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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 phosphorus 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, 0.35 mmol/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.

References

1. Hayek ME, Eisenberg PG. Severe hypophosphatemia following the institution of enteral feedings. *Arch Surg*. 1989;124(11):1325–8. Epub 1989/11/01. [PubMed: 2510701]
2. Keys A The residues of malnutrition and starvation. *Science*. 1950;112(2909):371–3. Epub 1950/09/29. [PubMed: 14781769]
3. Maier-Dobersberger T, Lochs H. Enteral supplementation of phosphate does not prevent hypophosphatemia during refeeding of cachectic patients. *JPEN Journal of parenteral and enteral nutrition*. 1994;18(2):182–4. Epub 1994/03/01. [PubMed: 8201756]
4. Mezoff AG, Gremse DA, Farrell MK. Hypophosphatemia in the nutritional recovery syndrome. *Am J Dis Child*. 1989;143(9):1111–2. Epub 1989/09/01. [PubMed: 2773890]
5. Sheridan PH, Collins M. Potentially life-threatening hypophosphatemia in anorexia nervosa. *Journal of adolescent health care : official publication of the Society for Adolescent Medicine*. 1983;4(1):44–6. Epub 1983/03/01. [PubMed: 6841239]
6. Beumont PJ, Large M. Hypophosphataemia, delirium and cardiac arrhythmia in anorexia nervosa. *The Medical journal of Australia*. 1991;155(8):519–22. Epub 1991/10/21. [PubMed: 1943930]
7. Kaysar N, Kronenberg J, Polliack M, Gaoni B. Severe hypophosphataemia during binge eating in anorexia nervosa. *Archives of disease in childhood*. 1991;66(1):138–9. Epub 1991/01/01. [PubMed: 1899785]
8. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *The American journal of clinical nutrition*. 1981;34(3):393–9. Epub 1981/03/01. [PubMed: 6782855]
9. Hall DE, Kahan B, Snitzer J. Delirium associated with hypophosphatemia in a patient with anorexia nervosa. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 1994;15(2):176–8. Epub 1994/03/01. [PubMed: 8018692]
10. Birmingham CL, Alothman AF, Goldner EM. Anorexia nervosa: refeeding and hypophosphatemia. *The International journal of eating disorders*. 1996;20(2):211–3. Epub 1996/09/01. [PubMed: 8863075]
11. Kohn MR, Golden NH, Shenker IR. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*. 1998;22(3):239–43. Epub 1998/03/21. [PubMed: 9502012]
12. Fisher M, Simpser E, Schneider M. Hypophosphatemia secondary to oral refeeding in anorexia nervosa. *The International journal of eating disorders*. 2000;28(2):181–7. Epub 2000/07/18. [PubMed: 10897080]
13. Norris ML, Pinhas L, Nadeau PO, Katzman DK. Delirium and refeeding syndrome in anorexia nervosa. *The International journal of eating disorders*. 2012;45(3):439–42. Epub 2011/10/20. [PubMed: 22009708]
14. Solomon SM, Kirby DF. The refeeding syndrome: a review. *JPEN Journal of parenteral and enteral nutrition*. 1990;14(1):90–7. Epub 1990/01/01. [PubMed: 2109122]
15. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. *Medicine*. 2000;79(1):1–8. Epub 2000/02/12. [PubMed: 10670405]
16. O'Connor LR, Wheeler WS, Bethune JE. Effect of hypophosphatemia on myocardial performance in man. *The New England journal of medicine*. 1977;297(17):901–3. Epub 1977/10/27. [PubMed: 904668]
17. Planas RF, McBrayer RH, Koen PA. Effects of hypophosphatemia on pulmonary muscle performance. *Advances in experimental medicine and biology*. 1982;151:283–90. Epub 1982/01/01. [PubMed: 7180654]
18. Jacob HS, Amsden T. Acute hemolytic anemia with rigid red cells in hypophosphatemia. *The New England journal of medicine*. 1971;285(26):1446–50. Epub 1971/12/23. [PubMed: 5122895]

