Module 6.3

Refeeding Syndrome and Methods for Safe Nutritional Intervention

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Learning objectives:

- To specify particular clinical conditions related to a high risk of refeeding syndrome;
- To learn how to recognize patients at high risk of refeeding syndrome;
- To know the mechanisms contributing to the development of refeeding syndrome in specified clinical states;
- To learn how to prevent the refeeding syndrome.

Contents:

Key messages:

- The biochemical hallmark of the refeeding syndrome is hypophosphataemia, which can occur in hospitalized patients with an incidence of 0.2%-3.1%, with clinical manifestations ranging from mild to life-threatening;
- At highest risk of hypophosphataemia are patients with uncontrolled diabetes, cancer cachexia, anorexia nervosa, sepsis and chronic alcoholism;
- Early identification of patients at risk, for which the best means seems to be the NICE criteria, and prevention of the refeeding symptoms are crucial to its successful management;
- Before refeeding, electrolyte disorders should be corrected and the circulatory volume carefully restored;
- Careful monitoring of electrolytes on a daily basis is required;
- Slow, gradual feeding reaching goal rates in 4–7 days is recommended;
- If the refeeding syndrome occurs – stop nutrition and correct imbalances before next attempt at feeding.

1. Introduction

The refeeding syndrome is a life-threatening complication accompanying restoration of the delivery of nutrients, independently of route of their administration, in patients who are severely malnourished. It was described for the time in 1948 in a group of prisoners released from concentration camps following the Second World War (1). The start of oral feeding in these starved individuals often resulted in severe diarrhoea, heart failure, convulsions, coma and even death. In those patients the implementation of apparently optimal diet including vitamins resulted in the cardiac failure death of one fifth of them (2). After a long break, in 1981, other cases of refeeding syndrome were presented in the literature, again ending with death (3). It riveted attention to the problem.

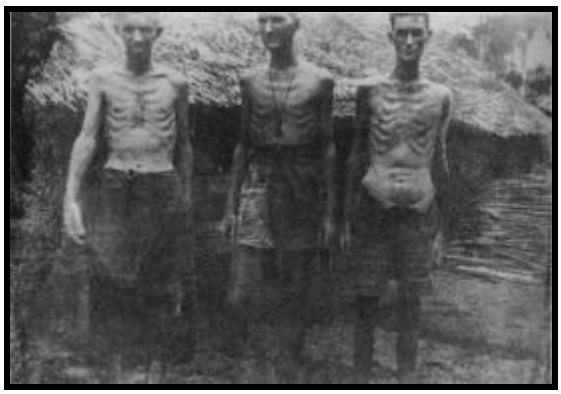

Fig. 1 Starved American prisoners in Japan during WW II.
http://www.forties.net/WWIIPOWs.html.

1.1. Definition

Refeeding syndrome can be defined from severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients after reinstating the administration of nutrients, independently of the route: oral, enteral, or parenteral (4). Severe hypophosphatemia is a predominant feature of the refeeding syndrome, but there are other metabolic consequences that are equally important such as fluid-balance abnormalities, hypokalaemia and hypomagnesaemia, altered glucose metabolism, and certain vitamin deficiencies, e.g., thiamine.
In 1990 in their review Solomon and Kirby (5) proposed the following definition for this medical condition: "the metabolic and physiologic consequences of the depletion, repletion, compartmental shifts and interrelationships of phosphorus, potassium, magnesium, glucose metabolism, vitamin deficiency and fluid resuscitation". According to the recent review published by Skipper in 2012 (6) the refeeding syndrome may be understood as "a result when oral, enteral, or parenteral nutrients, primarily carbohydrate, fluid, and sodium, are administered to starved or malnourished patients in amounts greater than a weakened cardiopulmonary system can accommodate". Usually it occurs within the first 2 to 5 days after the start of the nutrition.

2. Prevalence of refeeding syndrome in various clinical states

Unfortunately, there are no solid data on the prevalence of the refeeding syndrome. This may be due to unclear definitions of the syndrome and the diversity of its clinical features. There is no unequivocal consensus on how many abnormalities, of those named below, are required to diagnose the refeeding syndrome. It seems, however, that the main biochemical marker of refeeding syndrome is hypophosphataemia, because it was almost universally present (96% of cases) (6). This is a common finding in critically ill patients, particularly in those receiving nutritional support, and can result in serious complications. Hypophosphataemia leads to an energy deficit in the form of ATP

depletion, resulting in cardiac failure, pulmonary failure, haemolysis, rhabdomyolysis and neurologic disorders. Hypophosphataemia may develop as a result of phosphorus depletion or due to a shifting of phosphorus to the intracellular compartment. Depletion of total body phosphorus occurs in undernourished patients, such as those with cancer cachexia, HIV infection, anorexia nervosa and chronic excess alcohol consumption. In non-depleted patients, risk factors for hypophosphataemia are: glucose infusion, medications (antacids, diuretics), trauma (especially severe head injury), burns and sepsis (4). Among the mechanisms leading to the development of hypophosphataemia, the following can be distinguished:

- decreased intestinal absorption:
— starvation or anorexia;
— malabsorption and chronic diarrhoea;
— antacids;
— vitamin D deficiency;
— alcoholism;
- increased urinary losses:
— diuretics;
— extracellular fluid volume expansion;
— glycosuria (diabetic ketoacidosis);
— post-obstructive or resolving acute tubular necrosis diuresis;
— primary hyperparathyroidism;
— after renal transplant;
- redistribution:
— refeeding syndrome;
— respiratory alkalosis;
— alcohol withdrawal;
— severe burns;
— leukaemic blast crisis.

In the general hospital population, the incidence of hypophosphataemia may range from 0.2% to 3.1%, depending on how it is defined, however in selected patient populations it can reach over 20%, with clinical manifestations ranging from mild to life-threatening (6). In large studies conducted among hospitalized patients the prevalence of severe hypophosphataemia (serum phosphate ≤ 0.33 mmol/l) was estimated at approximately 0.43% overall, but respectively at:

— 14.6% in patients with diabetic ketoacidosis;
— 10.4% in patients with malnutrition;
— 2.42% in septic patients;
— 0.91% in alcoholics (5).

In parenterally fed patients the incidence of hypophosphataemia (the major abnormality during refeeding syndrome) ranged from 30%–38% when phosphorous was provided in the feed, to 100% when PN without phosphorous was administered (5). In another prospective study of sixty-two patients in the intensive care unit who were re-nourished after being starved for 48 hours, 34% of them experienced refeeding hypophosphataemia. There was an association between low serum phosphate level and low prealbumin concentration (8). Another notable condition is cancer and its treatments including operative procedures, chemotherapy, and radiotherapy (9, 11). In cancer patient's severe hypophosphatemia has been reported to be as frequent as 25% (12, 13, 14).

