Refeeding syndrome: What does it really mean?

Refeeding syndrome from the laboratory perspective

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Abstract:

The aim of this review is to explain the development of refeeding syndrome from a laboratory standpoint. This includes a brief explanation of the pathophysiology of the development of RFS, a reflection on the metabolic and biochemical changes in laboratory blood analytes concentration, and the usefulness of the "reference change value" in the longitudinal assessment of laboratory test results. This work is the result of the review of the literature that has been applied in a laboratory environment.

Key words: refeeding syndrome, diagnoses and examinations, reference change values

Introduction:

Refeeding Syndrome (RFS) is a set of clinical symptoms (heart, lung, liver, kidney, neurological, metabolic and haematological) that occur as a result of fluid and electrolyte shifts in malnourished patients in response to an inappropriately high-calorie diet. This applies to any form of complementary foods after several hours of fasting. It includes enteral or parenteral nutrition, as well as uncontrolled and unlimited oral intake. Changes in fluids and electrolytes are caused by hormonal and metabolic changes that can cause severe complications and death. The main biochemical feature of refeeding syndrome is hypophosphataemia, although the syndrome is complex and may include a disruption in the balance of water and nitrate content, alterations in the metabolism of glucose, fat and protein, thiamine deficiency, hypokalaemia and hypomagnesaemia. These deficiencies vary from case to case.

They depend on the severity of the health status of the organism (type and duration of primary disease), on the nutritional status or on the severity of the malnutrition of the organism which suffers from the amount of the retained energy, vitamins and minerals "reserve" as an effect. Their deficiency is visible by measuring their concentrations in the blood. In doing so, a deficiency in all minerals is not necessarily pronounced; all combinations are possible with various severity levels for each. Thus, the symptoms that occur as a consequence of this deficiency are unpredictable and can range from asymptomatic cases to the dysfunction of any of the vital organs; inasmuch as they are not treated (with a correction of electrolyte imbalances) they can cause a coma and death (1,2,3,4,5).

Over the last sixty years, since RFS was first clinically described and published, what we in fact call RFS has still not been clearly defined.

A clear international consensus has not been set on when we can truly say that RFS has been developed, on whether this is a laboratory diagnosis or a case of clinical symptoms. A laboratory diagnosis of RFS refers to moment when during the feeding of malnourished patients, the decline in the concentration of one or more major electrolytes (particularly in phosphates) can be noticed in the serum, without any symptoms or without any clearly expressed symptoms, while the appearance of symptoms in laboratory findings implies disturbance in vital function that are primarily show low phosphates (6,7).

In a review of the published literature, we can find individual case reports or reports on series of cases, cohort studies and expert opinions. The level of evidence (LOE) of the published studies is III and IV. On this basis, in 2006 the National Institute for Health and Clinical Excellence (NICE) claimed that the recognition and timely

inclusion of compensatory mechanisms is essential to reduce, if not completely eliminate the morbidity and mortality associated with this phenomenon. Guidelines for the management of RFS in adults have been published. These guidelines define the criteria for at at-risk and high risk patients (Table 1), as well as instructions for the implementation of compensation mechanisms in case of occurrence of electrolyte deficits. However, in medical practice, RFS still frequently occurs (2,4).

RFS is generally a term associated with marked malnutrition, primarily with anorexia. However, many clinical conditions represent a risk for RFS. There are three basic groups of patients that are at risk of developing RFS: (1) individuals with a low intake of nutrients, (2) individuals with an increased loss of nutrients, and (3) individuals with a reduced absorption. These groups include a wide range of individuals for whom various medical conditions as well as social, economic and psychological statuses that affect all age groups are responsible for malnutrition and risk (6,7).

The incidence of refeeding syndrome

The lack of a clear definition of RFS entails the lack of randomized controlled trials and published data on its frequency. Moreover, as was already mentioned, often mild symptoms frequently remain unrecognized, and low electrolytes are often associated with secondary diseases. For these reasons, the frequency of RFS remains unknown. According to a study by Camp and Allon, in 10197 hospitalized patients, the incidence of severe hypophosphatemia was 0.43% (8). The published results of studies on patients who were on total parenteral nutrition (TPP) revealed that 30 to 38% of patients who received phosphate had hypophosphataemia, as did 100% of patients who received no phosphates in the parenteral nutrition (9), while the

frequency RFS in oncological patients was observed in more than 25% of patients (10).

