Prophylactic Phosphate Supplementation for the Inpatient Treatment of Restrictive Eating Disorders

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ABSTRACT

Purpose: The medical stabilization of adolescent patients with restrictive eating disorders can be associated with refeeding syndrome, a potentially fatal complication preceded by refeeding hypophosphatemia (RH). Whether RH can be prevented by routine prophylactic phosphate supplementation has not been previously examined. This study sought to determine the safety and efficacy of a refeeding strategy that incorporates prophylactic phosphate supplementation to prevent RH.

Methods: Retrospective chart data were collected for patients aged younger than 18 years with restrictive eating disorders admitted to a tertiary pediatric inpatient ward between January 2011 and December 2014. All patients were refed with a standardized protocol that included prophylactic oral phosphate supplementation (1.0 ± 0.2 mmol/kg/day).

Results: During the 4-year study period, 75 admissions (70 patients) were included for analysis. The mean age and percent median body mass index of included patients were 15.3 years and 83.5%, respectively. Seven out of 75 (9%) had percent median body mass index of < 70% and 26 out of 75 (35%) had percent body weight loss > 20%. All patients were normophosphatemic at the time of admission (mean serum phosphate 1.24 ± 0.2 mmol/L). Serial laboratory evaluation revealed that all supplemented patients maintained serum phosphate levels > 1.0 mmol/L during the initial 7 days of refeeding. Eleven patients became mildly hyperphosphatemic (range 1.81–2.17 mmol/L) with no associated clinical consequences. Additional analysis of 11 patients presenting with hypophosphatemia before refeeding revealed that with supplementation, phosphate values normalized by Day 1, and this group experienced no further RH episodes during initial refeeding.

Conclusions: Prophylactic oral phosphate supplementation appears safe, and no episodes of RH occurred in patients with restrictive eating disorders undergoing inpatient refeeding.

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Anorexia nervosa (AN) is a complex, potentially life-threatening illness frequently affecting adolescents. The condition can be associated with complications such as cardiac dysrhythmias, hypotension, decreased bone mineral density, and growth arrest [1]. Affected individuals may necessitate hospital admission for medical stabilization and nutritional rehabilitation to prevent serious or fatal complications.
Guidelines for the management of AN have been published by various organizations including the Society for Adolescent Health and Medicine [2], the Canadian Pediatric Society [3], and the American Academy of Pediatrics [4]. There is general consensus on indications for hospital admission; however, there remains significant clinical equipoise regarding the approach to inpatient management.

The primary goal of a medical hospitalization for patients with AN is physiologic stabilization through weight restoration. The need to correct weight loss must be balanced against the potentially fatal risk of refeeding syndrome (RS). RS is defined as fluid and electrolytes shifts secondary to insulin surges brought on by refeeding severely malnourished patients [1]. These electrolyte abnormalities can result in muscle weakness, delirium, cardiac dysrhythmias, and failure. An early sign of RS is a drop in serum phosphate or refeeding hypophosphatemia (RH). The depletion of total body phosphorus stores during malnutrition coupled with increased cellular influx of phosphorus during refeeding places AN patients at risk for profound extracellular hypophosphatemia. Low serum phosphorus is thought to cause a deficiency of intracellular phosphorylated compounds (i.e., adenosine triphosphate, 2,3-diphosphoglycerate) necessary for normal cellular metabolism, which, in turn, produces the cardiac, neuromuscular, hematologic, and respiratory dysfunction seen in full RS [5,6].

