Refeeding syndrome in a woman with pancreatitis: a case report

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Abstract
Refeeding syndrome can occur in malnourished patients with acute pancreatitis who have electrolyte imbalances. Refeeding syndrome is characterized by severe electrolyte imbalances (mainly hypophosphatemia, hypomagnesemia, and hypokalemia), vitamin deficiency (mainly thiamine deficiency), fluid overload, and salt retention resulting in organ dysfunction and cardiac arrhythmias. We herein report a case involving a patient with severe pancreatitis and gallbladder stones who developed refeeding syndrome with shock and loss of consciousness. The patient was treated by opportune vitamin and electrolyte supplementation therapy and showed substantial improvement after 2 weeks of hospitalization, gaining the ability to eat small bites of solid food orally. Early diagnosis and treatment of refeeding syndrome may reduce morbidity and mortality in patients with acute pancreatitis. Patients should be fasted only if alimentation is contraindicated, and electrolyte values must be closely monitored.

Keywords
Refeeding syndrome, nutritional therapy, metabolism, pancreatitis, electrolyte imbalance, case report

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Introduction
Acute pancreatitis (AP) is an inflammatory disorder of the pancreas. Its diagnosis is
based on severe abdominal pain, a lipase concentration three times higher than the upper limit of the reference range, and characteristic pancreatic imaging findings.\textsuperscript{1} AP is the most common cause of acute hospitalization among all gastrointestinal disorders, with a prevalence of 10 to 100 per 100,000 cases worldwide.\textsuperscript{2} The two most common causes of AP are gallstones and excessive alcohol intake, but AP can also be caused by infectious disease, drugs, and metabolic causes such as hypercalcemia and hypertriglyceridemia.\textsuperscript{3}

No specific treatments are available for AP; management is focused on supportive interventions such as fluid resuscitation and nutritional intervention with the aim of reducing complications and modifying the course of the disease.\textsuperscript{4} A potential risk associated with nutritional therapy in undernourished patients is the development of refeeding syndrome (RFS), a lethal clinical complication caused by metabolic disturbances and electrolyte shifts that occur during early nutritional rehabilitation.\textsuperscript{5} Notably, RFS reflects the change from catabolic to anabolic metabolism and involves severe electrolyte imbalances (low serum concentrations of phosphate, magnesium, and potassium) as well as metabolic abnormalities in malnourished patients during refeeding by oral, enteral, or parenteral routes.\textsuperscript{6,7} The pathophysiology of RFS is unclear, but most symptoms occur within the first 72 hours after the beginning of refeeding.\textsuperscript{8}

Glucose oxidation is reduced during fasting, and the secretion of insulin consequently decreases while the glucagon and catecholamine concentrations increase.\textsuperscript{9} This leads to abnormal metabolism resulting in resting energy expenditure. Gluconeogenesis, lipolysis, and proteolysis are activated to maintain energy production; as a result, muscle proteins are used and vitamins and electrolytes are consumed.\textsuperscript{10} However, the lipolysis process increases the blood concentrations of free fatty acids, stimulating ketogenesis in the liver. Indeed, the visceral adipose tissue is commonly involved in AP, exhibiting stranding around the inflamed organ.\textsuperscript{11} However, acute and excessive lipolysis by pancreatic lipase can cause systemic injury. A study by de Oliveira et al.\textsuperscript{12} showed that during AP, pancreatic triglyceride lipase leaks from the injured pancreas into the surrounding adipocytes, and its entry is facilitated by multiple mechanisms. Pancreatic triglyceride lipase-mediated lipolysis results in the release of large quantities of non-esterified fatty acids, which cause inflammation and elevated cytokines, thus worsening both lung and kidney injuries and culminating in multisystem organ failure. More recently, research has shown a significant similarity in cytokine elevations between patients with severe AP and those with severe COVID-19.\textsuperscript{13} This suggests that therapeutic removal of cytokines through early supplementation with calcium and albumin may improve outcomes in patients with both diseases.\textsuperscript{13}

The concentration of glucose increases during refeeding, leading to hyperglycemia. As a consequence, insulin secretion increases, stimulating the anabolic pathway and leading to intracellular uptake of phosphate, which is significant for cellular metabolism of macronutrients for energy production.\textsuperscript{14} Hypophosphatemia is the most common symptom of RFS and can lead to neurologic, neuromuscular, respiratory, and/or hematologic adverse effects. Indeed, low levels of calcium and magnesium can induce arrhythmia, confusion, paresis, rhabdomyolysis, and respiratory insufficiency.\textsuperscript{15,16} Similarly, deficiencies in electrolytes and vitamins, which are mainly due to the lack of thiamine, lead to metabolic acidosis, which is a risk factor for neurologic disorders such as Wernicke encephalopathy or cardiovascular disorders together with water retention.\textsuperscript{6,7}
We herein report a case involving a patient with AP and gallbladder stones who developed RFS after 3 days of severe illness.

