RESEARCH
Review

Nutrition Therapy during Initiation of Refeeding in Underweight Children and Adolescent Inpatients with Anorexia Nervosa: A Systematic Review of the Evidence

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ARTICLE INFORMATION

Article history:
Accepted 20 November 2013
Available online 7 February 2014

Keywords:
Anorexia nervosa
Children and adolescents
Inpatients
Nutrition therapy
Refeeding

2212-2672/$36.00
http://dx.doi.org/10.1016/j.jand.2013.11.022

ABSTRACT

Restoration of weight and nutritional rehabilitation are recognized as fundamental steps in the therapeutic treatment of children and adolescent inpatients with anorexia nervosa (AN). However, current recommendations on initial energy requirements for this population are inconsistent, with a clear lack of empirical evidence. Thus, the aim of our study was to systematically review, assess, and summarize the available evidence on the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed AN. Searches were conducted in Scopus, Web of Science, Global Health (CABI), PubMed, and the Cochrane database for articles published in English up to May 2012, and complemented by a search of the reference lists of key publications. Seven observational studies investigating a total of 403 inpatients satisfied the inclusion criteria. The range of prescribed energy intakes varied from 1,000 kcal to >1,900 kcal/day with a progressive increase during the course of hospitalization. It appeared that additional tube feeding increased the maximum energy intake and led to greater interim or discharge weight; however, this was also associated with a higher incidence of adverse effects. Overall, the level of available evidence was poor, and therefore consensus on the most effective and safe treatment for weight restoration in inpatient children and adolescents with AN is not currently feasible. Further research on refeeding methods is crucial to establish the best practice approach to treatment of this population.
J Acad Nutr Diet. 2014;114:897-907.

ANOREXIA NERVOSA (AN) IS AN EATING DISORDER with a high morbidity and mortality rate.[1] AN is characterized by a significantly lower-than-expected body weight, intense fear of becoming overweight, and a distorted body image.[2] The disorder primarily affects adolescent girls aged 15 to 19 years[3]; however, incidences of early onset AN in children aged 5 to 13 years has been reported.[4] Although the overall prognosis for recovery from AN is better in younger patients than in adults,[5,6] the treatment for AN is a complex and protracted process, involving a multidisciplinary approach across a range of health care settings.[7,8] Life-threatening consequences of malnutrition as a result of AN may lead to one or more admissions for inpatient treatment.[1,9,10]

Weight restoration through continuous increases in energy intake is one of the priorities in the initial stages of inpatient care and is an essential step for overall rehabilitation and recovery.[11-13] Regaining weight during hospitalization has been shown to be one of the major factors predicting favorable short-[14] and long-term outcomes,[15] and has been associated with improvement in a number of psychological and medical complications.[16-18] In adolescents, weight restoration has been shown to significantly improve cognitive impairment compared with pretreatment, thus facilitating psychological or psychiatric therapy.[19] Restoring weight in young patients can also reverse growth retardation, developmental delay, and compromised bone density.[7,20] Conversely, failure to gain weight before discharge can increase the likelihood of the symptomatic progression of the disorder and the chance for consecutive readmissions.[10,18,21] Thus, timely and effective nutrition treatment for weight restoration is crucial to ameliorate the debilitating consequences of AN.[6,22]

Currently there is no consistent approach in recommendations for optimal refeeding practices or nutrition-related treatment of patients with AN.[6,8,13] Most guidelines[8,23-25] for young patients advocate for conservative energy intake at the initiation of treatment (800 to 1,000 kcal/day)[24] due to the risk of refeeding syndrome (RS),[26] a potentially life-threatening disturbance of electrolytes that can occur in severely malnourished individuals following the reintroduction of food.[11,27,28] Although RS is a relatively rare condition (previously reported in <6% of hospitalized

adolescents[29]), it can affect the cardiovascular, pulmonary, renal, hepatic, and neuromuscular systems, potentially leading to multiple organ failure and death.[27] Severely malnourished patients (those with <70% of expected body weight), are at most danger of developing the syndrome, particularly during the first week of nutrition treatment.[11] Therefore, energy recommendations for the initiation of refeeding are commonly set lower than the estimated energy requirements of the individual.[30] However, there is an opposing view that this approach could potentially postpone weight recovery, thus delaying the therapeutic process[9,30] and initiation of refeeding should commence at around 2,000 kcal whilst closely monitoring vital signs.[30] Research on the current practice of refeeding reflects the lack of consistent recommendations on treatment for weight restoration in this population. A 2008 survey of North American physicians treating adolescents with AN suggested a "tremendous variation in care"[31] with refeeding regimens at initiation of treatment ranging from 100 to 1,500 kcal/day.[31] Similarly, a recent study of Australian dietitians revealed discrepancies in estimation of the initial energy requirements for children and adolescent inpatients with AN.[32]