RH typically develops during the initial 3–7 days of nutritional rehabilitation [7]. For hospitalized adolescents with AN, a drop in serum phosphate level <1 mmol/L (<3 mg/dL) is considered significant [8]. The factors predisposing to RH remain poorly understood, but it is believed that severe malnutrition is thought to portend the highest risk [7–10]. Recent guidelines from the Society of Adolescent Health and Medicine propose using a combination of percent median body mass index (%mBMI) <70%, body mass index (BMI) z score >−3 or % body weight loss (%BWL) of >20% in 1 year to define severe malnutrition [2]. Studies reporting that the frequency of RH among adolescents hospitalized with AN is limited, and estimates of this complication vary widely. A recent systematic review reported a 14% mean incidence of RH among 17 studies from 1980 to 2012 which included 1,039 patients (mean %mBMI = 78%) [9]. One of the studies included in this review observed a rate of RH as high as 38% [10].

At present, it is unclear whether refeeding patients should receive prophylactic phosphate to prevent RH or receive phosphate treatment only once laboratory-confirmed RH has been detected. Some authors advocate daily phosphate supplementation for all hospitalized patients being refed [11,12], whereas others recommend close early monitoring and supplementation only when phosphate levels begin to decline [7,13]. Since 2010, the Montreal Children’s Hospital has followed a standardized, short-term, continuous nasogastric (NG) refeeding protocol for all patients admitted with restrictive-type eating disorders [14]. This protocol incorporates the determination of baseline electrolyte values and immediate daily prophylactic phosphate supplementation beginning at the time of admission for all patients, including those that are normophosphatemic. Electrolytes are monitored daily for the first week.

To our knowledge, no study has assessed the impact and outcomes of a refeeding strategy that utilizes prophylactic oral phosphate supplementation during refeeding. We hypothesized that oral phosphate supplementation could safely be used to prevent RH among at-risk, normophosphatemic adolescents hospitalized for nutritional rehabilitation. We undertook a 4-year retrospective chart review with the specific aims of (1) determining the efficacy of prophylactic phosphate supplementation to prevent RH and (2) reporting on any harms associated with prophylactic phosphate supplementation among our inpatient population.

Methods

Study design setting and participants

Ethical approval for this study was obtained from the Montreal Children’s Hospital Research Ethics Board. A retrospective chart review was conducted among patients admitted to the Montreal Children’s Hospital for restrictive eating disorders during the 4-year study period between January 1, 2011, and December 31, 2014. The Montreal Children’s Hospital is a tertiary pediatric referral center that admits eating disorder patients aged younger than 18 years for medical stabilization. Patients are treated via a standardized continuous NG tube refeeding protocol as described previously [14]. Admitted patients are prescribed an initial daily caloric intake of 1800 kcal/day. All patients have electrolytes drawn within the first 24 hours of admission and are started on prophylactic phosphate supplementation, regardless of initial phosphate values. Supplementation is administered for a minimum of 7 days, and electrolytes are monitored daily during this period. After 7 days, phosphate supplementation is tapered over 2–3 days and subsequently discontinued at the discretion of the admitting physician. Phosphate supplementation is provided in the form of an oral phosphate solution, containing 1.5 mmol (48 mg) of elemental phosphorous per mL, administered at a dose of 1 mmol/kg/day (31 mg/kg/day) divided in four daily doses. A multivitamin (Centrum, Pfizer Inc.; 125-mg elemental phosphorous) is prescribed at the time of admission at the discretion of the admitting physician.

The study population was identified using the International Classification of Diseases, Ninth Revision (ICD-9) and discharge summary coding for the terms anorexia nervosa, atypical anorexia nervosa, bulimia nervosa, vomiting associated with other psychological disturbances, other eating disorder, eating disorders unspecified, and specified eating disorders. Patients were included if they were between the age of 10 and 18 years, admitted for protocol-based NG refeeding, and met criteria for AN or a restrictive form of eating disorder based on the DSM–5 criteria. For patients with multiple admissions, each admission was analyzed separately. Patients admitted with the diagnosis of bulimia nervosa, pre-existing medical comorbidities affecting phosphate metabolism (e.g., kidney disease, malabsorption, thyroid dysfunction) or patients with a restrictive eating disorder admitted for reasons other than nutritional rehabilitation (e.g., depression or suicidality) were excluded.

