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Review Article

Refeeding Syndrome: A Review

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Introduction

Refeeding syndrome (RS) was first described among prisoners of far east after the second world war[1]. Eating again after a long period of prolonged starvation seems to precipitate cardiac failure. It develops in malnourished patient who receives nutritional support after a long period of inadequate intake. It usually develops within four days of initiation of dietary therapy[2]. Although no consensus definition exists, refeeding syndrome can be defined as the consequences of severe fluid and electrolyte shifts in malnourished patient when they are refed[3-5]. It can develop after oral, enteral (through a tube) or parenteral (Intravenous) nutritional therapy. Phosphate plays an important role in the pathogenesis of various manifestations of refeeding syndrome. The biochemical hall mark of refeeding syndrome is hypophosphataemia[6].

Historical aspects

Some of the adverse consequences of refeeding were well-described in the medical literature in the 1940[3]. Key et al[3,7] reported a new classical study, the Minnesota Experiment, which studied the effect of drastic food restriction and subsequent oral feeding in previously healthy subjects. Subjects who had undergone 6 months of starvation showed no evidence of dyspnoea, increased venous pressure or cardiac dilatation. However, during the recovery phase, as the volunteers were refed, the cardiovascular reserve was diminished to the point that cardiac failure occurred in some subjects. The observation in this experiment correlated with the prior unintentional refeeding experiments undergone by victims of World War II. Hypertension and cardiac insufficiency increased markedly in the populace of Leningrad after the post-siege restoration of normal food and liquid intake in patients apparently healthy until the appearance of feature of refeeding syndrome. Peripheral oedema was also seen in the Leningard patients as well as in hospitalized recovering Japanese prisoners of war. Neurological complications coincident with refeeding, including coma and convulsions, were noted in the victims of the war in the Netherlands.

In 1972, Silvis and Paragas[8] reported three cases of refeeding syndrome with paresthesia, weakness and seizure occurring within 4 to 5 days of beginning TPN in patients with weight loss secondary to regional ileitis or prolonged gastric outlet obstruction. In 1982, Weinsier et al[3] reported two cases of the refeeding syndrome. The first case was a severely malnourished patient with anorexia nervosa who suffered acute myocardial infarction and subsequent death which was associated with institution of TPN 44 hours before the tragedy. The second patient, a case of malnutrition secondary to malabsorbtion developed acute respiratory failure 48 hours after starting TPN. It is important to note that both patients had normal serum phosphate levels before beginning TPN therapy but had extremely low phosphate levels (1.1 mg/dl and 0.7 mg/dl, respectively) at the time of their initial decompensation.

Pathogeneses of refeeding syndrome

The pathophysiology of refeeding syndrome has now been established[9]. In starvation the secretion of insulin is decreased in response to a reduced intake of carbohydrates and glucagone level increased. Consequently body fat and protein are catabolised to produce energy by the process of gluconeogenesis (Fig.-1).

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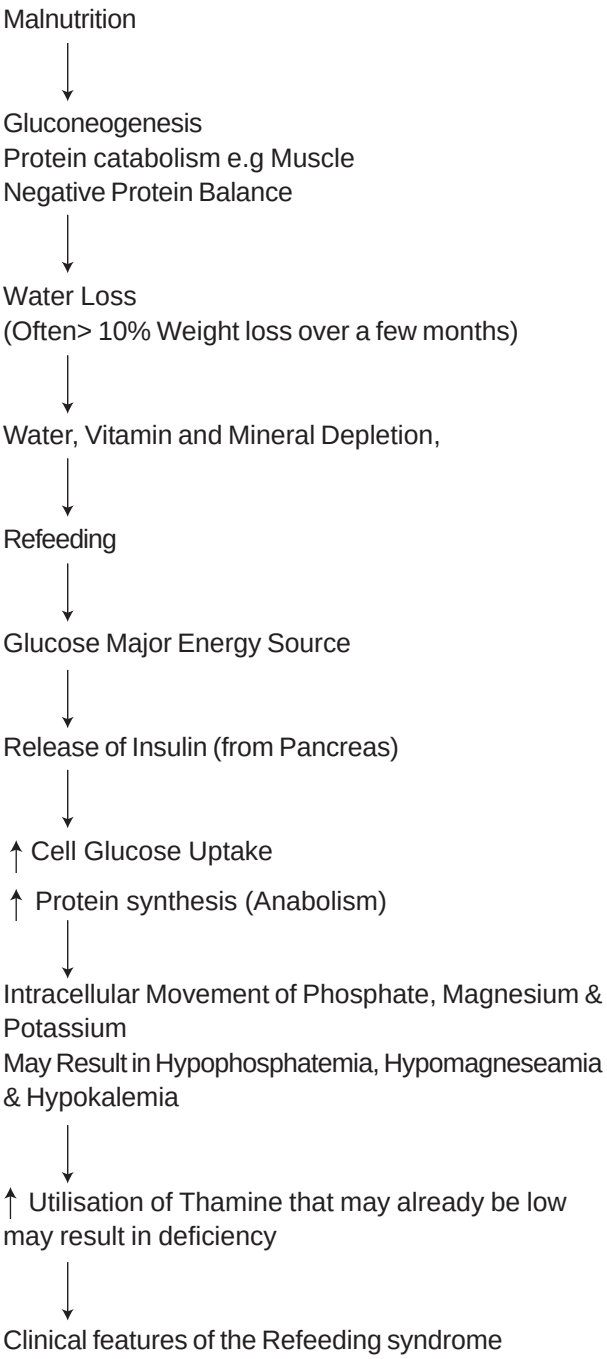

