Hyperglycemic emergencies: Clinical features and diagnostic criteria. A systematic literature review

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ABSTRACT
Diabetes Mellitus is a chronic condition in which the manifestation occurs when blood glucose levels are elevated due to the inability of the body to produce insulin in adequate quantity or efficiently use the insulin produced. This metabolic dysfunction can be attributed to several mechanisms, varying according to the specific type of diabetes. Methodology: This is a systematic literature review constructed by searching the PUBMED, VHL and CAPES Periodicals Portal, using the terms "Diabetic Ketoacidosis", "Hyperglycemic Hyperosmolar State", "Hypoglycemia", "Diabetic Emergencies" in Portuguese, English, Spanish and German. Results: Of the 229 articles found, only 10 were selected according to the guiding question and the eligibility criteria. Conclusion: The study conducted on hyperglycemic emergencies brought a wide range of fundamental information to understand and manage these conditions. Through the analysis of the selected studies, it was possible to obtain insights into the complications and possible sequelae associated with these emergencies. In short, research on diabetic emergencies establishes a solid knowledge base for health professionals and researchers, contributing to improve the early identification, appropriate treatment and prevention of these complications, aiming to improve the quality of life of individuals living with diabetes.

Keywords: Diabetic ketoacidosis, Hyperosmolar State, Hyperglycemic, Hypoglycemia, Diabetic Emergencies.

1 INTRODUCTION

Diabetes Mellitus (DM) is a condition characterized by the manifestation of several signs and symptoms, which involve the impairment of the metabolism of fats, proteins and carbohydrates. This metabolic dysfunction occurs due to different mechanisms, depending on the specific type of DM. As a result, there is an increase in blood glucose levels and a reduction in the ability of cells to properly utilize glucose. Consequently, there is a significant increase in the use of proteins and fats as alternative energy sources, which leads to weight loss (GUYTON; HALL, 2002 apud LADEIA et al, 2020).

It can be characterized as a chronic condition that manifests itself when blood glucose levels are elevated due to the body's inability to produce insulin in adequate quantity or to effectively utilize the insulin produced. This dysfunction can be classified according to its pathophysiology, that is, the underlying mechanisms involved.

Type 1 Diabetes Mellitus (T1DM) is an autoimmune and polygenic disease that results in the destruction of the β cells of the pancreas, leading to deficiency in insulin production. This condition mainly affects children and adolescents, and about 88,000 Brazilians are diagnosed with T1D, representing about 10% of diabetes cases. Importantly, people with T1D need to make use of insulin throughout their lives to control blood glucose levels (BRAZILIAN DIABETES SOCIETY, 2019-2020).

The development of T1DM is thought to be triggered by the presentation of peptides from the β cells of the pancreas by antigen-presenting cells (APCs). These APCs, carriers of these autoantigens, migrate to the pancreatic lymph nodes, where they interact with self-reactive CD4+ T lymphocytes. This interaction triggers the activation of self-reactive CD8+ T cells. After activation, these CD8+ T cells return to the pancreatic islets and destroy β cells expressing immunogenic autoantigens on the surface of the class I molecules of the major histocompatibility complex. The destruction of β cells is further aggravated by the release of pro-inflammatory cytokines and reactive oxygen species by innate immune cells. These inflammatory processes contribute to a cycle of continuous destruction of β cells and the progression of the disease (DIMEGLIO; EVANS-MOLINA; ORAM, 2018).

Type 2 Diabetes Mellitus (DM2) has a multifactorial etiology, which involves genetic and environmental factors, with inadequate diet, sedentary lifestyle, lifestyle and lack of physical exercise being the main triggering elements. T2DM has a higher incidence in middle-aged people, usually from the age of 40, and corresponds to approximately 90 to 95% of all cases of diabetes. Importantly, in T2DM, there is a combination of insulin resistance (when the body's cells do not respond adequately to the action of insulin) and deficiency in insulin secretion by the pancreas. This condition results in high blood glucose levels. The adoption of a healthy lifestyle, with a balanced diet and regular practice of physical exercises, is essential for the control of DM2 (FERREIRA et al. 2020).

The pathophysiology of type 2 diabetes mellitus (T2DM) is largely driven by the induction of insulin resistance in skeletal muscle, liver and adipose tissues. Insulin resistance in skeletal muscle is particularly relevant, since this tissue is responsible for the efficient removal of glucose after meals. In T2DM, insulin resistance in skeletal muscle significantly limits the ability to clear glucose from the blood. At the cellular level, insulin resistance in skeletal muscle manifests itself through several mechanisms. This includes a deficit in the recruitment of GLUT-4 glucose transporter proteins to the plasma membrane, which is mediated by the action of insulin. In addition, there is a reduced glycogen storage capacity, a decrease in glucose oxidation and impaired mitochondrial function (JAVEED and MATVEYENKO, 2018 apud MAGNUSSON et al. 1992).

These changes impair glucose metabolism, resulting in elevated blood glucose levels in T2D. In addition, the liver also plays an important role in the pathophysiology of T2DM, since insulin resistance in this organ leads to an excessive production of glucose by the liver, further contributing to the hyperglycemia observed in this condition (JAVEED and MATVEYENKO, 2018 apud MAGNUSSON et al. 1992).

Pregnancy can also be a diabetogenic catalyst, causing the emergence of Gestational Diabetes Mellitus through the activity of the placenta, which produces hyperglycemic hormones and placental enzymes that degrade insulin, and triggers an increase in insulin production and resistance, which may evolve with dysfunction of pancreatic β cells. This condition can be temporary, existing only during some periods of pregnancy, most often in the second and third trimesters, or persist even after childbirth being an important risk factor for the development of DM2, requiring immediate intervention of the multidisciplinary health team (SOCIEDADE BRASILEIRA DE DIABETES, 2019-2020).

