

Metabolic Assessment of Menstruating and Nonmenstruating Normal Weight Adolescents

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ABSTRACT

Objective: Resumption of menses (ROM) is a key indicator of recovery in AN, but patients may remain amenorrheic despite weight restoration. The objective of this study is to better understand the mechanism of amenorrhea in patients with eating disorders.

Method: A retrospective chart review was conducted of 382 normal weight adolescents with a history of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified, who had been referred for indirect calorimetry tests. Resting energy expenditure (REE) was compared between amenorrheic ($n = 60$) and regularly menstruating females ($n = 121$).

Results: Participants with amenorrhea had a mean REE of 1,103 kcal/24 h (79% predicted), whereas participants who

were menstruating regularly had a mean REE of 1,217 kcal/24 h (85% predicted; $p = 0.001$). The amenorrheic group was found to be at a lower mean body weight (53.7 ± 5.6 kg vs. 57.5 ± 7.4 kg; $p \leq 0.001$), at a lower percent ideal body weight ($98.5 \pm 8.3\%$ vs. $102.8 \pm 10.2\%$; $p = 0.005$), and at a lower BMI (20.5 ± 1.7 vs. 21.5 ± 2.2 ; $p = 0.002$).

Discussion: This study highlights that amenorrheic participants with a history of eating disorders who are at normal body weight are hypometabolic, suggesting an adaptive response to dietary restriction. © 2009 by Wiley Periodicals, Inc.

Keywords: resting energy expenditure; metabolism; amenorrhea; eating disorders; indirect calorimetry

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Introduction

Amenorrhea is prevalent in adolescents with eating disorders, and is one of the diagnostic criteria for anorexia nervosa. About one-third of weight-restored patients with anorexia nervosa remain amenorrheic despite weight restoration.¹ While it is known that amenorrhea is secondary to dysregulation of hypothalamic function, the exact mechanism is not known. One theory proposes that amenorrhea is an adaptive response to an energy deficit, where energy intake is insufficient for energy expenditure. The body then compensates for this energy deficit by altering metabolic rate

and turning off nonessential functions such as reproduction.²

According to the “critical body weight hypothesis,” patients with anorexia nervosa must be at a sufficient weight to initiate and/or maintain menses.^{3–5} However, this hypothesis has been challenged more recently, as amenorrhea can persist, despite weight restoration, often in the context of abnormal eating patterns.^{5,6} Obese women can become amenorrheic when following a hypocaloric diet, despite being at a sufficient weight.⁷ Likewise, patients who eventually develop anorexia nervosa can become amenorrheic several months prior to weight loss, and conversely, may remain amenorrheic despite weight restoration. Thus, a low calorie diet, rather than body weight alone, seems to be one of the key factors in understanding prolonged amenorrhea.

In this study, we explored energy balance using indirect calorimetry conducted in adolescent females with eating disorders who were 90–130% of expected body weight, according to the National Center for Health Statistics Percentiles.⁸ Indirect calorimetry is a noninvasive technique that assesses resting energy expenditure (REE) through

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the measurement of oxygen consumption and carbon dioxide production. REE accounts for ~ 60% of total energy expenditure in healthy human participants. REE in malnourished participants with anorexia nervosa is lower than expected but can return to normal with nutritional rehabilitation.^{9,10} Interestingly, in patients with bulimia nervosa, REE may be low, unpredictable, and variable.¹⁰

The purpose of this study was to investigate a possible mechanism for amenorrhea in adolescents who were 90–130% expected body weight with a history of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified. Using indirect calorimetry, we examined the metabolic differences between participants who were menstruating regularly compared with those who were amenorrheic. Our hypothesis was that participants with amenorrhea would have a lower REE than those with regular menses. We also proposed that both groups would have a lower REE than would be expected for age, weight, and height due to their dieting, calorie restriction, and eating disorder behaviors.

