equations. The mean differences between REE values estimated with Harris-Benedict, Mifflin-St. Jeor and LARN equations, and the value measured with IC was significantly different from zero. Moreover, a significant difference was found between the mean REE values measured with the IC and the mean values estimated with the three equations.

Conclusions
Equations commonly utilised for the assessment of REE are not alternatives to IC in female patients treated for bipolar I disorder.

Key words

Bipolar disorder • Calorimetry • Energy expenditure • Equation methods

Introduction

Weight gain, glucose intolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia are unwanted effects that can occur during psychopharmacological treatment of bipolar disorders [1 2]. The mechanism underlying weight gain that frequently occurs with the psychopharmacological treatment of bipolar disorders is still under debate. It has been hypothesised, for example, that atypical antipsychotics may trigger weight gain not only for the combined affinity for 5-HT2c serotonin and H1 histamine receptors [3], but also for the induction of a positive energy balance [4]. The management of excessive weight gain and obesity in patients treated with atypical antipsychotics is currently emphasized in the literature, and includes pharmacological interventions, dietary suggestions and several behavioural strategies, such as nutritional counselling and cognitive behaviourally-oriented programmes [5-7].

The assessment of resting energy expenditure (REE) can play an important role in the management of these patients, consenting the quantification of the energy necessary to reduce excessive weight gain and obesity.

REE is usually calculated in the general population with predictive formulae (i.e., Harris-Benedict, Mifflin-St. Jeor, or LARN equations) based on age, stature, body weight and gender. The reliability of such predictive formulae for patients with psychiatric disorders has been recently disputed, especially for patients with eating disorders [8]. To our knowledge, very few studies have systematically investigated the reliability of these formulae to calculate REE in patients who are taking psychotropic medications [9 10].

Indirect calorimetry (IC) has been proposed to overcome the potential limits of predictive formulae when they are applied to special populations of patients, which measures oxygen consumption and production of carbon dioxide [11]. To our knowledge, few studies have measured REE with the IC devices on patients with bipolar disorder [12-14].

The aim of this study was to compare the REE obtained us-

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ing a portable metabolic IC device (VO2000) with those calculated by the Harris-Benedict, Mifflin-St. Jeor and LARN equations in a cohort of patients undergoing stable psychopharmacological treatment for at least 6 months, and who were already followed-up in a naturalistic setting dedicated only to females with bipolar I disorder. We were interested in determining whether IC and predictive formulae could be considered as alternative methods for assessing REE in a clinical sample different from the general population.

Subjects

Seventeen female subjects with bipolar I disorder consecutively admitted to the outpatient section of the Psychiatric Clinic of the University of Pisa, Italy, between July 2004 and June 2008, were enrolled. Diagnosis of Bipolar I disorder was made according to the DSM-IV criteria, as listed in the SCID-IV section dedicated to mood disorders. Patients with psychiatric comorbidity were included in the study. Only one patient met diagnostic criteria for a second psychiatric disorder, namely obsessive-compulsive disorder (OCD).

All participants were provided with a complete description of the study, and gave written informed consent for participation, in accordance with the institutional requirements of the Azienda Ospedaliero-Universitaria Pisana. Patients with medical diseases interfering with metabolism (i.e., hypo/hyper-thyroid's functioning, pituitary diseases, diabetes, adrenal gland diseases), acute inflammatory states (e.g. infections), or chronic autoimmune disease were not enrolled.

Measurements

Data collection included weight and height measurement and IC with the portable metabolic calorimeter VO2000. The predictive regression equations of Harris and Benedict (1919) for current body weight (CBW) [15], LARN (1987) [16] and Mifflin-St. Jeor (1990) [17] were used to calculate REE.

Body weight and height

A physician involved in the study measured body weight on a medical balance and height with a stadiometer. Patients were standing, with heels together, arms to the side, legs straight, shoulders relaxed and head on the horizontal plane (looking straight ahead). Patients were weighed standing in the middle of a monthly-calibrated digital scale, wearing only underwear and without shoes, before breakfast. BMI was determined according to the usual formula of body weight divided by the square of height in meters.

