REVIEW ARTICLE

Hypophosphatemia in Adults with Nutritional Support, a Literature Review

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Abstract

Introduction: Hypophosphatemia is a common event in clinical practice. Although it appears in the context of diverse clinical and pharmacological situations, the refeeding syndrome / refeeding hypophosphatemia stand out for their relevance. The aim of this review is to provide a global vision on hypophosphatemia during nutritional support (both parenteral and enteral nutrition): definition, epidemiology, etiology, physiopathology, clinical manifestations and management.

Methods: Scientific articles published in Medline (Pubmed), Scopus, Web of Science and Embase were electronically search. English and Spanish articles published in the last ten years were included.

Conclusions: Hypophosphatemia is a common and underdiagnosed adverse event in hospitalized patients, with a multifactorial etiology. The degree of hypophosphatemia correlates with symptoms. Treatment for hypophosphataemia depends on its severity, the route of administration and the underlying cause. There is no evidence based guidelines regarding neither the amount and timing of phosphorus replacement nor the optimal time to recheck serum phosphorus levels after supplementation.

Keywords: Hypophosphatemia, Refeeding Syndrome, Refeeding Hypophosphatemia, Parenteral nutrition, Enteral nutrition, Nutritional support, Tube feeding.

1. Background

Disease-related malnutrition is a common condition in medical and surgical inpatients and is associated with detrimental clinical outcomes including mortality, complications, and prolonged hospital stay.[1,2] Instigating nutritional therapy is commonly recommended in malnourished patients to prevent these adverse outcomes, although large clinical trials demonstrating benefit in the polymorbid inpatient population are

largely lacking.[3] A potential risk for nutritional therapy in malnourished or food-deprived patients is the refeeding syndrome (RFS), an under-diagnosed and life-threatening,[4] but entirely avoidable condition.[5]

The classic study describing RFS was carried out by Keys et al in healthy males who were conscientious objectors during World War II.[6] The participants subjected themselves to semi-starvation during 6 months, after which normal oral feeding was resumed. The result was decreased cardiovascular reserve with heart failure in some cases. Similar clinical outcomes were seen after restoring normal nutrition to individuals who had been besieged or held in concentration camps during World War II.[7] Subsequently, with the arrival of parenteral (PN) and enteral (EN) nutrition, similar complications were seen in malnourished patients who received aggressive nutritional therapy.[8]

In 2001 Crook et al. referred to a syndrome of severe electrolyte and fluid shift associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally.[9] The fundamental condition in RFS is severe hypophosphatemia,[9] which is accompanied by sodium and fluid balance abnormalities, alterations in glucose, protein and fat metabolism, thiamine deficiency, as well as hypopotassemia and hypomagnesemia. Clinical consequences include neurological, respiratory, cardiovascular and haematological abnormalities, among others. They occur only a few days after resuming feeding, increasing patient morbidity and even mortality. Optimal risk assessment, establishment of a nutritional care plan, and monitoring of patients at risk reduce the morbidity and mortality associated with RFS.[10]

RFS is still understudied in the inpatient population, although nutritional therapy is one of the most commonly used inhospital treatments. No standardized and evidence-based guidelines with a common definition as well as treatment recommendations exist.[10]

In one recent systematic review, it was noted that definitions for RFS were highly heterogenous with most studies relying only on blood electrolyte disturbances, and others also includying clinical symptoms. Hypophosphatemia was considered, either as a cutoff or as a relative decrease from baseline, as a part of the definition. Cutoffs used for hypophosphatemia diagnosis differed among studies (the range varied from phosphate below normal range to <1mg/dL or decreased rate from baseline >30% or >0.5mg/dL).[11]

Hypophosphatemia is the adopted surrogate marker for diagnosing RFS, though low serum phosphate is not pathognomonic.[12] RFS is not associated with a consistent pattern of biochemical or clinical abnormalities and many cases described in the literature may be more appropriately termed refeeding hypophosphatemia (RH).[13] There are many other causes of hypophosphatemia not related to RFS. So we need to be aware that hypophosphatemia does not necessarily mean the presence of RFS.[14] Low plasma electrolytes levels, especially in critically ill inpatientes, may be a consequence of numerous causes that should be taken into account when performing differential diagnosis.[15] These speculations would favour using clinical symptoms, in addition to electrolyte disturbances, as a gold standard for the diagnosis of RFS.[11]

RH can be defined as the hypophosphatemia following refeeding. Hypophosphatemia in the event of PN or EN, or RH, have different serum phosphate concentration cutoffs–depending on the studies, with no universally accepted definition.[4]

The normal serum phosphorus level in adult patients stays within 2.5 to 4.5 mg/dL (1 mg/dL = 0.32 mmol/L). Marinella et al. in a recent review about RFS in cancer patients define hypophosphatemia by a serum level of < 3 mg/dL and severe hypophosphatemia by a serum level less than approximately 1.5 mg/dL.[16] Generally, hypophosphatemia is defined as a serum phosphate level of <2.5 mg/dL and may be considered severe when serum phosphate is <1 or 1.5 mg/dL, moderate when the values are between 1 and 2 mg/dL or 1.5 and 2.2 mg/dL and mild between 2.3 and the lower normal limit.[10,17-19] The degree of hypophosphatemia is correlated with symptoms.

2. Methods

A bibliographic search was performed in Medline (Pubmed), Scopus, Web of Science and EMBASE databases in march 2018, using the following terms: "refeeding syndrome", "hypophosphatemia", "enteral nutrition", "tube feeding" and "parenteral nutrition", in combination with the operators "AND", "OR". Case reports, controlled trials, narrative reviews, systematic reviews, position statements and clinical guidelines were included. Additionally we examined the reference lists of included articles. We restricted the search to English and Spanish articles that were published in the last ten years. Animal studies and articles related to paediatric and neonate populations were excluded.

Our aim was to review hypophosphatemia during enteral or parenteral nutrition, particularly the following questions:

- Phosphorus metabolism
- Incidence
- Etiology and risk factors
- Physiopathology
- Clinical features
- Evaluation
- Management

3. Phosphorus metabolism

Phosphate is the main intracellular anion. The intracellular concentration is maintained using sodium-coupled transport proteins, where extracellular high sodium gradient is used to cotransport phosphate against its concentration gradient into the cellular space.[20] Phosphate deposits are over 700 g in an average adult body, 80% of which are located in the skeleton, nearly 20% in soft tissue and muscle and only 1% in extracellular liquid.[9] Most extracellular phosphorus exists as inorganic phosphate.[21]

The normal serum phosphorus level stays within a narrow margin of 2.5 to 4.5 mg/dL, although its concentration does not always reflect the total body content. Regulation of phosphorus and calcium (Ca) is influenced primarily by serum phosphorus and ionized Ca concentrations and the actions of parathyroid hormone (PTH), vitamin D (1,25-dihydroxyvitamin D3), and calcitonin in the bones, kidneys, and intestines.[22,23]

The phosphorus Recommended Dietary Allowance (RDA) for healthy adults is approximately 700 mg (~23 mmol) per day.[24] The average consumption is between 1000 to 1400 mg daily for a Western diet. 80% of ingested phosphorus is absorbed, most through the jejunum by passive transport, and a small percentage through vitamin D-dependent active transport.[25] 90% of phosphorus is excreted through the urinary tract and only 10% through the gastrointestinal tract.

