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# Refeeding Syndrome

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**Abstract:** Refeeding syndrome is a life-threatening condition that often goes unrecognized. Refeeding syndrome precipitate when fatal shifts in fluids and electrolytes occur in malnourished patients is artificially re-fed. These shifts result from hormonal and metabolic changes and may cause serious clinical complications. The precise definition of of refeeding syndrome incidence is hindered by the lack of a concise definition. The NICE recommendations offer guidelines to identify and manage high risk RFS patients. They do, however warrant the need for detailed assessments by a dietitian or nutrition specialist. Further updated recommendations are needed to take into account some of the newer concepts emerging from more recent literature.
**Keywords:** Refeeding syndrome, starvation, hypophosphatemia

## INTRODUCTION

Refeeding syndrome (RS) is often a neglected condition despite been recognized in the literature for over fifty years [1]. Clinicians are often not aware of the problem though there are guidelines that use best available evidence for managing the condition [2]. Refeeding syndrome is a life-threatening hematological abnormalities and dysfunction of cardiovascular, pulmonary, hepatic, renal neuromuscular, respiratory, metabolic systems, following inappropriate alimentary feeding in the severely malnourished, stressed, elderly, starved individuals [3].

The aim of this review is to raise awareness on refeeding syndrome identification, treatment and prevention strategies. This article also focuses on the National Institute for Heath and Clinical Excellence (NICE) guidelines on nutritional support in adults [4], with reference to new implications and recommendations for refeeding syndrome.

### Definition of refeeding syndrome:

There seems to be no internationally agreed definition of RFS [2]. First reports of the syndrome appeared in the 1950s after observations of malnourished prisoners of war who developed cardiac and neurological symptoms soon after the recommencement of feeding [5]. Since then, refeeding syndrome has been used to describe a series of metabolic events precipitated by the provision of nutrients, primarily carbohydrate, to a patient in a nutritionally compromised state [6].

Refeeding syndrome precipitate when fatal shifts in fluids and electrolytes occur in malnourished patients receiving artificial refeeding; whether enterally (EN) or parenterally (PN) [7]. These shifts result from hormonal and metabolic changes and may cause serious clinical complications [7]. The biochemical hallmark of refeeding syndrome is Hypophosphataemia [8]. Nevertheless, the syndrome is multifarious and could manifest abnormal fluid and sodium balance; alterations in protein, glucose, and fat metabolism; hypokalemia, hypomagnesaemia and thiamine deficiency [8].

### Incidence of Refeeding Syndrome

The precise investigation of refeeding syndrome occurrence is hindered by the lack of a concise definition. Hence, the criteria used to define refeeding syndrome vary across studies which results in a considerable variation in the reported incidence rates. A systematic review exploring reported incidence rates published in 2016 [9], included 45 studies of mixed populations and hypophosphataemia (either as a cut-off or a drop from baseline) was the most common component of refeeding syndrome definition across the studies included, there were great discrepancies in hypophosphataemia used cut-offs to define RFS, ranging from <1 mmol/L to <0.32 mmol/L, and differences in the required drop from baseline by 30% or >0.16mmol/L. In as much as 34% of studies, there were no patients recognized as presenting with any sign

or symptom of RFS. This could be due to the very rigorous definitions of RFS employed to include both clinical and biochemical manifestations. When definitions were less rigorous focusing on electrolyte disturbances only, predominately hypophosphatemia. RFS was reported up to 80%.

In a single-center study investigating 62 intensive care patients [10], 21 (34%) were diagnosed with refeeding-induced hypophosphatemia. The study revealed that the only significant risk factor was pre-treatment pre-albumin; 81% of patients with low phosphate level had a pre-albumin level of < 110 g/L. Remarkably, length of hospital stay and mechanical ventilation time of those with hypophosphatemia was significantly higher. "A Mixed Bag" published In 2010 by The National Confidential Enquiry into Patient Outcome and Death of the United Kingdom (NCEPOD UK) [11], investigating 877 records of adult patients who received PN showed that 39.3% had metabolic complications, and hypophosphatemia was designated the most common electrolyte abnormality, developed in 117 (13.3%) of patients, hypokalemia in 8% and low magnesium in 7%. With regard to refeeding syndrome identification among these patients, sixty percent (455) of cases was deemed at risk upon reviewing case records. Only 50 of these were recognized as being at risk by the PN prescription teams. When close case review was conducted 33 (14.7%) from those patients-identified to be at risk- are thought to have started developing signs of refeeding syndrome.

