

Nutritional rehabilitation of anorexia nervosa. Goals and dangers

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Abstract: Nutritional rehabilitation of adolescents with anorexia nervosa is both a science and an art. The goals are to promote metabolic recovery; restore a healthy body weight; reverse the medical complications of the disorder and to improve eating behaviors and psychological functioning. Most, but not all of the medical complications are reversible with nutritional rehabilitation. Refeeding patients with anorexia nervosa results in deposition of lean body mass initially, followed by restoration of adipose tissue as treatment goal weight is approached. The major danger of nutritional rehabilitation is the refeeding syndrome, characterized by fluid and electrolyte, cardiac, hematological and neurological complications, the most serious of which is sudden unexpected death. The refeeding syndrome is most likely to occur in those who are severely malnourished. In such patients, this complication can be avoided by slow refeeding with careful monitoring of body weight, heart rate and rhythm and serum electrolytes, especially serum phosphorus. This paper reviews our clinical experience.

Keywords: Nutritional rehabilitation, anorexia nervosa, refeeding, United States

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INTRODUCTION

Nutritional rehabilitation and weight restoration are early goals in the treatment of patients with anorexia nervosa. While refeeding a malnourished patient may seem like an easy task, in patients with anorexia nervosa who by definition are very resistant to weight gain, nutritional rehabilitation can be extremely challenging. Furthermore, refeeding a patient too rapidly is fraught with dangers and can be potentially fatal. The aim of this paper is to review both the science and the art of nutritional rehabilitation in patients with anorexia nervosa. At the end of the review, a timeline for the resolution of some of the medical complications of anorexia nervosa will be developed, based on the available evidence.

I. Goals of nutritional rehabilitation

Nutritional rehabilitation can be defined as "the restoration of normal eating habits, body weight and bodily functions". More specifically this involves:

0. A. Metabolic recovery (changing from a catabolic to an anabolic state);
0. B. Weight restoration;
0. C. Reversal of the medical complications;
0. D. Improved psychological functioning and
0. E. Improvement in eating behaviors.

A. Metabolic Recovery

Total energy expenditure is comprised of resting energy expenditure (REE), accounting for approximately 60% of total energy expenditure; diet induced thermogenesis (DIT), accounting for approximately 10% of total energy expenditure; and physical activity,

accounting for approximately 30% of total energy expenditure. Resting energy expenditure can readily be measured using indirect calorimetry. Measured values can then be compared with predicted values obtained using standard formulae based on age, height and body weight. Several formulae are available but the one most frequently used is the Harris-Benedict equation (1). Diet induced thermogenesis can be determined by measuring energy expenditure, both before and 2 hours after a standard meal. The difference between the basal and the post-prandial readings represents DIT.

In states of malnutrition, such as anorexia nervosa, basal metabolic rate slows down as an adaptive response to starvation. Resting energy expenditure decreases and may be as low as 50 to 70% of predicted values (2,3). Consequently, in the malnourished state, initial caloric requirements are low. With nutritional rehabilitation and metabolic recovery, caloric requirements increase dramatically (4,5). Schebendach et al (4) showed that in a sample of 21 adolescents with anorexia nervosa admitted to an inpatient unit for nutritional rehabilitation, measured REE was significantly lower than the Harris-Benedict predicted REE, 781 ± 263 kcals/d versus $1,205 \pm 99$ kcals/d, $p < 0.001$. Mean values of measured REE were 62 ± 18 % of predicted. The authors proposed a corrective formula for predicting REE in anorexia nervosa in the clinical setting, where indirect calorimetry may not be available (4). In a recent study from Italy, Marra et al (6) performed indirect calorimetry on 237 female patients with anorexia nervosa, 43 of whom were adolescents, and confirmed that both the Harris-Benedict equation and the World Health Organization equations overestimate REE in patients with anorexia nervosa. The Schebendach correction accurately predicted measured REE in the adolescents, but not in the adults.

