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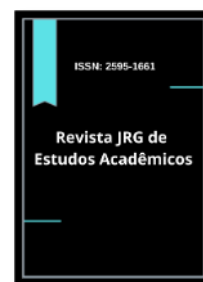
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Refeeding Syndrome in Critically Ill Patients: An Integrative Review on Diagnostic Complexity and the Applicability of Cautious Protocols

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Abstract

Refeeding Syndrome (RS) is a severe metabolic complication that mostly occurs in malnourished patients after the initiation of nutritional support. This integrative review aimed to synthesize evidence on risk factors, diagnostic criteria controversy and management of adults and elderly in the setting of intensive care units (ICUs). Results showed a large variability of incidence of RS due to the lack of universal definition and divergence between purely electrolytic criteria and those requiring clinical features. Hypophosphatemia is the hallmark of RS, and risk factors include low BMI, severe weight loss, low caloric intake and pre-existing electrolyte disturbances. Management includes mandatorily initial caloric restriction (5 to 10 Kcal/Kg/day for high risk patients) and gradual progression of the diet. Prophylactic thiamine supplementation and daily monitoring of electrolytes in the first 72 hours are essential.

Key-words: Refeeding Syndrome. Nutritional support. Caloric restriction.

1. Introduction

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Refeeding Syndrome (RS) is a potentially lethal complication characterized by electrolytical imbalances and metabolic dysfunctions that occurs fundamentally in severely malnourished patients subjected to the reintroduction of nutritional support, either oral/enteral or parenteral^(1,2).

Historically, the syndrome was first described amongst oriental prisoners during World War II who developed cardiac failure after being fed following prolonged fasting⁽¹⁾.

The incidence of RS is highly variable, depending on the population studied, the study methodology and, primarily on the diagnostic criteria employed⁽³⁾.

The present study was conducted as an Integrative Review (IR), which is the broadest methodological approach among reviews and is recognized as a tool to aid healthcare professionals in synthesizing available research on a specific topic⁽⁴⁾. Our primary goal was to synthesize and critically analyze the most recent evidence on the risk factors, controversies in diagnostic definition, and nutritional management strategies for RS in hospitalized adult and elderly patients, with an emphasis on the critically ill population.

2. Methodology

The current study employed the Integrative Literature Review method, adhering to the six phases of the development process: 1) formulation of the guiding question; 2) literature search or sampling; 3) data collection; 4) critical analysis of the included studies; 5) discussion of results; and 6) presentation of the integrative review⁽⁴⁾.

2.1. Formulation of the guiding question (Phase 1)

The guiding question determines the studies to be included and the information to be collected. The research question was formulated to encompass the conceptual and practical components of Refeeding Syndrome: What are the most recent pieces of evidence regarding the risk factors, the validity of diagnostic criteria, and the impact of nutritional management (including caloric restriction and supplementation) on the clinical evolution of adult and critically ill patients with Refeeding Syndrome?

2.2. Sampling and Critical Analysis (Phases 2, 3, and 4)

Literature search was conducted using studies with diverse designs to provide a comprehensive understanding of the knowledge. Included studies comprised: Randomized Clinical Trials, Retrospective Cohort Studies, Reviews and Consensus Guidelines (NICE, ASPEN), and Case Reports.

Data collection (Phase 3) involved abstracting relevant data, such as subject definition, methodology, results, and implications of the findings. The comparison of studies on specific details, such as problems and sample characteristics, was facilitated by organizing the findings in a visual format (Table 1).

The critical analysis (Phase 4) required an organized approach to weigh the rigor and characteristics of each study, classifying them hierarchically based on the research design:

Level 2: Evidence obtained from individual studies with an experimental design, such as a randomized clinical trial.

Level 4: Evidence from descriptive (non-experimental) or qualitative approach studies.

Level 5: Evidence derived from case reports or experience.

Level 6: Evidence based on expert opinions or consensus guidelines.

3. Results and Discussion

3.1. Pathophysiology and Risk Identification

RS results from the abrupt transition from the catabolic state, imposed by prolonged fasting, to the anabolic state promoted by nutrient reintroduction. The secretion of insulin stimulates the cellular uptake of glucose, water, and, critically, intracellular electrolytes, such as phosphate, potassium, and magnesium, leading to serum depletion. Hypophosphatemia (< 2.5 mg/dL) is the most significant alteration and the hallmark of RS^(2,5,6).

The risk factors for RS are clearly delineated by guidelines such as those from the National Institute for Health and Care Excellence (NICE). High-risk patients include those with a BMI < 16 kg/m², unintentional weight loss $> 15\%$ in 3 to 6 months, minimal or no nutritional support for more than 10 days or low baseline levels of phosphorus, potassium, or magnesium. Alcohol abuse and advanced age are also important predictors⁽⁶⁾.

3.2. The Controversy of Diagnostic Criteria

One of the major gaps in literature is the variability in diagnostic criteria, which results in variations in reported incidence rates. The absence of a gold-standard test hinders the true description of refeeding syndrome^(5,6).