Currently there is no evidence for the best approach to weight restoration in this population, because most recommendations are based solely on clinical experience and expert opinion.[22,24,33] Empirical evidence to support best practice in this field is lacking.[13,34] A systematic review of randomized controlled trials (RCTs) by Bulik and colleagues in 2007[35] found that no clinical trials on weight restoration in AN had been conducted, with the authors concluding that the literature "…has failed to address the optimal approach to renutrition…" in AN across the age groups. Therefore, due to the lack of empirical research on this topic, the aim of our study was to systematically review, assess, and summarize the available evidence on the effect of energy prescriptions during refeeding on weight restoration in hospitalized children and adolescents aged 19 years and younger with diagnosed AN.

METHODS

Methodology

This study was guided, where applicable, by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[36] One key question and one subquestion were developed using the Patient, Intervention, Comparators, Outcome, Study Design criteria[37] as follows:

1. What is the strength of the evidence for the effect of the starting energy intake prescribed during refeeding on weight gain in inpatient underweight children and adolescents aged 19 years and younger with AN?
   1.1 What is the evidence of any adverse effects of refeeding conducted in an inpatient setting in an attempt to restore weight in underweight children and adolescents aged 19 years and younger with AN?

Inclusion and Exclusion Criteria

RCTs and observational studies published in English up to June 2012 were included in our review. RCTs are regarded as the best evidence for treatment; however, based on a preliminary review of the literature and consultations with the experts, a lack of RCTs was expected; thus, observational studies were included per the inclusion/exclusion criteria listed in Figure 1.

Literature Search

References were identified by an online search conducted between March and May 2012. Three electronic databases were searched: Scopus, Web of Science, and Global Health (CABI) for articles published up to May 2012 with a combination of broad key terms *anorexia nervosa, children or adolescent**, *inpatient*, *nutrition therapy*, and *hospital** (modified as required) to maximize article retrieval. The PubMed database and Cochrane Collaboration libraries were searched using Medical Subject Heading terms *anorexia nervosa* and *dietary therapy*, and *anorexia nervosa*, respectively. A citation search of the identified key studies was performed in the Web of Science database. Individual authors were contacted for further information where required.

The titles and abstracts of the retrieved articles were imported into a commercial reference management software package (EndNote version X4.0.2, 2010, Thomson Reuters) and all duplicates were excluded. One author reviewed the references to identify potentially eligible studies, with full articles obtained for the latter. The full articles where examined using a priori exclusion and inclusion criteria (Figure 1) by two authors using a previously developed form with any disagreement resolved through discussion. The categories for the data extraction were based on Patient, Intervention, Comparators, Outcome, Study Design criteria[37] (Figure 1). The primary measures sought were: energy intake at initiation of refeeding, maximum energy intake during hospitalization, methods of delivery, weight gain, and reported adverse effects. A meta-analysis could not be conducted due to the small number of studies that met the inclusion criteria as well as the lack of heterogeneity in their study designs, energy intake prescribed, feeding methods used, and duration of the follow-up. Rather, our systematic review focused on the description of the intervention and outcome measures, including weight changes during treatment and presence or absence of reported adverse events. A qualitative synthesis of the strength of available evidence was also conducted.

Quality Assessment

There is currently no agreed upon gold-standard tool for the quality assessment of observational studies.[41-44] Furthermore, the variety in design and methodology of studies included in our review introduced a propensity to bias; thus, a single tool was not applied. Instead, the quality assessment of the included studies was guided by the Cochrane risk of bias tools.[45] The risk of bias was rated in two areas that were applicable to all of the selected studies: study design and study reporting.

RESULTS

Results of the Literature Search

Overall, 593 nonduplicated publications were identified during the initial search, with nine additional articles identified through snowball sampling. A total of seven studies[46-52]

PICOS[a]	Inclusion and exclusion criteria	Data extraction
Patient	Included: • Children or adolescents of both sexes up to age 19 y • Anorexia nervosa diagnosed according to DSM-IV[b] or ICD-10[c] Excluded: • Adults aged >19 y • Studies with mixed population (eg, participants aged <19 y and >19 y)	Study population, including: • No. of participants • No. of admissions • Sex • Mean age and age ranges • Baseline weight • Baseline BMI[d] • Diagnosed comorbidities
Intervention	• Reports containing details regarding nutrition therapy, including initial energy intake and feeding methods used • Reports containing sufficient details on monitoring of weight gain progress	Nutrition treatment provided: • Total daily energy intake at commencement of refeeding • Advance in intake and maximum number of calories consumed • Macronutrient distribution • Feeding modalities • Duration of the intervention
Comparator	Studies with or without comparator group	Allocation of participants to groups if applicable
Outcome	Prime outcome measures: • Weight/BMI changes • Adverse events	• Weekly weight changes • Weight at discharge/point of intercept • BMI at discharge/point of intercept • Presence or absence of adverse events related to treatment • Length of treatment
Study design	Included: • Prospective or retrospective cohort, cross-sectional, case-control, or RCT[e], if available • ≥10 participants • Any length of follow-up • Studies conducted in inpatient settings, including medical and psychiatric wards and specialized eating disorder services Excluded: • Case studies	• Study design and study setting • Consent procedures • Length of follow-up

[a]PICOS=patient, intervention, comparator, outcome, study design.

