

Physiology of Starvation and Refeeding Syndrome

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Abstract

Refeeding syndrome represents a series of metabolic complications that sometimes results by provision of nutrients, primarily carbohydrate, to a patient in a nutritionally compromised state. Refeeding syndrome is associated with hypophosphatemia, hypokalemia and hypomagnesaemia, fluid retention and vitamin deficiencies including thiamin are also of concern. If severe, refeeding syndrome may result in respiratory, cardiac, and neuromuscular dysfunction, especially in the stressed, elderly, or severely malnourished patient. This article discuss the physiology of starvation and the pathophysiology behind refeeding syndrome, identify the patients at greatest risk, and provide practical tips for prevention. As increased awareness and understanding of refeeding syndrome may help, prevent further such incidents and clinicians learn to recognize patients at risk and avoid over-aggressive nutrition support regimes.

Key words: Starvation, Refeeding Syndrome

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Introduction

Knowledge of the dangers of refeeding famine victims dates back many centuries. Historically, problems such as cardiac dysfunction, edema and neurological changes were observed when malnourished refugees were suddenly provided with adequate food. Such problems have also been observed when relief efforts provide food to victims of famine. After world war-II a number of investigators reported the unexpected death of starved prisoners of war (POW) shortly after reintroduction of high-caloric, high-carbohydrate food. Autopsies on those individuals did not reveal any obvious cause.¹⁻³

These potentially life threatening refeeding complications became apparent once again in the 1970's and 1980's with the widespread use of total parenteral nutrition (TPN) in hospitalized patients who were often malnourished⁴.

An increased awareness and understanding of Refeeding Syndrome may help to prevent further such incidents as clinicians learn to recognize

patients at risk and avoid over aggressive nutrition support regimes.

Incidence of refeeding syndrome

The incidence of Refeeding Syndrome is unknown. In studies of patients on total parenteral nutrition (TPN), the incidence of hypophosphatemia ranged from 30%-38% when phosphorous was provided in the solution, to 100% when TPN without phosphorous was administered⁵. In cancer patients, it has been reported as high as 25%⁶. It is more common in the elderly, although it may be masked by comorbid conditions⁷.

There are no reports of randomized clinical trials, controlled trials looking at the incidence of Refeeding Syndrome itself. Mild symptoms often go unnoticed or may be attributed to other cause. Conversely, low serum levels of phosphorus, potassium and magnesium thought to be due to Refeeding Syndrome may be due to other factors including decreased dietary intake, insufficient gastrointestinal absorption, increased renal or non-renal losses and transcellular shifts. (Table-I).

Table I: Potential Causes of Hypokalemia, Hypophosphatemia, and Hypomagnesemia²²**(A) Hypophosphatemia**

General	Metabolic	Medications
Malabsorption	Hypomagnesemia	Diuretics
Glucose administration	Hypokalemia	Beta-agonists
vitamin D deficiency	Hypocalcemia	Epinephrine
Volume repletion	systemic alkalosis	Insulin
Rhabdomyolysis	Hyperparathyroidism	Antacids
Hemodialysis	Hyperaldosteronism	Carafate
Initiation of CVVHD		Glucagon
Diabetic ketoacidosis		Bicarbonate
Alcoholism		Corticosteroids
Sepsis		Cisplatin
Gram-negative bacteremia		Theophylline
Refeeding Syndrome		

(B) Hypokalemia

General	Metabolic	Medications
Vomiting / Diarrhea	Hypomagnesemia	Albuterol Diuretics
Insulin delivery	Metabolic Alkalosis	Insulin
Refeeding syndrome		Carbenicillin
		Terbutaline
		Ticarcillin

(C) Hypomagnesemia

General	Metabolic	Medications
Diarrhea	Diabetes Mellitus	Amphotericin B
Malabsorption		Cisplatin
Alcoholism		Cyclosporin
Refeeding Syndrome		Ticarcillin
		Carbenicillin
		Digoxin
		Alcohol
		Gentamycin
		Insulin
		Diuretics

What is refeeding syndrome?

Re feeding Syndrome represents a host of metabolic complications that sometimes results when

feeding a malnourished patient. By definitions, Re feeding Syndrome describes a potentially fatal medical condition that may affect malnourished/ill patients in response to an inappropriately high protein-caloric intake. This commonly occurs following the institution of nutritional support, either parenteral or enteral or unrestricted oral intake.

