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Hyperglycemia in Hospital: Diagnosis, Classification, Clinical Implications and Treatment

Hastanede Yatan Hastada Hiperglisemi: Tanı, Sınıflama, Klinik Önemi ve Tedavisi

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Abstract

Hyperglycemia is a well-recognized risk factor for hospital-related complications, prolonged stay in the hospital and even mortality. The patients with in-hospital hyperglycemia may be categorized into three groups: i) Patients who have been diagnosed as having diabetes mellitus (DM) before admission; ii) Patients with newly diagnosed DM; and iii) Patients with stress hyperglycemia. The release of stress hormones, such as cortisol, catecholamines, glucagon, growth hormone and the related acceleration in gluconeogenesis and glycogenolysis, medications used for the treatment of primary diseases, such as glucocorticoids and vasopressors, are all claimed to be responsible for the development of in-hospital hyperglycemia. Glucose normalization with insulin therapy has been demonstrated to significantly decrease the morbidity and mortality in all the three groups. Therefore, it is recommended to monitor blood glucose levels for all hospitalized patients irrespective of the accompanying DM diagnosis.

Keywords: Hyperglycemia; hospital; stress

Özet

Hiperglisemi; hastane ilişkili komplikasyon sıklığını, hastanede kalış süresini ve mortaliteyi artırmaktadır. Hastanede yatan hastalarda, genel olarak üç farklı hiperglisemi grubu ile karşılaşılmaktadır: i) Yatış öncesinde diyabet tanısı olanlar, ii) İlk kez diyabet tanısı alan hastalar, iii) Stres hiperglisemisi olan hastalar. Hastanede yatan hastalarda, stres hormonlarının salınımının artışı (kortizol, katekolamin, glukagon, büyüme hormonu gibi), artmış glukoneogenez ve glukojenoliz, tedavi amaçlı glukokortikoit ve vazopresör ajan kullanımı gibi nedenler hiperglisemi gelişiminden sorumludur. Her üç grupta da insülin tedavisi ile glukoz normalizasyonu sağlanması ile mortalite ve morbidite de belirgin azalma sağlandığı gösterilmiştir. Bu nedenle, diyabet tanısı varlığından bağımsız olarak, hastanede yatan bütün hastaların kan glukoz takipleri yapılmalıdır.

Anahtar kelimeler: Hiperglisemi; hastane; stress

Introduction

Diabetes Mellitus (DM) is a devastating syndrome that is usually accompanied by co-morbidities, like, cardiovascular disorders, nephropathy, cancer, amputation of the extremities, etc.; all of which enhance the rate of hospitalization by three times than the people with normal glucose homeostasis (1). However, generally, one-third of the affected cases, in a given population, are not even aware that they have diabetes. In a recent retrospective study, 38% of the hospitalized patients exhibited hyperglycemia; 26% of whom had been diagnosed with DM before admission, whereas 12% had no diagnosis (2).

It is a well-known fact that hyperglycemia poses a potential risk for the hospital-related complications, may lead to prolonged hospital stay and may even cause mortality. For a simplified analysis, the patients with in-hospital hyperglycemia may be categorized into the following three groups (3):

i) Patients diagnosed with DM before admission to the hospital;

ii) Patients who do not report DM history, but are found to be hyperglycemic during hospital stay [fasting plasma glucose (PG) ≥ 126 mg/dL and/or random PG ≥ 200 mg/dL] and exhibit persistent hyperglycemia after discharge from the hospital. These patients are considered as newly diagnosed DM cases.

ii) Patients who do not report DM history, but are found to have hyperglycemia during their stay in hospital (fasting PG ≥ 126 mg/dL and/or random PG ≥ 200 mg/dL). Restoration of normal glucose homeostasis, with any intervention, takes place post hospital dis-

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Table 1. Classification of hyperglycemia in hospital

Known diabetes
Diabetes diagnosed before admission
Newly diagnosed diabetes
Fasting plasma glucose [PG]≥126 mg/dL and/or random PG≥200 mg/dL during hospital stay and confirmed after discharge
Hospital-related hyperglycemia
Fasting plasma glucose [PG]≥126 mg/dL and/or random PG≥200 mg/dL during hospital stay and that reverts to normal range after discharge

charge. This group is termed as the 'stress hyperglycemia' (Table 1).

