Nutritional Support in
Intensive Care Unit (ICU) Patients

Module 18.1

How to Maintain Homeostasis by Nutrition Care in the ICU

Michael. J. Hiesmayr
Division of Cardiothoracic & Vascular Anesthesia and Intensive Care
Währingergürtel 18-20
Medical University Vienna
Austria

Learning objectives
- Understand the metabolic & endocrinological consequences of underfeeding
- Determine target for energy supply
- Methods to determine energy consumption
- Determine or estimate target for protein supply
- Identify patients at risk for the refeeding syndrome
- Learn key features of the refeeding syndrome
- Learn how to prevent the refeeding syndrome

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1. Introduction

Nutrition Care is considered to be a basic and mandatory (essential) element of modern intensive care treatment. Recommendations and guidelines exist from several professional organizations: ASPEN, Canadian Critical Care Group and ESPEN. Their focus is on the indication for EN vs PN, amount of nutrient to be given, composition of all-in-one mixtures, and specific nutrients such as glutamine. No guidelines give any practical advice on how to maintain homeostasis during nutrition care or clinical problem solving in case of problems. Several large nutrition trials (1-5) have questioned some recommendations and are now integrated into this educational material.

Nutrition Care in the ICU has several challenges because the usual control mechanisms such as hunger, thirst may be missing during critical illness. On the one hand the control of the intake is under external control and on the other hand nutrients may have a complex interaction with various organ systems. A further challenge is that acute illness triggers an internal production of nutrients, usually called catabolism, that does not immediately stop when external nutrients are given. This "catabolic response" to injury is an essential mechanism to survive periods of missing intake. The availability of certain nutrients impairs essential repair mechanisms such as autophagy, an internal mechanism to sequester injured organelles in autophagosomes (6). These four factors indicate that an integrative view is essential.

The patient groups at highest risk for complications associated with nutrition care are obviously those at the extremes of body size, nutrient intake and actual disease:

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<td>- BMI very low or very high</td>
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<td>- Higher age</td>
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<tr>
<td>- Prolonged starvation</td>
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<td>- High level of organ support in the ICU</td>
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<td>- Severe physiological impairment</td>
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The common denominator of all these conditions is an altered body composition. Most conditions are associated with a decrease in lean body mass. This decrease may not be easily apparent because still maintained body fat is hiding the decrease in lean body mass. Various methods such as body impedance assessment (BIA), ultrasound, CT and MRI scans, but also functional measurements of muscle function, are used in specialist centres. Sarcopenia research has addressed this issue extensively (7).

The challenge of nutrition science and care is to define to margins: the minimal requirement for macro- and micronutrients necessary for recovery from acute illness and the maximum tolerable margin. A new concept is that minimal requirements and maximum tolerable concentrations vary during the course of an acute illness.

This concept is shown for health and disease in Fig. 1a and b. During health a minimum of glucose (G) is needed for glucose dependent tissues such as the central nervous
system, suprarenal glands, erythrocytes. If glucose supply from intake is not sufficient gluconeogenesis from protein (red arrow) can prevent a shortage. If glucose is available above needs and glycogen stores are full, storage into (yellow arrow) fat (F) occurs. High levels of amino acids (AA) are either oxidized and excreted or enter gluconeogenesis and are stored as fat. Saturated (yellow bar) and unsaturated (green bar) fat are necessary in different amounts as energy sources but also to build e.g. cell membranes, hormones, etc. During acute illness needs change and endogenous mobilisation of macronutrients combines with external supply of nutrients. Thus the danger limit and the minimum may be changed. Recent research has shown that early large provision of nutrients is associated with storage of fat even in organs such as muscle where storage usually does not occur (8). Any level of nutrients below the minimum will induce an increased catabolic response mostly of the muscle.

