Severe Acute Malnutrition, Refeeding and Insulin

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The symptoms of severe acute malnutrition and of refeeding syndrome were already known to the Romans, as we can learn from the report on the siege of Jerusalem by the Roman historian Flavius Josephus of the first century AD:[1]

> *„Hereupon some of the deserters, having no other way, leaped down from the wall immediately, while others of them went out of the city with stones, as if they would fight them; but thereupon they fled away to the Romans. But here a worse fate accompanied these than what they had found within the city;* ***and they met with a quicker despatch from the too great abundance they had among the Romans, than they could have done from the famine among the Jews; for when they came first to the Romans, they were puffed up by the famine, and swelled like men in a dropsy; after which they all on the sudden overfilled those bodies that were before empty, and so burst asunder****, excepting such only as were skilful enough to restrain their appetites, and by degrees took in their food into bodies unaccustomed thereto.“*

Until today, all evidence of international food aid clearly demonstrates the very dangers of any too rapid and inappropriate refeeding in cases of severe acute malnutrition. For a full understanding of the underlying physiology in malnutrition and in re-alimentation one has to be familiar with the central and governing role of the hormone insulin.

Understanding of insulin mechanism is essential for a full understanding of malnutrition and refeeding.

The widely used phrase that insulin is being released in order to lower the blood glucose level is not helpful for really understanding the insulin effects. Similarly, we could state that humans use their lungs in order to lower the surrounding oxygen level. Indeed, insulin, when injected as a medical drug does

[1] Flavius Josephus: The War of the Jews or History of the Destruction of Jerusalem; book V; chapter 13: 548-549. (accentuations: JG) Online available: http://www.documentacatholicaomnia.eu/03d/0037-0103,_Flavius_Josephus,_De_Bello_Judaico,_EN.pdf [accessed March 21, 2019]

lower blood glucose levels, but this form has only been available since 1922.[2]

Consequently, the question arises about the central function of the insulin hormone in the metabolism of animals. During almost four billion years of life and metabolic evolution on earth[3] the challenges and hazards to any living organism were predators, infections and malnutrition. Overnutrition or obesity only recently has become a health problem for humans (and their domestic animals). Why then should Mollusca or worms of the Cambrian period almost 500 million years ago or Homo sapiens of the ice ages actively reduce their blood glucose levels? What really was the central function of insulin during millions of years in the evolution of life?

The insulin mechanism developed in millions of years of hunger and stress.

Biology already finds insulin-like factors in invertebrates such as worms[4] and flies[5]. These hormones regulate development, upgrowth, life span and behaviour depending on individual nutritional status. Only when insulin is present, are most cells able to import glucose from the serum. Only when insulin is present, can cells grow, multiply and assemble organs and other structures in ontogenesis. Up to the present human beings, insulin adapts any metabolic activity and development to nutritional status. In human children, chronic undernutrition will result in hypoinsulinemia and reduced body height (stunting)[6].

Insulin, being a protein hormone (a chain of amino acids) is produced and released by specialized cells of the digestive system into venous blood vessels. In mammals, the pancreatic beta-cells are the insulin production facility. Insulin is released into the portal vein and consequently directly into the liver.

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[2] Banting FG, Best CH (1922) The Internal Secretion of the Pancreas. The Journal of Laboratory and Clinical Medicine Vol. 7, Issue 5, 251–266

[3] Knoll AH (2005) Life on a young planet; the first three billion years of evolution on earth. Princeton NJ: Princeton Sciences Library

[4] Tissenbaum HA, Ruvkun G (1998) An Insulin-like Signaling Pathway Affects Both Longevity and Reproduction in Caenorhabditis elegans. Genetics vol. 148 no. 2: 703-717

[5] Delanoue R, Meschi E et al. (2016) Drosophila insulin release is triggered by adipose Stunted ligand to brain Methuselah receptor. Science 30,Vol. 353, Issue 6307, 1553-1556

[6] Martins PA, Sawaya AL (2006) Evidence for impaired insulin production and higher sensitivity in stunted children living in slums. Br J Nutr. 95(5):996-1001