Chronic diseases, such as: malabsorption syndromes, gastrointestinal fistulae, chronically uncontrolled diabetes mellitus, and alcoholism, but also the perioperative period, surgery for non-malignant diseases (e.g. treatment of obesity), old age, pregnancy, and paediatric illness, all predispose to hypophosphataemia and refeeding syndrome(15-25). Unfortunately, metabolic abnormalities remained unrecognized or inappropriately treated in many - 42% of patients in one study (14). Although hypophosphataemia is the predominant issue, it must be taken into consideration that the refeeding syndrome is a complex issue. Apart from hypophosphataemia also hypokalaemia and

hypomagnesaemia, thiamine deficiency, abnormal sodium and fluid balance, changes in glucose, protein, and fat metabolism may occur. All are addressed presented below.

3. Pathogenic mechanisms involved in the refeeding syndrome

Review of some basic physiological processes that take place during starvation helps to explain some of the clinical manifestations observed during the refeeding syndrome.
During starvation the insulin concentration decreases while glucagon increases. This results in the utilisation of glycogen stores to form glucose. Other adaptations to starvation include gluconeogenesis: the synthesis of glucose from non-carbohydrate sources, and the production of other lipid and protein breakdown products (fatty acids, glycerol, ketone bodies and amino acids).
Adipose tissue releases large quantities of fatty acids and glycerol while skeletal muscles release mainly amino acids. Ketone bodies and free fatty acids replace glucose as a major energy source under these circumstances. Overall, catabolism of adipose tissue and muscle results in absolute and relative loss of lean body mass. Intracellular and extracellular ions, including phosphate, potassium, and magnesium, are lost over time, but as there is the concurrent loss of total body water that also accompanies malnutrition, their measured concentrations in blood may remain misleadingly normal. Up to 150 g of lean muscle is lost daily during simple starvation, resulting in the release of 15 to 20 mmol of potassium and 110 ml of water from the intracellular to the extracellular fluid. Stress or injury increases the lysis of lean tissue and may result in the loss of 1.2g of phosphorus, 60 mmol of potassium, and 450 ml of water per day (26).

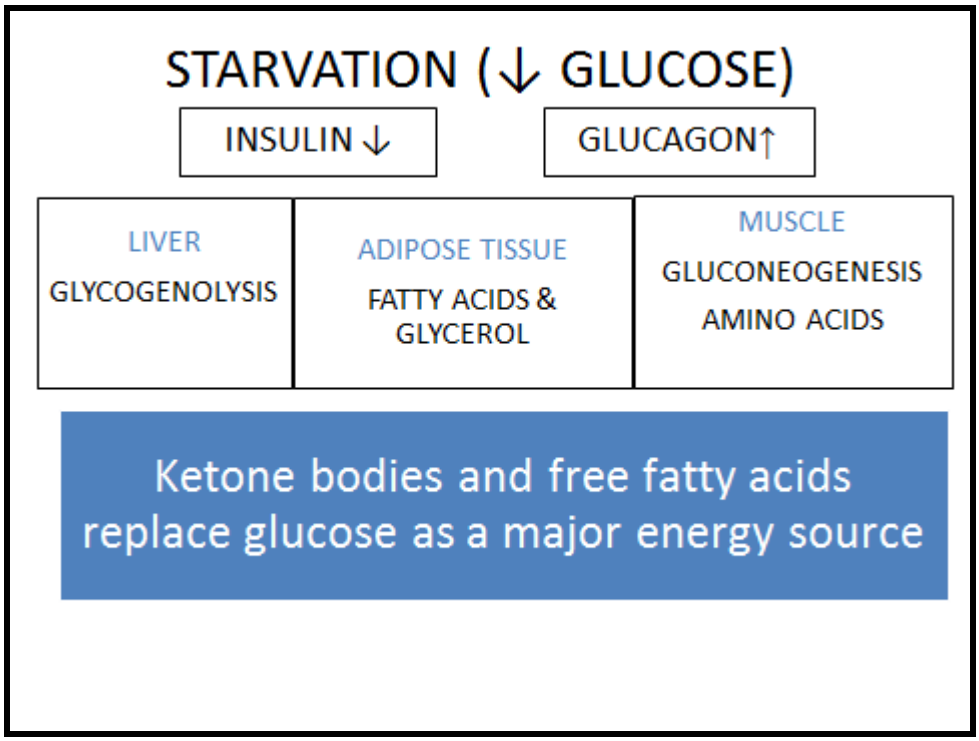

Fig.2 Metabolism during starvation

During refeeding, a rapid shift from fat to carbohydrate metabolism occurs. A glucose load evokes insulin release. Insulin stimulates glycogen, fat and protein synthesis. This process requires minerals such as phosphate and magnesium and cofactors such as thiamine. Insulin stimulates the absorption of potassium into cells through the sodium-potassium ATPase symporter, which also transports glucose. Magnesium and phosphate are also taken up into the cells. Water follows by osmosis. These processes result in a decrease of the serum levels of phosphate, potassium, and magnesium, all of which are

already depleted (even if the prior concentrations were normal). The clinical features of the refeeding syndrome occur as a result of functional deficits of these electrolytes aggravated by the rapid change in basal metabolic rate (27).

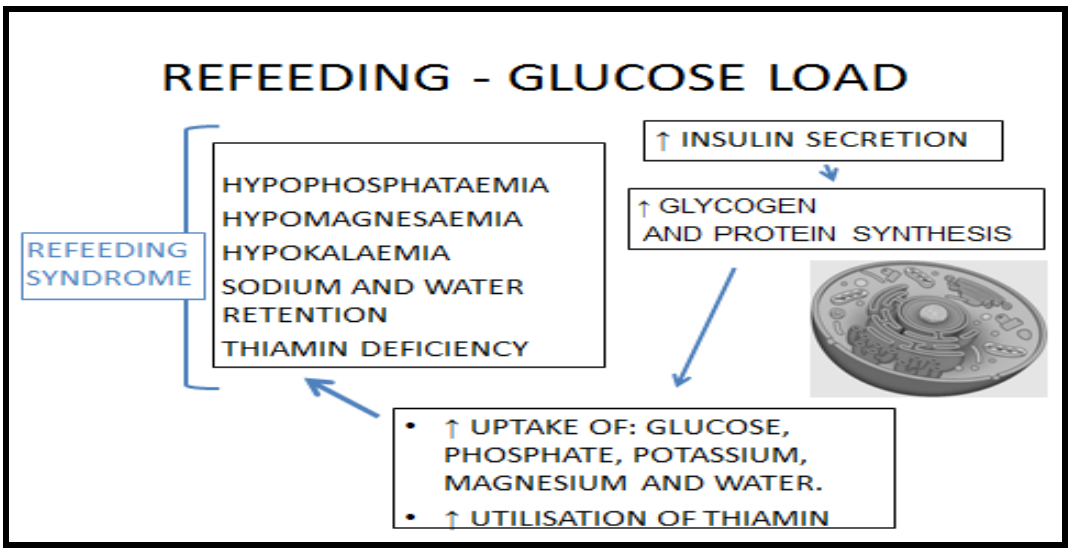

Fig. 3a Metabolism after refeeding.

