Hypophosphatemia and Refeeding Syndrome

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Hypophosphatemia is an uncommon condition in dogs and cats. Normal serum phosphate concentrations are often maintained in the face of severe systemic phosphate depletion through the actions of renal tubular reabsorption and bone resorption.

Potential causes for hypophosphatemia are decreased intestinal absorption (decreased intake, malabsorption, vomiting, diarrhea, phosphate-binding antacids, vitamin D deficiency), increased urinary excretion (primary hyperparathyroidism, diabetes mellitus with or without ketoacidosis, hyperadrenocorticism, renal tubular disorders, diuretic administration, hyperaldosteronism, parenteral fluid administration, hypercalcemia of malignancy), and transcellular shifts (insulin administration, parenteral glucose administration, enteral or parenteral hyperalimentation, respiratory alkalosis, hypothermia).

Hypophosphatemia is the most significant disturbance of refeeding syndrome. "Refeeding syndrome" is a description of multiple metabolic disturbances that occur during and complicate the reinstatement of oral, enteral, or parenteral nutrition in malnourished or starved patients. In contrast to the human literature, which states that hypophosphatemia is frequently associated with reinstatement of alimentation in at-risk patients, only a handful of reports document the same occurrence in veterinary patients.

Refeeding syndrome in humans encompasses a number of fluid and electrolyte disorders affecting multiple body systems such as the hematologic, cardiac, pulmonary, neurologic, and neuromuscular systems. Refeeding syndrome in cats affects mainly the hematologic and neurologic systems; in dogs, the hematologic, cardiac, and neurologic systems are affected.

The development of hypophosphatemia in a malnourished patient when alimentation is restored can be explained by the pathophysiology of starvation. During the initial period (24 to 72 hours) of a negative energy balance (catabolic state), the liver becomes a net exporter of glucose, using glycogen stores (glycogenolysis) and skeletal muscle for amino acids (gluconeogenesis). This process provides the energy requirements for the glucose-dependent bodily tissues (erythrocytes, kidney, and brain). After 72 hours of a negative energy balance, the predominant source of energy is ketone production via oxidation of free fatty acids that spares amino acid mobilization from skeletal muscle. There is also a decrease in gluconeogenesis, a reduction in insulin secretion, and a decline in basal metabolic rate in the body's effort to survive long-term starvation.

As soon as a positive energy balance (anabolic state) is created with carbohydrates by either enteral or parental alimentation, there is a sudden shift back to glucose utilization as the principal energy source, creating a huge demand for phosphorus in order to generate adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (2,3-DPG). Furthermore, an increase in endogenous insulin secretion in response to the carbohydrate load causes a significant shift of phosphorus and other electrolytes (potassium, magnesium) from the extracellular space to the intracellular space. The combination of these physiologic responses may result in severe hypophosphatemia.

The most common sequela to hypophosphatemia in animals is hemolytic anemia. ATP is necessary to maintain erythrocyte membrane integrity, cell shape, and deformability. Because erythrocytes can only generate ATP through glycolysis, a process that depends on the presence of inorganic phosphate, decreased concentrations of phosphorus limit ATP production. Decreased ATP production may cause malfunction of the Na^+-K^+ pump, leading to osmotic lysis and failure of the membrane-associated actin and myosin fibers that help maintain erythrocyte shape and plasticity. Also, low concentrations of inorganic phosphate and ATP may directly affect the structure of the erythrocyte membrane, which is composed largely of phospholipids. This makes the membrane rigid and decreases deformability. In addition, cats are susceptible to Heinz body formation secondary to decreased levels of glutathione caused by low ATP levels that may also contribute to hemolysis. Because of this, the potential consequences of hemolysis in cats can be severe. In

humans and dogs, a decrease in erythrocyte 2,3-DPG results in increased fragility and a high hemoglobin oxygen affinity, contributing to intravascular hemolysis and tissue hypoxia.

Other abnormalities may be present in patients with refeeding syndrome. In cats, hyperglycemia, hypokalemia, and potentially hypomagnesemia may be present. In dogs, abnormalities such as myocardial depression, platelet dysfunction, leukocyte dysfunction, hypokalemia, and potentially hypomagnesemia may be present, but hyperglycemia is rarely encountered.

Malnourished patients and those with refeeding syndrome may be deficient in thiamine as well regardless of whether the deficiency was preexisting or secondary to increased metabolism of carbohydrates after reinstatement of alimentation.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition

- None.

Age Predisposition

- None.

Breed Predisposition

- None reported.
- Cats may be more susceptible to refeeding syndrome than dogs because their hepatic glycogen stores are low and gluconeogenesis is accelerated within the first day of malnutrition.

