International Journal of Nutritional Sciences

Open Access

Austin Publishing Group

Special Article - Malnutrition

Refeeding Patients with Moderate and Severe Eating Disorders: A Retrospective Cohort Study

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Received: March 26, 2021; **Accepted:** April 28, 2021; **Published:** May 05, 2021

Abstract

Background: Anorexia Nervosa (AN) is a life-threatening mental illness that can cause significant medical complications, including the potentially fatal refeeding syndrome. Registered dietitians (RDs) are a critical part of an eating disorder multidisciplinary team that focuses treatment on safe weight restoration and nutrition rehabilitation.

Method: This study is a description of how the nutrition rehabilitation protocol of 395 adult patients diagnosed with AN and admitted to residential eating disorder treatment is implemented, how the protocol is sustained throughout a patient's treatment stay to achieve desired weight gain, and how the patients' biochemical and clinical progress proceeded between admission and discharge, including laboratory results and body mass index (BMI).

Results: One hundred twenty-six patients required phosphorus supplementation for refeeding hypophosphatemia (RH); admission BMI was not significantly different between those with and without RH. The 15% of patients who required enteral nutrition at any point during their admission gained significantly less weight than patients who only received an oral meal plan. 34.4% of patients admitted with starvation induced hepatitis, 28.6% experienced refeeding hepatitis at some point, 21.0% of patients had elevated liver function tests 2 weeks into refeeding and 28.6% at discharge.

Conclusions: This study demonstrated overall effectiveness in achieving weight restoration goals with aggressive kcal increases without a single incidence of refeeding syndrome and infrequent RH. No significant biochemical changes were observed during refeeding. With close medical supervision and concurrent RD oversight, a refeeding approach with consistent calorie increases that is more aggressive than previously recommended appears to be safe.

Keywords: Anorexia Nervosa, Eating Disorders, Refeeding Syndrome, Nutritional Care Plan

Introduction

Anorexia Nervosa (AN) is a multidimensional life-threatening mental illness. The American Psychiatric Association (DSM-V) diagnostic criteria for AN are defined by three components: 1) Restriction of energy intake relative to requirements, leading to significantly low body weight; 2) Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain; and 3) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight [1]. AN is classified into two different subtypes: restricting type and binge-eating/purging type. Restricting type (AN-R) is characterized by severe food restriction. Binge-eating/purging type (AN-BP) is characterized by calorie restriction as well as purging behavior. AN severity can be defined by using an individual's body mass index (BMI; kg/m^2), with a BMI less than 15kg/m^2 deemed severe AN and a BMI of 15-16 deemed moderate AN [1].

AN has one of the highest mortality rates of all psychiatric disorders, and the highest rate of medical complications out of all the psychiatric disorders [2,3], causing disruption to most organ systems including cardiovascular, gastrointestinal, endocrine, and other metabolic alterations. Another potentially fatal medical complication that can occur is termed refeeding syndrome, which is biochemically characterized by hypophosphatemia, hypomagnesemia, hypokalemia, glucose intolerance, fluid overload, and thiamine deficiency as a result of inadequate monitoring during the early phase of refeeding a patient with AN [4]. Table 1 outlines the major medical consequences of full-blown refeeding syndrome.

Individuals with AN are at a high risk for refeeding syndrome due to their low body weight and chronic poor nutritional intake. The "start low and advance slow" approach to calorie administration in AN has historically been the preferred nutrition rehabilitation protocol for these individuals to avert refeeding sequelae and continues to be espoused in Europe [5]. In recent studies, this approach has been challenged, and some studies have more recently determined that using a more aggressive approach to refeeding by starting these individuals on a higher calorie meal plan can be carried out safely, without an increased risk of refeeding syndrome and with shorter hospitalizations [6]. In 2013, Garber and colleagues found that the start low and advance slow approach could actually delay nutrition repletion, increase lengths of hospitalization, and even lead to initial

Citation: Rabito GS, Blalock DV, Beaty LR, Harr BL, Manwaring J, Rienecke RD, et al. Refeeding Patients with Moderate and Severe Eating Disorders: A Retrospective Cohort Study. Int J Nutr Sci. 2021; 6(2): 1050.

weight loss due to "underfeeding" in some cases [7].

