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Comparison of energy expenditure between women with anorexia nervosa in outpatient treatment and healthy controls

Comparação do gasto energético entre mulheres com anorexia nervosa em tratamento ambulatorial e controles saudáveis

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ABSTRACT

Objective

Resting metabolic rate is an important measure for nutritional monitoring in anorexia nervosa. This study aims to investigate the differences in resting metabolic rate measurements across various methods between underweight and recovered anorexia nervosa patients, as well as healthy controls.

Methods

Participants were categorized into three groups: active anorexia nervosa, recovered anorexia nervosa, and healthy individuals. Indirect calorimetry, the gold standard for resting metabolic rate measurement, was used to evaluate the performance of the Harris-Benedict, Schebendach, FAO/WHO, and Buchholz equations. Body mass index and fat free mass were also measured. Mean and median resting metabolic rate values across evaluation methods were compared, and Bland-Altman plots along with percent difference tables were employed to compare the different methods.

Results

In the active anorexia nervosa group, the Buchholz, Harris-Benedict, and FAO/WHO equations overestimated resting metabolic rate, whereas the Schebendach equation did not. In the recovered anorexia nervosa group, Schebendach's equation underestimated resting metabolic rate, while the other equations, with the exception of FAO/WHO, did not. Bland-Altman analysis supported the adequacy of the Schebendach equation in active anorexia nervosa. In recovered anorexia nervosa, proportional biases observed for the Harris-Benedict, Buchholz, and FAO/WHO equations indicated its inadequacies for this group.

Conclusion

In patients with active anorexia nervosa, the results indicate that the Schebendach equation may be adequate for estimating resting metabolic rate. However, none of the equations showed adequacy for estimating resting metabolic rate in recovered patients.

Keywords: Anorexia nervosa. Body composition. Body mass index. Electric impedance. Resting metabolism.

RESUMO

Objetivo

A taxa metabólica de repouso é uma informação importante para o monitoramento nutricional na anorexia nervosa e buscou-se investigar diferenças nas medidas da taxa metabólica de repouso por diferentes métodos entre pacientes de anorexia nervosa com baixo peso e recuperados e controles saudáveis.

Métodos

Os participantes foram distribuídos em grupos de anorexia nervosa ativa, anorexia nervosa recuperada e indivíduos saudáveis. A calorimetria indireta, medida padrão ouro da taxa metabólica de repouso, foi utilizada para comparar o desempenho das equações de Harris e Benedict, Shebendach, FAO/OMS e Buchholz. O índice de massa corporal e a massa livre de gordura também foram medidos. Foram comparadas médias e medianas dos métodos de avaliação da taxa metabólica de repouso e também foi empregado análise de Bland Altman e tabelas de diferenças percentuais para comparar os diferentes métodos.

Resultados

No grupo de anorexia nervosa ativa as equações de Buchholz, Harris e Benedict e FAO/WHO superestimaram a taxa metabólica de repouso, o que não foi observado com a equação de Schebendach. No grupo de anorexia nervosa recuperada, a equação de Schebendach subestimou a taxa metabólica de repouso, enquanto as outras equações, com exceção da FAO/OMS, não o fizeram. A análise de Bland Altman sugeriu a adequação da equação de Shedenbach na anorexia nervosa ativa. Na anorexia nervosa recuperada, os vieses proporcionais observados para as equações de Harris e Benedict, Buchholz e FAO/OMS indicaram sua inadequação para este grupo.

Conclusão

Em pacientes com anorexia ativa, os resultados indicam que a equação de Schebendach pode ser adequada para estimar a taxa metabólica de repouso. Nenhuma das equações mostrou adequação para estimar a taxa metabólica de repouso em pacientes recuperados.

Palavras-chave: *Anorexia nervosa. Composição corporal. Índice de massa corporal. Impedância elétrica. Metabolismo de repouso.*

INTRODUCTION

In Anorexia Nervosa (AN), significant weight loss affects body composition, leading to reductions in Fat Mass (FM) and Fat-Free Mass (FFM) [1]. Resting Metabolic Rate (RMR) decreases as well, primarily due to the loss of FFM, which is responsible for most of the energy expenditure. The RMR represents about 50 to 70% of total energy expenditure, making its calculation an important measure for nutritional monitoring in AN [2]. Besides FFM, factors such as sex, age, physical activity, and changes in thyroid, adrenal, and leptin hormones may also contribute to the reduction in RMR, albeit to a lesser degree [3].