In a prospective research conducted in a tertiary hospital in the UK, 243 patients receiving nutrition support (87% enteral feeding, 13% parenteral), 3 were considered to have developed RS signs. A strict definition of severe electrolyte depletion was used in the study (phosphate < 0.5 mmol/L, magnesium <0.5 mmol/L, potassium < 2.5 mmol/L) + evidence of organ dysfunction + edema/fluid overload which were confirmed by the researchers before accepting the diagnosis. Only pre-feeding low magnesium level was significantly correlated with the risk of developing RS [12].

In a detailed review of database at North Shore Hospital, in Auckland, New Zealand, 292 consecutive episodes of PN in 272 patients were analyzed. RS Was defined as being "definite" if there was a decrease in serum phosphate level adjacent to the pathological development of extracellular fluid shift, and "possible", if it was accompanied by a drop in either serum magnesium and/or potassium along with the development of edema. a combined incidence of both "definite" and "possible" RS was found in 9.9% (95% CI 6.8–14%) and of "probable" of 5.1% (95% CI 2.9–8.3). Low prefeeding phosphate and increasing age were significant risk factors in this group [13].

It appears that across current literature summarized Hypophosphataemia is considered the most common component of definition and identification of RFS, and in some cases it is regarded as the only defining tool. Some suggestions state that many reported cases of RFS in the literature could be more properly categorized as 'refeeding hypophosphataemia' [14]. The difficulty with having hypophosphataemia as the solitary indictor of RFS is that clinical causes of low phosphate also have to be considered [15].

**Pathophysiology of Refeeding Syndrome**

The main causative element of refeeding syndrome is the hormonal and metabolic changes caused by prompt refeeding, whether enteral or parenteral. The main metabolic and hormonal changes in early starvation include the change from using carbohydrate as the main source of energy to using fat and protein, the basal metabolic rate decrease but as much as 20-25% [16].

Clinical manifestations of refeeding syndrome prevail when carbohydrate is reintroduced into the body. The unexpected swipe from protein and fat catabolism to carbohydrate metabolism fuels a catastrophic rise in insulin level. The resultant increase in insulin secretion causes an intracellular shift of glucose with enforced cellular uptakes of phosphate, potassium, and magnesium. Furthermore, this rapid introduction of carbohydrate can lead to reduced water and sodium excretion, causing an expansion of extracellular fluid and thus fluid overload, pulmonary edema and/or cardiac decompensation [6].

Numerous other clinical manifestations may also be detected during this phase, including hypophosphatemia, hypomagnesemia, hypokalemia, hyperglycemia, thiamin and water soluble vitamin deficiency [17].

**Hypophosphatemia**

Phosphorus is primarily an intracellular mineral. It is required for the structural integrity of cell membranes and all intracellular processes. Furthermore, several enzymes and second messengers are activated through phosphate binding. Prominently it is also vital for storage of energy in the form of adenosine triphosphate (ATP). It is also significant in the renal acid-base buffer system and regulates the oxygen affinity of haemoglobin and thus controls oxygen delivery into tissues [17].

In refeeding syndrome chronic whole body depletion of phosphorus occurs. Also, the insulin surge causes a greatly increased uptake and use of phosphate in the cells. These changes lead to deficit in intracellular as well as extracellular phosphorus. In environment, even small decreases in serum phosphorus may lead to widespread dysfunction of cellular

processes affecting almost every physiological system [18].

Hypophosphatemia (eg, serum phosphorus concentration_1.0 to 1.5 mg/dL (0.3 to 0.5 mmol/L), can lead to cardiac arrhythmias, respiratory failure, rhabdomyolysis, and confusion [7].

**Hypokalemia**

Potassium, the main intracellular cation, is also depleted in under-nutrition. However, serum concentration may stay normal. Upon the change to anabolic state in refeeding, as a consequence of insulin secretion potassium is taken by cells as they increase in volume and number. This result in severe hypokalemia [17]. Severe hypokalemia (eg, serum potassium concentration _2.5 mEq/L _2.5 mmol/L) causes derangements in the electrochemical membrane potential, resulting in, for example, arrhymias and cardiac arrest [17], as well as paralysis, respiratory compromise, rhabdomyolysis, muscle necrosis, and changes in myocardial contraction and signal conduction [6].

**Hypomagnesaemia**

Another predominantly intracellular cation is Magnesium, is an important cofactor in most enzymatic reactions, including ATP production and oxidative phosphorylation, it is also essential for the structural integrity of DNA, RNA, ribosome and membrane potential [19].

