REVIEW ARTICLE

The Importance of the Refeeding Syndrome

M. A. Crook, BSc, MB, BS, PhD, FRCPath, V. Hally, BSc, SRD, and J. V. Panteli, BSc, SRD

From the Department of Chemical Pathology, Guy's and St Thomas' Hospital and University Hospital, Lewisham, London, UK; the Department of Dietetics and Nutrition, University College Hospital, London, UK; and the Department of Dietetics, University Hospital Lewisham, Lewisham, London, UK

In this review we discuss the refeeding syndrome. This potentially lethal condition can be defined as severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally. It can be associated with significant morbidity and mortality. Clinical features are fluid-balance abnormalities, abnormal glucose metabolism, hypophosphatemia, hypomagnesemia, and hypokalemia. In addition, thiamine deficiency can occur. We describe which patient groups are more at risk for this syndrome and the clinical management of the condition. *Nutrition* 2001;17:632–637. ©Elsevier Science Inc. 2001

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INTRODUCTION

In urbanized industrialized countries, where obesity is now becoming more commonplace, it might appear paradoxical that patients can still present with the "refeeding syndrome." This potentially lethal condition can be defined as severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding orally, enterally, or parenterally.[1,2]

Although previous reports had emphasized severe hypophosphatemia as a predominant feature of the refeeding syndrome, it has now become apparent that there are other metabolic consequences that are important such as fluid-balance abnormalities, altered glucose metabolism, and certain vitamin deficiencies, e.g., thiamine, as well as hypokalemia and hypomagnesemia (Table I).

TABLE I.

MAIN PATHOPHYSIOLOGIC FEATURES OF THE REFEEDING SYNDROME

Abnormalities of fluid balance
Abnormalities of glucose metabolism
Vitamin deficiency, e.g., vitamin B1 (thiamine)
Hypophosphataemia
Hypomagnesaemia
Hypokalaemia

PATIENTS AT HIGH RISK FOR THE REFEEDING SYNDROME

Historically, some of the earliest reports of the refeeding syndrome occurred in starved patients in wartime such as Japanese prisoners and victims of the Leningrad or Netherlands famines.[3] In general, those individuals with marasmus or kwashiorkor are at risk for the refeeding syndrome, particularly if there is greater than 10% weight loss over a couple of months. Patients are at risk if they have not been fed for 7 to 10 d, with evidence of stress and depletion. However, more specifically, this syndrome also has been described after prolonged fasting, massive weight loss in obese patients including after duodenal-switch operations, chronic alcoholism, prolonged intravenous fluid repletion, and anorexia nervosa. Anorexia nervosa is one of the more common modern clinical presentations of the refeeding syndrome, as are oncology patients undergoing chemotherapy, the refeeding of malnourished elderly individuals, and certain postoperative patients (Table II).[4–15]

It is important to emphasize that the clinical features of the refeeding syndrome can be seen after parenteral or enteral feeding; indeed, the key prerequisite is chronic nutritional deprivation regardless of the route of calorie administration. The degree of refeeding is important in the etiology of the condition, and, as we will discuss later, calorie repletion should be given slowly, particularly during the first week, at about 20 kcal/kg of body weight per day. The duration of refeeding also might be important, particularly if prolonged. Therefore, nutrition support may need to be modified over time in accordance with the patients' clinical conditions.[16] Electrolyte disturbances can take place within the first few days of refeeding, cardiac complications within the first week, and delirium and other neurologic features generally afterward.[17,18]

PATHOGENIC MECHANISMS INVOLVED IN THE REFEEDING SYNDROME

It is useful to review some basic physiologic processes that take place during starvation because this will help to explain some of the clinical manifestations observed in the refeeding syndrome.

Insulin concentrations decrease while glucagon increases during starvation. This results in the rapid conversion of glycogen

Disclaimer: It is recommended that readers check drug and electrolyte dosages and concentrations with their pharmacies before patient administration. The authors accept no responsibility for errors in the article.

Correspondence to: M. A. Crook, BSc, MB, BS, PhD, FRCPath, Senior Lecturer and Consultant Chemical Pathologist, Chemical Pathology, 5th Floor Tower, Guy's Hospital, London SE1 9RT, UK. E-mail: martin.crook@gstt.sthames.nhs.uk

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TABLE II.