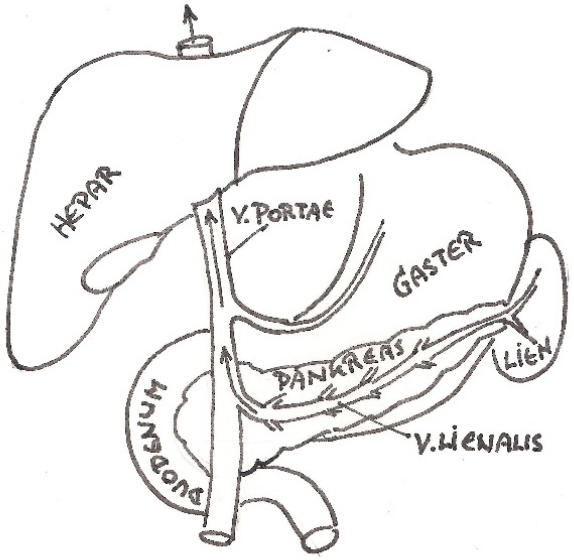

Fig 1: venous transport of insulin via splenic vein and portal vein into the liver

- Insulin inhibits hepatic glucose synthesis on the basis of amino acids (gluconeogenesis). (Glucose synthesis using fatty acids will not be performed in animal cells anyway).
- Insulin inhibits hepatic release of glucose from glycogen storage molecules.
- After liver perfusion, insulin allows for peripheral glucose uptake into muscle and fat cells.

At large, insulin effects on the metabolism will induce downsizing of serum glucose level in resting and anabolic periods, while the hormones glucagon, epinephrine, cortisol and the growth hormone somatotropin will raise blood glucose in periods of activity and energy requirement.

Increased serum glucose levels after food intake for instance directly induce the release of insulin from pancreatic beta cells. The insulin mechanism, being of great antiquity, is totally independent of the considerably younger brain or nervous system.

Pancreatic beta-cells represent both analyser and producer of insulin. In insulin-dependent cells like in fatty and muscle tissue insulin stimulates the placement of glucose transporting molecules (GLUT4) into the cell membrane and thus enables cellular glucose uptake.

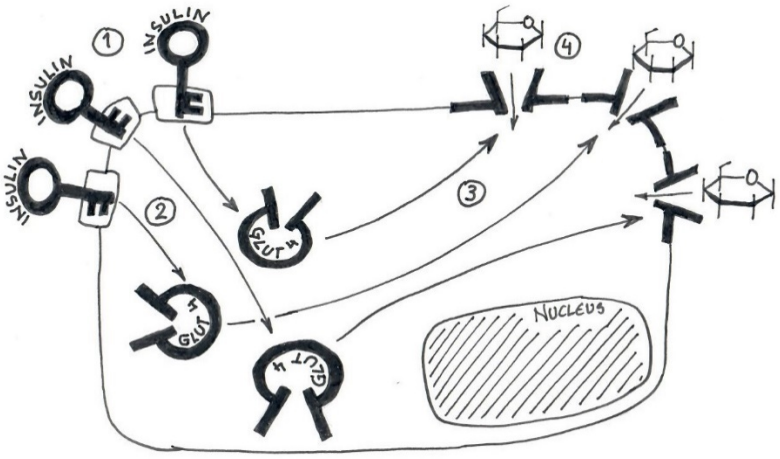

Fig 2: ① insulin joins to the cell membrane, ② messenger molecules move intracellular vesicles containing GLUT4 towards the cellular membrane, ③ GLUT4 are being integrated into the cellular membrane, ④ GLUT4 start transporting glucose into the cell

Brain cells and red blood cells are not dependent on insulin, because their glucose transport systems (GLUT1) are already incorporated into their cell membranes. The GLUT1-system allows for continuous glucose uptake even in absence of insulin.

The different distribution of GLUT4 and GLUT1 transporters guarantees a safe distribution of glucose to the different organs and tissues. Without insulin present, muscle cells cannot consume any glucose, so this most valuable energy source is allocated exclusively to the vitally important brain and blood cells. This mechanism of energy distribution in periods of undernutrition and starvation was lifesaving during millions of years in the evolution of life.

The interaction of insulin, GLUT1- and GLUT4-transporters distributes glucose between the different tissues and organs.

