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TITLE PAGE

Body composition and resting energy expenditure in women with anorexia nervosa: is hyperactivity a protecting factor?

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ABSTRACT:

Background. In subjects with anorexia nervosa (AN) physical exercise may cause or even prevent weight loss, body composition alterations and adaptive thermogenesis. To investigate the influence of behavioral patterns on body composition and energy expenditure in women with AN, we conducted a retrospective analysis in 62 patients with AN referring to our outpatients' clinic.

Materials and Methods. We assessed anthropometric measurement of weight, height, and BMI; body composition was assessed by bioelectrical impedance analysis; resting energy expenditure was measured through indirect calorimetry. Patients' characteristics were assessed at the time of first evaluation.

Results. The subjects were both restricting type (ANR, n=39) and binge-eating/purging type (ANBP, n=23) according to DSM-5. We observed a lower reactance (58.63 (11.9) vs. 66.5 (15.5) Ohm, $p < 0.05$) and higher total body water in ANR subjects. No differences were found in phase angle, fat mass or fat-free mass, nor in REE measures. Within ANR subgroup, we identified two behavioral patterns, with or without physical hyperactivity. Compared to dieting and fasting subjects, hyperactive subjects showed higher phase angle [5.6(0.7) vs. 4.8 (0.8), $p < 0.05$], lower fat-free mass [82.5(6.8) vs. 89.9 (7.5)%, $p <0.05$], greater proportion of fat mass [17.5(6.8) vs. 10.1(7.5)%, $p <0.05$] and body cell mass[46.6(5.1) vs. 42.5(5.5)%, $p<0.05$]. Finally, hyperactive subjects had greater BMI than dieting or fasting subjects[18.2 (1.7) vs. 15.8 (1.7), $p<0.005$].

Conclusion. With limitations due to the small sample size, hyperactive subjects show body composition and energy metabolism features that seem protective in terms of prognosis.

Keywords: anorexia nervosa, body composition, energy metabolism, hyperactivity, physical activity

Introduction

Anorexia nervosa (AN) is a relatively common eating disorder characterized by difficulty in maintaining minimal weight, fear of gaining weight and distorted body image.

In patients with AN, undernutrition is responsible for weight loss and body composition (BC) alterations. Weight loss is due to diminished fat, lean and bone mass: assessing alterations of these compartments can be helpful in evaluating the disease stage[1–3].

In patients with AN, measurement of resting energy expenditure (REE) is an useful tool to investigate the entity of calorie restriction, to assess the clinical stage of the disease and to help develop a successful therapeutic plan. Restriction of energy intake relative to requirement is responsible for both a fat-free mass (FFM)-dependent and a FFM-independent reduction of REE[4]: the former originates from a loss of metabolically active cellular mass, the latter is known as adaptive thermogenesis and its features remain to be further investigated. Elegant studies have showed that adaptive thermogenesis is related to the extent of energy deficit and it may persist after the restoration of a normocaloric diet[5–7].

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5)[8] identifies two types of AN: anorexia nervosa restricting type (ANR) and anorexia nervosa binge-eating/purging type (ANBP). In ANR, the weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise, while the main feature of ANBP are recurrent episodes of binge eating and purging behaviors.

ANR is a fairly heterogeneous group as regards physical activity, ranging from sedentary patients that control weight only through dieting and fasting to sport-oriented, hyperactive subjects. Hyperactivity is a frequent symptom in the course of AN, but potential benefits of physical exercise have been found in the treatment of AN. A few studies have suggested that moderate exercise may ameliorate BC and be protective against osteoporosis in women with AN, whereas pathological hyperactivity may be harmful.

Since physical activity is one of the main determinants of BC and may help regulate REE, we hypothesized a correlation between clinical status, body composition, metabolic adaptation and eating/exercise behavior.

Materials and methods

Study design

The study population included 62 females with Anorexia Nervosa (AN) attending our outpatient service between years 2007 and 2017. AN was diagnosed by physicians experienced in the diagnosis and treatment of Eating Disorders (EDs) on the basis of physical and psychological evaluations according to the criteria for diagnosis as defined in the DSM-5. Since the DSM-5 was released in mid-2013[8], the diagnosis of AN patients enrolled prior to this date has been reformulated according to the new DSM-5 criteria as previously described[9].

