Equine Refeeding Syndrome: A Clinical Review of the Physiology, Diagnosis, and Management

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Introduction

Refeeding Syndrome is the designation for the clinical signs, physiologic abnormalities, and mortality that can occur following refeeding of a chronically or severely starved patient.[1] This syndrome was first described in humans following the liberation of World War II concentration camps.[2,3] The abnormalities associated with refeeding a chronically starved person were further studied as part of the Minnesota Experiment.[4] Rehabilitation of the severely malnourished animal is an important topic for veterinarians, caretakers, and rescue organizations. Prevention, recognition, and treatment of this disease can help save those patients at risk.

History and Presentation

As the name suggests, Refeeding Syndrome typically presents following resumption of feeding after a period of starvation or malnutrition.[1] Starvation may be caused by multiple factors including deficient quantity of feed, deficient quality of feed (energy, protein, minerals, vitamins), seasonal declines in feed source such as pasture, malabsorption (e.g. from diarrhea, poor dentition, or geriatric conditions), or parasitism.[5] Concurrent conditions such as neoplasia, insulin resistance, infection, or systemic diseases can contribute to emaciation.[5]

Behavior changes, such as decreased response to stimuli, and immune compromise can occur as soon as 3-4 days after total feed deprivation.[5] Bacterial infections such as salmonellosis can occur due to a compromised immune system.[5,6] Weight loss becomes noticeable after 1 to 2 weeks of feed deprivation.[5] Abrupt refeeding of these horses can lead to a sudden decline in their condition within 3 days.[5] Even in horses fed more conservatively, hypophosphatemia can occur in the first 10 days.[6]

Horses presenting with Refeeding Syndrome present with severe manifestations of starvation and with signs precipitated by the refeeding. These signs may include anemia, cardiovascular dysfunction, or neurological dysfunction.[5] Hypophosphatemia may manifest as weakness, disorientation, anorexia, and joint pain.[7] Evidence of a severe deficiency includes intravascular hemolysis, respiratory failure, neurologic dysfunction, seizures, and cardiac arrhythmias such as ventricular tachycardia.[7] Starvation can also lead to cachexia, muscle wasting, and a poor Body Condition Score (2 or lower).[8] Subcutaneous fat is minimal and the skin coat is unthrifty.[8] In severe or chronic cases (60-90 days), the patient may be recumbent and unable to raise their head.[8]

The hallmark laboratory finding of Refeeding Syndrome is hypophosphatemia, often accompanied by hypomagnesemia and hypokalemia.[1,8] Anemia, hypoalbuminemia, hypertriglyceridemia, hyperbilirubinemia (unconjugated), elevated nonesterified fatty acid concentrations, lymphopenia, decreased BUN, and RBC membrane instability are also common in these patients.[8]

Pathophysiology

An overview of the pathophysiology of starvation and refeeding is illustrated in Figure 1

Phosphorus:

Phosphorus is a macromineral element essential to normal growth and metabolism which, physiologically, is most commonly found as a phosphate anion (PO_4^{3-}).[10,11] The terms "phosphorus" and "phosphate" are often used interchangeably, but the latter is a more accurate description of the biologically relevant form.[11] Intracellular phosphorus concentrations are 10-20 times higher than extracellular concentrations allowing for increased structural and metabolic

