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Rapid refeeding does not worsen anxiety in adolescents with anorexia nervosa: a pilot study

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ABSTRACT

The study aimed to describe the progression of state anxiety in adolescents with anorexia nervosa (AN) hospitalized on a high calorie refeeding (HCR) protocol. Participants, 12–21 years, admitted for malnutrition due to AN were placed on a HCR protocol in which calories were advanced by 300 kcal/day. The State-Trait Anxiety Inventory for Children (STAIC) was given to participants within 24 hours of hospitalization and the state anxiety component of the STAIC was administered daily immediately before and after breakfast until discharge. Of 22 patients enrolled, 86% were female, mean age was 14.9 ± 2.0 years, and 95% had AN-restrictive type. The median state and trait anxiety scores at time of admission were 37.0 (28–55) and 35.5 (23–51), respectively. There was no significant difference in median pre-meal state anxiety from hospital day 1 to 6 (34.0(26–55) vs. 38.5(25–55), p-value = 0.079) or in median post-meal state anxiety from hospital day 1 to 6 (35.5(29–56) vs. 37(24–56), p-value = 0.484). Similarly, we found minimal correlation between change in caloric intake and change in pre-meal S-anxiety (Spearman correlation coefficient = −0.032) or post-meal S-anxiety (Spearman correlation = 0.032). While this was a small sample observing anxiety over one week, we found no evidence that state anxiety increased with advancing calories, providing additional support for the use of more rapid refeeding protocols.

Clinical Implications

- High calorie refeeding (HCR) protocols aim at correcting acute medical complications associated with anorexia nervosa (AN).
- Although current literature supports their medical safety and efficacy, studies examining their psychological effects are scarce.

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- The study found no evidence that HCR causes increased state anxiety among hospitalized adolescents with AN in the first week of refeeding.

Introduction

Anorexia nervosa (AN) may lead to significant malnutrition due to caloric restriction, purging, excessive exercise and other unhealthy behaviors (Katzman, 2005). Hospitalization for acute medical stabilization is recommended for adolescents with severe malnutrition, characterized by bradycardia, hypotension, hypothermia, electrolyte disturbances and/or cachexia (Golden et al., 2015).

Historically, the approach to refeeding malnourished adolescents has been a conservative one, starting with a low caloric intake and advancing calories slowly over several days. The rationale for this "start low, go slow" approach is to minimize the risk of refeeding syndrome, characterized by rapid fluid and electrolyte shifts that can have severe medical consequences and may be lethal (Whitelaw et al., 2010). Lower calorie refeeding, however, has been shown to be associated with initial weight loss and longer hospitalization (Garber et al., 2012). More recently, higher calorie refeeding (HCR) protocols have been described and demonstrate faster weight restoration, shorter length of stay, and no increase in incidence of refeeding syndrome (Garber et al., 2013; Golden et al., 2013; Smith et al., 2016). HCR approaches have been widely adopted (Guarda et al., 2020; Madden et al., 2015; Parker et al., 2015) despite the lack of a standardized, evidence-based approach to their use.

AN is associated with high levels of comorbid anxiety (Kaye et al., 2004). Furthermore, the presence of anxiety has been shown to be a negative prognostic factor among patients with AN (Swinbourne & Touyz, 2007). An interesting study looking at factors associated with recovery in a group of adult AN patients found that participants had a lower probability of recovery when they endorsed more trait anxiety (Zerwas et al., 2013). Other studies have reported on the relationship between anxiety and remission. One study found that an increase of one unit on the trait anxiety scale reduced the chance of remission from AN by a factor of 1.15 (Yackobovitch-Gavan et al., 2009). The core features of AN, primarily food restriction and exercise are hypothesized to have an anxiolytic effect (Dellava et al., 2010; Kaye, 2008). Anxiety may increase in patients undergoing treatment as these features are compromised especially if the patient is hospitalized.