In order to successfully reduce the mortality rate and avoid the progressive medical complications of AN, immediate treatment with safe weight restoration and nutrition rehabilitation is strongly recommended. Because nutritional rehabilitation is the key to the recovery of AN, Registered Dietitians (RDs) play a critical role within the multidisciplinary treatment team consisting of RDs, therapists, and physicians. RDs are responsible for determining an appropriate meal plan to initiate the process of weight restoration, monitoring daily weight trends, and making meal plan adjustments throughout the weight restoration process, including the use of enteral feeds when needed. RDs provide medical oversight, nutrition education, meal coaching, and emotional support throughout the refeeding process.

Eating Recovery Center (ERC) is a large residential eating disorder facility located in Denver, Colorado. At ERC, RD practices in working with moderately to severely ill patients with AN on the residential (RES) units were reviewed. The refeeding protocol for ERC was created with the intent to safely refeed malnourished patients with eating disorders effectively and efficiently to restore towards Ideal Body Weight (IBW). Data were collected on 395 ERC patients, with the diagnosis of either AN-R or AN-BP upon admission, 2 weeks after admission, and at discharge. The aims of this study were to: (1) Describe the implementation of the nutrition rehabilitation protocol by the RDs; (2) Describe how this protocol is sustained throughout a patient's treatment stay to achieve desired weight gain; and (3) Examine the changes in patients' biochemical and clinical progress at admission, 2 weeks after admission, and discharge of their residential treatment stay.

Methods

The sample consisted of N=399 adult patients with AN admitted to a residential level of care at ERC in Denver, CO between 2013 and 2018. Patients had to be at least 17 years old, admitted directly to residential level of care (as opposed to transferred from another treatment facility), have a length of stay ≥14 days, and have no period of time off the unit greater than one week. Four patients were removed from the sample due to requiring abnormally low calories at admission (defined as <1200kcal/day). Our final analytic sample is N=395 unless otherwise stated.

The patients' multidisciplinary care team made the initial diagnosis of AN-R or AN-BP consistent with DSM-5 criteria (American Psychiatry Association, 2013). For residential level of care, RDs saw patients weekly for two individual sessions of 45-60 minutes each. During sessions, RDs worked with patients on meal plans to increase calories and variety in food choices and implement food-related challenges and exposures. Food-related challenges and exposures typically involved RDs having 1:1 meals or snacks with patients, redirecting mealtime behaviors, and supporting challenging meals. RDs were also present in weekly multidisciplinary team rounds with each patient, managed orders for enteral feeding, and coordinated care with registered nurses and the medical team in the event that there were medical reasons necessitating a change in the course of weight restoration.

Refeeding procedures involved starting at 1500-1800 kilocalories (kcal) per day and increasing by 300-500 kcal/day every two to three days based on weight trends. The weekly weight gain goal was 1.3-1.8 kg/wk. Patients were given the opportunity to eat planned meals (15-20% protein, 50-60% carbohydrates, 20-25% fat), and if they were unable to complete their calorie requirement in a timely manner (≤30 minutes for meals and ≤15 minutes for snacks), then they were provided with a liquid oral supplement (14-15% protein, 50-86% carbohydrates, 0-35% fat). If patients were unable or unwilling to meet calorie goals with an oral meal plan, then Enteral Nutrition (EN) was added (16-18% protein, 43-50% carbohydrates, 30-41% fat), to achieve their current caloric prescription via a nasogastric tube at a continuous rate for 24 hours, either nocturnally, or via bolus feeds. Rarely, nasojejunal tubes were used if nausea, vomiting, or gastroesophageal reflux were a problem. The percent oral versus enteral was based on patient preference with RD input, as long as the daily kcal goal was being met and weight gain was being achieved.

A Comprehensive Metabolic Panel (CMP) and serum phosphorous level were obtained at admission, with phosphorous monitored daily for the first five days after admission. CMP and phosphorous were monitored weekly thereafter, unless more frequent monitoring was indicated based on abnormal lab results or provider concerns. Liver function was tested, including Alanine Transaminase (ALT) and Aspartate Transaminase (AST), with elevated ALT defined as >45 units/Liter (U/L), elevated AST defined as >40U/L, and "hepatitis" defined as having either elevated ALT or elevated AST. Hypophosphatemia was defined as serum phosphate level of <2.7 milligrams/deciliter (mg/dL). Critical hypophosphatemia was defined as a serum phosphorus level <2.0mg/dL. Normal levels of albumin were 3.2 to 5.6 grams/deciliter (g/dL) and normal levels of prealbumin were 17.6 to 36 mg/dL. Degree of malnutrition was determined using the Classification of BMI in Adults [8]. Participants either provided informed consent to participate in a broad research study, or their data are covered by an exemption determination request for those who have not provided informed consent, both approved by ERC governing Institutional Review Boards.