Short-term regulation of phosphorus levels is done by transcellular flow between intracellular and extracellular compartments.[26] Skeletal muscle and bone are

endogenous phosphorus reservoirs. In case of hypophosphatemia, muscular phosphorus is recruited to supply vital organs. Long-term regulation depends on the kidney. Phosphorus is filtered in the glomerule and 85% of the filtrate is reabsorbed. Reabsorption is regulated by serum phosphate concentration: mild phosphate depletion directly triggers increased phosphate reabsorption.[20]

Phosphate exerts essential functions, including bone homeostasis, cell membrane (phospholipids) composition as well as numerous metabolic processes.[27] It is involved in glycolisis,[10] protein phosphorylation/dephosphorylation, mitochondrial energy production, energy transfer, acid base buffering;[14] and it is a component of 2, 3-diphosphoglycerate, which regulates the oxygen-haemoglobin dissociation curve. It also is important for chemotaxis and phagocytosis, platelet function (aggregation), nervous system conduction and muscle function,[28] especially in the myocardium and diaphragm.[29]

4. Epidemiology

RFS is not an unusual complication of artificial nutrition,[30] but its true incidence is unknown – partly owing to the lack of a universally accepted definition.[31] RFS is generally poorly understood and underdiagnosed, particularly by trained doctors, thus leading to an underestimation of prevalence figures.[32] The development of RFS has been reported in the 5-25% of the patients receiving nutritional support,[30] corresponding the highest figures to cancer patients.

Multiple studies have been completed to evaluate the incidence of hypophosphatemia in hospitalized patients.[33] The incidence varies widely depending on the different definitions of RH and the patient population.[34,35] Hypophosphatemia is uncommon in the general population, but occurs in up to 5% of hospitalized patients and the incidence may be as high as 30%-50% in clinical settings such as alcoholism, sepsis, or patients in intensive care units (ICUs).[36,37] Kagansky et al. investigated episodes of hypophosphatemia in a group of 2,307 patients aged 65 years or older who were hospitalized in a geriatric division. 14.1% of them had documented hypophosphatemia.[33] Fifty-four head and neck cancer patients referred for surgery were investigated by Rasmussen et al.: 52% developed RH.[38] Marik et al. showed that 34% of severely ill patients in ICUs that were not alimented for at least 48 h showed some degree of hypophosphatemia (less than 1.5 mg/dL) with the restarting of feeding.[39] Hoffman et al. reported 45% of 621 patients who developed hypophosphatemia of less than 1.5 mg/dL in a large academic hospital, were in an intensive care setting.[12] Incidence appears to be less on general wards. In a study of 10197 hospitalized patients the incidence of severe hypophosphatemia was 0.43%, with malnutrition being one of the strongest risk factor and an associated increased mortality (18.2 vs 4.6%, $P < 0.001$).[40]

30-40% of inpatients with specialized nutritional support show hypophosphatemia, in general during the first 2-4 days after restarting the feeding.[41] In a prospective study of 243 critically and not critically ill patients with enteral or parenteral nutrition 6% showed severe hypophosphatemia on the third day.[42]

4.1. Hypophosphatemia and parenteral nutrition

Studies report a 100% incidence of hypophosphatemia in patients receiving total parenteral nutrition (TPN) solutions that do not contain phosphorus. When solutions containing phosphate are used, the incidence can decrease to 18%.[43]

In 2010, the National Confidential Enquiry into Patient Outcome and Death of the United Kingdom (NCEPOD UK) published "A Mixed Bag", the results of a wide-ranging enquiry into the delivery of PN in the UK. Of 877 records of the adult patients who received PN during 3 months, metabolic complications were seen in 39.3%. The most common electrolyte abnormality was hypophosphatemia, developed in 117 cases (13.3%). Sixty percent (455) of cases were deemed to have been at risk by advisors reviewing case records. Of these, only 50% were recognized as being at risk by the teams prescribing the PN. From those patients recognized to be at risk, 33 (14.7%) were thought to have developed signs of RFS on close case review.[44]

In a prospective observational study of 100 medical and surgical patients at a university teaching hospital, Weinsier et al. observed hypophosphatemia in 30% of patients during PN administration.[45] A retrospective study by Anderson et al. demonstrated that 55% of patients receiving PN developed a metabolic complication with the most common abnormalities being hyperglycemia (32%) and hypophosphatemia (29%).[46] A multicenter, descriptive, prospective study in patients with nutritional support in ICUs showed 38.5% of patients receiving PN developed hypophosphatemia.[47]

4.2. Hypophosphatemia and enteral nutrition

Fernandez et al. assessed during seven days 181 not critically ill patients started on EN. The incidence of hypophosphatemia (phosphate <2.5 mg/dL) was 31.5%, but only 1.1% of the patients developed severe hypophosphatemia (phosphate <1.5 mg/dL).[48] Lubart et al. observed values of phosphorus <1.6 mg/dL in 25% of 40 patients with feeding problems for at least 72 h before restarting EN. The decreases in phosphorus levels were maximal in the 2–3 days of refeeding.[49] A prospective observational cohort study conducted at a mixed medical-surgical ICU reported a 42.6% incidence of hypophosphatemia in patients receiving enteral feeding. RH was defined as plasma phosphate <2 mg/dL and a drop of more than 0.5 mg/dL following feeding. 4.6% of the patients had severe hypophosphatemia.[34]

A retrospective study in patients with nutritional support showed 21.4% of patients receiving EN and 8.5% of patients receiving PN developed hypophosphatemia (phosphate <1.9 mg/dL).[52]

5. Etiology

Causes of hypophosphatemia are multifactorial and include: insufficient intake or impaired absorption, redistribution or shift from extracellular phosphate into the intracellular space and increased excretion of phosphorus.[51] Intravenous glucose administration is the most common cause of hypophosphatemia in hospitalized patients.[52] Table 1 lists some potential causes of hypophosphatemia in adult patients.[15,17, 20,27,51,52]

