

Refeeding Syndrome: When Good Food Goes Bad
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Introduction

A phenomenon has been noted in historical records in humans describing epidemics of death when starving people gained access to food. When allowed to engorge themselves, they became severely ill and died. Those people that did not engorge themselves, but consumed small amounts of food did not suffer the same fate.¹ In human medicine this metabolic derangement is still seen with severe anorexia nervosa, chronic alcoholics, diabetic ketoacidosis or those having gone on hunger strikes.^{1,2}

More importantly to us in veterinary medicine, this metabolic derangement can also be seen in our patients. Typically these patients present with a prolonged history of anorexia or other metabolic condition such as diabetic ketoacidosis or hepatic lipidosis.^{1,3} When a body goes into a starvation situation, a complex set of changes or adaptations occur. By understanding these changes we are better able to understand what happens when we start to "refeed".² The metabolic rate slows down decreasing the energy necessary to run the basic needs of the body, in addition a reduction in the functional reserve of most if not all the organ systems occur. Significant reductions occur in cardiac output, hemoglobin level and therefore oxygen carrying capacity, renal concentrating capacity, gastrointestinal villous atrophy and slowing of GI motility.² These reductions in functional reserves are not severe enough to cause failure of any one organ system during starvation.

In humans, potential complications of refeeding include generalized muscle weakness, tetany, myocardial dysfunction, cardiac arrhythmias, seizures, excessive sodium and water retention, hemolytic anemia and death from cardiac and respiratory failure.^{2,4} While seen rarely in veterinary medicine, it is seen most often in those patients receiving enteral or parenteral nutritional support.⁴

Keeping in mind the changes the body has undergone while in starvation, when reintroducing food several areas need to be monitored closely to prevent the "Refeeding Syndrome". During recovery, excessively rapid refeeding (or hyperalimentation) can overwhelm the patient's already limited functional reserves.²

Refeeding causes a shift in the body from a catabolic state where protein is the primary energy source to an anabolic state where carbohydrates are the preferred energy source.^{2,5} Administration of enteral or parenteral nutrition stimulates the release of insulin; this causes dramatic shifts in serum electrolytes from the extracellular space to the intracellular space, primarily phosphorus, potassium and to a lesser degree magnesium.^{2,5,6} Insulin also promotes intracellular uptake of glucose and phosphorus for glycolysis.⁵

Prior to reintroducing food the serum electrolyte levels are usually within normal ranges, and may even be elevated.^{2,4,5} During catabolism as body cell mass shrinks, the intracellular ions; phosphorus, potassium and magnesium move in to the extracellular space.² From there they are excreted through the kidneys as they reach the renal threshold. This loss through the kidneys will continue to happen even with continued depletion.²

During refeeding, these ions move back into the re-expanding intracellular space, and the serum levels can fall dangerously low within 24–72 hours.^{2,5} Treatment of uncontrolled diabetes with insulin can lead to identical electrolyte shifts.²

In addition to electrolyte abnormalities another potential problem is fluid overload. Because of the decrease in functional reserve in the heart and kidneys death from congestive heart failure is a possibility. If carbohydrates are reintroduced too quickly, the resulting fluid retention can overwhelm the patient's limited cardiac reserve causing heart failure.² Carbohydrate intake stimulates the release of insulin, one of the actions of insulin in addition to regulating glucose is to reduce sodium and water excretion.^{2,6} Dextrose containing intravenous fluids can also cause the same problems without having food being given due to the rise in serum insulin levels driving the dextrose into the cells.

Those patients most "at risk" for developing Refeeding Syndrome are:

- Cats with hepatic lipidosis-the more severe the more "at risk"
- Diabetic ketoacidotics
- Severe malnutrition/starvation
- Hyperadrenocorticism (Cushing's Disease)³

Phosphorus

Phosphorus in the form of phosphate is the most abundant intracellular anion.^{3,7} Most intracellular phosphorus exists as organic compounds, such as creatine phosphate, adenosine monophosphate (AMP), and adenosine triphosphate (ATP).¹ Organic phosphate is also present in many compounds in the body such as phospholipids, phosphoproteins, nucleic acids, enzymes, cofactors and biochemical intermediaries.³ Phosphorus is involved in cell membrane integrity (the phospholipid layer), muscle and neurologic function, carbohydrate, fat and protein metabolism, oxygen delivery from the red blood cell (RBC) to the tissue, and the acid-base buffering system.⁷ Phosphorus also aids in the transfer of energy to cells through the formation of ATP and is an essential component of bones and teeth.⁷

Most extracellular phosphorus is in the form of inorganic phosphorus, approximately 12–15% of this is protein bound, and the remaining 85–88% exists unbound as either monohydrogen phosphate or dihydrogen phosphate.^{3,7} Only inorganic phosphate ions are measured when

serum is analyzed for the presence of phosphorus.³ Serum should be separated from cells within 1 hour of sample collection; leakage of cellular organic phosphate into the serum may increase the inorganic phosphate concentration. Hemolysis can have the same effect.³

As with any ion found predominately in the intracellular space, serum concentrations do not represent total body stores.³ Phosphorus normally shifts freely between the extracellular, intracellular and boney compartments.³ Hypophosphatemia does not imply that phosphorus depletion exists; just that it has shifted out of the measurable extracellular space.