The most reliable method for measuring RMR is Indirect Calorimetry (IC). Although it provides reliable data, IC relies on expensive equipment, making it impractical for routine use by health services. As an alternative to IC, predictive equations are widely used [4]. They are, however, lacking standardized references for individuals with AN, which could lead to both overestimation and underestimation of energy expenditure requirements [5]. In cases of weight recovery, the extent of energy expenditure needs further clarification.

Studies on the behavior of energy expenditure in AN were largely carried out in controlled, inpatient, or experimental environments [6]. The present study aimed to investigate the RMR of women with AN in the active and recovery phases undergoing outpatient treatment, and to compare it with the RMR of women with normal body weight, using the Harris-Benedict (HB), Food and Agriculture Organization/World Health Organization (FAO/WHO), Buchholz, and Schebendach equations [7-10] with IC as the gold-standard reference.

METHODS

Patients were selected from a specialized university outpatient public service. All patients had an AN diagnosis as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [1]. Groups were formed according to the following criteria: an active group (ANact), with a Body Mass Index (BMI) <18.5kg/m^2 and/or weight adequacy <85% of ideal weight, and the presence of key symptoms (intense fear of gaining weight and body image disturbance); a recovered group (ANrec), composed of previous AN patients, BMI value ≥18.5kg/m^2 and/or weight adequacy ≥85% of ideal weight calculated according to the minimum normal BMI of 18.5kg/m^2 [1], maintained for a sustainable period, as well as partial or full remission of the key symptoms cited above. The presence of key symptoms was determined by a multidisciplinary team of psychologists and psychiatrists of the institution. Healthy Individuals (HI) were selected according to the absence of AN symptoms, female sex, age between 18 and 40 years, and BMI between 18.5 and 24.9kg/m^2 [11]. The classification for adolescents between 10 and 19 years old employed the z-score of BMI/age, with the following cutoff points: underweight, ≤-2 z-score; adequate weight, >-2 <1 z-score [12].

Weight and height were measured by a Filizola® mechanical scale calibrated with ±0.1 kg accuracy, coupled to a stadiometer with ±0.1cm accuracy. BMI was calculated according to the quotient of weight in kilograms and the squared height in meters. Two patients who presented improvement in key symptoms, recovery of the menstrual cycles, and BMI of 18.1 and 18.5kg/m^2 were included in the ANrec group, since they reached the level of 85% weight adequacy [11,12]. A low-intensity (800µA/50 kHz) Quantum X® (RJL System) bioelectrical impedance (BIA) device measured the FFM through the manufacturer's Body Composition program, using the Resistance and Reactance data [13]. The FFM was employed for the calculation of the Buchholz equation. MetaCheck® calorimeter was employed for IC, at a comfortable room temperature of 22 to 25ºC. All participants were instructed to fast for at least 5 hours before testing. The device estimates the individual's RMR in kcal/day from VO2, according to the equation by Weir [14]. Measurements were performed at the same time of the day to avoid fluctuations in weight. Women who had diseases known to influence energy expenditure, such as those that affect thyroid metabolism, were excluded from the study. To estimate the RMR, the predictive equations of Schebendach, HB, FAO/WHO, and Buchholz [7-9], with IC as the reference method, were applied (Chart 1).

Chart 1 – Predictive equations used to calculate energy expenditure.

Harris-Benedict[7] (1918): BMR (kcal) = 655.09+ (9.563xWeight (kg) + 1.85xHeight (cm)-4.676×age (years)
Schebendach[10] (1995): BMR (kcal) = 1.84×HB (kcal)-1435 (kcal)
Buchholz[9] (2003): RMR (kcal) = 2268+ (86.6xFFM) × 0.239
FAO/WHO[8] (1989): 10 – 18 years: BMR (kcal) = 7.4Weight (kg) + 482Height (m) + 217;
18 – 30 Years BMR (kcal) = 13.3Weight (kg) + 334Height (m) + 35;
30 – 60 Years BMR (kcal) = 8.7Weight (kg) + 25Height (m) + 865.

Note: RMR: Resting Metabolic Rate; BMR: Basal Metabolic Rate; FFM: Fat-Free Mass. Obs.: RMR and BMR were used interchangeably; the results of the equations, apart from Buchholz, express the BMR.

Participants were informed about the study's objectives and protocols upon joining, and signed the Informed Consent Form previously approved by the institutional Ethics Committee under number 53641815.6.0000.5149.

