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Refeeding syndrome: Problems with definition and management

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ABSTRACT

Refeeding syndrome (RFS) broadly encompasses a severe electrolyte disturbance (principally low serum concentrations of intracellular ions such as phosphate, magnesium, and potassium) and metabolic abnormalities in undernourished patients undergoing refeeding whether orally, enterally, or parenterally. RFS reflects the change from catabolic to anabolic metabolism. RFS sometimes is undiagnosed and unfortunately some clinicians remain oblivious to its presence. This is particularly concerning as RFS is a life-threatening condition, although it need not be so and early recognition reduces morbidity and mortality. Careful patient monitoring and multidiscipline nutrition team management may help to achieve this goal. The diagnosis of RFS is not facilitated by the fact that there is no universal agreement as to its definition. The presence of hypophosphatemia alone does not necessarily mean that RFS is present as there are many other causes for this, as discussed later in this article. RFS is increasingly being recognized in neonates and children. An optimal refeeding regimen for RFS is not universally agreed on due to the paucity of randomized controlled trials in the field.

Introduction

Refeeding syndrome (RFS) broadly encompasses a severe electrolyte disturbance (principally low serum concentrations of the predominately intracellular ions; phosphate, magnesium, and potassium) and metabolic abnormalities in undernourished patients undergoing refeeding whether orally, enterally, or parenterally. In essence, RFS reflects the change from catabolic to anabolic metabolism [1,2].

It has been reported that RFS is a medical condition that can occur despite identification of risk, prompt treatment and hypocaloric nutritional therapy [3]. Results of one study demonstrated that the most reliable predictor of developing RFS is starvation and intravenous (IV) glucose infusion before artificial nutrition support in undernourished patients. However, there is no universal agreement on the definition of RFS, although the following clinical criteria for determination of its risk have been proposed [3].

One of the following features is required:

- Body mass index (BMI) <16 kg/m^2
- Unintentional body weight loss $>15\%$ in the preceding 3 to 6 mo
- Minimal or no significant nutritional intake for >10 d
- Low concentrations of plasma potassium, phosphate, or magnesium before feeding

Or two of the following features are required:

- BMI <18.5 kg/m^2
- Unintentional body weight loss $>10\%$ in the preceding 3 to 6 mo
- Minimal or no significant nutritional intake for >5 d
- Medical history of alcohol or drug abuse [3]

It has been suggested that a precise definition of RFS is difficult as this is a spectrum of abnormalities and that the so-called "full-blown" RFS should be defined by the presence of symptoms [4]. It has also been suggested that a category of potential or biochemical RFS should be recognized that is asymptomatic [4]. However, exactly what is meant by symptoms is debatable and symptoms in RFS may be non-specific, thus making a suggestion for a definition problematic.

In one systematic review, it was noted that RFS is not associated with a consistent pattern of biochemical or clinical abnormalities and that many cases described in the literature may be more appropriately termed *refeeding hypophosphatemia* [5].

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Although this is an important point, there are many other causes of hypophosphatemia that are not necessarily related to RFS. Thus, we need to be aware that hypophosphatemia does not necessarily mean the presence of RFS.

How common is RFS?

The prevalence of RFS has been variably quoted with estimations as wide as 0.43% to 34% in different hospital populations [1,2]. The actual prevalence figure is debatable, however, as some definitions of RFS state the presence of hypophosphatemia, which is relatively common in hospital populations and its presence does not necessarily mean that RFS has occurred. Undernutrition is also variably reported and sometimes misdiagnosed, although its prevalence may be as high as 65% in some hospitalized patients [6,7].

One large hospital-based study [8] reported that the prevalence of severe hypophosphatemia was 0.43% and undernutrition was one of the strongest risk factors for hypophosphatemia; however, this does not necessarily mean the patient has RFS. In a prospective cohort research study [9] of patients in intensive care units, 34% experienced hypophosphatemia soon after refeeding. One study demonstrated that RFS was generally poorly understood and underdiagnosed particularly by trainee doctors, thus leading to an underestimation of prevalence figures [10].