Table 1. Potential causes of hypophosphatemia in adults

Insufficient intake or impaired absorption	Redistribution or intracellular shifting	Increased renal excretion
Malnutrition Diarrhea Vomiting Gastrointestinal losses Vitamin D deficiency Intestinal malabsorption Inadequate phosphorus maintenance/supplementation Drugs: - Antacids (eg, calcium-, magnesium- and aluminum-containing antacids) - Phosphate binders (eg, calcium acetate, sevelamer, lanthanum) - Sucralfate	Refeeding syndrome Administration of carbohydrate loads Recovery from diabetic ketoacidosis Rapid cell proliferation Hungry bone syndrome Respiratory alkalosis Gram-negative sepsis Intoxication: - Salicylates Drugs: - Insulin - Intravenous glucose - Catecholamines (epi and Norepinephrine, dopamine) - Beta-agonists - Terbutaline - Erythropoietins - Colony stimulating factors	Primary hyperparathyroidism Secondary hyperparathyroidism Hyperaldosteronism Alcoholism Hypercalcaemia Hypomagnesemia Metabolic acidosis Volume expansion Osmotic diuresis: glucosuria Alcohol Intoxication: - Iron - Cadmium - Paracetamol Dialysis therapy Renal tubular acidosis Primary renal phosphate- wasting syndromes: - X-linked hypophosphatemic rickets - Fanconi syndrome - Hypophosphatemic osteomalacia Drugs: - Diuretics (loop, thiazide and osmotic diuretics) - Carbonic anhydrase inhibitors (acetazolamide) - Calcitonine - Corticoesteroids - Estrogens - Theophylline - Bicarbonate - Iphosphamide - Cysplatin - Foscarnet - Pamidronate - Litium

Hypophosphatemia secondary to inadequate intake of phosphate occurs in the setting of prolonged poor dietary sources of phosphate, intestinal malabsorption, and intestinal binding by exogenous agents. Almost all diet types contain a surplus of phosphate sufficient to maintain needs, and renal adaptations can compensate for the short-term deficiency.[20]

Intracellular shifting of phosphate stores may occur in a variety of clinical scenarios. Acute respiratory alkalosis probably is the most common cause of severe hypophosphatemia in inpatients.[20]

Aditional drugs inducing hypophosphatemia, not included in Table 1, are: anti-rejection drugs used in organ transplant (basiliximab, mycophenolate, tacrolimus),

anti-viral drugs (tenofovir), bisphosphonates (ibandronic acid, zoledronic acid), cancer chemotherapy drugs (bortezomib, sorafenib, sunitinib, cisplatin, imitinab), gallium, growth hormone analogue, Interferon alfa 2a (pegolated), Interleukin II, leflunomide and parenteral iron.[16,53,54,55]

5.1. Risks factors of RFS and RH

Patients at high risk of RFS and RH are those with anorexia nervosa, uncontrolled diabetes mellitus (electrolyte depletion, diuresis), chronic alcoholism, chronic malnutrition (marasmus, prolonged fasting or low energy diet), morbid obesity with profound weight loss, malabsorptive syndrome (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome), prolonged vomiting and diarrhea, depression, long term users of antacids, long term users of diuretics, oncology patients, elderly (comorbidities, decreased physiological reserve), high stress patients unfed for >7 days, postoperative patients and hunger strikes.[31,56]

Phosphorus levels often decline with trauma and postoperatively, especially in cardiac, abdominal aortic, obesity and hepatic surgery. Extreme weight loss following obesity surgery has been shown to be associated with undernutrition. These patients are at high risk for evolving RFS, even though they may still be obese.[57] Hypophosphatemia is particularly common after hepatic surgery, possibly because the liver metabolizes phosphaturic factors.[37]

Severe hypophosphatemia have been described in patients who did not receive appropriate phosphate supplementation with nutrition support. Hypophosphatemia occurs frequently in patients on PN, mainly when malnutrition is present, and it is related to phosphorus concentration in the solution and increasing total caloric load.[27,58] Most standard EN formulations contain approximately 700–1,200 mg (22–39 mmol) of phosphate per liter of formula. Severely malnourished patients will have higher daily phosphate requirements when initiating nutrition support and should be supplemented accordingly to prevent hypophosphatemia.[19] A systematic review that studied patients with anorexia nervosa showed that the severity of malnutrition seems to be a marker for the development of RH more so than total energy intake.[59]

Reported risk factors for hypophosphatemia include: Acute Physiology and Cronic Health Evaluation II score (APACHE II), hypoalbuminemia, prealbumin <110 g/L, and forearm circumference and muscular area in the 5th percentile. It is likely that these factors represent a previous state of malnutrition and do not play a real pathogenic role in the appearance of hypophosphatemia. Risk factors for RFS do not predict the decrease in serum phosphate properly.[14]

The National Institute for Health and Clinical Excellence (NICE) recommends risk assessment for RFS.[60] Patients at risk are:

- Patient has one or more of the following:
    - Body mass index (BMI) <16 kg/m2
    - Unintentional weight loss >15% within the last 3-6 months
    - Little or no nutritional intake for more than 10 days
    - Low serum concentrations of potassium, phosphate or magnesium prior to feeding
- Or patient has two or more of the following:
    - BMI <18.5 kg/m2

- Unintentional weight loss >10% within the last 3-6 months
- Little or no nutritional intake for more than 5 days
- A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

6. Physiopathology of RFS and RH

RFS pathogenesis is complex, since it involves metabolic and physiological changes that occur during the substrate depletion and repletion phases, resulting in compartmental shifts of electrolytes, changes in glucose and vitamin metabolism and changes in the use of corporal water.

