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REVIEW

Refeeding syndrome

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Thiamine

Abstract
Refeeding syndrome is a complex syndrome that occurs as a result of reintroducing nutrition (oral, enteral, or parenteral) to patients who are starved or malnourished. Patients can develop fluid-balance abnormalities, electrolyte disorders (hypophosphataemia, hypokalaemia, and hypomagnesaemia), abnormal glucose metabolism, and certain vitamin deficiencies. Refeeding syndrome encompasses abnormalities affecting multiple organ systems, including neurological, pulmonary, cardiac, neuromuscular, and haematological functions. Pathogenic mechanisms involved in the refeeding syndrome and clinical manifestations have been reviewed. We provide suggestions for the prevention and treatment of refeeding syndrome. The most important steps are to identify patients at risk, reintroduce nutrition cautiously and correct electrolyte and vitamin deficiencies properly.

PALABRAS CLAVE
Síndrome de realimentación;
Hipofosfatemia;
Hipopotasemia;
Hipomagnesemia;
Tiamina

Síndrome de realimentación

Resumen
El síndrome de realimentación (SR) es un cuadro clínico complejo que ocurre como consecuencia de la reintroducción de la nutrición (oral, enteral o parenteral) en pacientes malnutridos. Los pacientes presentan trastornos en el balance de fluidos, anomalías electrolíticas —como hipofosfatemia, hipopotasemia e hipomagnesemia— alteraciones en el metabolismo hidrocarbonado y déficits vitamínicos. Esto se traduce en la aparición de complicaciones neurológicas, respiratorias, cardíacas, neuromusculares y hematológicas. En este artículo se han revisado la patogenia y las características clínicas del SR, haciendo alguna sugerencia para su prevención y tratamiento. Lo más importante en la prevención del SR es identificar a los pacientes en riesgo, instaurar el soporte nutricional de forma prudente y realizar una corrección adecuada de los déficits de electrolitos y vitaminas.

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Definition

We use the term "refeeding syndrome" (RS) to describe the metabolic alterations that occur when administering nutrition, whether by oral, enteral, or parenteral means, to severely malnourished or food-deprived individuals.[1] The fundamental condition in RS is severe hypophosphataemia,[2] which is accompanied by fluid balance abnormalities, carbohydrate metabolism alterations, certain vitamin deficiencies such as thiamine deficiency, as well as hypopotassaemia and hypomagnesaemia.[2] Clinically, this signifies the appearance of neurological, respiratory, cardiovascular, haematological, and other abnormalities a few days after resuming feeding, which increases patient morbidity and even mortality.[3]

The classic study describing RS was carried out by Keys et al[4] in healthy males who were conscientious objectors during World War II. 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 results were seen after restoring normal nutrition to individuals who had been besieged or held in concentration camps during World War II.[5] Subsequently, with the arrival of parenteral (PN) and enteral (EN) nutrition, the same types of complications were seen in malnourished patients who received aggressive nutritional therapy.[6]

There are numerous causes of hypophosphataemia, hypomagnesaemia, and hypopotassaemia apart from RS, especially in severe cases with hospitalised patients. The most common are listed in Table 1, and should be taken into account when performing differential diagnosis.

Epidemiology

RS is a common phenomenon in malnourished patients with a previous depletion of lean body mass. Its incidence rate varies according to the series and the diagnostic criteria that are used. Hernández Aranda et al[7] reported an RS incidence rate of 48% in a cohort of 148 patients receiving nutritional therapy whose malnourishment ranged from mild to severe. González et al[8] diagnosed RS in 25% of 107 oncology patients who received PN or EN; the incidence rate was higher in the subgroup receiving EN. Flesher et al[9] evaluated the appearance of abnormalities consistent with RS in 51 patients receiving EN in whom the nutritional goal was reached in only 17 hours. Eighty percent of the patients