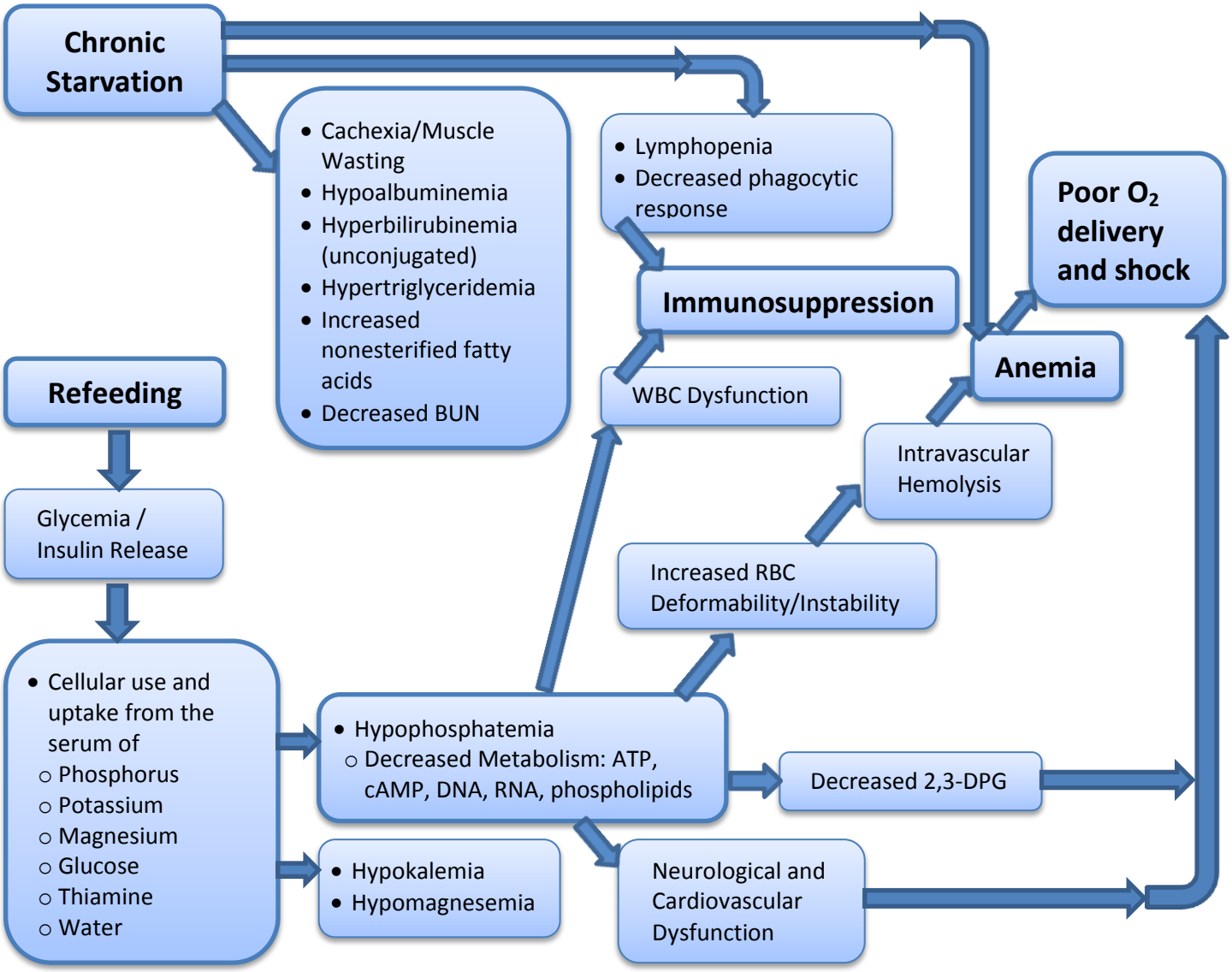
cellular utilization.[10,11] Phosphate is essential for structural and energy needs including phospholipids, phosphoproteins, nucleic acids (DNA, RNA), and energy transferring molecules such as adenosine triphosphate (ATP), guanosine triphosphate (GTP), cyclic adenosine monophosphate (cAMP), and phosphocreatine.[7,10,11] These energy transferring molecules and organic phosphates play vital roles in metabolism and membrane stabilization through forming and cleaving their high-energy phosphate bonds.[7] Additionally, phosphate is a major component in the formation of 2,3-diphosphoglycerate (2,3,-DPG), which allows for the normal release of oxygen from hemoglobin at the tissue level.[7]

Phosphorus concentrations are regulated by 1,25-dehydroxyvitamin D_3 which allows for the intestinal absorption of available calcium and phosphorus.[11] However, parathyroid hormone (PTH) is regulated by calcium levels, not phosphorus levels, and can work at odds with phosphorus levels.[11] PTH increases plasma levels by small intestinal phosphorus absorption through 1,25-dehydroxyvitamin D_3, bone resorption, and urinary reabsorption of phosphorus through the type II sodium-dependent phosphate transporter (NDPT2a).[7,11] Ninety percent of phosphorus intake is excreted in the urine, while the remainder is excreted by the gastrointestinal tract.[7] Under normal conditions, phosphorus levels are tightly regulated with little variation from diet changes.[7]