A complex approach to the mechanism of refeeding syndrome was also proposed by Boateng et al. (28)

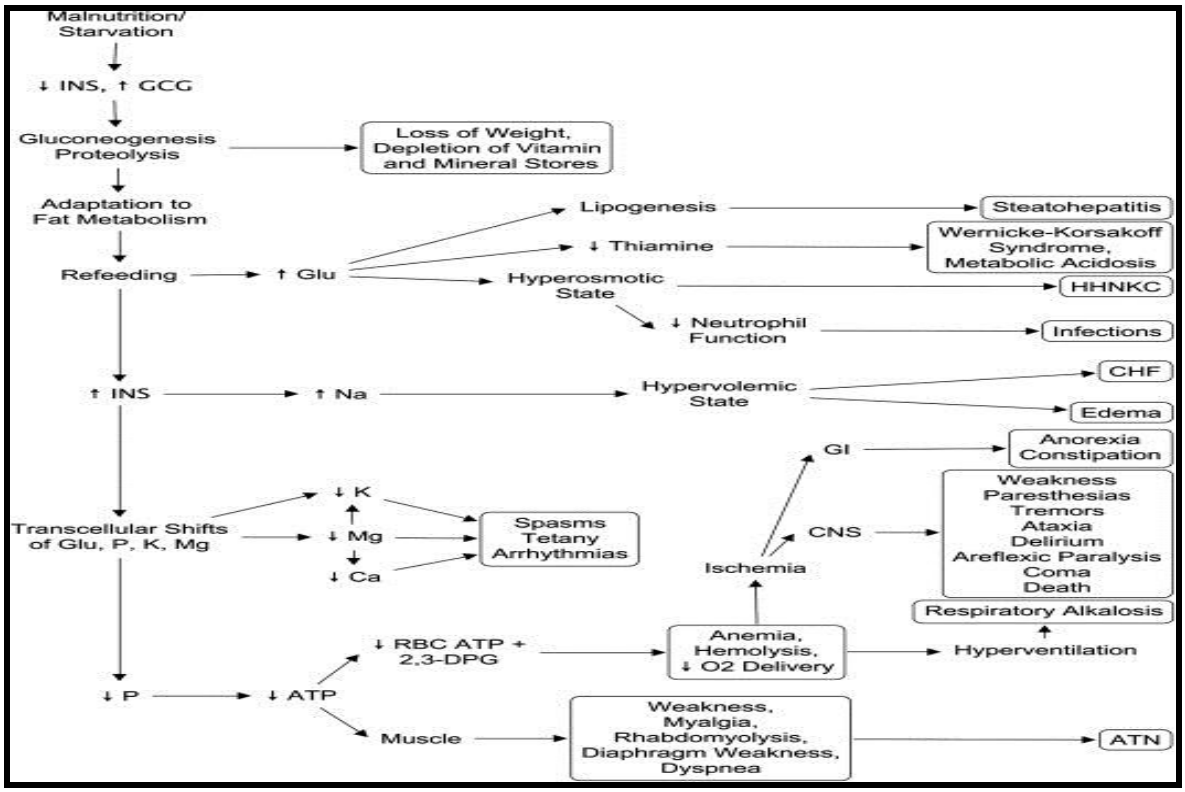

Fig. 3b Pathophysiology of refeeding syndrome. Boateng et al. 2010 (8)**.**

INS, insulin; GCG, glucagon; Glu, glucose; P, phosphorus; K, potassium; Na, sodium; Ca, calcium; ATP, adenosine triphosphate; RBC, red blood cell; CHF, congestive heart failure;

ATN, acute tubular necrosis; HHNKC, hyperosmolar hyperglycemic nonketotic coma; GI, gastrointestinal system; CNS, central nervous system.

3.1. Patients at risk of refeeding syndrome

To prevent the development of the refeeding syndrome identification of high risk patients is crucial. The low incidence of refeeding syndrome reported in various studies may be the result of insufficient biochemical monitoring and subsequent insufficient recognition of this condition (6). All patients in the following categories should be considered at high risk:

- anorexia nervosa;
- chronic alcoholism;
- cancer;
- perioperative period;
- chronic infectious diseases (AIDS, tuberculosis);
- elderly patients;
- uncontrolled diabetes mellitus;
- chronic malnutrition:

— Marasmus;
— Prolonged fasting or low energy diet;
— Chronic swallowing problems and other neurological disorders;
— Morbid obesity with profound weight loss;
— High stress patient unfed for >7 days;
— Malabsorptive syndromes (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome);

- Long term users of antacids;
- Long term users of diuretics.

NICE criteria to identify patients at risk

In the guidelines developed by the National Institute for Health and Clinical Excellence - NICE (published in 2006 in England) criteria for identifying patients at high risk of refeeding problems were precisely defined:

- Either the patient has one or more of the following:

— Body mass index (kg/m^2) <16;
— Unintentional weight loss >15% in the past three to six months;
— Little or no nutritional intake for >10 days;
— Low levels of potassium, phosphate, or magnesium before feeding;

- Or the patient has two or more of the following:

— Body mass index <18.5;
— Unintentional weight loss >10% in the past three to six months;
— Little or no nutritional intake for >5 days;
— History of alcohol misuse or drugs, including insulin, chemotherapy, antacids, or diuretics (27).

3.2. Signs and symptoms of refeeding syndrome

Signs and symptoms are secondary to the electrolyte and metabolic disorders mentioned above **(Table 1).**

Table 1. Manifestations of refeeding syndrome according to organ systems (modified from Boateng et al.(28)):

System	Sign/symptom
Cardiovascular	Arrhythmias Congestive heart failure Sudden death
Respiratory	Diaphragm/Intercostal muscle weakness Respiratory failure Ventilator dependency
Metabolic	Hyperglycaemia Metabolic acidosis Metabolic alkalosis Respiratory alkalosis
Neurological	Wernicke's encephalopathy Weakness Paraesthesias Tremors Ataxia Delirium Acute encephalopathy Coma Guillan-Barré-like syndrome Central pontine myelinolysis
Musculoskeletal	Weakness Myalgias Rhabdomyolysis Osteomalacia
Gastrointestinal	Anorexia Abdominal pain Constipation Vomiting
Others	Acute tubular necrosis Liver failure

3.3. Pathological mechanisms leading to refeeding syndrome in various clinical states

Uncontrolled diabetes

There are similar pathological changes observed in uncontrolled diabetes mellitus and in the refeeding syndrome, particularly when disturbances are prolonged and severe (9). During prolonged starvation or catabolism, loss of muscle, fat, and water results in a disproportional loss of phosphate and, subsequently, of ATP, creatine phosphate, and 2,3-diphosphoglyceric acid (2,3-DPG) depletion. With the start of high-caloric feeding (oral, enteral and especially intravenous) endogenous insulin causes increased phosphate uptake into the cells, and serum concentrations of phosphorus fall suddenly and dramatically.

In uncontrolled diabetes associated with a prolonged osmotic diuresis, when a hyperglycaemic hyperosmolar state persists over a period of days or weeks, total body phosphate stores are depleted. These patients develop a catabolic state and, as in the case of prolonged starvation, use fat and protein as their main metabolic substrates.