Physical activity, eating and purging behavior

AN behaviors were investigated on the basis of a clinical interview, and coded as follows: 1 = dieting, 2 = fasting, 3 = excessive exercise, 4 = vomiting, 5 =use of laxatives, 6 = use of diuretics, 7 = use of enemas, 8 = recurrent episodes binge eating. Accordingly to the DSM-5, we defined exercise "excessive" whenever it significantly interfered with important activities, occurred at inappropriate times or in inappropriate settings, or when the subject continued to exercise despite injury or other medical complications.

ANBP and ANR, according to DSM 5, were coded 8, and 1-3 in absence of 8 respectively.

Anthropometrics

All the subjects underwent a medical and nutritional status examination, during which the following anthropometrics measures were recorded: standing height (without shoes) stadiometrically measured to the nearest 0.1 cm; body weight in underwear using a calibrated mechanical balance accurate to ± 0.1 kg[10] by means of a professional scale (Wunder San A model; Wunder SA.BI. s.r.l, Trezzo sull'Adda - Italy).

Body composition

BC was assessed by bioelectrical impedance (BIA-101 model; Akern, Florence, Italy) analysis (BIA), using an alternating electric current at low intensity (800 µA) and fixed rate frequency at 50 kHz. According to a previously described procedure[11-12], two electrodes were positioned 5 cm apart at the wrist and two electrodes at the ipsilateral ankle bony prominences. Before the placement of the electrodes, the skin was prepared with alcohol. In order to allow a homogeneous distribution of body fluids and to avoid short-circuiting of the pathway, the patient was instructed to remain in horizontal position for 10 min with the arms and the legs abducted at a 30 to 45-degree angle from the trunk. Resistance, reactance and phase angle were measured. Fat mass percentage, fat-free mass and total body water were estimated by the manufacturer's BIA equations[13,14].

Resting energy expenditure measurement

REE was measured by open-circuit indirect calorimetry (IC), (V-max model; SensorMedics Italia, Milan, Italy). Gas and flow calibration were performed before each testing session with a fixed gas concentration. REEs were measured in the morning, on the subjects instructed to abstain from food and drink overnight (12h) and from physical activity in the morning. The measurements were performed in the morning, for a 45 min period, on the participants laid on a medical bed, instructed to remain awake and to avoid fidgeting and hyperventilating. Inspired and expired O_2 and expired CO_2 concentrations, as well as the volume of expired gas per minute to calculate the VO_2(L/min) and

VCO_2(L/min), were measured [13]; urinary nitrogen excretion reference value of 13 g/24 h for females was used. EE(kcal/day) was subsequently estimated by using the Weir's equation[15].

Statistical methods

Student's t test was used to compare anthropometric, body composition and resting energy expenditure measures by anorexia types. ANOVA was used to perform a similar analysis among the anorexia subtypes (ANR vs. ANBP) considering weight or BMI. The significance threshold was set at 0.05. Results are presented as frequencies, mean values and standard deviations. Data description and statistical analysis was carried out using STATA/MP software version 11.1 (College Station, TX, USA).

Results

Descriptive characteristics of the overall sample and by AN type are reported in table 1. Sixty-two women were considered, 39 with a diagnosis of ANR and 23 with ANBP.

Table 2 shows BC and REE measures by AN type. We found significant differences in bioelectrical Impedance measurement between ANR and ANBP subjects, in particular we observed a lower reactance (58.63 (11.9) vs. 66.5 (15.5) Ohm, $p < 0.05$) and higher total body water in ANR subjects. No significant differences were found in phase angle, fat mass or fat-free mass. Similarly, no differences were observed in REE measures.

Within ANR subgroup, we could identify two behavioral patterns, with or without physical hyperactivity, accordingly to the DSM-5 description of "excessive exercise": 15 ANR women associating excessive physical exercise to dieting (behavior 1+3 or 1+2+3) (ANRe), and 24 just dieting or fasting (ANRd)(Table 3). We used analysis of variance (ANOVA) to identify differences in body composition measures between ANRd, ANRe and ANBP women (Table 4). ANRe subjects showed the highest phase angle, greatest proportion of fat mass and highest body cell mass. However, when considering weight-adjusted analysis, only phase angle values approached the classical level of statistical significance (p = 0.06).