Phosphorus serum levels less than 2.5 mg/dL are generally considered to be decreased.[7] Mild to moderate hypophosphatemia (1.0-2.0 mg/dL) typically results in generalized weakness, disorientation, anorexia, and joint pain.[7] Severe hypophosphatemia (<1.0 mg/dL) is life-threatening and may result in acute respiratory failure, seizures, coma, cardiac arrhythmias, and hemolysis.[7] At <0.5 mg/dL, there is interference with glycolysis resulting in decreased phospholipid and ATP production.[7] Thus, when phosphorus levels are low membranes are

unstable and the Na/K/ATPase pumps no longer maintain normal ion gradients.[7] This instability can result in cardiac arrhythmias such as ventricular tachycardia, neurologic dysfunction, and hemolysis.[7] Red blood cells may hemolyze due to membrane deformability and decreased ATP availability.[7] Hypophosphatemia has also been shown to reduce leukocyte function.[7] Hypophosphatemia also reduces production of 2,3-DPG in red blood cells, resulting in decreased oxygen delivery to tissues through a left-shift of the hemoglobin-oxygen dissociation curve.[7]

Fig. 1: Starvation and Refeeding Syndrome Diagram



Starvation and Refeeding:

Starvation or malnutrition in horses can be caused by disease, intentional neglect, ignorance, economic hardship of owner, or seasonal variation in available pasture feed.[6] Failure to meet a horse's energy needs results in weight loss.[8] Prolonged nutritional deficiencies (energy, protein) result in emaciation and, in severe cases, death.[8] These horses have a poor Body Condition Score with minimal subcutaneous fat and reduced muscle mass.[8] They often have a poor hair coat, and they may be recumbent from weakness.[8] Healthy horses take approximately 60 to 90 days of being starved to become recumbent.[8] After 36 to 48 hours of recumbency, this progresses to lateral recumbency, inability to raise their head, and seizure-like activity.[8]

Laboratory findings in chronically starved horses may include anemia, hypertriglyceridemia, hyperbilirubinemia (especially unconjugated bilirubin), high nonesterified fatty acid concentrations, lymphopenia, hypophosphatemia, and hypomagnesemia.[8] Protein deficiency that often occurs simultaneously can result in hypoalbuminemia and low BUN concentration.[8] Primary thiamine (Vitamin B1) deficiency (Beriberi) is another possible feature of starvation and Refeeding Syndrome documented in humans.[8]

Prolonged or severe starvation depletes intracellular concentrations of phosphorus, potassium, and magnesium while serum concentrations often remain within normal limits.[8] Upon refeeding, metabolism switches from catabolic to anabolic metabolism abruptly.[18] Glycemia causes an insulin release which stimulates glycogen, fat, and protein synthesis.[8] These processes require phosphate, magnesium, and thiamine as co-factors.[8] Insulin then stimulates cellular uptake of potassium, phosphate, magnesium, and water from the serum.[6,8] Thus, these electrolyte derangements can lead to cardiac dysfunction (e.g., arrhythmias, cardiac arrest), neuromuscular complications, and shock.[8] The exact same uptake does not occur in red blood cells (RBC) as

their glucose uptake is non-insulin dependent.[12] The above electrolytes, particularly phosphorus as part of metabolism (e.g., ATP synthesis, etc.), are siphoned from the serum, and are no longer as available for RBC use.[13] As a result, in severe cases (<1.0 mg/dL), RBC ATP synthesis and metabolism are retarded, Na/K/ATPase pumps lack sufficient ATP, membranes destabilize, and intravascular hemolysis can occur.[9,13] As discussed, hypophosphatemia also reduces white blood cell function contributing to immunosuppression.[7] Additionally, hypophosphatemia's reduction of 2,3-DPG concentration in red blood cells, the anemia from chronic disease, possible hemolysis, and the above combined factors can reduce oxygen delivery to tissues and precipitate shock.[7,13]

Differential Diagnoses

Clinically, Refeeding Syndrome has clinical signs similar to starvation. However, starvation electrolyte levels, including phosphorus, are typically normal or only mildly decreased. Additionally, in the depressed or recumbent patient, it should also be differentiated from similar causes including sepsis, muscle weakness, neurologic disorders, and cardiovascular disorders. A thorough history should identify those patients that were at risk of Refeeding Syndrome such as rescuing a chronically starved horse or aggressive non-structural carbohydrate feeding. The history should also identify those who may be at future risk once treatment begins. Diagnosis of Refeeding Syndrome should not be the extent of diagnostics or the scope of treatment. Many concurrent ailments and diseases could have initiated the events leading up to presentation, or opportunistically manifested during the disease course – such as salmonellosis.[5,6] Additionally, neglected horses may have other problems that impact their health and quality of life such as internal parasites, external parasites (e.g., lice), poor dentition, poor hair coat, geriatric conditions, or hoof disorders.[8] The diagnosis of Refeeding Syndrome should not cease the investigation of an

underlying cause of the emaciation or any contributing factors. Any other illnesses must also be diagnosed and treated in order to fully recover a patient with Refeeding Syndrome.