19. Practice guideline for the treatment of patients with eating disorders (revision). American Psychiatric Association Work Group on Eating Disorders. The American journal of psychiatry. 2000;157(1 Suppl):1–39. Epub 2000/01/22.
20. Treatment of patients with eating disorders, third edition. American Psychiatric Association. The American journal of psychiatry. 2006;163(7 Suppl):4–54. Epub 2006/08/24. [PubMed: 16925191]
21. Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders Clinical Guideline 9. London: 2004.
22. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical Guideline 32. London: 2006 Contract No.: Clinical Guideline 32.
23. Psychiatrist RCo. Guidelines for the nutritional management of anorexia nervosa (Clinical Report 130). London: 2005.
24. Psychiatrists RCo. Management of Really Sick Patients with Anorexia Nervosa: MARSIPAN (Council Report 162). London: 2010.
25. Psychiatrists RCo. Junior MARSIPAN: Management of Really Sick Patients under 18 with Anorexia Nervosa (Council Report 168). 2012.
26. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. European journal of clinical nutrition. 2008;62(6):687–94. Epub 2007/08/19. [PubMed: 17700652]
27. Garber AK, Mauldin K, Michihata N, Buckelew SM, Shafer MA, Moscicki AB. Higher calorie diets increase rate of weight gain and shorten hospital stay in hospitalized adolescents with anorexia nervosa. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2013;53(5):579–84. Epub 2013/09/24. [PubMed: 24054812]
28. Whitelaw M, Gilbertson H, Lam PY, Sawyer SM. Does aggressive refeeding in hospitalized adolescents with anorexia nervosa result in increased hypophosphatemia? The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2010;46(6):577–82. Epub 2010/05/18. [PubMed: 20472215]
29. Kohn MR, Madden S, Clarke SD. Refeeding in anorexia nervosa: increased safety and efficiency through understanding the pathophysiology of protein calorie malnutrition. Current opinion in pediatrics. 2011;23(4):390–4. Epub 2011/06/15. [PubMed: 21670680]
30. Leclerc A, Turrini T, Sherwood K, Katzman DK. Evaluation of a nutrition rehabilitation protocol in hospitalized adolescents with restrictive eating disorders. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2013;53(5):585–9. Epub 2013/07/31. [PubMed: 23891242]
31. Garber AK, Michihata N, Hetnal K, Shafer MA, Moscicki AB. A prospective examination of weight gain in hospitalized adolescents with anorexia nervosa on a recommended refeeding protocol. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2012;50(1):24–9. Epub 2011/12/23. [PubMed: 22188830]
32. Katzman DK. Refeeding hospitalized adolescents with anorexia nervosa: is “start low, advance slow” urban legend or evidence based? The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2012;50(1):1–2. Epub 2011/12/23. [PubMed: 22188827]
33. Golden NH, Keane-Miller C, Sainani KL, Kapphahn CJ. Higher caloric intake in hospitalized adolescents with anorexia nervosa is associated with reduced length of stay and no increased rate of refeeding syndrome. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2013;53(5):573–8. Epub 2013/07/09. [PubMed: 23830088]
34. O’Connor G, Nicholls D. Refeeding hypophosphatemia in adolescents with anorexia nervosa: a systematic review. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2013;28(3):358–64. Epub 2013/03/06. [PubMed: 23459608]
35. Ornstein RM, Golden NH, Jacobson MS, Shenker IR. Hypophosphatemia during nutritional rehabilitation in anorexia nervosa: implications for refeeding and monitoring. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2003;32(1):83–8. Epub 2003/01/01. [PubMed: 12507806]
36. Schwartz BI, Mansbach JM, Marion JG, Katzman DK, Forman SF. Variations in admission practices for adolescents with anorexia nervosa: a North American sample. The Journal of

- adolescent health : official publication of the Society for Adolescent Medicine. 2008;43(5):425–31. Epub 2008/10/14. [PubMed: 18848669]
37. Worley G, Claerhout SJ, Combs SP. Hypophosphatemia in malnourished children during refeeding. *Clinical pediatrics*. 1998;37(6):347–52. Epub 1998/06/25. [PubMed: 9637898]
 38. Gaudiani JL, Sabel AL, Mascolo M, Mehler PS. Severe anorexia nervosa: outcomes from a medical stabilization unit. *The International journal of eating disorders*. 2012;45(1):85–92. Epub 2011/12/16. [PubMed: 22170021]
 39. Gentile MG, Pastorelli P, Ciceri R, Manna GM, Collimedaglia S. Specialized refeeding treatment for anorexia nervosa patients suffering from extreme undernutrition. *Clin Nutr*. 2010;29(5):627–32. Epub 2010/04/27. [PubMed: 20416994]
 40. Rigaud D, Brondel L, Poupard AT, Talonneau I, Brun JM. A randomized trial on the efficacy of a 2-month tube feeding regimen in anorexia nervosa: A 1-year follow-up study. *Clin Nutr*. 2007;26(4):421–9. Epub 2007/05/15. [PubMed: 17499892]