Refeeding in anorexia nervosa: increased safety and efficiency through understanding the pathophysiology of protein calorie malnutrition

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Purpose of review

This paper reviews recent publications about the physiology associated with adaptation to malnutrition and refeeding (including the refeeding syndrome) and clinical outcomes of refeeding paradigms.

Recent findings

A number of recent reviews and original publications have highlighted important differences from the assumptions underpinning the current refeeding guidelines for patients with anorexia nervosa. The notion of 'starting low and going slow' with the prescription of daily calories seems unlikely to be important in preventing refeeding syndrome. Recent publications suggest this approach does not necessarily add to safety in the refeeding process but rather the contrary. It typically results in weight loss and protracts hospitalization and nutritional recovery. Rather, the composition of macronutrients, in particular avoiding a high proportion of calories from carbohydrates, appears to be more important than the absolute number of calories. The means of initial refeeding appears increasingly important in this process, particularly following descriptions of postprandial hypoglycemia.

Summary

The study supports a review of the current guidelines. Evidence for the use of continuous feeding strategies with less than 40% of calories from carbohydrates is presented. This approach has important implications for the prevention of the refeeding syndrome as well as the safety and efficiency with which refeeding may occur for children and adolescents with anorexia nervosa in hospital.

Keywords

anorexia nervosa, children and adolescents, feeds nasogastric, hospital, refeeding

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Introduction

The occurrence of anorexia nervosa during adolescence and the impact this has on peak growth and development continue to demand improvements in the safety and efficiency with which nutritional recovery and weight gain can be achieved. Many such patients are admitted to hospital with life-threatening medical instability (i.e., a fall in core body temperature, heart rate, and blood pressure below accepted minimum values) [1], with initial refeeding increasingly occurring in the context of medical based 'adolescent' wards. Recent publications recognize the contribution of early care and successful weight gain to improved outcomes and decreased morbidity in adolescent anorexia nervosa [2,3].

Standard care as described in current clinical guidelines [4–7] has not been shown to eliminate the occurrence of the refeeding syndrome. The use of these paradigms has routinely been demonstrated to result in weight loss until the second week of treatment [8••].

Refeeding syndrome was initially described by Weinsier and Krumdiek [9] and included the occurrence of sudden death within 2 weeks of commencing refeeding to treat protein calorie malnutrition. This paper followed the clinical experience of a range of patients admitted to intensive care units. The clinical experience and scientific reports from this period contain descriptions of refeeding complications, including delirium, cardiac failure, and death, though few authors linked these outcomes to an understanding of the underlying biology of refeeding. Subsequently, a range of 'defensive approaches to refeeding' have ensued. By ostensibly appearing conservative in their recommendations, these have the face validity of seeming to reduce the risk of the

refeeding syndrome, but, however, are inconsistent with the increasing awareness of the physiological mechanisms by which these adverse outcomes occur. Additionally, there has been a tendency to indiscriminately lump a range of abnormal biological measures reported to occur during the refeeding process with the refeeding syndrome. This approach has been unhelpful in informing improvements in safety and efficiency for optimal refeeding.

These issues have been clarified by O'Connor and Goldin [8••], who report that 'refeeding syndrome is instigated by the influx of enteral glucose during starvation, causing an insulin surge, driving glucose, fluid, and electrolytes into the intracellular space'. This then results in hypophosphatemia, cardiac and neurological events, and sudden death. O'Connor and Goldin [8••] also concluded that 'regardless of how cautious refeeding is commenced, whether it is 10 or 60 kcal/day, those individuals at high risk will still develop refeeding syndrome without appropriate interventions'.

This paper will review the physiology underlying the refeeding process with recommendations based on this and recently published clinical experience. We will suggest alternate strategies for refeeding than those espoused in current clinical guidelines, which may prove to be more effective in promoting weight gain and decrease the length of hospital admission without increases, and possibly with decreases, in the incidence of refeeding syndrome.

Key points

- If the pathophysiology of protein calorie malnutrition is addressed, refeeding patients with anorexia nervosa can be achieved with avoidance of refeeding complications as well as increases in safety and efficiency.
- Current guidelines do not adequately address this issue.
- A new treatment paradigm is proposed from review of current clinical experience and exposition of the pathophysiology of refeeding in the scientific literature.

Physiology of refeeding

Disturbances in both insulin and serum phosphate levels have been implicated in development of the refeeding syndrome.

Insulin and the refeeding syndrome

Insulin secretion and its effects have been targeted as the 'key' to appreciating the metabolic stressors and changes that occur when patients with protein calorie malnutrition are re-fed. During starvation, insulin concentrations decrease and glucagon levels rise, resulting in the rapid conversion of glycogen stores to glucose, exhausting glycogen stores in muscles and liver, and the induction of gluconeogenesis, utilizing lipids and proteins to form glucose.