In a follow-up prospective study of 50 patients with anorexia nervosa, Schebendach et al (4) measured resting and post-prandial REE every two weeks throughout hospitalization and found that fasting REE was low initially, increased significantly during hospitalization and reached the normal range by week six of hospitalization. Post-prandial REE, which was initially 17.5% above basal levels, increased dramatically to over 30% above basal levels, by week four of treatment. It is not clear why the post-prandial increases in energy expenditure are so much higher in anorexia nervosa than the 10% increase expected in a healthy population. What is clear, however, is that during the first few weeks of refeeding, caloric requirements increase dramatically.

A number of studies have investigated the energy cost of weight gain for patients with anorexia nervosa who are undergoing nutritional rehabilitation on inpatient or in clinical research units (7-11). While there is wide variability in individual cases and in different studies, on average, approximately 3,400 kcals of energy are required for a weight gain of one pound (approximately 7,500 kcals/kg of weight gain). As already discussed, the energy cost of weight gain depends on the patient's metabolic status and whether or not nutritional rehabilitation has already been initiated.

B. Weight Restoration

Weight gain can be achieved in inpatient, partial hospitalization, and outpatient settings. Rate of weight gain should be 0.9-1.4 kg (2 to 3 lb.) per week for inpatient programs, 0.5 to 0.9 kg (1 to 2 lb.) per week for partial hospitalization programs (when such programs are step-down programs from inpatient units) and 0.2 to 0.5 kg (0.5 to 1 lb.) per week for outpatient management (12). For most inpatient units, a behavioral contract is the backbone of the program. Weight gain is rewarded by an increase in privileges and weight loss accompanied by a loss of privileges. Such programs work without necessarily needing to resort to nasogastric feeding or to total parenteral nutrition. When a contract mandating weight gain of 0.4 kg (.8 lb.) in four days was utilized, patients gained weight at that rate. When the contract was subsequently changed to a rate of 0.54 kg (1.2 lb.) in four days, patients gained weight at the higher rate (13). What was clear, however, is that during the first 5-7 days of nutritional rehabilitation there was no weight gain. In fact, initially there was even some weight loss to levels below admission weight. These 5-7 days, termed the "phase of stabilization," is the time during which the body changes from a state of

catabolism to a state of anabolism. Weight gain cannot be expected to occur during this time.

In the malnourished state, caloric requirements may be as low as 1,000-1,400 kcals per day initially but increase rapidly as metabolic recovery occurs. A total energy intake of 130% of either measured or predicted energy expenditure should be prescribed (2) and requirements may reach 3,600 to 4,000 kcals per day. Gradual increases in caloric prescription should be made every 24 to 48 hours as tolerated. Most patients with anorexia nervosa can be refeed orally (either by eating regular meals or by liquid supplements). The advantage of eating regular meals is that it teaches the patient to eat normally. This method, however, requires a greater need for nutritional or dietary input to ensure that the meals provide the correct amount of calories. Liquid supplements alone provide the necessary calories in a balanced formula but this method does not necessarily reinforce normal eating behavior. Different programs have different preferences over whether to provide regular meals, liquid supplements alone, or a combination of the two. Short-term nasogastric feeding may be necessary in some patients who require large amount of calories or who are failing to gain weight on oral foods alone. Nasogastric feeding should never be used as punishment. Voluntary nasogastric feeding, in conjunction with oral feeding, does increase the rate of weight gain but does not impact on psychological recovery (14). Total parenteral nutrition should rarely be necessary for nutritional rehabilitation in anorexia nervosa.

Independent of the type of nutritional rehabilitation, the content should provide a balanced diet containing 45-65% of intake from carbohydrates, 10-35% from protein and 20-35% from fat (15). Care needs to be taken to ensure adequate calcium intake, which for an adolescent is 1,200 to 1,500 milligrams a day (16,17). A multivitamin containing 100% of the DRI should be prescribed to provide adequate intake of vitamin D, other fat-soluble vitamins and trace elements in order to compensate for the increased requirements during metabolic recovery. The expertise of a nutritionist is recommended (18,19).

