Nutrition 30 (2014) 1448–1455

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Special article

Refeeding syndrome: Problems with definition and management

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ARTICLE INFO

Article history:
Received 10 March 2014
Accepted 31 March 2014

Keywords:
Nutrition
Refeeding syndrome
Phosphate
Magnesium
Potassium

ABSTRACT

Refeeding syndrome (RFS) broadly encompasses a severe electrolyte disturbance (principally low serum concentrations of intracellular ions such as phosphate, magnesium, and potassium) and metabolic abnormalities in undernourished patients undergoing refeeding whether orally, enterally, or parenterally. RFS reflects the change from catabolic to anabolic metabolism. RFS sometimes is undiagnosed and unfortunately some clinicians remain oblivious to its presence. This is particularly concerning as RFS is a life-threatening condition, although it need not be so and early recognition reduces morbidity and mortality. Careful patient monitoring and multidiscipline nutrition team management may help to achieve this goal. The diagnosis of RFS is not facilitated by the fact that there is no universal agreement as to its definition. The presence of hypophosphatemia alone does not necessarily mean that RFS is present as there are many other causes for this, as discussed later in this article. RFS is increasingly being recognized in neonates and children. An optimal refeeding regimen for RFS is not universally agreed on due to the paucity of randomized controlled trials in the field.

Introduction

Refeeding syndrome (RFS) broadly encompasses a severe electrolyte disturbance (principally low serum concentrations of the predominately intracellular ions; phosphate, magnesium, and potassium) and metabolic abnormalities in undernourished patients undergoing refeeding whether orally, enterally, or parenterally. In essence, RFS reflects the change from catabolic to anabolic metabolism [1,2].

It has been reported that RFS is a medical condition that can occur despite identification of risk, prompt treatment and hypocaloric nutritional therapy [3]. Results of one study demonstrated that the most reliable predictor of developing RFS is starvation and intravenous (IV) glucose infusion before artificial nutrition support in undernourished patients. However, there is no universal agreement on the definition of RFS, although the following clinical criteria for determination of its risk have been proposed [3].

One of the following features is required:

- Body mass index (BMI) <16 kg/m^2
- Unintentional body weight loss $>15\%$ in the preceding 3 to 6 mo
- Minimal or no significant nutritional intake for >10 d
- Low concentrations of plasma potassium, phosphate, or magnesium before feeding

Or two of the following features are required:

- BMI <18.5 kg/m^2
- Unintentional body weight loss $>10\%$ in the preceding 3 to 6 mo
- Minimal or no significant nutritional intake for >5 d
- Medical history of alcohol or drug abuse [3]

It has been suggested that a precise definition of RFS is difficult as this is a spectrum of abnormalities and that the so-called "full-blown" RFS should be defined by the presence of symptoms [4]. It has also been suggested that a category of potential or biochemical RFS should be recognized that is asymptomatic [4]. However, exactly what is meant by symptoms is debatable and symptoms in RFS may be non-specific, thus making a suggestion for a definition problematic.

In one systematic review, it was noted that RFS is not associated with a consistent pattern of biochemical or clinical abnormalities and that many cases described in the literature may be more appropriately termed *refeeding hypophosphatemia* [5].

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http://dx.doi.org/10.1016/j.nut.2014.03.026

Although this is an important point, there are many other causes of hypophosphatemia that are not necessarily related to RFS. Thus, we need to be aware that hypophosphatemia does not necessarily mean the presence of RFS.

How common is RFS?

The prevalence of RFS has been variably quoted with estimations as wide as 0.43% to 34% in different hospital populations [1,2]. The actual prevalence figure is debatable, however, as some definitions of RFS state the presence of hypophosphatemia, which is relatively common in hospital populations and its presence does not necessarily mean that RFS has occurred. Undernutrition is also variably reported and sometimes misdiagnosed, although its prevalence may be as high as 65% in some hospitalized patients [6,7].

One large hospital-based study [8] reported that the prevalence of severe hypophosphatemia was 0.43% and undernutrition was one of the strongest risk factors for hypophosphatemia; however, this does not necessarily mean the patient has RFS. In a prospective cohort research study [9] of patients in intensive care units, 34% experienced hypophosphatemia soon after refeeding. One study demonstrated that RFS was generally poorly understood and underdiagnosed particularly by trainee doctors, thus leading to an underestimation of prevalence figures [10].