Moderate to severe hypomagnesemia usually defined as serum magnesium concentration 1.0 mg/dL (0.5 mmol/L) [24] can cause cardiac dysfunction and neuromuscular complication [23], tetany electrocardiographic changes, seizures, and convulsions [16].

**Hyperglycemia**

Depending on the method of delivery and rate of carbohydrate infusion, hyperglycemia from insufficient insulin secretion might occur [6].

Glucose intake after period of starvation suppresses gluconeogenesis through the release of insulin. Excessive administration may therefore lead to hyperglycemia and its squeal of osmotic diuresis, dehydration, metabolic acidosis, and ketoacidosis. Glucose excess also lead to lipogenesis (resulting from insulin stimulation), which could cause fatty liver, hypercapnoea, increased carbon dioxide production, and respiratory failure [20].

**Vitamin Deficiency**

Though all vitamin deficiencies can happen at variable rate with inadequate vitamin intake, thiamine is the most important vitamin complication of refeeding. Thiamine is an essential coenzyme in carbohydrate metabolism. Its deficiency lead to Wernicks encephalopathy characterized by mental status, (ocular abnormalities, confusional state, gait ataxia, hypothermia, coma) or Korsakoffs syndrome (confabulation, retrograde and anterograde amnesia) [21].

**Sodium, Nitrogen, and Fluid**

Changes in carbohydrate metabolism can lead to a profound change in sodium and water balance. The introduction of the carbohydrate results leads in a rapid decrease in sodium and water renal excretion rate [22]. if fluid repletion is instituted in order to maintain a normal urine output, patients may promptly develop fluid overload. Which lead to pulmonary oedema, congestive cardiac failure, and cardiac arrhythmia [2].

**Screening for Refeeding Syndrome**

The risk of RS is directly correlated with the degree of weight loss in patients as a result of developing anorexia nervosa [23]

At present; anorexia nervosa is considered one of the most frequent clinical presentations that place patients at risk of refeeding syndrome. Nevertheless, malnourished elderly, postoperative patients, oncology patients, and patients receiving chemotherapy, are also at risk [6].

In general, any patient with negligible food intake for more than five days is at risk of developing refeeding problems, especially chronically undernourished patients, and those with limited physiological reserves [4], elderly patients with multiple comorbidities, patients with chronic malnutrition symptoms such as marasmus, chronic alcoholics, patients with malabsorptive diseases e,g cystic fibrosis, those with severe inflammatory bowel disease or short bowel syndrome, or morbidly obese patients with rapid weight loss [24].

Rigaud and his colleagues published an illustrative example of how vulnerable patients with anorexia nervosa and severe malnutrition could develop RS. They outlined in detail their experiences of refeeding 41 anorexia nervosa patients (BMI < 11 kg/m2). Refeeding was not as proscriptive as recommended in guidelines, on the first day intravenous dextrose was given, and enteral feeding at 25 Kcal/kg/day was started on the second day. And electrolytes were assertively replaced, nonetheless there was one death, two cases of pancreatitis, two myocardial infarctions, and five patients with mental confusion. All clinical scenarios could be argued as manifestations of RS [24].

The National Institute for Clinical Excellence (NICE- UK) produced guidelines on Adult Feeding (2006) with specific criteria for identifying high risk patients [4].

These criteria are summarized in the table below. It should be noticed however that these evidences are D level evidence, i,e the advice of experts in the field only

**Refeeding syndrome Risk Factors**

- BMI< 16kg/m2*
- >15% unintentional weight loss in previous 3-6 monthsLittle/no nutrient intake for more

Than 10 consecutive day's Low potassium, phosphate, and magnesium levels prior to feedings.
BMI< 18kg/m2

- >10% unintentional weight loss in previous 3-6 months
- Little/no nutrient intake for more than 5 consecutive days
- Misuse of alcohol and drugs, including insulin, antacids, chemotherapy or diuretics.

*Presence of one major risk factor or two minor risk factors indicates that the patient might be at a high risk of refeeding syndrome. *BMI, body mass index [4].

Although the NICE recommendations are extensively implemented in clinical practice, some studies have found them to have low specificity and sensitivity and propose that there might be other risk factors to take into consideration [9]. The additional risk factors proposed include older age, patients who are enterally fed, higher nutritional intake during feeding, low albumin or pre-albumin, and low insulin-like growth factors. However, none of these have yet been included in national guidelines.

One study suggests that early intravenous glucose infusion before any nutrition support is started can precipitate RFS, which highlights the importance of careful selection of intravenous fluids for at high risk of developing patients [12]. The same study also classified low baseline serum levels of magnesium and starvation as independent predictors of RFS.