Without the insulin mechanism, during any sustained activity our muscle tissue would sponge every molecule of glucose and leave the brain without energy, thus causing unconsciousness even by just climbing stairs. Low insulin levels protect the vital organs like brain and blood from energy shortage. In general, elevated serum insulin levels are found in situations of adequate nutrition and satiation and of tissue build-up and energy storage (anabolic active principle). Reduced serum insulin levels are found in hunger situations and in tissue degradation for energy generation (catabolic active principle). For these reasons, patients suffering from Type 1 diabetes mellitus, who totally lack any insulin, massively lose weight unless they are treated

with exogenous insulin. In situations of severe distress and/or severe infections a state of insulin resistance develops at several steps of the insulin mechanism. Insulin resistance disables the GLUT4-mobilization and by this mechanism stops glucose uptake into muscular tissue cells. The serum glucose remains in the blood, where it can be used as energy supply for the blood cells during the activation of immune response.[7] Hence, insulin resistance neither is a metabolic disease nor a morbid pathway, but quite the contrary; it is a highly successful evolutionary mechanism of energy allocation in distress or infections[8].

Insulin resistance provides glucose exclusively for the blood and nervous system, where it is needed in infection and stress.

Likewise, the non-alcoholic fatty liver disease of humans dates back to the early hominides, who developed the ability of storing fructose in the form of fat in the liver in order to survive during a cooling climate with only seasonable availability of fruit around 15 million years ago.[9]

For the early hominids a fatty liver served as physiological energy store during seasons of unavailability of fruit.

Excessive intraabdominal fatty tissue however releases inflammatory messenger molecules that induces causeless long lasting insulin resistance and in the long run type 2 diabetes mellitus. In long lasting insulin resistance permanently elevated serum glucose levels will induce permanently maximum insulin production until the production capacity of the pancreatic beta-cells will be exhausted.[10] In early stage of the disease, reduction of body weight may be medicative.

[7] Soeters MR, Soeters PB (2012) The evolutionary benefit of insulin resistance. Clin Nutr 31: 1002–1007

[8] Straub R (2014) Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases: Arthritis Research & Therapy, 16(Suppl 2): S4

[9] Johnson RJ, Andrews P (2010) Fructose, uricase, and the Back-to-Africa hypothesis. Evolutionary Anthropology 19 (6): 250-257

[10] Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale Versorgungsleitlinie Therapie des Typ-2-Diabetes – Langfassung, 1. Auflage. Version 4. 2013, zuletzt geändert: November 2014. AWMF-Registernummer: nvl-001g

Fig 3: typical aspect in type 2 diabetes mellitus with obesity and insulin resistance

Type 1 diabetes mellitus, on the other hand, is an acute immunological and not preventable disease that rapidly destroys all insulin producing pancreatic beta cells. All patients suffering from type 1 diabetes mellitus are in lifelong need of insulin substitution therapy.

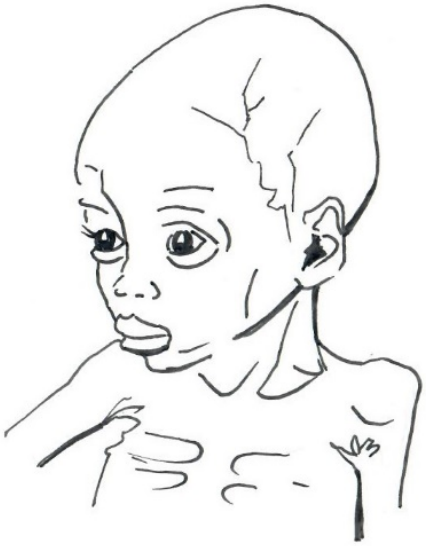

Fig 4: typical aspect of a child suffering from untreated type-1-diabetes mellitus and demonstrating severe malnutrition and dehydration as an effect of total insulin deficiency

In type 1 and in type 2 diabetes mellitus the low insulin levels inhibit cellular glucose uptake, thus raising serum glucose level outside the cells and causing energy deficiency within the cells. Degradation of fatty tissue (lipolysis), fatty acid transport into the cells and fat oxidation are used as an alternative energy source. Free fatty acids in the liver provide acetyl-coenzyme A (C2-molecules) and trigger the synthesis of keto bodies (C4-molecules), being the transport form of acetyl-coenzyme A

from liver to muscle, where they are used for ATP-production within the mitochondria by oxidative phosphorylation.

Finally, in untreated type 1 diabetes mellitus, excessively high serum glucose levels in combination with excessively high keto body levels cause severe metabolic acidosis and dehydration, known as diabetic ketoacidosis that may cause diabetic coma and death.