Fig.-1: *Schematic diagram of some of the metabolic consequences of malnutrition & refeeding syndrome*

In severe malnourished individual, the catabolism of fat and muscle lead to loss of lean muscle mass, water and minerals. The serum concentration of these depleted components including phosphate, generally remain normal due to adjustments in renal rates of excretion. With the conversion to carbohydrate as the major source of energy during refeeding, insulin release is stimulated. Carbohydrate repletion and insulin release together enhance uptake of glucose, phosphate, water and other components to intracellular compartments often resulting in oedema (e.g. pulmonary)[3,11]. The combination of depletion of total body phosphate stores during catabolic starvation and increased cellular influx of phosphate during anabolic refeeding leads to severe extracellular hypophosphatemia[13,14]. Low serum phosphate levels are directly related to depletion of phosphorylated intermediates and compound, such as red cell 2,3-DPG, ATP, G-3-PD etc which are important for metabolism.

The major clinical manifestations of refeeding syndrome are the results of reduced ATP in metabolic pathways and reduced 2,3 DPG in erythrocytes. Refeeding syndrome can affect every system in the body. Phosphate is vital for cellular respiration. The first step, glycolysis, involves the phoshorylation of glucose (the addition of a phosphate). Cellular respiration also needs adequate phosphate stores to form the energy storing molecule adenosine triphosphate (ATP), which contains three phosphate groups. Phosphate also plays a part maintaining intracellular enzyme functions including the synthesis of 2,3 diphosphoglycerate (DPG) which regulates oxygen dissociation from haemoglobin. So severe phosphate depletion disrupts almost every cellular physiological process.

Decreased level of ATP causes reduced respiratory muscle contraction which has been suggested as a mechanism of acute respiratory failure. Decreased level of WBC ATP content interferes with chemotactic and phagocytic activity causing increase chance of infections.

The common pathway to refeeding syndrome may be ascribed to hypophosphatemia. There is also depletion of magnesium, potassium and vitamins (specially thiamine) which also plays important role in the development of refeeding syndrome [16,27, 28] (Fig.-1).

Clinical Features of Refeedng Syndrome[10, 21-25]

Serum phosphate concentration of less than 0.5 mmol/L (Normal 0.88-1.40 mmol/L) can produce the clinical features of refeeding syndrome[8,12]. Importantly, the early clinical features of refeeding syndrome are nonspecific and may go unrecognised.

Cardiac[24]	Altered myocardial function, arrhythmia, congestive cardiac failure, cardiac arrest, sudden death.

Haematologic[10,25]	Altered RBC morphology, haemolytic anaemia, WBC dysfunction, thrombocytopenia, depressed platelet function, haemorrhage
Neurological[23]	Acute areflexic paralysis, confusion, coma, cranial nerve palsies, diffuse sensory loss, Guillain-Barre like syndrome, lethargy, tetany, tremor, paresthesia, seizures, weakness
Respiratory[21,22]	Acute ventilatory failure
Gastro-intestinal	Paralytic ileus
Musculo-skeletal	Osteomalacia, rhabdomyolysis

Prevention & Management

Refeeding syndrome is often under diagnosed and as a consequence remains untreated[26]. The first step towards preventing it is to increase awareness among hospital clinicians so that patients can be assesed for their risk and hence managed appropriately. Nutritional repletion should begin with less than full restoration of salt, fluid and caloric needs. Circulatory volume and caloric requirements should be advanced slowly and gradually to avoid cardiac overload and rapid electrolyte shifts respectively. Before refeeding, electrolyte disorders, vitamin and trace-element deficiencies (e.g. thiamine) should be corrected. Electrolytes including phosphate, potassium, magnesium, glucose should be monitored both before & after refeeding. A gradual increase in calories over the first week is prudent untill the patient becomes metabolically stable[3]. Severe hypophosphatemia should be treated by phosphate supplementation. A little nutrition support is good, too much is lethal[4].

Conclusion

The refeeding syndrome is poorly recognized or understood. As the biochemical derangements usually occur in the first 3-4 days of initiating nutritional therapy careful monitoring the serum levels of phosphate along with electrolytes during this period will help to recognize this preventable syndrome. A nutrition specialist can help to provide advice in its prevention, recognition and treatment. Eventually this will help to prevent the PEM related morbidity and mortality in our country.

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