Case report

This report is presented in accordance with the CARE guidelines. A 79-year-old Caucasian woman was diagnosed with AP based on a high fever, involuntary weight loss, inadequate nutrient consumption, two episodes of vomiting, and severe pain in the upper right abdomen. The anamnesis revealed comorbid diabetes and hypertension in addition to a history of atrial fibrillation and cholestasis. On admission, the patient weighed 50 kg and was 168 cm tall; her body mass index (BMI) of 17.8 kg/m² indicated an underweight status. Because her BMI was <18 kg/m² and involuntary weight loss of >10% had occurred in the previous 3 to 6 months, the patient was identified as at risk for RFS. She developed sudden pain that became intense within a few minutes, and the pain was associated with nausea and lack of appetite. She received ciprofloxacin and metronidazole for treatment of the AP with clinical signs of inflammation; an elevated C-reactive protein concentration, erythrocyte sedimentation rate, and leukocyte count; and signs of inflammation around the pancreas structure on computed tomography. The patient reported no alcohol consumption, and her clinical history did not include organ failure. She was diagnosed with steatosis and cholelithiasis, and we hypothesized that refeeding was the principal cause of her rapid deterioration; however, the patient’s resources were partly consumed by her inflammatory state. We believe that multiple factors (poor oral intake, weight loss, pancreatitis) contributed to RFS in this case. Three days is generally not long enough for the development of RFS. In our case, however, the patient had been severely debilitated by malnutrition and did not eat enough because food consumption caused nausea; moreover, her septic state had caused hypercatabolism, and the intervention was a stressful situation that compromised her general state and triggered the development of RFS.

Although the patient was uncomfortable and sweating with wheezing and accelerated breathing, her clinical examination revealed full mental awareness. Notably, she was dehydrated and had a pulse rate of 90 beats/minute, blood pressure of 135/75 mmHg, and body temperature of 38.5°C. However, thoracic examination revealed no pathologic findings, and cardiac auscultation revealed only a modest mitral murmur. The patient exhibited local tenderness in the right upper abdomen without muscular defense with positive Murphy and Blumberg signs. Ultrasonography showed gallbladder enlargement with stones and common bile duct expansion of about 14 cm, while the pancreas showed a finely inhomogeneous echostructure. Thus, the bile calculi, lack of appetite, reduced dietary intake for more than 5 days, and low concentrations of potassium, phosphate, and magnesium (Table 1) impaired her organ function, leading to respiratory and cardiac failure. The patient was treated with intravenous antimicrobial therapy (ciprofloxacin at 0.4 g twice a day and metronidazole at 0.5 g twice a day), intravenous rehydration therapy, intravenous 0.5% glucose at 500 mL three times a day, and spasmytic drugs.

A nutritional assessment was performed on day 2 of hospitalization to correct the patient’s micro/macronutrient deficits and manage her nutritional therapy, which was maintained as oral feeding until 6 hours before retrograde endoscopic cholangiopancreatography to remove the stones in the common bile duct on day 3 of hospitalization. During the postoperative phase (i.e., from the third to fourth day), the
patient was enterally fed through a nasogastric tube although the International Association of Pancreatology/American Pancreatic Association guidelines for mild and severe AP recommend restarting oral feeding once the abdominal pain has decreased and inflammatory markers begin to improve.\textsuperscript{18,19} However, the patient refused oral feeding, and she was therefore treated with low-speed normocaloric enteral feeding (100 kcal/100 mL). This enteral preparation included 12.3 g of carbohydrates, 3.9 g of fat, 4.0 g of protein, and no fiber. Unfortunately, the enteral feeding was not well tolerated and was therefore interrupted after a few hours. Indeed, after the first administration, the patient became confused and developed tachycardia, respiratory insufficiency (oxygen saturation of 85\%), and severe hypotension. Therefore, she was treated with rapid fluid supplementation together with oxygen supplementation at 2 L/minute and dopamine at 4 mcg/kg/minute. Laboratory examination showed severe alterations of electrolytes (phosphate, potassium, and magnesium) and vitamins (especially thiamine) as well as a hydric balance dysfunction (Table 2). Thus, RFS was diagnosed and the enteral feeding was immediately suspended. The patient was scheduled to undergo new nutritional therapy by insertion of a parenteral feeding bag from 1920 to 60 mL/hour with appropriate intake of phosphorus, magnesium, potassium, and B-group vitamins. She exhibited mild recovery at the beginning of the parenteral feeding. After 24 hours, the patient started to feed orally. On the first day of oral feeding (i.e., day 4 of hospitalization), her calorie intake was 10 kcal/kg (50\% carbohydrates, 35\% lipids, and 15\% protein) with supplementation of phosphorus at 0.5 to 0.8 mmol/L, potassium at 1.3 mmol/L, magnesium at 0.3 to 0.4 mmol/L, and sodium at <1 mmol/L. During the next 3 days (i.e., from day 5 to 7 of hospitalization), her daily calorie intake was increased by 5 kcal/kg and she received thiamine supplementation according to the ASPEN guidelines.\textsuperscript{20} During the next 3 days, the patient’s daily calorie intake was increased by 20 to 30 kcal/kg, her liver and kidney functions were monitored and controlled, and fluids and electrolytes were supplemented as necessary. During the following 2 days (i.e., days 11 and 12 of hospitalization), her calorie intake further increased until she reached an adequate