The pathophysiology and characteristics of RFS

Under normal circumstances, the body uses glucose as a primary source of energy. This requires a continuous intake of carbohydrates. Two to three hours after the intake of carbohydrates, blood glucose becomes available and is retained as glycogen. The amount of glycogen is limited and provides a short-term source of energy to the body in situations where food intake fails. The body thus retains proteins that would not be used for energy purposes. Excessive food intake, that is, excessive energy intake, is stored by the body as fat, which represents the most important energy reserve in the human body (11).

In a short period of fasting (24 hours), glycogenolysis takes place in the liver and in muscles to compensate for glucose. After the glycogen is expended, the gluconeogenesis process begins. Amino acids from muscle protein and fatty acids from fatty tissues provide the organism glucose as an energy source through metabolic reconstruction. With gluconeogenesis pyruvate and lactate may also provide glucose. This initial fasting period marks an increased protein degradation (11).

If fasting continues, the body will slow down and reduce its basal metabolism rate by about 20 to 25%. Most organs and tissues in these conditions switch to fatty acids as an energy source. The brain is the organ that primarily uses glucose, and can only partially switch to ketones as an energy source. By switching to fat as an energy source in the body, protein and muscle mass are maintained. The reduction of the

proteolysis rate, an increased migration of fatty acids and formation of ketone is characteristic of this period. In addition, at this stage there is also a decrease in intracellular concentrations of minerals (electrolytes) and vitamins. Serum electrolyte concentrations usually remain normal because of intracellular space contraction, decreased renal excretion and withdrawal from storage in the body. Under these conditions, the body slowly begins to consume itself and this is its mode of survival. Bearing these metabolic changes in mind, they are changes that mostly occur in thin or emaciated and malnourished people. However, they can also occur in overweight people who resort to starvation as a means to decrease their body weight (11).

During the supplemental feeding process, the increase in blood glucose leads to increased insulin secretion and decreased glucagon secretion. This hormonal shift results in the stimulation of the synthesis of glycogen, protein and fat. Minerals such as phosphor and magnesium, as well as cofactors such as thiamine, are necessary for these processes. Insulin stimulates the absorption of potassium and glucose into the cell, and magnesium and phosphates enter the cell. This leads to a reduction in serum concentrations of phosphates, potassium and magnesium which are already in deficit in the body. Clinical symptoms of refeeding syndrome occur as the result of a lack of these minerals and rapid changes in the basal metabolism rate (1,11).

Phosphor is the primary intracellular mineral. It is found in blood in the form of free and protein-binding inorganic phosphate. It is essential for many intracellular processes: it activates enzymes and messengers, stores energy in the form of adenosine triphosphate (ATP), regulates the affinity of haemoglobin for oxygen and thus regulates the supply of oxygen to the tissues, participates in the regulation of acid-base balance, is an integral part of DNA, RNA and cellular membranes and is responsible for its integrity. The depletion of phosphor in the whole body occurs in the

"refeeding" syndrome and insulin secretion leads to increased absorption and utilization of phosphate in the cell. This leads to a deficit of intracellular and extracellular phosphor. In these conditions, even slight decrease in serum phosphate levels can lead to a significant dysfunction of cellular processes that affects virtually every physiological system. Hypophosphatemia is a surrogate marker for RFS, but may be present before the feeding of undernourished patients with malnutrition, in diabetes, alcoholism, or in prolonged severe respiratory alkalosis and in vitally endangered patients. Moreover, antacids can also be a cause of hypophosphatemia. (12,13,14).

Potassium, the main intracellular cation, is also deficient in malnutrition, although its serum concentrations may remain normal. Starting anabolic processes leading to the absorption of potassium into the cell stimulated with insulin, which results in severe hypophosphatemia, changes in electrochemical membrane potential, abnormal heart rhythm and heart failure. Hypophosphatemia is probably the most common electrolyte deficit in clinical practice. The causes of hypophosphatemia, besides in refeeding, are an increased loss of stool (diarrhea), an increased loss of urine, metabolic alkalosis, or secondarily as a result of taking many drugs (diuretics, b-adrenergic agents, high-dose glucocorticoids, insulin) (12,14,15).