Owner Observations

- Anorexia.
- Weight loss.
- Lethargy.
- Weakness.
- Nausea or vomiting.
- Diarrhea.
- Pigmenturia.
- Restlessness.
- Seizures.
- Coma.
- Death.

Animals at Risk

- Patients with chronic malnutrition receiving alimentation.
- Patients with diabetes mellitus being treated with insulin therapy.
- Cats with hepatic lipidosis.
- Patients with chronic disease, including hepatic dysfunction, cancer or cardiac cachexia, or renal failure.
- Patients with poor body condition.
- Patients in certain physiologic states such as growth, gestation, or lactation.
- Patients with endocrine disease, including hyperparathyroidism, hyperadrenocorticism, hyperaldosteronism, and hyperthyroidism.
- Patients receiving medications, such as phosphate binders, diuretics, and glucocorticoids, that can potentially lower serum phosphorus levels.
- Patients with respiratory alkalosis or metabolic acidosis.
- Patients with eclampsia.
- Burn patients.

Physical Examination Findings

- Poor body condition (not in all patients).
- If the patient has anemia because of hypophosphatemia:
  - — Pale mucous membranes.
  - — Tachycardia.
  - — Tachypnea.
  - — Bounding pulses.
  - — Lethargy.

Laboratory Findings

Serum Chemistry $

- Hypophosphatemia (adult reference range, 2.5–6.0 mg/dl):
  - — Mild: 2.0–2.4 mg/dl.
  - — Moderate: 1.5–2.0 mg/dl.
  - — Severe: <1.5 mg/dl.
- Hypokalemia (adult reference range, 3.6–5.5 mEq/L):
  - — Mild: 3.0–3.5 mEq/L.
  - — Moderate: 2.5–3.0 mEq/L.
  - — Severe: <2.5 mEq/L.
- Hypomagnesemia (adult reference range, 1.5–2.5 mEq/L):
  - — Total: <1.5 mEq/L.
  - — Ionized: <0.48 mEq/L.
- Hyperglycemia.
- Hyperbilirubinemia.
- Hypoproteinemia.
- Possibly elevated liver enzymes in cats.

Complete Blood Count $

- Anemia (adult reference range for cats, 29%–48%; for dogs, 36%–55%).
- Heinz bodies in cats.
- Possibly spherocytosis in dogs.

TABLE 1
Potassium Supplementation Guidelines

Serum Potassium Concentration (mEq/L)	mEq KCl to Add to 1 L Fluid at a Fluid Rate of 66 ml/kg/day
<2.0	80
2.1–2.5	60
2.6–3.0	40
3.1–3.5	28
3.6–5.0	20

Other Diagnostic Findings

- Left ventricular systolic dysfunction in dogs via echocardiography. **$$**
- Prolonged buccal mucosal bleeding time in dogs (>4 minutes). **$**

Potential Future Tests to Assess Nutritional State

- Delayed-type hypersensitivity reaction.
- Lymphocyte function testing.
- Acute-phase protein testing.
- Gene expression testing.

Summary of Diagnostic Criteria

- Malnourished patient.
- Poor body condition or recent weight loss.
- Hypophosphatemia.
- Anemia may be present or absent.

Diagnostic Differentials

- Insulin administration is ruled out with patient history obtained from the owner or medical record.
- Diabetes mellitus is ruled out with serum glucose or fructosamine levels.
- Diabetic ketoacidosis is ruled out with serum glucose and ketone levels and urine ketone levels.
- Hospitalized patients that have or develop anemia:
  - Immune-mediated hemolytic anemia is ruled out with slide agglutination or Coombs test.
  - Hemorrhage is ruled out with physical examination or paracentesis if third-space fluid is present.
  - Coagulopathy is ruled out with a blood coagulation profile (prothrombin and activated partial thromboplastin times).
- Primary hyperparathyroidism is ruled out with parathyroid hormone, parathyroid-related protein, and ionized calcium levels.
- Renal tubular disorders are ruled out with a urine profile to look for low urine pH, glucosuria, proteinuria, and ketonuria.
- Sepsis is ruled out with physical examination, finding the source of infection, and a white blood cell count.

TREATMENT RECOMMENDATIONS

Initial Treatment

Initial Alimentation **$$**

- The mainstay of treatment to avoid refeeding syndrome is to institute the initial alimentation slowly and at a fraction of the calculated resting energy requirement (RER), increasing over 3 to 5 days to full RER. Calculations for RER are as follows:

For animals 3 to 25 kg: (30 × Current body weight in kg) + 70 = kcal/day

For animals <3 and >25 kg: 70 × (Current body weight in kg)$^{0.75}$ = kcal/day

- Alimentation should be instituted at 25% to 30% of calculated RER for the first 24 hours and then slowly increased over 3 to 5 days until the full RER is being delivered. Routes of alimentation include oral, enteral, and parenteral.