The tendency of complications and mortality rates are higher among in-hospital patients with newly diagnosed DM and stress hyperglycemia than the others who have known DM. The glucose normalization with insulin therapy has been demonstrated to considerably reduce the mortality and morbidity in all the three hyperglycemic groups. Therefore, it is vital to monitor blood glucose levels of all the hospitalized patients irrespective of the accompanying DM diagnosis.

Hemoglobin A1c (HbA1c) is a valid method for the estimation of mean blood glucose levels within the preceding three months. Thus, this measurement should be performed in all the in-hospital cases with hyperglycemia (4). The HbA1c levels above 6.5% may indicate a diagnosis of DM in the in-hospital subjects. The former helps to discriminate between the unrecognized DM and the stress hyperglycemia. However, it should be noted that the blood loss and transfusion, hemoglobinopathies or hemolytic anemia may interfere with the HbA1c measurements. The diagnosis of diabetes becomes a challenge when the HbA1c levels are either normal or between the 5.6–6.4% range. The workup should be repeated following hospital discharge after the resolution of acute stress (5).

Mechanisms of hyperglycemia in hospital

The release of the stress hormones, such as cortisol, catecholamines, glucagon, growth hormone and the related acceleration in gluconeogenesis and glycogenolysis, medications used for the treatment of primary diseases, such as glucocorticoids, vasopressors, are all claimed to be responsible for the occurrence of in-hospital hyperglycemia (Figure 1). Glucose elevation in response to the acute disease in patients without any glucose metabolism disorders is known as 'stress hyperglycemia' (6). The affected individuals have been shown to have a worse prognosis than the ones with diabetes, normoglycemia or the newly diagnosed diabetes. High glucose, itself, may further lead to clinical deterioration via the impairment of immune functions and aggravated oxidative stress. However, it is not clear whether hyperglycemia, itself, is a marker for poor prognosis or it is a marker for severity of the underlying disease (7).

Under physiological circumferences, normoglycemia is maintained via uptake of glucose in tissues, increase in glycogen synthesis and the suppression of gluconeogenesis in response to the insulin secretion. The metabolic processes that stimulate hyperglycemia under stressful conditions are very complex. The stress hormones, which are together called as the contra-insulinergic system, increase the plasma glucose via the stimulation of glycogenolysis and gluconeogenesis and the inhibition of peripheral glucose uptake (8). Glucagon and epinephrine inactivate glycogen synthase via increasing cyclic adenosine monophosphate (c-AMP), thereby increasing the levels of glycogen phosphorylase. Glucagon also induces increased synthesis of a rate-limiting enzyme, phosphoenolpyruvate carboxykinase (PEPK), which is involved in gluconeogenesis.

Under critical conditions, following acute phase, a devastating period begins, which is characterized by low energy consumption with high protein catabolism, peripheral vasoconstriction and increased sympathoadrenal activity. Hyperglycemia is provoked via the release of catecholamines and the induction of hepatic glycogenolysis (9). Following this period, an increase in protein catabolism in skeletal muscles, energy consumption, and systemic vasodilatation occurs. During this period, hyperglycemia is maintained via increased hepatic glucose production and insulin resistance (10). The proinflammatory cytokines, viz., tumor necrosis factor (TNF), interleukin–1 and interleukin–6, are secreted in response to critical disease and lead to the development of insulin resistance (11). Lactate and alanine are the main substrates of hepatic gluconeogenesis. Alanine, which is also released from skeletal muscles, enters into the alanine-glucose cycle and potentiates glucose production. The stress-induced fatty acid mobilization causes the production of glycerol, which is then converted into glucose. Insulin-mediated glucose disposal is decreased in the peripheral tissues as a result of decreased glucose transporter–4 (GLUT–4) production at the peripheral tissues (12).