The Statistical Package for Social Sciences IBM®SPSS® (version 25) was used for statistical analysis. Data on age, time since diagnosis, weight, and BMI were evaluated in relation to their distribution (Shapiro-Wilk method) and compared among the three study groups. Means were compared with ANOVA with post hoc Bonferroni correction (parametric distribution). Medians were compared by the Kruskal-Wallis or Mann-Whitney method (non-parametric distribution). RMR derived from the four equations were compared with IC, employing ANOVA or Mann Whitney test with post hoc Bonferroni correction, according to the type of distribution. Bland-Altman [15] plots were built to verify the agreement between the equations and IC with the percent differences between each equation and calorimetry on the y-axis {[(equation-RMR)/(equation+RMR)/2]*100} and equation and calorimetry mean [(equation+RMR)/2] on the x-axis. Distributions of percent differences and their correlation with equation and calorimetry means were also analyzed to verify the proportionality bias. The graphs for ANact, ANrec, and HI were plotted together for the same equation in order to allow a visual comparison of each group for the same equation. As an additional verification of the agreement, t-tests for single samples were performed with the percent differences obtained for each equation and for each clinical condition, in order to verify to what extent the mean differences observed were different from zero.

RESULTS

Eighteen AN patients undergoing outpatient follow-up were analyzed, 9 participants from the ANact group and 9 from the ANrec group. The HI group included 16 volunteers after excluding 2 participants with constitutional thinness (BMI: 18.1kg/m^2 and 18.3kg/m^2).

The mean age did not show significant differences among the ANact, ANrec, and HI groups (25.0±8.6 years, 22.1±6.9 years, 25.8±5.1 years; *p*=0.335, respectively). The time since diagnosis of ANact and ANrec also showed no differences (medians =48.0 and 28.5 months, respectively; *p*=0.470, Mann Whitney). The BMI of ANact and ANrec was significantly different (15.9±2.6kg/m^2 x 20.3±2.2kg/m^2, *p*=0.000), and there was no statistical difference between ANrec and HI (20.3±2.2kg/m^2 × 22.28±1.75kg/m^2, *p*=0.112). Mean weight was 39.4±5.9kg (ANact), 51.4±5.3kg (ANrec), and 60.3±6.7kg (HI), with *p*=0.000 (ANOVA). A lower, but not significantly different FFM was observed in ANact compared to ANrec (31.01±4,56kg x 37.59±1,89 kg, *p*=0.053), but a statistically significant difference was present when comparing FFM between ANrec and HI (37.59±1.89kg x 44.56±4.64kg, *p*=<0,001). In relation to IC (900.78±132.89kcal) in ANact, the RMRs calculated by the HB equation (1229.44±54.99, *p*=0.003), the Buchholz equation (1183.83±94.31 kcal, *p*=0.006), and the FAO/WHO equation (1159.70±61.5 kcal, *p*=0.012) were significantly higher. The Schebendach equation (781.98±46.80kcal, *p* 0,513) showed no statistical difference compared to IC. Analysis of HI did not show significant differences between IC and the HB and Buchholz equations, but both the Schebendach and the FAO/WHO equations showed significantly lower values than IC. Regarding ANrec, in comparison to IC (1337.55±352.66kcal), the Schebendach equation showed significantly lower values (1025.08±95.21kcal, *p*=0.003). The other methods did not display significant differences from those obtained by IC (Table 1).

The single-sample T-test analysis of the percent difference between equation and calorimetry [(equation-RMR)/(equation+RMR)/2]×100, together with the correlation of this percentage with the equation and calorimetry means, which are described in Table 2, allows for the description of the behavior of the equations in each state. A significant correlation (r≠0) between the percent differences and calorimetry and equation means suggests the existence of a proportionality bias. The analysis of Table 2 and the graphs allows observation of the proportionality bias in the use of the four equations in ANrec. For ANact, this type of bias was observed for the FAO/WHO equation. Additionally, it indicates the existence of a fixed bias, which is the obtaining of values that are persistently higher or lower, as a result of using one method compared to another; in this case, compared to IC.

Table 1 – Results of multiple comparisons of means (or medians) of resting metabolic rate as measured by indirect calorimetry with predictive equations, by study group.