In one of the few studies examining the psychological experience of adolescent patients with AN over the course of an inpatient treatment implementing a rapid-refeeding protocol, Kezelman et al. examined participants with surveys and weekly interviews to assess the severity of their anxiety. Patients

were progressed through a five-staged meal plan initiated at 1800 kcal/day with maximal oral caloric intake at 3800 kcal/day. Although participants initially described experiences of anxiety, this decreased and stabilized during the course of treatment (Kezelman et al., 2016).

The extent to which acute anxiety is affected by the quantity of food presented during medical stabilization for AN has not been well studied. Studies examining the relationship between pre-meal anxiety and food intake have shown that greater pre-meal anxiety is associated with lower calorie intake and that the strength of this association differed by meal type (Steinglass et al., 2010). A systematic review by Lloyd et al. evaluated the longitudinal associations between anxiety and AN. They concluded that anxiety in general may predict increased AN risk. However, they stated that main outcomes of the studies produced conflicting findings, highlighting the need for further investigation into the relationship of anxiety and AN (Lloyd et al., 2019).

The objective of the current study was to describe the progression of state anxiety reported by malnourished adolescent patients with AN who are hospitalized in a medical setting and placed on a HCR protocol. The secondary objective was to examine differences between pre- and post-meal state anxiety in this population. We hypothesized that HCR protocols would provoke severe anxiety symptoms in patients with AN by presenting larger quantities of food quickly.

Methods

Study population

Patients 12–21 were eligible to participate if they met DSM-5 criteria for AN, were hospitalized at our quaternary care children's hospital for sequelae of malnutrition and were able to complete the study measurement tools. Criteria for hospitalization include one or more of the following: severe protein energy malnutrition (<75% expected body weight), bradycardia (heart rate <50 beats/minute during the day or 45 beats/minute at night), hypotension (blood pressure <90/45 mm Hg), hypothermia (temperature <36.0□), orthostatic changes in pulse and blood pressure, dehydration, electrocardiographic abnormalities, or electrolyte disturbances (Golden et al., 2015). The study was approved by the institutional review board at Nationwide Children's Hospital (NCH). Written consent was obtained from all participants 18 years of age and older. Written assent and parental consent were obtained for participants under the age of 18.

HCR protocol

All patients were admitted between October 2017 and September 2018 to the Adolescent Medicine service and treated in accordance with our HCR protocol. Patients typically are started on 1500 kcal daily and advanced by 300 kcal daily until consistent weight gain is achieved or they reach the estimated caloric goal required to achieve 1 kg of weight gain weekly. The managing physician may alter the protocol as they see fit. Food is presented as a standardized menu of three meals and three snacks daily. A liquid nutrition supplement is given to replace the caloric value of food not eaten within an appropriate timeframe. If the patient is unable to consume the supplement orally, it is administered via nasogastric tube. The protocol includes daily weights, orthostatic vital signs, continuous cardiac monitoring, EKG on admission, and daily blood draws for electrolyte monitoring for at least the first several days of admission (or more frequently if indicated). Therapeutic eating disorder care is not provided during hospitalization, which focuses strictly on nutritional rehabilitation. However, behavioral elements of the protocol include maintenance of a calm and safe environment to limit the patient's opportunities to engage in eating disorder behaviors such as hiding food, exercising or purging. Supportive psychological care is available as needed, as well as massage therapy and a variety of age-appropriate sedentary activities for distraction. Psychiatric consultation is accessible and additional safety measures are activated for patients expressing suicidal thoughts. Patients are discharged from the hospital when medically stable and transitioned to day treatment or outpatient care. Discharge criteria include improvement of bradycardia, temperature >36.0 C for at least 24 hours, and appropriate daily weight gain.

Study measurement tools

The following measurement tools were conducted at baseline (within 24 hours of admission) on all patients who agreed to participate:

(a) State-Trait Anxiety Inventory for Children (STAIC), which is comprised of separate, self-report scales for measuring two distinct anxiety concepts: state anxiety (S-Anxiety) and trait anxiety (T-Anxiety). Scores on both the S-Anxiety and T-Anxiety subscales range from a minimum of 20 to a maximum of 80 with higher scores indicative of increased anxiety. The mean S-anxiety and T-anxiety scores age- and gender-matched to our study population are 38.0 ± 6.68 and 30.7 ± 6.01, respectively. The psychometric properties of STAIC showed high reliability for both the state (Cronbach's alpha = 0.91–0.95) and trait (Cronbach's alpha = 0.91) subscales (Spielberger & Edwards, 1973).