Method

A retrospective chart review was conducted of the charts of normal weight adolescent females with a history of eating disorders who were referred to the Schneider Children's Hospital for indirect calorimetry tests between February 2000 and July 2006. Normal weight was defined as a weight between 90–130% of median weight for height and age, using the National Center for Health Statistics Percentiles.⁸ Participants had past histories of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified. Eating disorder behaviors varied across groups. This study included both previously underweight adolescents who were weight restored, as well as adolescents whose weight had always been within 90–130% of expected body weight but were still struggling with eating disorder symptomatology.

Indirect calorimetry was conducted in this population as a clinical tool to determine caloric requirements during nutritional rehabilitation. This allows for the customization of treatment plans for each patient as well as for ongoing metabolic monitoring throughout the recovery process.

Participants were eligible for inclusion in the study if they were between the ages of 14 and 19 years and postmenarchal. There are limited data available according to the National Center for Health Statistics percentiles for the expected body weight of females less than 152.0 cm

and greater than 178.0 cm; therefore, only participants between 152.0 and 178.0 cm (60 and 70 in.) were included. If REE was measured multiple times on a given patient, only the first measurement where the participant met criteria for this study was considered. Exclusionary criteria were as follows: pregnancy, hormone therapy (i.e. oral contraceptives, depot-medroxyprogesterone acetate, thyroid replacement, steroid therapy), an underlying chronic medical condition (i.e. renal disease, inflammatory bowel disease, diabetes), and/or any organic causes of amenorrhea (i.e. polycystic ovarian syndrome, hyperprolactinemia, and premature ovarian failure), or primary amenorrhea, defined as the absence of menses by 15 years of age in the presence of normal development.¹¹ Indirect calorimetry tests conducted within 1 month of a patient's resumption of menses were also excluded.

Participants were divided into two groups by menstrual status: the amenorrheic group (defined by the absence of menses for at least 3 consecutive months after regular menstruation has been established) and regular menses group (defined as consecutive menstrual cycles for at least 3 months after regular menstruation has been established). All charts were reviewed by at least two investigators, a registered dietitian and a physician, to determine menstrual group and eating disorder diagnosis. Any disagreement was resolved by a third investigator.

The following data were collected based upon the data of the participant's first indirect calorimetry test: age, height, weight, % ideal body weight (IBW), body mass index (BMI), BMI percentile, date of indirect calorimetry test, REE (kcal/24 h), expected REE (based on the Harris-Benedict equation for each female's height, weight, and age, where normal equals 90–110%), percent expected REE ($mREE/expected\ REE \times 100$), respiratory quotient (RQ; volume of carbon dioxide produced/volume of oxygen consumed), menstrual history, pertinent medical history, eating disorder history, maximum weight, and eating disorder diagnosis.

Measurement of REE

REE was measured using an open circuit, computerized indirect calorimetry machine (Datex Delta-Trac II, Sensor Medics, Anaheim, California) after a 12-h fast in a thermo-neutral environment. Exercise was prohibited for at least 24 h, and a 15-min rest period was implemented prior to testing. During testing, participants remained awake and in a supine position with a plexiglass hood over the head and neck. The duration of each test was ~25 min.

Statistics

The Student *t* test was used to detect differences in height, weight, age, REE, percent expected REE, and the RQ between the amenorrheic and regular menses groups;

$p < 0.05$ was considered statistically significant using a two-tailed test.

The study was approved by the North Shore-Long Island Jewish Health System Institutional Review Board.

Results

Three hundred and eighty-two females met the inclusion criteria for this study. Two-hundred and one participants were excluded. Participants were excluded for the following reasons: primary amenorrhea ($n = 21$), irregular menses (those participants who did not meet precise criteria for either amenorrhea or regular menses; $n = 20$), not enough information to determine menstrual or medical history ($n = 61$), use of hormone therapy ($n = 41$), resumption of menses within 1 month of the test date ($n = 34$), underlying chronic medical condition and/or any organic cause of amenorrhea ($n = 23$), and pregnancy ($n = 1$). Of the eligible par-

ticipants, 60 were in the amenorrheic group and 121 were in the regular menses group (Fig. 1).