Individuals at particular risk for RFS

One of the first descriptions of RFS was in individuals who were starved in Japanese World War II prison camps on a long-term basis [11]. After being liberated and then refed, some of the prisoners developed RFS associated with peripheral edema and neuropathy [12]. The term *refeeding syndrome* may first have been used after the tragic deaths of two undernourished patients who were apparently refed and developed RFS. In this study, the patients received from glucose approximately 75 kcal/kg of estimated edema-free body weight [13]. Further insight in to the RFS was made in pioneer studies on human starvation and refeeding in healthy volunteers [14]. Although this work was essentially in normal starved volunteers, anorexia nervosa often is used as a “human model” for RFS and valuable information regarding the pathophysiology of refeeding has been gathered by studying this condition, although it may not be representative of all patients with RFS [15].

About half of psychiatric patients are at risk for undernutrition. This patient group is also more at risk for RFS [16]. Indeed, one study [17] showed that early detection and management of refeeding patients with anorexia nervosa who are treated in an intensive care unit might prevent RFS. More recently, researchers in Africa found an association between pretreatment of hypophosphatemia and early antiretroviral therapy in HIV and mortality among undernourished individuals and associated RFS [18,19].

There have been some reports of RFS in children, although more recently cases are being presented in the medical literature. One group [20] described RFS in two children—one with celiac disease and the other cerebral palsy. Another group [21] reported severe hypophosphatemia in severely malnourished children <5 y of age, including those with sepsis and diarrhea. These groups showed that treatment of the hypophosphatemia might have reduced mortality in these children. RFS has been described in children with celiac disease who live in developing countries [22] ad has also been reported to occur in very low-birth-weight babies who had interuterine growth restriction and were born to mothers with preeclampsia [23]. A good predictor of developing RFS in pediatric patients is a body weight <80% of the ideal [24]. RFS in a small-for-date micropreemie initiated on parenteral nutrition [25] also has been reported. Enhanced feeding of very low-birth-weight neonates may induce electrolyte imbalances such as hypophosphatemia and hypokalemia and these electrolyte disturbances may be associated with sepsis [26].

As Table 1 depicts, there are numerous patient groups at risk for RFS. Recently topical and also perhaps ironic is the observation that RFS may be seen after bariatric surgery for severe obesity. Hunger strikers and those who undergo prolonged fasting also may be more susceptible to RFS [1,2,14,15]. Clinicians in a variety of medical specialities, therefore, need to be vigilant in recognizing and appropriately managing RFS.

Pathophysiology of RFS

Starvation can be broadly defined as a catabolic state where the body shifts to fat and protein metabolism from carbohydrate utilization. Plasma insulin concentrations decrease while glucagon increases during starvation, resulting in the rapid conversion of glycogen stores to form glucose for cell energy. Additionally, gluconeogenesis, resulting in glucose synthesis via lipid and protein breakdown products increases. The essential amino acid alanine has a central role in gluconeogenic pathways. The brain, renal medulla, and erythrocytes, for example, are obligate utilizers of glucose as an energy source [1–3]. Adipocytes release fatty acids and glycerol, whereas muscle myocytes release amino acids such as alanine to help fuel these metabolic pathways [1–3]. Ketone bodies and free fatty acids replace glucose as a major energy source in human starvation. Overall, in starvation there is catabolism of adipose tissue and muscle, resulting in loss of lean body mass [1–5,9].

Undernutrition is a predominant feature in patients with RFS. In prolonged starvation (usually weeks to months), glycogen stores are depleted. This allows conservation of proteins as these have essential metabolic and structural functions and thus lipids preferentially become the principle source of energy in prolonged starvation [1–5].

Cell volume of various organs such as the brain, heart, and liver, as well as muscle, decreases as a result of undernutrition; the reason for this is postulated as being due to the loss of intracellular storage macromolecules such as protein and glycogen as part of adaptation of the cells to fat metabolism. Additionally, intracellular ions, principally those of phosphate,

Table 1
High risk for refeeding syndrome

Conditions
Bariatric surgery
Chronic alcoholism or drug abuse
Chronic infection (e.g., HIV)
Dysphagia and esophageal dysmotility
Eating disorders (e.g., anorexia nervosa)
Hyperemesis gravidum
Inflammatory bowel disease
Low-birth-weight and premature birth
Malabsorptive states (e.g., celiac disease)
Malignant disease
Older age (e.g., > 70 years)
Prolonged fasting (e.g., individuals on hunger strikes)
Protracted vomiting
Short bowel syndrome
Undernourishment such as is present in kwashiorkor and marasmus

magnesium, and potassium, are lost from the body. Once metabolic adaptation has occurred, survival may be maintained for several months, the exact duration of which is in part dependent on the size of useable adipose deposits [1–5]. To conserve energy during starvation, the human body may become bradycardic and hypotensive, whereas the basal metabolic rate decreases by about 25% [9].