(b) Eating attitude test (EAT-26), which is a valid, sensitive and specific measure for detecting individuals at high risk for eating disorders. The total score ranges from 0 to 78 but a cut-point score of 20 or higher is considered significant, requiring further assessment. Cronbach's alpha as a measure of internal consistency is 0.87 for the EAT-26 (Garner & Garfinkel, 1979).

(c) Compulsive Exercise Test (CET), comprised of 24 self-report items that are designed to assess the core cognitive, behavioral and emotional features of compulsive exercise. A cut-off score of 15 on the CET has resulted in acceptable values of both sensitivity and specificity and higher scores are indicative of greater pathology. The Cronbach's alpha for the overall scale is 0.85 (Taranis et al., 2011).

(d) The Patient Health Questionnaire (PHQ-9) was used to provisionally diagnose depression and grade severity of symptoms, generating a severity score of 0–27. Cut-offs suggesting mild, moderate and severe depression are 5–9, 15–19 and above 20, respectively. Higher PHQ-9 scores are associated with decreased functional status and increased symptom-related difficulties. The internal reliability of the PHQ-9 is excellent with a Cronbach's alpha of 0.89 (Spitzer et al., 1999).

In addition to the above baseline survey measures, the S-Anxiety component of the STAIC questionnaire was administered daily immediately before and after the first meal of the day until time of discharge.

Electronic medical record review

Clinical information prior to hospitalization was collected and included: duration of illness, rate of weight loss, minimum and maximum weight, demographic factors (age, sex, race/ethnicity and insurance type), current exercise (hours/week), other mental health diagnoses, use of anxiolytic medications (SSRIs, benzodiazepines, antipsychotics, other), significant past medical history, and last menstrual period.

Admission information was reviewed and included: reason(s) for admission (e.g., bradycardia, acute food refusal, long QT/abnormal EKG, electrolyte abnormality, suicidal ideation), baseline weight (weight obtained at 0600 hours on the first full day after admission), heart rate on admission, reported caloric intake prior to hospitalization, starting HCR protocol caloric intake, and the difference between reported daily caloric intake prior to hospitalization and initial HCR protocol caloric intake.

Additionally, the following information was recorded daily starting with hospital day 1 until time of discharge: weight in kilograms (measured in a gown daily before breakfast, after urination), change in weight from admission, lowest heart rate in the past 24 hours, caloric intake, use of liquid

supplementation (24-hour volume), use of NG tube, and use of pre-meal anxiolytics. Length of stay was defined as the number of full days from admission to discharge.

Statistics

Descriptive statistics were utilized to characterize the study participants. Continuous variables were examined via means, standard deviations, medians, minimums, and maximums, and categorical variables via counts and percentages. Mood's median test (chosen over a *t*-test due to the small sample size and skewed outcome distribution) was utilized to describe the progression of state anxiety over the course of hospitalization. Due to hospital discharge, the number of participants significantly decreased after hospital day 6. As such, we used Mood's median test to compare pre-meal S-Anxiety between days 1 and 6 and post-meal S-Anxiety between days 1 and 6. For our secondary objective, the median difference between daily pre-meal and post-meal S-Anxiety was calculated starting with hospital day 1 and found to be nearly constant at zero. Baseline S-anxiety (day 0) was not included in the aforementioned procedures as timing of administration was not standardized in relation to mealtime. All calculations were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Electronic medical record review

A total of 35 patients were assessed for eligibility. Of these, 8 patients did not assent, 1 patient did not acquire parental consent, 2 patients did not complete the initial assessment within 24 hours of admission, and 2 patients did not complete the daily S-Anxiety questionnaire. As such, 22 participants were included in the current analyses (Table 1).

