PRACTICAL ASPECTS OF NUTRITIONAL THERAPY AND BLOOD GLUCOSE LEVEL IN CRITICALLY ILL PATIENTS

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Summary
The main goal of nutritional support in critically ill patients is to minimize the negative protein balance by avoiding starvation, with the purpose of maintaining muscular, immune, and cognitive function, as well as to enhance recovery. Nutrition can be given either by the enteral or the parenteral route. Patients should be provided with nutritional substrates, because starvation or underfeeding in intensive care unit (ICU) patients is associated with increased morbidity and mortality. The guidelines of European Society for Clinical Nutrition and Metabolism (ESPEN) and Canadian Society for Clinical Nutrition (CSCN) recommend the initiation of enteral nutrition within 24-48 hours after the admission to ICU. Total parenteral nutrition (TPN), if indicated, should also be initiated within the first 24-48 hours after ICU admission. The minimal amount of carbohydrate required is about 2 g of glucose/body weight per day. Hyperglycemia above 180 mg/dl (>10 mmol/l) may have fatal consequences for critically ill patients and should also be avoided. Insulin therapy should be initiated for persistent hyperglycemia, with decision threshold no greater than 180 mg/dl, with a target glycemia range of 140 to 180 mg/dl for the majority of critically ill patients. Intravenous insulin infusions adjusted according to validated protocols with demonstrated safety and efficacy are preferred.

Keywords: nutritional therapy, blood glucose concentration, intensive care unit

INTRODUCTION
The metabolic response of trauma patients in critical condition includes the dysfunction of the carbohydrate metabolism, leading to the increase in blood glucose level. The response is exacerbated by the release of the counterregulatory hormones (1). Metabolic changes in critically ill patients lead to lower immunity and increased morbidity and mortality (2). Glucose blood level measurements and glycemia control, as well as choosing appropriate nutritional therapy, can improve the metabolism and decrease the risk of infection (3). Early nutritional therapy in critically ill patients is the standard care in ICUs (intensive care units) around the world. Critical condition is characterized by metabolic disorders, which result in increased muscle catabolism, reduced lean body mass, and hyperglycemia. Nutritional therapy in critically ill ICU patients should prevent both negative protein balance and overfeeding. Doing so improves nutritional outcomes. The indications for parenteral nutritional treatment should be narrowed. It is indicated when enteral nutrition is contraindicated or inadequate. Blood glucose fluctuations are an independent risk factor for infections and increased mortality in ICU patients (4, 5). Therefore, it is suggested that standard enteral formulas should be modified in order to achieve stable glucose levels. In order to avoid dangerous consequences of hyperglycemia, many ICUs lowered the acceptable lower limit of blood glucose (6, 7). The optimal blood glucose range, however, is not specified (8, 9). The prevention of hyperglycemia in ICU patients during nutritional treatment consists of applying special dietetic formulas, and the treatment of hyperglycemia – by insulin administration (10). Standard enteral formulas that are high in carbohydrates and low in fat may hinder glycemic control (11, 12). The modification of carbohydrate content and the addition of monounsaturated fats and fiber enables better glycemia control when compared with standard enteral diets (13-15).

TARGET GLYCEMIA RANGE
The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association recommend blood glucose range between 140 and 180 mg/dl in critically ill patients (16). In the majority of patients that are not in life-threatening condition, preprandial blood glucose level of 100-140 mg/dl and random blood glucose level under 180 mg/dl is recommended, under the condition that this range is safely achievable. It is recommended to maintain a higher glycemia in patients prone to hypoglycemia. However, it is advised that
patients with severe medical conditions have a narrower glycemia range. Despite the lack of prospective randomized controlled trials that would justify the benefits of intensive glycemic control in nutritionally treated patients, several observational and interventional studies in ICU patients suggest that maintaining blood glucose level under 150 mg/dl improves the outcomes of the patients (17).