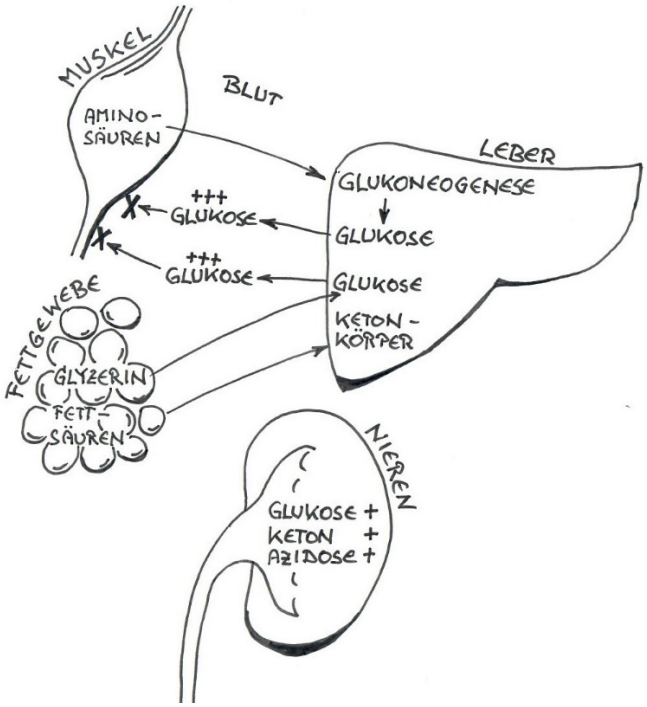

Fig 5: pathophysiology leading to diabetic ketoacidosis

Use of keto bodies from storage fat for energy supply in malnutrition is initiated by low serum insulin and high serum glucagon. Glucagon is produced in the alpha cells of the pancreas in situations of low serum glucose. Glucagon stimulates glycogenolysis and gluconeogenesis, thus boosting serum glucose level. It is for this effect that glucagon is used as an injectable emergency drug in cases of serious hypoglycaemia in patients with diabetes mellitus (GlukaGen® HypoKit).

Low serum insulin and high serum glucagon will trigger fat mobilization and ketogenesis.

In addition to type 1 and type 2 diabetes mellitus we know diabetes in pregnancy and diabetes on the basis of total pancreas loss (pancreoprivic diabetes). Therapy of this diabetes is exceptionally difficult, because these patients lack both insulin and glucagon for glucose regulation. Globally, serum glucose level is

specified by using the SI-unit of mmol/l. Only the western German states, Austria and few other countries still use the outdated unit mg/dl. Standard fasting value of serum glucose in healthy individuals on a normal diet is[11]:

3.6–5.6 mmol/l equivalent to **65–100 mg/dl**

In healthy individuals, ingestion of 10g glucose will initiate release of about 1 IU of insulin from the pancreas.

Insulin, being the hormone for connecting growth and development with nutritional status, plays a paramount role in hunger metabolism as well. However, many of the physiological details of malnutrition and refeeding still await full scientific disclosure.[12] At least the following hypotheses are scientifically documented and highly probable:

In energy malnutrition, diminishing serum glucose levels consequently down-regulate serum insulin levels. In the absence of insulin, the glucose present in the serum only enters the vitally important organs (with GLUT1-transporters) like brain and blood cells („selfish brain“)[13]. Just as in diabetes mellitus, low serum insulin levels induce keto body utilisation from storage fat for energy allocation to muscles, organs and even nervous system. These pathways of ketogenic energy provision have been subject of paediatric clinical research, taking the ketogenic diet in cerebral convulsive disorders for example.[14]

[11] Deutsche Diabetes Gesellschaft (DDG) (2015) Diagnostik, Therapie und Verlaufskontrolle des Diabetes mellitus im Kindes- und Jugendalter. S3-Leitlinie der DDG und AGPD 2015. AWMF-Registernummer 057–016

[12] Spoelstra MN, Mari A, Mendel M, et al (2012) Kwashiorkor and marasmus are both associated with impaired glucose clearance related to pancreatic β-cell dysfunction. Metabolism 61:1224–1230.