Hospital chart data were extracted to determine baseline patient characteristics at the time of admission and included: gender, age, temperature, BMI, and percent median BMI (%mBMI; current BMI/50th percentile BMI for age and sex × 100), %mBMI was calculated utilizing World Health Organization standardized growth curves [15]. %BWL was obtained from the hospital nutritionist consultation when available and was based on premorbid growth curves or self-reported weight loss during the preceding year. Patient self-reported duration of symptoms was also noted.

Refeeding protocol treatment parameters and daily laboratory values were collected. The normophosphatemic range was defined as a phosphate level between 1.0 mmol/L (3.1 mg/dL) and
1.8 mmol/L (5.6 mg/dL). Adverse events were defined as clinical symptoms requiring medical intervention (i.e., imaging, pharmacological treatment, hydration) that occurred concomitant to an episode of either hypophosphatemia (<1.0 mmol/L) or hyperphosphatemia (>1.8 mmol/L). Hypokalemia was defined as a serum potassium <3.0 mmol/L and hypoglycemia as a serum glucose <2.6 mmol/L. The duration and any dosing adjustments of phosphate supplementation during the first week of admission were also recorded for each patient.

**Statistical analysis**

Descriptive statistics are presented for relevant baseline patient characteristics and treatment measures. Continuous variables are expressed as means ± SD and were analyzed using a student’s t test; categorical variables are expressed as proportions and were analyzed using chi-square testing (GraphPad Prism software, version 6.03). A two-tailed p value < .05 was considered statistically significant.

**Results**

Broad chart review identified 261 admissions (representing 208 patients); of which, 109 met inclusion criteria (Figure 1). Of the 152 admissions excluded, 35 were not assigned the standardized NG refeeding protocol, 16 did not meet the DSM criteria for restrictive eating disorders, and 101 were patients with restrictive eating disorders admitted for reasons other than nutritional rehabilitation. Of the remaining 109 charts, an additional eight were excluded due to missing data (≥2 unavailable phosphate values during the first week of admission). To ensure analysis of only normophosphatemic patients, 15 patients were eliminated; two that were hyperphosphatemic at the time of presentation and 13 that had phosphate supplementation administered before baseline blood work was performed. Eleven additional patients found to be hypophosphatemic at the time of admission were also excluded and analyzed separately.

Seventy-five admissions (representing 70 patients) were included for analysis. Patient demographic data are presented in Table 1. On admission, patients had a mean age of 15.3 ± 1.5 years and %mBMI of 83.5 ± 12.8%. Data on estimated %BWL were available in 56/75 (74%) of admissions. Seven of 75 (9%) of included patients had %mBMI <70% at the time of admission.

Of these, %BWL data were available for 4/7, and all four presented %BWL >20%. There were an additional 26/56 (46%) patients with %BWL >20% in the preceding year, and the overall group mean %BWL was 20.3%.

Details of nutritional rehabilitation treatments are presented in Table 2. Mean energy prescribed on admission (1781 ± 89 kcal/day) and mean maximum caloric intake (2422 ± 170 kcal/day) closely approximated targeted goals of the standardized treatment protocol. Orally administered phosphate supplementation mean was 1.0 ± .2 mmol/kg/day. Phosphate dosing ranged from 0.5 to 1.9 mmol/kg/day as 5/75 patients received incorrect doses that were corrected to 1 mmol/kg/day within 24 hours of admission. A multivitamin was prescribed at the time of admission for 22/75 (29.3%) of patients.