Whereas refeeding strategies utilizing high carbohydrate concentrations provide ready usable energy in the form of glucose, low basal insulin levels in starvation result in a delayed insulin response with clinically significant postprandial hypoglycemia and its associated complications (Gniuli [10], Yasuhara [11], Kinzig *et al.* [12•], and O'Connor and Goldin [8••]). Gniuli [10] investigated glucose-induced thermogenesis (GIT) and the glucose and insulin responses after a 75-g glucose load in 10 restricted anorexia nervosa women and 10 normal individuals. Fasting blood glucose levels in anorexia nervosa patients were low. Glucose and insulin time courses differed in the two groups, with delayed insulin release and hypoglycemia in the anorexia nervosa group. These metabolic alterations may represent a way to preserve calories by enhancing energy storage; however, they potentiate the risk of developing recurrent hypoglycemia with intermittent oral feeding, and are more pronounced with calories in the form of carbohydrate, as compared with protein or fat. As well as glucose, insulin drives fluid and electrolytes, including phosphate, into the intracellular space, exacerbating the risks of low serum glucose.

The risk of a combination of low serum glucose and low serum phosphate was first highlighted by Patrick [13]. He identified the central role of sodium flux through the activity of Na/K ATPase as determining both risk of developing refeeding syndrome and causing organ dysfunction due to its importance in the maintenance of the integrity of the intracellular environment and hence cell function. His work described the depletion of 'precursor ''fuel'' sources and phosphated adenosine, as being the mechanism by which Na-K ATPase activity is diminished'.

A recent review of the literature by O'Connor and Goldin [8••] highlighted the possible deleterious effects that carbohydrates may have in exacerbating the refeeding syndrome. They concluded it is difficult to postulate what the ideal carbohydrate content of a feed should be at this stage, but, 'by ensuring that carbohydrate is not the predominant energy source, may be enough to reduce the insulin surge which goes on to elicit the refeeding syndrome'. Additionally, these findings highlight the potential benefits of continuous refeeding (most commonly nasogastric refeeding) that mitigates against the impacts of delayed insulin release and postprandial hypoglycemia through the constant supply of calories.

The role of phosphate

Hypophosphatemia occurring with oral refeeding was observed in patients refed after the Second World War (Solomon and Kirby [14]), and by Keys *et al.* [15] in individuals who underwent voluntary starvation [14,15]. Hypophosphatemia is a common metabolic complication in patients receiving specialized nutrition support and is well recognized to occur in patients receiving nutritional treatment for anorexia nervosa (Fisher *et al.* [16]). Low phosphate levels have been shown to cause weakness, cardiac failure, and arrest [14], a central component of the refeeding syndrome. Reports describing hypophosphatemia occurring in the context of the refeeding syndrome in patients with anorexia nervosa include those of Sheridan and Collins [17], Schoken and Holloway [18], Beumont and Large [19], and Kohn *et al.* [20].

Ornstein *et al.* [21] performed a retrospective review of 69 patients to determine the incidence of hypophosphatemia in adolescents with anorexia nervosa hospitalized for nutritional rehabilitation and to examine factors predisposing to its development. The only consistent finding their study identified was that those with low serum phosphate prior to refeeding or those whose phosphate dropped below 1.0 mg/dl were at higher risk of developing hypophosphatemia and its associated complications. Ornstein *et al.* recommended daily monitoring of serum phosphate with supplementation as needed during the first week of hospitalization. These findings were consistent with those of Gaudiani *et al.* [22], who in a review of 25 consecutive patients admitted for medical stabilization found no clinical features predicted hypophosphatemia, including admission BMI.

The need for phosphate monitoring is, thus, well established, as is the importance of commencing phosphate supplementation when levels of serum phosphate either are already decreased at the beginning of refeeding or drop during the initial refeeding process. Some units have taken the approach of universal phosphate supplementation during the initiation of refeeding in anorexia nervosa due to its role in preventing the refeeding syndrome and its lack of toxicity. How much phosphate is required to prevent hypophosphatemia during refeeding remains to be determined. Brown *et al.* [23] evaluated the safety and efficacy of a revised weight-based phosphate-dosing algorithm (0.3–1.0 mmol/kg) in critically ill trauma patients receiving specialized nutrition support. Mean serum phosphorus concentrations were normal in all three dose groups. The generalizability of these results to malnourished patients with anorexia and the dose of phosphate required to maintain normal blood levels during refeeding are yet to be established.

Current clinical guidelines

Over the past 10 years, treatment guidelines for the nutritional rehabilitation of patients with anorexia nervosa have been published by professional organizations. In all of these guidelines, initial caloric intake is below daily requirements, with slow increases recommended. It is important to emphasize that there is no evidence-based research behind recommendations in the current refeeding guidelines, which range from an initial rate of 10 to 60 kcal/kg per day. These figures have been based on 25–75% of total energy intake (TEI).

Provision of daily calories greater than REE (resting energy expenditure), the thermal effect of food, insensible losses, and physical activity is required for weight gain to occur. An excess of around 7000 kcal is required to achieve a weight gain of approximately 1 kg.