[b]DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.[39]

[c]ICD-10=*International Classification of Diseases*, 10th edition.[40]

[d]BMI=body mass index.

[e]RCT=randomized controlled trial.

Figure 1. The study inclusion and exclusion criteria and data extraction in a review examining the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed anorexia nervosa. Format adapted from Whelan and Myers.[38]

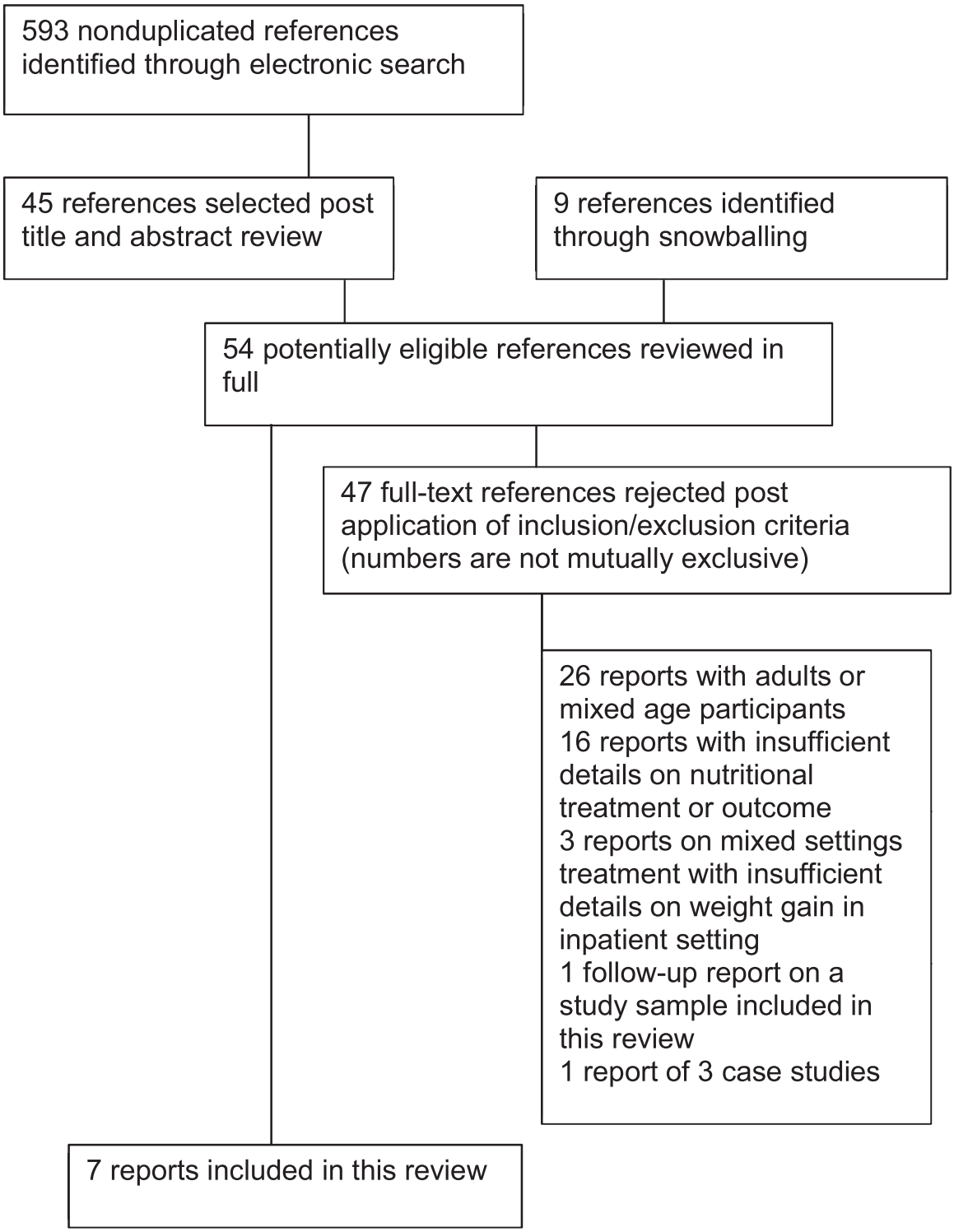

Figure 2. The search process used to identify and assess relevant references in a study examining the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed anorexia nervosa.