Table 1. Laboratory test results.

| Laboratory test | Result |
|-----------------|--------|
| Leukocyte count | $16.3 \times 10^9$/L with 92.7\% neutrophils (4.5–11.0 $\times 10^9$/L) |
| Hemoglobin      | 12.2 g/dL (12.0–16.5 g/dL) |
| Platelet count  | $320 \times 10^3$/mm$^3$ (130–400 $\times 10^3$/mm$^3$) |
| Sodium          | 139 mmol/L (136–145 mmol/L) |
| Potassium       | 4.2 mmol/L (3.5–5.0 mmol/L) |
| Creatinine      | 1.1 mg/dL (0.60–1.30 mg/dL) |
| Serum phosphate | 5.0 mmol/L (1.0–1.5 mmol/L) |
| Total bilirubin | 3.2 mg/dL (0.2–1.2 mg/dL) |
| GOT             | 176 U/L (5–35 U/L) |
| GPT             | 154 U/L (5–45 U/L) |
| Lipase          | 3250 U/L (11–50 U/L) |
| CRP             | 14.5 mg/dL (<0.5 mg/dL) |

Reference ranges are provided in parentheses.

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; CRP, C-reactive protein.
daily caloric requirement.\textsuperscript{20} The patient’s condition showed clinical improvement on day 13 with a decrease in her body temperature to 36.8°C and normalization of her laboratory parameters. An electrocardiogram showed no sign of ischemia, while an echocardiogram showed a low ejection fraction (49%). Thoracic computed tomography showed a small amount of bilateral pleural effusion. After 24 hours, the patient resumed eating small amounts orally. Moreover, her hemodynamic status stabilized, her vasopressor therapy was discontinued, and her electrolyte imbalance disappeared. Figure 1 shows the timeline of the patient’s hospitalization. We have de-identified all patient details, and the patient provided written informed consent for treatment and publication of this report.

### Discussion

The real incidence of RFS is unknown. However, recent findings emphasize that clinicians should be aware of the possibility of RFS in malnourished patients with AP who have electrolyte imbalances.\textsuperscript{5} Indeed, malnutrition often exhibits features of RFS upon hospital admission, which is associated with long-term mortality and other adverse clinical outcomes.\textsuperscript{21} Therefore, the identification of high-risk patients is important; patients at high risk are those who have been chronically undernourished and those with diminished physiological reserve. A prospective cohort study of a heterogeneous group of patients admitted in intensive care units showed that about 34% of patients had hypophosphatemia after beginning feeding.\textsuperscript{22} A low albumin concentration may be an important predictor of hypophosphatemia, although albumin is not a nutritional marker.\textsuperscript{6–10} Similarly, Francisco et al.\textsuperscript{23} reported a 12% rate of intolerance to refeeding in a cohort of 232 patients with AP, observing an association between intolerance to refeeding and choledocholithiasis, the

| Laboratory test results after refeeding. | Reference ranges are provided in parentheses. |
|-----------------------------------------|-----------------------------------------------|
| **Potassium** | 2.4 mmol/L (3.5–5.0 mmol/L) |
| **Sodium** | 105 mmol/L (136–145 mmol/L) |
| **Phosphate** | 1.6 mmol/L (1.0–1.5 mmol/L) |
| **Calcium** | 7.6 mg/dL (8.4–10.0 mg/dL) |
| **Magnesium** | 1.3 mg/dL (1.6–2.6 mg/dL) |
| **Albumin** | 2.1 mg/dL (3.5–5.0 mg/dL) |
| **Blood gas analysis** | Respiratory alkalosis |

*Performed with an Emogas analyzer (Radiometer Medical, Copenhagen, Denmark).
fasting time, the length of symptoms before admission, and the metamizole dose.