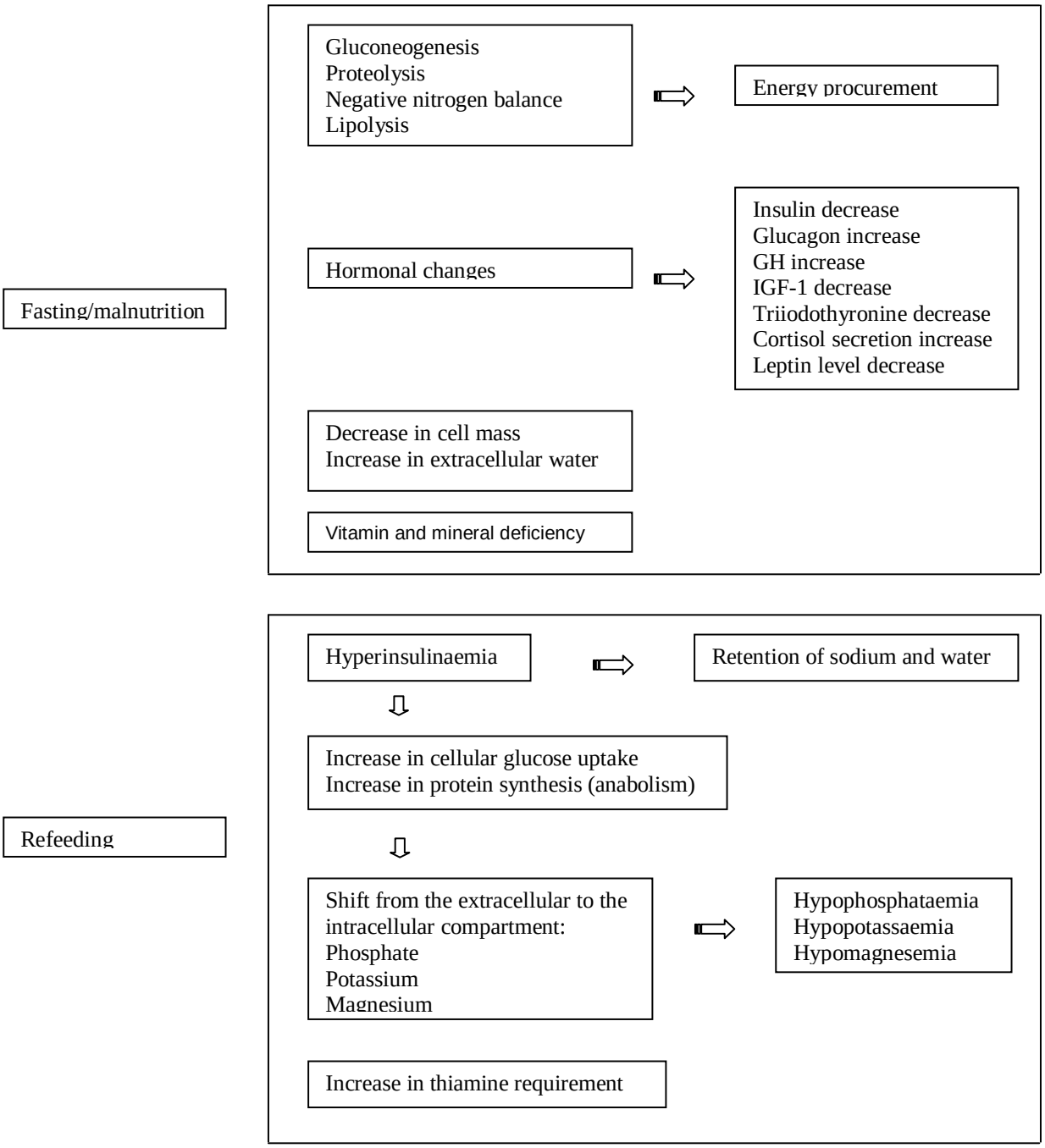
The preferred sources of energy used by tissues are carbohydrates. Our bodies dispose of a limited reserve, as glycogen stored in liver and muscle tissues. During the initial fasting period, glycogen deposits are used as an energy source. When these deposits are exhausted, the proteolysis process begins. After 72 hours of fasting, the metabolic routes change to lipolysis and obtain free fatty acids in order to prevent the recruitment of proteins from skeletal muscle. In addition to the metabolic features certain hormonal changes intended to maintain vital functions also occur during this adaptive process (Figure 1).[61,62,63] In this situation basal metabolic rate decreases by as much as 20–25%.[64] Fasting prolongation eventually leads to catabolism and loss of lean body mass. The most important effects of starvation are:

- Increased intracellular and whole body sodium and water
- Whole-body depletion of potassium, magnesium and phosphate
- Deficiency of vitamins (especially water-soluble vitamins) and minerals
- Renal, cardiovascular and intestinal dysfunction, with reduced ability to excrete excess sodium and water.[65]

A consequence of catabolic processes (fasting, stress reaction, inflammation) is a loss of intracellular ions (potassium, phosphate, magnesium), which results in a transient increase of their circulating levels, and is followed by a bodily loss due to immediate urinary excretion in exchange with sodium, which is retained.[10] Homeostatic mechanisms maintain serum concentrations of these ions: serum levels may remain normal despite a marked reduction in total body levels.[66]

RFS is an anabolic reaction caused by nutritional therapy, resulting from metabolic changes and a fluid imbalance. It is a potentially life-threatening condition that occurs in malnourished patients or in patients recovering from severe catabolic diseases after starting nutritional therapy.[67] The main trigger for RFS is the switch from a catabolic to an anabolic state, which is a physiological reaction in the initial phase of replenishment.[10] When malnourished and starved individuals receive high-carbohydrate feeding suffer a sudden change of the energy sources, from fat to carbohydrates, which causes a sustained increase in insulin secretion (Figure 1).[5,68,69]

Figure 1. Refeeding syndrome physiopathology.



Adapted from: Fernandez MT et al. Refeeding Syndrome.

Hypophosphatemia results from cellular uptake of phosphorus and inorganic phosphates for the synthesis of ATP, DNA, RNA, proteins, and 2,3-diphosphoglycerate, and from the increased phosphorylation of glucose. Cell membrane formation by phospholipids, cellular growth and replication by nucleoproteins and nucleic acids, regulation of cellular functions such as leukocyte chemotaxis, phagocytosis and

platelet clot formation require phosphate.[70] Hypophosphatemia may occurs even in patients with renal failure.

Enteral feeding appears to predispose to RH more commonly than parenteral nutrition. There are two potential reasons for this. The enteral feed given is often initiated at a slow rate to reduce the carbohydrate load on the basis that this is less likely to stimulate the insulin response that drives the RH. The delivering of low phosphate concentrations when refeeding is initiated is not enough to correct intracellular phosphate shifts. In adition, enteral feeding stimulates a greater insulin secretion through the incretine effect than parenterally so the mechanism that drives RH is amplified. The incretin effect is related to the production of enteral gastroinsulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), both increasing insulin secretion from the pancreatic islet B cells.[50]

7. Clinical manifestations of hypophosphatemia

Clinical manifestations of hypophosphatemia derive from the effects of phosphorus deficiency on systems and organs. The degree of hypophosphatemia correlates with symptoms. Mild to moderate hypophosphatemia is often asymptomatic and may go unrecognized. Typically hypophosphatemia causes adverse effects when phosphorus serum level is <1.5 mg/dL, and life-threatening complications may occur when it drops below 1.0 mg/dL. RH is most common within 2 to 4 days of refeeding.[16]

Clinical consequences of hypophosphatemia differ between acute and chronic conditions. Acute effects are due to intracellular depletion; however, chronic effects can be seen in bones. Prolonged hypophosphatemia leads to osteopenia, osteoporosis, rickets, or osteomalacia due to decreased bone mineralization.[20] Intracellular phosphorus deficit causes shortage of the high-energy chemical ATP and 2,3 diphosphoglycerate (2,3-DPG) resulting in reduced energy stores and impaired oxygen delivery, respectively and, finally, in numerous clinical sequelae.[37,71] Even when severe, acute hypophosphatemia from redistribution may have little consequence in the absence of phosphate depletion.[18] Severe acute hypophosphatemia with phosphate depletion results in clinical manifestations. In some cases of hypophosphatemia from an intracellular shift (insulin and glucose infusion and respiratory alkalosis) patients may remain asymptomatic because intracellular phosphate levels are sufficient for ATP and 2,3-DPG production.[72] If phosphate is sequestered in extracellular sites or intracellular pathways that do not produce ATP or 2,3-DPG symptoms of hypophosphatemia may be profound.[37]

Multiple organ systems, including cardiac, respiratory, neurologic, and hematologic can be affected by severe hypophosphatemia and this may lead to multisystem organ failure and death in the most severe cases.[70] The clinical emergence of these conditions varies in timing, with cardiac signs and arrhythmias occurring often within hours, and neurological signs and symptoms days to weeks later.[63] The most common cause of death is the presence of cardiac arrhythmias. The mortality rate in patients with severe hypophosphatemia is 30%. There is, also, a significant increase in hospital length of stay (LOS).