met the inclusion criteria (Figure 2). These studies were published between 2002 and 2010; however, because the data were reported retrospectively in four studies, participants may have been admitted for inpatient treatment as early as January 1990. All but one study were single-centered, conducted in child and adolescent psychiatric units[46-49,51] and a specialized eating disorder unit[52] in five countries: Australia, Italy, Germany, Spain, and the United States. In the

multicenter study,[50] 28 patients were initially treated in an adolescent medical unit for medical stabilization before being transferred to an adolescent psychiatric unit. Two studies[48,49] sought informed consent from the participants and their caregivers, four studies[47,50-52] reviewed all consecutive admissions, and one[46] study did not specify consent procedures.

Characteristics of the Studies

No randomized controlled trials on this topic were identified during the search. All seven studies included in this review were observational and included four retrospective chart reviews[47,50,51,52] (Tables 1 and 2), three prospective,[46,48,49] and one case control study[49] (Table 2). Two of the retrospective cohort studies[50,51] compared the short-term outcomes of oral refeeding with and without supplementary nocturnal nasogastric (NG) feeding in girls[50] and boys.[51] The criteria for administration of NG feeding was specified in Robb and colleagues[50] as the following: a primary diagnosis of AN, weight at or below 85% of ideal body weight (IBW), and no physiologic contraindication to NG refeeding. In an article by Silber and colleagues,[51] the initiation of nocturnal NG feeding was described as a standard hospital procedure for inpatients with AN receiving treatment in the center after 1995.

An additional retrospective cohort study by Diamanti and colleagues[47] included an evaluation of the indications for and clinical safety of parenteral nutrition (PN) in the treatment of underweight patients with AN by comparing short- and long-term outcomes according to feeding modality received during rehabilitation. In this study, inpatients were grouped as either having received oral refeeding combined with PN refeeding or an exclusive oral refeeding regimen.[47] The criteria for the use of PN were specified as electrolyte disturbance, dehydration, and cardiac dysfunction. In addition, PN treatment was used in inpatients with inadequate oral intake.[47] For the purpose of our review, in all three studies reporting a comparison of treatment modalities, the groups of patients receiving additional tube feeding were considered to be the intervention group (Table 1). The final retrospective study, by Whitelaw and colleagues,[52] reported results of audited medical records of patients admitted for weight restoration to an adolescent ward over a 12-month period. This study aimed to examine the incidence of hypophosphatemia in children and adolescents who were treated according to a relatively hypercaloric protocol during the first 2 weeks of hospitalization[52] (Table 2).

Three prospective studies[46,48,49] included in this review conducted investigations in children and adolescents with AN; however, the primary aims of these particular studies did not include examining energy intake prescription. Nevertheless, weight change was reported as one of the primary outcomes and, therefore, these studies were considered appropriate to include in our systematic review. The first of these investigations was a case control study by Mika and colleagues[49] that compared nutritional status and body composition changes assessed by multifrequency bioelectrical impedance analysis during dietary treatment of inpatients with AN compared with normal-weight age-matched controls.[49] The data for the controls were not extracted for our review. The second prospective case series study by Heer and colleagues[48] investigated bone turnover over 11 weeks of inpatient hypercaloric nutrition-related treatment supplemented by calcium and vitamin D.[48] Finally, the third prospective case series study, by Guerda and colleagues,[46] measured the changes in resting energy expenditure (REE) during weight rehabilitation of adolescent inpatients using indirect calorimetry. A secondary aim of this study was to evaluate the accuracy of calculated predictions of REE by comparing measured REE with calculated REE using predictive equations (eg, Fleisch, Harris-Benedict, FAO, Schofield-HW, and Schebendach).[46]

Patients

Overall, 403 children and adolescents inpatients with AN were included in the reviewed studies; most were white females (96%). Mean age ranges and body mass index (BMI) were reported to be 13.8 to 15.7 years and 14.2 to 17.4, respectively (Tables 1 and 2). The number of admissions was reported as means in two studies[50,52] and ranged from 1.3 to 5.1, and the duration of illness as 11.4 to 25.2 months across three studies.[47,48,50] In addition, diagnosed psychosocial comorbidities were reported in all three studies comparing feeding modalities.[47,50,51]

Interventions

The three studies that compared tube-feeding modalities reported a varied approach. In the study by Diamanti and colleagues[47] energy intake of 40 kcal/kg/day was initially implemented in the exclusive oral feeding group, while this was complemented with additional PN in the intervention group (Table 1). Alternatively, in the studies by Robb and colleagues[50] and Silber and colleagues,[51] the oral protocol was not described in terms of a specific energy intake, but as a gradually increasing feeding regimen that allowed for a required weight gain. Detailed tube feeding regimens were described in all three studies comparing treatment modalities.[47,50,51] However, in the study by Silber and colleagues,[51] the refeeding protocol was referenced to previously published work.[53] Energy delivered via tube feeding were progressively increased at the initiation of refeeding, and then decreased according to an increase in oral intake (Table 1).