Of the patients included, at baseline, three patients had missing menstrual patterns, one did not complete the S-Anxiety instrument, and another the CET. There were no missing values for daily weights. When each variable of interest was analyzed, records with missing values were excluded.

Most of the participants were female (86%) with a mean age of 14.9 ±2.0 years (11–18 years), and 95% had AN-restrictive type. All were admitted due to protein calorie malnutrition, and a majority had other reasons for admission, the most common being bradycardia (91%). Anxiety was the most common additional mental health diagnosis reported (32%), followed by depression (14%) and obsessive-compulsive disorder (14%). Psychotropic medication taken by the patient at the time of admission are given in Table 1; no changes were made during hospitalization.

Table 1. Baseline characteristics of study participants (N = 22).

Characteristic	n	%
Sex		
• Female	19	86
• Male	3	14
Race/ethnicity		
• White non-Hispanic	21	95
• Black non-Hispanic	1	5
Insurance type		
• Private	19	86
• Public	3	14
DSM-5 diagnosis		
• AN-Binge/Purge	1	5
• AN-Restrictive	21	95
Reason for admission		
• Protein calorie malnutrition	2220	100
• Bradycardia	2	91
• Electrolyte abnormality	1	9
• Acute food refusal	1	5
• Hypotension	1	5
• Hypothermia		5
Mental health diagnosis		
• Anxiety	7	32
• Depression	3	14
• Obsessive compulsive disorder	3	14
Medication		
• Selective serotonin uptake inhibitor	3	14
• Atypical antipsychotic	2	9
• Anxiolytic	1	5
	Mean ±SD	Min-Max
Age (years)	14.9 ±2.0	11.0–18.0
Onset of weight loss (months)	8.5 ±4.9	2.0–22.0
Minimum weight (kg)	43.3 ±10.3	22.0–67.1
Maximum weight (kg)	57.3 ±15.2	27.5–88.8
BMI at admission (kg/m^2)	17.3 ±3.0	12.2–23.9
Caloric intake prior to admission (kcal)	784.1 ±459.1	100–2000
Caloric intake at admission (kcal)	1540.9 ±140.3	1200–1800
Difference in caloric intake (kcal)	756.8 ±411.2	−200-1400
Baseline heart rate (beats per minute)	43.9 ±5.9	29.0–57.0
Exercise (hours per week)	9.4 ±7.5	0.0–21.0

The mean reported onset of weight loss was 8.5 ± 4.9 months prior to admission (Table 1). Mean estimated caloric intake just prior to admission was 756.8 ± 411.2 kcal/day. At time of admission, mean BMI was 17.3 ±3.0 kg/m^2 and mean heart rate 43.9 ± 5.9 bpm. Mean starting caloric intake was 1540.9 ± 140.3 Kcal. The intake of all participants was increased by 300 kcal/day until adequate daily weight gain was achieved. No participants required nasogastric feeding. Mean duration of admission was 6.2 ± 1.6 days (3–9 days). At time of discharge, average caloric intake was 2768 ± 225.5 Kcal, and mean weight gain over the course of admission was 2.09 ± 1.20 kg.

Study measurement tools

The median state and trait anxiety scores at time of admission (day 0) were 37.0 (28–55) and 35.5 (23–51), respectively. The results of all baseline measures are in Table 2.

Table 2. Study survey measures at baseline (N = 22).