Table 1 Causes of hypophosphataemia, hypomagnesaemia, and hypopotassaemia

- Hypophosphataemia
  - Causes that provoke extra-intracellular mobility
    - Refeeding syndrome
    - Alkalosis
    - Gram-negative sepsis
    - Intoxication: salicylates
    - Drugs: insulin, intravenous glucose, adrenaline, salbutamol, terbutaline, dopamine, erythropoietin, G-CSF
  - Causes that decrease intestinal absorption
    - Drugs: antacids containing aluminium
  - Causes that increase renal excretion
    - Primary hyperparathyroidism
    - Secondary hyperparathyroidism
    - Renal tubular disorders
    - Hyperaldosteronism
    - Poorly controlled diabetes
    - Alcoholism
    - Hypercalcaemia
    - Hypomagnesaemia
    - Intoxication: iron, cadmium
    - Drugs: diuretics, corticosteroids, bicarbonate, oestrogens in high doses, iphosphamide, cysplatin, foscarnet, pamidronate
  - Other causes: vomiting, diarrhoea, and surgery
- Hypomagnesaemia
  - Causes provoking exit from the extracellular space
    - Refeeding syndrome
    - Correction of respiratory acidosis
    - Correction of diabetic ketoacidosis
    - Other: pancreatitis, transfusions, burns, sweating
  - Causes that decrease gastrointestinal absorption
    - Malabsorption syndrome
  - Causes that increase gastrointestinal losses
    - Vomiting, diarrhoea, fistulae
  - Causes that increase renal excretion
    - Tubular disorders
    - Hyperaldosteronism
    - Inappropriate secretion of antidiuretic hormone
    - Diabetes mellitus
    - Hyperthyroidism
    - Hypercalcaemia
    - Alcoholism
    - Drugs: diuretics (loop, thiazides, osmotics), cysplatin, pentamidine, cyclosporin, aminoglycosides, foscarnet, amphotericin B, tacrolimus
- Hypopotassaemia
  - Causes that provoke extra-intracellular mobility
    - Refeeding syndrome
    - Alkalosis
    - Hypothermia
    - Theophylline intoxication
    - Drugs: insulin, b-stimulants
  - Causes that provoke extrarenal losses
    - Profuse sweating
    - Diarrhoea, vomiting
    - Drugs: laxatives
  - Causes that increase renal excretion
    - Hyperaldosteronism
    - Diabetic ketoacidosis
    - Polyuria
    - Hypomagnesaemia
    - Drugs: diuretics (loop, potassium-sparing), penicillin, amphotericin B, aminoglycosides

presented phosphate, magnesium, or potassium deficiencies after beginning EN. The incidence rate ranged between 74% in the patient group considered "not at risk," and 93% in the "at risk" group[9] (Table 2).

Hypophosphataemia is a relatively frequent finding in hospitalised patients; it affects between 3% and 42% of them. The incidence rate is especially high in intensive care and infectious disease units.[10] Marik and Bedigian[11] detected hypophosphataemia related with refeeding in 34% of intensive care patients after a fast of only 48 hours.

Table 2 Patients at risk for developing refeeding syndrome

Kwashiorkor or marasmus
Anorexia nervosa
Malnutrition linked to chronic diseases, (cardiac cachexia, COPD, cirrhosis)
Chronic alcoholism
Cancer patients
Those with a 7-10 day fast associated with stress or depletion
Post-op patients
Morbidly obese patients following massive weight loss
Hunger strikers
Diabetic hyperosmolar decompensations

COPD indicates chronic obstructive pulmonary disease.

Physiopathology

The preferred sources of energy used by tissues are carbohydrates. Our bodies dispose of a limited reserve, in the form of glycogen stored in the liver and muscle tissue. During the initial fasting period, glycogen deposits are used as an energy source. When these deposits are exhausted, the proteolysis process begins. It provides amino acids for gluconeogenesis, which makes glucose available to those issues that depend on it (the cerebrum, renal medulla, and red blood cells). After 72 hours of fasting, the metabolic channels change to lipolysis and obtain free fatty acids in order to prevent the recruitment of proteins from skeletal muscle. These free fatty acids can follow 2 channels: on a peripheral level, they are used by cells to produce energy, and on a hepatic level, they are used as substrates for synthesising ketone bodies (acetyl-acetic acid, β-hydroxybutyric acid, and acetone) by ketogenesis. The brain can use ketone bodies that cross the haematoencephalic barrier as an energy source. However, these cells' ability to oxidise ketone bodies is limited, which leads to a condition of ketosis, followed by metabolic acidosis.

In addition to the metabolic response described above, certain hormonal changes intended to maintain vital functions also occur during this adaptive process: a decrease in insulin and an increase in glucagon,[12] increased secretion of the growth hormone (lipolytic and ketogenic action), decrease in insulin-like growth factor (IGF-1), decrease in triiodothyronine, increased cortisol secretion, decreased leptin[13,14] concentrations, and an increase in catecholamines. All of these hormonal changes lead to a diminished baseline metabolism and increase the availability of certain energetic substrates.

In addition to weight loss, a decrease in cell mass and an increase in extracellular water also occur during fasting. Plasma values for electrolytes such as potassium, phosphorus, and magnesium remain at normal levels; however, their total body amount decreases.

RS pathogenesis is complex, since it involves metabolic and physiological changes that occur during the substrate depletion and repletion phases, with resulting compartmental deviations of electrolytes, changes in glucose and vitamin metabolism and the use of corporal water. When feeding is resumed, particularly if it is carbohydrate-based, there is an increase in insulin secretion that favours anabolism and the entry of certain elements (phosphorus, potassium, and magnesium) into the cell interior, which gives rise to decreased plasma concentrations for those elements.[15] The exact mechanism by which the fluid imbalance occurs is unknown, but it is believed that water and sodium retention could be due to an anti-natriuretic effect caused by hyperinsulinaemia.[16] Thiamine is an essential cofactor in carbohydrate[17] metabolism, and therefore introducing high quantities of carbohydrates increases the demand for thiamine. Although it is difficult to know if the thiamine deficiency is due to refeeding or to the fasting state, malnourished patients are at risk of developing a deficiency and its associated complications. There is also an increase in T4 to T3 conversion,[18,19] which leads to an increase in energy output. Figure shows RS physiopathology.

