Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

The refeeding syndrome. Importance of phosphorus☆

Marta Araujo Castro[a,*], Clotilde Vázquez Martínez[b]

[a] Servicio de Endocrinología y Nutrición, Hospital Universitario Rey Juan Carlos, Madrid, Spain
[b] Servicio de Endocrinología y Nutrición, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

ARTICLE INFO

Article history:
Received 29 September 2017
Accepted 2 December 2017
Available online xxx

Keywords:
Refeeding syndrome
Hypophosphataemia
Starvation
Hypokalaemia
Hypomagnesaemia
Prevention

ABSTRACT

Refeeding syndrome (RS) is a complex disease that occurs when nutritional support is initiated after a period of starvation. The hallmark feature is the hypophosphataemia, however other biochemical abnormalities like hypokalaemia, hypomagnesaemia, thiamine deficiency and disorder of sodium and fluid balance are common.

The incidence of RS is unknown as no universally accepted definition exists, but it is frequently underdiagnosed.

RS is a potentially fatal, but preventable, disorder. The identification of patients at risk is crucial to improve their management.

If RS is diagnosed, there is one guideline (NICE 2006) in place to help its treatment (but it is based on low quality of evidence).

The aims of this review are: highlight the importance of this problem in malnourished patients, discuss the pathophysiology and clinical characteristics, with a final series of recommendations to reduce the risk of the syndrome and facilitate the treatment.

El síndrome de realimentación. Importancia del fósforo

Palabras clave:
Síndrome de realimentación
Hipofosfatemia
Ayuno
Hipopotasemia
Hipomagnesemia
Prevención

RESUMEN

El síndrome de realimentación es una enfermedad compleja que ocurre cuando se inicia el soporte nutricional después de un periodo de ayuno. La característica principal es la hipofosfatemia, sin embargo, también son comunes otras alteraciones bioquímicas como la hipomagnesemia, el déficit de tiamina y las alteraciones hídrico-electrolíticas.

Su incidencia es desconocida, ya que no existe una definición universalmente aceptada, pero con frecuencia está infradiagnosticado.

El síndrome de realimentación es un trastorno potencialmente fatal pero prevenible. Identificar a los pacientes en riesgo es crucial para mejorar su manejo.

Si se diagnostica existen unas guías (NICE 2006) para orientar su tratamiento (pero basadas en un bajo grado de evidencia).

Los objetivos de esta revisión son: destacar la importancia de este problema en pacientes desnutridos, discutir su fisiopatología y características clínicas y dar una serie de recomendaciones finales para disminuir el riesgo de desarrollarlo y facilitar su tratamiento.

Introduction and definition

The refeeding syndrome (RS) is a complex disorder, in which the key event is the development of severe hypophosphataemia after reintroduction of nutrition, whether oral, enteral or parenteral in malnourished or deprived patients. Anomalies also occur in the water balance and hydrocarbon metabolism, deficiency of vitamins (especially thiamine) and other electrolytes.[1,2] All this translates

☆ Please cite this article as: Araujo Castro M, Vázquez Martínez C. El síndrome de realimentación. Importancia del fósforo. Med Clin (Barc). 2018. https://doi.org/10.1016/j.medcli.2017.12.008

* Corresponding author.
E-mail address: martaazul.2a@hotmail.com (M. Araujo Castro).

Table 1
Causes of hypophosphataemia, hypokalaemia and hypomagnesaemia.

Hypophosphataemia	Hypomagnesaemia	Hypokalaemia
Increase extra-intracellular mobility	*Increase output to the extracellular space*	*Increase intra-extracellular mobility*
RS	RS	RS
Alkalosis	Respiratory acidosis correction	Alkalosis
Gram-negative sepsis	Diabetic ketoacidosis correction	Hypothermia
Salicylate toxicity	Other: pancreatitis, transfusions, burns, sweating	Theophylline intoxication
Drugs: insulin, intravenous glucose, adrenaline, salbutamol, terbutaline, dopamine, etc.		Drugs: insulin, foscarnet, amphotericin B, tacrolimus
Decreased intestinal absorption	*Decreased absorption or increase intestinal losses*	*Increase extrarenal losses*
Drugs: antacids with aluminium	Malabsorption syndrome	Profuse sweating
	Vomiting, diarrhoea, fistulas	Diarrhoea, vomiting
		Drugs: laxatives
Increased renal excretion	*Increased renal excretion*	*Increased renal excretion*
Primary and secondary hyperparathyroidism	Tubular disorders	Hyperaldosteronism
Tubular disorders	Hyperaldosteronism	Diabetic ketoacidosis
Hyperaldosteronism	SIADH	Polyuria
Poorly controlled diabetes	Diabetes mellitus	Hypomagnesaemia
Alcoholism	Hyperthyroidism	Drugs: diuretics (loop, distal), penicillin, amphotericin B, aminoglycosides
Hypercalcaemia	Hypercalcaemia	
Hypomagnesaemia	Alcoholism	
Toxicity: iron, cadmium	Drugs: diuretics (loop, thiazide, osmotic), cisplatin, pentamidine, cyclosporine, aminoglycosides, foscarnet, amphotericin B, tacrolimus	
Drugs: diuretics, corticosteroids, bicarbonate, oestrogens at high doses, ifosfamide, cisplatin, foscarnet, pamidronate		
Other: vomiting, diarrhoea and surgery		