Characteristic	Median	Mean	Std. Dev.	Minimum	Maximum	BMI corr.	Dur. corr.	Cal. corr.
S-Anxiety[a]	37.0	38.3	6.7	28.0	55.0	0.362	0.051	−0.175
T-Anxiety	35.5	36.6	7.9	23.0	51.0	0.248	0.255	−0.008
PHQ-9	7.5	8.5	5.6	1.0	22.0	0.167	0.289	−0.163
EAT-26	20.0	26.5	18.0	3.0	63.0	0.281	0.255	−0.195
CET[a]	62.0	63.1	26.0	15.0	109.0	0.426	0.176	0.092

[a]One participant did not complete this instrument. PHQ-9: Patient Health Questionnaire, EAT-26: Eating attitude test, CET: Compulsive Exercise Test
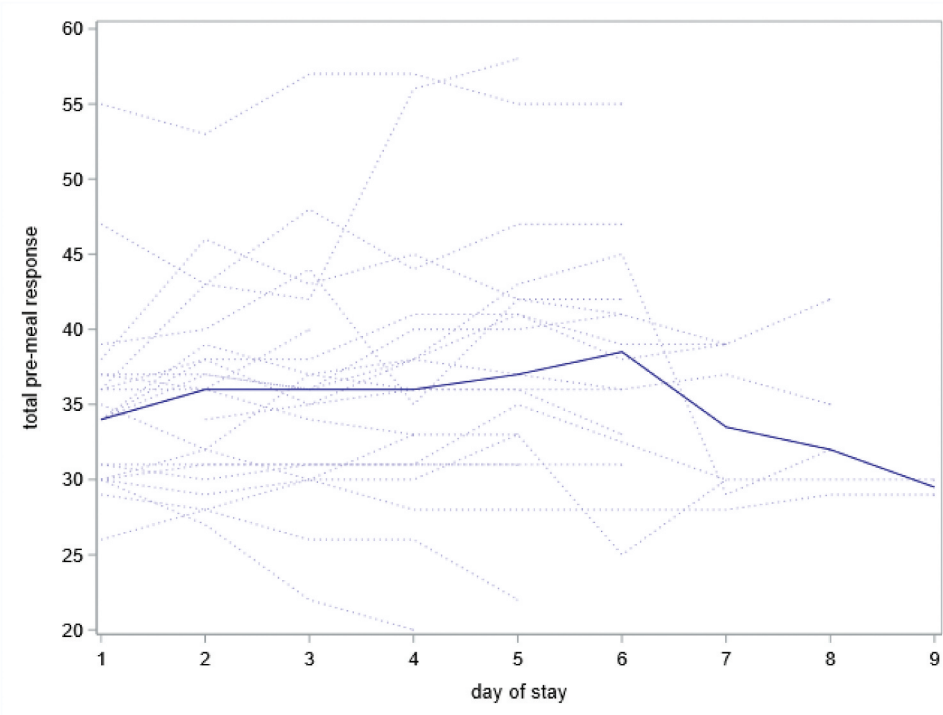

Figure 1. Trajectories of total pre-meal state anxiety responses (median curve highlighted) over course of hospitalization.

Trajectory of pre-meal and post-meal S-anxiety over the course of hospitalization are shown in Figures 1 and 2. Based on Mood's median test, there was no significant difference in median pre-meal S-anxiety from hospital day 1 to 6 (day 1: 34.0 (26–55) vs. day 6: 38.5 (25–55), p-value = 0.079) or post-meal S-anxiety from hospital day 1 to 6 (day 1: 35.5 (29–56) vs. day 6: 37 (24–56), p-value = 0.484).

Comparison of daily pre-meal and post-meal S-anxiety found the median difference to be approximately zero throughout the hospitalization, i.e. no significant difference (Figure 3).