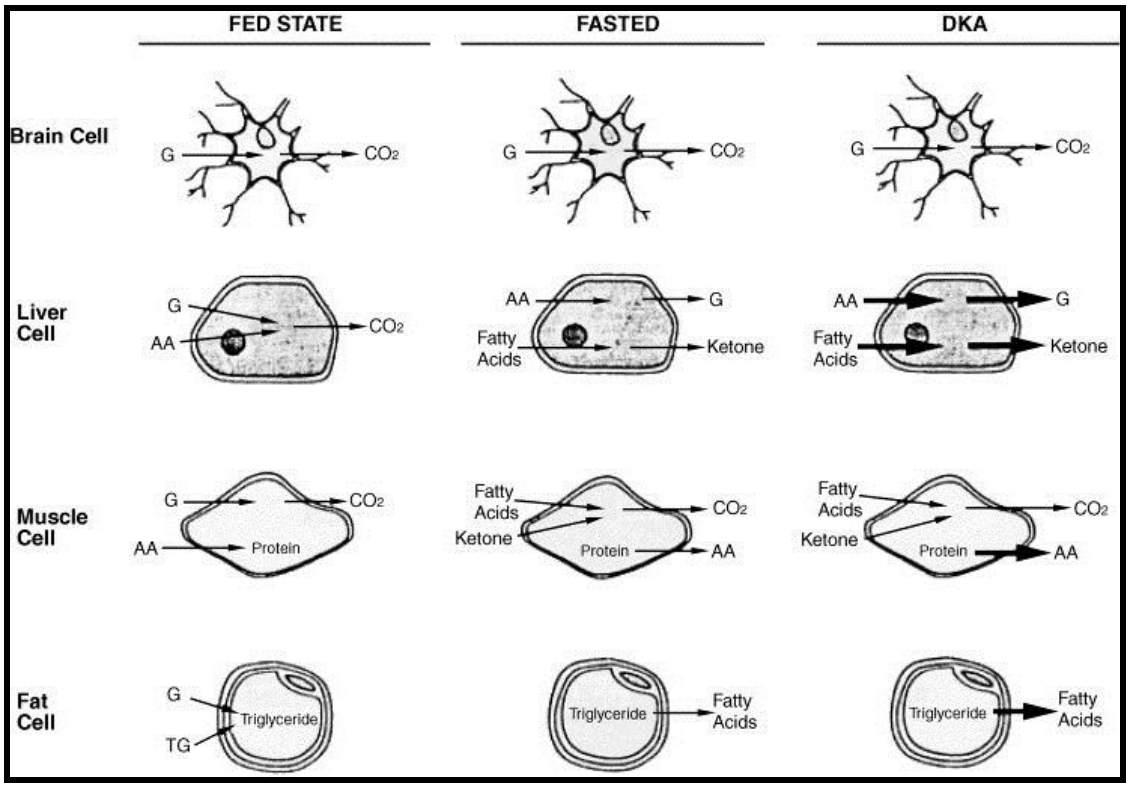

Fig. 4 Substrate utilization in the fed and fasting states and in diabetic ketoacidosis in insulin-insensitive tissue (brain cells) and in insulin-sensitive tissue (live, muscle, and fat) (Charfen, Fernández-Frackelton 2005) (29). DKA, diabetic ketoacidosis; G, glucose; AA, amino acid; TG, triglyceride.

When exogenous insulin is given to these patients in order to bring the serum glucose level back to normal, the result is similar to that observed during refeeding in starved patients: a rapid shift to glucose as the predominant fuel and a severe decrease in serum phosphate. During the treatment of diabetic ketoacidosis the serum phosphate level decreases significantly after as little as 12 hours of therapy (29, 30).
The hyperosmolar non-acidotic state (usually in Type 2 diabetes), typically develops over a longer period of time than diabetic ketoacidosis, but is associated with more serious total body phosphate depletion. It is also associated with a higher mortality.
In uncontrolled diabetes, total body potassium and magnesium are depleted as in chronic catabolic states or in starvation. Insulin therapy causes an intracellular shift of potassium and magnesium, and hypokalaemia may become clinically apparent. Moreover, hypokalaemia may inhibit insulin secretion and decrease insulin sensitivity, and hypomagnesaemia may be responsible for refractory hypokalaemia, despite provision of supplemental potassium (29, 30). The serum concentrations of potassium and magnesium are unreliable markers of total body stores of these mainly intracellular electrolytes.
In the uncontrolled diabetic patient’s rapid weight gain associated with salt and water retention and oedema may occur during treatment. It is sometimes called "insulin oedema". The same phenomenon is seen in the refeeding syndrome as a result of an antinatriuretic effect of insulin on the renal tubule (29, 30).
Many diabetic patients are not well managed on a chronic basis or have uncontrolled diabetes for a long time before diagnosis and therefore they are likely to be chronically catabolic. Although they are often well adapted to their catabolic state, they can develop serious symptomatic undernutrition rapidly in stress conditions such as concomitant critical illness or trauma. These catabolic, chronically ill patients are most prone to the development of the full-blown refeeding syndrome (13, 29).

Cancer

Cancer patients with solid or haematologic malignancies have many risk factors for the development of the refeeding syndrome. The main risk factors are:

- Poor oral intake/ malnutrition:
— Cancer anorexia;
— Anorexia during chemotherapy;
— Stomatitis/ mucositis;
— Disease / chemotherapy related dysguesia;
- Nausea/ vomiting induced or related to:
— Chemotherapy
— Hyponatraemia
— Brain metastases/ increased intracranial pressure;
— Visceral cancer/ metastasis (e.g. linitis plastica, peritoneal carcinomatosis);
— Malignant gastric-outlet obstruction;
— Malignant bowel obstruction;
- Total parenteral nutrition/ glucose based fluid therapy;
- Enteral tube feeding;
- Tube decompression of stomach;
- Malignant gastrointestinal fistulae;
- Fever:
— Sepsis;
— Tumour–related;
- Increased circulating cytokines (31).

A majority of cancer patients (up to 80%) suffer from undernutrition sooner or later in the course of the disease. Patients often develop mucositis during chemotherapy which, in stage 3 and 4 according to the WHO complications scale (ulceration), causes inability to chew and swallow due to pain. Anorexia is very common in this group of patients and may be due to the disease itself (circulating cytokines released from the tumuor) and due to the cancer treatment (including taste and smell disturbances induced by chemo- or radiotherapy). Without prophylaxis, vomiting affect up to 100% of patients undergoing high dose chemotherapy (e.g. for marrow or stem cell transplantation) leading to depletion of phosphate, magnesium and potassium. Electrolyte depletion may also result from some specific treatments. For instance, granulocyte/macrophage colony stimulating factor (GM-CSF) may be responsible for significant hypophosphataemia, ongoing magnesium wasting has been described secondary to the EGFR-inhibitor cetuximab, and cisplatin and ifosfamide can also cause a hypomagnesaemia which may result in persistent loss of other electrolytes (32). Cancer patients often take medications that can affect electrolyte concentrations, such as antiacids (in gastric protection during corticosteroid therapy). Also diuretics prescribed for patients with oedema can increase losses of phosphate, magnesium and potassium. Fever, which is common in neutropaenic cancer patients and patients with lymphoma and renal cell cancer, affects release of phosphate-depleting cytokines such as TNF and IL-2. It is unclear, however, whether circulating cytokines released from tumour cells can induce hypophosphataemia as much as they do in sepsis (33). Head and neck cancer patients are at particular risk of refeeding syndrome because so many of them have not one, but multiple risk factors, including periods of prolonged poor nutritional intake due to dysphagia, chronic alcohol abuse and high metabolic demands through cancer cachexia, perioperative trauma, chemo-and radiotherapy (34).

