Chapter 44

Hyperglycemic emergencies - epidemiological, physiopathological aspects and therapeutic management

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ABSTRACT
Diabetes mellitus (DM) corresponds to a metabolic immunity in which there is a definition of resistance1, corresponding to peripheral resistance to DM, respectively. The disease has a high prevalence and can lead to acute and numerous complications worldwide, as well as chronic; in this sense, diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHE) correspond to the main acute complications of the disease; diagnosis and immediate treatment due to the severity of the same condition by them. In addition, both complications are called hyperglycemic emergencies, precisely because of their signs and symptoms, high blood glucose can occur in a diabetic patient. Furthermore, there are several causes of CAD and EHH; however, the main causes established in the literature are the presence of infections and the inappropriate use of insulin in patients with DM. In addition, proper patient management in these circumstances involves early administration of intravenous fluids, insulin therapy, electrolyte replacement, and recognition and treatment of precipitating causes. However, despite the existence of numerous protocols involved in the diagnosis and treatment of DKA and HHE, little has been done to prevent these complications; thus, there is an urgent need to better clarify diabetic patients about their disease and its likely complications, as well as alert them to possible warning signs, so that they can seek assistance as early as possible, reducing the likelihood of negative outcomes.

Keywords: acute complications, diabetic ketoacidosis, diabetes mellitus, hyperosmolar hyperglycemic state, metabolic disorders.

1 INTRODUCTION

Diabetic ketoacidosis (Cad) and hyperosmolar hyperglycemic status (HHS) correspond to frequent complications of diabetes mellitus (DM) and have high morbidity and mortality - despite the existence of well-established diagnostic and treatmentprotocols. Moreover, in epidemiological terms, the annual incidence of Cad in the United States of America (USA) is about 8 episodes per 1,000 admissions of patients with DM; it should also be highlighted that the costs of CAD care for patients in the U.S. increased to US$5.1 billion in 2014, corresponding to US$20-26,000 per admission (GOSMANOV et al., 2018; REWERS et al., 2018; ELZOUKI; ELEDRISI, 2020; GOSMANOV et al., 2021).

Moreover, bothcomplications are related to dm decompensation factors, and the main causes are inadequate insulin therapy and the presence of infections. In these circumstances, there is marked reduction of circulating insulin in plasma, which promotes the action of hormones contract gluttonythat lead to the production of ketone bodies and metabolic acidosis. The common clinical presentation of Cad and HHS occurs by hyperglycemia, its signs and symptoms include polyuria, polyphagia, polydipsia and weight loss, in addition to weakness and physical signs d anddecrease in intravascular volume - such as dry oral mucosa, sunken eyeballs and deficient skin turgor, in addition to hypotension and shorthand. Finally, for the correct management of the patient, adequate insulin therapy and strict control of glycemia, as well as vascular volume and electrolyte concentrations - mainly potassium - (GOSMANOV et al., 2018) are essential; REWERS et al., 2018; ELZOUKI; ELEDRISI, 2020; GOSMANOV et al., 2021).

2 OBJECTIVE

The aim of this article is to gather information, through analysis of recent studies, about the aspects inherent to hyperglycemic emergencies, especially diabetic ketoacidosis and hyperosmolar hyperglycemic status.

3 METHODOLOGY

Scientific articles indexed in the Latindex and MEDLINE/PubMed databases were conducted between 2017 and 2021. The descriptors used, according to "MeSH Terms", *were: diabetic ketoacidosis, diabetes mellitus and hyperglycemic hyperosmolar state.* A total of 281 articles were found, according to the inclusion criteria: articles published in the last 5 years, full texts, free and type of study. Papers paid and with publication date in a period longer than the last 5 years were excluded from the analysis, sand 11 articles pertinent to the discussion were collected.

4 EPIDEMIOLOGY

Hyperglycemic emergencies are acute metabolic complications that have important morbidity and mortality in patients with type 1 diabetes mellitus (DM1) and diabetes mellitus (DM2) in addition to high economic expenditure with hospitalizations. Cad and HHS represent the two ends of the spectrum of

clinically decompensated diabetic patients, differing mainly in the severity of acidosis, dehydration and ketosis. In contrast to CAD in which acidemia and ketonemia are the greatest characteristics, these are more limited in HHS (MILANESI et al., 2018; GOSMANOV et al., 2021).