Clinical manifestations

Clinical manifestations of RS derive from the effects that the hydroelectrolyte alterations and vitamin deficiencies have on different systems and organs (Table 3).

Hypophosphataemia

Phosphate is the main intracellular anion. There are approximately 700 g of phosphate deposits in an average adult body, 80% of which are located in the skeleton, nearly 20% in soft tissue and muscle,[2] and only 1% in extracellular liquid. The average consumption of phosphorus is between 1000 to 1400 mg daily for a Western diet. Eighty percent of the ingested phosphorus is absorbed, most through the jejunum by passive transport, and a small percentage through vitamin D-dependent active transport.[20] The main elimination channel for phosphorus is the kidney; 90% of all phosphorus is excreted through the urinary tract and only 10% through the gastrointestinal tract.[21]

The normal serum phosphorus level stays within a narrow margin of 2.5 to 4.5 mg/dL (1 mg/dL = 0.32 mmol/L), although its concentration level does not always reflect the total body content. Short-term regulation of phosphorus levels is done by transcellular flow between intracellular and extracellular compartments, depending on the carbohydrates and lipids ingested, and on any modifications in the acid-base balance.[22] Skeletal muscle and bone are endogenous phosphorus reservoirs; therefore, in the event of hypophosphataemia, muscular phosphorus is recruited to

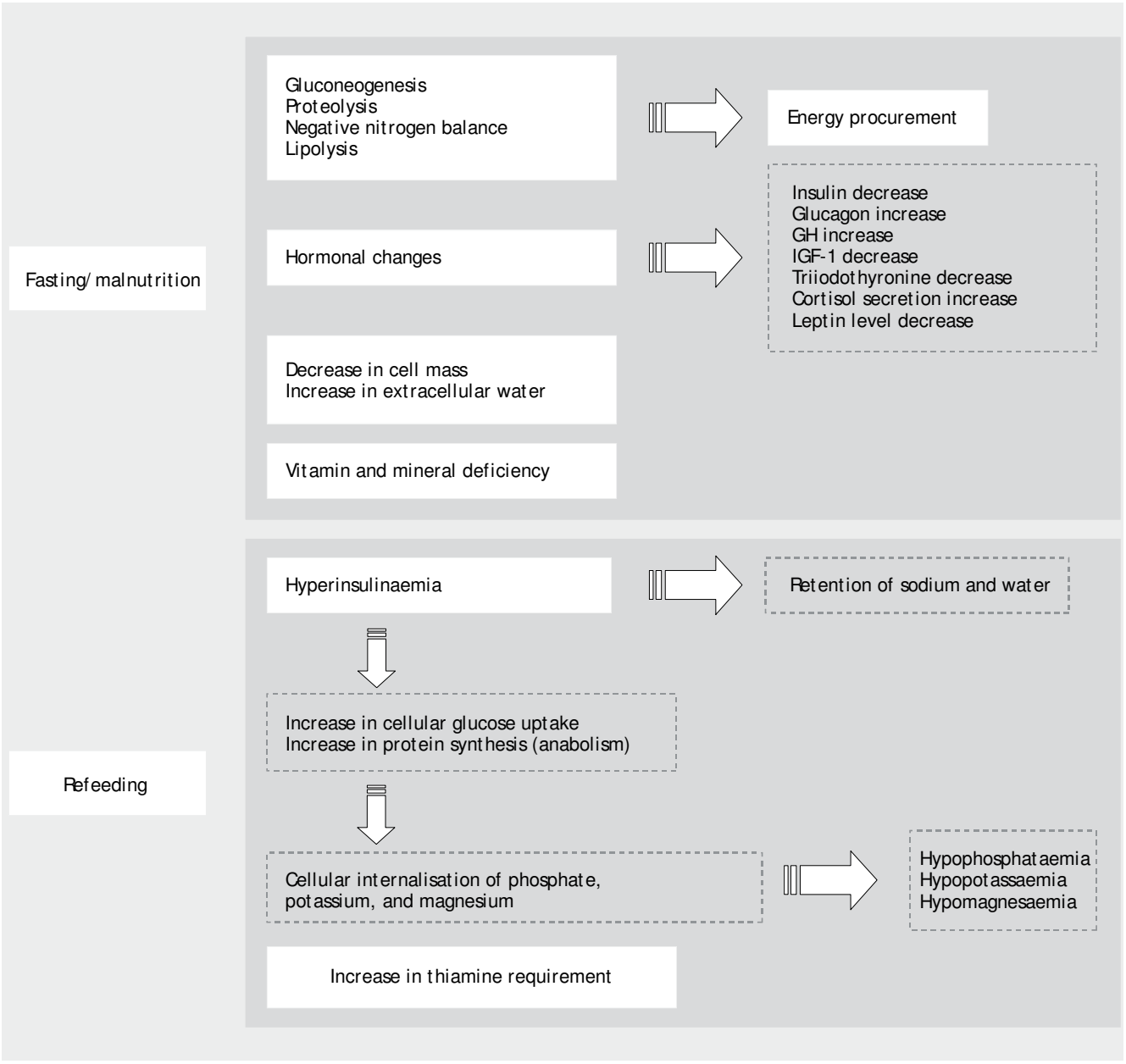

Figure Refeeding syndrome physiopathology.