The clinical manifestation of refeeding syndrome in cancer patients may be aggravated in comparison to other groups of patients due to pre-existing organ damage. Many cancer patients experience loss of cardiac myocytes (i.e. due to cardiotoxic chemotherapy), and therefore have poor contractile reserves and are prone to acute heart failure. In some cases hypophosphataemia may lead to haematopoietic dysfunction with acute haemolytic anaemia and thrombocytopenia, which may be difficult to attribute to this condition, because these cancer patients can have many competing aetiologies for thrombocytopenia (32).

Anorexia nervosa

Eating disorders are known to result in serious medical complications and to lead to death in extreme cases. These consequences are usually most severe in patients with anorexia nervosa due to prolonged starvation. The most predominant are: changes in fluid balance and electrolyte concentrations (sodium depletion and hypovolaemia are common). However, hypophosphataemia seems to be most threatening (35). In their study Birmingham et al. (36) reported a series of 50 patients with anorexia nervosa. Sixty percent of them developed hypomagnesaemia at some point during nutritional therapy. Huge differences between predicted and measured resting energy expenditure (REE) in anorexia patients have been found in various studies (37). REE is lower at the admission (after a long period of starvation) as an adaptive response to starvation, than during refeeding. After the start of nutrition REE increases rapidly, probably due to increase in fat-free mass, increase in physical activity or in diet-induced thermogenesis and is apparent already after 1 week of therapy. Consequently, initial caloric requirements are low. However, with nutritional rehabilitation and metabolic recovery, caloric requirements increase to over 30% of the basal value. Management of patients with anorexia nervosa is difficult, because on the one hand it is hard to estimate energy expenditure properly and, on the other, inappropriate nutritional support is associated with a high prevalence of refeeding syndrome. Most at risk are all the patients with a very low BMI (below 12 kg/m^2), with a history of severe dietary restraint, vomiting, and/or taking laxatives, and those with associated co-morbidities, such as diabetes, infection or major organ failure.

In the retrospective study performed by Vignaud e al. (38) it was proven, that the main reasons for admission to ICU were profound metabolic abnormalities or the need to monitor vital signs during refeeding. Hypophosphataemia affected 16% of patients and hypokalaemia occurred in 24% of them. The mortality rate was 71% for patients who developed a full clinical refeeding syndrome and only 3% in patients without the syndrome.

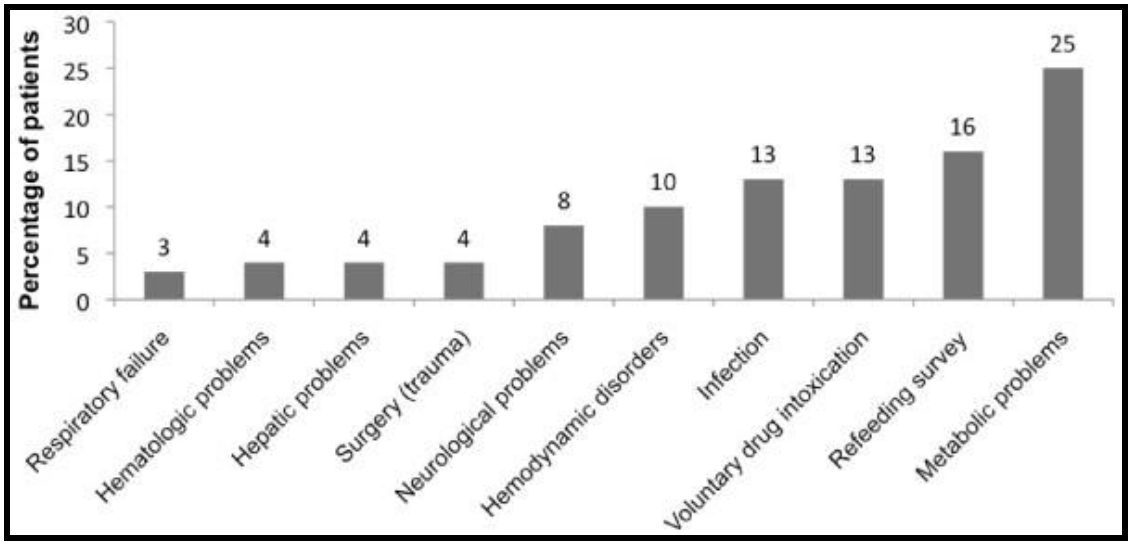

Fig. 5 Reasons for admission to the ICU. Vignaud e al. 2010 (38).

Occasionally some rare complications of nutrient deficiency may also occur, such as corneal disease resulting in blindness due to vitamin A deficiency (39) or centropontine myelinolysis most likely due to hypophosphataemia, due in turn to the refeeding syndrome (40).

Sepsis

During sepsis, especially Gram-negative infections, hypophosphataemia is a common condition, which develops already in the early stages of the disease and correlates closely with the severity of the patient's clinical condition (41). From the meta-analysis of Shor

et al (42) it appears that having severe hypophosphataemia (serum phosphate levels < 0.30 mmol/l; <1 mg/dl) is related to a nearly 8-fold increased risk of death. Severe hypophosphataemia may be considered as an independent predictor of mortality in sepsis. The main mechanism by which hypophosphataemia develops in these condition involves redistribution of phosphate from the extracellular fluid into the cells. Acute respiratory alkalosis occurring in sepsis causes an increase in intracellular pH, which subsequently stimulates phosphofructokinase activity and glycolysis. Intensive glycolysis increases intracellular formation of phosphorylated carbohydrate compounds, which attract phosphate from the extracellular fluid.

Associations have also been demonstrated between high levels of inflammatory cytokines such as tumour necrosis factor (TNF) α and interleukin (IL) 6 and their receptors (soluble IL (sIL) 2 receptor and sIL-6R) and serum phosphate levels (43). In the systemic inflammatory response syndrome (SIRS), principally secondary to infection or sepsis, a release of proinflammatory cytokines occurs, contributing towards hypophosphataemia. Results of the study of Barak et al. (13) indicated the presence of hypophosphataemia associated with very high levels of TNFα, IL-6 and of sIL-2R and sIL-6R in approximately 80% of septic patients, especially in those with positive blood cultures. Additionally, cytokine concentrations and hypophosphataemia may be included in sepsis evaluation and prognosis. However, a full understanding of all the mechanisms involved in the origin of hypophosphataemia in sepsis remains lacking.

Metabolism during sepsis combines features of starvation and the stress response. Sepsis is associated with hypermetabolism and negative nitrogen balance. Hypophosphataemia may also occur if nutrition is given in order to prevent further deteriorations in metabolic status. In the majority of cases insulin resistance occurs in the presence of high serum insulin levels. It is not exactly clear, whether these patients are therefore at greater risk of refeeding syndrome than those in whom insulin resistance is less marked. Anyway, it is often necessary to use exogenous insulin in order to bring serum glucose levels back into the normal range. The net result is a severe decrease in serum phosphate, potassium and magnesium. The intensive insulin regimen proposed by van den Berghe might therefore have been expected to increase risks of hypophosphataemia and hypokalaemia and to increase the refeeding effect, but there is no evidence to confirm this supposition (41).