Fig. 1 Margins for macronutrients between minimum and danger zone

Energy expenditure remains relatively stable during the early phase of starvation and is only decreased by roughly 10% after 3 weeks of starvation. Energy expenditure is mostly determined by a few organs that have a high energy demand such as brain, liver, intestine, heart and kidney that represent 5% of body mass and 66% of energy expenditure. Only the brain maintains its weight during severe starvation. Thus the functional capacity of vital organs (especially heart, kidney, intestine) is decreased because structural protein has been lost during starvation. Individuals with a regularly decreased lean body mass such as the elderly have a decrease in energy expenditure, which is about 1% per year above the age of 60 years. Of course these general estimates need to be adapted if functional status is different from the age group. In addition to these basic rules related to lean body mass, synthesis of acute phase proteins by the liver, faster turn-over of immune cells, uncontrolled muscle activity in delirium and repair of injured tissues modify energy expenditure.

Protein handling follows another basic structure. Protein turnover is not similar to energy expenditure. The brain has a low protein turnover but a high energy expenditure, the kidney a relatively lower energy expenditure but a higher protein turnover. During health protein balance is equilibrated. Proteolysis of 300 g/day is balanced by protein synthesis (Fig. 2).
The largest contribution (100g/day) to proteolysis comes from muscle that has a daily turnover rate of 2%, in contrast to the liver that contributes about half (50g/day) with a turnover rate of 25%. The largest turnover rate is in the intestine (Fig. 3). This turn-over of protein decreases at higher age and is related to less efficient repair mechanisms and accumulation of less functional organelles. In a quite general sense this is the process of ageing.

During acute illness there is a net deficit in protein despite an increased whole body protein synthesis because there is an increase in breakdown that is relatively higher. The major site of protein synthesis in acute illness is the liver and the major site of breakdown is the muscle. The take-up of amino acids from the pool of free amino acids by the liver serves the generation of acute phase proteins and gluconeogenesis. There appears to be a priority of organs according to the needs of acute illness.
2. Amount of Protein Needed

In principle the amount of protein needed should be sufficient to cover usual protein turn-over plus the additional needs related to the increased protein synthesis in the liver and in injured tissues. The usual recommendations are that a supply of $1-1.5 \text{ g.kg}^{-1}.\text{day}^{-1}$ is sufficient. Protein breakdown associated with starvation needs several days before a decrease occurs. This is the point where ketogenesis increases and ketones partially replace glucose as preferred fuel. There is an additional breakdown associated with the inflammatory process but also with bed-rest and disuse of muscle. The amount of protein loss was shown to be independent of the energy expenditure when many observational studies were combined in a recent systematic review. (9). Most probably there is an association between protein loss and lean body mass, the muscle being the largest part. Lean body mass typically decreases with age and thus protein need may depend on age and lean body mass. No practical methods to relate measurements of lean body mass with protein supply have been proposed to date.

There are no large trials that have modified the amount of protein independently from the amount of energy given. Many observational trials have suggested that patients with a higher protein supply and a good coverage of calculated energy needs have the best prognosis. This observation could also be seen as showing that a good tolerance of large amounts of enteral nutrition is associated with a better prognosis. It has repeatedly been shown that patients needing prolonged ICU care rarely have more than 60% of calculated needs covered by enteral nutrition. The special benefit of meeting calculated protein and energy target was only seen for 28 day mortality and was associated with the highest mortality in the ICU and the hospital (10).

Moreover some recent trials suggest that providing larger amounts of protein and glucose impair the repair mechanism associated with autophagy. A trial with large amounts of glutamine also failed to show a positive effect (11).
Thus a progressive increase in protein supply over a few days up to a level of 1-1.5 g.kg\(^{-1}\).day\(^{-1}\) is probably safe. Given the usually low amounts given in clinical practice, achieving 1g.kg\(^{-1}\).day\(^{-1}\) is already ambitious. Larger amounts should not be considered until randomized trials have shown their efficacy and benefit.

3. Amount of Nutrients Needed

A general physiological rule is that energy consumption is tightly related to lean body mass (12). In shock of any origin energy consumption is lower than estimated (13) by up to 50%; during reconvalescence when patients begin to be effectively mobile and anabolic energy consumption will increase above estimated resting energy expenditure. Modification of estimated energy consumption should not be applied during ICU stay because these factors tend to change during critical illness, often below but also sometimes above estimations. Use clinical judgment and consider that 2/3 of energy is consumed by brain, liver, kidney and heart representing 5% of total body weight. Only the brain weight does not decrease during starvation and catabolism of acute illness. Another ¼ of energy is consumed by muscles that, in healthy young adults, represent about 20-35 kg or 30% to 50% of body weight. A recent trial showed that during the first two weeks of critical illness 220-250 g of nitrogen or 5-6 kg of muscle have typically been lost (14).