Magnesium, predominantly an intracellular cation, is an important cofactor in most enzyme systems, such as in those involved in oxidative phosphorylation and ATP production. It is essential to the structural integrity of DNA, RNA and ribosomes, it affects the membrane potential of cells and its deficiency can lead to changes in neuromuscular excitability and heart disorders. Besides in refeeding, where we find acute hypomagnesemia, the cause of reduced magnesium levels may be diarrhea, pancreatitis, malnutrition, alcoholism, metabolic acidosis, or secondarily as a result of

therapy (amphotericin B, furosemide, aminoglycosides, cisplatin, cyclosporin). Hypomagnesemia can cause hypocalcemia and hypokalemia (K activator, the ATP-ase pump, and impairs the release of parathyroid hormones). It can also be falsely lowered in cases of significant hypoalbuminemia. The correction of a potassium deficiency along with magnesium values (the lower reference range or lower) is not possible without correcting the magnesium. (12,14,16).

Hypocalcemia is a sign of lower total serum calcium levels and is present relatively often in different states (sepsis, pancreatitis, trauma). Serum calcium concentrations return to normal values 5 to 6 days after recovery from an acute illness. The etiology of hypocalcemia is multi-factorial and not fully understood. However, the interpretation of findings of total serum calcium may be incorrect in situations where there is markedly reduced albumin, which is often found in malnourished patients. Under conditions in which the concentration of serum albumin is low, it is necessary to determine the ionized calcium level (12,17).

Thiamine deficiency is the most common vitamin deficiency that occurs as a re-alimentation complication. Thiamine is an essential cofactor of key enzymes in the metabolism of carbohydrates and synthesis of ATP. Its deficiency leads to Wernicke's encephalopathy (ataxia, ophthalmoplegia, confusion, hypothermia, coma) or Korsakoff's syndrome (amnesia, confabulation)(4,18).

Changes in carbohydrate metabolism lead to changes in sodium and water balance. The introduction of carbohydrates in the diet leads to a decrease in the renal excretion of water and sodium. If fluid intake is increased to maintain dieresis, this can lead to fluid overload, congestive heart failure and pulmonary edema (1,3).

An excessive intake of glucose can lead to hyperglycaemia, osmotic diuresis and dehydration. There can also be a stimulation of lipogenesis, which can lead to fatty changes in the liver, increased production of carbon dioxide, hypercapnia and respiratory failure (1).

Mutual hormonal and biochemical relations and the consequences that arise during feeding after starvation can be seen on Figure 1 (1).

During fasting, due to the reduced food intake and the minerals and vitamins in the body, there is a lack of them in the body. Nevertheless, through control mechanisms and their redistribution between compartments, concentrations of electrolytes in the blood are mainly normal. Baseline concentrations of electrolytes were measured before refeeding; this is why they are not a true reflection of the state of the organism. Reduced basal electrolyte concentration values can be found when due to other disturbances compensatory mechanisms are no longer sufficient. The principle of complementary foods in such cases requires a specific approach, but is basically clear.

Laboratory monitoring during the supplemental feeding of malnourished patients are an integral part of NICE guidelines and come in the form of protocols. The protocols include biochemical tests along with the dynamics of definition and also note explanations and interpretations. These protocols were developed by a group of professionals (Guideline Development Group, GDP) on the basis of good practice point (GPP) and as a recommendation for the best practice based on experience (LOE 3 or 4) and/or formal consensus (2,3). According to this protocol, laboratory monitoring includes:

1. Sodium, potassium, urea and creatinine for the assessment of renal functions as well as the status of water, Na and K. The interpretation of results includes insight on therapies and fluid balance.
    a. After the initial values, the dynamics of determination include monitoring once a day until the results are stable, and then 1 to 2 times a week. The determined of K and Na in the urine can be of use when tracking and replenishing electrolytes that are lost gastrointestinally is necessary.
2. Glucose for monitoring glycaemia and due to possible resistance to glucose, which is not a rare occurrence.
    a. After the initial value, values need to be determined twice a day or more if necessary, until the results are stable; then they are to be determined once a week.
3. Magnesium and phosphates in the body are often depleted despite initial values that are often within the reference range.
    a. After the initial values are determined, once a day during the first week (there is risk of developing refeeding syndrome), then 2 to 3 times a week until the values are stable, then once a week.
4. Liver function tests including International Normalised Ratio (INR): deviation of normal values is common, although the reasons can be complex and should be interpreted taking this into consideration. Deviation in laboratory tests could be a result of parenteral nutrition, sepsis or other disorders.
    a. The initial values are determined, then again twice a week until values are stable, then once a week.