7.1. Cardiovascular system

Cardiovascular complications appear within the first week of refeeding. Prolonged fasting leads to atrophy and depletion of ATP of myocardial cells, which results in contractile dysfunction. In this situation, fluids replacement and retention of sodium

and water secondary to hyperinsulinemia give raise a volume overload that can bring about heart failure. Severe hypophosphatemia leads to depressed myocardial function due to ATP depletion and direct myocardial damage. The outcomes are decreases in volume per beat, mean arterial pressure, and cardiac output and an increase in pulmonary capillary pressure.[73] In this situation, hypotension, pericardial effusion, shock, arrhythmias and sudden death may occur. Hypophosphatemia is a direct cause of ventricular arrhythmias. Arrhythmias appear in up to 20% of hypophosphatemic patients with no underlying heart disease and in the event of an acute myocardial infarction, there is an increased risk of ventricular tachycardia.

7.2. Haematological system

Hematopoietic dysfunction may result from hypophosphatemia, including the well-described acute haemolytic anemia. Depletion of erythrocyte ATP and 2,3-DPG levels have been suggested as a pathogenic factor in the development of acute haemolysis. Depletion of ATP impairs several membrane pumps, such as the sodium-potassium-ATPase pump, as well as cellular energetic pathways, such as the anaerobic Embden-Meyerhof pathway which is the primary mechanism for erythrocyte ATP production.[74] 20%-50% decrease in intraerythrocytic ATP with respect to its normal value causes reversible spherocytosis with increased cell membrane rigidity. This contributes to tissue hypoxia due to the inability of the erythrocytes to pass through the capillaries, which also leads to the onset of haemolytic anaemia.

Hypophosphatemia causes a decrease in intraerythrocytic 2,3-DPG which increases haemoglobin affinity for oxygen, thus shifting the dissociation curve to the left and consequently decreasing oxygen liberation to peripheral tissues.[9] Hypophosphatemia severely alters platelet survival and function and can cause thrombocytopenia, platelet aggregation disorders and secondary haemorrhages. White blood cells are also affected, with chemotactic, phagocytic and bactericide function disorders, which may increase the probability of sepsis in high-risk patients.

7.3. Respiratory system

Respiratory dysfunction in patients with hypophosphatemia usually occurs with serum levels of < 1.0 mg/dL and is secondary to the glycolysis decrease and the drop in ATP levels in respiratory muscles. Severe hypophosphatemia alters diaphragm and intercostal muscle contractility.[75] This weakness leads to decreased vital capacity, acute hypoxic or hypercapnic respiratory failure or failure to wean patients from mechanical ventilation.[76] A prospective observational study by Alsumrain et al. reported an association between hypophosphatemia and failure-to-wean from mechanical ventilation (MV) when compared with patients with normal serum phosphorus concentrations.[77]

7.4. Nervous system

The mechanism for neurological dysfunction in hypophosphatemia is not well-defined, but it has been suggested that tissue hypoxia secondary to haemolytic anaemia and haemoglobin increased affinity for oxygen could be the cause.

Hypophosphatemia may cause peripheral neuropathy with paresthesias, paralysis of cranial pairs, fatigue, tetany, hallucinations, delirium, seizures and metabolic encephalopathy, a disorder marked by confusion, seizures, and coma. Phosphate depletion-induced encephalopathy probably originates from direct impairment of cerebral electrophysiological activity.[78] Guillain-Barré-like paralysis, hyporeflexia

and quadriparesis have also been described.[79] Polyneuropathy during hemodialysis is associated with loss of phosphate by the dialysate.

Phosphorus depletion is also associated with central pontine myelinolysis (CPM). CPM, which was originally considered to be the result of rapid correction of chronic hyponatremia, is not necessarily accompanied by hyponatremia or drastic changes in serum sodium level. The mechanism of how hypophosphatemia causes CPM has not been fully elucidated. One hypothesis is that the lack of energy supply to glial cells because of the reduction of ATP production might lead to widespread dysfunction of Na+/K+-ATPase pumps, resulting in apoptosis.[80] Another possible mechanism may be the reduction of cell-protective organic osmolytes, such as phosphocreatine and glycerophosphorylcholine, as phosphate is required for their synthesis.[81]

7.5. Musculoskeletal system and others

Musculoskeletal system dysfunction secondary to hypophosphatemia can manifest clinically as weakness, myalgia or rhabdomyolysis. Some patients present proximal myopathy with difficulty walking. Depletion of ATP in myocytes, and probably the creatine kinase alterations as well, lead to muscle weakness and sarcolemmal rupture with rhabdomyolysis, which is especially common in alcoholic patients.[79] Rhabdomyolysis can lead to acute tubular necrosis due to myoglobinuria.

Hypophosphatemia can also trigger psychiatric symptoms, such as anxiety or visual or auditory hallucinations. On a gastrointestinal level, anorexia, nausea, vomiting, or changes in liver function tests may also appear. As a result of ATP deficiency dysphagia or ileus are possible.[20] Phosphorus depletion is also associated with insulin resistance and with hypomagnesemia due to magnesium excretion increases through the kidneys.

8. Diagnosis

Most patients with hypophosphatemia are asymptomatic, and it is an incidental finding. A clinician should have suspicion for phosphate abnormalities whenever an hypophosphatemia associated etiology is present. Hypophosphatemia is diagnosed with a simple serum measurement and etiology is typically evident from the history.[20]

If hypophosphatemia etiology is unknown we should determine renal phosphate excretion. It can be measured either from a 24-hour urine collection or by calculation of the fractional excretion of filtered phosphate (FEPO4). A 24-hour urine phosphate excretion greater than 100 mg or FEPO4 greater than 5% indicates renal phosphate wasting.