supply vital organs (brain, heart, suprarenal veins, kidneys, thyroid, pancreas, and spleen). Long-term regulation depends on the kidney. Phosphorus is filtered in the glomerule and 85% of the filtrate is reabsorbed in the proximal tubule through the type II sodium-phosphate transporter (NaPi-2a). The tubular phosphate reabsorption rate depends on the number of transporters. Parathyroid hormone (PTH) causes intracellular internalisation and degradation of transporters, which leads to a decrease in phosphate reabsorption and the appearance of phosphaturia.[23] In addition to PTH, other hormonal factors also influence NaPi transporters: insulin, glucagon, growth hormone, glucocorticoids, and 1-25 dihydroxyvitamin D.[24]

The phosphate is essential for cell function. It has a structural role as a component making up phospholipids, nucleoproteins and nucleic acids; it plays a key part in metabolic pathways, such as glycolysis and oxidative phosphorilation,[25] and it is implicated in the control of enzymatic processes through protein phosphorilation. Phosphate acts as a cofactor of glyceraldehyde 3-phosphate dehydrogenase. Therefore, in the event of hypophosphataemia, it decreases production of 2,3 diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP).[26] 2,3-DPG makes up 80% of the organic phosphate composition of erythrocytes and it is involved in regulating the oxygen-haemoglobin dissociation curve, and therefore, the liberation of oxygen to tissues.[27]

Hypophosphataemia in RS typically appears in the 3 first days after beginning nutritional therapy. The factors that various studies have related to its appearance are as follows:

Table 3 Clinical manifestations of refeeding syndrome

System	Hypophosphataemia	Hypopotassaemia	Hypomagnesaemia	Thiamine deficiency	Na+ Retention/ fluid overload
Digestive	Anorexia Nausea Vomiting	Vomiting Ileum Constipation Worsening of hepatic encephalopathy	Anorexia Nausea Vomiting Diarrhoea		
Cardiovascular	Heart failure Arrhythmias Sudden death	Myocardial contractility alteration Electrocardiographic changes (depressed ST, flattened or inverted T waves, U waves), arrhythmias (auricular tachycardias, bradicardia, block auriculoventricular, tachycardia or ventricular fibrillation) increase from sensibility to digital intoxication, hypothension, sudden death	Electrocardiographic changes (long PR, wide QRS, long QT, decrease ST, waves T pointed or flattened), arrhytmias (auricular fibrillation, ventricular arrhytmias, torsade de pointes, extrasistoles ventricular)	Heart failure	Heart failure
Respiratory	Altered diaphragm contractility Respiratory failure	Respiratory insufficiency			
Haemato-logical	Increased haemoglobin affinity for oxygeno Haemolytic anaemia Thrombocytopaenia Altered platelet function Altered white blood cell function				
Skeletal muscular	Weakness Myalgias Rhabdomyolysis Proximal myopathy	Weakness, rhabdomyolysis, muscular necrosis	Weakness Fasciculations Tetany		
Nervous	Paraesthesia Acute flaccid paralysis Cranial pair paralysis Convulsions Drowsiness Disorientation Coma	Paraesthesia, arreflexia, paralysis	Ataxia Irritability Convulsions Vertigo Personality alterations Coma	Peripheral neuropathy Wernicke's encephalo-pathy Korsakov's syndrome	
Kidney	Acute tubular necrosis	Polyuria			
Metabolism	Hypomagnesaemia	Carbohydrate intolerance, metabolic alkalosis	Hypocalcaemia Hypopotassaemia	Lactic acidosis	

hypoalbuminaemia, prealbumin <110 g/L, and forearm circumference and muscular area in the 5th percentile. It is likely that these factors merely represent the patient's previous severely malnourished state and do not play a pathogenic role in the appearance of hypophosphataemia.[26]

Hypophosphataemia is considered severe when serum phosphate is <1 or 1.5 mg/dL,[26] moderate when the values are between 1.5 and 2.2 mg/dL and mild when serum phosphate levels are between 2.3 and the lower normal limit.[1] Symptoms appear when phosphorus levels are <1.5 mg/dL, or at higher levels if the decrease is rapid, and they are very apparent when levels are <1 mg/dL. Severe hypophosphataemia induces significant alterations on the neurological, cardiac, respiratory, and haematological levels, and can lead to death.[1] The mortality rate in patients with severe hypophosphataemia is 30%.[28]

Cardiovascular system. Cardiovascular complications appear in the first week in which nutrition is resumed. Prolonged fasting leads to the atrophy and depletion of ATP in myocardial cells, which results in contractile alteration. In this situation, the replacement of liquids in conjunction with the retention of sodium and water secondary to refeeding with carbohydrates creates a volume overload that can give rise to heart failure. Severe hypophosphataemia leads to changes in cardiac function that are related to a depressed myocardial function due to ATP depletion and direct myocardial damage.[3] In a group of patients with phosphate levels between 0.7 and 1.4 mg/dL, O'Connor et al[29] describe decreases in volume per beat, mean arterial pressure, and cardiac output and an increase in pulmonary capillary pressure that improve significantly when phosphate is replaced.

