Pivotal Paper

Death Resulting From Overzealous Total Parenteral Nutrition: The Refeeding Syndrome Revisited

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Financial disclosure: none declared.

Commentary is provided on the pivotal paper by Weinsier and Krumdieck from 1981 describing 2 patients who developed profound and fatal refeeding syndrome following initiation of aggressive total parenteral nutrition. This classic description was among the first to describe the overwhelming cardiovascular and pulmonary manifestations that can accompany parenteral refeeding with carbohydrate in chronically malnourished patients. The syndrome has also been described with oral and enteral nutrition. One of the hallmarks of the syndrome is hypophosphatemia. Since 1981, dosing schemes for addressing hypophosphatemia have been refined. Other manifestations of the syndrome include other electrolyte abnormalities such as hypokalemia and hypomagnesemia, hyperglycemia, fluid and sodium retention, and neurologic and hematologic complications. Case reports of refeeding syndrome continue to be published, particularly in the anorexia nervosa population. Stressed, critically ill patients may be at risk of refeeding following short periods of fasting; hypophosphatemia is commonly encountered in this situation. It behooves the current nutrition support practitioner to keep in mind the types of patients at risk of refeeding syndrome and to approach refeeding of such patients with caution and careful monitoring. (Nutr Clin Pract. 2008; 23:166-171)

Keywords: refeeding syndrome; hypophosphatemia; protein-energy malnutrition

In 1981, Weinsier and Krumdieck published a paper that outlined dramatic and rapidly evolving refeeding syndrome in 2 chronically malnourished patients who received aggressive dextrose-based parenteral nutrition (PN). Emphasis was placed by these authors on the hypophosphatemia (reported nadirs of 0.4 and 0.7 mg/dL) that developed in these 2 patients. This paper has been used extensively by nutrition support educators to emphasize the importance of recognizing patients at risk for refeeding syndrome and to approach the feeding of such patients with due caution. Patients who are typically at increased risk of refeeding syndrome are those who are extremely malnourished at the time of refeeding. The syndrome is characterized by severe shifts of electrolytes and fluids accompanied by metabolic abnormalities that may include, among other things, hyperglycemia and thiamine deficiency. In severe cases, cardiac arrhythmias, respiratory failure, congestive heart failure, hematologic abnormalities, and neurologic complications may occur; Weinsier and Krumdieck’s 2 patients manifested cardiovascular and respiratory abnormalities resulting in death in the third and first weeks of hospitalization, respectively.

Prevaling Belief

Weinsier and Krumdieck’s case descriptions were by no means the first descriptions of refeeding syndrome, nor were they the first descriptions of the syndrome in parenterally fed patients, although they were among the first to describe the cardiovascular and pulmonary manifestations of the syndrome in parenterally fed patients. Misadventures occurred during World War II in Leningrad and the Netherlands when, following famine and short food supplies, normal oral feeding was resumed. From Leningrad, reports of cardiac insufficiency and peripheral edema occurred, whereas severe neurological complications were seen in some residents of the Netherlands. Similar unfortunate events, especially edema, were seen in Japanese prisoners of war who were refed during this same era. Intentional starvation and refeeding studies of previously healthy men were also conducted in the 1940s by Keys. After 6 months of significant food restriction,
Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited

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ABSTRACT Although cachectic patients are relatively well adapted to their calorically deprived state, they are prone to acute metabolic imbalances when infused with hypertonic solutions of dextrose and amino acids. Of particular concern is hypophosphatemia and its associated disorders of cardiac, pulmonary, hematological, and neuromuscular functions. This report describes two chronically malnourished but stable patients who were given aggressive total parenteral nutrition support, which was rapidly followed by acute cardiopulmonary decompensation associated with severe hypophosphatemia and other metabolic abnormalities. Despite attempts at correction, progressive multiple systems failure led to death. In light of the high prevalence of hospital malnutrition and the ready availability of total parenteral nutrition, attention is brought to these examples of how overzealous nutrition repletion can paradoxically precipitate deterioration in clinical status. Am. J. Clin. Nutr. 34: 393–399, 1981.