Serum phosphate levels were measured daily during the first 7 days of admission and are shown in Figure 2. No episodes of hypophosphatemia were noted for patients supplemented with prophylactic phosphate during any of the 75 admissions. Individual daily serum phosphate values ranged between 1.00 and 2.17 mmol/L. Eleven patients (14.7%) receiving phosphate supplementation had one or more documented episodes of hyperphosphatemia (>1.8 mmol/L); 2/11 cases had elevated values on more than a single day, and 9/11 cases occurred by Day 2. Among the 11 patients with documented hyperphosphatemia, the mean presupplementation phosphate level was 1.29 ± .2 mmol/L (range 1.01–1.52 mmol/L). In addition, we examined the potential effect of (phosphorous-containing) multivitamin administration. Subanalysis revealed that there was no difference in the occurrence of hyperphosphatemia among patients receiving a multivitamin (3/22, 13.6%) and patients not receiving a multivitamin (8/53, 15.1%; p = 1.00).

There were no adverse events or clinical symptoms requiring medical intervention among any patients who became hyperphosphatemic during refeeding. Physician response to elevated serum phosphate was highly variable; 3/11 patients (27%) had their supplementation dose reduced by 50% within 24 hours, 3/...
We compared the prophylactic phosphate group to the 11 excluded patients who were hypophosphatemic at the time of admission. Demographic data are summarized in Table 3. The hypophosphatemic cohort differed only by their admission phosphate values (.8 ± .1 mmol/L vs. 1.2 ± .2 mmol/L; p < .001). %BWL was 15.5 ± 10.0% and available for 8/11 patients. This group was treated with the equivalent phosphate dose as the prophylaxis cohort (1.1 ± .4 mmol/kg/day vs. 1.0 ± .2 mmol/kg/day, p = .19). Normophosphatemia was achieved in 10/11 patients on Day 1 (mean Day 1 serum phosphate, 1.3 ± .3 mmol/L), and all 11 patients reached and remained in the normophosphatemic range by Day 2. No adverse events were noted in this group.

### Discussion

To our knowledge, this is the first study to specifically assess the effects of prophylactic phosphate supplementation in adolescent patients with restrictive eating disorders hospitalized for nutritional rehabilitation. Our cohort was administered routine phosphate solution throughout the initial week of inpatient refeeding treatment, and no incidences of RH were observed. Reported rates of RH vary among adolescents comparable to our study population but not receiving prophylactic phosphate supplementation. Ornstein et al. [7] reported that 27% of adolescent patients being refeeding with 1,200–1,400 kcal/day required phosphate supplementation for phosphate nadirs < .99 mmol/L during the first week of hospitalization. Comparatively, 38% of patients required phosphate supplementation in a study by Whitelaw et al. [10] utilizing a high refeeding protocol of 1900 kcal/day. A recent systematic review of refeeding practices in anorexic adolescents found a 14% overall incidence of RH with an average initial caloric intake of 1500 kcal/day (range 1200–1900 kcal/day) [9]. This may even be an underestimate, as some patients were supplemented in the presence of declining but still normal serum phosphorus levels. Among these studies, mean %mBMI was 78%, similar to our study cohort’s %mBMI of 83%. Most of the studies included in this review defined hypophosphatemia as a phosphate level < .9 mmol/L. No patient in our study developed RH on a nutritional protocol of 1800 kcal/day despite a more strict definition of hypophosphatemia (<1.0 mmol/L).

The factors predisposing to RH are poorly understood. The National Institute for Health and Clinical Excellence has identified several risk factors in the adult population for the development of RS that include any of the following: (1) BMI < 16 kg/m²; (2) unintentional weight loss >15% within the prior 3–6 months; (3) little or no nutrition intake for >10 days; and (4) low levels of phosphate, potassium, or magnesium before refeeding [16]. Adolescent-specific guidelines now advocate for a more comprehensive assessment of the degree of malnutrition, defining severe malnutrition as any of %mBMI < 70%, BMI z scores < -3, and %BWL in the preceding year >20% [2,17]. Using these metrics of malnutrition, a patient can be severely malnourished even at a normal weight, and several studies have drawn attention to the number of adolescents with life-threatening complications of eating disorders and a normal BMI at presentation [18,19]. In the present study, patients were not severely underweight at admission with a %mBMI of 83%; however, the mean %BWL over the preceding year was 20.3%, and 7/75 (9%) patients had %mBMI < 70%. Overall, at least 33/75 patients (44%) met the Society of Adolescent Health and Medicine’s criteria for severe malnutrition. This number is potentially underestimated by %BWL data missing in 19/75 patients. Although we cannot extrapolate what would happen in a purely low BMI population, none of these 33 patients meeting severe malnourishment criteria experienced RH while supplemented with prophylactic phosphate during the first week of refeeding.