- Biochemical vs. Clinical Definitions: Some studies selectively consider only hypophosphatemia, while others require deviations of multiple electrolytes or the presence of clinical symptoms (neurological, cardiorespiratory)^(1,6).
- Association with Mortality: Naik et al. (2023) compared different RS definitions (including ASPEN's) and concluded that definitions based purely on electrolyte abnormalities showed a modest or no association with 30-day mortality in critically ill patients. The authors suggest that strict attention to electrolyte correction within the cohort may have prevented severe outcomes, thereby obscuring the statistical association between the biochemical alteration and death⁽⁷⁾.

In light of this variability, the recommendation by Stanga et al. (2008) to define RS as a spectrum disorder (distinguishing the purely biochemical entity from symptomatic RS) gains relevance⁽⁸⁾.

3.3. Nutritional Management and Intervention Evidence

Management focuses on prevention and early identification, with the slow and gradual refeeding protocol being the consensus strategy⁽²⁾.

- Caloric Restriction: The Randomized Clinical Trial by Doig et al. (2015) provided robust evidence indicating that caloric restriction (intake $< 50\%$ of the target) during RS management in critically ill adults was associated with a difference in survival at 60 and 90 days^(2,9).
- Provision Protocols: Guidelines recommend initiating refeeding with a maximum of 10 kcal/kg/day for high-risk patients, gradually increasing the provision over 3 to 7 days. For extremely malnourished patients (BMI < 14 kg/m² or fasting > 15 days), initiation should be at 5 kcal/kg/day⁽⁶⁾.
- Provision Calculation: Calorie calculations must include not only nutritional calories but also the provision from intravenous and medicinal solutions (such as propofol and glucose), which can by themselves exceed cautious recommendations^(3,10).

- **Electrolytes and Vitamins:** Prophylactic supplementation with intravenous thiamine (100–300 mg/day) is mandatory before initiating the diet and should be maintained for 5 to 10 days. Daily monitoring of serum electrolytes (P, K, Mg) and weight is essential during the first 72 hours^(2,10,11).
- **Administration Route:** Studies observe that hypophosphatemia (a risk marker for RS) increases significantly after the initiation of Nutritional Therapy, being more frequently associated with Parenteral Nutrition (PN) than with Enteral Nutrition (EN), reinforcing the need for rigorous monitoring when PN is utilized^(12,13).

Table 1 summarizes the main findings of the included studies:

Table 1 – Synthesis of Critical Analysis of Selected Studies on Refeeding Syndrome

Author (Year) / Design	Objective / Main Variables	Principal Finding	Level of Evidence
Doig et al. (2015) / RCT	Compare restricted vs. standard caloric intake in RS management in critical patients.	Caloric restriction (< 50% of target) associated with improved survival at 60 and 90 days.	Level 2
Naik et al. (2023) / Retrospective Cohort	Evaluate the association between different RS definitions (electrolytic) and 30-day mortality.	Purely electrolytic definitions (including ASPEN) showed modest or no association with mortality, suggesting early management prevents severe outcomes.	Level 4
Ribeiro et al. (2020) / Retrospective Cohort	Frequency of hypophosphatemia (RS risk) before and after Nutritional Therapy (NT) in critical patients.	The risk of hypophosphatemia increases significantly after NT, being more frequent with Parenteral Nutrition (PN).	Level 4
Stanga et al. (2008) / Review/Guidelines	Provide guidelines for prevention and treatment.	Proposes that RS should be defined as a spectrum disorder due to diagnostic inconsistency.	Level 6

Santos et al. (2023) / Management Protocol	Construct a protocol for nutritional management of RS (adults and elderly) based on NICE/ASPEN.	Presents a structured protocol with progressive caloric and fluid provisions (e.g., 5-10 kcal/kg/day) for high risk).	Level 6
Patita et al. (2021) / Case Report	Describe a case of severe RS due to Total Parenteral Nutrition (TPN) prescription error.	Administration of 100% of caloric needs within 24h resulted in overt RS (hypophosphatemia, myoclonus, peripheral edema).	Level 5
Pucci et al. (2008) / Retrospective Study	Evaluate a refeeding regimen after prolonged voluntary fasting.	The high-energy provision regimen (mean 49 kcal/kg/day in the 1st week) was considered excessive, associated with fluid retention and gastrointestinal disturbances.	Level 4

4. Conclusions

Refeeding Syndrome is a serious condition that requires immediate attention due to the fact that it is associated with high morbidity and mortality⁽⁵⁾.

The primary limitation in the field of study is the diversity of diagnostic criteria, which leads to clinical uncertainty and makes determining the true incidence difficult. The suggestion of adopting a spectrum definition emerges as a path toward unifying the description of the entity^(2,5,6).

Nonetheless, the synthesis of evidence reaffirms that management must be primarily prophylactic. It is essential to use protocols that determine risk (based on NICE/ASPEN) and guide the initiation of nutritional therapy with marked caloric restriction (5–10 kcal/kg/day) and gradual diet progression. Daily monitoring of electrolytes (P, K, Mg) and prophylactic thiamine supplementation are essential to prevent multiple organ failure^(2,6,13).

The development of and rigorous adherence to institutionalized nutritional protocols, as well as the training of the multidisciplinary team, are crucial for the prevention and adequate management of RS. Further clinical studies are necessary to provide advanced information on preventive protocols and therapeutic measures, as well as to adjust energy provision and define the optimal time for the complete reintroduction of macronutrients^(3,5).

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