Hypophosphatemia can present as part of several disease processes and should not be equated to Refeeding Syndrome. In general moderate hypophosphatemia (1.0 – 2.5 mg/dL) has been associated with renal tubular defects (chronic renal disease), gram-negative bacteremia / sepsis, diuretic therapy, hypomagnesemia, starvation, hypothermia, hyperparathyroidism, volume expansion (hyperaldosteronism, saline infusion, hypokalemia), osteomalacia, pregnancy/eclampsia, malabsorption, Vitamin D deficiency, hemodialysis, acute gout, and androgen therapy .[7,14,15] It is also associated with glucose, fructose, glycerol, lactate, bicarbonate, insulin, gastrin, glucagon, epinephrine, and corticosteroid administration that draw phosphorus intracellularly.[14] Severe hypophosphatemia has been generally associated with Refeeding Syndrome, hyperalimentation, severe respiratory alkalosis, phosphate binders, antacids, the recovery/diuretic phase after severe burns, diabetes mellitus treatment, and alcoholic withdrawal (in humans).[14] It has also been associated with hyperadrenocorticism, early hypercalcemia of malignancy, acute liver failure, head trauma, severe tissue trauma, total parenteral nutrition, and malabsorption.[7,15] Thus, while refeeding syndrome should be kept in mind with hypophosphatemia, it is not the only explanation.

Diagnostic Approach/Considerations

The clinician must evaluate a thin or emaciated horse's condition for underlying or contributing factors. Patients may not present for starvation or with clinical signs after refeeding; patients presenting with other diseases should be evaluated to determine if they are at risk for Refeeding Syndrome. For example, horses chronically unable or unwilling to eat due to another

disease may be at risk of Refeeding Syndrome if corrected and aggressively refed. A thorough diet history should be taken, though this may be difficult if the animal has been neglected. Overgrazed pasture, poor or insufficient hay, or harsh environmental conditions (dry summer, cold winter) can contribute to starvation and forming a clinical diagnosis.

There is no set standard for the diagnosis for Refeeding Syndrome, and diagnosis is usually made through a summary of evidence, identification of risk, and using hypophosphatemia as the surrogate marker.[8,13,18] Diagnosis is suspected and supported through history and physical exam findings which determine if a patient is at risk. It is more specifically supported through a complete blood count and serum chemistry. Although certainly not pathognomonic, the hallmark sign of Refeeding Syndrome is hypophosphatemia which is often accompanied by hypokalemia and hypomagnesemia.[8,13,16]

Recent research may help identify at risk patients prior to initiation of refeeding. In January 2015, a human trial was published that attempted to validate an assay as a marker for Refeeding Syndrome risk.[17] Insulin Growth Factor 1 (IGF-1) and leptin were proposed as biochemical markers of hypophosphatemia risk following refeeding.[17] Baseline IGF-1 was found to be a superior marker with 91% sensitivity and 65% specificity at 63.7 µg/L.[17] The role of this assay in veterinary medicine has not been evaluated.

Treatment and Management Options

Treatment of a horse with refeeding syndrome primarily revolves around supportive care (electrolyte replacement, fluids, partial parenteral nutrition), frequent monitoring, dietary control, and quality nursing care. Phosphorus and potassium deficiencies can be corrected using a potassium phosphate infusion. Magnesium levels can also be restored using a magnesium sulfate

infusion. Hypoalbuminemia, if present, can be improved by plasma transfusions. Additionally, any underlying or contributing conditions should also be addressed. This may involve deworming, applying lice spray, floating teeth, or administering antibiotics. Recumbent patients may develop pressure sores which should be prevented by changing the horse's position frequently and by providing soft bedding.