KEY WORDS Total parenteral nutrition, hyperalimentation, hypophosphatemia, hospital malnutrition, protein-calorie malnutrition, marasmus

Introduction

Central venous total parenteral nutrition has already proven to be one of the major advances in medicine, many times being life-saving for patients who would otherwise have died of malnutrition. With the availability of this new tool our awareness and understanding of human nutrient requirements and their interactions have rapidly increased. As with other innovations, however, it often requires years of application until the potential dangers are recognized. Hypophosphatemia has emerged as perhaps one of the most frequent and potentially dangerous consequences of total parenteral nutrition, particularly among patients being therapeutically refed after severe weight loss (1). This report describes two chronically ill, severely malnourished patients who, within hours of the initiation of total parenteral nutrition, rapidly developed cardiopulmonary failure resulting in death. The possible contributory role of hypophosphatemia is discussed.

Case history 1

A 28-yr-old white female was transferred to the general medical service from the psychiatric service because of severe malnutrition initially believed to be caused by anorexia nervosa. Since early childhood she had had recurrent diarrhea and abdominal pain with nausea and vomiting. Repeated diagnostic evaluations including two small bowel biopsies failed to disclose a specific underlying disease. Over the past 7 yr she had progressive weight loss with exacerbation of her diarrhea but had no acute changes and was stable at the time of admission.

On physical examination she was alert, oriented, and in no acute distress but was severely emaciated with a body weight of 23 kg (height 162 cm), 40% of her ideal weight. Blood pressure was 90/60, without orthostatic changes; pulse was 92 and regular; heart sounds were normal; no galls, murmurs, or rubs were audible. Bowel sounds were hyperactive and the abdomen was nontender. The neurological exam was normal except for decreased extracranial movement and generalized weakness.

Laboratory data included a hematocrit of 35%, white blood count 8000, blood urea nitrogen 30 mg/dl, serum creatinine 1.6 mg/dl, potassium 2.9 mEq/l, calcium 5.1 mg/dl, phosphorus 2.7 mg/dl, albumin 2.3 g/dl, and glucose 103 mg/dl. Liver function tests were normal. Chest x-ray was within normal limits.

Hospital course

On the day of admission the patient was transferred from the psychiatric to the general medical service. Cen-
blood pressure and heart rate decreased significantly. In addition, heart size decreased but to a lesser extent than total body weight. With oral refeeding, some subjects experienced cardiac decompensation.

Following the groundbreaking work on central PN access in the late 1960s, reports of what was first known as the hypophosphatemic hyperalimentation syndrome appeared in the 1970s. In 1980, Silvis et al. compiled references of 20 reported cases of patients receiving PN who had paresthesias, seizures, and/or coma accompanying severe hypophosphatemia. This was followed the next year by the pivotal paper of Weinsier and Krumdieck that emphasized the effects of refeeding hypophosphatemia on cardiovascular and pulmonary function. Notably, in 1978, Heymsfield and colleagues reported cardiac decompensation in 2 of 5 severely malnourished patients refed with 4 to 6 weeks of enteral or parenteral nutrition.

Many of the early reports of PN-related refeeding syndrome emphasized the importance of hypophosphatemia in the pathophysiology of the manifestations of the syndrome. However, the effects of refeeding on fluid and sodium retention were well known prior to publication of Weinsier and Krumdieck's case reports in 1981 and should not be overlooked as important components of a full-blown refeeding syndrome. Studies conducted in the 1960s and 1970s showed that refeeding with carbohydrate (but not fat or protein) leads to antinatriuresis (sodium retention) and fluid retention. This probably explains the peripheral edema (sometimes termed refeeding edema) seen in most of the early descriptions of refeeding syndrome. Although serial weights were not recorded in Weinsier and Krumdieck's case reports, it is notable that the patients they described received a rather large amount of sodium (100 mEq/L) in their high-carbohydrate PN solution and were noted to develop pulmonary edema with refeeding. Also notable are the amounts of carbohydrate administered to Weinsier's patients: 21 and 23 g/kg per day far exceed our current maximum recommendation of 7 g/kg per day of carbohydrate.