Additionally, we found minimal correlation between weight gain over hospitalization and change in pre-meal S-anxiety (Spearman correlation
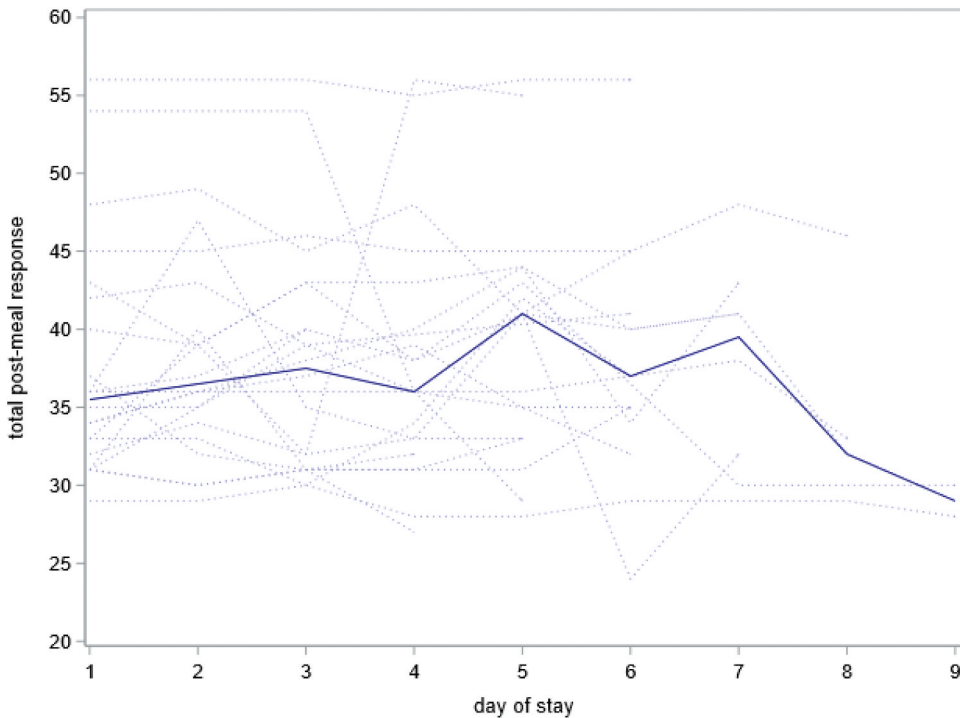
Figure 2. Trajectories of total post-meal state anxiety responses (median curve highlighted) over course of hospitalization.

coefficient = −0.032) or post meal S-anxiety (Spearman correlation = −0.301). Similarly, we found minimal correlation between change in caloric intake over hospitalization and change in pre-meal S-anxiety (Spearman correlation coefficient = −0.032) or post meal S-anxiety (Spearman correlation = 0.032).

Discussion

In this study, we examined the trajectory of state anxiety in patients with AN hospitalized on an HRC protocol and evaluated the difference between anxiety before and after a meal. Contrary to our hypothesis, state anxiety did not increase during the admission as calories were rapidly increased, nor did anxiety levels differ before or after a meal.

The increasingly widespread use of higher calorie protocols has raised concerns that presenting larger quantities of food more quickly to patients with severe AN could provoke more severe anxiety symptoms than advancing intake more gradually, and more aggressive protocols have even been described as aversive to the psychological state of the patient (Offord et al., 2006; Vandereycken, 2003). Studies evaluating the effect of employing a more
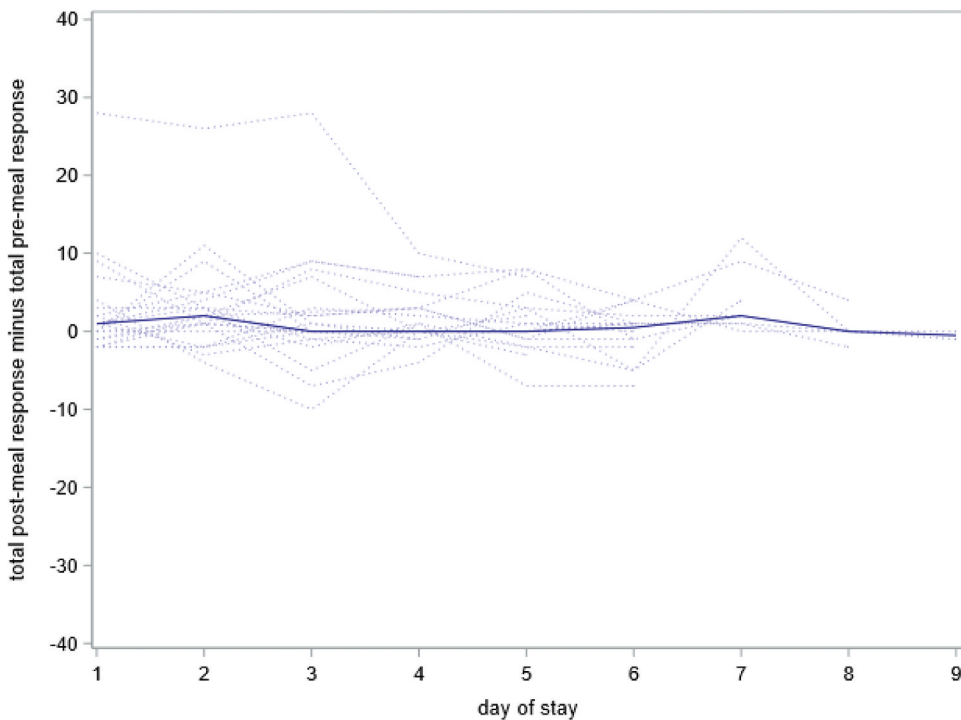
Figure 3. Trajectories of differences between total post-meal and total pre-meal state anxiety responses (median curve highlighted) over the course of hospitalization.