The ESPEN guidelines state that:
- 20-25 kcal.kg\(^{-1}\).h\(^{-1}\) in the acute and initial phase of critical illness and
- 25-30 kcal.kg\(^{-1}\).h\(^{-1}\) in the anabolic recovery phase should be given to patients. ACCP guidelines recommend 25 kcal.kg\(^{-1}\).h\(^{-1}\).

![Fig. 4 Individualized estimated daily caloric need versus body weight](image)

Actual body weight is replaced by normal body weight (kg) derived from height (cm) as height -100 and 25% of the difference between actual and normal body weight is added. All coloured fields have an associated BMI>25, orange (daily calories > 2500), pink (daily calories> 3000).

A further suggestion is to decrease energy provided by 1% for each year above 60 years. This suggestion may correct actual formula for the decreasing lean body mass with age. A decrease of energy need by 20% between the age of 60 and 80 has been reported. As an example a frail octagenerian with a BMI of 27 had a measured energy consumption of 800-1400 kcal.day\(^{-1}\) whereas estimated energy consumption was 1600-2100 (15). One of the most accurate formulae for estimation of energy need has been proposed by Faisy et al. (16) and includes weight, height and minute-ventilation. Minute-ventilation may serve as a good surrogate for CO\(_2\) production.
Little information about individualization of therapy is given and thus only two options exist: measuring energy expenditure with indirect calorimetry or using clinical observation, lab values and judgment to adjust nutrition care. The observation of trends is of crucial importance as is also the combination of several signs and symptoms in any of these situations. Guidelines currently do not offer problem solving algorithms for diagnosis of under- or overnutrition. We consider that most of the recommendations apply for “mean” patients and that clinical judgment needs to be used for patients outside this category. A cartoon shows conceptually the adaptation of nutrient intake that may be considered for the young and very old as well as in the acute and the stable phases of illness. The duration until stabilization certainly varies from patient to patient. Age is also an important factor for energy requirements. Energy requirements decrease at higher age (17).

**Fig. 5** Conceptual graph: actual body weight vs caloric intake:
The arrows represent the progressive increase in calories that may be appropriate after initial stabilization and when patients are becoming anabolic.
Fig. 6 Conceptual graph relating body weight (actual or normal depending on BMI) to caloric intake:
The arrows represent the progressive increase in calories that may be appropriate after initial stabilization and when patients are becoming anabolic.

4. Excessive Nutrient Intake

Excessive nutrient intake is considered to be much less frequent than undernutrition but recent observational data from the NutritionDay ICU project 2007-2008 suggest that almost as many patients receive an amount of nutrients below or above a target zone of 20-30 Kcal.kg$^{-1}$.h$^{-1}$. Prescription of parenteral nutrition may be associated with overfeeding in more than half of the patients (18).

Measured energy consumption may suggest an excessive intake if RQ is > 0.85 for patients that are not exercising during the measurement period. An elevated RQ suggest an increased CO$_2$ production that may be related to either high energy intake or high glucose load and ongoing lipogenesis (19).

The organ systems most affected by excessive intake are the lung, the heart and the endocrine system but a few general symptoms such as fever or decreased level of consciousness may also relate to larger than tolerated intake of single nutrients.

4.1 The Lung and Ventilation

Elevated minute volume e.g. above 150 ml.kg$^{-1}.min^{-1}$, persistently elevated arterial pCO$_2$ despite normal minute ventilation or difficulty to wean from the ventilator in otherwise unstressed patients should trigger thoughts about nutrient intake. In the case that an excessive nutrient intake appears to be a possibility, a trial of decreasing intake by 30% for a few days to allow weaning may be necessary (20).