**Unique Scientific Contribution**

As outlined above, the paper by Weinsier and Krumdieck emphasized the gravity of refeeding syndrome and reiterated that it could occur in chronically malnourished patients begun on aggressive PN. Silvis's previous descriptions had emphasized neurologic complications associated with refeeding hypophosphatemia. Weinsier and Krumdieck's cases hearkened back more to the World War II descriptions of refeeding complications, with the spotlight on the cardiovascular and pulmonary manifestations. Investigators during and immediately following World War II had not fully recognized the importance of hypophosphatemia in refeeding complications; this recognition largely emerged after the introduction of PN administered via central vein in the late 1960s and 1970s, and Weinsier and Krumdieck's reports also emphasized this aspect of the syndrome.

**Validation**

Many subsequent reports of refeeding syndrome in orally, enteral, and parenterally fed patients published since Weinsier and Krumdieck's paper have validated that the syndrome is real and can still occur. Hayek and Eisenberg studied 25 patients receiving postoperative enteral feedings in the surgical intensive care unit. Within 2 to 5 days after initiation of enteral feedings (600 to 1200 kcal/d initially increased based on patient tolerance), serum phosphorus levels decreased from 2.4 to 4.8 mg/dL to 0.5 to 1.2 mg/dL. The authors concluded that highly stressed patients may have higher requirements for phosphorus than the amount present in standard isotonic enteral feedings. Note that this study focused on refeeding hypophosphatemia rather than the larger constellation of manifestations of refeeding syndrome.

Marik and Bedigan also studied refeeding hypophosphatemia in 62 surgical and medical intensive care patients refed with enteral or parenteral nutrition following at least 48 hours without feeding. Twenty-one patients (34%) exhibited refeeding hypophosphatemia, defined as a drop in serum phosphorus by at least 0.5 mg/dL to less than 2 mg/dL. In 6 of these patients (10%), serum phosphorus levels dropped to less than 1 mg/dL. (Interestingly, Weinsier and Krumdieck had commented in the discussion section of their paper that in their institution, they had noted serum phosphorus values less than 2 mg/dL in 30% of their medical and surgical patients receiving PN and values less than 1 mg/dL in 6% of these patients.) The nadir for serum phosphorus occurred after about 2 days of feeding. A low serum prealbumin concentration was the only risk factor identified that predicted the development of refeeding hypophosphatemia. Patients who developed hypophosphatemia had significantly prolonged lengths of mechanical ventilation and hospital stay.

Aubier and colleagues made some interesting observations in 8 mechanically ventilated patients with hypophosphatemia. In these patients with a mean serum phosphorus level of 1.7 mg/dL, diaphragm function was measured before and after administration of 10 mmol of potassium phosphate over 4 hours. This infusion resulted in an elevation in the mean serum phosphorus level to 4.2 mg/dL, which correlated with a marked improvement in diaphragm function.

Most of the reports of refeeding syndrome published since Weinsier and Krumdieck's reports have involved chronically malnourished patients. (The notable exceptions to this were most of the patients studied by Hayek and Eisenberg and Marik and Bedigan as outlined above.) However, these 2 studies focused on hypophosphatemia...
only.) Quite a number of these case reports have been patients suffering from anorexia nervosa.10-13 These patients were fed orally, enterally, parenterally, or by some combination of these 3 modalities. In some of these cases, hypophosphatemia was the main marker reported as evidence of the refeeding syndrome, whereas in others, cardiovascular and neurologic complications were reported. The phosphorus nadir tended to occur within the first week of initiating refeeding. As had been noted in the older literature, cardiovascular complications were more likely to occur during the first week of refeeding, whereas neurologic complications tended to occur a bit later.13 Authors of these more recent case reports have reiterated the recommendations given by Weinsier and Krumdieck to gradually increase these chronically malnourished patients to their caloric goals, monitor serum electrolytes (especially phosphorus) frequently with initiation of refeeding, and supplement phosphorus liberally.