Indirect Calorimetry

IC was performed at room temperature in a single session before breakfast using the VO2000 a portable metabolic measuring system. For this study, patients were asked to abstain from smoking, eating and drinking caffeinated and alcoholic beverages for at least 12 hours before the session, and to not perform physical exertion before the test. Upon arrival in the test room, patients were placed in a comfortable position on a medical seat, while the instrument was prepared immediately before measurements. The VO2000 uses an auto-calibration mode that calibrates the analysers using room air and proprietary software. The VO2000 uses a three-point harness system or single belt configuration for data collection in a field setting. The O2 analyser is a galvanic fuel cell with an accuracy of ±0.1%, while the CO2 analyser is a NDIR analyser with an accuracy of ±0.2%. The preVent pneumotach measures ventilation from expiratory flow volumes. A neoprene facemask used during data collection has an aluminium nosepiece that is adjusted at the bridge of the nose, a silicone coupler in front of the mouth for attaching the pneumotach and two strips of neoprene with Velcro to secure the facemask to the crown and nape of the neck.

Statistical analysis

Data are presented as means and standard deviations (SDs) for continuous variables and percentages for discrete variables. The associations between BMI and the measured and predicted REEs were analysed using Spearman correlation coefficients to take into account the skewed distribution of some variables. The Bland-Altman method [18] was used to study concordance between the VO2000 method with the Harris-Benedict, Mifflin-St. Jeor and LARN equations. The z-test was used to evaluate whether the mean of the differences between the values obtained by the three methods, with respect to VO2000, was or was not significantly different from zero. Furthermore, the Wilcoxon Signed-Ranks Test was performed to compare the mean REE values of the VO2000 method with those of the Harris-Benedict, Mifflin-St. Jeor and LARN equations. Statistical analyses were performed with SPSS 15 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Table I shows the demographic and clinical characteristics of the study sample. The mean age was 37 years and mean BMI was 28.8, ranging from 21.4 to 41.5, with 64.7% of the patients having a BMI ≥ 25, and 29.4% having a BMI ≥ 30.

TABLE I.
Anthropometric and clinical characteristics of the sample (n = 17). *Caratteristiche antropometriche e cliniche del campione (n = 17).*

Anthropometrics	Mean (SD)	Range
Height (cm)	166.1 (7.5)	155.0-184.0
Weight (kg)	79.5 (15.2)	57.0-105.5
Body Mass Index (kg/m^2)	28.9 (5.7)	21.4-41.5
Age (yr)	37.3 (11.4)	21.0-57.0
Resting Energy Expenditure		
VO2000 (kcal/day)	1122.1 (228.6)	790.0-1500.0
Harris-Benedict equation (kcal/day)	1547.8 (156.7)	1356.9-1809.4
Mifflin-St. Jeor equation (kcal/day)	1485.3 (177.9)	1295.0-1788.0
LARN et al. equation (kcal/day)	1559.3 (168.7)	1333.9-1863.1

TABLE II.
Atypical antipsychotics and mood stabilisers administered. *Antipsicotici atipici e stabilizzatori dell'umore somministrati ai pazienti.*

Patient #	Atypical Antipsychotic	Dosage (mg/day)	First Mood Stabilizer	Dosage (mg/day)	Second Mood Stabilizer	Dosage (mg/day)
1	Olanzapine	5	Oxcarbazepine	300	-	-
2	Olanzapine	3.75	Lithium	900	-	-
3	Olanzapine	7.5	Lithium	750	-	-
4	Olanzapine	10	Valproate	1200	-	-
5	Olanzapine	5	Carbamazepine	300	-	-
6	Olanzapine	15	-	-	-	-
7	Olanzapine	2.5	Lithium	600	-	-
8	Olanzapine	5	Valproate	500	-	-
9	Olanzapine	5	Valproate	1000	-	-
10	Olanzapine	2.5	Lithium	600	-	-
11	Olanzapine	5	-		-	-
12	Quetiapine	25	Lithium	750	Valproate	600
13	Aripiprazole	15	Pregabalin	225	-	-
14	Aripiprazole	2.5	-	-	-	-
15	Quetiapine	100	-	-	-	-
16	Quetiapine	100	Lithium	300	-	-
17	Aripiprazole	10	Lithium	600	Valproate	750

Table II summarizes treatments with atypical neuroleptics and mood stabilisers at the time of measurements. Figure 1 shows the Bland-Altman plots reporting the differences between REE values measured with VO2000 and those obtained using the other methods (Harris-Benedict, Mifflin-St. Jeor and LARN equations).
The mean of the differences between the REE values estimated with the Harris-Benedict equation and those measured with VO2000 (bias = 425.6 kcal/day) was significantly different from zero ($t = 8.48$; $p < 0.001$). Moreover, for the other two comparisons, the means of differences between Mifflin-St. Jeor method and VO2000 method was significantly different from zero (bias = 363.2 kcal/day; $t = 6.29$, $p < 0.001$) and also between LARN equation and VO2000 method (bias = 437.2 kcal/day, $t = 7.34$, $p < 0.001$).