Phosphorus moves into the cells with refeeding to support the increased production of phosphorylated intermediary components of energy metabolism. Severe hypophosphatemia, hemolytic anemia and death can occur within 12–72 hours of refeeding.

Because of the phosphorus requirements for formation of ATP, signs of hypophosphatemia are often related to decreased energy stores and may include muscle weakness; anorexia, dysphagia and respiratory failure caused by decreased diaphragmatic contractility and decreased cardiac output. Decreased oxygen delivery to cells, depleted cell energy stores, seizures and coma may result.⁷

Severe hypophosphatemia may impair heart function by reducing the energy generating ability of the left ventricle. This is thought to be the result of depleted intracellular ATP stores and/or impaired calcium metabolism.³ Approximately 20% of human patients show cardiac arrhythmias, even when underlying heart disease was not present. After repletion of phosphorus, the severity of the arrhythmias improved.^{1,3}

The red blood cell is the only tissue in the body that produces 2,3-diphosphoglycerate (2,3-DPG). 2,3-DPG is bound to hemoglobin and helps to enhance dissociation of oxygen from the hemoglobin molecule.^{1,3} A deficiency of RBC 2,3-DPG impairs release of oxygen from the hemoglobin molecule causing tissue hypoxia.^{1,3}

Muscle contraction also requires ATP as an energy source, low concentrations of intracellular phosphorus results in depletion of these energy stores causing muscular weakness and respiratory failure.³

ATP depletion is also the proposed mechanism by which hypophosphatemia may cause hemolysis. ATP is needed to maintain RBC membrane integrity, cell shape and deformability. Glycolysis is the only means by which RBCs generate ATP. Decreased concentrations of inorganic phosphate therefore limit ATP production. ATP depletion may cause malfunction of the sodium-potassium pump, which causes decreased cell deformability and osmotic lysis. This can lead to severe hemolytic anemia.⁵

Phosphorus depletion can occur in the absence of hypophosphatemia in diabetic ketoacidosis. This is due to the effects of insulin on extracellular phosphorus and potassium and not necessarily due to the effects of "refeeding". Supplementation should be done in animals than

have low normal or moderate hypophosphatemia prior to starting insulin therapy. Monitoring of serum phosphate is critical during the first 12–24 hours after starting insulin and fluid therapy.^{1,3}

Cats have low levels of hepatic glucokinase, the enzyme that phosphorylates glucose for hepatic use. This deficiency makes cats particularly susceptible to hyperglycemia when either fed diets high in glucose or receiving fluids containing glucose.⁵ This elevated serum glucose further stimulates the production of insulin, which causes an increased shift of phosphorus from the extracellular space into the intracellular space.⁵ Enteral diets high in simple carbohydrates can have the same effect.⁵

Potassium

Potassium is the primary intracellular cation, with at least 90% of the total body stores located in the intracellular space.⁷ Since potassium like phosphorus is located primarily intracellularly, serum levels often do not accurately represent the extent or severity of potassium deficiency, especially in cases of chronic disease.⁷ Potassium has a direct impact on cell, nerve and muscle function by maintaining the cell's electrical neutrality and osmolality, aiding in neuromuscular transmissions, assisting skeletal and cardiac muscle contractility, and affecting the acid-base balance.⁷

Since potassium is an integral part of the sodium-potassium pump, hypokalemia usually results in muscle weakness and decreased GI motility. (7) An ECG will show prolonged repolarization (the period of time in which the $\text{Na}^+\text{-K}^+$ pump moves the potassium back into the cell and the sodium out), this causes a prolonged PR, QRS and QT intervals, a decreased ST segment and a flattened inverted T wave. When the deficiency is severe enough, sinus bradycardia and heart block with atrioventricular dissociation can be seen.⁷