Hypothalamic-pituitary-adrenal axis (HPA) is stimulated in response to the stress caused by the acute disease, which in turn activates the sympathetic adrenomedullary system. The corti-

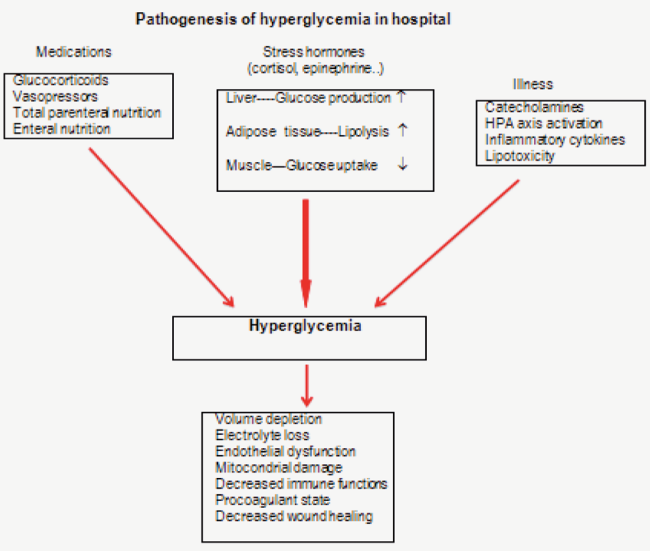

Figure 1: Pathogenesis of hyperglycemia in hospital

cotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) stimulate the secretion of cortisol from the adrenal glands. The proinflammatory cytokines also potentiate the induction of HPA (13).

Pathological conditions, like hypokalemia and pancreatitis, may halt insulin secretion and result in hyperglycemia. Hepatic fibrosis that is observed during cirrhosis may cause hyperglycemia via the prevention of glucose storage.

The medications that are used for the treatment of the acute disease may also cause in-hospital hyperglycemia; among which, glucocorticoids are the major ones, owing to their powerful anti-inflammatory properties. These exert diabetogenic effect via promoting gluconeogenesis, peripheral insulin resistance, and the production of free fatty acids. These may increase the risk of diabetic ketoacidosis and hyperglycemic hyperosmolar non-ketotic state for the in-hospital patients. Beta-blockers (metoprolol, propranolol, etc.) may cause hyperglycemia via decreasing the secretion of pancreatic insulin. They may further minimize the peripheral clinical signs of hypoglycemia that may cause fatal outcomes in the unconscious intensive care unit (ICU) patients who have been treated for hyperglycemia. Thiazide diuretics can impair the cellular uptake of glucose and pancreatic insulin secretion. Octreotide, vasopressor agents, and total parenteral nutrition may also cause hyperglycemia in the ICU patients. Quinolone antibiotics (levofloxacin and gatifloxacin) are known to cause hyperglycemia via unknown mechanisms. Calcineurin inhibitors (cyclosporine, sirolimus, and tacrolimus), which are used to prevent of allograft rejection, inhibit calcineurin and thereby, the pancreatic beta cell production, which may result in elevated glucose levels in the organ transplant recipients. Protease inhibitors, which are used as antiretroviral agents, are also proposed to decrease insulin sensitivity (14).

Thus, to conclude, it can be stated that there are several underlying diseases and treatment-related contributing factors that cause hyperglycemia in the hospitalized patients.