Taking into account ANRd and ANRe groups, we found that ANRe women showed a higher phase angle [5.6(0.7) vs. 4.8 (0.8)], lower fat-free mass [82.5(6.8) vs. 89.9 (7.5)%], greater proportion of fat mass [17.5(6.8) vs. 10.1(7.5)%] and body cell mass[46.6(5.1) vs. 42.5(5.5)%]. Noteworthy, ANRe patients had higher BMI than ANRd subjects[18.2 (1.7) vs. 15.8 (1.7), p<0.005].

Within ANBP group, we did not run analysis on individual behaviors because of the high heterogeneity and the relatively small sample size.

A similar analysis was run to identify REE differences within ANR group. Measured REE was higher in ANRe subjects compared to ANRd ones [978.8(135.6) vs. 918.9(172.2) kcal/day] but failed to reach statistical significance.

Discussion

At the time of first evaluation in our outpatients' clinic, ANR patients showed a similar mean BMI compared to ANBP subjects. We were not able to confirm differences in body composition between the two types of AN, as reported in bigger population studies[16,17]. However, phase angle values and fat mass percentage were higher in ANBP compared to ANR subjects, although did not quite attain conventional levels of significance. Since ANBP subjects do not completely "purge" their intakes following the binge episode[18,19], it is not surprising that compared to ANR, they show a relatively higher percentage of fat mass, a higher phase angle and therefore be less damaged with regard to tissue integrity.

In contrast with previous studies[17,20], the analysis of REE between the two types of AN failed to highlight significant differences in energy expenditure.

To better characterize the two types of AN, we studied BC and REE variables in the light individual exercise behavior. As mentioned above, within ANR group, two behavioral patterns were observed: patients with hyperactivity (ANRe) and patients without hyperactivity (ANRd). In contrast with the analysis on AN types (ANR vs. ANP), we were able to find several statistically significant differences in BC when hyperactive behavior was considered (ANRd vs ANRe). Data about excessive exercise were obtained from the patients' medical record since the Italian version of validated tools were not available or not commonly used in clinical practice at the time of evaluation. Further studies should include structured interviews to evaluate excessive exercise.

It is noteworthy that between the three subgroups (ANRe, ANRd and ANBP), ANRe subjects exhibit the highest phase angle values. Phase angle is a nutritional prognostic marker that is related to the integrity of cell membranes and tissue quality. As mentioned in a previous work from our research group[11], results from trials on patients with AIDS[21] or colon-rectal cancer [22] suggest that a lower phase angle is associated with loss of integrity of cell membrane and worse prognosis, whereas a higher phase angle is associated with healthy cell membranes. This is because phase angle is positively correlated with capacitance and negatively associated with resistance[11]. This is consistent with the findings that underweight ballet dancers and constitutionally lean subjects have a higher phase angle and different BC features compared to weight-matched patients with AN[23,24]. Accordingly, within our study population, we expected ANRd women to be disadvantaged in terms of prognosis, since they had the lowest values of phase angle. The higher BMI observed in ANRe patients may be responsible for the BC differences between ANRe and ANRd subjects. Still, it is noteworthy that BMI is the simple method to classify underweight, overweight and obesity in adults and it is widely used to assess the severity of the disease however a subtle but significant information was retrieved in the present study: although no difference in BMI was registered between ANR (in toto) and ANBP sample, ANRe patients had higher BMI compared to ANRd. In other words, within the ANR group, we found two subgroups of patients differing in behavioral features, BMI and BC.

Altogether, our results confirm previous indication on the protective effect of physical exercise in some patients with AN and suggests that that in recovery from AN, exercise (under strict supervision) may be beneficial[25–27]. In subjects with AN, positive effects of physical activity have been described on exercise capacity[28], muscle strength[29] and restoration of lean body mass, but it remains unclear whether physical activity helps in maintaining bone mineral density[30]. Also, physical exercise increases circulating myokine levels, which have proved to provide beneficial metabolic effects on endothelial function[31].