Group	IC (kcal)	Method		
		Equations	RMR (kcal)	*p*
ANact*	900.78±132.89	Buchholz	1183.83±94.31	0.006
		HB	1229.44±54.99	0.003
		Schebendach	781.98±46.80	0,513
		FAO/WHO	1159.70±61.51	0.012
HI**	1510.25±213.10	Buchholz	1464.28±96.05	1.000
		HB	1414.63±72.83	0.419
		Schebendach	1167.91±134.01	0.000
		FAO/WHO	1364.56±86.37	0.023
ANrec**	1337.55±352.66	Buchholz	1320.04±39.19	1.000
		HB	1337.00±51.74	1.000
		Schebendach	1025.08±95.21	0.003
		FAO/WHO	1290.54±77.61	1.000

Note: *Mann-Whitney (Bonferroni correction); **ANOVA (Bonferroni correction). HB: Harris-Benedict; ANact: Active Anorexia; ANrec: Recovered Anorexia; HI: Healthy Individuals; IC: Indirect Calorimetry; RMR: Resting Metabolic Rate.

Table 2 – Behavior of the equations according to the study group: percent difference values and analyses of proportionality biases.

	Equations	ANact	ANrec	HI
Single sample t-test mean (IC)*	Buchholz	27.6 (18.8;36.5)	1.7 (-18.9;22.3)	-2.3 (-10.5;5.9)
	HB	30.4 (21.7;39.1)	3.8 (-15.2;22.8)	-4.8 (-12.8;3.2)
	Scheb	-12.1 (-25.0;0.8)	-21.5 (-39.2;-3.8)	-23.2 (-32.4;-14.1)
	FAO/WHO	25.8 (15.2;36.3)	-0.6 (-20.5;19.3)	-9.3 (-17.3;-1.3)
R^{2**} (*p*)	Buchholz	0.252 (0.169)	0.908 (0.000)	0.435 (0.005)
	HB	0.442 (0.051)	0.927 (0.000)	0.620 (0.000)
	Scheb	0.069 (0.452)	0.731(0.003)	0.122 (0.184)
	FAO/WHO	0.499 (0.033)	0.853 (0.000)	0.494 (0.002)

Note: *For percent difference values (y axis on Bland Altman plot): [(equation-IC)/(equation +IC)/2] x 100; **R2 for correlation between percent difference (y axis on Bland Altman plot) and equation and calorimetry mean (x axis on Bland Altman plot): (equation +IC)/2. ANact: Active Anorexia; ANrec: Recovered Anorexia; HB: Harris-Benedict; HI: Healthy Individuals.

It is possible to infer the presence of this type of bias for HB, Buchholz, and FAO/WHO equations for the ANact group, in which a concentration of percent difference values in the upper left regions of the graphs is observed, indicating overestimation of calorimetry values close to 40%, a fact that occurs to a lesser extent with the Shebendach equation. This situation is also supported by the analysis of the mean and median differences, in which, for the ANact group, the overestimation of the HB, Buchholz, and FAO/WHO equations and the absence of significant difference in relation to the Shebendach equation for the calculations of the RMR are observed.

The HB, Buchholz, and FAO/WHO equations showed the single-sample *t*-test with p values below 0.05 and percent difference values greater than 25% for the ANact group, as a result of the overestimation of the RMR. Conversely, the percent difference value of the Shebendach equation of -12.1% indicates a tendency to underestimate the RMR; however, this value is not significantly different from zero (Table 2). The Schebendach equation does not vary significantly as energy expenditure changes, and does not display a proportionality bias, determined by the linear correlation between the percent differences and the mean of the equations and calorimetry (R2=0.069, *p*=0.452).

Regarding the ANrec group, the graphs show that the equations, with the exception of Schebendach's, result in RMRs that are distributed more or less evenly around the zero percent difference line, as indicated by the means of the percent differences and non-significant p values in the single-sample T-test, a behavior similar to that of the HI group (Table 2). Of note, however, are the confidence intervals for the three equations, which are wider in the ANrec group than in the HI, denoting greater variation in RMR compared to the control group, with the finding of extreme values, positive or negative, in the graphs of the three equations. In the ANrec group, the Shebendach equation reveals an underestimation of RMR, and it is the only equation with a negative mean of percent differences and p values below 0.05 in the single-sample *t*-test, a situation similar to that observed in relation to the use of this equation in the HI group. The proportionality bias was observed in all equations for the ANrec group.