rapid-refeeding protocol on a patient's psychological well-being, particularly anxiety, are scarce.

It has been suggested that individuals who develop AN have elevated levels of anxiety resulting from a dysfunctional serotonin system and that restrictive eating serves to reduce baseline levels of anxiety to a more manageable level (Kaye et al., 2003). It was therefore hypothesized that starting with higher calories and increasing at a faster pace would lead to an increase in anxiety.

Contrary to this hypothesis, patients in this study were able to adhere to the treatment protocol, adapting to increasing daily caloric intake without an increase in measured anxiety. During medical hospitalization, the patient relinquishes all food-related decision-making to the medical team, and nutritional intake is strictly non-negotiable. Relieving the patient of this responsibility may have a mitigating effect on state anxiety. In addition, our lack of observed change in the trajectory of anxiety may have been be due to the setting and aim of our program. Patients are hospitalized for the purpose of medical stabilization rather than achieving a target weight. Results may vary in a setting where the patient is hospitalized for a longer period and is expected to achieve a certain amount of weight gain before discharge, as is often the case in a psychiatric or eating disorder inpatient setting.

Similar to the current study, Kelzman et al. examined anxiety in adolescent patients hospitalized and treated with a rapid-refeeding protocol. In this study anxiety decreased and stabilized during the course of treatment. The mean duration of admission was longer in this study (26.9 days) as compared to the current investigation, and all patients received both group and individual psychotherapy during their admission while our patients did not (Kezelman et al., 2016) . Our findings may be particularly relevant to medical settings in which inpatient treatment is focused almost entirely on nutritional rehabilitation, with only minimal psychological support available. As patients often are admitted shortly after their initial diagnosis of malnutrition due to an eating disorder, they may lack the skills needed to tolerate the distress caused by food and eating.

An additional goal of the study was to examine whether anxiety differed before or after a meal. Some patients may experience pre-meal anxiety, due to meal anticipation. A study by Steinglass et al (Steinglass et al., 2010) looked at pre-meal anxiety and food intake in patients with AN and found that greater pre-meal anxiety was associated with lower caloric intake. For other patients, the physiologic sensations after eating, such as feelings of fullness and discomfort, pose a significantly greater challenge (Kezelman et al., 2016). In our study, there was no correlation between state anxiety pre- or post-meal and caloric intake.

Weight loss and anxiety both can impair cognitive functioning in patients with AN (Jones et al., 1991). Weight gain during hospitalization may enhance cognitive resources which may in turn led to a better control of anxiety (Kezelman et al., 2015) . Although, in our study, there was no correlation between weight gain and change in total pre- or post-meal S-anxiety during admission, it could be argued that anxiety caused by rapid refeeding counteracts improved cognitive control of anxiety through re-nourishment of the brain, resulting in no change in the experience of anxiety. Furthermore, the short length of admission (mean 6 days) in the current study may have precluded full evaluation of the relationship between weight gain and anxiety. However, a recent study examining the relationship between anxiety symptoms and weight gain for AN patients hospitalized on a HCR protocol similarly found no evidence to support a relationship between anxiety change and weight restoration even though the length of stay in this study was longer (26.9 days) (Kezelman et al., 2018).