5. Calcium and albumin: a possible presence of hypo and hyperkalemia. Albumins are not a measure of the status of protein, rather a measure of malnutrition or disease. It is necessary to correct serum calcium levels because of albumin.
    a. The initial values are determined, then again once a week.
6. C-reactive protein (CRP) is necessary to assess the presence of acute phase reaction. The CRP value is important in interpreting, but can also be helpful in assessing the results of other parameters (proteins, trace elements, vitamins).
    a. The initial values are determined; then again 2 to 3 a week until results are stable.
7. Zinc (Zn) and copper (Cu), trace elements, are often lacking in malnutrition, even when the loss is increased. When interpreting the results it should be borne in mind that the acute phase (an elevated CRP level) can be reflected in a reduced Zn level and an increased Cu level.

a. The initial values are determined, then, depending on the results, again every 2 to 4 weeks.

8. A selenium (Se) deficiency is found in severe disease and sepsis, but also in long-term nutrition support. The acute phase lowers Se values.
    a. Is determined only when a deficiency is suspected, and further determinations depend on the initial one.
9. Complete blood count (CBC) and MCV: Anaemia due to iron deficiency or folic acid is common in malnourished patients. Sepsis significantly affects the results of the CBC.
    a. The initial values are determined; then again 1 to 2 times a week until results are stable, then once a week.

10. Iron (Fe) and ferritin. Iron deficiency is common in long-term parenteral nutrition. When interpreting the results, the acute phase reaction should be paid close attention to, when the Fe is reduced and ferritin elevated.
    a. The initial values are determined, then again every 3 to 6 months.
11. Folate, B12: Serum folate/B12 sufficient, with full blood count.
    a. The initial values are determined, then again every 2 to 4 weeks.
12. Manganese and 25-OH vitamin D. These tests are rarely needed, unless there is cause for concern (2,3).

RFS from a laboratory perspective

RFS is a complication that arises during the supplemental feeding of malnourished patients. The dynamics of laboratory monitoring of these patients according to the protocols of published guidelines (NICE, 2006)(2) allows the identification of the development RFS before the onset of symptoms and with the correction of the deficiency symptoms are prevented from being developed. In this respect, RFS is a laboratory diagnosis. This understanding includes laboratory professionals in and commits them to the team that treats and cares for such patients. What can a laboratory expert do in this regard? What is important for good laboratory monitoring? How can he or she help a physician in interpreting the laboratory test results?

From a laboratory perspective, the most important feature of RFS is the rapid and uncertain change in the concentration of glucose and electrolytes in serum, which depends on the applied therapeutic procedure. These treatments are generally not known to the laboratory professional, and neither is the weight of the underlying disease, which may or may not be present.

Standardized methods of determination, standardized complete pre-analytical procedures and analytical phases of laboratory work, as well as the implementation of quality control are the basic requirement for good laboratory practices (according to ISO 15189). Laboratory errors were thus reduced to a minimum. The interpretation of the laboratory test results is part of the post-analytical phase, and it is common to both biochemists and clinicians.

In medical practice, most often the obtained laboratory tests results are compared with the reference values that are determined by the age and sex of patients. This is the so-called longitudinal evaluation of laboratory test results. The usefulness of such assessments in laboratory monitoring may be calculated through an index of individuality (II) for each analyte. It represents the ratio of inter-individual (CV_I) and intra-individual variability (CV_{intra}). The smaller the ratio (II), the more pronounced the individuality of each analyte is, and hence the usefulness of the reference interval lessens (19,20).