In its 2003 position paper on eating disorders in adolescents, the Society of Adolescent Health and Medicine (SAHM) [1] recommended a progressive increase in calorie prescription of patients in order to avoid the 'refeeding syndrome' along with close monitoring of their weight, vital signs, and fluid and electrolyte levels. Among those with severe malnutrition, the SAHM guidelines suggested the use of short-term nasogastric feeding. Guidelines released by National Institute for Clinical Excellence (NICE) [7], in 2004, similarly advocated for a gradual increase in calorie prescription along with regular physical monitoring, but with adjunctive oral multivitamin/multimineral supplements. Specifically, NICE recommends average weekly weight gains of 0.5–1 kg in inpatient settings, equivalent to 3500–7000 extra kcals per week. In 2006, the American Psychiatric Association (APA) [4] recommended the same weight gain goals as NICE, but provided no specific refeeding strategies.

Risks of weight loss in medically unstable patients

Weight loss at the commencement of refeeding in hospitalized patients is commonly reported, and to be expected, from observance of the current recommendations. The initial calorie recommendations are less than the energy required for daily metabolic requirements. Initial underfeeding increases the period in which refeeding complications are most likely to occur, contributing to both increased cardiac risk and mortality. As patients are typically bed rested till they are medically stable and gain weight, the increased time on bed rest contributes to loss of lean tissue mass and poorer long-term outcomes with regard to bone health, as well as increasing hospital length of stay.

Published clinical outcomes

O'Connor and Goldin [8••] note to date there have been a total of 23 patients identified in the literature as developing refeeding syndrome during treatment for anorexia nervosa [20,21]. All of these patients are described as receiving a calorie prescription in accordance with published guidelines. The refeeding syndrome presented itself with hypophosphatemia, hypotension, and cardiac abnormalities while refeeding at an average rate of 27 kcal/kg per day. On most occasions, patients are described as having been commenced on to a standard polymeric enteral feed, which comprises 100 kcal/100 ml, with nearly half of the caloric content of the feeds derived from glucose.

The issue raised by O'Connor and Goldin [8••] relates directly to safety when commencing feeding based on kcal/kg. Hence, regardless of how cautiously refeeding is commenced, whether it is 10 or 60 kcal/day, those individuals at high risk may still develop the refeeding syndrome. O'Connor and Goldin [8••] question whether the refeeding syndrome is preventable through manipulation of caloric intake.

Published clinical outcomes by Kohn and Madden [24] and Whitelaw *et al.* [25] support the view that it is safe and in fact desirable to increase the rate of calorie increase and total daily calorie amount, contingent upon limiting the proportion of calories from carbohydrate and maintaining a normal level of serum phosphate. Kohn and Madden [24] also assert that protection from hypoglycemia occurring from the mismatch between glucose load and insulin phase may be attained by initiating feeds via a continuous (nasogastric) approach prior to introducing intermittent (oral) intake.

Kohn and Madden [24] reported refeeding over 300 adolescents with anorexia nervosa (mean age 13.8 years and mean BMI 14.1 kg/m^2) using continuous nasogastric tube feeds at the outset of refeeding, graduating to intermittent daytime oral feeds with phosphate supplementation, as outlined below (modifications to refeeding guidelines):

(1) Continuous (nasogastric) feeding at the outset of refeeding.
(2) Use of feeds and meal plan limited to a maximum of 40% of total energy from carbohydrates.
(3) Minimum initial daily energy intake of approximately 2000 kcal (8400 kJ) per day.
(4) Daily energy intake of 2700 kcal (11000 kJ) per day by the end of week 1.
(5) Oral phosphate 20–25 mg/kg daily (divided into two doses).
(6) Reintroduction of oral feeding once medical stability has been achieved, as observed from 6 hourly measurements of vital signs.

Monitoring of vital signs and daily blood tests should be undertaken during the first week of treatment.

Caloric prescription commenced at or greater than 2000 kcal/day and was increased to 2700 kcal/day by the end of the first week. Average patient weight gain in the first week of treatment was greater than 2.1 kg. No episodes of refeeding syndrome occurred in these cohorts. Whitelaw *et al.* [25] similarly reported no incidents of refeeding syndrome in a retrospective chart review of 46 admissions (29 adolescents commenced on 2000–2700 kcal/day).

The patient experience of nasogastric tube feeding has been recently reported by Halse *et al.* [26]. Consistent with other studies commenting on the experience of nasogastric tube feeding, no difficulties were experienced in re-establishing a diet with regular food, patients and families tolerated this treatment approach, and no psychological trauma was described in qualitative assessments of patients receiving this form of treatment.

Conclusion

These studies highlight the importance of the maintenance of blood glucose and phosphate levels, and provision of adequate calories at the outset of refeeding, to establish early weight gain. The avoidance of low blood sugar from the effects of delayed insulin phase and metabolic changes with regard to glycogen storage and fatty oxidation support the use of continuous feeding strategies, such as nasogastric tube feeding at the outset of refeeding as well as limiting the proportion of daily calories from carbohydrates to less than 40%. Oral phosphate supplementation should be routine and blood phosphate levels should be maintained above 1.0 mg/dl (as mentioned above in 'modifications to refeeding guidelines').

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 494).

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