In this situation, hypotension, pericardial effusion, shock, arrhythmias, and sudden death may occur. Hypophosphataemia is a direct cause of ventricular arrhythmias; the risk increases if hypomagnesaemia and hypopotassaemia are simultaneous.[30] Arrhythmias appear in up to 20% of hypophosphataemic patients with no underlying heart disease and in the event of an acute myocardial infarction, there is an increased risk of ventricular tachycardia.

Haematological system. Hypophosphataemia causes a decrease in ATP and intraerythrocytic 2,3-DPG. The decrease in 2,3-DPG increases haemoglobin's affinity for oxygen, thus shifting the dissociation curve to the left and consequently decreasing oxygen liberation to peripheral tissues.[2] The 20%-50% decrease in intraerythrocytic ATP with respect to its normal value causes the appearance of reversible spherocytosis with an increase in cell membrane rigidity.[31] This contributes to worsening tissue hypoxia because it impedes the passage of erythrocytes through the capillaries, which also leads to the onset of haemolytic anaemia.

Hypophosphataemia severely alters platelet survival and function and can cause thrombocytopaenia, 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.[32]

Respiratory system. Respiratory dysfunction in patients with hypophosphataemia is secondary to the glycolysis decrease, and probably also to the drop in ATP levels in respiratory muscles. Severe hypophosphataemia alters diaphragm contractility.[33] The clinical profile may present as decreased vital capacity, respiratory failure or difficulty disconnecting patients from mechanical ventilation.

Nervous system. The mechanism for neurological dysfunction in hypophosphataemia is not well-defined, but it has been suggested that tissue hypoxia secondary to haemolytic anaemia and haemoglobin's increased affinity for oxygen could be the cause.[3] Neurological alterations described in relation with hypophosphataemia are as follows: paralysis of cranial pairs, paraesthesia, fatigue, tetany, hallucinations, delirium, convulsions, lethargy, confusion, and coma. Some patients may present a profile similar to Guillan-Barré syndrome, which manifests as acute flaccid paralysis.[32] For RS patients who develop neurological dysfunction, we must consider the possibility of Wernicke's encephalopathy.

Musculoskeletal system Musculoskeletal system dysfunction secondary to hypophosphataemia can manifest clinically as weakness, myalgia, rhabdomyolysis, or diaphragm weakness. 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 with RS.[32] Rhabdomyolysis can lead to the appearance of acute tubular necrosis.

Others. Hypophosphataemia can also provoke 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.[26] Magnesium excretion increases in the kidneys, and hypomagnesaemia appears.[34]

Hypopotassaemia

Potassium is the main intracellular cation. Ninety-eight percent of the body's total calcium is located in the intracellular space. Excretion takes place through the kidneys (80%), and the rest is eliminated in faeces and sweat. Potassium has various physiological functions and contributes to the maintenance of membrane potential and the regulation of glycogen and protein synthesis. Hypopotassaemia alters the transmembrane action potential, resulting in its hyperpolarisation and altered muscle contractility.[35] The body's potassium content is regulated by the kidneys. The distal neuron secretes potassium in response to aldosterone, alkalosis, a potassium-rich diet or an increase in sodium delivery to the distal convoluted tubule.[36]

We speak of mild to moderate hypopotassaemia when serum potassium levels are between 2.5 and 3.5 mEq/L. The patient may present gastrointestinal symptoms, such as nausea, vomiting, and constipation as well as weakness. If it is untreated, it can progress to severe hypopotassaemia (serum potassium <2.5 mEq/L) with the appearance of neuromuscular dysfunction (flaccid paralysis, paraesthesia, rhabdomyolysis, muscle necrosis, respiratory failure, confusion) and disorders affecting myocardial contractility and signal conduction. Severe hypopotassaemia provokes electrocardiographic changes, such as ST segment depression, flattened, or inverted T wave, or presence of U waves.[37] The patient may present cardiac arrhythmias, from atrial tachycardia, bradycardia, atrioventricular block

and ventricular extrasystoles to tachycardia, ventricular fibrillation, and even sudden death. Other clinical signs of hypopotassaemia are the appearance of glucose intolerance, metabolic alkalosis, worsening of hepatic encephalopathy and increased digitalis toxicity.[26]

Hypomagnesaemia

Magnesium is the second most abundant intracellular cation (the most abundant divalent cation). Ninety-nine percent of the body's total magnesium is intracellular and located fundamentally in bone and muscle. Therefore, as with phosphate or potassium, serum levels do not properly reflect the body's total magnesium or magnesium levels in intracellular fluid.