Statistical analysis

Paired-samples *t*-tests were used to examine raw changes in patient values from admission to discharge. Multivariate generalized linear models were used to examine associations controlling for additional variables or including interactions between variables (standard regressions were used for continuous outcomes and logistic regressions were used for dichotomous outcomes). Associations between two continuous variables were examined with Pearson correlations, associations between a continuous and a dichotomous variable were examined with independent-samples t-tests, and associations between two dichotomous variables were examined with a non-parametric chi-square test of independence with a Phi coefficient for effect size. Alpha for significance was set at $p<0.05$.

Results

Demographic and clinical characteristics at admission

Demographic and clinical characteristics of patients and treatment are described in Table 2. Changes in relevant lab values from admission to discharge are presented in Table 3. There were 395 patients; 236 (59.7%) with a diagnosis of AN-R and 159 (40.3%) with a diagnosis of AN-BP. Three hundred and sixty (91.1%) of the patients were female, and 28 (7.1%) were male. Three (0.7%) were

Table 1: Refeeding Syndrome a pentad.

Refeeding Syndrome: A Pentad
• Hemolysis
• Rhabdomyolysis
• Respiratory Failure
• Heart Failure
• Seizures

Table 2: Sample and Treatment Characteristics.

	Total (N=395)	ANR (N=236)	ANBP (N=159)
Age (yrs, SD)	27.82 (10.07)	28.33 (11.08)	27.06 (8.32)
Female (N, %)	360 (91.1%)	210 (89.0%)	150 (94.3%)
White (N, %)	372 (94.2%)	220 (93.2%)	152 (95.6%)
Inpatient (N, %)	316 (80.0%)	188 (79.7%)	128 (80.5%)
LOS (weeks, SD)	5.72 (3.37)	6.20 (3.79)	5.01 (2.47)
Illness Duration (yrs, SD)	11.32 (9.56)	10.68 (10.02)	12.27 (8.78)
Degree of Malnutrition			
Severe (N, %)	239 (60.5%)	160 (67.8%)	79 (49.7%)
Moderate (N, %)	64 (16.2%)	29 (12.3%)	35 (22.0%)
Mild (N, %)	58 (14.7%)	33 (14.0%)	25 (15.7%)
Normal (N, %)	34 (8.6%)	14 (5.9%)	20 (12.6%)
Phos During Tx (mg, SD)	2278.78 (5221.44)	2623.94 (6127.49)	1766.48 (3420.53)
Refeeding Hypophos (N, %)	126 (31.9%)	74 (31.3%)	52 (32.7%)
Oral Only Refeeding (N, %)	336 (85.1%)	204 (86.4%)	132 (83.0%)
Albumin (g/dL, SD)	4.48 (2.01)	4.51 (2.57)	4.44 (0.47)
Nadir Wt (kg, SD)	43.00 (7.28)	42.14 (7.49)	44.27 (6.78)
Avg Daily Calories (SD)	2692.87 (476.33)	2786.28 (504.79)	2554.24 (392.96)
Freq calories increase/wk (SD)	1.10 (0.39)	1.06 (1.17)	1.17 (0.39)
Avg calorie increase/wk (SD)	322.07 (159.48)	330.63 (201.09)	309.36 (54.88)
Highest calories/ kg (SD)	70.94 (14.09)	74.27 (14.29)	66.01 (12.25)
Max calories (SD)	3312.87 (604.41)	3415.05 (642.46)	3161.20 (508.25)
On Spironolactone (N, %)	55 (13.9%)	14 (5.9%)	41 (25.8%)

transgender female and four (1.0%) were transgender male. Based on BMI, 239 (60.5%) patients admitted with severe malnutrition, 64 (16.2%) patients had moderate malnutrition, 58 (14.7%) had mild malnutrition, and 34 (8.6%) were not malnourished upon admission. The average admission BMI was 15.7 (SD=1.98) with a range of 10.6-20.7, and the average BMI at discharge was 18.06 (SD=1.77). Admission percent expected body weight (%EBW) was 75.03 (SD=9.49), which was significantly higher for females (M=75.38) than males (M=70.69, t=2.65, p=0.01). The average initial calorie level was 1688 kcal (range of starting kcals was 1200-2560).