PARENTERAL NUTRITIONAL TREATMENT

The relationship between hyperglycemia during parenteral treatment and worse treatment outcomes is known. The patients with hyperglycemia during total parenteral nutrition (TPN) are more likely to be admitted to ICU and to die, and their stay in the hospital is longer. It is not clear whether diabetes is an additional risk factor for complications in patients on nutritional treatment. In one study, patients with diabetes had higher risk of death, cardiac complications and systemic infections when compared with non-diabetic subjects (18). Other papers did not confirm the increased risk of complications and mortality in patients with diabetes, concluding that diabetes could even have a protective effects in spite of the higher glycaemia (19). The analysis of two prospective studies on a high number of patients on TPN revealed that diabetes does not increase the risk for complications of hyperglycemia in ICU patients (20). Nutritional guidelines recommend that early nutritional treatment should be considered in every patients who will be unable to eat for three or more days in ICU and 5-10 days in other department (21). Parenteral nutrition, if indicated, should be initiated within the first 24-48 hours after the admission to the ICU, because it has been proven that it does not increase mortality when compared with enteral nutrition (22). The metabolic demand of most patients can be met with the supply of 25-35 kcal/kg body weight/day depending on the severity of the disease (23), whereas some patients in critical condition may require 15-25 kcal/kg body weight/day (24). This diet requires providing about 200 grams of carbohydrates per day. Carbohydrates are the main source of calories in most TPN formulas. Glucose is the major metabolic fuel for the human body. Brain and peripheral nerves, renal medulla, leukocytes, erythrocytes, and bone marrow use glucose as their main source of oxidative energy. The minimal glucose intake per day that allows to meet the demand of the brain is estimated to be 100-120 grams. In stress conditions, such as disease or trauma, if the glucose is not provided with exogenous nutrition, the glucose will be generated in gluconeogenesis from the aminoacidic precursors obtained from proteolytic processes of skeletal muscle. During starvation, providing glucose intravenously helps to spare body protein, as it reduces the need for the proteolytic energy substrates for gluconeogenesis. In a patient exposed to stress, the maximum rate of glucose oxidation is 4-7 mg/kg body weight/min (i.e. 400-700 g/day for a patient weighing 70 kg). Both enteral and parentral nutritional treatment is effective in preventing the complications of starvation and malnutrition in hospital patients. In clinical practice, enteral nutrition is preferred due to higher risk of hyperglycemia and infection during TPN. The strategy of hyperglycemia treatment in patients requiring nutritional treatment should include diet modification, as well as effective and safe pharmacological treatment. Unfortunately, the fear of inducing hypoglycemia and the complexity of treatment of critical patients frequently excludes the introduction of such treatment. In order to prevent dangerous hypoglycemia, interdisciplinary training programs are conducted (25).

ENTERAL NUTRITIONAL TREATMENT

A few prospective randomized trials have evaluated the efficacy of strategies of prevention and treatment of hyperglycemia in patients fed enterally (26-32). The strategy of hyperglycemia control during enteral nutrition should include an assessment of caloric intake as well as pharmacological treatment with insulin. Enteral treatment is administered via a nasogastric tube, or rarer, a gastrostomy. A standard formula contains 1.2 kcal/ml and consists of protein, fat in the form of long-chain triglycerides, and carbohydrates. In contrast to the standard diet, in which carbohydrates provide 55-60% of total energy content, new formulas for diabetic patients provide more calories from nonsaturated fatty acids, with 35% of total energy provided from fat (33). Moreover, they contain more fiber (10-15 g/l) and fructose (33). Research on patients with diabetes indicated that lowering the carbohydrate intake in enteral diet decreased hyperglycemia and levels of HbA1c, as well as decreased insulin demand when compared to standard diet (34). However, there are no randomized trials on critical diabetic patients comparing standard enteral diets and diabetic enteral diets (35). Enteral nutritional treatment may lead to complications, such as bacterial colonization of the stomach and gastric retention, which may lead to aspiration of the gastric content into the lungs, as well as diarrhea. Additionally, an unexpected removal of the nasogastric tube and periodic cessation of enteral nutrition due to nausea or diagnostic process of gastrointestinal tract may increase the risk of hypoglycemia in patients treated with insulin (36).

