Prevention and Management of Refeeding Syndrome

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ABSTRACT

Refeeding Syndrome is a syndrome which occurs as a result of food administration in poorly nourished individuals. In this syndrome, there are wide range of biochemical alterations, clinical manifestations, and complications, starting from mild (asymptomatic) to severe (death). This syndrome was initially proposed in 1950s; however, there is still no agreement for its clear definition, causing clinicians to be less aware and tend to overlook this condition. Clinical manifestations which usually appear include electrolyte imbalances (hypophosphatemia, hypokalemia, hyponatremia, hypomagnesemia) and vitamin B1 deficiency. The main principle in management of refeeding syndrome is prevention, where clinicians need to identify this condition in the early stage in high risk individuals, supervision during refeeding, and administration of appropriate diet.

Keywords: *refeeding syndrome, electrolyte imbalance, vitamin B1 deficiency*

ABSTRAK

Refeeding Syndrome merupakan sindrom yang terjadi akibat pemberian makan pada individu kurang gizi. Pada sindrom ini terjadi perubahan biokimia, manifestasi klinis dan komplikasi yang rentangnya sangat luas, mulai dari ringan (tidak bergejala) sampai berat (kematian). Sindrom ini pertama kali dikemukakan pada tahun 1950-an, namun sampai sekarang masih belum ada kesepakatan untuk definisi yang jelas, sehingga membuat klinisi tidak waspada dan cenderung terlupakan. Manifestasi klinis yang biasanya muncul adalah gangguan elektrolit (hipofosfatemia, hypokalemia, hiponatremia, hipomagnesemia) dan defisiensi vitamin B1. Prinsip utama dalam penanganan Refeeeding Syndrome adalah pencegahan, dimana klinisi harus mengidentifikasi dini individu berisiko tinggi, adanya pengawasan saat pemberian makan kembali, dan pemberian diet yang tepat.

Kata kunci: *refeeding syndrome, gangguan elektrolit, defisiensi vitamin B1*

INTRODUCTION

Refeeding syndrome (RS) describes biochemical alterations, clinical manifestations, and complications which can happen due to food administration in individuals with catabolic malnutrition. RS has been known and recorded in literature since more than 50 years ago and may cause serious injury and death. RS may happen in all individuals, but more often to occur in population at risk.[1] RS was reported for the first time in 1950s, after observation performed to malnourished war prisoners who suffered from cardiac and neurological symptoms soon after food re-

administration.[2] Until now, there is still no international consensus regarding the definition of RS. As there is no precise definition, it is anticipated that the incidence of RS is unclear.[1] Specific characteristic of RS is the presence of hypophosphatemia in patients; however, because this is a complex syndrome, it may also lead to symptoms of fluid imbalance, abnormal sodium level, alteration of glucose, protein, and fat metabolism, vitamin B1 deficiency, hypokalaemia, and hypomagnesemia.[3]

The spectrum of clinical manifestations of RS is very wide, with various symptoms, unpredictable, that may occur without any warning signs, and may also appear later. Its symptoms occur as a result of alterations in blood electrolytes causing disturbance in cell membrane potential, thus interrupts the function of neurons, heart, and skeletal muscle. The presentations of symptoms start from mild nausea and vomiting to breathing problems, heart failure, hypotension, arrhythmia, delirium, coma, and death.[1] Although the physiology and pathophysiology of RS is well known, conditions causing the appearance of RS, clinical manifestations, and management of this patient are still unclear. It leads many clinicians to be unaware and even forget RS; hence, this condition is still happening.[1,3]

This article aims to increase the awareness of RS and acts as a discussion material for prevention and management of RS. Thus, in the future clinicians have good ability in diagnostic approach and can manage RS in comprehensive and holistic manner.

DEFINITION OF REFEEDING SYNDROME

The first report regarding RS is published in 1950s, after observation performed in malnourished war prisoners who suffered from cardiac and neurological symptoms soon after food re-administration.[2] For the universal definition of RS, until now there is still no approved consensus.[4] In their study performed in year 2001, Crook et al stated that RS is a syndrome marked by the presence of severe fluid and electrolyte imbalance accompanied by metabolic dysfunction in malnourished individuals who underwent food re-administration, either in the form of oral, enteral, or parenteral.[5]

As there is still no strict definition, it is not surprising that the incidence rate of RS remains unclear.[1,3] The number of studies of RS is still limited because there is no internationally approved diagnostic criteria or guidelines to detect RS.[6] Most published data is obtained from prospective and retrospective case series; thus, do not reflect the incidence rate in general.[1,6]

Hypophosphatemia is the most common marker used in RS, although low phosphate level in the blood is not a pathognomonic condition.[7] In a prospective cohort study in ICU patients conducted by Marik and Bedigian, 34% patients suffered from hypophosphatemia soon after patients were given food re-administration (mean (standard deviation) 1.9 (1.1) days).[8] However, this condition is frequently undetected, or even do not receive appropriate management, particularly in patients treated in regular wards.[3]