However, since malnutrition is the most compelling risk factor for RFS agreed upon in literature, the importance of adequate screening for this is then paramount. Malnutrition is common in hospitals. The Nutrition Screening Survey has shown that 34% of hospital adult inpatients are at risk of malnutrition [25].

One emerging theory is that RFS depends on the extent of malnutrition at the start of refeeding and not on the quantity of calories delivered; as BMI is reduced the severity of refeeding hypophosphataemia increases [25]. One effective way that could quickly identify patients potentially at high RFS risk is the 'Malnutrition Universal Screening Tool' ('MUST'), which is a validated, feasible screening tool that takes into consideration BMI [25].

The NICE guidelines requires the application of a detailed and accurate diet history and weight measurements to correctly identify at risk patients. Whereas calculating BMI is simple and can be taken by screening tools, to accurately determine 'percentage weight loss' and 'little or no nutritional intake', a detailed assessment by a dietitian or nutrition support team is necessary. Collecting this information involves accurate weight histories, which can be hard to obtain, with diet recall assessment which could be subjective. The question arises here is whether the difficulty of precisely obtaining these information leads to being "too cautious " and thus over diagnosing refeeding syndrome risk? And could this mean that patients identified as high risk could be unnecessarily underfed? [14].

**Treatment and Prevention Strategies for Patients Identified at Risk of RS**

There is a scarcity of published guidelines on preventive strategies targeting at those at risk of metabolic complications. The NICE guidelines are the most comprehensive guidelines available. The guidelines recommend starting refeeding of high risk patients at 10 kcal/kg/day, then increasing, over a minimum of 4 days, to full requirements, coupled with supplementation of (vitamin B1) at 200–300 mg/day for the first 10 days. And with close monitoring of serum phosphate, potassium, and fluid requirements. Limiting sodium input, and supplementing adequate amounts of magnesium and potassium and phosphate should also be performed [4].

To this date, there are limited number of studies supporting these recommendations; however, some support is provided by the NCEPOD UK audit [12]. According to the audit, among the total 174 at high risk patients identified 19% developed RS. 20 of those patients occured despite taking precautions while no precautions were attempted in the remaining patients. The exact definition of at risk cases or RS was not defined in the audit. Over 5 years period using the NICE criteria [24], 80% of at-risk patients who received PN met the criteria for high risk of RS. And according to researchers' definition for RS, the sensitivity of NICE criteria was 86.7%, while specificity was only 20%, which reflecting a positive predictive value of a minute 5.6%, and a negative predictive value of 96.5%.

A recent RCT in intensive care patients reported that energy restriction in patients who developed RFS (as identified by their phosphate <0.65

mmol/L) reduced infectious complications, improved survival, and reduced hospital length of stay [26].

Nevertheless, despite NICE recommendations, refeeding practices do vary. One emerging impression is that the overall quantity of nutrition delivered at the start of refeeding may not be quite as important as assumed [14].

A systematic review investigated feeding practices in adolescents diagnosed with anorexia nervosa (AN) report different energy intakes at the start of feeding (125-1900 kcals/day) and, remarkably refeeding hypophosphatemia incidence did not appear to be affected by total calorie intake but rather by the lower BMI (i,e degree of malnutrition) [27], in study investigating the incidence rate of RS in a non-anorexia population, a similar theory was proposed; hypocaloric feeding did not prevent the development of RFS in at risk patients [12].

It appears wise to tailor refeeding practices for different clinical areas. The main uneasiness against strict adherence to the NICE guidelines is the risk of unnecessarily underfeeding patients, delaying nutrition and having a negative impact on patients that are already malnourished [14].

Other perception is that the main consideration should be given to the source of nutrition rather than quantity alone. One suggestion is that RFS may be more likely to manifest when the nutrition provided is predominately from carbohydrates [14]. Whether nutrition mainly comprise less carbohydrates and mainly fats and proteins is an area that needs further quality research.

## CONCLUSION

Refeeding syndrome is a potentially fatal condition, caused by rapid initiation of refeeding after a period of under-nutrition Based on this review and literature summarized it is essential to properly train health care professionals on the importance of detecting at risk patients and train them on the proper managements recommended. The NICE recommendations offer guidelines to identify and manage high risk RFS patients. They do, however warrant the need for detailed assessments by a dietitian or nutrition specialist. Further updated recommendations are needed to take into account some of the newer concepts emerging from more recent literature. We also recommend conducting field audits and studies to examine these widely ignored medical phenomena in Libya, to determine its magnitude and to evaluate the treatment and prevention approaches taken, if any.

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