Introduction of energy can evoke RFS because during refeeding the body converts from catabolism to anabolism and switches back to carbohydrate metabolism. Thus, during refeeding, a physiological shift from fat to carbohydrate metabolism takes place. This elicits insulin release, resulting in cellular uptake of glucose, phosphate, potassium, and magnesium ions (the latter three being predominately intracellular ions). Sometimes fluid retention occurs, thereby increasing the extracellular fluid volume.

It has been suggested that plasma insulin-like growth factor (IGF)-1 and leptin concentrations may be diagnostic markers of RFS and its associated mortality; this is relevant and further research would be helpful to establish whether the measurement of IGF-1 and leptin may be useful in the diagnosis and definition of RFS [27]. It has been suggested [28] that monitoring serum leptin concentration also may be useful in diagnosing RFS. Ghrelin, a gastric hormone, has been recommended as a possible therapy and plasma marker for RFS because it may slow body weight loss and enhance weight gain [28,29]. Adiopocyte fatty acid-binding protein (AFABP) 1 has been reported [30] as being abnormal in an animal model of refeeding, thus offering potential as a diagnostic test if confirmed in humans. Another possible biochemical marker is prealbumin whose plasma concentrations could predict the development of refeeding hypophosphatemia in the critically ill. In one study low plasma concentrations of prealbumin reflected protein malnutrition [31]. Additionally, abnormal liver function occurred and serum IGF-1 and insulin concentrations were reduced, as were the appetite-regulating hormones leptin and ghrelin. It was also reported that refeeding caused reduced serum free fatty acid concentrations and an abnormal increase in serum ketone bodies [31]. Results from another study showed that undernutrition resulted in higher concentrations of monocarboxylic carnitine fatty acids and upon refeeding, a decrease in all carnitine fatty acids was observed [32].

Clinical features of refeeding syndrome

There are various features of RFS that have been discussed previously [1–5]. However, broadly speaking, the features of RFS consist of severe electrolyte disturbance (principally low plasma concentrations of intracellular ions phosphate, magnesium, and potassium) and various metabolic abnormalities. Some of the changes of serum electrolyte concentrations may be a normal response to refeeding and may not necessarily cause patient harm and symptoms. However, there are numerous reports in the literature of clinical sequelae that may present in RFS. Table 2 depicts some of these clinical features of RFS.

Hypophosphatemia

Hypophosphatemia (<0.80 mmol/L) is a major feature of RFS, although its presence in undernourished patients does not necessarily mean that RFS has occurred. In fact, there are many causes of hypophosphatemia (Table 3). Aggressive refeeding in patients with anorexia nervosa using up to 2200 kcal did not result in severe hypophosphatemia (<0.30 mmol/L) [33]. The severity of undernutrition is more a marker of refeeding hypophosphatemia than the total energy intake (TEI) when refeeding adolescents with anorexia nervosa [34].

Table 2
Clinical features of refeeding syndrome

Features
Acute encephalopathy
Acute tubular necrosis
Anemia
Ataxia
Cardiac arrhythmias
Central pontine myelinolysis
Coma
Congestive heart failure
Constipation
Delirium
Diaphragm and intercostals and other muscle weakness
Hyperglycemia
Increased risk for infections
Increased risk for renal impairment; acute or chronic kidney disease
Korsakov's psychosis
Liver failure or hepatic function tests abnormality
Metabolic acidosis; lactic acidosis
Myalgia or lassitude
Osteomalacia
Parasthesia
Peripheral neuropathy
Respiratory failure
Rhabdomyolysis
Sudden death
Thrombocytopenia
Ventilator dependency
Vomiting or nausea
Wernicke's encephalopathy

Changes in serum magnesium and phosphate concentrations in older patients do not correlate with changes in muscle strength and risk factors for RFS do not predict the decrease in serum phosphate or magnesium concentration [35]. High energy refeeding has been associated with reduced hospital length of stay, but not increased rate of body weight gain or likelihood of hypophosphatemia, hypomagnesemia, or hypokalemia [36]. Refeeding hypophosphatemia thus appears to depend on the degree of undernutrition but not the refeeding energy intake per se. These observations have been supported previously in a study that also demonstrated that a higher initial caloric refeeding intake achieved rapid and safe nutritional rehabilitation in undernourished patients [37].