In four of the other included studies,[46,48,49,52] the initial prescribed energy intake for weight restoration varied from 1,000 to 3,600 kcal/day (Table 2). In three of these studies,[48,49,52] most of the inpatients commenced refeeding on at least 1,860 kcal/day; however, there was variation in the commencement time. Mika and colleagues[49] reported starting all (100%) participants on this regimen from admission, whereas the study by Heer and colleagues[48] reported a period of initial observation of 2 to 3 days before commencing. Whitelaw and colleagues[52] described initial regimens starting from 1,900 kcal in the majority (91%) of inpatients. In contrast, Cuerda and colleagues[46] reported an admission diet of 1,000 to 1,600 kcal/day (30 to 40 kcal/kg) (Table 2).

Three studies[48,49,52] reported NG tube feeding at the initiation of refeeding (Table 2), which was in addition to the studies specifically on nocturnal NG feeding.[50,51] Four studies[47-49,52] specified the distribution of macronutrients in the refeeding diets of patients as approximately 15% to 20%

Table 1. Characteristics of retrospective, intervention studies with a comparator group examining the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed anorexia nervosa

	Patients			Intervention		Outcome		
Reference	Patient (n)/sex (n)	Mean age (y±SD[a])	Baseline weight (kg±SD)/BMI[b]±SD	Energy intake at commencement/ maximum energy intake/d±SD	Duration (d±SD)	Weight gain (kg±SD)	Point of intercept weight (kg±SD)/BMI±SD	Adverse events (yes/no)
Robb and colleagues, 2002[50]	n=100/F[c]=100							
	Intervention: n=52 (NNG[d])	14.8±1.9	41.1±4.7/15.5±1.7	O+NNG (Night 1: 600 kcal, Night 3 and post 1,200 kcal)/3,255±668 kcal[f]	22.3±13.5	5.4±4.0[g]	46.5±5.1/17.5±1.3[g]	Yes
	Comparator: n=48 (O[e])	15.0±1.8	42.5±7.6/16.0±1.8	Not reported/2,508±478 kcal	22.1±9.4	2.4±1.8	44.8±7.4/16.8±1.6	No
Silber and colleagues, 2004[51]	n=14/M[h]=14							
	Intervention: n=6 (NNG)	13.8±2.0	42.9±10.7/15.3±1.7	O+NNG (Night 1: 600 kcal, Night 3 and post 1,200-1,440 kcal)/4,350 kcal[ij]	36.0±11.0	10.9[ij]	53.7/19.1[ij]	Yes
	Comparator: n=8 (O)	14.9±1.7	46.2±11.0/17.4±2.3	Not reported/3,400 kcal[j]	39.9±22.0	3.0[j]	49.1/18.5[j]	No
Diamanti and colleagues, 2008[47]	n=198/F=198							
	Intervention: n=104 (PN[k])	14.9±1.4	36.3±0.5/14.3±0.2	O+PN at 40 kcal/kg, ↑ PN to 60 kcal/kg; PN ↓as O ↑, suspended at O ≥50 kcal/kg/ 2,175±26 kcal[l]	30.7±2.2[m]	0.7±0.01[n]	39.6±0.5/15.6±0.2	Yes
	Comparator: n=94 (O)	15.2±1.0	41.0±0.6/16.0±0.2	O: 40 kcal/kg, ↑ to 60 kcal/kg/2,078±37 kcal	15.6±1.0	0.5±0.008	41.5±0.7/16.3±0.3[o]	Yes

[a]SD=standard deviation.
[b]BMI=body mass index.
[c]F=female.
[d]NNG=additional nocturnal nasogastric feeding.
[e]O=exclusive oral feeding.
[f]Significantly higher maximum intake (<0.05 with Bonferroni correction).
[g]Significantly greater weight gain (<0.05 with Bonferroni correction).
[h]M=male.
[i]No statistical calculation of significance was reported.
[j]No SD was reported.
[k]PN=additional parenteral nutrition.
[l]Significantly higher maximum intake ($P<0.0001$).
[m]Significantly longer hospital stay ($P<0.0001$).
[n]Significantly greater mean weekly weight gain, reported in grams ($P<0.0001$).
[o]Significantly greater weight ($P<0.0001$)/BMI ($P<0.02$).