Moreover, moderate physical activity could have beneficial effects on mental health alleviating anxiety for patients with AN[32]. In addition, a recent trial suggested that exercise induces a transient anorexigenic effect in obese patients, but not in lean subjects[33]. Although evidence is uncertain[34], a part from the physical benefits that it may bestow, physical activity could provide AN patients with a further tool to allow a greater acceptance of food.

Nevertheless, it should be considered that excessive exercise could be associated with increased energy requirements to achieve weight restoration and poorer clinical outcome, especially during refeeding[35], and that subjects may develop a psychological dependence on exercise, transforming physical activity into “unhealthy” exercise behavior.

On the other hand, ANRe subjects showed a greater proportion of fat mass when compared to ANRd. Primarily this is due to the greater BMI we found in this subgroup of patients. Moreover, compared to dieting or fasting subjects, it is likely that ANRe present a greater 'energy flux' that may result in a protective BMI and BC. Since exercise may be perceived as a compensatory behavior, ANRe subjects could have a higher energy intake compared to ANRd ones[36] and their undernutrition could be less severe. Psycho-educational therapy about features of healthy, non-compulsive exercise could reinforce exercising for enjoyment and fitness, rather than being focused on weight and shape.

Finally, a small difference in REE emerged when hyperactivity was considered. As expected, a higher REE was measured in ANRe, even if these patients had a smaller proportion of fat-free mass compared to non-hyperactive subjects. It has been known for a long time[5] that adaptive thermogenesis is a defensive mechanism against starvation. Showing the tendency to have higher REE, hyperactive women seem not to require adaptive thermogenesis as much as ANRd patients. In hyperactive subjects, we can identify at least two mechanisms responsible for REE maintenance: the trained muscle and an increase in brown adipose tissue. The former is quite simple, since exercise promote muscle growth and attenuate the voluntary weight-loss-induced reduction in muscle mass[31]. As regards brown adipose tissue, in recent studies[37,38], chronic exercise has demonstrated the ability to promote the "browning" of adipose tissue, but this effect is debatable[39], and no data are available in undernourished, underweight AN subjects.

In the process of disease diagnosing and staging, some doubts should arise when using the DSM-5 classification of AN types; it is worth noting that ANR and ANBP classification might not be sufficient and one might need to further distinguish by specific behavioral features in ANR subgroups. Being ANRe are hyperactive subjects with higher BMIs, they showed BC and REE characteristics that seem protective in terms of prognosis (higher BMI, greater proportion of fat mass conserved, higher phase angle, less adaptive thermogenesis), compared to ANRd. In our experience these behavioral features should be exploited for a faster and long lasting outcome, including in the multidisciplinary team sports medicine specialists and exercise trainers.

Limitations

Although this was not the main objective of the study, we could not statistically confirm existing results on differences in BC and REE between AN types, due to the small sample size.

Moreover, BIA may not be the ideal BC assessment tool for severe grade AN[40], but several studies[1,41,42] found it to be appropriate in mild-to-moderate AN patients referring to outpatients' clinics.

In addition, the retrospective nature of the study does not allow establishing cause-and-effect relationship between hyperactivity and the observed body composition features.

Conclusions

Despite the limitations acknowledged above, this single center study confirms that subjects with ANR may be very different between them especially when it comes to behavioral features that go far beyond the mere classification. It is important to emphasize that behavioral features merit more attention within the same subgroups of eating disorder pathology, since they may influence prognosis and treatment. Particularly, physical activity deserves to be taken into consideration and be transformed from compensatory compulsive exercise in programmed and selected physical activities to enhance recovery from AN, building a healthy relationship with exercise, reducing anxiety and negative mood and improving self-esteem and cognitive function.

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Table 1. Mean characteristics of the study population.

	ANR N =39 mean (SD)	ANBP N =23 mean (SD)
Age (years)	21.5 (8.9)	27.1 (10.1)
Weight (kg)	43.6 (6.1)	44.4 (5.4)
BMI (kg/m^2)	16.7 (2)	16.9 (1.9)

ANBP = anorexia nervosa – binge-eating/purging type, ANR = anorexia nervosa – restricting type, BMI = Body Mass Index, SD = standard deviation

Table 2. Body composition and resting energy expenditure measures by anorexia type. P-value refers to t-test on differences in mean values.