Hyperphosphatemia is a potential consequence of oral phosphate supplementation and can lead to gastrointestinal
complications such as abdominal pain, diarrhea, and inconsistent absorption [7]. No guidelines currently exist for prophylactic phosphate dosing. Treatment recommendations for moderate hypophosphatemia (<0.8 mmol/L) are variable and include oral supplementation at a starting dose of 30–60 mg/kg/day [8]. Our patients were renourished on a protocol that included phosphate supplementation at the lower end of the recommended treatment range (31 mg/kg/day). A minority of patients (14.7%) became hyperphosphatemic; only 2/11 had phosphate elevations that persisted >24 hours, and no patients experienced adverse events requiring a change in management. Moreover, patients receiving a multivitamin (approximate additional elemental phosphorus of 2.5 mg/kg/day) were at no greater risk of hyperphosphatemia.

Hypophosphatemic patients were analyzed separately to ensure that the study group was exclusively a prophylactic treatment model. It is not readily evident why these patients were hypophosphatemic on admission, as their baseline characteristics did not differ from the normophosphatemic group. While not reaching statistical significance, the hypophosphatemic cohort was of slightly lower zBMI when compared with the normophosphatemic group (79.8% vs. 83.5%). This may have contributed to their hypophosphatemia on presentation as suggested by previous studies [7–10]. The hypophosphatemic patients were treated with equivalent phosphate doses as the prophylactic group. With this dose, the hypophosphatemic group rapidly reached and maintained normophosphatemia without complication despite their low phosphate level before refeeding. The only hypophosphatemic patient to take >24 hours to reach a normal serum phosphate presented with the most profound level of hypophosphatemia (.51 mmol/L) and normalized by Day 2 of admission.

Certain limitations of the present study reflect the inherent nature of the retrospective design. A large proportion of patients (19.3%) were excluded for missing data (n = 8) or for a lack of baseline labs (n = 13). We cannot exclude the possibility that rare adverse events might not have been documented. Moreover, adverse events that occurred but were not documented would not have been captured in our study. Although other authors have proposed baseline levels of prealbumin [20] and magnesium [21] as risk factors of RH, we did not routinely collect them in our population. Physician response to hyperphosphatemia was highly variable, making it difficult to interpret subsequent measured phosphate values among hyperphosphatemic patients. However, this occurred in only 14% of patients; among whom, 5/11 had no change in supplementation dose. In addition, it was not possible to know the temporal relationship and possible effect of dose administration and blood sampling. In addition, in the present study, we have attempted to determine the extent to which phosphate supplementation prevented RH in the context of a protocol that incorporates NG feeding. An NG-based approach is not standard for the inpatient management of AN and is advocated by some authors to theoretically decrease the risk of RS [22]. It is not possible from our study design to determine the true added incremental value of phosphate supplementation compared with either intervention alone. Finally, given the retrospective nature of the study, we cannot assume causality between prophylactic phosphate supplementation and the prevention of RH.

Although this study supports the use of prophylactic phosphate supplementation to prevent RH, there is a need for well-designed prospective studies further evaluating this strategy and its applicability in severely underweight populations. Additional work is still required to define optimal phosphate dosing for prophylaxis and the appropriate response to hypophosphatemic values. Although beyond the scope of the present study, it remains to be determined if the prevention of RH by phosphate supplementation is sufficient to prevent full RS. This fundamental question is an important area of future research that may provide the foundation for clinical practice guidelines and standardized inpatient treatment protocols.

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References