Table 2. Characteristics of studies without a comparator group in a review to examine the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed anorexia nervosa

	Patients			Intervention		Outcome		
Reference	Patient (n)/Sex (n)	Mean age (y±SD[a])	Baseline weight (kg±SD)/BMI[b]±SD	Energy intake at commencement/ maximum energy intake/d±SD Feeding methods	Duration (d±SD)	Weight gain (kg±SD)	Point of intercept weight (kg±SD)/ BMI±SD	Adverse events yes/no
Heer and colleagues, 2002[48]	n=19/F[c]=19	14.2±1.4	39.4±5.4/14.2±1.4	1,860±140[d] kcal/ 2,220±170[d] kcal O[e], initial NG[f] n=18	77	Not reported	Not reported/ 17.1±0.7	No
Mika and colleagues, 2004[49g]	n=21/F=21	14.4±1.5	42.3±3.9/15.5±1.1	1,860±140[d] kcal/ 2,220±170[d] kcal O, initial NG n=20	105	0.5-1.0[h]	Not reported/ 17.4±0.7	No
Cuerda and colleagues, 2007[46]	n=22/F=22, n=11[i]	14.7±1.2	40.4±3.3/15.1±1.5	30-40 kcal/kg or 1,000-1,600 kcal/40-60 kcal/ kg or 2,000-2,500 kcal Not reported	54.1±22.3	Not reported	45.3±2.0/17.1±0.7	No
Whitelaw and colleagues, 2010[52]	n=29/F=26, M[j]=3	15.7±1.4	41.8±7.3, 40.9±6.4/ 15.6±1.5, 15.1±1.9[k]	61%-1,900 kcal; 28%-2, 200 kcal; 2%-3,600 kcal; n=3-rehydration; n=1-1,400 kcal/≥2,700 kcal O, 15%-bolus NG	14	2.6±1.3[l]	Not reported	Yes

[a]SD=standard deviation.
[b]BMI=body mass index.
[c]F=female.
[d]Derived figures, calculated based on 1 J=0.239 kcal.
[e]O=oral feeding.
[f]NG=nasogastric feeding.
[g]Comparative data were not extracted for a control group of healthy participants matched for age.
[h]Expected weekly weight gain reported.
[i]Twenty-two patients were assessed on admission, with anthropometry and calorimetry measurements repeated in 11 patients before discharge.
[j]M=male.
[k]Admission weight and BMI were reported separately for patients with normophosphatemia and hypophosphatemia.
[l]Two weeks' weight gain reported.

of energy from protein, 30% from fat, and 50% to 55% from carbohydrates. The maximum energy intake achieved during hospitalization was reported in all seven studies, with means ranging from 2,000 to 4,350 kcal/day. In all three studies reporting comparative feeding modalities,[47,50,51] the maximum energy intake achieved was greater in groups with additional tube feeding (Table 1). Periods of investigation varied from 2 to 15 weeks, and in most studies depended on the overall length of hospitalization of patients (Tables 1 and 2).

Outcomes

Outcome assessment criteria varied among all studies. For example, assessment of and change in body composition were assessed using absolute weight gain during inpatient treatment,[50,51] weekly weight changes,[47,52] weight at discharge or point of intercept,[46,47,50,51] and lean or fat mass.[46,48,49] Gains in lean or fat mass were reported in kilograms[48,49] or as a percentage of overall increase in BMI[46] or weight.[49] The differences in reporting reduced the ability to present an overall summary of the outcome criteria. Nevertheless, in six studies[46-50,52] BMI was included as the primary outcome, and increased significantly after treatment (Tables 1 and 2). In two of the comparative studies,[50,51] mean weight gain and changes in BMI were greater in the groups with oral intake and additional NG feeding. In contrast, in the study investigating PN,[47] discharge weight and BMI were greater with oral refeeding when compared with the PN group. However, the reported difference in mean weekly weight gain between exclusive oral and mixed modalities was $<$0.2 kg (Table 1).

Other reported primary outcomes of treatment included length of stay,[47,50,51] body composition,[48,49] skinfold thickness,[46] bone formation markers,[48] and serum phosphorus levels.[52] In the three studies that compared feeding modalities[47,50,51] the overall length of hospitalization of inpatients was also reported. In the studies with nocturnal NG feeding,[50,51] there was no significant difference between the groups. In the study that used PN,[47] a significantly shorter hospital stay was reported in participants who were on an exclusive oral refeeding program (Table 1).

