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Refeeding Hypophosphatemia in Hospitalized Adolescents with Anorexia Nervosa

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POSITION:

Refeeding hypophosphatemia in hospitalized adolescents with anorexia nervosa (AN) is correlated with degree of malnutrition.

Refeeding syndrome describes the clinical and metabolic derangements that can occur during the refeeding of a malnourished patient. First described over 60 years ago, refeeding syndrome occurs in conditions associated with malnutrition (1–4), including anorexia nervosa (AN). (5–13) Refeeding syndrome is complex and consists of a variety of metabolic and clinical features. The clinical features include cardiac arrhythmias, cardiac failure or arrest, muscle weakness, hemolytic anemia, delirium, seizures, coma and sudden death that can occur days to weeks after the initiation of nutritional rehabilitation (14). The hallmark biochemical feature of refeeding syndrome is hypophosphatemia, also referred to as refeeding hypophosphatemia (RH).

Refeeding hypophosphatemia is thought to play an important role in the refeeding syndrome (14). During starvation, after glycogen stores have been depleted, catabolism of fat, protein and muscle provides the major source of energy. Once refeeding is initiated, carbohydrates become the major substrate for energy production. With reintroduction of carbohydrates, insulin secretion causes an influx of electrolytes into the cells. Phosphorus is required for

glucose metabolism to produce phosphorylated intermediates of glycolysis such as adenosine triphosphate and 2,3 diphosphoglycerate. The combination of cellular uptake of phosphorus together with depletion of total body stores during starvation causes extracellular hypophosphatemia.

Phosphate deficiency impacts on metabolic processes affecting all organs and systems (15). Effects of hypophosphatemia on the myocardium include impaired contractility and a reduction in cardiac output leading to heart failure (11, 16). Hypophosphatemia can also increase the risk for ventricular arrhythmias. In addition, there have been cases of respiratory failure due to impaired diaphragmatic contractility (17). Other reported clinical manifestations of muscular dysfunction include ophthalmoplegia, dysphagia or ileus. Hypophosphatemia can also cause rhabdomyolysis, which may be asymptomatic, manifested only by an increase in serum creatine phosphokinase, or may cause severe muscle pain and weakness or acute renal tubular necrosis. Hypophosphatemia can cause a range of impaired neurologic functions including confusion, delirium, seizures, tetany or coma (11, 13). Peripheral neuropathy and ascending motor paralysis have also been reported. Hematologic function may be impaired causing hemolytic anemia and leukocyte dysfunction resulting in impaired chemotaxis and phagocytosis (18).

Weight restoration and nutritional rehabilitation are fundamental components in the treatment of adolescents with AN. In the past, nutritional rehabilitation was based on conservative, consensus-based recommendations for lower calorie refeeding because of concerns about the refeeding syndrome . In the U.S., lower calorie approaches typically begin between 900–1200 kcal/d and advance by 200 kcal every other day (19, 20), however recommendations start as low as 200–600 kcal/d in Europe and the United Kingdom. (21–26) These “start low and go slow” approaches have been linked to the so-called “underfeeding syndrome”, characterized by poor weight gain, prolonged illness and even death due to overly cautious refeeding (25). The resulting shift in clinical practice toward higher calorie diets, starting between 1400–2400 kcal/day (27–33), has raised new questions about how to balance the potential risks of RH with the need to maximize weight gain and nutritional rehabilitation.

In a recent systematic review of hospitalized adolescents with AN (34), the average incidence of RH in adolescents was 14% (range 0–38%), although this may be an underestimate because some patients were supplemented with oral phosphate in the presence of declining but normal serum phosphorus levels. Methodological limitations to existing studies preclude direct comparisons of the relationship between calorie intake and prevalence of RH among different centers. Studies examining both lower calorie (31, 35) and higher calorie approaches (27, 28, 30, 33) have shown that the degree of RH is correlated with degree of malnutrition (% ideal body weight or % median body mass index (BMI)) on admission to hospital. These findings suggest that the degree of malnutrition at presentation may be more important than the amount of energy intake in mitigating the risk for RH. Thus, physicians should have a high index of suspicion for RH when severely malnourished patients (<70% median BMI) are admitted to hospital.

The reference range for serum phosphorus varies by age and laboratory, being higher in children and adolescents than in adults. For hospitalized adolescents with AN, most authors consider an episode of hypophosphatemia to be a serum phosphorus level ≤3 mg/dl (≤1 mmol/L) (33–35). (34) Refeeding hypophosphatemia usually develops during the first week of nutritional rehabilitation (35). The majority of hospitalized adolescents with AN have serum phosphorus levels within the reference range prior to refeeding (34) and therefore monitoring of serum phosphorous every 24–48 hours is recommended during the first week of hospitalization. To date, there have been no published studies examining the risk-benefit derived from prophylactic oral phosphate supplementation during refeeding. In clinical practice, there is wide variability regarding the use of prophylactic oral phosphate supplementation during refeeding, with some programs supplementing all patients undergoing nutritional rehabilitation (36). Further studies on the use of prophylactic phosphate supplementation are required to examine the need, efficacy and safety of this intervention in adolescents with AN during refeeding.

Standard phosphate replacement regimens for RH in adolescents with AN have not been established. Current clinical practice is based on reports of malnourished pediatric and adults populations (37). Based on this literature, a treatment suggestion for moderate hypophosphatemia (1.1 to 3.0 mg/dL) includes oral supplementation at a starting dose of 30 to 60 mg/kg/day, divided three to four times per day. (35) In one study in adolescents with AN, patients with RH were treated with 250 mg of oral phosphate replacement, 2–3 times per day and this was found to be sufficient. The authors noted that it was important to adjust the dose based on results of serial blood testing. Intravenous phosphate replacement should be considered for severe hypophosphatemia (<1.0 mg/dL, 0.35mmol/L), and should only be undertaken in an intensive care unit. A dose of 20–30 mg/kg/d in divided doses usually infused over 6 hours, has been recommended. (35)

Over the past few years there has been increasing evidence on the approach to refeeding hospitalized adolescents with AN. These approaches have highlighted the important implications for the prevention of RH as well as for the safety and efficiency of refeeding of hospitalized adolescents with AN. Notwithstanding, there is more work to be done. To date, the range of BMIs across study samples has been relatively small and there is a paucity of information about how chronicity and rapidity of weight loss may interact with BMI to impact refeeding risk. There is also the question of how calories should be delivered and how this may affect the risk of RH. For instance, meal-based approaches are used widely in the United States (27, 33) and Canada (30), whereas enteral feeding is reported in Europe (38–40) and Australia (29) and purported to attenuate the risk of refeeding by avoiding the wide glucose and insulin variations associated with meal boluses (29). More evidence is needed to understand the macronutrient and micronutrient content of the diet, its impact on refeeding and the safety and efficacy of different refeeding protocols.

Conclusion

Based on the evidence to date, RH in hospitalized adolescents with AN is correlated with degree of malnutrition at presentation. Recognizing that RH can occur at any body weight after a period of malnutrition, physicians should have a high index of suspicion for RH when

severely malnourished patients (<70% median BMI) are admitted to hospital and nutritional rehabilitation is initiated.

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