Phosphate Supplementation **$**

- Phosphate supplementation is warranted in asymptomatic patients at risk for development of hypophosphatemia, patients with clinical signs believed to be a result of hypophosphatemia, and truly hypophosphatemic patients.
- When formulating enteral or parenteral nutrition solutions for patients with normal serum phosphorus levels, phosphates should be added to the solution to meet the patient's estimated daily requirements. The estimated daily phosphorus requirement is 200–400 mg in cats and 75 mg/kg in dogs.
- For patients with severe hypophosphatemia and patients exhibiting hemolytic anemia, IV potassium or sodium phosphate should be administered at 0.01 to 0.06 mmol/kg/hr until the patient is no longer severely hypophosphatemic or until serum phosphorus is >2 mg/dL. Refer to the Patient Monitoring section for guidelines on monitoring phosphorus levels.

Potassium Supplementation **$**

- Potassium supplementation is warranted in patients that develop hypokalemia.
- Potassium chloride or potassium phosphate may be added to parenteral fluid therapy based on the level of hypokalemia (Table 1).

- For patients with severe hypokalemia, a KCl IV infusion can be given at 0.5 mEq/kg/hr for 6 hours. The KCl should be diluted in an equal volume of normal saline.
- Regardless of the type of potassium supplementation, the overall potassium infusion should not exceed 0.5 mEq/kg/hr. The clinician should be aware of the contribution of potassium phosphate to the overall potassium supplementation if this solution is being used to correct hypophosphatemia.

Magnesium Supplementation $

- Magnesium supplementation is warranted in patients that develop hypomagnesemia.
- Magnesium chloride or sulfate may be added to parenteral fluid therapy at 1 mEq/kg/day for the first 24 hours.
- If further magnesium supplementation is needed past the initial 24 hours, the rate should be decreased to 0.5–0.75 mEq/kg/day.

Thiamine Supplementation $

- Thiamine supplementation is warranted in all malnourished patients with reinstatement of alimentation.
- Cats and dogs should receive 10–100 mg/day SC during the refeeding period.

Blood Transfusions $$–$$$

- Whole blood or packed red blood cell (RBC) transfusions in patients with severe anemia (<20%) or rapid change in packed cell volume (PCV) or hematocrit (Hct) (>50% decrease in a 24-hour period).
  - — 20 ml/kg whole blood given IV over 1–4 hours.
  - — 10 ml/kg packed RBCs given IV over 1–4 hours.

Insulin Therapy $

- Insulin therapy is warranted in patients that develop persistent hyperglycemia.
- Insulin therapy can be administered in intermittent bolus injections or by continuous-rate infusion, depending on the patient's needs.

Supportive Treatment

- Most critically ill animals that require nutritional support also require IV fluid support.
- Antibiotic therapy should be provided if indicated.
- Gastroprotectant medications should be administered if indicated.

Patient Monitoring

- Food intake or administration of nutritional support should be reviewed at least daily.
- The patient's body weight and body condition score should be recorded at least daily.
- For patients undergoing treatment with IV phosphates, serum phosphorus and serum calcium concentrations should be evaluated every 6 to 12 hours.
- Serum phosphate, glucose, potassium, and magnesium levels should be monitored on at least a daily basis during the refeeding period (≥5 days) or more frequently for patients receiving potassium, magnesium, or insulin supplementation.
- PCV and Hct should be monitored for evidence of anemia, and serum should be monitored for evidence of hemolysis in animals with hypophosphatemia.
- Patients should be monitored daily for signs of fluid overload and congestive heart failure.

Home Management

- Owner-administered enteral tube feedings should be provided for patients that require continued nutritional support.
- Oral phosphorus supplementation should be given if indicated.

Milestones/Recovery Time Frames

- Resolution of hypophosphatemia in 12 to 24 hours with supplementation.
- Stabilization or improvement of PCV or Hct in patients with anemia.
- Improvement in the patient's mentation and level of activity.
- Serum chemistry, complete blood count, PCV, and total solids should be rechecked at 5 to 7 days and 21 to 28 days after discharge from the hospital if indicated.

Treatment Contraindications

- When refeeding at-risk patients, solutions deficient in phosphorus should not be given.
- Patients with vomiting or diarrhea should not be given oral phosphate supplementation.
- Parenteral phosphate supplementation should not be added to fluids containing calcium because it may cause calcium phosphate to precipitate.

PROGNOSIS

Favorable Criteria

- Simple starvation malnutrition.
- Patients that do not develop hypophosphatemia or anemia.

Unfavorable Criteria

- Critical or chronic illness.
- Patients that develop hypophosphatemia.
- Patients with evidence of hemolytic anemia.

RECOMMENDED READING

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