PATIENTS AT PARTICULAR RISK FOR THE REFEEDING SYNDROME

Kwashiorkor or marasmus
Anorexia nervosa
Chronic malnutrition, e.g., from carcinoma or in the elderly
Chronic alcoholism
Prolonged fasting
Duodenal switch operation for obesity
Hunger strikers
Oncology patients
Postoperative patients

stores to form glucose as well as gluconeogenesis, resulting in glucose synthesis via lipid and protein breakdown products. Adipose tissue releases large quantities of fatty acids and glycerol and muscle releases amino acids. Ketone bodies and free fatty acids replace glucose as a major energy source under these circumstances. Overall, there is catabolism of adipose tissue and muscle, resulting in loss of lean body mass.

During refeeding, a shift from fat to carbohydrate metabolism occurs. A glucose load evokes insulin release, causing increased cellular uptake of glucose, phosphate, potassium, magnesium and water, and protein synthesis (Fig. 1).[19–25]

FIG. 1. Schematic diagram of some of the metabolic consequences of starvation and the refeeding syndrome.[90]

CLINICAL MANIFESTATIONS OF THE REFEEDING SYNDROME

Disturbances of Body-Fluid Distribution

The metabolic abnormalities, principally electrolyte and fluid disturbances, resulting from the refeeding syndrome can influence many body functions.

The fluid intolerance can result in cardiac failure, dehydration or fluid overload, hypotension, prerenal failure, and sudden death. Refeeding with carbohydrate can reduce water and sodium excretion, resulting in expansion of the extracellular-fluid compartment and weight gain, particularly if sodium intake is increased. Refeeding with predominately protein or lipid can result in weight loss and urinary sodium excretion, leading to negative sodium balance. High protein feeding also can result in hypernatremia associated with hypertonic dehydration, azotemia, and metabolic acidosis.[26–30]

Abnormal Glucose and Lipid Metabolisms

Glucose ingestion can suppress gluconeogenesis, resulting in reduced amino-acid (predominately alanine) usage and leading to a less-negative nitrogen balance. However, once the glucose infusion suppresses gluconeogenesis, then further administration can cause hyperglycemia. This in turn can evoke hyperosmolar nonketotic coma, ketoacidosis and metabolic acidosis, osmotic diuresis, and dehydration.

Further, glucose can be converted to fat through lipogenesis, which can evoke hypertriglyceridemia, fatty liver and abnormal liver-function tests, a higher respiratory quotient resulting in increased carbon dioxide production, hypercapnia, and respiratory failure.[31–33] It is important that the administered fat does not exceed the maximum lipid-elimination capacity, which is about 3.8 g of lipid/kg of body weight per day. This is particularly relevant because this capacity can be reduced in critically ill patients.[34,35]

Thiamine Deficiency

Thiamine (vitamin B1) deficiency can be associated with refeeding. Patients previously malnourished can have various vitamin deficiencies, including thiamine, which can be restored by refeeding. However, thiamine deficiency can result in Wernicke's encephalopathy or Korsakov's syndrome. The former is associated with ocular disturbance, confusion, ataxia, and coma, and the latter with short-term memory loss and confabulation. It is thought that carbohydrate refeeding causes increased cellular thiamine utilization because it is a cofactor for various enzymatic activities, e.g., transketolases.[36,37] Provision of thiamine with refeeding might reduce symptoms of postrefeeding thiamine deficiency.[2]

Hypophosphatemia

One of the predominant features of the refeeding syndrome is hypophosphatemia. The body stores of phosphate are between 500 and 800 g in an adult human. About 80% is in the bony skeleton and 20% is distributed in the soft tissues and muscle. Phosphate is the major intracellular anion and shifts between the intracellular and extracellular compartments.[38] Such transcellular movement can result from the ingestion of carbohydrate or lipid and from acid–base alterations. In the case of the latter, an acidosis can result in shifts of phosphate out of cells into the plasma.[39]

The intake of phosphate in the diet is about 1 g/d, with approximately 80% being absorbed in the jejunum. Protein-rich food is a major source of phosphate intake, as are cereals and nuts. Normally dietary phosphate deficiency is unusual; in fact, intake is often in excess of requirements. Between 60% and 70% of dietary

phosphate is absorbed. The output is essentially renal, with more than 90% being excreted by this route.

Most of the phosphate filtered at the glomeruli is reabsorbed by the proximal tubules, and this system is important for the control of phosphate homeostasis. Gastrointestinal loss of phosphate accounts for about 10% of the body's phosphate excretion.[40]

Phosphate is essential for cell function and has many physiologic actions. It is an important intracellular buffer and is essential for buffering hydrogen ions in urine. Phosphate has a structural role as a component of phospholipids, nucleoproteins, and nucleic acids. In addition, phosphate plays a central role in cellular metabolic pathways including glycolysis and oxidative phosphorylation.[41] A byproduct of glycolysis is 2,3-diphosphoglycerate. This compound is a regulator of the dissociation of oxygen from hemoglobin and subsequently the delivery of oxygen to the tissues and accounts for about 80% of organic phosphate in erythrocytes.[42] Further, phosphate is involved in many enzymatic processes, with protein phosphorylation being an important control mechanism for enzyme action. Nucleotides such as adenosine triphosphate contain phosphate.