Recently, patients with G1 fistulae have been identified as another population likely to develop refeeding syndrome. Fifteen of 158 patients (9%) with this diagnosis were reported to develop refeeding syndrome during parenteral and enteral refeeding; refeeding syndrome was nebulously defined as “symptoms and signs of electrolyte disturbances.”16 It appears that all of these diagnoses were made on the basis of hypophosphatemia, as serum potassium and magnesium were reported to remain within the reference range during refeeding. The patients developing hypophosphatemia had lost an average of 7 kg before admission. The nadir for serum phosphorus was reached in a mean of 3.3 days following initiation of refeeding. Cardiovascular and neurologic abnormalities were fairly common in this group of refeeding syndrome patients.

Protocols for repletion of hypophosphatemia have been refined since the early reports of refeeding syndrome in recipients of nutrition support. An intravenous phosphorus repletion regimen proposed by Vannatta et al7 became popularized at about the same time as the refeeding syndrome reports from Weinsier and Krumdieck. This regimen used 9 mmol of potassium phosphate infused continuously every 12 hours for patients with severe hypophosphatemia, defined as serum phosphorus less than or equal to 1 mg/dL. A more aggressive phosphorus repletion regimen was proposed by Kingston and Al-Siba’i in 1985.18 In this approach, 0.5 mmol/kg of phosphorus was recommended for serum phosphorus less than 0.5 mg/dL and 0.25 mmol/kg for serum phosphorus between 0.5 and 1 mg/dL. Two different phosphorus repletion regimens were published in 1995. Rosen and colleagues19 studied 15-mmol dosages given over 2 hours. This dosage could be repeated 2 times in a 24-hour period if serum phosphorus remained less than 2 mg/dL. Clark and colleagues20 designed a graduated phosphorus-dosing scheme based on the initial degree of hypophosphatemia; it should be noted that patients with serum phosphorus levels less than 1.6 mg/dL were included in this study, whereas they were not included in the Rosen et al study. The graduated scheme gave dosages of 0.16 mmol/kg to patients with mild hypophosphatemia (2.3-3 mg/dL), 0.32 mmol/kg to patients with moderate hypophosphatemia (1.6-2.2 mg/dL), and 0.64 mmol/kg to patients with severe hypophosphatemia (<1.6 mg/dL). In a recent modification of the above regimen, the same research group studied and subsequently recommended dosages of 0.32 mmol/kg for mild hypophosphatemia, 0.64 mmol/kg for moderate hypophosphatemia, and 1 mmol/kg for severe hypophosphatemia.21 With any of these regimens, it must be recognized that serum phosphorus levels may not correlate with total body phosphorus stores.

**Future Considerations**

At first glance, the reader might be tempted to consider refeeding syndrome largely of historical importance. In the decades since Weinsier and Krumdieck’s reports, nutrition support practitioners have become acutely aware of the dangers of overfeeding and would not feed patients at >7 g/kg per day of carbohydrate, much less the 23 to 25 g/kg per day initially provided in the 1981 report. However, the recent reports of refeeding complications that continue to appear in the literature, especially in anorexia nervosa patients, reiterate that the syndrome and in particular, refeeding hypophosphatemia, can occur even with more conservative dosages of carbohydrate. Not all clinics and institutions have nutrition support teams, so it is still important to educate health care practitioners as to the potential danger of too aggressively refeeding a chronically malnourished patient. Several informative reviews and discussions of the refeeding syndrome that have been published in the past 20 years were located in the literature.6,15,22-29 Although a few of these were published in mainstream medical journals, most of them were published in nutrition journals, where one might posit that the authors were preaching to the choir. Fortunately, many of the recent reports of refeeding syndrome occurring in anorexia nervosa patients have been published in journals likely to be read by health care practitioners taking care of this type of patient, which should help to raise and maintain the awareness of the potential for this complication.