Table 3
Other causes of hypophosphatemia [1,42]

Causes
Cellular phosphate redistribution
• Administration of insulin
• Alkalemia (metabolic or respiratory alkalosis)
• Intravenous glucose (most common cause)
Poor phosphate intake
• Chronic alcoholism
• Malabsorption states
• Phosphate binding medications
• Post-trauma
Renal tubular phosphate loss
• Fanconi syndrome
• Hypophosphatemic osteomalacia
• Oncogenic hypophosphatemia
• Paracetamol poisoning
• X-linked hypophosphatemia
Miscellaneous
• Hyperparathyroidism or parathyroid hormone-related peptide release
• Liver disease
• Septicemia

Hypophosphatemia can occur surprisingly quickly, sometimes within 48 h of undernutrition followed by refeeding in critically ill intensive care patients. As such, clinicians need to be vigilant. Hypophosphatemia is associated with reduced patient survival in RFS. This may not be surprising given the ubiquitous actions of phosphate in humans [38]. Phosphate is the major intracellular divalent anion and is a vitally important intracellular buffer as well as essential for buffering hydrogen ions in urine. Additionally, it has a major structural role as a component of phospholipids, nucleoproteins, and nucleic acids.

Phosphate has a mandatory role in essential metabolic pathways, including glycolysis and oxidative phosphorylation. Indeed, 2,3-diphosphoglycerate is a metabolite of glycolysis and is a regulator of hemoglobin oxygen dissociation. Nucleotides, essential for cell function, such as adenosine triphosphate also contain phosphate. Other actions of phosphate include excitation-stimulus response coupling and nervous system conduction, as well as chemotaxis and phagocytosis. Phosphate also is important for platelet function such as aggregation [39–42].

There is no universal agreement as to the optimal method of treating severe hypophosphatemia in RFS. Some phosphate replacement regimens are not always adequate in correcting hypophosphatemia. Oral phosphate salts have been used in non-severe cases of hypophosphatemia, although diarrhea and nausea may be problematic. The Vannatta regimen uses 9 mmol of monobasic potassium phosphate in half-normal saline by continuous IV infusion over 12 h. This is contraindicated in patients with hypercalcemia because of the risk for metastatic calcification and to patients with hyperkalemia given its potassium content. The administration of potassium phosphate 15 mmol to patients with hypophosphatemia was reported to be efficient when some replacement therapies are based on a graduated dosing scheme using patient body weight. Another phosphate replacement regimen that may be useful in RFS is 50 mmol of IV phosphate infusion, given as a "Phosphates Polyfusor" to those with hypophosphatemia [41] (Table 3).

Hypomagnesemia

The development of hypomagnesemia (<0.70 mmol/L) is a predictor of developing RFS [3]. Some of the numerous causes of hypomagnesemia, apart from RFS, are shown in Table 4 [1,42]. Magnesium, like phosphate and potassium, is mainly an intracellular ion and an essential cofactor for various enzymes as well as involved in cell membrane function and cell structure.

Hypomagnesemia can result in potentially lethal cardiac arrhythmias and seizures. Additionally, abdominal pain and anorexia may occur, as well as neuromuscular abnormalities including ataxia, confusion, paraesthesia, tetany, tremor, vertigo, and weakness. Severe hypomagnesemia can lead also to hypocalcemia probably as a result of decreased parathyroid hormone action and also refractory hypokalemia [1,42].

Severe hypomagnesemia (<0.50 mmol/L) can be corrected by oral magnesium therapy but this may be poorly absorbed and lead to gastrointestinal (GI) disturbance such as diarrhea. A possible regimen could be oral magnesium gluconate 12 mmol/d, in three or four divided doses. However, IV replacement in RFS often is given as magnesium sulphate such as 0.5 mmol/kg daily. Close monitoring of plasma magnesium is essential to avoid undertherapy or overshoot hypermagnesemia [1,42]. It has also been reported that more than 25% of patients with RFS manifested hypocalcemia [5]. The mechanism is unclear although magnesium is needed for the optimal action of parathyroid hormone.