Adverse Events/Complications

No deaths were reported in the short-term outcomes of any study. In the study assessing nutritional status by bioelectrical impedance analysis,[49] one participant with AN was excluded due to lack of weight gain. Complications were reported in all four retrospective studies,[47,50-52] but were resolved with an appropriate treatment. In the nocturnal NG feeding study in girls,[50] two individuals out of a total of 52 patients required antianxiety medication to relieve anxiety about tube placement, six patients had epistaxis, whereas 15 patients had tube-related nasal irritation. In addition, three patients removed their own tube. In the study on nocturnal NG feeding in boys,[51] one participant had nasal irritation and epistaxis. There were no cases of RS or aspiration pneumonia in either of these studies.[50,51] Two studies[47,52] reported hypophosphatemia in treated participants with the former study[47] also reporting incidence of hypopotassemia, increase in liver transaminase enzyme, leg edema, and tube-related infection in patients treated with supplementary PN.[47] In addition, abdominal pain, bloating, and constipation were reported with oral refeeding.[47] Notably, in the PN study,[47] the overall number of complications was significantly higher in the intervention group (oral and PN feeding) than in the comparator group (oral feeding only). In the study by Whitelaw and colleagues,[52] the decrease in serum phosphorus during treatment was shown to be significantly correlated with the percent of IBW on admission. Moreover, a significant inverse relationship between the number of admissions and the development of hypophosphatemia was reported.[52]

Long-Term Outcomes

Long-term outcomes were reported in the study by Diamanti and colleagues[47] and included rehospitalization and recovery rate, and failure of the first nutrition treatment. The long-term outcomes were assessed in 59% and 71% of the intervention (oral and PN refeeding) and comparator (oral) groups, respectively, at a mean time frame of 33.3±14.3 months (range of assessment=9 to 70 months) after intervention. Overall, the reported recovery rate was 63%. Failure of the first nutrition-related treatment was similar in the two groups, with 27 patients repeating nutrtion treatment.[47]

Quality Assessment

The observational studies included in our review had a number of methodologic shortcomings in both study design and reporting leading to potential bias (Table 3). The description of several of the studied populations was incomplete, with the duration of illness and number of admissions reported by only three[47,48,50] and two[50,52] studies, respectively. Initial nutrition treatment was poorly defined in terms of oral energy intake in the two nocturnal NG studies.[50,51] There was no random assignment of participants to treatment conditions in the comparative studies[47,50,51] due to the retrospective methodology and the intervention groups were more compromised in terms of weight at baseline (Figure 1). In the study by Diamanti and colleagues,[47] the intervention group had a significantly higher percent of diagnosed psychiatric comorbidities (29.4% compared with 12.6%), while the study by Robb and colleagues[50] reported a significantly higher number of prior hospitalizations in inpatients receiving NG feeding (means of 2.0 and 1.3 prior admissions), and earlier age of onset of the disorder in this group (mean 12.7 years compared with 13.5 years in the comparator group).[50] In the study by Silber and colleagues,[51] the sample size was insufficient to test statistical significance of the outcome measures. Cuerda and colleagues[46] only reported repeating anthropometry and indirect calorimetry measurements in half of participants before discharge, without an explanation as to why this had occurred. Finally, in the long-term outcome assessment of the PN intervention study, 41% of the PN group and 29% of the oral group were not evaluated.[47]

DISCUSSION

Summary of Evidence

The results of our systematic review confirm the paucity of empirical evidence on the most appropriate refeeding treatment for weight restoration in children and adolescent inpatients with AN. All included studies were observational

Table 3. Assessment of bias in the studies included to examine the effect of differing nutrition therapies prescribed during refeeding on weight restoration in hospitalized children and adolescents (aged 19 years and younger) with diagnosed anorexia nervosa

	Reference and Bias Score Allocated						
Assessment criteria	Heer and colleagues, 2002[48]	Robb and colleagues, 2002[50]	Mika and colleagues, 2004[49]	Silber and colleagues, 2004[51]	Cuerda and colleagues, 2007[46]	Diamanti and colleagues, 2008[47]	Whitelaw and colleagues, 2010[52]
Study design							
Representative sample	+[a]	+	+	+	++[b]	−[c]	−
Matching/randomization	NA[d]	++	−	++	NA	++	NA
Comparable characteristics	NA	+	NA	++	NA	++	NA
Confounding factors	+	+	+	+	+	+	+
Study reporting							
Patient characteristics	+	+	+	+	+	+	+
Treatment data	−	++	−	++	+	−	−
Outcome data (attrition bias)	−	−	+	−	++	++	−

[a] +=moderate risk of bias.
[b] ++=high risk of bias.
[c] −=low risk of bias.
[d] NA=not applicable.