4.2 The Heart and Circulation

Nutrient intake induces a typical response with an increase in oxygen consumption that is followed by an increase in cardiac output and a slight decrease in peripheral vascular
resistance and thus no major change in blood pressure. In patients with decreased cardiovascular reserve, patients with congestive heart failure or patients who have lost heart muscle because of prolonged starvation, e.g. anorexia nervosa, this increase in demand for cardiac work may be associated with new or worsening heart failure (21-23). Pulmonary oedema and new cardiac rhythm disturbances such as atrial fibrillation are possible. Cardiac inotropic support and careful volume adjustment may be the treatment of choice.

4.3 Endocrine System

Hyperglycaemia and hyperlipidaemia can be symptoms of excessive nutrient intake. In this case a decrease in nutrients needs to be considered. This decision is particularly difficult since acute disease states, injury and starvation for a few days are associated with increased insulin resistance (24). This phenomenon is by far the most likely reason for hyperglycaemia. Tolerance to glucose also decreases with age (25).

4.4 General Signs and Symptoms

Fever may be a sign of an excessive load of amino acids with their thermogenic effect (26). In some patients, especially those with a severe catabolic state, an increased load of amino acids that may appear indicated to prevent a further deterioration in nutritional status, may lead to a decreased level of consciousness due to a sharp rise in blood ammonium. Hyperlipidaemia may occur in some patients and can be related either to a high glucose load or to poor lipid clearance. Lipid should probably only be reduced if triglyceride levels are very high and excessive glucose intake has been excluded.

5. Insufficient Nutrient Intake

A cumulative deficit of nutrients compared with actual energy consumption has been found to be associated with an increase in complications (27 28). Especially, infectious complications have been shown to be increased in patients with an energy deficit of >50% of needs compared with the recommendations for energy supply in the ACCP guidelines. Few centres routinely use indirect calorimetry to assess patients’ energy needs, thus most centres have to rely on formulae and clinical judgment (29-31). Discrepancies between measurements in different groups of critically ill patients were between 1300 and 2200 calories (31).

The effect of an energy supply below needs is not easily detected since the clinical manifestation of semi-starvation needs time to be obvious in an individual patient. Moreover the effect of semi-starvation is similar to the effect of severe catabolism induced by the acute disease process.

Sleepiness, loss of physical strength, repeated skin defects, or pressure sores should raise the suspicion of a severe energy deficit.
6. Composition of the Diet

Modifications in the composition of the diet are considered in three clinical situations:

- Difficult to handle hyperglycaemia
- Excessive hyperlipidaemia (\(> 400 \text{ mg.dl}^{-1}\))
- High CO\(_2\) values and weaning problems

In the case of difficult to control hyperglycaemia (usually considered when insulin need is \(>100 \text{ IU. day}^{-1}\)) there are several options. The first option is excessive energy intake, the second an unbalanced nutrition regimen with a relatively high glucose content or a poorly controlled septic process.

Elevated lipids (usually triglycerides \(> 400 \text{ mg.dl}^{-1}\)) happen from time to time in the ICU. There are several possibilities that need to be considered:

- Excessive lipid intake (maximum clearance \(3.5 \text{ g.kg}^{-1}.\text{day}^{-1}\))
- Excessive glucose intake
- Acquired poor lipid clearance
  - Acute renal failure
  - Chronic renal failure
  - Hypodynamic sepsis
- Inborn poor lipid clearance or abnormal metabolism

In all cases where lipid intake is limited the minimal requirement in LCT of 10 g. week\(^{-1}\) should be considered. LCT are an essential component for cell membranes.
In patients with respiratory failure and elevated CO\(_2\) values there has been the idea to move from a balanced nutrition solution to a more lipid-based nutrition because the RQ of lipids is 30% lower than the RQ for glucose. Research in this field could demonstrate that a reduction in CO\(_2\) is only achieved with limitation of energy intake to consumption, but cannot be modified by modification of the composition of the diet (20, 32, 33). In the obese severely obese patient a modification of the diet with low calories and 1.2 g of protein per kg actual body weight had a similar nitrogen balance without difficulty to control hyperglycaemia (34).