Longer total duration of illness was significantly associated with lower weight at intake (r= -0.13, p<0.01) and fewer average kcals received throughout treatment (r=-0.13, p=0.01). Duration of illness was not associated with average weight gain max kcal/day and max kcal/kg mode of feeding or gender. More severe malnutrition was significantly more likely in females than males and significantly more likely in patients with AN-R than patients with AN-BP. Severity of malnutrition at admission was not associated with starting kcal. Patients who admitted with severe malnutrition were discharged on a higher meal plan and received more kcal/kg.

Calories, weight gain and refeeding during treatment

The average maximum kcal was 3312.87 (range=1850-5655 kcals). Average maximum kcal was 4047.50 for males and 3252.67 for females, and average final kcal was 4047.50 for males and 3244.07 for females. On average, kcals were increased 1.10 times per week, by an average of 322.07 (SD=159.48) kcals. Patients were fed a maximum of 70.94kcal/kg (range=39-112 kcal/kg). The average difference in kcals from admission to discharge was 1616.92, which was significantly higher among patients with AN-R (M=1692.54) than patients with AN-BP (M=1504.69, t=3.22, p=0.001). Similarly, the average difference in kcals from admission to discharge was significantly higher for males at 2178.39 than females at 1571.64 (t=5.62, p<0.001).

Patients' length of stay was on average 5.72 weeks (SD=3.37). During their admission, patients gained an average of 1.43kg/week (SD=0.44). Patients' BMI increased by an average of 2.33 (SD=1.46) and %IBW by an average of 11.11 (SD=6.95). Weight gain was significantly associated with lower admission BMI, but admission diagnosis was not significantly associated with weight gain apart from admission BMI. Patients who required EN at any point during treatment gained an average of 1.19kg/week, which was significantly lower than the 1.47kg/week for patients who only received an oral meal plan (t=4.58, p<0.001). Males had a significantly higher rate of weight gain (1.60kg/wk) compared to female patients (1.41kg/wk; t=2.65, p=0.01). Transgender patients were not included in this comparison due to the low number of patients. Average rate of weight gain was significantly associated with degree of malnutrition (r=0.32, p<0.001). Average rate of weight gain was not significantly associated with age or duration of illness.

Fifteen percent of patients received any EN during their treatment, with a similar proportion requiring EN between patients with AN-R (14%) and AN-BP (17%, t=0.92, p=0.36). No patients were completely dependent on enteral feeding for their entire admission stay. Mode of feeding was not associated with rate of kcal increases, length of stay, diagnosis or gender. There were no patients that discharged on EN.

Lab values during treatment

The average phosphorous level on admission was 2.42mg/dL. Only 30 (7.6%) patients had a low serum phosphorous on admission. One hundred twenty-six (31.9%) patients required phosphorous supplementation for RH. RH typically was present by day 2 of admission. These patients received an average of 2,278mg (SD=5221.44) of phosphorous; it took an average of 1.23 (SD=0.58) days to correct hypophosphatemia. There was not a significant difference in numbers of days to correct RH based on admission diagnoses. RH was more common in patients with AN-R (36%) than in AN-BP (28.9%) and in patients that required enteral feeding (36% versus 32% for those who did not require enteral feeding). However, these differences were not significant. BMI at admission was not significantly different between those with and without RH (Table

Table 3: Sample Changes during Treatment.