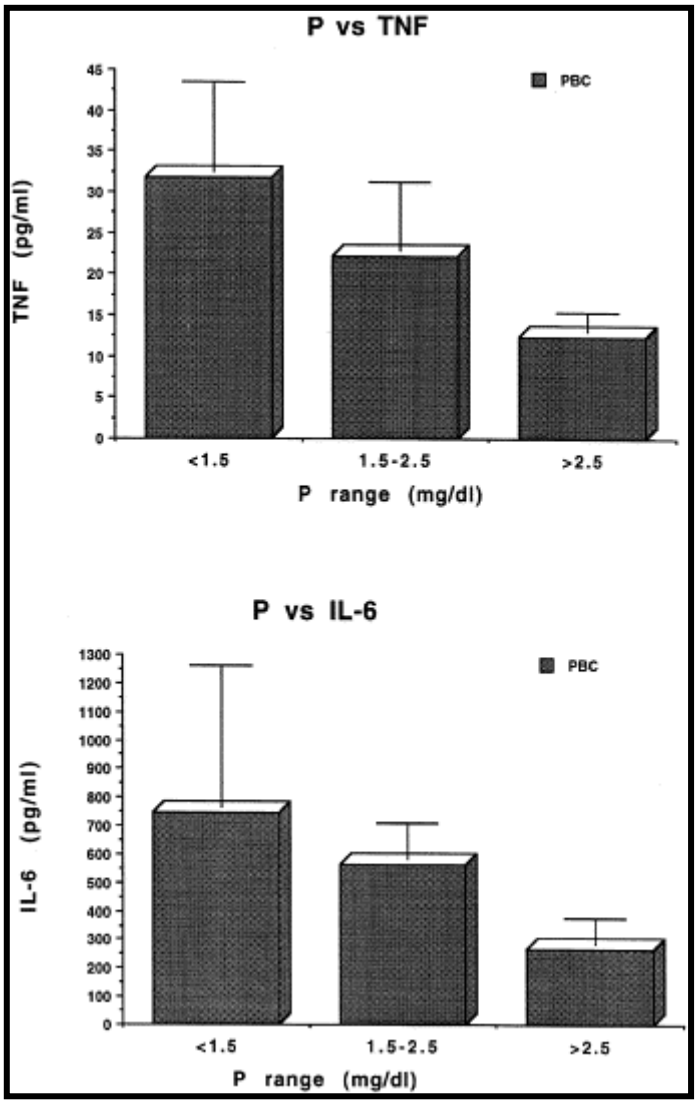

Fig. 6 Concentrations of IL-6 and TNF at different serum phosphate levels in septic patients. Barak et al. 1998 (13).

Alcoholism

Although a high risk of the refeeding syndrome in alcoholics is unquestionable, there are few publications relating to this topic, probably because alcoholics are treated not for alcohol abuse itself, but mainly for accompanying acute or chronic diseases. It is common knowledge, that electrolyte disturbances occur very frequently in this population. Therefore a history of alcohol use should be obtained in every case of reasonable suspicion of refeeding syndrome.

Hypophosphataemia can occur when there is decreased phosphorus intake/decreased intestinal phosphate absorption or excess renal wasting. Both of the above can occur in chronic alcohol abusers. Depletion of phosphate is very rare in properly nourished individuals, because the content of phosphorus in a standard diet is high (all proteins and dairy products contain it and additional amounts are taken as preservatives added to food). In alcoholics, however, it can be present due to poor oral intake of both phosphate and vitamin D, and poor food quality following social isolation and poverty or reduced intestinal phosphate absorption due to chronic diarrhoea. Chronic alcoholism is also associated with increased urinary flow and hyperphosphaturia - reduced proximal phosphate reabsorption resulting from secondary hyperparathyroidism (induced by

deficiency of vitamin D) and/or a direct effect of alcohol. Therefore hypophosphataemia is observed in 10% of hospitalized alcoholic patients (43).
The next well-known common finding in acute and chronic alcoholism, with an incidence of up to 30%, is hypomagnesaemia. Mechanisms contributing to magnesium depletion include poor oral intake and magnesium loss through the renal tubules, where alcohol acts as a diuretic causing increase in the urinary excretion of magnesium (44). Patients with hypomagnesaemia frequently have other electrolyte abnormalities, such as hypophosphataemia, hypokalaemia and respiratory alkalosis. Moreover, there are data suggesting that serum magnesium level play a central role in the homeostasis of the other electrolytes (45).
Another issue is thiamine deficiency. Thiamine is required for the intracellular transport of glucose. Chronic alcoholics use alcoholic drinks, which are often high in carbohydrate and with low or absent amounts of thiamine, as a substitute of food. The thiamine requirement, which is related to carbohydrate intake and ranges between 1–2 mg/d, increases with alcohol consumption. Several studies report level of thiamine reduced in 30%–80% of chronic alcoholics (46).

3.4. Description of major abnormalities involved in the pathogenesis of refeeding syndrome

Those factors include:

- Hypophosphataemia
- Hypomagnesaemia
- Hypokalaemia
- Thiamine (and other vitamin and trace element) deficiency

Hypophosphataemia
The most important facts about hypophosphataemia were presented in Section 2. It is also, however, important to remember that the body stores of phosphate are between 500 and 800g in an adult human. About 80% is located in the bony skeleton and 20% is distributed in the soft tissues and muscle. Phosphate is the major intracellular anion and shifts readily between the intracellular and extracellular compartments (49). Such transcellular movement can result from the ingestion of carbohydrate or lipid and from acid–base alterations. In the case of the latter, an acidosis can result in shifts of phosphate out of cells into the plasma (50).
The dietary intake of phosphate is about 1 g/d, with approximately 80% being absorbed in the jejunum. Protein-rich foods, such as cereals and nuts, are the major source of phosphate intake. Dietary phosphate deficiency is unusual; in fact, intake is often in excess of requirements. Between 60% and 70% of dietary phosphate is absorbed. The output is essentially renal, with more than 90% being excreted by this route. Most of the phosphate filtered at the glomeruli is reabsorbed by the proximal tubules, and this system is important for the control of phosphate homeostasis. Gastrointestinal losses of phosphate account for the remaining 10% of the body's phosphate excretion (51).
Phosphate is essential for cell function and responsible for many physiological actions. It is an important intracellular buffer and is essential for buffering hydrogen ions in urine. Phosphate has a structural role as a component of phospholipids, nucleoproteins, and nucleic acids. In addition, it plays a central role in cellular metabolic pathways including glycolysis and oxidative phosphorylation, and is involved in many enzymatic processes, with protein phosphorylation being an important control mechanism for enzyme action (52-54).
The normal range of serum phosphate concentration is 0.81-1.62 mmol/l (2.5-5 mg/dl). Severe hypophosphataemia, often considered as a plasma inorganic phosphate concentration <0.30 mmol/l (<1 mg/dl), can result in a plenitude of clinical manifestations (55). In most cases, effects are the result of impaired cellular energy pathways such as those involving adenosine triphosphate or reduced erythrocyte 2,3-diphosphoglycerate. Hypophosphataemia has been reported to impair diaphragmatic

contractility and this might help to explain the difficulty in weaning patients with low plasma phosphate concentration from mechanical ventilators (56, 57). The other complications of severe hypophosphataemia include: cardiomyopathy, rhabdomyolysis, impaired skeletal muscle function, including weakness and myopathy, renal tubular impairment and acute tubular necrosis secondary to rhabdomyolysis, seizures, perturbed mental state, paresthaesiae, thrombocytopenia, impaired clotting processes, reduced leukocyte phagocytosis and chemotaxis, haemolysis and osteomalacia (58-61). Those abnormalities became fatal after the implementation of total parenteral nutrition in some patients (62, 63).