7. Organs & Nutrition

7.1 Brain

The brain is affected by several nutrition related factors (22, 23, 35, 36):

- Glucose level
  - Hyperglycaemia
  - Hypoglycaemia
- High ammonium
- Electrolyte imbalance
7.2 Cardiovascular System

Hypophosphataemia, hypokalaemia and the consequences of muscle loss during reduced nutrient intake favour the occurrence of severe cardiac complications in patients with malnutrition, severe catabolism and refeeding.
7.3 Lung

The lung is affected by reduced cardiac function, diaphragmic strength and by the level of CO\textsubscript{2} that needs to be eliminated. Thus the main limiting factors are muscle loss during starvation or severe catabolism that impair both the heart and the respiratory muscles. The system is then stressed by the level of CO\textsubscript{2} that needs to be eliminated. CO\textsubscript{2} production is mainly affected by high energy intake or by a high glucose intake that, with a RQ above 1, is converted to fat (20). As a third consequence of inadequate nutrient intake the risk of pneumonia is increased.

7.4 Abdomen

The abdomen is not only affected directly by the disease and the tolerance of enteral feeding but also by other nutrition related factors.
7.5 Kidney Function

Reduced kidney function has a direct interaction with nutrition care. Poor excretion of waste products induces azotaemia. During acute illness it is usually not advisable to reduce protein intake or amino-acid infusion to a very low level. Thus renal replacement therapy is indicated to allow a sufficient protein intake. Other consequences such as hypokalaemia affect the capacity of the kidney to concentrate urine, or hinder the resolution of the metabolic alkalosis often seen after hypercapnic ventilatory failure or a shock state. Hypomagnesaemia has also been associated with renal failure (37). Uncontrolled hyperglycaemia may be associated with osmotic diuresis and hypovolaemia (38, 39).

7.6 Haematological System

Leucocytes, erythrocytes and platelets are affected by deviations from electrolyte homeostasis. The main reason for impaired blood cell function is hypophosphataemia. Infection control, clotting function and oxygen unloading may be affected (40-42).
7.7 Endocrine System/Metabolic Equilibrium

The endocrine system is affected by starvation, malnutrition and acute illness. After a few days of reduced intake the capacity to metabolize glucose is reduced by almost 50\% (24). This effect is even more pronounced in phases of acute stress such as surgical interventions. Hyperglycaemia is a common feature in acute illness even in a high proportion of non-diabetic patients (43-49). Hyperglycaemia is often associated with increased severity of illness and poorer prognosis especially in the group of patients without known diabetes before hospital admission.

In 2001 Greet van den Berghe from Leuven could show that intensive control of glycaemia to levels of 80-110 mg.dl\(^{-1}\) compared with treatment only for patients with glucose levels >180 mg/dl immediately after ICU admission significantly improved outcome and prevented morbidity (50). This effect could be found also in medical ICU patients staying longer in the ICU and in children (51). The Leuven approach combines early treatment of hyperglycaemia and simultaneous infusion of glucose, and early start of enteral and parenteral nutrition therapy. These studies bolstered the interest in hyperglycaemia and promoted research on treatment with continuous insulin to different targets and in specific populations. None of the multicentre trials could replicate the beneficial effects described by the Leuven group. Several trials were stopped prematurely because of a high proportion of hypoglycaemic events in the intensive treatment arm (52). A very large multicentre trial (NICE-SUGAR) in 6104 patients showed a small unfavourable effect of intensive insulin control. A large debate on the reasons for these conflicting results is still ongoing (51).