C. Reversal of medical complications

1) Electrolyte disturbances

The most common electrolyte disturbances are hypokalemia and hyponatremia. Hypokalemia occurs in those who are vomiting, abusing laxatives or diuretics, while hyponatremia is more likely to occur in those who drink excessive amounts of water either to satisfy hunger urges or to falsely elevate body weight prior to a medical visit. Water intoxication with hyponatremia can cause seizures, coma and death. Both hypokalemia and hyponatremia can be corrected within 24-48 hours using standard formulae.

Serum phosphorus levels may be normal on presentation but can drop precipitously on refeeding (20). A recent study showed that 27.5% of adolescents with anorexia nervosa hospitalized for nutritional rehabilitation, required phosphorus supplementation. Over three quarters of patients reach their phosphorus nadir within the first week of hospitalization (21). Hypophosphatemia is thought to be one of the more important etiologic factors in the development of the refeeding syndrome (described in more detail later in the chapter) (22).

2) Vital sign instability

Bradycardia and orthostatic pulse and blood pressure changes are frequent findings in anorexia nervosa and may be the reason for medical hospitalization (23). In a population of adolescents admitted with anorexia nervosa, Palla and Litt (24) showed that 48% of restrictors and 25% of those who vomited or purged, had heart rates less than 40 beats per minute. Bradycardia occurs as an adaptive response to reduced energy intake. With nutritional rehabilitation, the heart rate slowly increases and reaches normal levels by day 12 of hospitalization. Orthostatic blood pressure changes (defined as a drop in systolic blood pressure of more than 20 mm Hg and/or a drop in diastolic blood pressure of > 10 mm Hg) usually resolve within a day or two, but orthostatic pulse changes (defined as an

increase in pulse rate of more than 20 beats per minute on standing) are present in 60-85% of patients admitted with anorexia nervosa and take up to 21 days to resolve. Resolution of orthostatic pulse changes occurs when patients reach a weight approximately 80% of expected body weight (25).

3) *Cardiovascular abnormalities*

In anorexia nervosa, heart size is reduced (26,27), exercise capacity is diminished (28,29), but cardiac output and left ventricular function are usually preserved (26). Electrocardiographic abnormalities have been noted in up to 75% of hospitalized patients and include bradycardia, low voltage complexes, a prolonged corrected QT interval, T wave abnormalities, ST segment depression, first and second degree heart block and various atrial and ventricular arrhythmias (24,30). In those who are very malnourished, a pericardial effusion may be noted on echocardiography (31). With nutritional rehabilitation, there is normalization of heart rate, and an increase in left ventricular mass, cardiac diameter, cardiac output and exercise capacity suggesting that the cardiac structural and functional abnormalities are reversible after refeeding (27).

0.4) *Resumption of Menses*

Amenorrhea is one of the cardinal features of anorexia nervosa and is associated with suppression of the hypothalamic-pituitary-ovarian axis. Levels of gonadotropins and estradiol are low and revert to prepubertal levels (32). Weight restoration is accompanied by restoration of hypothalamic-pituitary-ovarian function and resumption of menses. A weight approximately 90% of ideal body weight is the average weight at which menses return and 86% of patient with anorexia nervosa who achieve this weight will resume menses within 6 months (33).

0. 5) *Structural brain changes*

Enlargement of the CSF spaces such as the cerebral ventricles and cortical sulci, with volume deficits of both gray and white matter of the brain, have been demonstrated in several computed tomography and magnetic resonance imaging studies of patients with anorexia nervosa (34-40). These findings imply loss of brain substance or cerebral atrophy. Cognitive impairment is well documented in anorexia nervosa but it is not clear whether the cognitive deficits are directly related to the structural brain changes (41). In general, the magnitude of the abnormality seen on imaging studies correlates with the degree of malnutrition. It is also unknown whether the structural brain changes are completely reversible with weight restoration. Earlier studies, with a follow-up period of 3-6 months, showed resolution of the sulcal widening with persistence of the ventricular enlargement (39,40). More recent studies, however, with a longer follow-up period of 1-3 years, have shown that the ventricular enlargement and white matter changes are reversible with nutritional rehabilitation (35,42), but that gray matter volume deficits and regional blood flow disturbances can persist despite weight restoration (42,43).