9. Treatment

The first step in the prevention of RFS development is to anticipate it. Guidelines for the prevention and treatment of RFS advise identification of individuals at risk, controlled hypocaloric nutritional treatment and supplementary electrolytes. However, not all vulnerable patients develop symptoms. A potential consequence of adherence to these untested guidelines is the delay of adequate nutrition to undernourished individuals.[42] The optimum timing for correcting biochemical abnormalities has been a source of controversy. The view that correction of electrolyte abnormalities must occur before commencement of feeding has been revised and NICE guidelines indicate that feeding and correction of biochemical abnormalities can occur in tandem without deleterious

effects to the patient.[66] Recently, based on the available evidence, Friedli et al. proposed an expert consensus algorithm for risk assessment, treatment, and monitoring of RFS in medical inpatients.[10]

To prevent RH we should supplement phosphate empirically before and during nutrition therapy. A minimum of 10-15 mmol of phosphate must be provided per 1000 kcal in order to maintain normal serum concentrations in patients with a normal renal function.[19] Most unstressed, well-nourished adult patients with normal renal function receiving PN require approximately 20–40 mmol/day. Patients with total body phosphate deficiency have higher needs. Severely malnourished patients may initially require 25%–50% higher doses of phosphate to prevent hypophosphatemia when initiating nutrition support. After starting nutrition therapy, electrolytes should be supplemented according to their serum levels and the response to the treatment.

Treatment for hypophosphataemia depends on its severity, the presence or absence of symptoms, the route of administration (enteral or parenteral) and the underlying causes.[19] It´s important to correct/remove the underlying cause when feasible. Some authors believe that treating hypophosphatemia is not necessary unless the patient has symptoms or the serum phosphate level is <1 mg/dL.[9] The amount of phosphate required to restore serum phosphorus and/or replect total-body phosphate is difficult to estimate because the volume of distribution of phosphate is highly variable and the serum phosphate level does not correlate with the body's total deposits.[37] Therefore, treatment with either oral or parenteral therapy is empirically determined and very close clinical and analytical monitoring are needed.

Phosphate repletion for phosphorus depletion can be given either orally or intravenously. Oral repletion is safer, but the absorption of oral phosphate is unpredictable and may cause diarrhea. Asymptomatic patients with functioning gastrointestinal tract who have mild or moderate hypophosphataemia can be treated with oral phosphates. When providing oral supplementation for mild to moderate hypophosphatemia, 32.3-64.6 mmol/d of phosphate for 7-10 days usually is adequate to replenish stores.[37] A liquid form is preferred in patients receiving EN. Although institutions may include an option for enteral supplementation as part of a correction protocol, there are limited published data describing the efficacy of this approach, especially in critically ill patients. In addition, enteral absorption may be decreased in patients with vitamin D deficiency.[27]

Patients with symptomatic moderate-severe deficiency and those who don´t tolerate oral supplements should receive intravenous (IV) supplementation.[27] A few regimens based on patient weight and serum phophorus concentration have been published, but these have been primarily in critically ill trauma and surgical patients with normal renal function.[82-84] Brown et al. designed a graduated phosphorus-dosing scheme based on the degree of hypophosphatemia: 0.32 mmol/kg for mild hypophosphatemia, 0.64 mmol/kg for moderate hypophosphatemia, and 1 mmol/kg for severe hypophosphatemia.[84] In patients with impaired renal function receiving nutrition support who are not being treated with continuous renal replacement therapy (CRRT), consider administering ≤ 50% of the empiric dose initially.[27] In patients undergoing CRRT hypophosphatemia can be prevented by using the dialysate and/or replacement solutions with phosphate.[85] When using weight-based dosing, "adjusting" weight should be considered to minimize the risk

of overdosing in obese patents (weight >130% of IBW or BMI ≥30 kg/m2).[27]

IV phosphorus products are available as either potassium or sodium salts. Potassium salts can be used in patients with simultaneous hypokalemia; otherwise, sodium salts are recommended. The calculated dose should be administered in 4 to 6 hours, without exceeding the limit of 7 mmol phosphate/hour to reduce the risk of calcium-phosphate precipitation and other infusion-related adverse effects. In patients with severe hypophosphatemia doses of 10-20 mmol/h were given for 1-3 hours without serious complications.[86]

IV repletion corrects hypophosphatemia faster, but adverse effects may include hyperphosphatemia, hypocalcemia, hypotension and arrhythmias related to faster rate of administration, hyperpotasemia (potassium salts), hypernatremia (sodium salts) and in patients with hypercalcemia calcium-phosphate intravascular precipitation, metastatic calcification, nephrocalcinosis and acute kidney injury.[37,63,87] A decrease in 1,25-dihydroxyvitamin D values occurs in phosphate-depleted patients after intravenous phosphate repletion which may contribute to hypocalcemia. Potassium salts may induce irritation or phlebitis with peripheral IV administration depending on the total dose, final potassium concentration and the rate of infusion.

Phosphorus can shift quickly between body compartments and serum concentrations can fluctuate. Data are lacking on the optimal time to recheck serum phosphorus concentration after supplementation. Arnold et al. recommend a serum phosphorus level be obtained 2-4 hours after the infusion and the dose be repeated until serum phosphorus level is >2 mg/dL.[37] Other published articles describe monitoring at the end of supplementation, 12-24 hours after or on a daily basis. Some authors recommend stopping repletion when serum phosphorus levels of 2 mg/dL is reached, but others continue the supplementatioin until the patient is asymptomatic or the serum phosphate concentration is within the normal range. Some patients will require multiple doses over several days to completely correct hypophosphatemia.[27]

10. Conclusions

Hypophosphatemia is a common and underdiagnosed adverse event in hospitalized patients, with a multifactorial etiology including insufficient intake, impaired absorption, redistribution and increased excretion of phosphorus. The degree of hypophosphatemia correlates with symptoms: mild to moderate hypophosphatemia is often asymptomatic while severe deficits can cause life-threatening complications. Treatment for hypophosphataemia depends on its severity, the presence or absence of symptoms, the route of administration and the underlying cause. There is no evidence based guidelines regarding neither the amount and timing of phosphorus replacement nor the optimal time to recheck serum phosphorus levels after supplementation.

Conflict of interest

Authors have no conflict of interest.

References

1. Pirlich M, Schütz T, Norman K, et al. The German hospital malnutrition study. Clin Nutr. 2006;25(4):563-572.

2. Felder S, Lechtenboehmer C, Bally M, et al. Association of nutritional risk and adverse medical outcomes across different medical inpatient populations. Nutrition. 2015;31(11-12):1385-1393.

3. Bally MR, Blaser Yildirim PZ, Bounoure L, et al. Nutritional Support and Outcomes in Malnourished Medical Inpatients: A Systematic Review and Meta-analysis. JAMA Intern Med. 2016;176(1):43-53.