Individuals at particular risk for RFS

One of the first descriptions of RFS was in individuals who were starved in Japanese World War II prison camps on a long-term basis [11]. After being liberated and then refed, some of the prisoners developed RFS associated with peripheral edema and neuropathy [12]. The term *refeeding syndrome* may first have been used after the tragic deaths of two undernourished patients who were apparently refed and developed RFS. In this study, the patients received from glucose approximately 75 kcal/kg of estimated edema-free body weight [13]. Further insight in to the RFS was made in pioneer studies on human starvation and refeeding in healthy volunteers [14]. Although this work was essentially in normal starved volunteers, anorexia nervosa often is used as a “human model” for RFS and valuable information regarding the pathophysiology of refeeding has been gathered by studying this condition, although it may not be representative of all patients with RFS [15].

About half of psychiatric patients are at risk for undernutrition. This patient group is also more at risk for RFS [16]. Indeed, one study [17] showed that early detection and management of refeeding patients with anorexia nervosa who are treated in an intensive care unit might prevent RFS. More recently, researchers in Africa found an association between pretreatment of hypophosphatemia and early antiretroviral therapy in HIV and mortality among undernourished individuals and associated RFS [18,19].

There have been some reports of RFS in children, although more recently cases are being presented in the medical literature. One group [20] described RFS in two children—one with celiac disease and the other cerebral palsy. Another group [21] reported severe hypophosphatemia in severely malnourished children <5 y of age, including those with sepsis and diarrhea. These groups showed that treatment of the hypophosphatemia might have reduced mortality in these children. RFS has been described in children with celiac disease who live in developing countries [22] ad has also been reported to occur in very low-birth-weight babies who had interuterine growth restriction and were born to mothers with preeclampsia [23]. A good predictor of developing RFS in pediatric patients is a body weight <80% of the ideal [24]. RFS in a small-for-date micropreemie initiated on parenteral nutrition [25] also has been reported. Enhanced feeding of very low-birth-weight neonates may induce electrolyte imbalances such as hypophosphatemia and hypokalemia and these electrolyte disturbances may be associated with sepsis [26].

As Table 1 depicts, there are numerous patient groups at risk for RFS. Recently topical and also perhaps ironic is the observation that RFS may be seen after bariatric surgery for severe obesity. Hunger strikers and those who undergo prolonged fasting also may be more susceptible to RFS [1,2,14,15]. Clinicians in a variety of medical specialities, therefore, need to be vigilant in recognizing and appropriately managing RFS.

Pathophysiology of RFS

Starvation can be broadly defined as a catabolic state where the body shifts to fat and protein metabolism from carbohydrate utilization. Plasma insulin concentrations decrease while glucagon increases during starvation, resulting in the rapid conversion of glycogen stores to form glucose for cell energy. Additionally, gluconeogenesis, resulting in glucose synthesis via lipid and protein breakdown products increases. The essential amino acid alanine has a central role in gluconeogenic pathways. The brain, renal medulla, and erythrocytes, for example, are obligate utilizers of glucose as an energy source [1–3]. Adipocytes release fatty acids and glycerol, whereas muscle myocytes release amino acids such as alanine to help fuel these metabolic pathways [1–3]. Ketone bodies and free fatty acids replace glucose as a major energy source in human starvation. Overall, in starvation there is catabolism of adipose tissue and muscle, resulting in loss of lean body mass [1–5,9].

Undernutrition is a predominant feature in patients with RFS. In prolonged starvation (usually weeks to months), glycogen stores are depleted. This allows conservation of proteins as these have essential metabolic and structural functions and thus lipids preferentially become the principle source of energy in prolonged starvation [1–5].

Cell volume of various organs such as the brain, heart, and liver, as well as muscle, decreases as a result of undernutrition; the reason for this is postulated as being due to the loss of intracellular storage macromolecules such as protein and glycogen as part of adaptation of the cells to fat metabolism. Additionally, intracellular ions, principally those of phosphate,

Table 1
High risk for refeeding syndrome

Conditions
Bariatric surgery
Chronic alcoholism or drug abuse
Chronic infection (e.g., HIV)
Dysphagia and esophageal dysmotility
Eating disorders (e.g., anorexia nervosa)
Hyperemesis gravidum
Inflammatory bowel disease
Low-birth-weight and premature birth
Malabsorptive states (e.g., celiac disease)
Malignant disease
Older age (e.g., > 70 years)
Prolonged fasting (e.g., individuals on hunger strikes)
Protracted vomiting
Short bowel syndrome
Undernourishment such as is present in kwashiorkor and marasmus