6) *Reduced bone mass*

Osteopenia, or reduced bone mass, occurs in over 90% of adolescents and young adults with anorexia nervosa and is associated with increased fracture risk (44,45). The cause of the osteopenia is multifactorial and is related to a combination of poor nutrition (dietary deficiencies of calcium, protein and vitamin D), low body weight, estrogen deficiency and excessive exercise (46). The degree of osteopenia is more severe than that seen in women with hypothalamic amenorrhea, suggesting that, in addition to estrogen deficiency, nutritional factors play an important role (47).

Osteopenia in anorexia nervosa may not be entirely reversible, despite medical and nutritional intervention. Weight gain is associated with some improvement in bone mineral density but levels do not return to normal (48). In fact, a recent study conducted on 19 women who had been weight restored and fully recovered from anorexia nervosa for an average of 21 years, found that at follow-up, bone mineral density of the hip still remained

significantly lower than that of healthy controls (49). There are no published studies that have documented the efficacy of either calcium or vitamin D supplementation in preventing or treating the osteopenia of anorexia nervosa. Nevertheless, despite the lack of hard data, it still makes sense to provide supplemental calcium if dietary calcium intake is insufficient and to prescribe a multivitamin containing 400 IU of vitamin D.

Two prospective studies have evaluated the role of estrogen supplementation in the treatment of osteopenia, and neither has found hormone supplementation to be effective (44,50). Ongoing studies are evaluating the use of newer modalities such as DHEA, IGF-1 (a nutritionally-dependent hormone) and the bisphosphonates.

D. Improved psychological function

Malnutrition is associated with depressed mood, cognitive impairment and preoccupation with food, weight and shape. In a classic study published in 1950, Keys et al (51) studied the effects of starvation and refeeding in healthy male volunteers who underwent 6 months of semi-starvation (the Minnesota Health Studies). As part of the study, they explored the effects of starvation on behavior, personality, psychological health, and eating patterns. During the semi-starvation period, subjects became progressively more preoccupied and obsessed with food. They played more with their food, ate over longer periods of time to savor the taste, spent more time reading cookbooks and menus, and spent most of their day planning their food intake. Though initially psychologically healthy, subjects reported feeling more depressed, irritable, angry, and anxious and became socially withdrawn and isolated during the semi-starvation phase (51).

Both Jones (52) and Kingston (41) found that patients with anorexia nervosa had impaired focusing, verbal memory and visuo-spatial reasoning. Similarly, Green et al (53) demonstrated that subjects with anorexia nervosa performed significantly worse than healthy subjects on a battery of cognitive performance tests including simple reaction time, tapping tasks, and immediate free recall. With nutritional rehabilitation there is improvement in mood and cognitive function, although it is not always possible to correlate the subtle neuropsychological changes with objective measures of nutritional status (53) or brain magnetic resonance imaging findings (41). A number of studies have shown improvement in attentional skills, cognitive function and depressive symptoms after inpatient treatment for anorexia nervosa (41,53-56). Despite the above, long-term follow up studies have demonstrated continued psychosocial morbidity in 30-60 % of subjects (57).

E. Improvement in eating behaviors

With nutritional rehabilitation, eating disorder symptoms such as food hoarding and abnormal eating behaviors lessen. Food choices improve and the obsessions about food decrease in frequency and intensity (12). It is well recognized that preoccupation with food and distortion of body image often are the last aberrant eating disorder behaviors to abate and may never resolve completely. Long-term follow-up studies of adult populations with anorexia nervosa have shown continued dieting and food restriction in 23-67% of patients and cross-over to bulimic symptoms in 10-64% (57).