4. Fung EC, Wickramasinghe SR, Panteli JV, Crook MA. Hypophosphataemia and parenteral nutrition; biochemical monitoring, incidence and outcomes. Br J Biomed Sci. 2017;74(1):48-51.

5. Ahmed S, Travis J, Mehanna H. Re-feeding syndrome in head and neck--prevention and management. Oral Oncol. 2011;47(9):792-796.

6. Keys A, Brozek J, Henschel A, Mickelson O, Taylor HD, editors. The Biology of Human Starvation. Vols. 1, 2. Minneapolis: University of Minnesota Press; 1950.

7. Brozek J, Chapman CB, Keys A. Drastic food restriction; effect on cardiovascular dynamics in normotensive and hypertensive conditions. J Am Med Assoc. 1948;137 (18):1569-1574.

8. Miller SJ. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Nutr Clin Pract. 2008;23(2):166-171.

9. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17(7-8):632-637.

10. Friedli N, Stanga Z, Culkin A, et al. Management and prevention of refeeding syndrome in medical inpatients: An evidence-based and consensus-supported algorithm. Nutrition. 2018;47:13-20.

11. Friedli N, Stanga Z, Sobotka L, et al. Revisiting the refeeding syndrome: Results of a systematic review. Nutrition. 2017;35:151-160.

12. Hoffmann M, Zemlin AE, Meyer WP, Erasmus RT. Hypophosphataemia at a large academic hospital in South Africa. J Clin Pathol. 2008;61(10):1104-1107.

13. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012;27(1):34-40.

14. Crook MA. Refeeding syndrome: problems with definition and management. Nutrition. 2014;30(11-12):1448-1455.

15. Fernández López MT, López Otero MJ, Alvarez Vázquez P, Arias Delgado J, Varela Correa JJ. Refeeding syndrome. Farm Hosp. 2009;33(4):183-193.

16. Marinella MA. Refeeding syndrome in cancer patients. Int J Clin Pract. 2008;62(3): 460-465.

17. Braun K, Utech A, Velez ME, Walker R. Parenteral Nutrition Electrolyte Abnormalities and Associated Factors Before and After Nutrition Support Team Initiation. JPEN J Parenter Enteral Nutr. 2016.

18. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. Crit Care. 2010;14(4):R147.

19. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005;20(6):625-633.

20. Sandeep Sharma, Danny Castro. Hypophosphatemia. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018

21. DeBiasse-Fortin MA. Minerals and trace elements. In: Matarese LE, Gottschlich MM, eds. Contemporary Nutrition Support Practice: A Clinical Guide. 2nd ed. Philadelphia, Pa: WB Saunders; 2003:164–172.

22. Bushinsky DA, Monk RD. Electrolyte quintet: Calcium. Lancet. 1998;352(9124): 306-311.

23. Khanal RC, Nemere I. Regulation of intestinal calcium transport. Annu Rev Nutr. 2008;28:179-196.

24. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy of Sciences, Institute of Medicine; 1997.

25. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. Lancet. 1998;352(9125):391-396.

26. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med. 1977;137(2):203-220.

27. Kraft MD. Phosphorus and calcium: a review for the adult nutrition support clinician. Nutr Clin Pract. 2015;30(1):21-33.

28. Crook MA. Management of severe hypophosphatemia. Nutrition. 2009;25(3): 368-369.

29. Peppers MP, Geheb M, Desai T. Endocrine crises. Hypophosphatemia and hyperphosphatemia. Crit Care Clin. 1991;7(1):201-214.

30. Lubos Sobotka. Basics in Clinical Nutrition: Refeeding syndrome. eESPEN, the European e-Journal of clinical Nutrition and Metaboism 2010;5:e146-e7.

31. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ. 2008;336(7659):1495-1498.

32. Hudson LD, Cumby C, Klaber RE, Nicholls DE, Winyard PJ, Viner RM. Low levels of knowledge on the assessment of underweight in children and adolescents among middle-grade doctors in England and Wales. Arch Dis Child. 2013;98(4): 309-311.

33. Kagansky N, Levy S, Koren-Morag N, Berger D, Knobler H. Hypophosphataemia in old patients is associated with the refeeding syndrome and reduced survival. J Intern Med. 2005;257(5):461-468.

34. Md Ralib A, Mat Nor MB. Refeeding hypophosphataemia after enteral nutrition in a Malaysian intensive care unit: risk factors and outcome. Asia Pac J Clin Nutr. 2018;27(2):329-335.

35. Lemon SJ, Zack SD, Voils SA. No difference in mechanical ventilation-free hours in critically ill patients who received intravenous, oral, or enteral phosphate replacement. J Crit Care. 2017;39:31-35.

36. Brunelli SM, Goldfarb S. Hypophosphatemia: clinical consequences and management. J Am Soc Nephrol. 2007;18(7):1999-2003.

37. Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. Am J Kidney Dis. 2012;60(4):655-661.

38. Rasmussen SO, Kristensen MB, Wessel I, Andersen JR. Incidence and Risk Factors of Refeeding Syndrome in Head and Neck Cancer Patients-An Observational Study. Nutr Cancer. 2016;68(8):1320-1329.

39. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. Arch Surg. 1996;131(10):1043-1047.

40. Camp MA, Allon M. Severe hypophosphatemia in hospitalized patients. Miner Electrolyte Metab. 1990;16(6):365-368.

41. Sacks GS, Walker J, Dickerson RN, Kudsk KA, Brown RO. Observations of hypophosphatemia and its management in nutrition support. Nutr Clin Pract. 1994;9(3):105-108.

42. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. BMJ Open. 2013;3(1).

43. Martínez MJ, Martínez MA, Montero M, Campelo E, Castro I, Inaraja MT. Hypophosphatemia in postoperative patients with total parenteral nutrition: influence of nutritional support teams. Nutr Hosp. 2006;21(6):657-660.

44. Stewart JAD, Mason DG, Smith N, Protopapa K, Mason M. A. Mixed Bag. An enquiry into the care of hospital patients receiving parenteral nutrition. 2010 May 5;1–102. Available from URL: http://www.ncepod.org.uk

45. Weinsier RL, Bacon J, Butterworth CE. Central venous alimentation: a prospective study of the frequency of metabolic abnormalities among medical and surgical patients. JPEN J Parenter Enteral Nutr. 1982;6(5):421-425.

46. Anderson D, Heimburger DC, Morgan SL, et al. Metabolic complications of total parenteral nutrition: effects of a nutrition support service. JPEN J Parenter Enteral Nutr. 1996;20(3):206-210.

47. Agudelo GM, Giraldo NA, Aguilar N, et al. Incidence of nutritional support complications in critical patients: multicenter study. Nutr Hosp. 2011;26(3):537-545.

48. Fernández López MT, Gómez Márquez Á, Casado Vázquez L, et al. Incidence of hypophosphatemia in not critically ill patients with enteral feeding. Nutr Hosp. 2017;34(4):761-766.