[13] Fehm HL, Kern W, Peters A (2006) The selfish brain: competition for energy resources. Progress in Brain Research (153): 129-140

[14] Och U, Fischer T, Marquardt Th (2017) Ketogene Diät - eine Herausforderung für Patienten und Fachkräfte. ErnährungsUmschau; 64(8): M444-M457

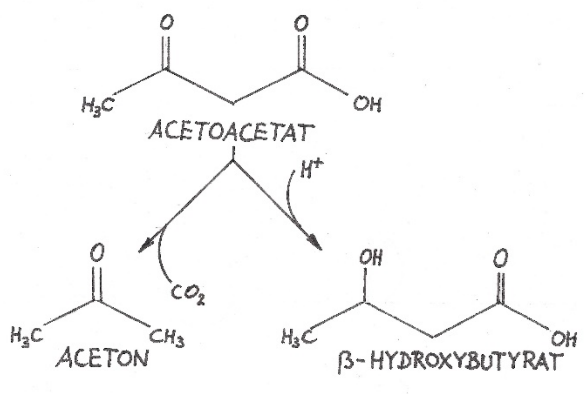

Fig 6: keto bodies for energy supply

The C4 keto bodies (especially ß-hydroxy butyrate) are high-energy substrates and additionally seem to function as specific messengers for metabolic adjustment in malnutrition.[15] Serum ketosis allows for a long-term utilization of storage fat and for avoiding substantial catabolism of proteins for glucose synthesis (gluconeogenesis). Fatty acids in human fat tissue constitute a reservoir of highly reduced electrons in molecules that are tightly packed and may be stored for long-term duration. In the metabolic condition of full ketosis humans can survive considerable periods of food shortage (marasmus) and will regain full health, if refeeding is appropriate.[16]

Healthy individuals are able to utilize protein-saving full ketogenesis during periods of food shortage.

The clinical symptoms of severe acute malnutrition without complications (Marasmus) with fat mobilization and ketosis, especially in children are:

- „little old man“
- massive loss of subcutaneous fatty tissue
- hunger
- no oedema
- normally pigmented hair

[15] Rojas-Morales P, Tapia E, Pedraza-Chaverri J (2016) β-Hydroxybutyrate: A signaling metabolite in starvation response? Cell Signal. 2016;28(8):917-923

[16] Keys A, Brožek J et al. (1950) The Biology of Human Starvation. Minneapolis: University of Minnesota Press

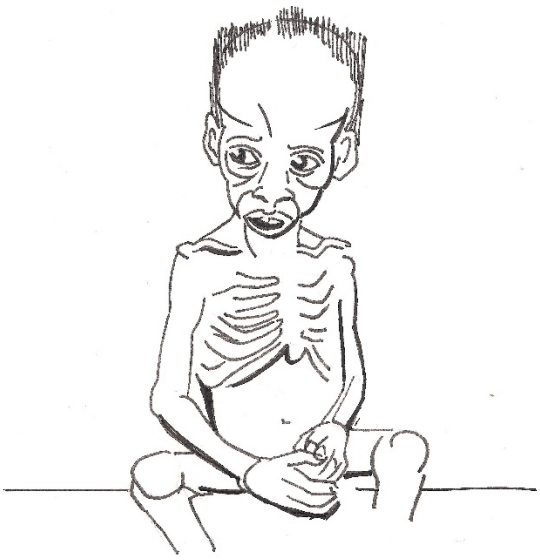

Fig 7: severe acute malnutrition without complications (Marasmus) (ICD 10 E41)

However, if pure food shortage is worsened by infections, burns, traumata or distress, the inflammation or stress markers will generate insulin resistance exactly like they do in type 2 diabetes mellitus. The insulin resistance will impair the glucose uptake into muscles and other organs.[17] As a consequence, serum glucose level will stay elevated or normal, so that serum insulin will stay elevated or normal likewise. Normal serum insulin will inhibit the metabolic shift to keto body utilisation and in the long run only glucose can be used as energy source. Since glucose formation needs amino acids as starting substance, this permanent gluconeogenesis will consume most essential proteins from muscle, blood and organs.[18]

Diseased or distressed individuals develop insulin resistance and cannot utilize protein-saving full ketogenesis during periods of food shortage.

Visible symptoms of massive protein losses are infections (lack of antibodies), depigmentation of hair and skin (lack of melanin), muscular weakness, organ failure, and eminently, oedema of lungs, abdomen and subcutaneous tissues (lack of serum albumin).