HYPERGLYCEMIA

It has been shown that TPN improves nutritional status and reduces the number of hospital complications in critical patients. Specialized nutritional therapy is an established and cost-effective way to improve the outcome of patients in critical condition, with severe burns, paralytic ileus, trauma, abdominal surgery, pancreatitis and in patients requiring prolonged
mechanical ventilation. However, excessive glucose supply during TPN can cause metabolic disorders manifested by an increase of lipogenesis in the liver and adipose tissue, an increase of thermogenesis, an increase in glucose oxidation to carbon dioxide, resulting in an increased respiratory effort. Moreover, TPN is associated with the atrophy of the intestinal mucosa, overfeeding, hyperglycemia, increased risk of infections, and increased mortality. Hyperglycemia during TPN in hospital patients in an independent risk factor for hospital mortality and complications. Total energy requirement of most of the adult patients is estimated to be 20-25 kcal/kg body weight/day in the early phase of the disease. The energy requirement generally increases afterwards in the so-called anabolic phase, amounting to 25-30 kcal/kg body weight/day. Similar increase is seen in a starved patient – up to 25-30 kcal/kg body weight/day. The guidelines of scientific societies and expert groups recommend at least 2 g/kg/d of glucose, 0.7-1.5 g/kg/d of fat, and 1.3-1.5 g/kg/d amino acids in the parenteral nutrition formula, based on ideal body weight (22). It has been shown that glucose intake of more than 4 mg/kg/min in TPN leads to hyperglycemia in critical patients without diabetes. In prospective and retrospective studies, it has been demonstrated that glucose infusion faster than 4 mg/kg/min was associated with a higher incidence of hyperglycemia and the need for insulin in ICU patients (37). The only way to reduce hyperglycemia during TPN is to reduce the amount of glucose delivered to 150 g/d, which is sufficient to cover the metabolic needs of the brain and basic metabolic demand of other cells (23). The results of another study suggest that the reduction of amount of glucose delivered in TPN improves survival in ICU patients (38). In a group of 88 ICU, non-diabetic patients, the use of glucose infusion rate of 1.8±1.3 g/kg/d was associated with lower incidence of hyperglycemia, less frequent use of insulin and lower mortality when compared with a group of patients who received glucose infusion at rate 2.6±1.4 g/kg/d (39). Prospective randomized studies assessing whether the reduction of glucose amount in TPN lowers the risk of hyperglycemia and improves outcomes in critical patients. The time of introduction of nutritional therapy is also to be considered as a potential strategy for reducing the complication rate in critical patients. Large, multi-center European study (40) compared the early nutritional therapy (consisting of administering 20% glucose solution on the first day in ICU, combined enteral and parenteral nutrition in the second day, and continuation of the therapy) with a delayed nutritional therapy (consisting of administering 5% of the first day in ICU, enteral nutrition in the second to seventh day, and parenteral nutrition from the eighth day). Delaying the administration of parenteral nutrition to the eighth day caused a decreased risk of infections in ICU, shortened the time of organ dysfunction, shortened the time of stay in the ICU and reduced treatment costs. It is important to note that blood glucose level was 102-107 mg/dl in both groups, however, the amount of insulin administered was significantly lower in the group of patients who received delayed nutritional therapy. Another study reports that adding enteral nutrition to TPN that covers more than 30% of nutritional requirements significantly reduced glucose concentration in tissues and decreased insulin resistance when compared with patients who were administered exclusively TPN (41). The increase in complication rate related to TPN can be related to the type of fat used in the formula. In North America, the only fat that is approved for use in TPN formulas is soya fat with high concentration of linoleic and polyunsaturated fatty acids ω-6 (ω-6 PUFA). Due to the high content of linoleic acid, fat emulsion delivered from soybean can increase the production of eicosanoids – arachidonic acid derivatives – and enhance the inflammatory response during stress and injury (41, 42). The infusion of ω-6 (ω-6 PUFA may also cause immunosuppression, impair endothelial function, reduce the production of nitric oxide, and impair the function of autonomic nervous system. Concerns about potential side effects of ω-6 PUFA resulted in the development of alternative fat emulsions for parenteral nutrition formulas. Fat emulsions with low linolenic acid content – with linolenic acid replaced by fish oil, improved the safety profile of TPN. In a study comparing the outcomes of 100 ICU departments, no significant differences in the rate of infectious and non-infectious complications, length of hospital stay and ICU stay, glycemia control, inflammatory markers, and oxidative stress were found between groups of patients receiving TPN containing either standard soy fat emulsion or olive oil emulsion (43). Some studies suggested that the addition of glutamine and chromium to the TPN formula can result in enhanced glycemia control and clinical outcomes in critical patients. It has been shown that glutamine reduces hyperglycemia and insulin resistance related to high-fat diet. Prospective randomized double-blind trial has shown that the addition of the dipeptide glutamine-alanine to the TPN formula decreases the need for insulin in hyperglycemia treatment by 54% compared with standard TPN formula (44). The treatment of choice in hyperglycemia during TPN is insulin. Subcutaneous and intravenous administration of insulin are effective methods of treating hyperglycemia in these patients (45). In critical and unstable patients, continuous intravenous infusion is preferred, as it allows for more frequent dose adjustments. The addition of insulin to TPN is a safe and effective way to control glycemia during TPN. Target glycemia in diabetic patients during TPN can be achieved by administering insulin and carbohydrates in a 1:4 ratio, i.e. 1 unit of insulin to 4 grams of glucose (46). Little data
on hyperglycemia treatment in non-diabetic patients on TPN is available. It is recommended to initiate insulin treatment in a 1:20 ratio with subsequent titration to a maximum dose of insulin in the 1:1:1.5 ratio, until target glycemia of under 140 mg/dl is achieved (47). Hypoglycemia in patients in critical condition is associated with more frequent complications, longer hospital stay, and an increase in mortality. Moreover, the fear of hypoglycemia in hospital patients remains the major barrier for achieving optimal glycemic control. Patients on nutritional treatment have an increased risk of hyperglycemia due to the masking of the clinical signs of hypoglycemia. Hypoglycemia may be caused by insulin overdose, interruption of nutrition, reduction of glucocorticoid dose, recovery processes in an acute illness, reduction in infusion of pressor amines, and progressive organ dysfunction. In cases of persistent hyperglycemia, the use of insulin is recommended, and insulin must be administered in all patients with glycemia higher than 180 mg/dl (10 mmol/l), and target glycemia should be 140–180 mg/dl (7.77–10 mmol/l) in most patients in critical condition. Lower values, 110–140 mg/dl (6.11–7.77 mmol/l), can be recommended for surgical patients staying in ICU, under the condition of minimizing the risk for hypoglycemia (48).