49. Lubart E, Leibovitz A, Dror Y, Katz E, Segal R. Mortality after nasogastric tube feeding initiation in long-term care elderly with oropharyngeal dysphagia--the contribution of refeeding syndrome. Gerontology. 2009;55(4):393-397.

50. Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr. 2011;30(3):365-368.

51. Liamis G, Milionis HJ, Elisaf M. Medication-induced hypophosphatemia: a review. QJM. 2010;103(7):449-459.

52. Iguchi Y, Mori K, Koike H, et al. Hypophosphataemic neuropathy during total parenteral nutrition. BMJ Case Rep. 2009;2009.

53. Marvin VA, Brown D, Portlock J, Livingstone C. Factors contributing to the development of hypophosphataemia when refeeding using parenteral nutrition. Pharm World Sci. 2008;30(4):329-335.

54. Fernández-Fernández FJ, Martín-Fernández A. Parenteral iron as a cause of hypophosphataemia. BMJ. 2014;349: g4616.

55. Fierz YC, Kenmeni R, Gonthier A, Lier F, Pralong F, Coti Bertrand P. Severe and prolonged hypophosphatemia after intravenous iron administration in a malnourished patient. Eur J Clin Nutr. 2014;68(4):531-533.

56. Adkins SM. Recognizing and preventing refeeding syndrome. Dimens Crit Care Nurs. 2009;28(2):53-58; quiz 59-60.

57. Chiappetta S, Stein J. Refeeding Syndrome: An Important Complication Following Obesity Surgery. Obes Facts. 2016;9(1):12-16.

58. Inaba Fernandes VP, Lomazi da Costa Pinto EA, Santana Ferreira Boin IF, Negrao Nogueira RJ. Phosphorus levels during infusion of parenteral nutrition with calorie-based phosphorus concentration: A case

series. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 2009;4:e252–6.

59. O'Connor G, Nicholls D. Refeeding hypophosphatemia in adolescents with anorexia nervosa: a systematic review. Nutr Clin Pract. 2013;28(3):358-364.

60. National Institute for Health and Clinical Excellence, Guideline for the Management of Refeeding Syndrome (Adults), NHS Foundation Trust, 2nd edition, 2009.

61. Marliss EB, Aoki TT, Unger RH, Soeldner JS, Cahill GF. Glucagon levels and metabolic effects in fasting man. J Clin Invest. 1970;49(12):2256-2270.

62. Klein S, Horowitz JF, Landt M, Goodrick SJ, Mohamed-Ali V, Coppack SW. Leptin production during early starvation in lean and obese women. Am J Physiol Endocrinol Metab. 2000;278(2): E280-284.

63. Boland K, Solanki D, O'Hanlon C. On behalf of IrSPEN's Standards and Guide-lines Committee. Prevention and Treatment of Refeeding Syndrome in the Acute Care Setting. 2013;www.irspen.ie.

64. McCray S, Walker S, Parrish CR. Much ado about refeeding. Pract Gastroenterol 2004;28:26–44.

65. Tsiompanou E, Lucas C, Stroud M. Overfeeding and overhydration in elderly medical patients: lessons from the Liverpool Care Pathway. Clin Med (Lond). 2013;13(3):248-251.

66. Khan LU, Ahmed J, Khan S, Macfie J. Refeeding syndrome: a literature review. Gastroenterol Res Pract. 2011;2011.

67. Preiser JC, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care. 2015;19:35.

68. Maiorana A, Vergine G, Coletti V, et al. Acute thiamine deficiency and refeeding syndrome: Similar findings but different pathogenesis. Nutrition. 2014;30(7-8):948-952.

69. Palesty JA, Dudrick SJ. Cachexia, malnutrition, the refeeding syndrome, and lessons from Goldilocks. Surg Clin North Am. 2011;91(3):653-673.

70. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition. 2010;26(2):156-167.

71. Gaudiani JL, Chu ES, Mehler PS. Clinical Issues Encountered in the Refeeding of the Patient with Anorexia Nervosa. Current Nutrition and Food Science 2009;5:13-6.

72. Datta HK, Malik M, Neely RD. Hepatic surgery-related hypophosphatemia. Clin Chim Acta. 2007;380(1-2):13-23.

73. O'Connor LR, Wheeler WS, Bethune JE. Effect of hypophosphatemia on myocardial performance in man. N Engl J Med. 1977;297(17):901-903.

74. Steinberg MH, Benz EJ, Adewoye HA, et al.Pathobiology of the human erythrocyte and its hemoglobins. In: Hoffman R, Benz EJ, Shattil SJ, et al, eds. Hematology: Basic Principles and Practice. 4th ed. Philadelphia, Pa: Elsevier Churchill Livingstone; 2005:442–454.

75. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313(7):420-424.

76. Marinella MA. Refeeding syndrome: an important aspect of supportive oncology. J Support Oncol. 2009;7(1):11-16.

77. Alsumrain MH, Jawad SA, Imran NB, Riar S, DeBari VA, Adelman M. Association of hypophosphatemia with failure-to-wean from mechanical ventilation. Ann Clin Lab Sci. 2010;40(2):144-148.

78. Håglin L. Using phosphate supplementation to reverse hypophos-phatemia and phosphate depletion in neurological disease and disturbance. Nutr Neurosci. 2016;19(5):213-223.

79. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. Medicine (Baltimore). 2000;79(1):1-8.

80. Ashrafian H, Davey P. A review of the causes of central pontine myelinosis: yet another apoptotic illness? Eur J Neurol. 2001;8(2):103-109.

81. Norenberg MD. Central pontine myelinolysis: historical and mechanistic considerations. Metab Brain Dis. 2010;25(1):97-106.

82. Clark CL, Sacks GS, Dickerson RN, Kudsk KA, Brown RO. Treatment of hypophosphatemia in patients receiving specialized nutrition support using a graduated dosing scheme: results from a prospective clinical trial. Crit Care Med 1995;23:1504-11.

83. Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM. Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. J Am Coll Surg 2004;198:198-204.

84. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. JPEN JParenter Enteral Nutr 2006;30:209-14.

85. Broman M, Carlsson O, Friberg H, Wieslander A, Godaly G. Phosphate-containing dialysis solution prevents hypophosphatemia during continuous renal replacement therapy. Acta Anaesthesiol Scand 2011;55:39-45.

86. Charron T, Bernard F, Skrobik Y, Simoneau N, Gagnon N, Leblanc M. Intravenous phosphate in the intensive care unit: more aggressive repletion regiments for moderate and severe hypophosphatemia. Intensive Care Med. 2003;29:1273-8.

87. Dwyer K, Barone JE, Rogers JF. Severe hypophosphatemia in postoperative patients. Nutr Clin Pract 1998;98:795-806.