Other roles are excitation–stimulus response coupling and nervous-system conduction. Clinically important is the role of phosphate in the optimal function of leukocytes, e.g., chemotaxis and phagocytosis, and platelets, where phosphate has a role in clot retraction.[43]

Severe hypophosphatemia, often considered a plasma inorganic phosphate with a concentration below 0.30 mmol/L, can result in a plethora of clinical manifestations. In most cases, the effects are the result of impaired cellular-energy pathways such as adenosine triphosphate or reduced erythrocyte 2,3-diphosphoglycerate. In practice, however, it is rare to see such a degree of severe hypophosphatemia; most cases are clinically insignificant.[44]

Rhabdomyolysis has been described, as impaired skeletal-muscle function, including weakness and myopathy. Hypophosphatemia has been reported to impair diaphragmatic contractility and might help to explain the difficulty in weaning patients from mechanical ventilators who have low plasma phosphate concentrations.[45] Cardiomyopathy is another possible complication of severe hypophosphatemia.

The nervous system does not escape hypophosphatemia, as shown by seizures, perturbed mental state, and paresthesia. Prolonged hypophosphatemia, not unexpectedly, can lead to osteomalacia. Renal tubular impairment can be precipitated by hypophosphatemia, and acute tubular necrosis can result secondary to rhabdomyolysis.

The hematologic effects caused by severe hypophosphatemia are thrombocytopenia, impaired clotting processes, and reduced leukocyte phagocytosis and chemotaxis. Hemolysis also can occur, as can erythrocyte 2,3-diphosphoglycerate depletion, resulting in a leftward shift in the hemoglobin/oxygen dissociation curve, i.e., hemoglobin has a greater affinity for oxygen (Table III).[46–52]

Two cases of fatalities possibly resulting from overzealous total parenteral nutrition provoking a refeeding syndrome have been described where severe hypophosphatemia was implicated.[53] Other reported cases were severe hypophosphatemia associated with the refeeding syndrome and implicated with increased morbidity.[54–58]

Hypomagnesemia

Magnesium is the most abundant intracellular divalent cation and is mandatory for optimal cell function.[59] Magnesium is an essential metal involved as a cofactor to many enzymes. In the body magnesium is found mainly in the bone and muscle. Magnesium is largely absorbed in the upper small intestine and, unlike calcium, its absorption does not depend on vitamin D. As much as 70% of dietary magnesium intake is not absorbed but eliminated in the feces. The major excretory route is through the kidneys.[60]

The refeeding syndrome is associated with hypomagnesemia. The mechanism is not clear and is possibly multifactorial, resulting from intracellular movement of magnesium ions into cells with carbohydrate feeding and poor dietary intake of magnesium. However, preexisting poor magnesium status might exacerbate the degree of hypomagnesemia.[2] Analogous to hypophosphatemia, many cases of hypomagnesemia are not clinically significant, but severe hypomagnesemia (usually plasma concentration < 0.50 mmol/L) can result in clinical complications.

Severe hypomagnesemia can result in cardiac arrhythmias including torsade de pointes. In addition, abdominal discomfort and anorexia have been described, as has neuromuscular features such as tremor, paresthesia, tetany, seizures, irritability, confusion, weakness, and ataxia (Table III).[61–63]

Hypokalemia

Potassium is a predominant monovalent intracellular cation essential for maintaining cell-membrane action potential. Total body potassium is regulated by the kidney. The distal nephron secretes potassium into the urine, which is increased by aldosterone, alkalosis, and a diet high in potassium, and increased delivery of sodium to the distal tubule.[64]

The features of hypokalemia are numerous and consist of cardiac arrhythmias, hypotension, and cardiac arrest. Gastrointestinal upset consists of ileus and constipation. The ability of the kidney to concentrate urine decreases, and there are neuromuscular dysfunctions such as weakness, paralysis, paresthesia, confusion, rhabdomyolysis, and respiratory depression. Other features include potentiation of digitalis toxicity, glucose intolerance, metabolic alkalosis, and worsening of hepatic encephalopathy (Table III).[65–68]