Hypomagnesaemia

Magnesium is the predominant intracellular cation, which is mandatory for optimal cell function (64). Magnesium is an essential metal involved as a cofactor in many enzyme systems (including oxidative phosphorylation and ATP production). It is also necessary for the structural integrity of DNA, RNA, and ribosomes, it affects membrane potential, and its deficiency can lead to cardiac dysfunction and neuromuscular complications (65). Magnesium is largely absorbed in the upper small intestine, and excreted through the kidneys (66). Up to 70% of dietary magnesium is not absorbed but eliminated in the stool. Although refeeding syndrome is strongly associated with hypomagnesaemia, the mechanisms involved are not completely clear. During high carbohydrate feeding and poor dietary intake of magnesium, intracellular movement of magnesium ions into cells lowers its level. Additionally, pre-existing poor magnesium status might exacerbate the degree of hypokalaemia and hypocalcaemia. Many cases of hypomagnesaemia are not clinically significant, but severe hypomagnesaemia (usually defined as plasma concentrations <0.50 mmol/l) can result in clinical complications, such as cardiac arrhythmias (including torsade de pointes), tremor, paraesthesiae, tetany, seizures, irritability, confusion, weakness, ataxia and anorexia (67, 68).

Hypokalaemia

Potassium is the predominant monovalent intracellular cation. It is essential for maintaining cell-membrane action potentials. During the change to anabolism on refeeding, potassium (with glucose and water) is taken up into cells as a direct result of insulin secretion. Severe hypokalaemia can be defined as a plasma potassium concentration of less than 3.0 mmol/l. The most important cardiac features of hypokalaemia consist of cardiac arrhythmias, hypotension, and cardiac arrest. There are plenty of neuromuscular dysfunctions such as weakness, paralysis, paresthaesiae, confusion, rhabdomyolysis, and respiratory depression. The ability of the kidney to concentrate urine decreases. Gastrointestinal upsets include ileus and constipation (68, 69, 70).

Thiamine Deficiency

Thiamine (vitamin B_1) deficiency can result in Wernicke's encephalopathy or Korsakov's syndrome. The former is associated with ocular disturbance, confusion, ataxia, and coma, and the latter with short-term memory loss and confabulation. It is thought that carbohydrate refeeding causes increased cellular thiamine utilization because it is a cofactor for various enzymatic activities, e.g., transketolases (71, 72). Provision of thiamine during introduction of feeding might reduce symptoms of post-refeeding thiamine deficiency. While deficiency is most often considered in patients with chronic alcohol abuse, its most severe manifestation, Wernicke's encephalopathy, can develop in any patient with a poor nutritional state (73). In addition, Wernicke's encephalopathy can also be precipitated by carbohydrate loading in patients with decreased thiamine stores (72). Although thiamine deficiency can be diagnosed by the demonstration of erythrocyte transketolase deficiency or the measurement of transketolase activity on exogenous thiamine pyrophosphate, Wernicke's encephalopathy is fundamentally a clinical diagnosis (73).

4. Prevention of refeeding syndrome

Patients need not develop the refeeding syndrome in the course of artificial nutrition. It is crucial to be aware of the condition and anticipate problems in order to prevent its occurrence. Four factors seem to be of fundamental importance:
- early identification of patients at risk;
- correction of abnormalities before refeeding;
- close monitoring during refeeding;
- an appropriate feeding regimen.

Identification of high-risk patients is possible by taking a detailed history, through clinical examination and by early involvement of the nutrition support team. The patients, who are at particular risk, were presented above. Those classified as belonging to one of high-risk groups should be screened for risk of developing refeeding syndrome on admission to hospital. Their successful management requires a multidisciplinary approach including nutritionists: physicians, nurses and dieticians. The basic element is the assessment of vital signs and physical examination, and prior to initiation of feeding in high-risk patients, levels of essential electrolytes must be assessed (phosphate, potassium, calcium, magnesium, sodium and chloride). The estimation of organ and system competence is also important. It includes several laboratory tests: complete/full blood count, gasometry/blood gases, serum proteins, liver tests (albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP), total bilirubin, gamma glutamyl transpeptidase (GGT), INR), renal tests (creatinine and urea), C-reactive protein and lipid profile. The urine sodium may be helpful in complex cases with gastrointestinal fluid loss.

4.1. Correction of abnormalities

Hypophosphataemia
Phosphate can be administered either in the form of sodium or potassium solution depending on the potassium concentration
- Mild (2.3–3 mg/dl or 0.75–1 mmol/l) - replace with 0.32 mmol/kg/d of intravenous or oral phosphate (during oral replacement diarrhoea can be a problem)
- Moderate (1.6–2.2 mg/dl or 0.5–0.74 mmol/) - replace with 0.64 mmol/kg/d of intravenous phosphate
- Marked and severe (<1.6 mg/dl or <0.5 mmol/l) - replace with 1 mmol/kg/d of intravenous phosphate (74).

The above dosages should not be applied to patients with renal impairment; renal function always should be evaluated beforehand (75). If the patient has renal failure, the standard doses should not be given. In general, it is suggested that about half of the normal dose or even less should be given to patients with renal failure. The monitoring of phosphate concentration is important as intravenous replacement is associated with neurological symptoms, mostly due to hypocalcaemia, which may occur during phosphate infusion (76). The serum calcium concentration should be checked regularly. Phosphate should be given very cautiously to patients with hypercalcaemia because of the risk of metastatic calcification. When the patient has a serum potassium of <4 mmol/l, a potassium phosphate salt should be used (3 mmol P accompanies 4.4 mmol K). When there is renal function impairment or serum potassium is >4 mmol/l, a sodium phosphate salt should be used (3 mmol P accompanies 4 mmol Na). The drug should be added to 0.9% saline or 5% glucose solution and given at a rate no faster than 7.5 mmol/h in an effort to prevent hypocalcaemia resulting from rapid phosphate infusion.