with various methodologic limitations and, therefore, the overall strength of the available evidence was poor, with a lack of consensus and inconclusive outcomes. Most studies were conducted at a single center, using female subjects, and had a range of sample sizes. The energy prescriptions at initiation of refeeding ranged from 1,000 to >1,900 kcal/day. In the studies comparing oral refeeding with and without NG feeding, the initial as well as the maximum energy intake during the inpatient treatment, was greater with both modalities (Table 1). However, the reported incidences of adverse effects were also higher in these groups. Furthermore, in the only study that included PN feeding, the incidence of adverse effects were significantly higher and included possible precursors of RS (eg, hypophosphatemia, hypopotassemia, increase in liver transaminase, and pedal edema).[54,55] The use of NG feeding at the initiation of refeeding was reported in five studies; however, the incidence of hypophosphatemia was only reported in the study that used a hypercaloric diet. That study showed a correlation between hypophosphatemia and lower percent of IBW upon admission. Thus, it appears that the factors associated with adverse effects included PN tube feeding and a lower presenting body weight. Weight gains were reported in all included studies; however, methodologic issues limit any recommendations on the most effective approach to renutrition.

The findings of our review agree with previous research conducted on AN. Previous systematic reviews have identified shortcomings in study design, including treatment-specific biases arising from small sample sizes, differences in study protocol, research conducted in single centers, and clinical rather than statistical interpretation of results.[35,56,57] These are commonly related to the difficulties in conducting well-designed research studies with this population.[35,56-58] Barriers include recruitment difficulties, diagnostic limitations, ethical issues in clinically relevant treatment, high attrition rates, and challenges in follow-up.[5,35] Moreover, the future prospect of research taking an empirical approach to therapeutic management of AN may be implausible due to the numerous presenting problems in both treatment and research.[59] Therefore, it is of particular importance for future studies to develop and observe robust methodologic frameworks of investigation. This could be achieved through explicit definition of cases, larger participation numbers, and matching of participants by disorder state and progression of illness (most likely achieved through multicenter interventions). Larger participation numbers could be also achieved by inclusion of underweight inpatients with restrictive types of eating disorders. For example, a 2013 study by Leclerc and colleagues[60] evaluated a rehabilitation protocol in adolescents inclusive of this population. Although this study was not included in our results due to the established search period, it is worth mentioning. The study is a retrospective review of medical charts and describes initial oral diets ranging from 1,500 to 2,500 kcal/day in 29 inpatients with AN and restrictive types of eating disorders not otherwise specified.[60] Although a small percentage of participants (3.5%) initially developed hypophosphatemia, the authors suggested that a proscribed refeeding protocol is effective and safe. Notably, all participants included in the study were admitted for their first hospital treatment and did not present with any clinical signs of RS. Similar to the majority of the studies included in the results of this review, 75% of participants in the Leclerc and colleagues[60] study were female. Overall, this review showed a clear lack of investigations conducted in male patients with AN. Thus, it is recommended for the future studies to focus on this population.

Furthermore, adequate reporting of the treatment plan, homogeneity and clarity in outcome reporting, and adequate length of follow-up should be considered. We recommend that future observational investigations conducted during refeeding for weight restoration include detailed descriptions of nutrition protocol and weight recovery markers, which will subsequently support and strengthen current evidence and form the basis for future recommendations on the best practice approach to treatment for weight restoration. In addition, availability of detailed treatment plans of interventions that have been successful in restoring weight will support practitioners working with inpatients with AN and provide a reference point in the absence of coherent and current clinical practice guidelines. Currently, practitioners appear to be using a range of sources to determine practice, including standard refeeding protocols established by their institution and protocols based on their individual expertise.[31,32]

Although we have attempted to follow rigor in the process of assessment of all studies included in this review, there are a number of limitations that need to be considered. The inclusion criteria were limited to studies conducted using inpatients aged 19 years and younger, excluding mixed-age studies. These strict age criteria were determined to identify age-specific treatments; however, this could have reduced the potential to conduct quantitative statistical analysis of the outcomes. Thus, the small number and a variable reporting style of the reviewed studies reduced the summary analysis to descriptive interpretation. In addition, due to the variability in design and methodologic features, the quality assessment of the included studies was challenging and likely biased.

CONCLUSIONS

Our review provides insight into the current evidence on nutrition therapy during initiation of refeeding in inpatient children and adolescents with diagnosed AN. However, the evidence summarized in our review is not sufficient to draw any consensus on the most effective quantity or delivery of energy intake. The studies included in our review varied in methodology and described different refeeding protocols with regard to both energy content and feeding modalities. Although in all reviewed studies the participants gained weight as a result of nutrition management during their hospital admission, it is not possible to suggest any initial energy prescription or method of nutritient delivery as the most safe, efficient, or preferential for treatment. Clearly, more research is needed in this challenging area of practice.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

FUNDING/SUPPORT

There is no funding to disclose.