Table 2
Glycaemia management elements

<table>
<thead>
<tr>
<th>Based on expert opinion and a recent meta-analysis current recommendations could be summarized:</th>
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<tr>
<td>- Hyperglycaemia should not be left uncontrolled in acute illness</td>
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<tr>
<td>- The target should be to achieve values &lt; 150 md.dl(^{-1})</td>
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<tr>
<td>- Avoid large changes in glucose values</td>
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<tr>
<td>- Avoid hypoglycemic events to values &lt; 60 mg.dl(^{-1})</td>
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<tr>
<td>- Do not withhold appropriate nutrition care to avoid giving insulin</td>
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<tr>
<td>- Use a protocol that includes the following elements</td>
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<tr>
<td>- Target glucose range</td>
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<td>- Insulin dosage for deviations from the target</td>
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<td>- Step changes in insulin for rapid glucose changes</td>
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<td>- Avoids insulin boluses being given intravenously</td>
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<tr>
<td>- Amount of glucose to be given in case of hypoglycaemia (usually 8-10 g as bolus)</td>
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<tr>
<td>- Intervals of glucose measurement adapted to the most recent changes in glucose and insulin dosage</td>
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<tr>
<td>- Definition of responsibilities</td>
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<tr>
<td>- Who measures glucose</td>
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<tr>
<td>- Who interprets glucose levels</td>
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<tr>
<td>- Who is allowed to modify insulin dosage</td>
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<tr>
<td>- Usually point of care glucose measurement is necessary unless glucose values can be obtained within 10 minutes of sampling 24h/24h</td>
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<tr>
<td>- Glucose measurement from blood gas machines are usually the most convenient, cost-effective and reliable point of care approach</td>
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The most important part is the analysis of the treatment process, to provide adequate training and to give the responsibility of measuring and modifying to one group of healthcare providers who work near to the patient (usually nurses but physicians possible depending on local organization).

**Fig. 11** An example for a glycaemia control protocol from the cardio-thoracic ICU at the medical university of Vienna
Treatment of stress induced hyperglycaemia outside ICU has not been formally assessed to date.

8. Refeeding Syndrome

The refeeding syndrome is a potentially lethal and often forgotten condition associated with feeding of chronic malnourished individuals or individuals with little or no nutrient intake for 5-10 days. The hallmark biochemical feature is hypophosphataemia but many other clinical signs are possible. The route of feeding does not have a specific effect on the refeeding syndrome (23, 53).

Table 3
Key pathophysiological features of the refeeding syndrome

| a- Fluid balance |
| b- Glucose homeostasis |
| c- Vitamin B1 deficiency .... Hyperlactataemia |
| d- Hypophosphataemia |
| e- Hypomagnesaemia |
| f- Hypokalaemia |

The incidence of the refeeding syndrome may be as high as 25% for cancer patients and as many as 34% of intensive care patients experienced hypophosphatemia within 2 days of starting artificial nutrition. The clinical presentation may be variable; some symptoms are even compatible with other disease and a poor general condition. Based on case reports the syndrome is potentially fatal, often unrecognized and poorly treated especially outside areas with close monitoring such as intensive care units.

According to the most recent NICE recommendations, refeeding should not be delayed until biochemical abnormalities have been corrected (54). Progressive increase in nutrient intake, correction of biochemical abnormalities and close monitoring allow early and safe refeeding.

Table 4
Refeeding syndrome: high risk patients (53)

- Patients with anorexia nervosa
- Patients with chronic alcoholism
- Cancer patients
- Postoperative patients
- Elderly patients
- Patients with uncontrolled diabetes mellitus
- Patients with chronic malnutrition
  - Marasmus
  - Prolonged fasting or low energy diet
  - Morbid obesity with profound weight loss
  - High stress patients unfed for > 7 days
  - Inflammatory bowel disease
  - Chronic pancreatitis
  - Cystic fibrosis
  - Short bowel syndrome
- Long term antacid use
- Long term diuretic use
Table 5
NICE recommendation to identify high risk patients based on cases and expert opinion (23)

- One or more
  - BMI < 16
  - Unintentional weight loss > 15 % in 3-6 months
  - Little or no nutritional intake for > 10 days
  - Low potassium, phosphate, magnesium before feeding
- Two or more
  - BMI < 18.5
  - Unintentional weight loss > 10 % in 3-6 months
  - Little or no nutritional intake for > 5 days
  - History of alcohol misuse or chronic drug use (insulin, antacids, diuretics)

8.1 Pathophysiology

The pathophysiology is determined by the occurrence of starvation followed by refeeding. During starvation the basal needs in glucose are supplied by gluconeogenesis from protein when glycogen stores have been depleted. The metabolic and hormonal changes aim to minimize protein break-down. The main source of energy is lipids, and increased levels of ketone bodies stimulate the brain to utilize ketone bodies instead of glucose. The metabolic rate progressively decreases by 20-25%. During this phase cells tend to shrink and lose large amounts of intracellular electrolytes. The serum levels may remain normal despite severe depletion.