Table 4
Other causes of hypomagnesemia [1,42]

Causes
Cellular magnesium redistribution
• Excess of catecholamines
• "Hungry" bone syndrome
Drugs
• Aminoglycosides
• β_2-adrenergic agonists
• Cyclosporin and tacrolimus
• Cytotoxics
• Diuretics
• Pamidronate, pentamidine, amphotericin B, foscarnet
• Proton pump inhibitors (e.g., omeprazole)
Increased renal loss of magnesium
• Bartter and Gitelman syndromes
• Postrenal transplantation
• Renal dialysis
Poor magnesium intake
• Gastrointestinal fistulae
• Intestinal resection
• Malabsorption states
• Starvation/undernutrition
Miscellaneous
• Alcoholism
• Diabetes mellitus
• Hyperaldosteronism
• Hypercalcemia
• Hyperthyroidism

Hypokalemia

Like phosphate and magnesium ions, potassium ions are also predominately intracellular and hypokalemia may be another metabolic feature of RFS, although not exclusively so and there also are many other causes for this (Table 5). Potassium is an essential univalent cation for optimal cell membrane function.

Table 5
Other causes of hypokalemia [1,42]

Causes
Redistribution of potassium ions
• Catecholamines
• Glucose and insulin
• Familial hypokalemic periodic paralysis
• Barium intoxication
• Vitamin B_{12} therapy
• Rapidly growing tumors
• Reduced intake (e.g., poor diet or geophagia)
Gastrointestinal loss of potassium
• Intestinal loss
• Diarrhea
• Intestinal fistual
• Purgative abuse
• Pyloric stenosis
• Vomiting
Renal potassium loss
• Mineralocorticoid excess conditions
• 11-hydroxylase and 17-hydroxylase deficiencies (rare)
• Bartter or Gitelman syndrome
• Cushing's syndrome
• Licorice excess
• Liddle syndrome (pseudohyperaldosteronism)
Renal tubule mechanisms
• Alkalemia
• Carbonic dehydratase inhibitors
• Fanconi syndrome
• Severe hypomagnesemia (see Table 4)
• Diuretics such as "loop"
• Renal tubular acidosis (Types I and II)

The sodium-potassium adenosine triphosphatase pump on cell surface membranes ensures a high intracellular potassium concentration and potassium ions are exchanged for protons and thus potassium is essential in acid–base balance [1,42].

Hypokalemia (<3.5 mmol/L) can be associated with numerous clinical features including arrhythmias, constipation, hypotonia, and muscular weakness. Severe hypokalemia (<2.5 mmol/L) can precipitate hepatic encephalopathy, paralytic ileus, renal tubule damage, and rhabdomyolysis as well as a metabolic alkalosis. There are numerous causes of hypokalemia, in addition to RFS, some of which are depicted in Table 5 [1,42].

Oral potassium therapy can cause GI upset. IV potassium replacement usually should not be given at an infusion rate of more than 20 mmol/h and ideally should be given closely monitored by blood testing and administered using an infusion pump because of the risk for overshoot hyperkalemia. In very severe potassium depletion, this dose may have to be exceeded; in such cases frequent plasma potassium estimations should be performed under electrocardiogram monitoring [1,42]. It is important to ensure that hypomagnesemia is treated in cases of refractory hypokalemia.

Thiamine and other vitamin deficiencies

Humans cannot synthesize thiamine (vitamin B_1) although it is a constituent of many foodstuffs such as certain cereals and yeast. Thiamine is an essential cofactor for various metabolic pathways such as the decarboxylation of 2-oxoacids; involved in the conversion of pyruvate to acetyl coenzyme-A and is also an essential cofactor for transketolase in the pentose-phosphate pathway. Thiamine deficiency can result in beri-beri as well as a metabolic acidosis and more specifically a lactic acidosis. Indeed, a high anion gap metabolic acidosis also has been reported in RFS [43].

Thiamine deficiency can be observed in RFS and responsible for its associated morbidity and mortality, for example, Korsakov's psychosis or Wernicke's encephalopathy syndrome. These clinical situations may result in ataxia, coma, confusion, ocular disturbance, and seizures, as well as with short-term memory loss and confabulation. Carbohydrate administration can cause increased cellular thiamine utilization because it is a cofactor for various enzymatic activities discussed previously [1,2]. Importantly, it has been shown that individuals on prolonged hunger strikers had lower morbidity and mortality when given vitamin B supplementation [44].

In addition to thiamine, vitamins B_{12} and B_6 were also reduced after refeeding in undernourishment [31]. Other biochemical findings of RFS also may consist of reduced folate and vitamin B_{12} concentrations, although the mechanisms for this are unclear and may reflect low body stores as a result of undernutrition before refeeding.