Laboratory monitoring is used to monitor the effects of therapeutic procedures on the health status of patients. This means that the assessment of laboratory test results is relevant to the comparison of the obtained values to the preceding results. The slightest differences between two obtained concentrations in the required medical reports that could be linked to actual changes in the patient's medical status are referred to as critical differences, or "reference change values" (RCV). The usefulness of this estimate is far greater because it involves biological (intra-individual) and analytical variation. The formula and method of calculating the RCV according to Ricos and colleagues can be found in literature (19). The database containing biological and analytical variations is continually updated and is available on the website (21). Ricos and colleagues calculated the RCV values for 216

analytes (22), while Table 2 shows the RCV values for laboratory tests that are used in the daily laboratory monitoring of RFS. The RCV values were calculated from changes in healthy subjects, and were present at a 95% probability level, provided that the $CV_A < CV_I$ (approximately CV_A CV_I x = 0.5). RCV values in diseased states in individual analytes were significantly higher, although studies have shown that RVC in diseased and healthy states do not significantly change (20,22,23). However, in clinical terms, this is not significant because it is better to register the change, and then to decide that this is clinically unimportant, rather than to ignore the change in the patient's condition. Furthermore, the analytical imprecision of the (CV_A) is replaced by the desired analytical quality specifications that is based on biological variation (CV_I 0.5). Of course, a prerequisite for this is the daily implementation of internal quality control on the laboratory's analytical phase to achieve the desirable specifications for imprecision, inaccuracy and allowable total error total (21). For the proper interpretation of the laboratory test results, knowledge of the possible interferences is also necessary. It is particularly important to reduce the impact of all the factors from the preanalytical phase on the results (potential errors in blood tests, transport conditions, separation, sample storage)(20,23). This is done by introducing clear and precise protocols in and outside of the laboratory, and is based on guidelines published by the Clinical and Laboratory Standards Institute (CLSI) and the World Health Organization (WHO) (24,25). Furthermore, the effects of the most common interferences (haemolysis, icterus, lipemia) should be clearly defined, as well as other known interferences (drugs), or states in which the analytes can be altered.

The determination of the initial or basic values of all laboratory parameters provided by the working diagnosis is of great importance. These are values that are determined prior to any therapeutic or diagnostic procedure.

The longitudinal assessment of the initial laboratory tests allows a series of therapeutic procedures. It also presents a comparative value along with the value of the next scheduled laboratory monitoring point.

Key points:

1. RFS is a pathophysiologically well-described condition, and in respects of the protocols of laboratory monitoring in published guidelines (NICE, 2006) it has become a laboratory diagnosis.
2. The RCV value in laboratory monitoring should be an aid in interpreting differences in serial laboratory test results from individuals.
3. The introduction of the RVC in the laboratory reports the value of the reference range would most certainly help the clinician in making medical decisions.
4. This requires good and organized policies implementation to control the quality of the laboratory work.

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Table 1. Criteria for determining people at high risk of developing refeeding syndrom.

Patient has one or more of the following:	Patient has two or more of the following:
• BMI less than 16 kg/m^2 • unintentional weight loss greater than 15% within the last 3–6 months • little or no nutritional intake for more than 10 days • low levels of potassium, phosphate or magnesium prior to feeding.	• BMI less than 18.5 kg/m^2 • unintentional weight loss greater than 10% within the last 3–6 months • little or no nutritional intake for more than 5 days • a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Modifed from National Institute for Health and Clinical Excellence (NICE) guideline − Nutrition support in adults)(2).

Table 2. Biological (intra- and interindividual) variation, analytical variation, index of individuality and reference change values for analytes in daily monitoring of refeeding syndrome.

Analyte	CV_I (%)	CV_{INTRA} (%)	Index of individuality (II) (CV_I/CV_{intra})	CV_A Desirable (%)	$RCV_{95\%}$ Desirable specification ($CV_A \sim 0.5CV_I$)(%)
Phosphate	8.5	9.4	0.90	4.3	26.3
Potassium	4.8	5.6	0.86	2.4	14.9
Magnesium	3.6	6.4	0.56	1.8	11.2
Calcium	1.9	2.8	0.68	1.0	5.9
Calcium ionized	1.7	1.9	0.89	0.9	5.3
Sodium	0.7	1.0	0.7	0.4	2.2
Glucose	4.9	6.1	0.80	2.5	15.2

Legend: CV_I intra-individual coefficient of variation; CV_{INTRA}: inter-individual coefficient of variation; CV_A: desirable coefficient of analytical variation; $RCV_{95\%}$: reference change values at a 95% probability level.