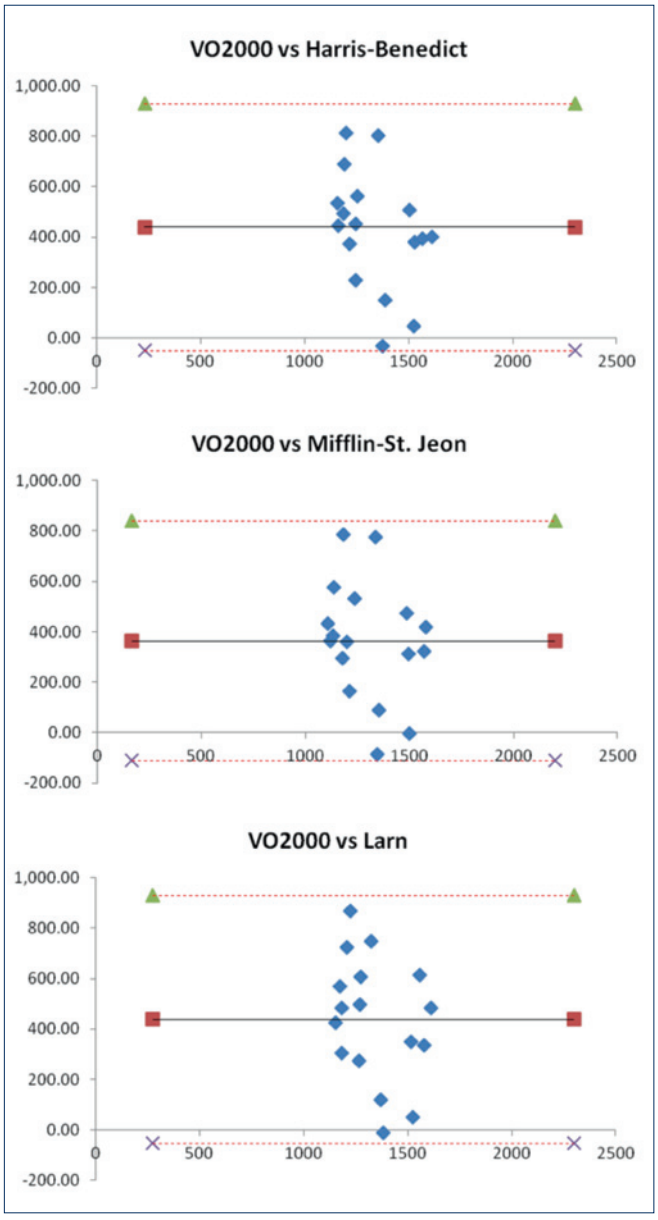

FIGURE 1.
Bland-Altman plots comparing the three methods of measuring REE considered together with IC. *Bland-Altman Plots che comparano i 3 metodi di misurazione del REE con la calorimetria indiretta.*

BMI was significantly correlated to REE measured using Harris-Benedict (rho = 0.77, p < 0.001), Mifflin-St. Jeor (rho = 0.69, p = 0.002) and LARN (rho = 0.78, p < 0.001) equations, but was not correlated to REE measured using the VO2000 method (rho = 0.08, p = 0.747).
The measured REE was not significantly correlated with the three methods (Harris-Benedict rho = 0.23, p = 0.376; Mifflin-St. Jeor rho = 0.24, p = 0.360; LARN rho = 0.17, p = 0.501).

The Wilcoxon Signed-Ranks Test showed significant differences between the mean REE values estimated with the VO2000 method and the mean values estimated with Harris-Benedict equation (Z = -4.23, p < 0.001), Mifflin-St. Jeor equation (Z = -4.06, p < 0.001) and LARN equation (Z = -4.17, p < 0.001).