Severe hypokalemia can be defined arbitrarily as a plasma potassium concentration of less than 3.0 mmol/L, at which point clinical complications can become manifest. In keeping with hypophosphatemia and hypomagnesemia, clinical manifestations are rare unless the electrolyte defect is severe. There is a relative paucity of data concerning the relative incidences of clinical manifestations due to electrolyte disturbances in the refeeding syndrome. The situation is not helped by the fact that the clinical features can be subtle and that plasma concentrations, predominantly intracellular ions, do not necessarily reflect their total body stores. Further, the clinical manifestations of these electrolyte disturbances can interact.[65]

CLINICAL RELEVANCE OF THE METABOLIC DERANGEMENTS IN THE REFEEDING SYNDROME

The total incidence of the refeeding syndrome has been put at as high as about 25% in cancer patients who are nutritionally supported.[69] That study also reported that the syndrome was more common in those fed enterally than parentrally and tended to manifest in the first few days after commencement of feeding. Further, it is more common in the elderly, although mortality figures per se are difficult to establish accurately because patients often have other underlying disease states.[70]

The body-fluid imbalances, vitamin deficiencies, and electrolyte disturbances can result in fatal cardiopulmonary dysfunction. Reduction in cardiac-muscle mass leading to impaired cardiac output can be seen in starvation. In particular, congestive cardiac failure can result if the patient is overhydrated and deficient in thiamine. Life-threatening cardiac arrhythmias have been described in anorexia nervosa.[71–73]

The electrolyte disturbances mainly involve intracellular ions, i.e., phosphate, magnesium, and potassium, and can result in potentially fatal cardiac arrhythmias and other clinical complications. Some patients might develop poor ventilatory function,

TABLE III.

CLINICAL CONSEQUENCES OF SEVERE HYPOPHOSPHATEMIA, HYPOMAGNESEMIA, AND HYPOKALEMIA

- Hypophosphatemia
  - Neurologic
    - Fits
    - Weakness
    - Parethesia
    - Altered higher functions
    - Acute encephalopathy
  - Muscular
    - Weakness
    - Myalgia
    - Rhabdomyolysis
    - Decreased cardiac contractility
    - Cardiomyopathy
  - Hematologic
    - Dysfunction of platelets and leukocytes
    - Thrombocytopenia
    - Hemolysis
    - Reduction of erythrocyte 2,3-diphosphoglycerate and adenosine triphosphate
  - Respiratory
    - Impaired respiratory muscle function sometimes resulting in respiratory failure or ventilator dependency
  - Bone
    - Osteomalacia
  - Renal
    - Acute tubular necrosis
    - Tubular defects
- Hypomagnesemia
  - Neurologic
    - Tetany
    - Paresthesiae
    - Seizures
    - Ataxia
    - Tremor
    - Weakness
  - Cardiac
    - Arrhythmias, e.g., torsade de pointes
    - Hypertension
  - Gastrointestinal
    - Anorexia
    - Abdominal pain
  - Electrolyte
    - Hypokalemia
    - Hypocalcemia
- Hypokalemia
  - Neurologic
    - Paralysis
    - Paresthesia
    - Rhabdomyolysis
    - Respiratory depression
    - Weakness
  - Cardiac
    - Arrhythmias
    - Hypotension
    - Digoxin toxicity
    - Cardiac arrest
  - Gastrointestinal
    - Constipation
    - Paralytic ileus
  - Renal
    - Decreased urinary concentrating ability
  - Metabolic
    - Metabolic alkalosis
    - Glucose intolerance

respiratory failure, or neurologic complications such as delirium, neuropathy, or seizures.[74,75]

These electrolyte disturbances per se seem to be similar to those observed in poorly controlled diabetes mellitus.[76,77] Where disorders of fluid balance and electrolytes are often seen. In addition, there may be derangements of trace elements in the refeeding syndrome, and this idea needs further research particularly with regard to low plasma selenium (Crook M, unpublished observations).

PREVENTION AND MANAGEMENT OF THE REFEEDING SYNDROME

Not all patients who are refed develop the refeeding syndrome. It is important to be aware of the condition and anticipate problems to help minimize its occurrence. Hospital nutrition teams have an important role in the recognition, education, and management of the refeeding syndrome.[78] It is important to closely monitor at-risk patients, in particular their vital functions, fluid balance, and plasma electrolytes including magnesium and phosphate. Electrocardiographic monitoring can be useful in facilitating the detection of life-threatening arrhythmias. A tachycardia has been reported to be a useful sign in detecting cardiac stress in the refeeding syndrome.