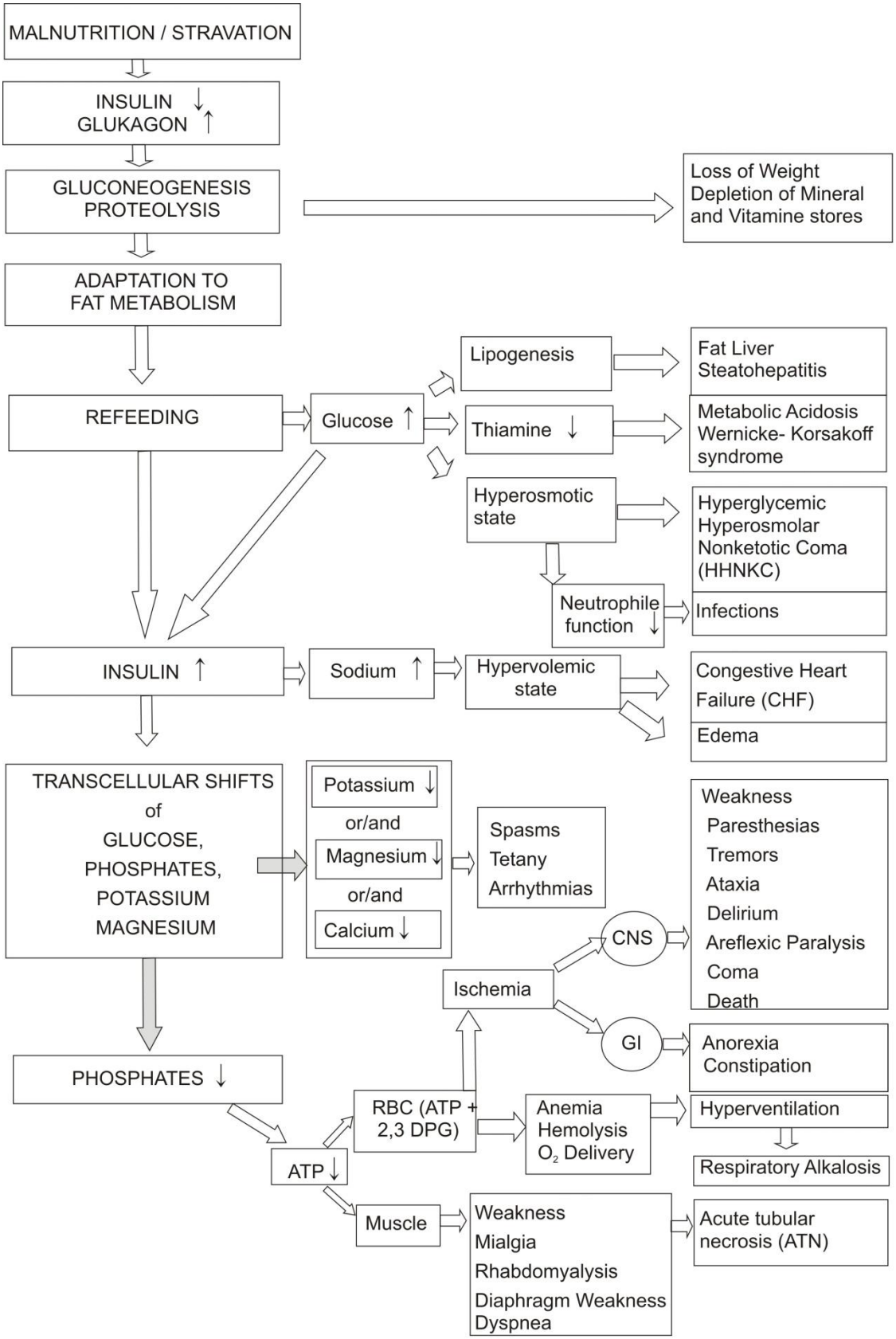

Figure 1. Consequences of the major metabolic and biochemical changes in the refeeding syndrome. Modified from Boateng (1)