Numerous Physiological changes occur during refeeding that may result in increased patient morbidity and mortality. Intracellular mineral depletion (eg. hypophosphatemia, hypomagnesemia, hypokalemia), body fluid disturbances (refeeding edema), vitamin deficiencies (eg. thiamine), life threatening cardiac arrhythmias, respiratory arrest and congestive heart failure are among the most often reported events associated with refeeding.^{4,8} Death may have been avoided by recognition of the patients risk for Refeeding Syndrome, appropriate nutritional support management, effective monitoring, and therapy for complications.

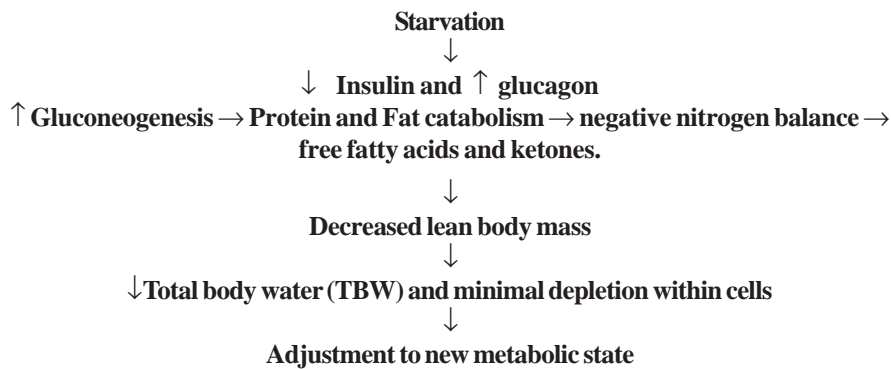
Physiology of starvation

Under normal conditions, glucose is the body's preferred fuel. Glucose is primarily derived from carbohydrates in the diet. The body depends on a consistent intake of carbohydrate for continued glucose supply. Glucose is available in the blood stream for fuel for 2-3 hours after ingestion and can be stored as glycogen, & 300gms of glucose are stored as glycogen in the liver and muscles. In absence of oral intake, glycogen can provide energy up to 24 hours. A minimum of 100-150 gm of glucose per day is needed to provide adequate glucose to the brain and to prevent protein breakdown for glucose production.¹⁰

When adequate glucose is available, protein is used for non-fuel functions, such as building muscle and the synthesis of enzymes, hormones, anti-bodies and transport proteins. Carbohydrate, protein and fat intake in excess of needs is stored as fat. Fat is the primary storage fuel in the human body.

During the short period of fasting (upto 24 hours.) obligatory glucose is obtained by glycogenolysis. After depletion of glycogen stores, amino-acids are mobilized from muscle and fatty acids are mobilized from adipose tissues. Both are degraded further to produce glucose and glycerol respectively from gluconeogenesis. Glucose is also produced via gluconeogenesis from lactate and pyruvate. The initial period of starvation is marked by increased protein catabolism. As the nutrient deprivation is prolonged, the rate of proteolysis decreases as the body further adapts to the decreased nutrient intake, basal metabolic rate slows by as much as 20% - 25%¹¹. Peripheral tissues and most organs can adapt to using fatty acids as a fuel source. The brain, as a primary end user of glucose, switches over to Ketones as a partial fuel source and decreases it's reliance on glucose as a substrate. These adaptive mechanisms, in the non-stressed state, decrease the need for glucose, thereby sparing muscle mass.