Only 30%of the magnesium that is ingested is absorbed. Absorption takes place in the proximal part of the small intestine and is not vitamin D dependent. Excretion is fundamentally renal.[26] It acts as a cofactor of numerous enzymes and participates in regulating different biochemical reaction, such as oxidative phosphorylation.

Hypomagnesaemia is frequent in critically ill patients, and it is associated with increased morbidity and mortality. Normal serum levels are between 1.8 and 2.5 mg/dL (0.65-1 mmol/L). Patients with mild to moderate hypomagnesaemia (serum magnesium level between 1 and 1.5 mg/dL) are generally asymptomatic, which is not the case for those with severe hypomagnesaemia (serum levels <1 mg/dL). It has diverse clinical manifestations: neuromuscular dysfunction (trembling, paraesthesia, tetany, hyperreflexia, fasciculations, convulsions, ataxia, nystagmus, vertigo, muscle weakness, depression, irritability, psychotic profile, etc), electrocardiographic changes (prolonged PR interval, long QRS complex, prolonged QT interval, depressed ST segment, pointed or flattened T waves), cardiac arrhythmias (atrial fibrillation, ventricular tachycardia, *torsades de pointes*), and even death.

At the same time, hypomagnesaemia can favour the appearance of hypocalcaemia or hypopotassaemia, or complicate the treatment of pre-existing disorders. Hypocalcaemia induced by hypomagnesaemia is the result of alterations in PTH secretion and action upon target cells in bone and kidney tissue.[38] Resistance to vitamin D is also characteristic of hypomagnesaemia; it is related to an anomaly in 1-α-hidroxylation of 25(OH)D in the kidney, and to tissues being resistant to $1,25(OH)_2D_3$. Hypomagnesaemia-induced hypopotassaemia is due to an alteration in Na+/K+-ATPase activity, and increased renal loss of that electrolyte.

Thiamine deficiency

Thiamine or vitamin B^1 is a hydrosoluble vitamin which is necessary for carbohydrate metabolism because it acts as a cofactor for pyruvate dehydrogenase and transketolases. Thiamine deficiency causes an increase in blood levels of pyruvate, which is transformed into lactate. This excessive lactate formation gives rise to lactic acidosis. The minimum recommended allowance in adults is 1 mg daily. The vitamin's absorption efficiency is greater than 80%, and absorption takes place by a specific active transport mechanism in the proximal part of the small intestine. There are about 30 mg of deposits in the body, and they become rapidly depleted in the event of malnutrition. The clinical conditions that are most commonly associated with thiamine deficit are chronic alcoholism, malabsorption syndromes, and pregnancy-related nausea and vomiting. Thiamine deficiency can lead to the appearance of heart failure, Wernicke's encephalopathy (eye disorders, confusion, ataxia, and coma), and Korsakov's syndrome (short-term memory loss and confabulation).[2]

Ingesting carbohydrates increases the need for thiamine. The appearance of Wernicke's encephalopathy has been described in malnourished patients with a thiamine deficit who received PN with a high carbohydrate content.[39]

Sodium retention and fluid overload

Sodium retention and expansion of extracellular fluid, with the accompanying risk of cardiac decompensation, may appear in early phases of RS.[40] The risk is greater in patients with severe malnutrition, due to possible myocardial atrophy and hypocontractility.

Prevention

RS not well understood by medical professionals outside of the nutritional specialty and it is probably underdiagnosed.[1] Factors commonly associated with the appearance of RS are the presence of malnutrition, aggressive refeeding methods in early stages without adequate phosphate, magnesium, potassium, and thiamine supplements, and the presence of associated conditions which exacerbate the micronutrient, mineral and electrolyte deficiencies.[41] To prevent the onset of RS and avoid the associated morbidity and mortality, we should follow a list of key steps, shown below:

1. Perform a complete medical and nutritional assessment of the patient before beginning nutrition therapy. This will enable us to identify patients at risk for developing RS (Table 2).
2. Monitor the patient analytically before and during refeeding. This includes a complete haemogram and biochemical profile. Serum levels of phosphorus, magnesium and potassium may not reflect the body's total deposits in a reliable way; testing urine may be useful for detecting deficiencies.
3. Correct the water balance and electrolyte anomalies (especially hypophosphataemia, hypopotassaemia, and hypomagnesaemia) before beginning to administer nutrients. In practice, this means delaying feeding between 12 and 24 hours.
4. Avoid overfeeding, regardless of the method used to estimate caloric objectives. The minimum amount of glucose required in a 70 kg adult to suppress gluconeogenesis, store proteins and provide the central nervous system with fuel is 100-150 g/day. The goal for protein is about 1.2 to 1.5 g/kg/day, although there will be patients with larger or smaller requirements.
5. Resume feeding with caution (25%of the calculated need on the first day) and gradually raise the food supply to the target level in 3 to 5 days.[1] Other authors recommend

beginning with 20 kcal/kg/day or an average of 1000 kcal/day, and slowly raising the amount during the first week until the patient is metabolically stable.[3]