Vitamin supplementation also should be started with refeeding and continued for at least 10 d [1–3]. It has been suggested that before feeding starts, 200 to 300 mg of oral thiamine be administered daily, as well as one to two tablets of high-potency vitamin B three times daily (or full-dose IV vitamin B), and a daily multivitamin or trace element supplement [45].

Trace metal deficiencies

It has been demonstrated that low plasma selenium and copper concentrations may occur in RFS [31]. However, it also can be difficult to interpret the results of certain trace element plasma concentrations, which may decrease in the presence of an acute-phase response that may occur in some patients at risk for RFS. It has been recommended that before feeding starts, in addition to thiamine replacement, trace element supplementation should be given daily, in addition to thiamine replacement [45].

Fluid balance abnormalities

RFS can result in fluid balance abnormalities, which can lead to cardiac failure, dehydration or conversely fluid overload, hypotension, acute kidney injury, and sudden death. Refeeding with predominantly carbohydrate replacement can reduce water and sodium excretion, resulting in expansion of the extracellular fluid compartment and weight gain.

High protein feeding can result in hypernatremia associated with hypertonic dehydration [1–5]. An insulin surge occurs after refeeding and this stimulates intracellular movement of potassium, magnesium, and phosphate ions, thus potentiating hypokalemia, hypomagnesemia, and hypophosphatemia, respectively. To maintain electroneutrality of the extracellular space, retention of sodium and water occurs and peripheral edema also can develop in RFS. A low-sodium diet is recommended as part of refeeding in patients with anorexia nervosa to help avoid RFS fluid overload [46]. Correction of electrolyte and fluid imbalances before refeeding is not necessary and may cause delay; thus ideally this should be done concomitantly [47].

Glucose and lipid imbalance

IV glucose infusion before artificial nutrition support can precipitate RFS [3]. After starvation, glucose administration can suppress gluconeogenesis, resulting in reduced amino acid (predominately alanine) usage and lead to a reduced negative nitrogen balance. Starvation can evoke hypoglycemia, although glucose can be converted to fat via lipogenesis and further administration can cause hyperglycemia, which can evoke hyperosmolar nonketotic coma, ketoacidosis, and metabolic acidosis, osmotic diuresis, and dehydration. There are thus similarities with RFS and diabetic ketoacidosis [48]. Severe illness such as sepsis may cause insulin resistance, thus exacerbating hyperglycemia. However, hyperglycemia can result in infection and impaired immune function [49]. High glucose-containing feeds can elicit a higher respiratory quotient resulting in increased carbon dioxide production, hypercapnia, and respiratory failure in some patients, particularly those with existing pulmonary disease [50].

It is important that the administered fat does not exceed the maximum daily lipid-elimination capacity, which is probably about 3.8 g of lipid/kg of body weight in adults. This is particularly relevant because this threshold can be reduced in critically ill patients. Excess of fat intake can evoke fat overload syndromes such as fatty liver, fever, hypertriglyceridemia, and thrombocytopenia; whereas excessive glucose administration can result in potentially lethal cardiac arrhythmias [51].

Management of patients with RFS

It is generally agreed that prevention and management of RFS includes identification of individuals at risk, thoroughly monitored nutritional intake, and careful electrolyte and fluid replacement by an experienced multidiscipline team. The following is a summary of the possible management of RFS [52–60].

Recognize patients at risk for RFS (Table 1)

Identification of high-risk patients and management by a multidiscipline nutrition team may help reduce complications of RFS [61–63].

Careful assessment of fluid balance, sodium balance, and renal function and watching for the various clinical features of RFS (Table 2)

Fluid balance should be adjusted as needed to achieve adequate hydration and daily weights should be carefully measured to prevent fluid overload. Some recent evidence shows that low sodium intake may reduce refeeding edema [46]. If hyponatremia is present, it is essential that rapid correction be avoided to reduce the risk for central pontine myelinolysis. Patients with RFS are also more at risk for renal abnormality and thus renal function should be carefully monitored.

Electrolyte deficiency and acid–base correction

Correction of electrolyte and fluid imbalances, as well as magnesium, potassium, and phosphate requirements before refeeding is not necessary. Instead this should be done alongside refeeding so as not to delay energy replacement [45].

Careful assessment of acid–base balance including plasma lactic acid concentration is important. Furthermore, plasma sodium, potassium, bicarbonate, and chloride concentrations are required so as to calculate a plasma anion gap. A high plasma anion gap metabolic acidosis such as a lactic acidosis can occur in thiamine deficiency.