DISCUSSION

This study reinforces the role of the Shebendach equation in the estimation of RMR of patients with active anorexia in settings where IC is not available, which may help to avoid overestimation of energy expenditure by other equations. The Schebendach equation showed the best agreement with IC in the ANact group with a mean percent difference (-12,1%) closer to zero than those of other equations (Figure 1), indicating a smaller fixed bias and an absence of proportionality bias (lower Table 2). In this group, the HB, FAO/WHO, and Buchholz equations showed both greater fixed bias and significant proportionality bias (Table 2; Figure 1). Also, Schebendach equation's median was the only one that did not show statistically significant differences with the IC mean in the ANact group. Recent studies [16] also recommend the Schebendach equation in the absence of IC or bioelectrical impedance-derived equations. In the ANrec group, the Schebendach equation showed the presence of fixed bias. The HB, FAO/WHO, and Buchholz equations are comparable in the ANrec and HI groups, with low or absent fixed bias and absence of proportionality bias, with the exception of FAO/WHO in the HI group, which underestimated RMR. However, the confidence intervals for the three equations presented wide variations in the ANrec group, denoting greater variation in RMR compared to the control group, which may be related to different stages of recovery. Analysis with the Bland-Altman method allowed for the demonstration of the presence of proportionality bias in the use of the equations, both in the ANrec and HI groups, with the exception of the Schebendach equation in the HI group. Nevertheless, this equation showed important fixed bias in this group, with an important underestimation of RMR. Previous work has highlighted adaptive hypometabolism before nutritional recovery, that is, a reduction in energy metabolism that occurs in the context of severe energy restriction. On the other hand, during recovery, there is not enough evidence about metabolic alterations yet, which still raises questions about energy requirements in this phase [16].

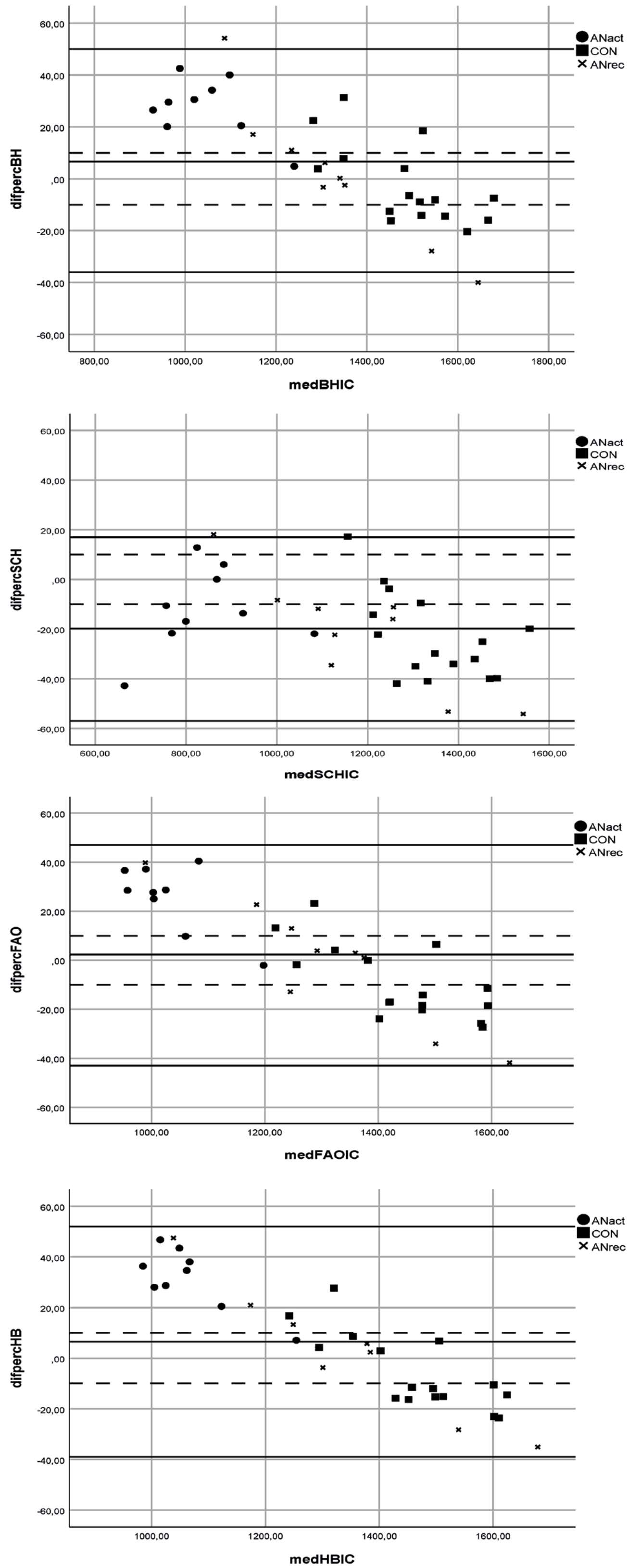

Figure 1 – Bland-Altman plots: analysis of agreement between equations and IC.