As shown in Table 1, the amenorrheic and regular menses groups were similar in age (16.1 ± 1.2 years vs. 16.5 ± 1.3 years; $p = 0.08$) and height (161.8 ± 6.1 cm vs. 163.3 ± 5.8 cm.; $p = 0.10$). However, the amenorrheic group had a lower mean body weight (53.7 ± 5.6 kg vs. 57.5 ± 7.4 kg; $p \leq 0.001$), lower percent IBW ($98.5 \pm 8.3\%$ vs. $102.8 \pm 10.2\%$; $p = 0.005$), and a lower BMI (20.5 ± 1.7 vs. 21.5 ± 2.2 ; $p = 0.002$). Participants with amenorrhea appeared to have lost more weight from their self-reported maximum weight than participants who were menstruating regularly (14 vs. 7.6% of their pre-morbid weight, or 8.8 ± 16.2 kg vs. 4.7 ± 16.2 kg); however, this did not reach statistical significance ($p = 0.14$).

The amenorrheic and regular menses groups differed in their REE, expected REE (Harris–Benedict values), percent expected REE, and RQ. Participants with amenorrhea had a mean REE of $1,103 \pm 161$ kcal/24 h, whereas participants with normal menses had a significantly higher mean REE of $1,217 \pm 159$ kcal/24 h differing by 114 kcal/24 h or 8% ($p \leq 0.001$). There was a significant difference found in expected REE (Harris–Benedict value) between groups, which is consistent with the fact that the groups differed in weight; a higher weight would increase expected REE. To minimize the effect that weight has on metabolism, REE is compared to a predictive standard (Harris–Benedict equation) to yield a percentage, where normal equals $90\text{--}110\%$ (Table 1). While both groups had a low percent expected REE, participants with amenorrhea had a statistically significant lower percent expected REE ($79.2 \pm 10\%$ vs. $85.2 \pm 9.7\%$; $p \leq 0.001$). Participants with amenorrhea had an RQ of 0.93 ± 0.08 , indicating consumption of a low fat diet, whereas participants with normal menses had an RQ of 0.88 ± 0.08 ($p \leq 0.001$), indicating more of a mixed diet.

FIGURE 1. Description of study population. Three hundred and eighty-two females met the inclusion criteria for this study. Of these, 60 were in the amenorrheic group and 121 were in regular menses group. Two-hundred and one participants were excluded (see “Method” section).

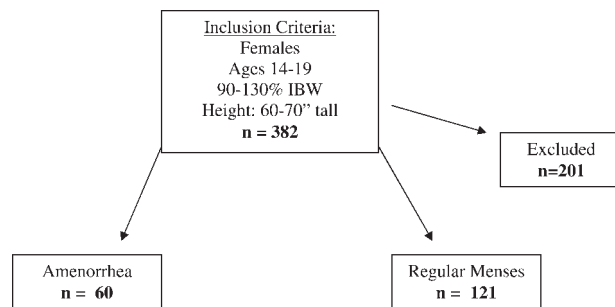


TABLE 1. Anthropometric variables and resting energy expenditure: Comparison between amenorrheic and regular menses groups

	Amenorrheic Group ($n = 60$)	Regular Menses ($n = 121$)	p Value
Age (years)	16.2 ± 1.2	16.5 ± 1.3	0.08
Height (cm)	161.8 ± 6.1	163.3 ± 5.8	0.10
Weight (kg)	53.7 ± 5.6	57.5 ± 7.4	<0.001
% IBW	98.5 ± 8.3	102.8 ± 10.2	0.005
BMI (kg/m^2)	20.5 ± 1.7	21.5 ± 2.2	0.002
BMI percentile	47.3 ± 19	55.5 ± 21	0.01
BMI Z-score	-0.07 ± 0.50	0.18 ± 0.64	<0.01
mREE (kcal/24 h)	$1,103 \pm 161$	$1,217 \pm 159$	<0.001
Predicted REE (kcal/24 h)	$1,391 \pm 60$	$1,429 \pm 78$	0.001
Percent expected HB ^a	79.2 ± 10	85.2 ± 9.7	<0.001
RQ (respiratory quotient)	0.93 ± 0.08	0.89 ± 0.08	<0.001
Change from maximum weight (kg)	8.8 ± 16.2	4.7 ± 16.2	0.14

^a Percent expected HB = $\text{mREE}/\text{Expected mREE} \times 100$, where normal equals $90\text{--}110\%$. The expected REE is based on the Harris–Benedict equation for women: $655.1 + (9.563 \times \text{weight}/\text{kg}) + (1.850 \times \text{height}/\text{cm}) - (4.676 \times \text{age})$.