Plasma electrolytes, in particular sodium, potassium, phosphate, and magnesium, should be monitored before and during refeeding, as should plasma glucose and urinary electrolytes. In the case of urinary electrolytes, a urine sodium concentration of less than 10 mmol/L might indicate saline depletion, and the determination of urine magnesium, phosphate, and potassium can be useful to help assess body losses of these electrolytes.[79–81]Before refeeding, electrolyte disorders should be corrected and the circulatory volume carefully restored. In practice this can delay administration of nutrition but usually can be accomplished within the first 12 to 24 h.

Vitamin and trace-element deficiencies also should be corrected; specifically, 50 to 250 mg of thiamine should be given at least 30 min before refeeding is instigated. More thiamine might be necessary until the patient is stabilized. Some preparations containing thiamine, e.g., Pabrinex, have been associated with anaphylaxis, thus facilities for treating this should be readily at hand. There is no universal agreement as to the exact dose of thiamine to administer, although it is possible to give one pair of Pabrinex ampules once daily for 48 h or until oral thiamine can be taken. Oral thiamine can be given as 100-mg tablets once daily. Some clinicians also give 5 mg of folate daily, although this does not necessarily prevent the refeeding syndrome.

The calorie repletion should be slow at approximately 20 kcal/kg per day or, on average, 1000 kcal/d initially. However, this rate may not meet patients' fluid, sodium, potassium, or vitamin requirements unless these are specifically addressed. The usual protein requirement is about 1.2 to 1.5 g/kg or about 0.17 g of nitrogen/kg per day. Gradual introduction of calories, particularly over the first week of refeeding, may be prudent until the patient is metabolically stable.[2]

Treatment of hypophosphatemia is usually not necessary unless the plasma phosphate concentration is less than 0.30 mmol/L or the patient is symptomatic. Assessment is not helped by the fact that phosphate is predominantly an intracellular ion and thus plasma levels do not necessarily reflect total body stores.

An editorial in 1981 suggested that severe hypophosphatemia should be treated.[82] Oral phosphate salts have been used, but diarrhea can be a problem. The recommendation was to use intravenous phosphate replacement with the Vannatta regime.[83] The Vannatta regime provides 9 mmol of monobasic potassium phosphate in half-normal saline by continuous intravenous infusion over 12 h. This should not be given to patients with hypercalcemia because of the risk of metastatic calcification or to patients with hyperkalemia.

Plasma phosphate, calcium, magnesium, and potassium should be monitored closely and the infusion stopped once the plasma phosphate concentration exceeds 0.30 mmol/L.[84] Monitoring urine output is also important. There has been continued debate about the treatment of severe hypophosphatemia, as illustrated by a patient who had been given 50 mmol/L of intravenous phosphate as recommended in the old British National Formulary in preference to the Vannatta regime.[85] This patient developed severe hyperphosphatemia with hypocalcemia and needed hemodialysis.

Hypomagnesemia, usually defined as less than 0.5 mmol/L or if symptomatic, can be corrected by oral magnesium salts, but these can be poorly absorbed and lead to gastrointestinal upset. Intravenous replacement often is given as magnesium sulfate (50% solution containing 2.1 mmol/mL). In general, 24 mmol of magnesium sulfate can be administered over 6 h. Close monitoring of plasma magnesium is necessary. The treatment of hypomagnesemia can facilitate the treatment of refractory hypokalemia.[86–88] Plasma calcium concentration also should be checked.

Hypokalemia can be corrected by cautious intravenous potassium administration. Ideally, the rate should not exceed 20 mmol/h and should not be greater than 40 mmol/L in the intravenous infusion mixture. Close monitoring of plasma potassium is important, preferably with electrocardiographic monitoring.[67,89]

CONCLUSIONS

The refeeding syndrome unfortunately is encountered in modern clinical practice and is relatively poorly recognized or understood. The pathophysiologic processes include disturbances of glucose and fluid balance and electrolyte disorders that involve mainly the intracellular ions, namely phosphate, potassium, and magnesium. Despite being potentially preventable, it is associated with high morbidity and mortality. Nutrition teams can help to provide advice and education in its prevention, recognition, and treatment. Local treatment guidelines should be established to facilitate this.[90]

POSTSCRIPT

Recently, a paper by Faintuch and colleagues in this journal looked at refeeding of hunger-strikers.[91] Using a modified refeeding regime[92,93] they were able to minimize electrolyte disturbances although episodes of diarrhea and some fluid retention were noticed. Interestingly, acute-phase markers were elevated during the refeeding time.

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