The National Institute for Health and Care Excellence guidelines recommend that refeeding begins with no more than 50% of the energy requirements in “patients who have eaten little or nothing for more than 5 days.” The calories can then be increased if no refeeding problems appear on clinical and biochemical monitoring (level D recommendation). Notably, for patients at high risk of developing RFS, the nutritional repletion of energy should be started slowly (maximum of 0.042 MJ/kg per 24 hours) and should be tailored to each patient. However, for very malnourished patients (BMI of ≤14 kg/m² or negligible intake for ≥2 weeks), refeeding should start at a maximum of 0.021 MJ/kg per 24 hours along with cardiac monitoring because of the risk of cardiac problems. In addition, vitamin supplementation should be started as soon as possible, before and for the first 10 days of refeeding. Oral, enteral, or intravenous supplementation of potassium, phosphate, calcium, and magnesium should be administered as necessary in patients without contraindications. The circulatory volume should also be replaced.

Symptoms of RFS can be various and unexpected, sometimes occurring late and without warning. These symptoms are due to changes in serum electrolytes that affect the cell membrane, impairing the functions of nerve, cardiac, and skeletal muscle cells. Thus, the specific clinical picture depends on the type and severity of the biochemical abnormalities, and the spectrum of clinical manifestations ranges from simple nausea, vomiting, and lethargy to respiratory insufficiency, cardiac failure, hypotension, arrhythmias, delirium, coma, and death. Clinical deterioration may occur rapidly if the cause is not established and appropriate measures are not applied. In the event of a severe deficiency, death may occur by multiple organ failure. Indeed, comorbidities and conditions in the anamnesis may influence the patient’s vulnerability to RFS, the diagnosis of which is based on hydro-electrolyte disorders including hypophosphatemia, hypocalcemia, hypokalemia, and hyperglycemia. Hyperglycemia is often found in patients with pancreatitis and results from insulin resistance, increased glucose production in the liver, and impaired insulin secretion caused by beta-cell damage. Hypocalcemia may be related to saponification of calcium, hypomagnesemia, decreased parathyroid hormone release, and an increased calcitonin concentration.

In our patient, the first signs of RFS were the onset of hypophosphatemia, hypocalcemia, and hyperglycemia. However, her compromised condition was also delineated by a BMI of <18.5 kg/m², which is a risk factor for complications and mortality in patients with AP, whereas hypertension is an independent risk factor for local complications, renal failure, an increased length of hospitalization, and newly diagnosed diabetes. Furthermore, patients may develop signs of congestive heart failure and neurologic disorders. Cardiac involvement has been well described in the literature, and its manifestations and mechanisms are diverse. However, the occurrence of authentic cardiogenic shock remains less frequent.

A recent meta-analysis revealed that an early oral refeeding strategy or a quickly increasing diet caused no damage to patients with mild AP, but rather early oral refeeding could significantly decrease the length of hospital stay. In fact, malnutrition in patients with AP can lead to anorexia, abdominal pain, vomiting, gastroparesis, gastric outlet obstruction, and fasting for pancreatic rest. Thus, nutritional support is a lifesaving modality. However, if nutrition is not delivered properly, refeeding the malnourished patient can
lead to serious complications or even death. Electrolyte concentrations should be checked prior to refeeding. Thiamine supplementation is recommended upfront refeeding in at-risk patients, and the gradual introduction of calories, especially during the first week, is prudent until the patient becomes metabolically stable. Fluid and salt intake should initially be limited because of the propensity to retain these. Once RFS has been diagnosed, caloric intake should be reduced, electrolyte abnormalities treated aggressively, and extra B vitamins administered.

Conclusion

This case report highlights the potential dangers of RFS and emphasizes cardiac-related complications. RFS is a poorly recognized multifactorial condition; all physicians caring for susceptible patients should be cognizant of the risks of refeeding to appropriately treat RFS and thus reduce morbidity and mortality in patients with AP. However, there are simple rules to prevent the development of RFS: order fasting only if alimentation is contraindicated, use a step-up approach (oral, enteral, or parenteral feeding), and monitor electrolyte concentrations.

Ethics statement

Ethics committee approval was not required because of the nature of this study (case report).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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