PATHOGENESIS AND PATHOPHYSIOLOGY

The main factor causing the occurrence of RS is hormonal and metabolic alterations which are triggered by rapid food re-administration, either enteral or parenteral. In starving condition, initially there are metabolic and hormonal changes where the body shifts its main source of energy from carbohydrate into protein and fat, and the basal metabolic rate decreases by approximately 20-25%.[9]

In prolonged fasting, the hormonal and metabolic changes which happen in the body aim to prevent

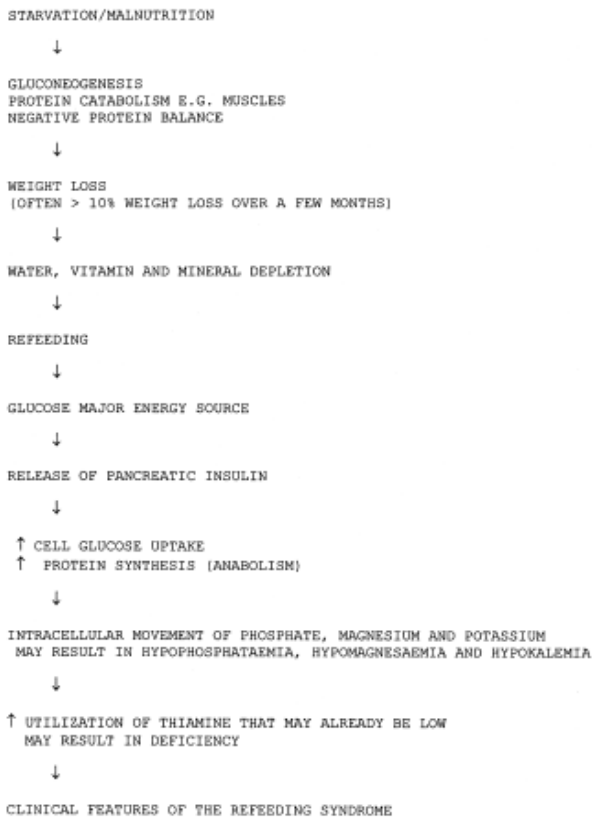

Figure1. Scheme of pathophysiology in refeeding syndrome[5]

protein and muscle breakdown. Muscle and other tissue organs decrease the use of ketone as main source of energy and instead use fatty acid. This can increase ketone level in the blood, thus stimulate brain to replace glucose with ketone as the main source of energy. Liver also decreases the rate of gluconeogenesis; thus, muscle protein can be preserved. In long-term starvation, several minerals which present in intracellular compartment will decrease dramatically. However, minerals concentration in the blood (including phosphate) will remain normal. This is due to the homeostasis mechanisms which maintain the concentration of those ions in the serum by sacrificing intracellular storage.[1,3]

Nutrition re-administration in malnourished patients will cause decreased gluconeogenesis and rapid anaerobic metabolism process. This is mediated by the rapid increase of insulin during refeeding.[10] Insulin will stimulate potassium, phosphate, and magnesium transfer from extracellular to intracellular. Since the level of these minerals are very low in the intracellular compartment, this transfer cause sudden decrease of mineral concentration in the extracellular space.[11] Osmotic imbalances which happen suddenly due to refeeding is compensated by the body by the presence of fluid and sodium retention to replace osmotic balance.[1] Reactivation of metabolic pathway associated with carbohydrate will increase thiamine requirement, a cofactor required for cellular enzymatic reaction. This process will lead to the decrease in the level of phosphate, potassium, magnesium, and thiamine in the serum. The degree of reduction varies and may cause different effects in every individual.

CLINICAL MANIFESTATIONS

Clinical manifestations of RS are varied, cannot be predicted, appear suddenly, and may also appear later. Those clinical manifestations appear as a result of drastic changes in serum electrolyte level which influences the potential of cell membrane and disturb the function of neurons, skeletal muscle cells, and cardiac muscle cells. The spectrum of clinical manifestations which appear due to RS is very wide, starting from complaints of nausea, vomiting, and fatigue until breathing problems, heart failure, hypotension, coma, and even death.[1,3,5] Clinical manifestations which are related to electrolyte imbalance due to RS is summarized in Table 1.

MANAGEMENT

The management principle of RS is correction of biochemical abnormality and fluid imbalance to reach their normal values, if possible. A guideline published by National Institute of Health and Clinical Excellence indicated that food administration and biochemical abnormality correction which happen in the RS may be performed simultaneously without giving bad effect to the patient.[3,6] However, until now there is still no randomized study to support this opinion.