Cad is the most common hyperglycemic emergency and occurs most often among those withDM1, but almost 1/3 of cases occur among those with DM2. Although CAD mortality rates have decreased to low levels overall, it remains high in many developing countries. Omission of insulin and infection are the two most common precipitantes of its cause. Non-adhering to insulin treatment may be responsible for up to 44% of CAD presentations, while infection is less frequently observed as a triggering factor. Proper management of Cad requires hospitalization for fluidreplacement, electrolytes, insulin therapy, as well as identification and treatment of the underlying precipitating event, along with frequent monitoring of the patient's clinical and laboratory states (GOSMANOV et al., 2018; ELZOUKI; ELEDRISI, 2020; REWERS et al., 2018).

Moreover, the rate of hospitalizations due to HHS is lower than that of Cad and is less than 1% of all hospitalizations related to DM. HHH mortality ranges from 5 to 20% and is higher at extremes of age and in those patientswith other associated comorbidities. In addition, HHS is more prevalent in type 2 diabetics and in about 7 to 17% of cases it is the initial presentation classically seen in institutionalized elderly patients with decreased perception of the home or inability to walk to obtain free water as needed. HHS is extremely rare as a first presentation in patients with DM1 and infections are the main precipitants of this complication (MILANESI et al., 2018; REWERS et al., 2018).

Moreover, decompensated DM imposes a heavy burden in terms of savings and outcomes for the patient. Timely diagnosis, comprehensive clinical and biochemical evaluation, and effective management are the key to successful resolution of Cad and HHS. Understanding and alerting to possible special situations, such as presentation of CAD or HHS in the comatose state, possibility of mixed acid-base disorders that are hindering the diagnosis of Cad, and risk of cerebral edema during therapy are important to reducethe risks of complications without affecting the recovery from hyperglycemic crisis. The identification of factors that precipitated CAD or HHS during hospitalization should help prevent subsequent episodes of hyperglycemic crisis (REWERS et al., 2018; GOSMANOV et al., 2021).

5 PHYSIOPATHOLOGY

HhS and Cad represent two outcomes of decompensated DM with similar pathophysiology: in both there is a decrease in insulin action, either by reducing insulin secretion in Cad or by its ineffective action onHH, with simultaneous elevation of counterregulatory hormones - against insulinopenia, glucagon, catecholamines, cortisol and growth hormone, which stimulate glucose production through glycogenolysis and glycogenogenesis in the liver, in addition tothe reduction of peripheral glucose use. However, HHS usually occurs with a lower degree of insulinopenia compared to Cad and they differ mainly in the severity of acidosis, ketosis and dehydration (GOSMANOV et al., 2018; MILANESI et al., 2018).

In CAD, the organism in catabolism promotes the breakdown of glycogen stocks, hydrolysis of triglycerides of adipose tissues and mobilization of muscle amino acids. The released triglycerides and amino acids become substrates for the production of glucose and ketone bodies by the liver. Hyperglycemia - the result of increased gluconeogenesis and glycogenolysis and decreased use of glucose by liver, muscle and fat - and ketonemy - resulting from the breakdown of triglycerides (lipolysis) in free fatty acids serving as a substrate for the formation of ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) - play central roles in the development of this metabolic decompensation that presents as metabolic acidosis with elevated anion gap (GOSMANOV et al., 2018; (GOSMANOV et al., 2021).

Moreover, in HHS there is enough insulin to contain lipolysis, ketogenesis and the sharp elevation of counterregulatory hormones, however, not enough to stimulate glucose use and to contain marked hyperglycemia, leading to loss of water and electrolytes due to glycosuria, which causes dehydration, decreased renal perfusion, decreased glucose clearance and exacerbation of hyperglycemia, may culminate in changes in the level of consciousness. In addition, in The AD, there is also the association between hyperglycemia and thrombotic state, consequent to high levels of pro-inflammatory cytokines, lipid peroxidation markers and procoagulant factors such asplasminogen-1 ativad or inhibitor (PAI-1) and C-reactive protein (CRP). In HHS, prothrombotic risk may also be high due to the increase in pro-inflammatory cytokines, reactive oxygen species and PAI-1 (MILANESI et al., 2018; GOSMANOV et al., 2021).