	ANR (n = 39) mean (SD)	ANBP (n = 23) mean (SD)	p-value
Resistance (Ohm)	660.39 (80.1)	706.54 (108.6)	0.0593
Reactance (Ohm)	58.63 (11.9)	66.5 (15.5)	0.0279*
Phase angle(°)	5.07 (0.9)	5.36 (0.9)	0.1935
Fat free mass (%)	87.32 (8.3)	84.62 (7.4)	0.2002
Fat mass (%)	12.68 (8.3)	15.84 (8.5)	0.1546
Total body water (%)	64.55 (6.9)	61.04 (4.9)	0.046*
Extra cell water (%)	45.73 (3.3)	44.43 (4.2)	0.2007
Cell mass (%)	43.9 (5.7)	44.88 (3.2)	0.4634
Muscular mass (%)	47.3 (6.3)	48.35 (8.2)	0.6164
Estimated REE (kcal/day)	1263.7 (90.7)	1246.65 (75.7)	0.4843
Measured REE (kcal/day)	934.18 (161.8)	994.95 (188.5)	0.2188
Measured REE/Estimated REE (%)	73.9 (11.6)	79.88 (15.1)	0.1109
RQ	0.9 (0.2)	0.88 (0.1)	0.6169

ANBP = anorexia nervosa – binge-eating/purging type, ANR= anorexia nervosa – restricting type, REE = resting energy expenditure, RQ = respiratory quotient, SD = standard deviation

Table 3. All observed combinations of behaviors by anorexia nervosa type

Behaviors	**ANR**	**ANBP**	**Total (%)**
1	22	0	22 (35.48)
1+2	2	0	2 (3.23)
1+3	14	0	14 (22.58)
1+2+3	1	0	1 (1.61)
1+5	0	1	1 (1.61)
1+8	0	2	2 (3.23)
1+3+4	0	1	1 (1.61)
1+3+8	0	2	2 (3.23)
1+4+8	0	6	6 (9.68)
1+2+3+5	0	1	1 (1.61)
1+2+3+8	0	2	2 (3.23)
1+2+4+8	0	1	1 (1.61)
1+3+4+8	0	4	4 (6.45)
1+2+3+4+8	0	1	1 (1.61)
1+3+4+5+8	0	1	1 (1.61)
Total	39 (62.90%)	23 (37.10%)	62 (100)

1 = dieting, 2 = fasting, 3 = excessive exercise, 4 = vomiting, 5 = laxatives, 6 = diuretics, 7 = enemas, 8 = binge eating, ANBP = anorexia nervosa – binge-eating/purging type, ANR= anorexia nervosa – restricting type

Table 4. Body composition measures by behavior subtype

	ANRd (n =24)	ANRe (n = 15)	ANBP (n=23)	ANOVA p-value	
BIA	**mean (SD)**	**mean (SD)**	**mean (SD)**	**Weight-adj**	**no adj**
Resistance (Ohm)	678.7 (88.3)	633.9 (49.2)	703.8 (111.4)	0.1429	0.0854
Reactance (Ohm)	57.1 (12.7)	62.1 (9.4)	66 (16)	0.1113	0.084
Phase angle (°)	4.8 (0.8)	5.6 (0.7)	5.3 (0.9)	0.0643	0.0102*
Fat free mass (%)	89.9 (7.5)	82.5 (6.8)	85 (8)	0.2853	0.0127*
Fat mass (%)	10.1 (7.5)	17.5 (6.8)	15.4 (9)	0.2846	0.016*
Total body water (%)	66.3 (6.5)	60.8 (4.2)	61.7 (6.5)	0.3662	0.0183*
Extra cell water (%)	46.6 (3.6)	44.7 (2.5)	44.2 (4.2)	0.2497	0.0976
Cell mass (%)	42.5 (5.5)	46.6 (5.1)	44.6 (3.1)	0.0978	0.0396*
Muscular mass (%)	48.4 (3.7)	45.7 (8.7)	48.3 (8.2)	0.8504	0.5388

ANBP = anorexia nervosa – binge-eating/purging type, ANOVA = analysis of variance, ANRd = anorexia nervosa – restricting type dieting or fasting, ANRe = anorexia nervosa – restricting type, with hyperactivity, BIA = Bioelectrical Impedance Analysis, SD = standard deviation.