Patients should be assessed carefully for hypophosphatemia, hypomagnesemia, and hypokalemia daily during refeeding until stable. Patients should be rehydrated carefully and supplemented and/or correct serum concentrations of potassium (give 2–4 mmol/kg), phosphate (0.3–0.6 mmol/kg), calcium, and magnesium (0.2 mmol/kg intravenously or 0.4 mmol/kg orally) should be given daily [45].

Vitamin supplementation

Some guidelines recommend that vitamin supplementation should be started immediately, before and for the first 10 d of refeeding. It has been recommended that before feeding starts, oral thiamine 200 to 300 mg daily, one to two tablets high-potency vitamin B three times daily, and once-daily multivitamin supplements be administered [45]. However, because there is a rare but potential risk for anaphylaxis with Pabrinex (thiamine-containing vitamin replacement), close supervision and resuscitation facilities should be available if administered.

Patients also should be monitored for serum ferritin, vitamin B_{12}, and folate concentrations.

It is rarely necessary to confirm thiamine deficiency with biochemical tests, as these are generally specialized assays not offered by all laboratories.

Energy replacement

There are some suggestions that RFS is more likely to occur when carbohydrate is given as the predominate refeeding energy source [64]. RFS also may be more common in those refed enterally than those refed parenterally [65]. It has been postulated that the reason for these observations is related to the incretin system's involvement in the GI tract involving glucose metabolism. Evidence has been found that the actual feed composition is important regarding development of RFS and that low amino acid intake may be less likely to be associated with hypophosphatemia [66].

Thus, the composition of the refeeding nutrition may be more important than the energy content and by giving less carbohydrate than previously recommended, for example, limits this to a maximum of 40% of the TEI. The usual daily protein requirement is about 1.2 to 1.5 g/kg, or about 0.17 g nitrogen/kg. Fat intake should not exceed the maximum daily lipid-elimination capacity, which is about 3.8 g of lipid/Kg of body weight in adult humans. Some patients may not clear the lipid component of the feed with parenteral nutrition. This can be monitored by measuring the patient's plasma triglyceride concentrations.

Current guidelines generally recommend slow, low-energy refeeding to avoid RFS; indeed the National Institute for Clinical Excellence (NICE) proposes a gradual increase in energy intake, with weekly body weight gain of 0.5 to 1 kg where the initial energy refeeding intake is below daily requirements [67]. The slow introduction of energy was also recommended in a review on RFS. The review suggested starting refeeding with 0.0418 MJ/kg daily given slowly and increasing over 4 to 7 d or if the patient is severely undernourished (e.g., BMI <14 kg/m^2) or if intake is minimal for >2 wk. Refeeding should then commence at a maximum of 0.0209 MJ/kg daily [45].

The danger is that refeeding that is too cautious can result in underfeeding syndrome, which is when patients can experience increased morbidity and mortality as a result of insufficient energy intake. However, the MARSIPAN (Management of Really Sick Patients with Anorexia Nervosa) report [68] and a number of studies in patients with severe anorexia nervosa have shown that high-energy intakes of 40 kcal/kg body weight did not result in RFS [33,69–72]. Before the NICE guidelines [67], some authors had recommended a far more conservative approach of 20 kcal/kg body weight or 50% of estimated energy requirements to avoid RFS.

Thus, some researchers have highlighted a dichotomy; namely treating undernutrition too aggressively and provoking RFS versus trying to avoid "underfeeding" caused by an overly cautious refeeding approach. In a perceptive paper [34], the authors noted that there is no evidence supporting some of the current guidelines that refeeding with 10 to 60 kcal/kg based on 25% to 75% of TEI reduces the risk for RFS. They also suggested that more important than energy amount may be the TEI from glucose. Thus, reducing the glucose and possibly increasing the fat content of refeeding regimens for undernourished patients may minimize the insulin surge associated with refeeding, thus in theory, reducing the risk for RFS.

On a similar theme, one study [73] has suggested modifications to current RFS guidelines so as to limit to a maximum of 40% the TEI from carbohydrate with a minimum daily intake of 2000 kcal titrated up to 2700 kcal after week 1 of refeeding. Further support for this comes from recent publications that suggest the risk for developing RFS may not be reduced by feeding slowly with low-energy feeds [33,34] and also goes against the conventional wisdom of starting energy refeeding "low and slow," as this may prolong nutritional recovery. These studies also imply that the type of feed, such as avoiding $<40\%$ energy as carbohydrate, is more important than energy given per se. Furthermore, it has been reported that refeeding hypophosphatemia was dependent on the severity of undernutrition but not the caloric intake given on refeeding [74]. However, currently one cannot recommend a change in the NICE guidelines [67] regarding this unless more high-quality randomized controlled trials rather than observational studies are performed.