6. Supplement electrolytes empirically before and during nutrition therapy. The increase in the calorie load decreases serum phosphorus levels. 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. Patients with severe malnutrition, critical illnesses, trauma or burns may suffer from a total body phosphate deficiency, and also potassium and magnesium deficiencies, so their needs will be higher. After starting nutrition therapy, electrolytes will be supplemented according to their serum levels and the response to the treatment.[1]
7. Restrict sodium (<1 mmol/kg/day) and liquids to avoid volume overload. Liquids will be restricted in such a way as to allow renal function to be maintained, replace lost liquids and avoid weight gain. Patients should not gain more than 0.5-1kg per week. Any weight gain above 1 kg/week is probably the result of retaining fluids.[42]
8. Administer vitamin supplements: parenteral multivitamin formulas provide the vitamin requirements recommended by the American Medical Association. They contain 3 or 6 mg thiamine. Thiamine requirements are higher in the malnourished, alcoholics, patients recovering from operations and patients who have undergone fasting or who have suffered serious episodes of vomiting. We recommend the empirical administration of 50 to 250 mg thiamine at least 30 minutes before beginning feeding.[2] Thiamine should be administered in doses of 50 to 100 mg/day intravenously (IV) or 100 mg/day orally during 5 to 7 days in patients at risk for this vitamin deficiency or for developing RS.[1] Patients may also be given 1 to 5 mg/day of folic acid during 5 to 7 days, although this does not seem to prevent RS.[2] Administering a multivitamin complex to these patients on a daily basis seems to be a safe and inexpensive way of preventing complications.
9. Monitor the patient strictly. The goal is early detection of any data suggesting RS. There should be routine checks of the heart and respiratory rates, arterial pressure and pulse oximetry. It is important to assess the water balance, weigh patients regularly and perform physical examinations to search for oedema or other signs that would indicate a volume overload. Detecting any symptoms or signs that would indicate neuromuscular dysfunction is also important, and electrocardiograph monitoring should be used when possible.[1]

Treatment

If a patient is diagnosed with RS, nutrition therapy must be discontinued immediately. Treatment will include taking the necessary supplementary steps (treating cardiovascular and respiratory manifestations, etc) and correcting electrolytic anomalies. In the event of neurological changes, a dose of 100 mg IV thiamine must also be administered. Nutrition may be reintroduced when the patient is asymptomatic and stable. A slow pace is recommended when resuming feeding (approximately 50% of the pace that had been followed previously), with gradual increases over 4 to 5 days, supplementing electrolytes and vitamins appropriately and carefully monitoring the patient.

Treating hypophosphataemia

Treatment for hypophosphataemia depends on its severity, the presence or absence of symptoms and the route of administration that we may use (enteral or parenteral).[1] Some authors believe that treating it is not necessary unless the patient has symptoms or the serum phosphate level is <0. 3mmol/L (1 mg/mL).[2] In Table 4, we can see some of the pharmacological forms, and their content, which we can use for treating hypophosphataemia, hypopotassaemia, and hypomagnesaemia.

Asymptomatic patients with functioning gastrointestinal tracts who have mild[1] or moderate[43] hypophosphataemia can be treated with oral phosphates, keeping in mind that it can cause diarrhoea. Symptomatic patients with a severe deficiency, or those whose digestive tract is not functional, will receive IV supplementation. The recommended doses are empirical, since the serum phosphate level does not correlate with the body's total deposits and there is no way of predicting the response to supplementation. For this reason, very close clinical and analytical monitoring is needed. One possible guideline for replacing IV phosphate would be administering 0.08-0.16 mmol/kg weight when serum phosphate is 2.3-2.7 mg/dL; 0.16-0.32 mmol/kg in patients with levels of 1.5-2.2 mg/dL and 0.32-0.64 mmol/kg if phosphate is <1.5mg/dL.[44] The calculated dose should be administered in 4 to 6 hours, without exceeding the limit of 7 mmol phosphate/hour. Administering IV phosphate in patients with hypercalcaemia or hyperpotassaemia is contraindicated, due to risk of metastatic calcification.[26] Side effects include hyperphosphataemia, hypocalcaemia, tetany, hypotension, hyperpotassaemia, hypernatraemia, and metastatic calcification.[45] Therefore, some authors recommend suspending its administration upon reaching serum levels of 1-2 mg/dL;[46] others, however, continue with the supplement until the patient is asymptomatic or the serum phosphate concentration is within the normal range.