Prolonged starvation leads to loss of lean body mass, adipose tissue and fluid. Eventually, starvation also affects the visceral protein mass and the function of vital organs. Respiratory function may decline due to respiratory muscle wasting which may limit CO₂ excretion¹². Cardiac mass and output are also decreased as well. In the absence of additional stressors, such as illness or injury, serum protein levels are maintained at relatively normal levels during pure protein, calorie malnutrition. A severely malnourished patient may have a normal albumin level despite prolonged starvation. This is due in part to decreased break down of serum proteins and to extravasations of fluid into the interstitial space that may make serum levels appear falsely elevated. In fact, it is not uncommon for a severely malnourished patient to initially loose weight after nutrition support is started due to diuresis of this additional extracellular fluid. (**Table II**)

Table II: Pathophysiology of Starvation

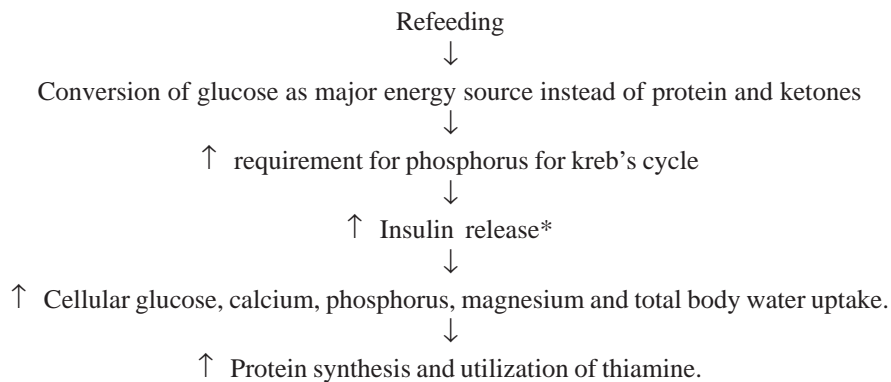
During starvation there is a change in the hormonal milieu in addition to a reduction in the basal metabolic rate, conservation of proteins, prolongation of organ function, preferential catabolism of skeletal muscles and loss of visceral cell mass⁹. The concentration of insulin is decreased whilst glucagon increases resulting in the conversion of glycogen to glucose in addition to gluconeogenesis from lipid and protein stores. Free fatty acids and ketones bodies replace glucose as the primary source of energy⁸

Decreased nutrient intake and poor nutritional status may lead to depleted vitamin and mineral status, including depletion of phosphorus, magnesium and potassium. Unlike glucose metabolism, fatty acid oxidation does not require

phosphorous intermediates; hence phosphorus requirements is decreased during starvation.

Metabolic response to refeeding

There are many consequences that occur when nutrition namely carbohydrate, is provided to a starved patient. (**Table III**).

Table III: Pathophysiology of Refeeding

Intracellular shifts of calcium, phosphorus, magnesium and potassium. Insulin release stimulates the sodium potassium ATPase pump (which requires magnesium as a co-factor). This drives potassium into the cells and moves sodium out. Carbohydrate load and insulin release stimulate phosphate shifts into the cells and phosphate depletion is associated with increased urinary magnesium excretion. This leads to low extracellular phosphate, magnesium and potassium may precipitate the symptoms of Refeeding Syndrome. Thiamine is an essential coenzyme in carbohydrate metabolism. The symptoms of thiamine deficiency e.g. Wernicke's encephalopathy, can be precipitated by feeding with carbohydrate in a vitamin B depleted patient.

Table IV: Complications associated with refeeding syndrome²²

Hypophosphatemia	Hypokalemia	Hypomagnesemia
Respiratory	Cardiac Dysfunction	Cardiac Abnormalities
- Failure	- Arrhythmia	- Arrhythmias
- Ventilator dependency	- Cardiac arrest	- Tachycardia
Cardiac	- EKG changes	Neurologic
- Arrhythmia	- Digoxin toxicity	- Altered mental status
- Congestive heart failure	Neurologic	- Weakness
- Cardiomyopathy	- Paralysis	- Tetany
- Decreased cardiac contractility	- Rhabdomyolysis	- Paresthesia- Seizures
- Hypotension	- Lethargy/confusion	- Ataxia
Skeletal	Metabolic	- Vertigo
- Rhabdomyolysis	- Metabolic alkalosis	- Tremors
- Weakness	Gastrointestinal	Gastrointestinal Problems
Neurologic	- Paralytic ileus	- Abdominal pain
- Altered mental status	- Constipation	- Diarrhea
- Paralysis		- Constipation
- Seizures		- Anorexia
Endocrine		Electrolyte
- Insulin resistance		- Hypokalemia
- Osteomalacia		- Hypocalcemia
Hematologic		Hematologic
- Leukocyte dysfunction		- Anemia
- Altered RBC morphology		
- Thrombocytopenia		
- Decreased platelet function		
- Hemolytic anemia		
- Decreased oxygen release from oxyhemoglobin		

The driving factor for refeeding complications is insulin secretion. Insulin promotes glucose uptake, along with phosphorus and other electrolytes into the cells. This intracellular shift, along with already depleted electrolyte pool, can lead to dangerously low levels of serum phosphorus, potassium and magnesium (but not necessarily all three). Serious respiratory, cardiac and neurological complications can occur. In most severe cases, they can be fatal (Table IV).