Hyperglycemia Among Critically Ill Patients in Intensive Care Units (ICU)

Hyperglycemia, irrespective of the diabetic status, is a potential risk factor for mortality and morbidity to both medical and surgical ICU patients. Hyperglycemia, with its toxic environment, may worsen the clinical presentation of the underlying disease (2). A retrospective study on 1826 critically-ill general ICU patients, revealed that the mortality rates of normoglycemic cases were lower than the hyperglycemic ones (15). Prognosis is even worse among the ones with stress hyperglycemia (2). In a meta-analysis, the mortality rates of the hyperglycemic ICU patients, who were hospitalized for acute stroke without prior DM diagnosis, were found to be higher (16).

Hyperglycemia may potentiate glucose levels via osmotic diuresis, thereby resulting in decreased glomerular filtration rate (GFR). The latter leads to mitochondrial and endothelial damage via the production of free oxygen radicals and inhibition of nitric oxide (NO), respectively. Hyperglycemia, itself, interrupts immune functions via production of proinflammatory cytokines, increases vascular permeability and activates leukocyte-thrombocyte functions (17). The elevated levels of plasminogen activator inhibitor–1 (PAI–1) and fibrinogen cause thrombocyte aggregation and hypercoagulability. Phagocytosis, chemotaxis and bactericidal functions of leukocytes diminish with increasing blood glucose levels (18). Inhibition of collagen synthesis may result in the retardation of wound healing process in patients with hyperglycemia.

Overall, if all the interfering factors (as mentioned above) are considered, the diagnosis of diabetes seems difficult in hospital cases. At times, it may become impossible to detect whether the case is of unrecognized diabetes or stress hyperglycemia in critically ill ICU patients. Nevertheless, whatever the case may be, the treatment for hyperglycemic condition must be initiated and the final diagnosis should be postponed, even after the patient's discharge from the hospital, until complete resolution of the stressful condition is achieved.

The treatment of Hyperglycemia in general ICUs

Subcutaneous (SC) insulin injection and oral anti-diabetics are not recommended in critically ill ICU patients, especially those with hypotension and shock. Since the insulin absorption rate cannot be foreseen, thus the risk of hypoglycemia is high among such subjects. Instead, intravenous insulin infusion is considered safer for the ICU patients, who may also have feeding problems. Insulin not only controls blood glucose levels but also lowers the high circulating proinflammatory cytokine levels, thus exerting anti-inflammatory effects (19).

As per the currently available medical literature, various protocols have been described for the infusion of insulin; the different protocols have similar guidelines for hypoglycemia frequency, duration of ICU and total hospital stay, and mortality (20). A clinician may select the most cost-effective protocol for his/her clinic. The paramedical staff must be educated and trained for properly following the chosen protocol. The insulin infusion rate should be corrected with the frequent bedside glucose monitoring in order to avoid hypoglycemia. Serum potassium levels should be checked and replaced wherever required.

In clinics, where intravenous infusion pumps are unavailable, glucose-insulin-potassium may be delivered in the same solution, which is known as the 'GIK' solution.

Although a tight control of blood glucose has been considered to decrease mortality in critically ill ICU patients, this approach brings the risk of severe hypoglycemia which may also be life-threatening for some patients. The studies that have been performed on coronary ICU patients, among the cases with acute myocardial infarction, have demonstrated that intensive insulin treatment aiming tight glucose control is capable of increasing mortality (21–24). The NICE-SUGAR study, which has compared the effects of tight glycemic control (PG = 81–108 mg/dL) with conventional control (PG < 180mg/dL), among the critically ill patients, has clearly shown that tight control leads to higher life-threatening hypoglycemia and mortality rates. In this high-impact trial, it was recommended that the glycemic targets should be kept in the range which can avoid poor prognosis and hypoglycemia for these cases (25). In another prospective study, conducted on 1548 surgical ICU patients, tight

glucose control was shown to increase mortality and morbidity. The clinical diagnosis of hypoglycemia can be very difficult in these cases, which are generally under sedation and mechanical ventilation. Unrecognized hypoglycemia may cause cardiac arrhythmia, convulsions, and irreversible brain injury (3). Accordingly, glycemic targets should not be kept too low for the critically-ill ICU patients.