With refeeding insulin levels increase and glucagon levels decrease. Protein, glycogen and fat synthesis is stimulated and cell volume increases again. This anabolic phase necessitates nutrients but also large amounts of phosphate and magnesium as well as cofactors such as thiamine. The role of depletion of micronutrients has not yet been well investigated.

Insulin stimulates glucose uptake into cells with the help of the Na-K ATPase symporter. Magnesium and phosphate are also taken up by the cells. Water follows by osmosis, and cell volume tends to increase. This is by itself an strong anabolic signal. As a consequence the serum levels of these electrolytes may decrease dramatically within a short period of time and the metabolic rate may increase above the physiological tolerance of the cardio-respiratory system.

8.2 Clinical Symptoms

8.2.1 Fluid Equilibrium

Refeeding with carbohydrate can induce reduced sodium and water excretion with extracellular volume expansion and weight gain. Volume expansion and poor fluid tolerance due to the reduced cardiac mass of malnutrition may result in cardiac failure (39, 55). Refeeding predominantly with protein and lipid may result in fluid loss.
8.2.2 Glucose and Lipid Metabolism

The capacity to metabolize glucose decreases within a few days of even partial starvation. During refeeding with glucose gluconeogenesis will be suppressed or at least reduced in critically ill patients but tolerance for glucose is limited. Hyperglycaemia with osmotic diuresis and metabolic acidosis is possible and should be detected early with proper monitoring. Thus relative overnutrition and insufficient treatment of insulin-resistance of starvation may promote lipogenesis. The maximal lipid tolerance is 3.8 g.kg\(^{-1}\).day\(^{-1}\) and can be much lower during critical illness (56).

8.2.3 Thiamine Deficiency

Thiamine is a cofactor of several enzymes such as transketolases. The vitamin deficiency of malnutrition may be exacerbated with refeeding and the increasing intracellular need for vitamins. Thiamine deficiency is associated with Wernicke’s encephalopathy (confusion, ocular disturbance, ataxia, coma) and Korsakov’s syndrome (short-term memory impairment and confabulation). Thiamine deficiency is also associated with hyperlactataemia without other shock symptoms (57).

8.2.4 Hypophosphataemia

Hypophosphataemia is the most frequent sign of the refeeding syndrome. Phosphate is the major intracellular anion and is involved in energy storage in the form of ATP, in intracellular buffering, as an essential initial step of glycolysis, and as a structural part of cell membranes. Many enzymes are activated by phosphate binding (40, 41).

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<td>- General cell function</td>
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<td>o Metabolic pathways</td>
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<tr>
<td>o Intracellular buffer</td>
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<tr>
<td>o Control of enzyme function</td>
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<tr>
<td>- Excitation-stimulus coupling and nervous system conduction</td>
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<tr>
<td>- Chemotaxis &amp; phagocytosis of leucocytes</td>
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<tr>
<td>- Platelets: clot retraction</td>
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<tr>
<td>- Erythrocyte oxygen affinity</td>
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<td>- Muscle function</td>
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<tr>
<td>- Neurological function</td>
<td></td>
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<tr>
<td>- Avoidance of thrombocytopenia</td>
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Phosphate is the major intra-cellular anion and is shifted rapidly between the intracellular and extracellular compartments. The driving force for these shifts is the metabolic rate, ingestion of carbohydrates and lipids and finally the acid-base balance. The majority of phosphate (85%) is stored in the organic matrix of bone as hydroxyl-apatite crystals, 14% is in cells and 1% in blood. The intracellular concentration is 100 mmol.L\(^{-1}\). A small portion is in the inorganic form and the majority is bound to intermediary carbohydrates, proteins and lipids. In the blood, phosphate is present in organic and inorganic forms at a concentration together of 3.5-4 mmol.L\(^{-1}\). Typically only the inorganic form is measured by standard laboratory methods and the normal concentration of phosphate is 0.9-1.3
mmol.L⁻¹. Phosphate is present in sufficient amounts in a mixed diet; phosphate balance is determined by the kidneys.