Excess glucose

Glucose is an important substrate in specialized nutrition support. As previously discussed

overfeeding carbohydrates (enteral or parenteral) may result in adverse consequences. Hyperglycemia is a common complication of specialized nutrition support. Critically ill patients are often hypermetabolic and insulin resistant because of the metabolic response to stress and infection. Gluconeogenesis continues in the stressed patient because of hormonal mediators in spite of high circulating levels of insulin. Hyperglycemia develops in non diabetic patients if given large amounts of glucose. This is especially true in the hypercatabolic, stressed state¹³. Uncontrolled hyperglycemia can lead to hyper osmolar non ketotic coma, which has a

mortality rate as high as 40%¹⁴. Hyperglycemia may also place the compromised, critically ill patient at higher risk of the development of sepsis¹⁵. Serum glucose levels should be kept in the range of 100-200 mg/dL¹⁵.

Phosphorus

Hypophosphatemia is one of the most serious metabolic complications observed in response to specialized nutrition support^{16,17}. Plummeting serum phosphorus levels may be seen within 24 to 72 hours after beginning of therapy. However, it is possible to see a delay in the development of hypophosphatemia of 5 to 10 days in patients who have normal body stores of phosphorus. In response to refeeding, there is a movement of inorganic phosphorus from the extracellular to the intracellular space because of utilization of phosphorus for the synthesis of phosphorylated compound. Insulin also promotes the uptake of both phosphorus and glucose in skeletal muscle and liver¹⁸. Severe hypophosphatemia (below 1.0 mg/dL) is associated with serious life threatening complications involving all major organ systems.^{1,18} It can lead to respiratory failure, cardiac abnormalities, central nervous system dysfunction including seizures, red blood cell dysfunction and leukocyte dysfunction^{4,6,19}.

One of the potential consequences of hypophosphatemia may be decreased oxygen delivery to the cell (ischemia) as hypophosphatemia leads to decreased levels of 2,3 diphosphoglyceride (2, 3 DPG) consequently impairing oxygen release from hemoglobin^{20,21}.

Potassium

Refeeding causes a shift of potassium into cell and may result in hypokalemia if potassium is not adequately supplied in the diet. Potassium moves into cells along with glucose and other energy substrates.

Symptoms of hypokalemia include muscle weakness, paralysis, paralytic ileus, cardiac arrhythmias, cardiac arrest, coronary ischemia, rhabdomyolysis, renal dysfunction, decreased urinary concentrating ability, polyuria, dysuria, constipation, respiratory depression, exacerbation of hepatic encephalopathy.^{4,6,19}

Magnesium

Magnesium shifts intracellularly with refeeding and new tissue synthesis. Hypomagnesemia is a frequent complication of both enteral and parenteral nutrition support.

Adequate magnesium is essential for normalizing phosphorus and potassium levels and is also required for over 300 metabolic pathways, including those involving ATP production. Therefore hypophosphatemia and hypokalemia associated with refeeding may be exacerbated by an underlying hypomagnesemia.²² Clinical deficiency symptoms are associated with serum level below 1.0mEq/L. Hypomagnesemia may lead to arrhythmias, tachycardia, respiratory depression, abdominal pain, diarrhea, ataxia, confusion, muscle tremors, weakness and tetany.^{4,6,19}

Thiamine

While not a hall mark of Re feeding Syndrome, thiamin deficiency can still be of significant importance to the malnourished patient at risk for refeed. Thiamine (B₁) is a water soluble vitamin with a biological half life of 9½ to 18½ days²³. In patients with suboptimal intake, it is estimated that deficiency can occur in less than 28 days.¹²