SIADH: Syndrome of Inappropriate ADH Secretion; RS: refeeding syndrome.
Source: Fernández López et al.[6]

into cardiovascular, respiratory, neurological and haematological manifestations, among others, which usually occur a few days after the start of refeeding.[3]

The first description of RS was made in connection with prisoners of the Second World War who had suffered prolonged fasting; a severe condition of congestive heart failure (CHF), seizures and even death occurred when a normal diet was reintroduced. The classic study that describes RS is the Minnesota experiment, in which healthy volunteers are subjected to food restriction for 6 months and subsequent refeeding, observing a similar but milder condition.[4] In 1980, the hypothesis of hypophosphataemia secondary to refeeding was proposed as a key aspect of RS, which is what is known today.[5]

The importance of RS lies in a significant associated morbidity and mortality; however, death is currently unusual in this context.

In the hospitalized and severe patient there are multiple causes of hypophosphataemia, hypomagnesaemia and hypokalaemia with which a differential diagnosis must be made[6] (Table 1).

Epidemiology

It is a relatively common problem in malnourished patients, which is important, since 30–50% of hospitalized patients have malnutrition or are at risk of developing it.[7]

The incidence is very variable according to the definition used and the different series, but it is usually underdiagnosed, especially by non-nutritionists.[2] Its true incidence is unknown, partly due to the absence of a universally accepted definition and that most of the studies are retrospective and do not evaluate all RS components, but rather the presence of hypophosphataemia.[1,8,9] It is estimated that it develops in 20–40% of malnourished patients undergoing NS.[10]

Patients with risk of RS are considered those with chronic malnutrition, chronic exacerbated or acute who are going to receive NS. The risk increases if there are long-standing nutritional deficiencies (as in alcoholism or elderly patients).[3] The morbidly obese with significant weight loss after bariatric surgery, oncology patients with total parenteral nutrition (PN) or patients undergoing prolonged intravenous fluid therapy are also risk groups.[3,8] Of special risk are patients with head and neck tumours, since they present multiple risk factors for a RS (fasting > 5 days in the context of dysphagia due to tumour progression, tumour cachexia, prolonged fasting in the postoperative period, previous history of alcohol abuse, among others).[11]

There is the possibility of developing a RS with any type of NS, even in patients undergoing oral nutrition at home. Some studies document a higher incidence with enteral nutrition (EN) than with PN (possible influence of incretin effect in EN that would produce a higher insulin secretion and less predictable absorption than in PN).[12]

Currently the main risk group is patients with anorexia nervosa (AN), given its high prevalence and high risk of RS: 14% (0–38%) of AN develop it.[13,14] The guidelines of the *National Institute for Health and Care Excellence* (NICE) 2006 establish a series of criteria that help identify risk groups[15] (Table 2).

On the other hand, hypophosphataemia is present in up to 40% of hospitalized patients, and even a higher percentage in the case of patients admitted to intensive care units and infectious disease services.[16] The RFs are basically the same as those of RS.[17]

Pathogeny

In *normal conditions* carbohydrates serve as the main energy source for tissues (hepatic and muscular glycogen stores).

During *fasting* the body tries to compensate for the lack of energy through changes in metabolism and hormonal regulation. The body enters a catabolic state, in which glycogen reserves are used until exhaustion. At that time, proteolysis (protein degradation in amino acids) starts, followed by gluconeogenesis (obtaining glucose from amino acids, lactate and glycerol). After 72 h of fasting other processes are initiated to minimize the mobilization of amino acids and decrease protein catabolism, including lipolysis, in which free fatty acids are released that can be used for the synthesis of ketone bodies. Ketoadaptation is one of the most important metabolic phenomena in the response to fasting.[1,6,8,18]