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Position statement

Refeeding Hypophosphatemia in Hospitalized Adolescents With Anorexia Nervosa

The Society for Adolescent Health and Medicine

A B S T R A C T

Refeeding hypophosphatemia in hospitalized adolescents with anorexia nervosa is correlated with degree of malnutrition, with a high index of suspicion for severely malnourished patients (<70% median body mass index). Weight history (greater magnitude or rate of weight loss prior to admission) regardless of presentation weight has also been associated with lower serum phosphate. Higher energy meal-based refeeding starting at 2,000 kcal has not been shown to be associated with higher rates of refeeding hypophosphatemia than the traditional standard of care, lower energy refeeding. Further research is needed to identify risk factors for refeeding hypophosphatemia and develop optimal delivery methods (oral vs. enteral), macronutrient content, and electrolyte replacement strategies to optimize weight gain without increasing the risk for refeeding hypophosphatemia.

Position of the Society for Adolescent Health and Medicine

Among hospitalized adolescents with anorexia nervosa (AN), those with severe malnutrition are at the highest risk for developing refeeding hypophosphatemia. The incidence of refeeding hypophosphatemia is not associated with higher caloric refeeding (starting at 2,000 kcal) in moderately malnourished patients.

Statement of the Problem

Refeeding syndrome describes the clinical and metabolic derangements that can occur during the refeeding of a malnourished patient. First described more than 70 years ago, refeeding syndrome occurs in conditions associated with malnutrition [1–4] including AN. Refeeding syndrome is complex and consists of a variety of metabolic and clinical features. To date, there is no universally accepted definition for refeeding syndrome [5]. Historically, a diagnosis of refeeding syndrome required clinical evidence of organ dysfunction such as cardiac arrhythmias, cardiac failure or arrest, muscle weakness, hemolytic anemia, delirium, seizures, coma, and sudden death that would occur days to weeks after the initiation of nutritional rehabilitation. However, many (most in fact) studies have used low serum phosphorus as the sole diagnostic criterion [5]. In an effort to provide clinical guidance for refeeding syndrome in hospitalized pediatric and adult populations, the American Society for Parenteral and Enteral Nutrition [4] proposed a new definition of refeeding syndrome that includes criteria for risk stratification. These criteria occur within 5 days of reintroduction of nutrition: decrease in serum phosphorus, potassium or magnesium levels by 10%–20% (mild), 20%–30% (moderate), or >30% (severe) and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamin deficiency [4]. It is important to note that these recommendations were based on consensus for hospitalized children and adults, including critically ill patients in the intensive care unit and do not necessarily pertain to hospitalized adolescents and young adults with AN.

Hypophosphatemia, also referred to as refeeding hypophosphatemia, is considered the hallmark biochemical feature of refeeding syndrome. Other electrolyte changes, including hypokalemia and hypomagnesemia, are also important and contribute to refeeding syndrome [6]. 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 rapid migration of electrolytes, including phosphate from the extracellular to intracellular space.

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Intracellular phosphate is used in metabolic pathways producing adenosine triphosphate. Together with depletion of total body phosphate stores during starvation, these metabolic shifts contribute to serum hypophosphatemia.

Hypophosphatemia impacts metabolic processes affecting all organs and systems [7]. Effects of hypophosphatemia on the myocardium include impaired contractility and a reduction in cardiac output leading to heart failure [8,9]. Hypophosphatemia can also increase the risk for ventricular arrhythmias. In addition, there have been cases of respiratory failure due to impaired diaphragmatic contractility [10]. 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 [9,11]. Peripheral neuropathy and ascending motor paralysis have also been reported. Hematologic function may be impaired causing hemolytic anemia and compromised immune function such as impaired leukocyte chemotaxis and phagocytosis [12].