Treating hypopotassaemia

The potassium supplement may be administered orally or intravenously. We use the IV route to treat patients who are symptomatic, have a severe deficit, or who cannot use their digestive tracts. In addition, we must keep in mind that oral potassium may cause gastrointestinal side effects (colic, diarrhoea). An initial dose of 1.2-1.5 mEq/kg is recommended, adjusting the dosage according the clinical response and serum concentration; in cases of severe deficiency, up to 2.5 mEq/kg may be needed.[47] IV potassium should not be administered quickly. Release speeds of 10-20 mEq/hour are considered safe, with a maximum of 40 mEq/hour. If the speed is above 10 mEq/hour, using a central line with simultaneous cardiac monitoring is recommended. Potassium concentration in solutions should not be higher than 80 mEq/L when administering by a peripheral vein and 120 mEq/L for central lines.[1]

Table 4 Main phosphate, potassium, and magnesium preparations

Product	Electrolyte contribution
Intravenous delivery	
Monopotassium phosphate 1 M 10 mL (magistral formula)	1 mEq/mL potassium, 1 mmol/mL phosphate (30.9 mg/mL)
Monopotassium phosphate 1 M 10 mL (magistral formula)	1 mEq/mL sodium, 1 mmol/mL phosphate (30.9 mg/mL)
Sodium glycerophosphate (Meinsol KP 242) 1 0mL	2 mEq/mL sodium, 1 mmol/mL phosphate
Dipotassium phosphate 1M 10 mL	2mEq/mL potassium, 1 mmol/mL phosphate
Potassium chlorate 1 M® 10mL	1 mEq/mL potassium (38.9 mg/mL); 1 mEq/mL chlorate
Potassium chlorate 2 M® 10mL	2 mEq/mL potassium (77.4 mg/mL); 2 mEq/mL chlorate
Potassium acetate 1 M® 10mL	1 mEq/mL potassium, 1 mEq/mL acetate
Ap inject. potassium chlorate solution® vial 20 mL	2 mEq/mL potassium, (78.25 mg/mL)
Potassium chlorate 18.4%® 10 mL	2.5 mEq/mL potassium (96.5 mg/mL); 2.5 mEq/mL chlorate
Magnesium sulphate 15%® 10 mL (foreign medication)	1.5 salt, 1.2 mEq/mL magnesium (0.6 mmol/mL; 14.8 mg/mL)
Oral delivery	
Sodium phosphate monobasic NM® in packets of 3.56 g salt	26 mmol phosphate (800 mg)
Phosphate Sandoz Forte® tablets (foreign medication)	20.4 mEq sodium; 3.1 mEq potassium, 16.1 mmol phosphate (500 mg)
Potasion 600 mg® capsules	8 mEq potassium (313 mg)
Potasion solution®	1320 mg/5 mL salt, 1 mEq/mL potassium (39 mg/mL)
Boi K® effervescent tablets	640 mg salt; 10 mEq potassium (390 mg)
Boi K® aspartic acid effervescent tablets	1825 mg salt; 25 mEq potassium (975 mg)
Magnesioboi® tablets	500 mg salt, 3.9 mEq magnesium, (1.95 mmol; 47.5 mg)
Actimag® oral solution	2000 mg/5 mL salt, 14.3 mEq/5 mL magnesium (7.15 mmol; 170 mg)
Magnesium Pyre® tablets	570.6 mg salt, 5.56 mEq magnesium, (2.78 mmol; 67.9 mg)
Magnogene® tablets	198.84 mg salt, 4.25 mEq magnesium, (2.12 mmol; 51.4 mg) 3,9 mEq de magnesio (1,95 mmoles; 47,5 mg)

Treating hypomagnesaemia

Severe hypomagnesaemia (magnesium <1 mg/dL) is associated with a total body magnesium deficiency of 1-2 mEq/kg. Oral supplements are absorbed poorly and cause diarrhoea and gastrointestinal distress. IV treatment should be administered to symptomatic patients or those with severe hypomagnesaemia. The empirical recommendation for asymptomatic patients with mild to moderate hypomagnesaemia is to administer 8-32 mEq magnesium up to a maximum of 1 mEq/kg. In symptomatic patients with severe hypomagnesaemia, the recommendation is 32-64 mEq magnesium, up to a maximum of 1.5 mEq/kg.[48] Renal elimination of magnesium is rapid (50% of the IV dose is eliminated in the urine) and reaching equilibrium between intra and extravascular space is a slow process,[49] which is why we recommend slow release and monitoring plasma levels 12-24 hours after replacement. Normally, doses of up to 6 g of magnesium sulphate (1 g of magnesium sulphate contains 8 mEq magnesium) are administered in 6-12 hours

and higher doses in 12-24 hours, without exceeding the maximum speed of 1 g magnesium sulphate and the maximum dose of 12 g.[1] In exceptional cases of severe symptomatic hypomagnesaemia, 32 mEq magnesium may be administered in 4-5 minutes.[50]

Replacing phosphate, potassium, and magnesium in patients diagnosed with RS who have altered renal function must be done carefully. This means that in patients with a creatinine clearance <50 mL/min, creatinine ≥2 mg/dL or oligoanuria, and who are not undergoing kidney replacement therapy, ≤50% of the calculated empirical dose for these electrolytes should be administered initially.[1]

Treatment for thiamine deficiency and the method to treat retaining sodium/fluids was discussed above in the "prevention" section.

Conclusion

Refeeding syndrome is a potentially serious clinical profile. Preventing the system requires identification of at-risk individuals, as well as providing nutrition therapy carefully with proper monitoring. Once a patient is diagnosed with RS, nutrition therapy must be suspended immediately, the supporting measures must be applied, and underlying electrolyte imbalances must be corrected.

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