Discussion

Our data indicate that the Harris-Benedict, Mifflin-St. Jeor and LARN equations overestimated REE in female patients with bipolar I disorder. The overestimation of REE using the above-mentioned equations in our sample was relatively consistent, and close to 400 kcal/day from the predicted REE value. A possible reason for the high overestimation error in the prediction of REE with the Harris-Benedict, Mifflin-St. Jeor and LARN equations is that they are tested in the nutrition field on the general population. Conversely, patients with bipolar I disorder are chronically in a significantly different condition compared to the general population. Bipolar disorder is characterised by extreme variations in mood, energy and in psychomotor activation *versus* retardation when bipolar patients shift from manic/mixed to depressive episodes. For example, abundant resources of energy characterise manic episodes; the increased physical activity has a significant impact on energy expenditure, accounting for 20–30% of the body's energy output [19]. A recent study suggested REE as a possible biological marker in the manic episodes of bipolar I disorder, considering the relevance of its variations when a manic/mixed episode occurs [14]. Given that, we evaluated only patients stabilised on medications for at least six months to avoid acute episodes that may have affected their energy expenditure. However, a stable condition requires long-term treatment with several psychotropic medications that have a profound impact both on metabolism and eating habits, as already noted by Skouroliakou and colleagues (2009) [10]. Our finding is concordant with that of Sharpe and colleagues (2005) [9] who reported that the Harris-Benedict equation overestimated the REE in a group of male patients taking clozapine. Nonetheless, there are several differences between the two studies, considering Sharpe's sample selection (only male patients) and the choice of enrolling patients who were taking clozapine. Thus, even if olanzapine and clozapine are both included in the same class of drugs, they have different receptor affinity profiles, and clozapine is considered as second-line treatment, when other antipsychotics (such as olanzapine) have already failed [20]. None of our female patients was taking clozapine. Our data are partially in line with Skouroliakou and Colleagues [10] who found that the Mifflin-St. Jeor and Harris-Benedict equations for adjusted body weight were accurate in estimating the energy needs of a sample of patients treated only

with olanzapine. However, the Harris-Benedict current body weight and Schofield equations showed significant overestimation error in the REE prediction ($p < 0.001$). Skouroliakou and Colleagues [10] concluded that the possible reasons for the high overestimation error in the prediction of REE with equations such as the Harris-Benedict and Schofield were the specific characteristics of this population, namely the effects of mental disease, antipsychotic medication use, mood changes and alterations in psychosocial rhythm. Nonetheless, they did make a narrow selection of patients, enrolling only those who were obese (body mass index > 30 kg/m^2) and treated with olanzapine. Patients in our sample were treated with olanzapine, quetiapine, aripiprazole and no selection was made on BMI. In general, there is a strong correlation between BMI and percentage of body fat. The positive relationship between energy expenditure and BMI has been previously reported [21]. In our study, we found a significant correlation between BMI and measured REE, but not between BMI and predicted REE, confirming the weakness of the predictive formulae in measuring REE in female patients with bipolar I disorder.

The main limitations of this study are the small sample size and the absence of a control group. Moreover, we are aware that a more refined measurement of metabolism should take into account several additional parameters, including urinary ammonia nitrogen, total nitrogen levels and body composition. However, these parameters were not included, considering the naturalistic setting of this preliminary study.

Conclusions

Our findings suggest that commonly-used formulas may not be considered as an alternative to the VO2000 method for assessment of REE in patients with bipolar I disorder. Clinicians are well aware that patients with a Bipolar Disorder are at higher risk than the general population for obesity and metabolic syndrome. Nonetheless, a resting energy expenditure assessment that includes IC is still lacking in the routine outpatient setting. We propose that IC become part of routine clinical evaluation when patients with bipolar disorder are followed-up, considering that formulae are not specific for this special population. Despite the limitations mentioned, our results are of interest because they demonstrate the feasibility and acceptability of a simple intervention in patients receiving psychotropic medications, who are usually concerned about the metabolic consequences of long-term treatment. Moreover, we agree with previous observations on the importance that REE studies in bipolar patients have for clinicians. For example, as suggested by Caliyurt and Altiay (2009) [14] the REE measurements might help psychiatrists to monitor bipolar patients in remission and to detect the development of manic episodes as they are characterised by increased energy levels that could be identified earlier if repeated REE measurements are performed.

Finally, we believe that future studies using gold-standard methods to assess REE in samples of patients with Bipolar disorder should take into account the different forms of Bipolar Disorders, including bipolar II Disorder, cyclothymic disorder and sub-threshold syndromes belonging to the overall spectrum of mood disorders [22].

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None.

Conflict of interests
None.

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