Thiamin is the precursor for the active metabolite thiamin pyrophosphate (TPP), essential for optimal glucose utilization and metabolism. TPP is a co-factor for three critical enzymes, in particular, pyruvate dehydrogenase. In thiamin deficiency, the conversion of pyruvate to acetyl coenzyme A (CoA) is blocked and the accumulating pyruvate is subsequently converted to lactate. This results in an overproduction of lactate and lactic acidosis follows. Inadequate levels of thiamin can also precipitate Wernicke's Encephalopathy (WE) in malnourished patients. Glucose load, whether delivered enterally or parenterally, will increase the demand for thiamin. Thiamine depletion may be exacerbated by dialysis, diuretics, diarrhea, alcohol, folate deficiency or malabsorption.²⁴⁻²⁶

The 2004 guidelines of the British Association of Pharmacology recommend a minimum of 500mg. IV TID for a minimum of two days, followed by

500mg IV daily for five days for patients with suspected or diagnosed WE.²⁷

Fluid retention

Insulin secretion associated with sudden carbohydrate infusion also lead to sodium fluid retention. This is thought to be due to insulin's effect on renal tubules leading to anti natriuresis. This antidiuretic effect causes an increase in extracellular fluid volume. Therefore, excessive sodium containing fluid infusion can lead to edema or, in severe cases, the combination of increased extracellular fluid volume and the cardiomyopathy often present in severely malnourished individuals & can lead to pulmonary edema, respiratory compromise and cardiac failure.

Prevention of the refeeding syndrome

The key to prevent the Refeeding Syndrome is to be aware of it and its consequences. Prevention begins with recognition of those patients at greatest risk of the development of potentially lethal complications from rapid overzealous feeding.

Initial assessment of refeeding syndrome:

Your patient is at risk of refeeding syndrome if there is: History of chronic malnutrition; acute weight loss of greater than 10% of pre-morbid body weight; little or no nutritional intake of any form for greater than 7-10 days.

The risks of refeeding syndrome are higher in patients with

Significant co-morbidity, e.g. infection, surgery, pressure sores, cancer; evidence of physiological stress, e.g. postoperatively or patients who require critical care input; prolonged fasting; anorexia nervosa; chronic alcoholism; electrolyte abnormalities (Potassium/Magnesium/Phosphate); the elderly (due to the increased risk of malnutrition in this patient group).

History and clinical examination

To record weight, rate of weight loss, dietary intake, reasons for malnutrition – physiological

impediment to oral or parenteral intake, swallowing difficulties, impaired intestinal function, heart rate, pulse rate, blood pressure,

respiratory rate and level of consciousness- 6 hourly for first 72 hours, daily temperature, ECG if patient has:

Irregular pulse, abnormal heart rate, serum potassium or phosphate level below normal range)

If evidence of cardiac abnormalities is present on assessment or during re feeding, patient will require cardiac monitoring. If necessary, transfer to ICU

Initial management of refeeding syndrome

Fluid resuscitation and monitoring fluid balance

Assess and carefully restore circulatory volume, monitor pulse rate, fluid intake and output. Malnourished patients have a reduced tolerance of intravenous fluid in moderate to high intake (i.e. more than 2 liters per 24 hrs.) can lead to heart failure.

Administration of intravenous fluids may be necessary in the initial 72 hours until sufficient oral intake is achieved.

If evidence of dehydration, for careful rehydration i.e. 1-2 liters in the first 24 hrs depending on response. Greater volumes only if severely dehydrated.

Total fluid intake (including i.v., enteral and oral) should aim for a maximum of 30ml/kg per day (i.e. commonly 1.5 liter or less).

At least 6 hourly monitoring of blood pressure, pulse and respiratory rate is necessary to detect evidence of heart failure or inadequate intra vascular volume.

Correction of electrolyte abnormalities

Ensure recent (last 48 hours) electrolyte levels are available. These should include: urea and electrolytes (Na⁺, K⁺), Phosphate, Magnesium, Calcium (add to standard blood profile) liver function tests, full blood counts. If electrolytes are deranged consider to treat possible cause.