Lest today’s nutrition support practitioner become complacent and believe that refeeding syndrome is unlikely in today’s environment of providing conservative amounts of enteral and parenteral calories, the words of Solomon and Kirby in their excellent 1990 review of refeeding syndrome should be heeded. They commented that anorexia nervosa “serves as a sobering model for the possible calamity inherent in refeeding severely malnourished hospitalized patients.” Although many of the patients encountered by contemporary nutrition support practitioners are obese, chronic illness with accompanying chronic malnutrition is still encountered, thus making the possibility of encountering refeeding syndrome still quite high. Although
the full-blown syndrome, with fluid retention and cardiovascular, pulmonary, neurologic, and hematologic manifestations, may be currently uncommon, most intensive care nutrition support practitioners will be able to attest to the common occurrence of electrolyte abnormalities such as hypophosphatemia, hypokalemia, and hypomagnesemia in patients receiving nutrition support in their units. These abnormalities, particularly hypophosphatemia, can probably at least sometimes be attributed partially to refeeding phenomena.

In the classic form of refeeding syndrome, carbohydrate overfeeding of a chronically malnourished patient often led to hyperglycemia. In extreme cases, this could lead to osmotic diuresis, dehydration, and hyperosmolar nonketotic coma. Both of Weinsier and Krumdieck’s case patients exhibited extreme hyperglycemia, one to a maximum of about 700 mg/dL and the other to about 1200 mg/dL. With what we now know about the downside of hyperglycemia in hospitalized patients, and particularly intensive care patients, this complication of refeeding syndrome is to be avoided.30,31

Several authors have described the types of patients currently seen by nutrition support practitioners who are at greatest risk of refeeding syndrome. In addition to anorexia nervosa patients, these include patients with cancer cachexia, chronic GI illness, prolonged fasting especially in the presence of stress, and chronic alcoholics. The possibility for development of refeeding syndrome in patients who have undergone bariatric surgery, particularly in those who develop chronic vomiting following the surgery, has been broached by Mason.32 The fact that multiple cases of severe thiamine deficiency have been reported following bariatric surgery and that thiamine deficiency was associated with classic refeeding edema causes the nutrition support practitioner to ponder this possibility.33

A variety of strategies have been suggested for the prevention of refeeding syndrome in patients at risk for these complications. These range from the very conservative recommendation of starting at 25% of estimated goal requirements on day 1 to a more common recommendation of about 20 kcal/kg per day or 1000 kcal per day to start.6,22,28 Most recommendations call for advancing kilocalories to goal amounts over the first 5 to 7 days and do not call for restricting the protein supplied initially. The amount of fluid and sodium initially supplied should be conservative because of the propensity to retain these complications. These range from the very conservative recommendation of starting at 25% of estimated goal requirements on day 1 to a more common recommendation of about 20 kcal/kg per day or 1000 kcal per day to start.6,22,28 Most recommendations call for advancing kilocalories to goal amounts over the first 5 to 7 days and do not call for restricting the protein supplied initially. The amount of fluid and sodium initially supplied should be conservative because of the propensity to retain these during initial carbohydrate refeeding of the chronically malnourished patient. Significant serum electrolyte abnormalities should be corrected prior to beginning nutrition support. Provision of supplemental potassium, magnesium, and phosphorus beyond amounts normally anticipated to be required for maintenance may be prudent in patients at risk for refeeding syndrome. Research to determine optimal electrolyte repletion regimens for obese patients would be useful as these patients have typically been excluded from, for example, the phosphate repletion studies mentioned earlier. Serum electrolytes should be monitored daily during the first week of refeeding in at-risk patients. Supplemental thiamine in amounts higher than found in most multivitamin preparations is also sometimes recommended for the first several days of refeeding of at-risk patients.

Conclusion

Weinsier and Krumdieck’s dramatic reports of refeeding syndrome in chronically malnourished patients receiving aggressive PN were a sobering warning to nutrition support practitioners. Today’s nutrition support practitioners should still be on the lookout for patients at risk for this syndrome, whether the method of nutrition repletion is oral, enteral, or parenteral. Even though current recommendations would prohibit the aggressive initial refeeding regimens used in the past, fragments of the syndrome, particularly hypophosphatemia, may be observed in at-risk patients. Nutrition support practitioners should strive to educate and remind the larger health care community regarding the dangers of aggressively refeeding certain patients.

References