II. Changes in body composition during refeeding

One of the most difficult aspects of refeeding is coping with changes in body shape and size that accompany weight gain. Recent research suggests that the weight gained during refeeding is disproportionate and is mostly fat mass, with the largest increase in fat mass being in the truncal area (58-62). A variety of anthropometric techniques have been used to assess body composition in the malnourished population. These techniques include measurements of skinfold thickness, mid-arm muscle circumference, total body nitrogen (in vivo neutron activation analysis, Potassium-40 assays), bioelectrical impedance, dual-energy X-ray absorptiometry (DEXA), dual-photon absorptiometry, and the gold-standard of under-water weighing. Most of these techniques are complicated and require sophisticated machinery and technical expertise. However, inexpensive, and more readily available

techniques such as skinfold thickness measurements (63,64), BMI and body weight (63) have been shown to be reliable tools for assessing nutritional status before and after refeeding.

As expected, patients with anorexia nervosa have less body fat and muscle mass than do healthy adolescents. Keys et al (51) documented a 25% decrease in body weight, with a 70% decrease in body fat, and a 40% decrease in lean body mass during semi-starvation in the Minnesota Health Studies. Similarly, Misra et al (65) noted that adolescents with anorexia nervosa had 57.7% less body fat and 8.9% less lean body mass than did healthy controls with a disproportionate loss of abdominal fat.

There has been some debate, however, about which type of tissue is gained during the course of refeeding of patients with anorexia nervosa. An early study conducted by Forbes et al (8) found that in the initial stages of recovery, about 64.4 percent of the weight gained was lean body mass, although this number decreased as ideal body weight was reached. However, more recent studies with a longer period of follow-up have found a preferential increase in fat mass (58,60,61,65,66). Probst et al (64) demonstrated that 55% of the 11.9 kg gained by adult patients with anorexia nervosa during a 23-week nutritional rehabilitation period was fat mass. Similar results were found by Iketani et al (60), who noted that over a 15 month follow-up period most of the weight gained was fat mass. It appears that the majority of weight gained during the first 1-2 months of recovery is lean body mass, and then as patients reach their treatment goal weights, a greater proportion of the weight gained will be fat. There is a need for additional studies to examine the progression of weight gain over discrete units of time in order to confirm which tissues are laid down first.

As weight is restored, it seems that a disproportionate amount of adipose tissue is deposited centrally in the abdomen and trunk (58,60-62,67). Iketani et al (60) found that when patients were less than 70% of ideal body weight, fat mass in the trunk and pelvis was 73.9% and 65.6% of that of controls. Upon refeeding, fat mass of the trunk and pelvis increased dramatically to 116.8% and 119% of that of the controls. Fat mass in the upper and lower extremities increased to a lesser degree and did not reach that of controls (81.6% and 91.2%) (60,65). Likewise, Grinspoon et al (58) found that 68% of the gain in total body mass was fat and that it was deposited centrally.

In addition, there are differences between adolescents and adults particularly in how weight is lost and then how weight is distributed upon weight recovery. The same investigators examined regional body composition in adolescents with anorexia and compared their findings to studies conducted in adults (65). They found that weight restoration was associated with central fat accumulation but, contrary to adults, the fat mass of their weight-restored adolescents did not exceed that of the healthy controls. The authors concluded that weight recovery in adolescents was associated with “normalization” of fat mass rather than central adiposity.

From the available literature, it is reasonable to conclude that during the course of nutritional rehabilitation, patients with anorexia nervosa will gain lean body mass during the early stages of recovery and fat mass during the later stages of recovery. Distribution of the fat mass may depend on age and which tissues were depleted during weight loss. These findings, which suggest a more favorable body composition after weight gain for adolescents, may be helpful in motivating adolescents towards recovery.

III. Dangers of nutritional rehabilitation

Aggressive nutritional rehabilitation is associated with a number of potentially dangerous medical complications, often referred to as the “refeeding syndrome”. These findings were first recognized after the Second World War when starved prisoners of war and survivors of concentration camps were liberated (51,68). On refeeding, some of the prisoners rapidly developed seizures, coma and died unexpectedly. In the classic experiments on starvation and refeeding conducted by Keys et al (51) in the 1940’s, healthy volunteers underwent semi-starvation for six months. During the refeeding process, some of the subjects

developed cardiac decompensation and even cardiac failure (51). The refeeding syndrome was subsequently noted in other states of malnutrition such as in patients with inflammatory bowel disease, in children with kwashiorkor (69), post-operative patients receiving total parenteral nutrition (70-72) as well as in those with anorexia nervosa (20,73-78). It can occur after intravenous, nasogastric or oral feeding.