Trace metals supplementation

"Loading" doses should be given when appropriate, followed by maintenance doses of, in particular, zinc (2.5–5 mg/d), selenium (20–70 mg/d), manganese (3.5–7 mg/d), and copper (0.3–0.5 mg/d) [75,76]. Plasma concentrations should be measured initially and then perhaps every 1 to 2 wk if these assays are available. It can sometimes be difficult to interpret plasma concentrations of certain trace metals in severely ill patients due to changes in their concentrations as a result of the acute-phase response (e.g., in the presence of a raised plasma C-reactive protein levels).

Patient monitoring

Mandatory close monitoring of patients should be undertaken for daily body weight, daily urine output, and optimization of fluid balance to prevent fluid overload such as cardiac failure (i.e., body fluid input versus fluid output) [75–77]. An apparently unique case of RFS in a marine recruit who was previously healthy but had undergone an arduous exercise program with energy restriction, has been reported, thus illustrating that RFS can occur quickly in formerly well individuals [78]. This case report illustrates that it can be difficult to predict who may develop RFS and that RFS can develop surprisingly quickly in even previously healthy individuals (in this case 8.8% of the patient's original body weight was lost).

Daily monitoring of patient's vital functions is essential. For example tachycardia might be a sign of impending cardiac failure. In this context electrocardiogram monitoring is useful during refeeding. Patients are more at risk for infection, which also should be vigilantly monitored. Plasma glucose should be monitored daily and maintained to prevent hypoglycemia or hyperglycemia. "Rebound" hypoglycemia can occur when parenteral feed is stopped unless it is titrated down gradually. Hypoglycemia also can occur during starvation.

Plasma albumin, protein, calcium, and the full blood count, including hemoglobin, white blood cells and platelets, also should be monitored. Similarly, liver function tests also should be monitored because hepatic dysfunction can occur in RFS [77].

Summary

RFS sometimes remains undiagnosed and unfortunately some clinicians are unaware of its presence. This is particularly concerning as RFS is a life-threatening condition, although it need not be so and early recognition may reduce complications, fatal or otherwise [33,66–71]. Close vigilance, careful patient monitoring, and management by a multidiscipline nutrition team may help to achieve this goal. The diagnosis of RFS is not facilitated by the fact that there is no universal agreement as to its definition. The presence of hypophosphatemia alone does not necessarily mean that RFS is present as there are many other causes. Furthermore, the optimal refeeding regimen for RFS is still not universally agreed on as slow low-energy feeding may prolong patient recovery and increase the risk for morbidity in some patients, whereas rapid high-energy feeding may worsen the associated metabolic sequelae. However, because of a lack of randomized controlled trials, it is currently premature to recommend a change in the NICE guidelines [67].

Conclusion

A significant number of cases in the literature reported to be RFS do not necessarily have associated symptoms as previously defined [4]. This poses the question as to whether these patients really did have RFS. Many of the reports of RFS in the literature may be more appropriately referred to as "refeeding hypophosphatemia" [5] because these patients do not always display all of the clinical features described for RFS. RFS is increasingly being recognized in neonates and children.

Uncertainties regarding the diagnosis and management of RFS may be improved by the following suggestions for possible future research:

1. A universal consensus on a definition for RFS.
2. The importance of low- versus high-energy intake refeeding should be studied in randomized controlled trials.
3. Determining the optimal refeeding nutritional composition (e.g., is less carbohydrate better for patients with RFS?).
4. What is the best way to correct refeeding hypophosphatemia?
5. Is there a place for biochemical markers such as AFABP, ghrelin, IGF-1, or leptin in the diagnosing of RFS and in assessing prognosis?
6. Increasing the awareness of clinicians toward earlier recognition and appropriate management of RFS.
7. Further study of different patient groups at risk for RFS including neonates and children could add to the understanding of this condition, as most research in RFS has been in adult patients.
8. Anorexia nervosa is frequently reported on in the literature as a cause of RFS and used as a model to investigate its etiology and management. However, this condition may not necessarily apply to other individuals susceptible to RFS.

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