The chronically starved horse should be fed a diet of primarily forage.[8] The goal of dietary therapy should be avoiding a glycemic insulin release that could precipitate a Refeeding Syndrome event (e.g., hypophosphatemia, hypokalemia, hypomagnesemia).[8] Forages generally contain less than 15% dry-matter (DM) non-structural carbohydrates (NSC).[8] Alfalfa hay is high in mineral content (phosphorus, calcium) and considered a good forage choice for the chronically starved horse.[8] Grains and sweet feeds are not recommended due to their high NSC content.[8] A balancer pellet or vitamin/mineral supplement should also be added to help reverse any deficiencies from starvation.[8] B-vitamins should also be supplemented to help prevent thiamine deficiency as a potential contributing factor.[8]

Adding vegetable oil (e.g., ¼ to 1 cup per day) or using a commercial fat-supplemented feeds (8-12% fat, NSC <20%) have been proposed as a means to increase feed energy.[8] However, in a study comparing alfalfa versus alfalfa with corn oil refeeding regimens, the corn oil supplemented diet was associated with lower phosphorus intake and lower serum phosphorus concentrations.[8]

Daily Energy (DE) requirements should be calculated using the resting energy requirements (RER) at the current body weight (22-23 kcal/kg/day) and the true maintenance requirements at the ideal body weight (30-36 kcal/kg/day).[8] DE intake should start at 25 to 50% of the resting requirements at current body weight building to 100% of resting requirements over

the following 2 to 3 days.[8] Over the next 7 to 10 days, theses should transition to maintenance energy requirements for the ideal body weight (can be 125-130% of original presentation weight).[8] To prevent a glycemic/insulin complication, the ration should be divided into four to six meals per day for the first 10 to 14 days and can later be transitioned to two to three meals per day.[8]

Postprandial serum glucose concentrations have been found to be significantly higher in chronically starved horses fed an oat hay/commercial ration diet versus an alfalfa diet.[6] Additionally, insulin levels in an oat hay/commercial ration diet were significantly higher than an alfalfa hay diet or an oat hay alone diet, especially once 100% DE requirement was provided.[6] In the same study, serum phosphorus concentrations were initially within reference range for the chronically starved horses (3.1-5.6 mg/dL), but decreased steadily during the refeeding trial.[6] Horses fed alfalfa hay had a significantly higher potassium and magnesium concentrations over the oat hay group.[6] Regardless of diet, there were also significant temporal declines in 2,3-DPG concentrations in this study.[6] In the study, one horse was euthanized following neurologic signs with no significant pathologic lesions at necropsy, but did have hypophosphatemia, hypocalcemia, and hypomagnesemia three days prior, suggesting a metabolic disturbance.[6] Another horse in the study was euthanized due to a colonic torsion, but also had hypophosphatemia and hypocalcemia.[6] Both horses had decreased 2,3-DPG concentrations. A third horse was euthanized due to salmonellosis.[6] If there are clinical signs of insufficient oxygen delivery such as tachypnea, tachycardia, weakness, or marked anemia, oxygen supplementation or whole blood transfusions may be indicated.

Serum phosphorus, potassium, magnesium, and blood glucose should be monitored at least every 1 to 2 days during the first 7 to 10 days of refeeding.[6] Hydration status and

gastrointestinal function should also be closely monitored.[6] Successful nutritional rehabilitation involves the resumption of normal body weight which may take 3 to 10 months.[6]

Expected Outcome and Prognosis

There are no available incidence studies of Refeeding Syndrome, likely due to its imprecisely defined diagnosis and uncommon clinical presentation. In the study of isoenergetic diets of chronically starved horses, not those with actual Refeeding Syndrome, 19 of 22 horses (86%) survived.[6] The prognosis for survival is very poor for horses who have been recumbent for more than 72 hours, even when appropriate nutritional support and nursing care are instituted.[8] In a study of 45 chronically starved horses placed with responsible caregivers with appropriate diet, 9 horses died, a 20% mortality rate.[19] Mortality after refeeding was associated with a worse Body Condition Score, but responses were variable.[19] Deworming and correcting dental problems will further improve prognosis.[6]

Conclusion

Refeeding Syndrome is a somewhat overlooked disease that can be fatal if not prevented or treated. Prevention, diligent monitoring, and proper treatment can help improve rehabilitation outcomes of starved and diseased horses. The information and confidence to treat these animals would benefit practitioners, owners, and rescue organizations. As clinicians and caretakers it is important to be cognizant of the welfare of animals and humanely address any suffering that may be occurring through starvation, disease, or neglect.

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