Participants were subdivided by eating disorder diagnosis. Participants in the amenorrheic group had past histories of anorexia nervosa ($n = 22$), bulimia nervosa ($n = 4$), and eating disorder not otherwise specified ($n = 34$). Participants in the normal menses group had past histories of anorexia nervosa ($n = 20$), bulimia nervosa ($n = 32$), and eating disorder not otherwise specified ($n = 69$). There were no significant differences found in REE between the amenorrheic and normal menses groups when comparing by eating disorder diagnosis. In addition, there was no significant difference found in REE between diagnoses within the amenorrheic group and within the normal menses group.

Discussion

Adolescents with eating disorders, in particular those with anorexia nervosa, have menstrual irregularities such as amenorrhea. Amenorrhea is one of the necessary diagnostic criteria for anorexia nervosa under the current classification system, the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV). The etiology of the amenorrhea is thought to be associated with disturbances in hypothalamic function.¹²

Many women previously diagnosed with “functional hypothalamic amenorrhea” have disordered eating and a low calorie diet.^{13–15} The female athlete triad, consisting of amenorrhea, disordered eating, and osteoporosis,^{16,17} is one such example. There have been several suggested causative factors for amenorrhea in the female athlete such as the physical stress of exercise or the psychological stress of competition, but evidence to date suggests that the primary cause is a chronic deficit in energy intake relative to energy expenditure.¹⁸

Leptin is a hormone that has been found to be a critical regulator of REE and plays an important role in hypothalamic amenorrhea and energy balance. Leptin levels are low in women with hypothalamic amenorrhea,^{19–22} and administration of recombinant leptin to these women can induce ovulatory menstrual cycles.²³ In weight-restored patients with anorexia nervosa, leptin levels are found to be lower in patients with amenorrhea as compared to those who are menstruating regularly.^{24,25} While leptin levels were not collected for this study, they may have provided some insight into the hypometabolic state found in our study population.

Secondary amenorrhea can persist independent of weight. We have previously shown that in patients with anorexia nervosa, the average weight at which resumption of menses occurs is $\sim 90\%$ of IBW.¹ Some participants resumed menses at a lower weight and some did so at a higher weight. In our present study, although both groups were weight-restored and nearly 100% IBW, participants with amenorrhea still weighed an average of 3.7 kg less than the group that was menstruating regularly ($p \leq 0.001$). These findings suggest that for these patients, further weight gain may have been necessary for resumption of menses. Our results are supported by studies conducted by Warren et al., who found that women with hypothalamic amenorrhea had a significantly lower weight, BMI, and percent body fat than normally menstruating controls.^{13,14}

On average, participants with amenorrhea had lost more weight than participants who were menstruating regularly (14 vs. 7.6% of their premorbid weight, or 8.8 ± 16.2 kg vs. 4.7 ± 16.2 kg). While this difference did not reach statistical significance, this trend emphasizes that premorbid weight may play a role in amenorrhea, and may be an important factor to consider in setting realistic goal weights.

Weight-restored participants with amenorrhea were also found to have a significantly lower REE than participants who were menstruating normally. Specifically, the REE of the amenorrheic group was 114 kcal/24 h or 8% lower than the group that was menstruating regularly. The difference in REE of 114 kcal/24 h does not reflect the difference in caloric requirements between the two groups, which would be much higher. In healthy individuals, REE accounts for $\sim 60\%$ of one's total energy expenditure and does not include daily activity, exercise, and diet-induced thermogenesis.²⁶ Our group has previously shown that in anorexia nervosa, during refeeding, diet-induced thermogenesis can be as high as 36% above REE, in contrast to 10% above REE, which is usually found in healthy individuals.⁸ The energy cost of weight gain and the expected rate of weight gain further increases caloric requirements. To determine one's total daily energy requirement, REE should be multiplied by a variety of activity and stress factors.²⁷