Methodological differences in phosphate supplementation make it difficult to estimate the occurrence of refeeding hypophosphatemia across existing studies. In a systematic review of 17 studies including 1,039 participants, the incidence of refeeding hypophosphatemia in adolescents with AN ranged from 0%–38% (average 14%) [13]. This wide variability is due in part to differences in clinical use and timing of oral phosphate supplementation during refeeding, with some programs initiating prophylactic treatment in all patients prior to refeeding, some treating normal but declining levels, and still others prescribing phosphate only when levels drop below a set threshold [14]. Phosphate prophylaxis and treatment of declining levels may result in underestimation of refeeding hypophosphatemia, while including patients who are admitted to hospital with low serum phosphate (in the starved state, prior to refeeding) likely results in overestimation. To date, there is only one published retrospective chart review in adolescents (aged <18 years) with restrictive eating disorders exploring the use of prophylactic oral phosphate supplementation (1.0 ± 0.2 mmol/kg/day) with a standard refeeding protocol [15]. This study reported no episodes of refeeding hypophosphatemia in patients receiving prophylactic oral phosphate supplementation during inpatient refeeding. Further studies, including randomized controlled trials (RCTs) are needed to examine the risk-benefit derived from prophylactic oral phosphate supplementation prior to and during refeeding.

Another methodological difference is the laboratory standards and reference range for serum phosphorus as it varies by laboratory and age, being higher in children and adolescents than in adults. For hospitalized adolescents with AN, the definition of hypophosphatemia is typically serum phosphorus ≤3 mg/dL (≤1 mmol/L) [13,16,17]. Although most hospitalized adolescents with AN have serum phosphorus levels within the reference range prior to refeeding [13,18–20], refeeding hypophosphatemia usually develops during the first week of nutritional rehabilitation [16] and often within the first 72 hours [5]. Standard phosphate replacement regimens for refeeding hypophosphatemia in adolescents with AN have not been established; current clinical practice is based on reports of malnourished pediatric and adult populations. Mild hypophosphatemia (2.5–2.9 mg/dL or 0.81–0.94 mmol/L) was treated with oral phosphate replacement (250 mg elemental phosphorus [8.06 mmol of phosphate]) 3 times a day; moderate hypophosphatemia (2.0–2.4 mg/dL or 0.65–0.77 mmol/L) was treated with oral phosphate replacement (500 mg elemental phosphorus [16.1 mmol of phosphate]) 3 times a day; and severe hypophosphatemia (<2.0 mg/dL or <0.65 mmol/L) was treated with intravenous phosphate replacement of sodium-potassium-phosphate 0.24 mmol/kg, maximum of 15 mmol per dose (Table 1) [18,21]. Evidence on the treatment of hypophosphatemia in adolescents with AN is scarce and further research is needed for the development of clinically relevant treatment guidelines.

Degree of malnutrition and weight history

Prior studies examining the relationship between refeeding hypophosphatemia and degree of malnutrition have focused on presentation weight or body mass index (BMI). Studies examining both lower [16,22] and higher calorie refeeding approaches [17,20,23,24] have shown that the degree of refeeding hypophosphatemia is correlated with lower weight, defined as lower percent of expected body weight on admission to hospital and expressed as percent of median BMI (%mBMI). Severely malnourished patients (<70% mBMI) have been shown to be at the highest risk for developing refeeding hypophosphatemia [16,17].

More recently, studies have also examined the role of weight history. In one study, among moderately malnourished patients with AN (average mBMI = 78%), the rate of weight loss prior to admission but not prescribed energy intake was associated with hypophosphatemia [17]. In both patients with AN and atypical AN who lost ∼20% body mass and were admitted to hospital for medical instability at a range of weights, greater magnitude of weight loss was associated with lower serum phosphorus upon admission [19] and during refeeding [25], independent of weight at presentation. While these studies suggest that patients with large or rapid weight losses warrant more concern regardless of admission weight, none used refeeding hypophosphatemia as an outcome. Nevertheless, the available data suggest that the degree of malnutrition at presentation (either by %mBMI or by

Table 1
Electrolyte replacement protocol[a]