	Total (N=395)			ANR (N=236)			ANBP (N=159)		
	Admission	Discharge	Change t/χ2	Admission	Discharge	Change t/χ2	Admission	Discharge	Change t/χ2
AST (U/L, SD)	41.95 (52.82)	26.28 (14.64)	t=-5.68, p<0.001	40.34 (42.35)	27.63 (16.29)	t=-4.30, p<0.001	44.33 (65.38)	24.27 (11.54)	t=-3.81, p<0.001
ALT (U/L, SD)	46.07 (44.21)	41.53 (35.74)	t=-1.58, p=0.11	48.32 (45.62)	46.47 (38.44)	t=-0.48, p=0.63	42.73 (41.93)	34.21 (29.95)	t=-2.09, p=0.03
Hepatitis (N, %)	136 (34.4%)	113 (33.7%)	χ^2=3.17, p=0.07	82 (34.7%)	79 (33.5%)	χ^2=0.78, p=0.38	54 (34.0%)	34 (21.4%)	χ^2=2.60, p=0.10
Weight (kg, SD)	43.85 (7.38)	50.22 (7.54)	t=11.99, p<0.001	43.11 (7.60)	49.82 (8.18)	t=9.24, p<0.001	44.97 (6.91)	50.81 (6.46)	t=7.80, p<0.001
BMI (kg/m^2, SD)	15.73 (1.98)	18.06 (1.77)	t=17.42, p<0.001	15.48 (2.01)	17.92 (1.83)	t=13.82, p<0.001	16.09 (1.90)	18.26 (1.66)	t=10.80, p<0.001
% IBW (SD)	75.03 (9.49)	86.14 (8.27)	t=17.55, p<0.001	73.68 (9.73)	85.33 (8.42)	t=13.90, p<0.001	77.02 (8.78)	87.34 (7.91)	t=11.01, p<0.001
Calories (SD)	1688.10 (210.49)	3305.03 (611.81)	t=49.67, p<0.001	1718.88 (219.76)	3411.42 (645.6)	t=38.13, p<0.001	1642.42 (187.46)	3147.11 (521.05)	t=34.26, p<0.001

Table 4: Refeeding Hypophosphatemia by Admission BMI Band.

Adm BMI Band	10-11.99	12-13.99	14-15.99	16-17.99	18-19.99	20-21.99
Total #	10	73	149	118	40	11
Refeeding Hypophos	2 (20.0%)	25 (34.2%)	49 (32.9%)	36 (30.5%)	14 (35.0%)	1 (9.1%)
No Refeeding Hypophos	8 (80.0%)	48 (65.8%)	100 (67.1%)	82 (69.5%)	26 (65.0%)	10 (90.9%)

Table 5: AST and ALT Trajectories.

Total Sample	Worsened	Improved	Remained High	Remained Norm
AST adm-dis	33 (8.4%)	89 (22.6%)	15 (3.8%)	257 (65.2%)
ALT adm-dis	71 (18.0%)	62 (15.7%)	39 (9.9%)	222 (56.3%)

4 for RH numbers by BMI band). Patients with AN-R received an average of 2614.50 mg phosphorus and AN-BP patients received an average of 1791.12mg to correct RH. This difference was not statistically significant. RH was not significantly associated with gender, duration of illness, severity of malnutrition upon admission, %IBW upon admission, starting kcals, frequency of kcal increases, and rate of kcal increases, total kcal increase, nadir weight, weight change, or the presence of refeeding hepatitis.

AST ranged from 4 to 581 at admission and 6 to 111 at discharge. ALT ranged from 7 to 280 at admission and 5 to 265 at discharge. Average AST (M= -15.66, SD=52.42) decreased significantly more during treatment than average ALT (M= -4.49, SD=51.94; p<0.001). Final kcals were significantly associated with changes in ALT (r=0.14, p<0.01) and changes in AST (r=0.12, p=0.01). Maximum kcals were also significantly associated with changes in ALT (r=0.14, p<0.01) and changes in AST (r=0.13, p=0.01). Changes in ALT and AST were not significantly related to admission diagnosis, degree of malnutrition upon admission, starting kcals, maximum kcal/kg, average rate of weight gain, mode of feeding, or gender. See Table 5 for ALT and AST trajectories across treatment for the total sample and by ED diagnosis.

Three-hundred eighty-six patients (97.7%) had serum albumin levels within normal limits on admission. Sixty-two of the 66 patients with prealbumin values (93.9%) had levels within normal limits. Average BMI for the 66 patients with prealbumin results was 15.22 (SD=2.10).

Fourteen percent of patients received spironolactone and its use was unrelated to weight gain outcomes. Spironolactone was significantly more commonly prescribed in patients with AN-BP (26% versus 6% in AN-R).

Discussion

This review of the aforementioned nutritional rehabilitation protocol, utilized at ERC for adults at the residential level of care, is the largest review to date of RD procedures for moderately ill adult patients with AN. The purpose of this study was to collect data on the nutrition protocol implemented at ERC, to describe how the protocol is sustained throughout an individual's treatment stay, and to outline the way in which biochemical status was monitored during this process. This study demonstrated overall effectiveness in achieving weight restoration goals with aggressive kcal increases without a single occurrence of refeeding syndrome and infrequent RH. The current study's timeframe was from 2013-2018. Thus, the very recently released 2020 ASPEN consensus definition of refeeding syndrome was not applicable to the current results [9]. This new definition of refeeding syndrome has a lower threshold to identify the syndrome based on the occurrence of a 10-30% decrease of serum phosphorous levels within five days of reintroduction of calories. If this new definition is applied to the current residential treatment center study, there would have been some cases of refeeding syndrome, but clinically it never occurred during the study period.