Our results are similar to findings of Lebenstedt et al. who examined metabolic differences among runners with and without menstrual disorders. They found that resting metabolic rate was significantly lower in athletes with menstrual disorders (114 kcal/24 h) and that there was a significant correlation between dietary restraint and a lower resting metabolic rate. They concluded that restrained

eating and low resting metabolic rate are associated with menstrual disturbances in athletes.²⁸

When comparing measured REE (mREE) to a predictive standard, the effect of the differences in height, weight, and age on metabolism is minimized. While there are several known standard equations, the one most commonly used is the Harris–Benedict equation, as described earlier. A comparison of the mREE to this expected value yields a percentage, where the normal range is 90–110% of expected. In this study, the metabolic rate of participants with amenorrhea was $79.2 \pm 10\%$ of expected, whereas participants with normal menses were $85.2 \pm 9.7\%$ of expected. It is not surprising that both groups were found to be hypometabolic, given their known history of calorie restriction and dieting behaviors. While both groups were found to be metabolically compromised, the percent expected REE was found to be significantly lower in participants with amenorrhea ($p \leq 0.001$). This highlights that a tangible energy imbalance exists, regardless of weight restoration, and results in a hypometabolic state.

There were additional metabolic differences found between participants regarding substrate utilization. Substrate utilization can be measured by comparing the ratio of the volume of oxygen consumed to the volume of carbon dioxide produced, which is known as the RQ, and it provides information regarding fuels being used by the body. An RQ of 1.00 reflects the complete oxidation of glucose and is suggestive of the consumption of a pure carbohydrate, low fat diet. An RQ of 0.70 is suggestive of a high fat/low carbohydrate diet and an RQ of 0.84–0.85 reflects a more mixed diet (a blend of both carbohydrates and fats).²⁹ Participants with amenorrhea had an RQ of 0.94, whereas participants with normal menses had an RQ of 0.88 ($p \leq 0.001$). The higher RQ found in the participants with amenorrhea is suggestive of the consumption of a low fat diet, which has been previously noted.^{14,30,31} In a study conducted by Laughlin et al., participants with hypothalamic amenorrhea consumed 50% fewer fat in grams than participants with normal menses. In the hypothalamic group, only $16.3 \pm 2.2\%$ of the total calories came from dietary fat, as compared to $31.6 \pm 1.9\%$ ($p \leq 0.001$) in the normal cycling controls.¹⁵ These results are consistent with the results in our study.

Future studies would need to be conducted to further explore strategies for resumption of menses in weight-restored adolescents with a history of eating disorders. It is unclear whether participants with amenorrhea, despite achieving a BMI percentile of 47.6 ± 18 , would require an additional, yet

modest, amount of weight gain to resume menses. Perhaps metabolic recovery alone, where the focus would be to correct the caloric imbalance and increase dietary fat, would be sufficient. In addition, it would be helpful to determine the impact of a participant's premorbid weight on influencing the chances for resumption of menses.

There were a few areas of limitation found in this study. First, we did not collect specific information about whether comorbid diagnoses, such as depression and anxiety, existed in this population. This would have been useful since depression³² and psychosocial stress can affect menstrual status.¹⁵ Another limitation was that we did not collect information about the duration of each patient's eating disorder as well as how much time had elapsed since weight restoration. This would have provided valuable historical points, which possibly could have affected menstruation.

Using indirect calorimetry to assess REE, we showed that a hypometabolic state persists despite weight restoration. There were significant metabolic differences found in weight-restored participants with amenorrhea as compared to participants who had regular menses. Participants with amenorrhea consumed a lower fat diet, had a lower REE, and were at a lower mean body weight. Since indirect calorimetry may not be readily available to many eating disorder patients and practitioners, eating disorder patients with amenorrhea may likely benefit from meeting with a registered dietitian, who can carefully analyze food records to assess whether in fact an energy imbalance exists.

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