RULES FOR THE IMPLEMENTATION OF NUTRITIONAL TREATMENT IN HOSPITAL

The rules for contractualization and implementation of nutritional treatments are frequently not understood by the medical community. The multiplicity of legal rules and their frequent changes cause many doubts regarding the way the Ministry of Health and National Health Fund formally defines the rules of implementation of nutritional therapy. The general rules of contractualization and implementation of nutritional treatment in hospital are described below. The general rules for implementation of nutritional treatment are defined in the Ordinance of the Minister of Health of the 28th August 2009 on guaranteed services in hospital care (Dz. U [Journal of Laws] 2009, No 140, item 1143, with further changes). In the Annex No. 1 to this Ordinance, it is specified that National Health Fund finances the following services: parenteral nutrition and enteral nutrition (49). Every hospital is obliged to assess the nutritional status:

§ 5a. 1. The healthcare provider providing services in the mode of hospitalization and planned hospitalization subjects all the beneficiaries admitted for treatment, with the exception of the hospital emergency department, to the screening assessment of their nutritional status (with the help of SGA – subjective global assessment, or NRS 2002 – nutritional risk score – for adults, and growth charts for children and youth), according to the regulations of the "Guidelines for parenteral and enteral nutrition" by the Polish Society of Parenteral and Enteral Nutrition or, in case of children, according to the regulations of the Polish Society of Clinical Nutrition of Children.

2. Beneficiaries who, based on the assessment referred to in paragraph 1., are diagnosed with an increased risk associated with nutritional status, should be subjected to nutritional assessment”.

Detailed rules for the implementation and settlement of the services are established by the National Health Fund in the Ordinance of the President of the National Health Fund No. 89/2013/DSOZ (50). Nutritional treatment services are the so-called summative services, i.e. they can be accounted for with other services, with the exception of nutritional treatment on the ICU unit, where the cost of the nutritional therapy is included in the cost of TISS points or TISS for children (Therapeutic Intervention Scoring System). The National Health Fund finances the following services related to nutritional treatment in the hospital care: enteral treatment, partial parenteral treatment, parenteral treatment, total parenteral treatment, immunomodulative parenteral treatment. Every hospital that provides nutritional services is obliged to keep additional records that are to be included in the medical history:

1. The screening nutritional assessment NRS or SGA (except for hospital emergency department),
2. Qualification for the enteral or parenteral nutrition (Annex 6a to the Ordinance 89/2013/DSOZ),
3. Card of parenteral nutrition / metabolic card (Annex 6b to the Ordinance 89/2013/DSOZ).

CONCLUSION

For each patient in a critical condition that is treated nutritionally, glucose blood level must be monitored and adequately modified. Target glycemia is achieved with the help of a developed protocol of glycemia control that is well known to the nursing and medical personnel. The frequency of blood glucose tests is dependent on the glycemia and the dynamic of its changes. The monitoring and control of glycemia during nutritional treatment of critical patients has a positive effect on the outcomes and reduces hospital mortality. It is essential to develop and implement standard procedures and protocols in order to achieve and maintain target glycemia during nutritional treatment of the ICU patients. In cases of persistent hyperglycemia, insulin should be administered, and the decision threshold must not be higher than 180 mg/dl (10 mmol/l), and target glycemia for critical patients should be 140–180 mg/dl (7.77–10 mmol/l). Lower target glycemia, 110–140 mg/dl, may be appropriate for patients on surgical ICUs, under the condition of minimizing the risk of hypoglycemia. Intravenous insulin infusion modified under a protocol with proven safety and efficacy is preferred. Frequent glycemia control are the basis of the treatment and minimize the risk of hypoglycemia.


49. Rozporządzenie Ministra Zdrowia z dnia 29 sierpnia 2009 r. w sprawie świadczeń gwarantowanych z zakresu leczenia szpitalnego (Dz. U z roku 2009 Nr 140, poz. 1143, ze zm.).

50. Zarządzenie Nr 89/2013/DSOZ Prezesa Narodowego Funduszu Zdrowia z dnia 19 grudnia 2013 r. w sprawie określenia warunków zawierania i realizacji umów w rodzaju: leczenie szpitalne (z załącznikami).

Conflict of interest
None

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