Insulin also pulls potassium along with phosphorus into the intracellular space with resumption of carbohydrate metabolism.^{2,4} When potassium and glucose move into the cells with insulin, the $\text{Na}^+\text{-K}^+$ pump and glycogen synthesis is stimulated. This further depletes the body of potassium, since 0.33 mEq of potassium is required for each gram of glycogen produced.⁴

Magnesium

Magnesium is the second most abundant cation in the intracellular space. Approximately 60% of the body's magnesium can be found in the bones and teeth, 39% in the intracellular space and less than 1% in the extracellular space.⁷ As with phosphorus and potassium, serum magnesium levels do not accurately reflect actual body stores because of the relatively small amounts found in the serum. Approximately 30% of the magnesium in the serum is protein bound; therefore reduced albumin levels may falsely decrease the serum reading even if actual levels are within normal limits.⁷

Magnesium promotes enzymatic reactions within cells during carbohydrate metabolism and helps the body produce and use ATP.⁷ Signs of hypomagnesemia are similar to those seen with hypokalemia, respiratory muscle paralysis, complete heart block and coma.⁷ Hypomagnesemia also causes an inappropriately high excretion of potassium through the urine, thus making worse any existing hypokalemia. This occurs because sodium-potassium ATPase which is required for reabsorption of potassium is magnesium dependent. This also prevents correction of the hypokalemia even with high doses of potassium supplements until the hypomagnesemia is corrected.^{2,4,7}

Hypomagnesemia can also cause a secondary hypocalcemia, which remains resistant to supplementation until magnesium is corrected.^{2,4} This happens because with magnesium depletion, parathyroid hormone (PTH) is unable to elicit calcium release from the bone. Even though the body initially continues to secrete increased levels of parathyroid hormone to stimulate calcium release, the continued hypomagnesemia will eventually inhibit PTH secretion.^{2,7} A patient with hypocalcemia due to hypomagnesemia may have a high, normal or low PTH level.² Animals with hypocalcemia can show signs of restlessness, muscle fasciculation's, tetany and convulsions.

Reintroduction of Food

Current recommendations assert that no animal should go longer than 5 days without food.⁸ As many of the animals that develop refeeding syndrome have already far exceeded this time frame, re-introducing food quickly is essential. It is important to keep in mind that the 5 day time frame is total days without food, not just hospital days.

It is essential that before starting nutritional support, rehydration, electrolyte and acid-base status be addressed. We want to provide the best chance of a favorable outcome to our patients and ensuring that everything starts off in the correct balance is essential to this.

When discussing nutritional support the first consideration is how much food to feed. Using conservative energy estimates, as is now the current recommendation, the most accepted formulas would be Resting Energy Requirements (RER) = 70 x (body weight in kg)^{0.75}, or for those who are logarithmically impaired as I am, RER= 70 + (30 x body weight in kg). This formula can be used for animals weighing between 2 and 30 kg). (8) For cats, some recommend the alternate formula of RER= 40 x body weight in kg.

The ultimate goal would be to have the animal receiving 100% of their RER either through a feeding tube or orally soon after discharge from the hospital; I would discharge an animal receiving 75% of their RER divided into 3 equal feedings with instructions to the owners for further increases in the food. Usually by this time, the animal is metabolically stable, tolerating the food well, off fluids and feeling better. Further nursing care can continue at home.

Recommendations for Avoiding Refeeding Syndrome

1. Anticipate the problem whenever a patient is "at risk" and refeed with formulations known to contain adequate levels of phosphorus, potassium and magnesium.
2. Use initial nutritional refeeding rates not to exceed the patient's resting energy requirements (RER) ($30 \times \text{weight in kilograms}$) + 70. Consider refeeding a high-fat low carbohydrate diet to patients who haven't eaten in greater than 5 days, if their condition would not contraindicate such a diet.
3. Do not add extra energy to the caloric requirements by using an Illness Energy Requirement adjustment to the RER
4. Monitor phosphorus, potassium, magnesium and PCV/TS at least daily, more often if indicated. Monitoring should start within 12 hours of refeeding.
5. Supplement electrolytes as needed, either IV or with the food.
6. Monitor closely for signs of fluid over load and congestive heart failure.^{2,4}

Conclusion

The take home message here is to be aware, monitor and when feeding "go slow, go low". I have found that starting feedings at 25% of RER with continuous rate infusion with a syringe pump to be the best way to address this. I use recovery diets exclusively, and supplement as needed. Some diarrhea is not unexpected in patient's that have undergone prolonged starvation due to GI villous atrophy. It does no one any good to try and rush the feedings to get the patient out of the hospital, especially if you create more problems that you already had!! If you've never seen a patient with refeeding syndrome, you haven't been looking in the right place. They're out there, and we need to find them so that they can be treated appropriately.

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