Hypokalaemia (<3.5 mEq/l or <3.5 mmol/l)
- replace with: 1–4 mmol/kg/d in the form of oral potassium (as KCl or other potassium formulae)
- Symptomatic or more severe deficiency may require intravenous supplementation with care to avoid hyperkalaemia (77, 78)

• 3.0–3.4 mmol/l - replace with 80 mmol K - check serum potassium 2 hours after, especially if losses are suspected to be high, then reassess
• 2.0–2.9 mmol/l – replace with 120 mmol K – check serum potassium 2 hours after 80 mmol infusion and reassess (75)
• the rate of infusion should not exceed 20 mmol/h, above this rate administration via a central line and ECG monitoring is needed

When examining the patient's laboratory findings, the potassium concentration should be readjusted for redistribution due to pH (for every 0.1 increase in serum pH, serum potassium will fall by approximately 0.6). Therefore an initial check of arterial pH must be performed. In patients with renal impairment or adrenal insufficiency the above doses should be modified and infusion closely monitored. The serum concentration of magnesium should also be checked as magnesium serves as a cofactor of the Na-K ATPase pump.

Hypomagnesaemia (<1.7 mg/dl or <0.7 mmol/l)
• Mild to moderate (1.2–1.7 mg/dl or 0.5–0.7 mmol/l) - replace with 10–15 mmol daily with oral Mg oxide or Mg citrate (during oral replacement diarrhoea can be a problem)
• Severe (<1.2 mg/dl or <0.5 mmol/l) - if asymptomatic, treat as above. If symptomatic, treat with 25 mmol/d of parenteral Mg with reassessments every 8–12 h (79-81).

Again, in patients with renal impairment, the above dosage must be adjusted. In general, it is suggested that half or less of the dose be given - depending on the extent of renal impairment and whether or not the patient is symptomatic. Hypomagnesaemia can also induce hypokalaemia and hypocalcaemia. Magnesium serves as a cofactor of the Na-K ATPase pump, and intracellular potassium cannot be retained in the presence of significant hypomagnesaemia. In the presence of hypomagnesaemia, there is also impaired end-organ responsiveness to parathyroid hormone and potentially impaired secretion of parathyroid hormone. As a result, the patient can become symptomatically hypocalcaemic. Magnesium concentrations are often elevated for 1 to 2 days following an infusion, because it takes about 36 to 48 hours for the magnesium to redistribute fully to the body tissues (75). It should be mixed in 0.9% saline or 5% glucose solution and given at a rate no faster than 8 mmol (or 1 g of magnesium sulphate) per hour. Rates above 8 mmol/h will exceed the renal threshold and will be disproportionately excreted in patients with normal renal function (75).

Vitamins and other micronutrients
Vitamins should be administered as follows (82):
• B_1 (thiamine) - loading dose of thiamine 300 mg intravenously before starting nutrition (at least 30 minutes beforehand). Maintenance dose of 200-300 mg/d during nutrition (orally or intravenously, at least till day 3 of refeeding)
• B_6 (pyridoxine) - 1.7 mg/d
• B_{12} (cobalamine) - 2.4 μg/d
• Folate - 400 μg/d, not to exceed 1 mg daily
Generally, the provision of 200% of dietary reference intakes of vitamins is recommended
Trace elements
• Selenium (Se) - loading dose of 100–400 μg/d; maintenance dose of 20–70 μg/d
• Zinc (Zn) - loading dose of 10–30 mg/d; maintenance dose of 2.5–5 mg/d
• Iron (Fe) - loading doses not needed. A maintenance dose of 10–15 mg/d via the oral route is sufficient, preferably a week after start of nutrition.

Fluid and sodium balance
Fluid retention can be a serious complication of the refeeding syndrome, although not all studies have proven this (83). Fluid volume excess may be correlated with hypoalbuminaemia because of dilution and may result in renal failure, cardiac failure, or even death. It is very important to evaluate sodium concentration and to monitor its

infusion carefully as the rapid correction of hyponatraemia may lead to central pontine myelinolysis. Therefore it is recommended that a low sodium should be corrected by no more than 12 mmol/l within a 24-h period (0.5 mmol/h) (84). Symptomatic hyponatraemia responds better to 0.9% or hypertonic saline therapy than fluid restriction but the latter is a safer course of action (85, 86).

Provision of energy
The gold standard for estimation of energy requirements is the indirect calorimetry.
In case it is unavailable, other methods should be used to estimate the goal. General rules for the provision of energy include:
• Use the indirect calorimetry whenever possible,
• At the beginning - no more than 20% of basal energy expenditure
• If calorimetry is unavailable:
A. in starved, undernourished or well-nourished patients use the actual body weight
B. in obese or overweight use the ideal body weight
• Start with 10 kcal/kg/d; use 5 kcal/kg/d in critically ill patients. Slowly increase to 25-30 kcal/kg/d within 5-7 days, increasing the provision by 5 kcal/kg per day, when well tolerated.
• The protein requirement is about 1.2-1.5 g/kg per day, start with 50% of target value on the first day and gradually increase the amount.
• Ratio: 50–60% carbohydrate, 15–25% fat, 20–30% protein. Refeeding with only protein and fat often results in losses in weight and urinary sodium.
• Increase or reduce energy provision based on resolution of symptoms and laboratory parameters.

4.2. Monitoring

Careful and systematic monitoring of clinical and laboratory parameters is essential part of nutritional intervention. Nutrition must also become an integral part of the whole treatment process. It must be accompanied by detailed recording of findings, results and the feeding regimen.
Basic monitoring includes:
On a daily basis:
• Nutrient intake from oral, enteral or parenteral nutrition (including any change in conditions that are affecting food intake)
• Body weight, urine output and chart monitoring to optimize fluid balance
• Clinical examination and vital signs (heart rate, blood pressure, presence of oedema) - tachycardia may be a sign of impending cardiac abnormality
• Plasma electrolytes: sodium, potassium, phosphate, magnesium, calcium, chloride (for first week or until clinically stable)
• BUN, creatinine concentration
• Plasma glucose: it must be monitored once or twice a day (or more if needed) and maintained between 100 and 150 mg/dl (5.5-8.3 mmol/l) to prevent hypoglycaemia and hyperglycaemia
• Blood gases (for first week or until clinically stable)
• Liver function tests (repeat after two days if abnormal)
Some of those laboratory tests should be performed even more frequently in critically ill patients. Cardiac complications generally occur within the first week of refeeding. During the first week, heart rate, cardiac monitor, and fluid balance must be monitored to prevent cardiac decompensation.

5. Summary

There are no robust data on the prevalence of refeeding syndrome, and there are no randomized controlled trials looking at its prevention. Hypophosphataemia, which occurs in hospitalized patients with an incidence of 0.2%-3.1% and with clinical manifestations ranging from mild to life-threatening should be considered as a biochemical hallmark of

refeeding syndrome. Patients at highest risk of hypophosphataemia are those with uncontrolled diabetes, cancer cachexia, anorexia nervosa, sepsis and chronic alcoholism. To prevent the development of a refeeding syndrome identification of the high risk patient is crucial. The most precisely defined criteria in common practice for identifying patients at high risk of refeeding syndrome are those published in 2006 in England by NICE. In order to prevent the occurrence of refeeding syndrome four factors appear fundamental: early identification of patients at risk, correction of abnormalities, close monitoring during refeeding and an appropriate feeding regimen. Slow, gradual initiation of nutrition over 4–7 days can also be recommended.

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