[17] Bandsma RH, Spoelstra MN, et al. (2011) Impaired glucose absorption in children with severe malnutrition. J Pediatr. 2011 Feb;158(2):282-7

[18] Heimburger DC (2006) Illness-Associated Malnutrition. In: Heimburger DC, Ard JD: Handbook of Clinical Nutrition, 4th ed., Philadelphia: Mosby Elsevier, 229-241

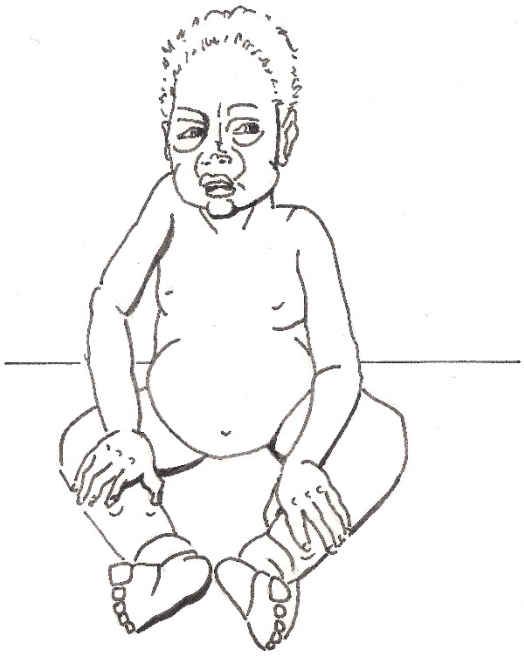

Fig 8: severe acute malnutrition with complications (Kwashiorkor) (ICD 10 E40)

The depletion of proteins additionally causes villous atrophy of the gut, complicating the situation even further by malabsorption and resulting chronic diarrhoea. The above described severe acute malnutrition with complications (Kwashiorkor) clinically has a very unfavourable prognosis. The typical symptoms of Kwashiorkor are:

- oedema of face, lungs, abdomen, subcutaneous tissue
- protruding abdomen
- depigmentation of hair and skin
- lethargy
- often no hunger

Numerous clinical observations of the different forms of severe acute malnutrition in the same family or group with exactly the same diet always indicated some other underlying metabolic disturbance like insulin resistance in addition to pure nutritional effects like „protein malnutrition“.

Fig 9: Marasmus (ICD 10 E41) (left) and Kwashiorkor (ICD 10 E40) (right) in the same family with the same nutrition in a Tanzanian refugee camp[19]

In any primary realimentation of severly malnourished patients the administration of small amounts of low carbohydrate food items like peanut butter (plumpynut®) is advisable in order to avoid any rapid insulin rise with resulting complications (refeeding syndrome).[20] Any re-alimentation with carbohydrates induces a rise of serum glucose and insulin. The insulin-facilitated uptake of any glucose molecule into the cells is convoyed by uptake of potassium, magnesium and phosphate. Life-threatening consequences in the serum are:

- hypopotassaemia
- hypomagnesaemia
- hypophosphataemia

Moreover, elevated insulin levels start anabolic pathways like glycogen synthesis, protein synthesis and lipogenesis, thus consuming phosphate, magnesium and thiamine (B1 vitamin). The insulin-mediated sodium retention in the kidneys completes the full-blown clinical picture of refeeding syndrome by severe hypernatraemia.

[19] clinical observation in IFRC Rwandan refugee camp referral hospital in Ngara / Tanzania in September, 1995, (J. Gardemann)
[20] Zauner C, Kneidinger N et al. (2005) Das Refeeding-Syndrom. Journal für gastroenterologische und hepatologische Erkrankungen 3 (4), 7-11

Any re-alimentation in severe acute malnutrition is at high risk of refeeding syndrome.

The details of biochemical pathways in severe acute malnutrition are not fully unravelled as yet. In addition to insulin and glucagon, the hunger-regulating hormone leptin seems to be of considerable importance in malnutrition, since low serum leptin correlates with a higher mortality rate.[21]

The corresponding guidelines of the World Health Organization still recommend carbohydrate-rich formula (F-75) at least for clinical in-patient realimentation in severe acute malnutrition.[22] This guidance does not fully reflect the current scientific discussion and evidence about malnutrition and refeeding.[23]

An evidence-based adjustment of the standard procedures of severe acute malnutrition and realimentation seems to be an important and urgently needed issue in nutritional paediatrics.

[21] Bartz S et al. (2014) Severe Acute Malnutrition in Childhood: Hormonal and Metabolic Status at Presentation, Response to Treatment, and Predictors of Mortality. J Clin Endocrinol Metab, 99(6), 2128-2137

[22] WHO (2013) Guideline: updates on the management of severe acute malnutrition in infants and children.

[23] Pulcini CD, Zettle S & Srinath A (2016) Refeeding syndrome. Pediatr. Rev. 37: 516–523