Table 1. Clinical manifestation of refeeding syndrome associated electrolyte imbalance[1]

	Clinical manifestation
Phosphate (PO_4^{2-})	Hypophosphatemia (normal range 0.8-1.45 mmol/L) presents as Cardiovascular: heart failure, arrhythmia, hypotension, cardiomyopathy shock, death Renal: acute tubular necrosis, metabolic acidosis Skeleton: rhabdomyolysis, weakness, myalgia, diaphragm weakness Neurology: delirium, coma, seizures, tetany Endocrine: hyperglycaemia, insulin resistance, osteomalacia Haematology: haemolysis, thrombocytopenia, leukocyte dysfunction
Potassium (K^+)	Hypokalaemia (normal range 3.5-5.1 mmol/L) presents as Cardiovascular: hypotension, ventricular arrhythmias, cardiac arrest, bradycardia or tachycardia Respiratory: hypoventilation, respiratory distress, respiratory failure Skeleton: weakness, fatigue, muscle twitching Gastrointestinal: diarrhea, nausea, vomiting, anorexia, paralytic ileus, constipation Metabolic: metabolic alkalosis
Magnesium (Mg^{2+})	Hypomagnesaemia (normal range 0.77-1.33 mmol/L) presents as Cardiovascular: paroxysmal atrial or ventricular arrhythmias, repolarisation alternans Respiratory: hypoventilation, respiratory distress, respiratory failure Neuromuscular: weakness, fatigue, muscle cramps (Trousseau and Chvostek) weakness, ataxia, vertigo, paresthesia, hallucinations, depression, convulsions Gastrointestinal: abdominal pain, diarrhea, vomiting, loss of appetite, and constipation Other: anaemia, hypocalcemia NB: many cases of hypomagnesaemia do not manifest clinically till very late
Sodium (Na^+)	Hyponatremia (normal range 136-145 mmol/L) ensues during RFS due to hyperglycaemia and presents as: Cardiovascular: heart failure and arrhythmia Respiratory: respiratory failure, pulmonary oedema Renal: renal failure Skeleton: muscle cramps, fatigue, fluid retention and swelling (oedema)
Vitamins	Deficiency of thiamine (especially in alcoholism) presents as Neurology: Wernicke-Korsakoff syndrome, Karsakoff's psychoisis, Cardiovascular: congestive heart failure and lactic acidosis, beriberi, disease Skeleton: muscle weakness

Prevention is the main key in the successful management of RS. In this prevention, there are 3 (three) main basic factors which need to be considered. These factors are identification of individuals at risk of RS, monitoring during refeeding, and appropriate regiment of diet. Anticipating risk of RS from the beginning will prevent the complications. This can be performed by detailed history taking accompanied with proper physical examination and identification of individuals at risk with early involvement of nutritionist (dietitian and/or clinical nutrition specialist).[1,3-5]

Table 2. High risk individuals for refeeding syndrome[1]

Anorexia nervosa	Chronic alcoholism
Radiation therapy	Major stressors without food for > 7 days
Oncology patients	Postoperative patients
Severe malnutrition (marasmus/ kwashiorkor)	Institutionalized patients
Pathological weight loss	Hunger strikes
Stroke (neurological problems)	Malabsorption diseases
Inflammatory bowel disease	Post bariatric surgery
Chronic pancreatitis	Elderly, poor social circumstance
Acquired Immunodeficiency Syndrome	Diabetes Mellitus

Table 3. Monitoring in patients with risk of refeeding syndrome[1]

Clinical monitoring	Biochemical monitoring
Early identification of high risk patients	Monitor biochemistry and electrolyte levels
Monitor blood pressure and pulse rate	Monitor blood glucose levels
Monitor feeding rate	ECG monitoring in severe case
Meticulously document fluid intake and output	Account other sources of energy
Monitor change in body weight	(dextrose, propofol, medications)
Monitor for neurologic signs and symptoms	
Patient education	

Currently, there are many publications regarding regiment for food administration in individuals at risk of RS. All of them are not evidence-based. In food administration of these at risk individuals, the main principle needs to be followed is underfeeding permissive principle.[1] Below is the recommendation of food administration based on guidelines, publication, and experts' opinions (Table 4).

CONCLUSION

All clinicians who treat patients at risk and require nutrition administration need to identify the risk of RS. The lack of randomized controlled trial study in this treatment means that the management of RS is still based on non-evidence based, anecdotal data. This highlights the importance of minimizing the risk of RS by carefully reintroducing food. RS is also a spectrum of disease happening in particular condition in high risk population.

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Table 4. Recommendation of food administration for individuals with risk of refeeding syndrome[1,6]

Day	Calorie intake (all feeding routes)	Supplements
Day 1	10 kcal/kg/day	Prophylactic supplement
	For extreme cases	PO_4^{2-}: 0.5-0.8 mmol/kg/day
	(BMI < 14 kg/m^2 or no food > 15 days)	K^+: 1-3 mmol/kg/day
	5 kcal/kg/day	Mg^{2+}: 0.3-0.4 mmmol/kg/day
	Carbohydrate: 50-60%	Na^+: < 1 mmol/kg/day (restricted)
	Fat: 30-40%	IV fluids-restricted, maintain "zero" balance
	Protein: 15-20%	IV Thiamine + vitamin B complex 30 minutes prior to feeding
Day 2-4	Increase by 5 kcal/kg/day	Check all biochemistry and correct any abnormality
	If low or no tolerance stop or keep	Thiamine + vitamin B complex orally or IV till day 3
	minimal feeding regime	Monitoring as required (Table 3)
Day 5-7	20-30 kcal/kg/day	Check electrolytes, renal and liver functions and minerals
		Fluid: maintain zero balance
		Consider iron supplement from day 7
Day 8-10	30 kcal/kg/day or increase to full requirement	Monitor as required (Table 3)