Furthermore, as stated above, inadequate insulin therapy (poor treatment or insufficient insulin dose) and the presence of infection are the two most common precipitating factors in the development of ADD or HHS. However, numerous other fatores can be cited: myocardial infarction, stroke, pulmonary embolism, pancreatitis, alcohol use and illicit drugs, drugs that cause the release of counterregulatory hormones, drugs such as corticosteroids, thiazoic diuretics, sympathetic mimetic agents and second-generation antipsychotic agents. More recently, two new classes of drugs have emerged as triggers of CAD, sodium-glucose cotransporter 2 inhibitors (ISGLT-2), such as canagliflozin, dapagliflozin and empagliflozin, and classes of immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab , used in the treatment of cancer (GOSMANOV et al., 2021).

6 CLINICAL MANIFESTATIONS

The clinical picture of Cad usually evolves rapidly, where symptoms begin within a few hours. On the other hand, in HHS, signs and symptoms have insidious onset, and may occur over days and weeks. The common clinical presentation of Cad and HHS occurs by hyperglycemia, where signs and symptoms include polyuria, polyphagia, polydipsia and weight loss, in addition to weakness and physical signs of decreased intravascular volume, such as dry oral mucosa, sunken eyeballs and efficient cutaneous turgor(MILANESI et al., 2018; REWERS et al., 2018; PEREZ-GUZMAN et al., 2021).

Due to the state of dehydration and acidosis, patients may experience hypotension and taquicardia. To compensate for acidosis, the patient manifests the Kussmaul breathing pattern, where the individual presents a slower and deeper breathing. In addition, other fairly common signs and symptoms are the presence of ketone breath, nausea, vomiting and abdominal pain. Patients usually have normal body temperature or mild hypothermia, regardless of the presence of infection. Therefore,a careful search for a source of infection should be carried out even in the absence of fever. In addition, neurological status in patients with CAD can range from full alert to deep lethargy and coma. However, changes in mental status in Cad areless frequent than in HHS and the relationship between the fall in the level of consciousness and severity of hyperosmolarity or causes of Cad has been controversial. Some studies have suggested that pH is the cause of mental status changes; others have concluded thatmolarity is responsible for the comatose state (MILANESI et al., 2018; REWERS et al., 2018; PEREZ-GUZMAN et al., 2021).

7 DIAGNOSIS

In view of the suspicion of Cad or HHS, it should initially be included for diagnostic confirmation, laboratory tests of plasma glicosis, electrolytes, ketonas, complete blood count and blood gas analysis. In a second moment, if necessary, additional tests such as electrocardiogram, chest X-ray, glycated hemoglobin and cultures should be requested. From this, Cad is characterized by hyperglycemia, presence of ketone bodies and acidosis; glycemic values usually exceed 250mg/dL, however, about 10% of patients may have levels within normal limits or even below normal. Ketone bodies will be present in urine and/or serum, in which it is recommended to evaluate beta-hydroxybutyrate levels due to their high levels of sensitivity and specificity. Therefore, acidosis is characterized by pH values $\leq$ 7.30 and bicarbonate $\leq$ 18mmol/L. However, unlike what happens in DOH, HHS is accompanied by severe hyperglycemia and hyperosmolarity with preservation of pH and bicarbonate values. Glucose levels are > 600mg/dL, pH > 7.30 and bicarbonate > 20mEq/L, with negative ketone bodies (BALDRIGHI et al., 2018; GOSMANOV et al., 2018; MARTIN; SURANI, 2019; SELF et al., 2020).

8 DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hyperglycemic seizures includes other causes of ketosis, acidosis, and hyperosmolarity. For example, metabolic acidosis may be severe in alcoholic ketoacidosis and total ketone bodies are typically higher than in diabetic ketoacidosis. Patients on diets with low food intakedevelop sanirate ketosis, but acidosis in these cases is mild. However, in these two situations, hyperglycemia does not exceed 200 mg/dL and bicarbonate is below 18 meq/L (GOSMANOV et al., 2018).