Insulin treatment, preferably intravenous insulin infusion, should begin if plasma glucose levels exceed 180 mg/dL in ICU patients. Glycemic targets should be kept between 140–180 mg/dL range. It can be kept between 110–140 mg/dL in some patients, if it does not increase the risk of hypoglycemia (20). Young patients with cardiac surgery, acute ischemic heart, and cerebrovascular disease may benefit from the 110–140 mg/dL targets (3, 26). Plasma glucose levels below 110 mg/dL have been shown to exert additional benefits (3,25–28).

The patients with diabetes undergo more surgical procedures and the stress caused by the surgeries triggers hyperglycemic state. Perioperative hyperglycemia has been demonstrated to increase morbidity and mortality (29,30). It is a well-established risk factor for post-operative sepsis and delayed wound healing. Counter–regulatory hormones, released in response to the surgical stress, predispose the susceptible patient to the hyperglycemic condition. Anesthesia, medications, and dehydration due to nausea and vomiting caused by stress-related vagal stimulation may provoke dehydration and worsen the clinical presentation of the afflicted person.

Appropriate medical nutrition therapy to provide sufficient calories, i.e., 15–25 cal/kg/day, is one of the most crucial key points in critically-ill patients. Surgical ICU patients require frequent enteral or parenteral feeding; solutions for which are rich in carbohydrates, thus potentiating hyperglycemia. Moreover, parenteral feeding solutions increase the blood glucose levels via bypassing the intestinal glucoregulatory system (31). Therefore, oral feeding is recommended as early as possible in hospital settings. Plasma glucose levels above 140 mg/dL are considered as a cut-off for initiation of insulin treatment in the ICU patients, who are under parenteral feeding. Insulin may be either added to the daily feeding solutions or given separately using infusion pumps (1). Eighty percent of the total daily insulin requirement may be administered via parenteral feeding solutions as regular insulin. Total daily insulin dose may be given as basal insulin as insulin glargine once daily or insulin Detemir twice daily to those who are fed on continuous enteral infusions. Likewise, similar recommendations may be followed for bolus enteral feeding via nasogastric or gastrostomy.

Multiple subcutaneous insulin injections are recommended for the patients who exhibit significant amelioration and can consume oral food under insulin infusion. Nutritional status, accompanying the medications and co-morbidities should be taken into consideration while calculating the SC insulin dose. There are various protocols for the transition from intravenous insulin infusion to multiple SC insulin regimes, as per the currently available medical literature (32,33). The most commonly recommended protocol is giving 80% of the total insulin infusion dose. Generally, half of the calculated dose is given as basal insulin at once, while the rest of the insulin is divided into three doses and administered as prandial insulin before meals. Basal insulin dosages comprise of insulin glargine, Detemir, and insulin neutral protamine Hagedorn-NPH, and may only rarely be given twice daily. Regular insulin, insulin Aspart, insulin lispro, and insulin glulisine may be chosen as the prandial insulin.

Intravenous insulin infusion should be stopped 1–2 h after the first subcutaneous insulin injection in an attempt to prevent hyperglycemia during follow-up (34). Carbonhydrate content of the meals may better be kept stable so as to provide a better glucose control. It is worth noting that the insulin requirement of the patients under glucocorticoid treatment is higher, which should be lowered in parallel to the decreasing glucocorticoid dosages.

It has been shown that an exclusive management of in-hospital hyperglycemic patients helps in reducing the duration of hospital stay and the frequency of recurrent hospitalization, along with increased patient satisfaction (35). Thus, it is recommended that the glucose regulation plan should be shaped and updated in parallel to the individual patient requirements, beginning from the admission to discharge from the hospital. Furthermore, appropriate patient treatment regarding medical nutrition therapy, hypoglycemia management, and insulin injection therapy must be properly provided.

Ethics

Externally peer-reviewed.

Authorship Contributions

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