Serum phosphate levels	Recommended treatment regimen
Mild hypophosphatemia 2.5–2.9 mg/dL or 0.81–0.94 mmol/L	Phos-NaK 1 packet (250 mg) TID[b]
Moderate hypophosphatemia 2.0–2.4 mg/dL or 0.65–0.77 mmol/L	Phos-NaK 2 packets (500 mg) TID[b]
Severe hypophosphatemia <2.0 mg/dL or <0.65 mmol/L	IV Na-K-Phos 0.24 mmol/kg; max 15 mmol/dose; contact PICU

IV = intravenous; PICU = pediatric intensive care unit; TID = three times a day.
[a] Adapted from the StRONG Trial Electrolyte Replacement Protocol [18].
[b] Phos-NaK = Sodium-Potassium Phosphate (contains 250 mg elemental phosphorus [8.06 mmol of phosphate]).

magnitude of weight loss) is important in the assessment of risk for refeeding hypophosphatemia.

Higher calorie refeeding

Concerns about patients' risk for refeeding hypophosphatemia have come to the fore as clinical practice is adopting evidence-based refeeding approaches where starting at higher energy levels and advancing faster is more efficacious at restoring medical stability. In the past, nutritional rehabilitation used conservative, consensus-based recommendations for lower energy refeeding because of concerns about the refeeding syndrome. In the United States, lower energy approaches typically began between 900 and 1,200 kcal/day and advanced by 200 kcal every other day [26]; however, recommendations started as low as 200–600 kcal/day in Europe and the United Kingdom [27–30] These "start low and go slow" [31] 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 [29]. Clinical practice is shifting toward higher energy refeeding, starting between 1,400 and 2,400 kcal/day, often starting around 1,500 kcal/day [17,20,22–24,31]. A recent RCT in adolescents and young adults hospitalized with AN found that higher calorie refeeding, starting at 2,000 kcal/day, restored medical stability 3 days earlier, reduced hospital stay by 4 days, saved $ 20,000 USD in hospital charges without an increased risk of refeeding hypophosphatemia or rehospitalization in the year following the initial admission, as compared to lower calorie refeeding starting at 1,400 kcal/day [18,21]. Using a consistent electrolyte monitoring and replacement protocols across treatments, the incidence of refeeding hypophosphatemia did not differ by group, providing strong evidence that the incidence of refeeding hypophosphatemia was not associated with a higher caloric load (2,000 kcal). On the other hand, serum phosphate nadir (but not refeeding hypophosphatemia) occurred at a mean of 4.6 days in the higher calorie group, which was 1.2 days earlier than in the lower calorie group [18]. This finding indicates that caloric load may impact the timing of refeeding hypophosphatemia.

Macronutrient distribution

While refeeding hypophosphatemia has long been assumed to occur in response to the reintroduction of nutrients, particularly carbohydrates, the potential role of macronutrient distribution is an important area of investigation. A lower carbohydrate intake, providing <40% total energy, has been recommended by some experts as a safer method for reintroducing nutrition to malnourished patients, to avoid excess postprandial insulin secretion, and reduce the risk of developing refeeding hypophosphatemia [32]. However, to our knowledge, only two published studies have tested this recommendation and findings have been mixed. One retrospective study examined nutrition prescriptions with a range of carbohydrate content and the occurrence of refeeding hypophosphatemia in adult inpatients with AN [33]. This study identified a cut-point of >58.4% carbohydrate as being associated with refeeding hypophosphatemia [33]. A pilot RCT of oral refeeding in children and adolescents with AN and atypical AN assigned patients to meal plans that were either low carbohydrate (<40% total energy from carbohydrate) or standard carbohydrate (50%–60% total energy from carbohydrate) and found that no patients in either group developed refeeding hypophosphatemia in the first seven days of admission but noted greater weight gain with higher carbohydrate feeding [34]. While the investigators concluded that providing 50%–60% of total energy from carbohydrates optimized nutritional rehabilitation without an increasing risk of refeeding hypophosphatemia, these findings should be interpreted with caution given the small sample size and the likelihood that energy intake differed between groups and participants.