Suggested guidelines for phosphorus replacement in adult I.V. ^{28, 29, 30}

Serum Po ₄ Level (mg/dL)	Recent Uncomplicated	Prolonged or Complicated
	mmol/kg. of Po ₄	mmol/kg of Po ₄
1.6–2.1	0.8–0.16	0.16–0.24
1.1–1.5	0.16–0.24	0.24–0.30
<1.1	0.24–0.30	0.50

Oral Repletion: Serum Phosphate > 1mg./dL, 1-2 g (32-64mmol) of Phosphorus/ day divided in 3 – 4 doses.

Suggestions for Magnesium Replacement ³¹

Condition	Magnesium – dose
Daily requirement	0.4m Eq/Kg./day
Mild to Moderate hypomagnesemia (Serum level 1.2 – 1.7 mg/dl)	Initial 1m Eq/Kg over 24 Hrs. Follow : 0.5 mEq/Kg over 24 Hrs. x 5 days
Severe Hypomagnesemia (Serum level < 1.2mg/dl)	Initial : 2g over 2 minutes Follow : 5g over 6 hours. Follow : 5g over 12 hrs. x 5 days

Suggestions for Potassium Replacement (If serum potassium < 3.0 mmol/L)

Administer: Potassium 0.3mmol/kg/hr for 4-6 hrs. Then 2-4mmol/kg/day; monitor ECG for arrhythmias during replacement therapy

If very low plasma electrolyte values are demonstrated e.g. phosphate < 0.32mmol/l, Potassium is <2.5mmol/l and Magnesium is <0.5mmol/l, then the institution of feeding or nutritional support may result in a further drop of these electrolytes to possibly critical levels. Electrolyte correction with oral/I.V. supplementation is required to achieve levels above these thresholds before institution of feeding.

Correction of Hypoglycemia:

Monitor blood glucose once to twice daily unless more frequent tests are indicated (i.e. for those patients with known diabetes or IGT).

If hypoglycemic replace intravenous fluids with 5% glucose.

Management of Hypothermia:

Monitor body temperature, and if necessary record temperature at least daily.

Hypothermia is commonly associated with malnutrition. It's correction should be simultaneously with fluid rehydration and can include provision of hot drinks and blanket.

Correction of micronutrient deficiencies

Administer thiamine 1-2mg/kg body weight IM. 100 mg IV should be administered in 50-100 ml 5% dextrose over 30 min., prior to refeeding as stat dose. Repeat the thiamine daily for 48 hours then weekly.

Administer vitamin B complex IV until oral route is available.

Commencing feeding in patients at risk of refeeding syndrome

Provision of calories should be done gradually during first 5- 7 days; 20Kcal-25Kcal/Kg/Day (5- 7 days) then after 7 day 25-35 Kcal./kg./day.⁴ or

no more than 20% above BEE.¹¹ or 1000Kcal/day.⁴ or 50% of total needs based on HBEx1.3-1.5.³²

For every 200-250 Kcal it is necessary to provide 6.25g Protein, 1.8mmol/Ca⁺⁺, 2.9mmol Phosphorus, 1.0mmol Magnesium, 10mmol Potassium, 7mmol Sodium and Chloride.

At the sight of a severely malnourished patient, the clinician should avoid the temptation to initiate excessive amount of nutrition support, rather, begin nutrition repletion slowly. While it is appropriate to start nutrition intervention as soon as feasible, it is dangerous to provide excessive calories or fluids to patients whose body has adapted to starvation.

In initial period 20Kcal/Kg. should be given to severely malnourished patients. A mixed fuel source of protein, fat and carbohydrate should be provided. Glucose infusion should not exceed 150-200 grams per day or 2mg/kg/min initially.¹¹ Protein can generally be initiated at full goal. (Up to 1.5g/Kg/day).¹¹ For estimating nutritional needs, the patients actual weight (or adjusted if obese) should be used rather than an ideal weight, which may be over (or under) estimate needs.

Conclusion

In many cases, nutrition support is a life saving modality. However, if nutrition is not delivered properly, Re feeding Syndrome represents a significant risk of morbidity and mortality in malnourished patients. Meticulous attention to the replacement of electrolyte imbalances and slow re-introduction of calories and protein will decrease the risk of cardiac and respiratory failure. Prospective, randomized controlled trials are needed to better identify patients prone to complications from Refeeding Syndrome. This, in turn will help to determine the best approach to Refeeding the malnourished patients.

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