In our study both S- and T-anxiety levels were measured at baseline. While S-anxiety levels (38.3 ± 6.7) were similar to historical healthy age- and gender-matched controls (38.0 ± 6.68), T-anxiety levels (36.6 ± 7.9) were above normal mean for this age group (30.7 ± 6.01) (10). The elevated level of T-anxiety is supported by the literature which indicates high rates of psychiatric comorbidity between anxiety disorders and AN in both adolescents and adults (Swinbourne et al., 2012; Swinbourne & Touyz, 2007). The finding that

S-anxiety levels measured at baseline were similar to healthy age matched norms was unexpected as we anticipated it to be elevated as hospitalization itself is a stressful event. State anxiety may not have increased for the same reason that we hypothesized above regarding why the trajectory of trait anxiety did not increase. When the patient is hospitalized, the control concerning eating is taken away; they are in an environment where the responsibility concerning food is given to the medical team, and this exchange of responsibility may have decreased anxiety levels from the onset. In addition, weight loss in eating disorder patients leads to autonomic dysfunction (Kollai et al., 1994). Perhaps this autonomic dysfunction impacts one's physiological response to stress, resulting in changes in how one then perceives their state of anxiety.

This study has several strengths. To the best of our knowledge this is the first study to look at the daily progression of anxiety in adolescents with AN on a HRC protocol during an admission solely for medical stabilization with no structured therapeutic eating disorder care. The sample was comprised of acutely ill adolescents, all with protein calorie malnutrition started on a set refeeding protocol with little variability between patients. Furthermore, we investigated the difference between pre- and post-meal, allowing for greater clarity regarding anxiety experienced by adolescents with AN during the refeeding process.

However, the study must also be considered in the context of its limitations. The number of participants in the study was small and comprised largely of white, non-Hispanic females, limiting our power to detect smaller differences in levels of anxiety, as well as generalizability. The trajectory of state anxiety was reported over only 6 days, and changes in anxiety may take longer to manifest themselves. We chose 6 days as a cut-off since the mean duration of admission in the current study was 6.2 days; the number of participants significantly decreased after day 6. In our program, patients are transitioned from the inpatient ward to a partial hospitalization day program as soon as they are medically stable, allowing for more comprehensive eating disorder treatment as soon as possible, resulting in a relatively short length of stay. Although the assessment tools used in this study are well validated and widely used, they were all self-report, which can introduce biases. Furthermore, baseline measures were collected within 24 hours of hospitalization and not precisely at the same time for each participant. To account for this variability, baseline values were not included in our comparison with day 6. Although a reported history of premorbid depression and anxiety was collected, participants were not formally evaluated for these conditions as part of this study. Some were already on psychotropic medications which are known to affect anxiety levels, such as selective serotonin reuptake inhibitors and antipsychotics. Our numbers were not large enough to control for these preexisting diagnoses or medication use. Interestingly, a recent study found that the

use of anti-psychotics did not play a role in reduction of anxiety in a group of patients hospitalized for AN and argued whether the routine use of these medications were indeed necessary for these patients (Kezelman et al., 2018). Finally, our study also lacked a control group. It would be ideal to compare anxiety levels in our patients to those receiving a lower-calorie, slowly progressive refeeding protocol. However, all patients hospitalized within our program are treated according to a protocol developed by a multidisciplinary team of eating disorder specialists. We believe this protocol allows for safe yet rapid medical stabilization, and alteration of this standard protocol was not supported by the medical team.

In conclusion, among adolescents with AN hospitalized for acute nutritional rehabilitation, state anxiety does not appear to worsen with advancing calories on a rapid refeeding protocol. This study provides additional support for the use of more rapid refeeding protocols in hospitalized patients with AN.

Disclosure statement

The authors have no conflict to declare.

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