Route and method of nutritional delivery

Route or method of nutritional delivery is another factor that may affect risk of refeeding hypophosphatemia. In the United States and Canada, meal-based approaches are used widely, whereas enteral feeding is more common in Europe and Australia. Continuous feeding strategies, such as nasogastric tube, has been purported to attenuate the risk of refeeding hypophosphatemia by avoiding the wide glucose and insulin variations associated with meal boluses [32]; however, studies to date have not directly compared nasogastric tube versus meal-based refeeding. Instead, research has focused on using nasogastric tube feeding to examine the role of carbohydrate content as a risk factor for the development of refeeding hypophosphatemia. A recent RCT [35] compared isocaloric nasogastric feeds in two groups of adolescents and young adults with AN on an inpatient unit; one group received 28% carbohydrate and 56% fat (n=14) and the standard feed (n=10) group received 54% carbohydrate and 29% fat. Serum phosphorus levels were significantly higher in the lower carbohydrate/high fat feed compared with standard feed treatment arm at week 1 (3.28 ± 0.46 mg/dL or 1.06 ± 0.15 mmol/L vs. 2.72 ± 0.37 mg/dL or 0.88 ± 0.12 mmol/L, $p < .001$). Weight gain did not differ between the two groups because total daily energy intake was similar in both groups. While findings from this trial support the hypothesis that lower carbohydrate nasogastric tube feeding may protect against refeeding hypophosphatemia, they contradict findings from the small RCT showing greater weight gain with higher carbohydrate meal-based refeeding discussed previously [34]. More evidence is needed to understand how macronutrient content and delivery methods (oral vs. enteral) impact the safety and efficacy of refeeding.

Conclusion

Based on the evidence to date, refeeding hypophosphatemia in hospitalized adolescents with AN is correlated with degree of malnutrition, with a high index of suspicion for severely malnourished patients (<70% mBMI). Weight history (greater magnitude or rate of weight loss prior to admission) regardless of presentation weight has also been associated with lower serum phosphate. Higher energy meal-based refeeding starting at 2,000 kcal has not been shown to be associated with higher rates of refeeding hypophosphatemia than the traditional standard of care, lower energy refeeding. Further research is needed to identify risk factors for refeeding hypophosphatemia and develop optimal delivery methods (oral vs. enteral), macronutrient content, and electrolyte replacement strategies to optimize weight gain without increasing the risk for refeeding hypophosphatemia.

Learning Points

1. Refeeding hypophosphatemia in hospitalized adolescents with AN is correlated with degree of malnutrition, with a high index of suspicion for severely malnourished patients (<70% mBMI).
2. Weight history (magnitude or rate of weight loss prior to admission) regardless of presentation weight has also been associated with lower serum phosphate.
3. Higher calorie refeeding starting at 2,000 kcal has not been shown to be associated with higher rates of refeeding hypophosphatemia than the traditional lower calorie refeeding standard of care.
4. Further research is needed to identify risk factors for refeeding hypophosphatemia and develop optimal delivery methods (oral vs. enteral), macronutrient content, and electrolyte replacement strategies to optimize weight gain without increasing the risk for refeeding hypophosphatemia.

Prepared by:

Debra K. Katzman, M.D.
Division of Adolescent Medicine, Department of Pediatrics, Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

Andrea K. Garber, Ph.D., R.D.
Division of Adolescent Medicine, University of California San Francisco, San Francisco, California

Elizabeth K. Parker, A.P.D.
Department of Dietetics and Nutrition, Westmead Hospital, Westmead, New South Wales, Australia

Michael Kohn, Ph.D.
Department of Adolescent and Young Adult Medicine, Faculty of Medicine Sydney University, Westmead Hospital, Westmead, New South Wales, Australia

Neville H. Golden, M.D.
Division of Adolescent Medicine, Stanford University School of Medicine, Palo Alto, California

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