In addition, it is important to rule out other causes of metabolic acidose with elevated anionic hiatus, such as lactic acidosis, advanced chronic renal failure, and the intake of drugs such as salicylate, methanol and ethylene glycol. The intake of isopropyl alcohol, in turn, can cause considered ketosisl with increased

anionic hiatus, in the absence of metabolic acidosis and with a tendency to hypoglycemia (GOSMANOV et al., 2021).

9 TREATMENT

Due to the lack of randomized controlled trials for the treatment of HHS, the American Diabetes Association (ADA) has developed guidelines that combine the treatment of HHS and CAD. In this sense, the pillars of the conduct in the face of a hyperglycemic emergency consist of circulatory volume replacement, hydroelectrolytic correction and hyperglycemia management. Initially intravenous fluid therapy (IV) should be done with normal saline solution (sodium chloride 0.9%) at a rate of 15–20 ml/kg (about 1–1.5 L) during the 1st hour; later, the correction flow and the type of fluid will be based on the patient'scondition. After correction of hypovolemia, volume replacement will be performed according to the corrected serum sodium level, if low concentration (<135 mmol/L), replacement will be done with sodium chloride at 0.9%; if high (≥135 mmol/L), it will be replaced by 0.45% sodium chloride (MILANESI, A. et al, 2018; ELEDRISI, M.S. & ELZOUKI, A.N., 2020).

Moreover, serum potassium concentration >5.2 mmol/L (5.2 mEq/L) does not indicate electrolyte supplementation, but serum levels should be monitored because potassium intake in cells, and consequent serum decrease, be facilitated by volumetric expansion, acidosis correction and insulin therapy. At ≤5.2 mmol/L levels, potassium replacement should be performed to achieve the goal of maintaining it at 4–5 mmol/L. Initially, replacement should be with 20–30 mEq of potassium in each liter of fluid IV. Concentration <3.3 mmol/L contraindicates insulin infusion as it may lead to decreased serum electrolyte concentration as previously cited (ELEDRISI, M.S. & ELZOUKI, A.N., 2020).

In addition, insulin is usually administered intravenously, starting with a regular insulin bolus at a dose of 0.1 unit/kg body weight, and then within 5 minutes followed by a continuous infusion of regular insulin of 0.1 unit/kg/h. When blood glucose reaches ≤ 11.1 mmol/L (200 mg/dL), 5% dextrose should be added together with 0.45% sodium chloride at a rate of 150–250 ml/h to maintain blood glucose concentration at 8.3–11.1 mmol/L (150–200 mg/dL) (ELEDRISI, M.S. & ELZOUKI, A.N., 2020).

10 EUGLYCEMICA KETOACIDOSIS

CAD is a medical emergency that deserves close attention in Intensive Care Units (ICUs) and should be diagnosed as early as possible to reduce the potential risk of life. In addition, diabetic patients - mostly type 1 - hiperglycemic, with metabolic acidosis and ketonemia diagnosed on arterial or venous blood gas may be diagnosed without major difficulties due to the exuberant clinic previously exposed. However, there is a type of CAD not so common that it can delayits diagnosis, which is euglycemic Cad (NASA et al., 2021).

Patients with DM1, or even patients with DM2, may present it, provided they are exposed to specific risk factors. They are: pregnancy, prolonged fasting, alcoholic libation, demais acute stressful conditions,

such as myocardial infarction, heart failure, infections, trauma, major surgeries, or prolonged physical activity. In these circumstances, there is disproportionate secretion of insulin counterregulatory hormones (glucagon, cortisol, catecholamines and GH). Hormonal imbalance in search of new urgent sources of glucose causes increased glycogenolysis, hepatic gluconeogenesis, ketogenesis by lipolysis in adipose tissue (from the metabolization of free fattyacids) and proteolysis (amino acids). The released ketone bodies (beta-hydroxybutyrate, acetoacetate and acetone) cause metabolic acidosis (NASA et al., 2021).