**Hypophosphataemia is categorized into**
- Mild 0.6-0.85 mmol/L
- Moderate 0.3-0.6 mmol/L
- Severe < 0.3 mmol/L

In moderate and severe hypophosphataemia immediate intravenous replacement therapy is indicated. Current guidelines recommend the administration of 9 or 18 mmol respectively within a 12 hour period (23). The next dose should be given after rechecking serum phosphate. In the setting of intensive care units supplementation of 45 mmol over a 3 hour period normalized phosphate in 98% of patients with moderate or severe hypophosphataemia (58). The amount proposed should always be seen in addition to continuous phosphate supplementation with typically 0.5 mmol.kg BW⁻¹.d⁻¹. Either inorganic phosphate or organic phosphate has been used. K PO₄⁻ has often been used when concomitant hypokalaemia has existed. Organic preparations such as glucose-1-phosphate or fructose-1-6-diphosphate have the advantage of minimizing the risk of precipitation when calcium is also present in the solution. In all cases where phosphate is added to parenteral nutrition mixtures the organic preparation should be preferred. Unfortunately organic preparations have not received approval in all countries.

Nutrition therapy should not be delayed until hypophosphataemia has been corrected. Both interventions - nutrition and correction of electrolytes - should be done in parallel (54).

### 8.2.5 Hypomagnesaemia

Hypomagnesaemia is also frequent with refeeding and several acute severe disease states. Magnesium is a predominantly intracellular divalent cation. Magnesium levels < 0.5 mmol.L⁻¹ are considered to be severe and are often accompanied by clinical symptoms. Magnesium is an important cofactor in many enzyme systems such as those involved in ATP production, maintains the structural integrity of DNA, RNA and ribosomes, and affects the membrane potential.

The most prominent clinical symptoms are cardiac arrhythmias including torsade de pointes, abdominal discomfort and anorexia, and neurological manifestations such as tremor, paresthaesiae, tetany, seizures, weakness, etc. (59, 60).

Supplementation is best achieved with a continuous infusion until normalization. The maintenance dose is 4-8 mmol.d⁻¹. Oral magnesium supplementation can be associated with diarrhoea.

### 8.2.6 Hypokalaemia

Hypokalaemia is frequently present in acute disease states especially those associated with increased catecholamine release, but also during aggressive refeeding. Potassium is the most abundant monovalent intracellular cation. Its main function is to maintain the electrochemical membrane potential. A potassium < 3 mmol.L⁻¹ is considered to be severely low. The most severe features are cardiac arrhythmias, but many other systems are also affected. Gastrointestinal symptoms include ileus and constipation, the kidney has impaired concentration capacity, compensation of metabolic alkalosis is delayed,
neuro-muscular function is impaired but also endocrine function is affected with impaired glucose tolerance.

8.3 Treatment and Prevention

<table>
<thead>
<tr>
<th>Table 7</th>
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<tbody>
<tr>
<td><strong>Treatment and prevention of the refeeding syndrome: a stepwise approach</strong></td>
</tr>
<tr>
<td>- Identify patients at risk</td>
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<tr>
<td>- Check electrolytes</td>
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<tr>
<td>- Start refeeding with 50% of recommended energy intake</td>
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<tr>
<td>o 8-10 kcal.kg(^{-1}).d(^{-1}) (actual body weight)</td>
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<tr>
<td>o Increase gradually to reach recommendations within 3-5 days</td>
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<tr>
<td>- Rehydrate carefully and monitor cardio-circulatory function</td>
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<tr>
<td>- Replace electrolytes in sufficient amounts</td>
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<tr>
<td>o Potassium 2-4 mmol.kg(^{-1})</td>
</tr>
<tr>
<td>o Phosphate 0.3-0.6 mmol.kg(^{-1})</td>
</tr>
<tr>
<td>o Magnesium 0.05-0.1 mmol.kg(^{-1})</td>
</tr>
<tr>
<td>o Calcium 0.05-0.1 mmol.kg(^{-1})</td>
</tr>
<tr>
<td>- Monitor electrolytes, metabolic tolerance and clinical situation closely during the first 5-10 days of refeeding</td>
</tr>
</tbody>
</table>

9. References


