Refeeding syndrome describes the clinical and metabolic de-
rangements 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).

RH is thought to play an important role in the refeeding syn-
drome [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 rein-
duction of carbohydrates, insulin secretion causes an influx of
electrolytes into the cells. Phosphorus is required for glucose
metabolism to produce phosphorylated intermediates of glycol-
ysis 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 extracel-
lar 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 manifes-
tations of muscular dysfunction include ophthalmoplegia,
dysphagia, or ileus. Hypophosphatemia can also cause rhabdo-
myolysis, which may be asymptomatic, manifested only by an in-
crease in serum creatine phosphokinase, or may cause severe
muscle pain and weakness or acute renal tubular necrosis. Hypo-
phosphatemia 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 funda-
mental 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 United
States, lower calorie approaches typically begin between 900 and
1200 kcal/day and advance by 200 kcal every other day [19,20];
however, recommendations start as low as 200–600 kcal/day in
Europe and the United Kingdom [21–26]. These “start low and
go slow” approaches have been linked to the so-called “under-
feeding syndrome,” characterized by poor weight gain, pro-
longed illness, and even death due to overly cautious refeeding
[25]. In clinical practice, some programs have been starting
around 1500 kcal/day and others are shifting toward higher
calorie diets, starting between 1400 and 2400 kcal/day [27–33].
raising 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 (percent ideal body weight or percent median body mass index [BMI]) on admission to hospital. One study found that in addition to percent median BMI, RH was also associated with rate of weight loss before admission but not prescribed caloric intake [33]. 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 (BMI < 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]. RH usually develops during the first week of nutritional rehabilitation [35]. Most hospitalized adolescents with AN have serum phosphorus levels within the reference range before refeeding [34] and therefore monitoring of serum phosphorus every 24–48 hours is recommended during the first week of hospitalization. To date, there have been no published studies examining the risk and/or 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 adult populations [37]. Based on this literature, a treatment suggestion for moderate hypophosphatemia (1.1–3.0 mg/dL) includes oral supplementation at a starting dose of 30–60 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, two to three 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, 0.35 mmol/L) and should only be undertaken in an intensive care unit. A dose of 20–30 mg/kg/day 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 and 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.

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

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