This mechanism associated with the depletion of glucose stocks, especially in situations of prolonged fasting - including preoperative fasting - , strenuous physical activity in patients with carbohydrate deficits - due to their insufficient intake, misuse of applied insulin or pregnancy - or use of new oral antidiabetics, cantrigger cad r without hyperglycemia. Moreover, the use of ISGLT-2 as the main cause of euglycemic Cad is noteworthy because the SGLT-2 cotransporter promotes 80 to 90% of glucose resorption in the proximal renal tubule and its inhibition is responsible for oslogour and osmimic diuresis with hypovolemia. Dehydration and carbohydrate deficit promote increased glucagon release with ketogenesis and this time, euglycemia. Thus, this class of antidiabetics therefore demands care and attention to prescrição. It is avoided for patients with DM1 and, when prescribed for DM2, requires careful guidance regarding the risks of CAD (NASA et al., 2021).

Treatment follows the same principle as Cad with hyperglycemia. Therefore, it demands close management of acidosis, glycemia and electrolytes. Volume replacement (with balanced crystalloides) with correction of dehydration and electrolyte disturbances, with intravenous weighted insulin and intermittent monitoring of capillary glycemia and arterial or ve nosa blood gases. The resolution is defined by pH > 7.3, > 15 mmol/L and ketone level in the blood < 0.6 mmol/L. In a nutsand, diabetic patients with metabolic acidosis in the emergency room or ICU and with risk factors deserve attention regarding ketonemia, equal euglycemic. The diagnosis, even if of exclusion, should be early (NASA et al., 2021).

11 CONCLUSION

DM is a chronic disease that can cause several health problems; ADM and HHS are acute complications of the disease that require immediate identification and management, due to the fact that they correspond to severe metabolic complications that lead to death, caso are not readily corrected. Moreover, the pathophysiology of these metabolic disorders is well understood and the treatment is all designed in protocols that guide the correct conduct in these cases. However, it is necessary that patients with DMbecome better aware about these complications and well oriented about the circumstances that can trigger Cad and HHS, as well as attentive to the signs and symptoms of severity that indicate a decompensation of the disease.

REFERENCES

BALDRIGHI, M. et al. **Hyperglycemic Hyperosmolar State: A Pragmatic Approach to Properly Manage Sodium Derangements.** Current Diabetes Reviews, v. 14, n. 6, p. 534–541, 10 out. 2018.

ELZOUKI, A.-N.; ELEDRISI, M. **Management of diabetic ketoacidosis in adults: A narrative review.** Saudi Journal of Medicine and Medical Sciences, v. 8, n. 3, p. 165, 2020.

GOSMANOV, A. R. et al. **Diabetic Ketoacidosis.** [Internet]. South Dartmouth (MA). 21 abr 2018.

GOSMANOV, A. R. et al. **Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.** [Internet]. South Dartmouth (MA). 9 maio 2021.

MILANESI, A. et al. **Hyperglycemic Hyperosmolar State**. [Internet]. South Dartmouth (MA). 1 aug 2018.

MORAES, A. G.; SURANI, S. **Effects of diabetic ketoacidosis in the respiratory system.** World Journal of Diabetes, v. 10, n. 1, p. 16–22, 15 jan. 2019.

MUSSO, G. et al. **Diabetic ketoacidosis with SGLT2 inhibitors.** BMJ, p. m4147, 12 nov. 2020.

NASA, P. et al. **Euglycemic diabetic ketoacidosis: A missed diagnosis.** World Journal of Diabetes, v. 12, n. 5, p. 514–523, 15 maio, 2021.

PEREZ-GUZMAN, M. C. et al. **Continuous Glucose Monitoring in the Hospital.** Endocrinology and Metabolism, v. 36, n. 2, p. 240–255, 30 abr. 2021.

REWERS, A. et al. A**cute Metabolic Complications in Diabetes.** Diabetes in America. 3rd edition. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018 Aug.

SELF, W. H. et al. **Clinical Effects of Balanced Crystalloids vs Saline in Adults With Diabetic Ketoacidosis.** JAMA Network Open, v. 3, n. 11, p. e2024596, 16 nov. 2020.