Moreover, and importantly, the program had low rates of RH, and no other significant biochemical changes during refeeding. Rates of RH did not differ between AN diagnoses, consistent with previous studies, or according to BMI, in contrast to previous studies finding that lower BMI is associated with RH [10-13]. However, Yamazaki et al. found a cutoff BMI of 12.6 to be associated with RH, which is lower than the average BMI of 15.7 in the current residential treatment center study [13]. Although some treatment centers may initiate prophylactic phosphorus supplements prior to refeeding, findings from the current study indicate that this would have been unnecessary for almost 70% of the patient population, especially given the reported finding of zero cases of refeeding syndrome [14]. With medical monitoring and close RD and nursing supervision at the residential level of care, an approach to initial meal plans with consistent calorie increases that are more aggressive than often

recommended appears to be safe, and is consistent with this emerging global trend [15,16].

It is interesting that notwithstanding significant malnutrition, serum albumin levels were normal. Thus, in contrast to other forms of malnutrition, such as HIV, cancer cachexia or sepsis, the current results suggest that albumin is a poor marker of disease severity in patients with AN. The findings in this patient cohort aligned with the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition consensus statement that serum albumin and prealbumin are not accurate indicators of malnutrition in patients with Anorexia Nervosa (AN), as evidenced by the 97.7% of our patient population having albumin levels within normal limits and in 93.9% of patients with prealbumin levels being within normal limits [17]. It is important to note that the average BMI of those patients with prealbumin levels was 15.22, so it is difficult to assess whether we may have seen lower prealbumin levels in patients with a lower average BMI. A study finding that prealbumin was a predictor of medical complications in AN examined patient with an average BMI of 12.9 [18].

Weight outcomes were predominantly achieved via an oral meal plan consisting of a 3-week cycle of standardized menus. It is important to note that 85% of patients in the current study achieved appropriate weight restoration results through progressive oral intake without the need for enteral feeding. Patients only received EN when noncompliance with oral feeding occurred. Results from this study show that weight restoration was slower in those who required and received enteral feedings in addition to their oral intake. This is in contrast to previous studies, which have shown that more rapid weight restoration occurs with the use of enteral feeds [19-21]. Findings from the current study may reflect that those patients needing EN were more resistant to oral feeding, thus affecting the average rate of weight restoration.

Strengths of this study include its large sample size and the first review to outline the role of RDs in implementing a nutrition protocol in residential care for adult patients with AN. The old adage of "start low and go slow", which for years was the accepted approach and still drives care in Europe (5kcal/kg) is refuted by this study. Patients were refed at a much more rapid rate and had no major untoward issues arise. This is increasingly the procedure used in the United States [22-24]. A limitation of this study is a lack of follow up after patients were discharged. Without this information, it is difficult to determine whether this protocol supported continued weight restoration or if full weight restoration was reached in an outpatient setting. Other limitations include an inability to obtain information on psychotropic medication data as well as an inability to examine meal macro-composition and its effect on certain biochemical markers, particularly phosphorus. Because some studies suggest that increased carbohydrate load can worsen RH, determining the meal composition of oral intake would be recommended as a future research direction [25,26].

In summary, the current protocol was designed to ensure early and rapid weight restoration at the residential level of care with moderate malnutrition. Findings suggest that the current protocol is safe and effective, with low incidence of unwanted outcomes such as RH and no incidence of the classic refeeding syndrome. Future research should continue to examine the optimal caloric starting level, the rate of increases needed to achieve positive outcomes safely and quickly, as well as the ideal macronutrient content for refeeding.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Acknowledgments

We would like to thank Millie Plotkin for her superb skills as an information scientist.

Author's Contribution

Ms. Harr wrote the Introduction. Dr. Blalock was responsible for data results and analysis. Ms. Trees, Ms. Beaty, and Dr. Rienecke helped co-author the discussion section with supervision and editing of that section and the overall paper from Dr. Mehler. Dr. Manwaring and Ms. Rabito were responsible for the compilation of the manuscript adhering to the journal's authors' instructions and for the preparation of the manuscript's final iteration.

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