Note: Continuous lines: average and +1.96 SD; dotted lines: +10% of percent difference; difperc = percent difference for Harris-Benedict (HB), Buchholz (BH), Schebendach (SCH), and FAO/WHO (FAO); med = (equation+indirect calorimetry recording)/2 for Harris-Benedict (HBIC), Buchholz (BHIC), Shebendach (SCHIC), and FAO/WHO.

All patients have been enrolled in an Outpatient Clinic; therefore, they cannot be considered representative of the whole population of patients with AN. For reasons of cost and ease of operation, a hand-held calorimeter, which provides only O_2 consumption and assumes a 0.85 respiratory coefficient, was employed. Another limitation is the small sample size, which indicates the need for the present findings to be replicated in larger samples. However, this limitation is not easy to overcome due to difficulties in recruiting patients who meet the inclusion criteria or to the low commitment of AN patients to take part in studies. It is important to highlight that even in groups of normal individuals, predictive equations, when compared to IC, can present significant variations in different study groups, both in terms of overestimating and underestimating the RMR. Because of the very nature of statistical laws, predictive regression equations work best in groups of people. When applied to an individual, significant errors can occur. If the individual does not share determining characteristics of the group for whom the equation was developed (age, sex, body composition, and ethnicity), the chance of clinically important errors increases [17].

When evaluating women with AN younger than 18 years and young adults aged 18 to 30 years, Scalfi et al. [18] demonstrated that the Schebendach equation can predict energy expenditure with a reasonable accuracy. This accuracy could be observed only in the group of patients under. In this same study, they showed an overestimation of RMR by the HB and FAO/WHO equations. Another study evaluated RMR and phase angle as markers of qualitative changes in FFM [19]. The RMR was significantly lower in subjects with AN compared to constitutionally lean subjects, dancers, and controls [19]. Additionally, Bailly et al. [20] confirmed in their systematic review a tendency for a higher RMR in individuals with constitutional thinness in comparison to those with AN.

Obarzanek et al. [21] showed that there was no difference in Total Metabolic Rate (TMR) between patients and healthy individuals after long periods of recovery. In the present study, despite the small sample size, analysis of the graphs indicates similarity in the behavior of recovered and control patients, with the exception of some cases that appear closer to patients with active disease in the upper left part of the graph (Figure 1), indicating, together with the wide confidence interval variations, possible ANrec group heterogeneity.

The difference between the predictive equations in AN may be due to significant changes in body composition, which may also be related to the duration of the disease and recovery [22,23] and the lack of precision of the four RMR equations studied (Harris-Benedict, Buchholz, FAO/WHO, and Schebendach) in this group of patients.

Individuals with greater weight loss and very low BMI should have their energy supply carefully evaluated, as it should allow weight gain without developing refeeding syndrome [24]. The recovery process is carried out until the patient reaches the weight that allows for the recovery of menstruation and ovulation, the normalization of growth, and the development of secondary sexual characteristics. This process is carried out according to the patient's tolerance, and to avoid refeeding syndrome in the initial stages of the process, aiming for a weight gain of 0.5 to 1.4kg/week in hospitalized patients and 250 to 500g/week in outpatients [6]. A review study favored the "start slow, advance slow" approach, translating into a slow rate of refeeding, especially in patients with very low BMI at admission. Conversely, another study suggests "start higher, move faster", which means a process of refeeding with phosphate supplements, usually in patients with moderate malnutrition. From a clinical point of view, the use of a predictive equation that is consistent with the IC is essential in the initial phase of recovery [24].

There is a lack of studies that evaluate the energy expenditure of weight-recovered individuals with anorexia. This is the first Brazilian study that compares different equations routinely used in clinical practice with a gold-standard method (IC) in patients with AN.

CONCLUSION

In the ANact group, the Schebendach equation, in view of the absence of biases and because it does not imply a risk of overestimating the RMR, appears more adequate to estimate energy expenditure. In recovered individuals with AN who return to normal BMI, energy expenditure expressed in RMR behaves differently from that of active-phase AN patients. In recovered patients, the predictive equations of HB, Schebendach, Buchholz, and FAO/WHO displayed a behavior similar to that of normal patients but showed proportionality biases. Nevertheless, energy expenditure may vary over recovery time, and overestimation of RMR may occur, especially during the initial phase.

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