The syndrome is characterized by a constellation of fluid and electrolyte shifts together with cardiac, hematological and neurological complications, the most serious of which is sudden unexpected death (22,71,77). The major fluid and electrolyte changes include fluid overload with refeeding edema and cardiac failure (79), hypokalemia and hyponatremia (presumably on the basis of hemodilution) and hypophosphatemia. Hypophosphatemia, in particular, is thought to have a major role in the development of the refeeding syndrome. One of the proposed theories is that during starvation there is total body depletion of phosphorus. Because phosphorus is predominantly an intracellular anion, normal serum phosphorus levels can be maintained until profound depletion occurs. During prolonged starvation catabolism of fat and protein provides energy. With refeeding, carbohydrates become the major source of energy, stimulating secretion of insulin. Insulin drives phosphate intracellularly where it is rapidly utilized for the production of phosphorylated intermediates such as adenosine triphosphate (ATP) which is required for protein synthesis and glycogen production. Because of increased metabolic demand for phosphorus, serum phosphorus levels, which may previously have been normal, now drop (22,71).

Hypophosphatemia can be induced experimentally in starving animals by administering a high caloric load (80). Cells with a high metabolic rate such as red blood cells, neurons and cardiac muscle cells are particularly vulnerable to depletion of phosphorylated intermediates (78). Severe hypophosphatemia is associated with hemolytic anemia, cardiac failure, ventricular arrhythmias, acute delirium, seizures, coma and sudden death.

Hypophosphatemia and the refeeding syndrome are more likely to occur in those who are severely malnourished (less than 70% of ideal body weight) and during the first 1-2 weeks of nutritional rehabilitation (21,81). Moderate to severe hypophosphatemia occurs in 6-7% of adolescents hospitalized for anorexia nervosa (21,82). Clinical signs and symptoms of the refeeding syndrome do not usually occur until serum phosphorus levels drop below 1.0 mg/dL, but they can occur at higher levels if there has been a rapid decline in phosphorus levels. The refeeding syndrome can be prevented by cautious nutritional rehabilitation with careful monitoring of heart rate and rhythm as well as serum phosphorus levels (see table 1). Typically, patients should be started on 1,000-1,400 kcals/day and caloric intake can be gradually advanced by 200-300 kcals every 24-48 hours.

There is no consensus as to whether to administer phosphorus prophylactically during the first weeks of refeeding or whether to provide supplementation as needed when and if the serum phosphorus drops (21,22,74,75,78). What is clear, however, is that in a severely malnourished patient undergoing nutritional rehabilitation, serum phosphorus levels should be carefully monitored during the first 1-2 weeks of nutritional rehabilitation. If available, during this same time period, patients should be monitored on cardiac telemetry to identify any life-threatening cardiac arrhythmias (81). Prompt administration of phosphorus supplementation may help avert the potentially fatal consequences of the refeeding syndrome.

CONCLUSION

Nutritional rehabilitation in subjects with anorexia nervosa results in metabolic recovery with improved mood and psychological functioning. Weight restoration is accompanied by reversal of most of the medical complications. A timeline for these events is shown in Figure 1. The electrolyte disturbances can be corrected within 24-48 hours, vital sign instability takes on average 21 days to resolve and resumption of menses occurs within 3-6 months of achieving a weight approximately 90% of ideal body weight. Some of the

medical complications such as the osteopenia and the structural brain changes, may not be entirely reversible. In addition, body image distortion and preoccupation with food may persist for many months or years. In the initial phases of nutritional rehabilitation lean body mass is gained but subsequently there is a predilection for deposition of adipose tissue centrally. In those who are very malnourished, nutritional rehabilitation must be performed with caution in order to prevent the refeeding syndrome. Caloric prescription should be low initially and slowly increased with careful monitoring of body weight, vital signs and serum electrolytes, especially serum phosphorus.

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