DM leads to acute and chronic complications, including Diabetic Ketoacidosis (DKA), Hyperosmolar Hyperglycemic Syndrome (HHS), and hyper- and hypoglycemia during treatment. DKA is the most common acute or hyperglycemic emergency complication of T1DM, but it also occurs in T2DM, happens as a result of peripheral resistance, partial or absolute insulin deficiency, and is commonly associated with triggering clinical conditions. (MÉNDEZ et al., 2018).

That said, the following question arises: what are the main characteristics, symptoms, causes and diagnostic criteria related to diabetic emergencies?

2 GENERAL OBJECTIVE

Identify and describe the main clinical features of diabetic emergencies.

2.1 SPECIFIC OBJECTIVES

- Understand the underlying causes of diabetic emergencies;
- Explore the diagnostic criteria used to identify and differentiate diabetic emergencies;

- Recognize the warning signs of diabetic emergencies.

3 METHODOLOGY

This is a systematic literature review. To answer the guiding question, a search was conducted in the following databases: National Library of Medicine (PubMed), Virtual Health Library (VHL), CAPES Periodicals Portal between January 2022 and March 2022, always using the Boolean operator AND for the pairing of the following Health Sciences Descriptors (DeCS): "Diabetic Ketoacidosis", "Hyperglycemic Hyperosmolar State", "Hypoglycemia", "Diabetic Emergencies" for the databases described above.

As inclusion criteria for the studies, we opted for articles available in full and free of charge, in the languages Portuguese, English, Spanish and German, published from 2017 to 2022. The exclusion criteria were: articles that did not address the research theme or that did not answer the guiding question, studies in editorial format and duplicate articles in more than one database **(Table 1).**

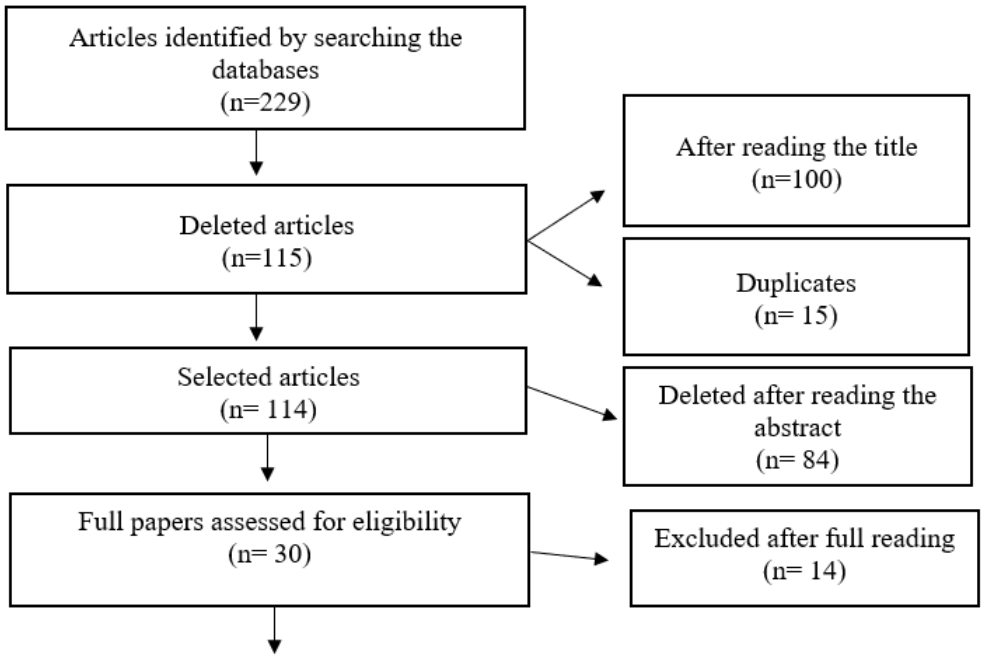
Table 1. Publications found between the years 2017 to 2022 according to the PUBMED, VHL and CAPES databases.

DESCRIPTORS	PUBMED	VHL	CAPES
Diabetic Ketoacidosis AND Hyperglycemic Hyperosmolar State AND Hyperglycemic Hyperosmolar State AND Hypoglycemia AND Diabetic Emergencies	08	13	198

After performing the electronic search, the publications were submitted to an initial pre-selection by reading the titles and, subsequently, based on the abstracts. Then, the previously selected articles were read in full, allowing the identification of the studies that composed the final sample of this review. A total of 229 studies were found and 10 articles were selected from the following databases:

Figure 1 shows the flowchart referring to the selection process of the articles that were part of the final sample of this selection.

Figure 1. Flowchart representative of the article selection process.



For data collection, the analysis of the full article occurred descriptively, in order to gather knowledge about the theme addressed in the review, for this a data collection form was filled out according to the previously validated model, which includes the identification of the article and methodological characteristics (SOUZA et al, 2010).

4 FINDINGS

Chart 1 presents the characterization of the 10 included productions, highlighting the predominance of studies published in the period from 2017 to 2022, covering several scenarios in the international context.

Table 1 - Presentation of the characteristics of the articles included in the Integrative Review.

N	Authors (year)	Main findings
1	FORTOFOIU M, et al. (2022)	New diagnostic strategies and therapeutic approach to emergencies in the evolution of patients with diabetes mellitus (Review)
2	SANTOMAURO, et al. (2022)	Euglycemic diabetic ketoacidosis (E-CAD) is an uncommon but potentially life-threatening condition and an emergency that can occur in people with T1D, T2D.
3	MODI, et al. (2017)	Euglycemic DKA represents a challenge for physicians, as patients who have normal BG levels in ketoacidosis may be neglected, leading to a delay in appropriate treatment strategies.
4	Mendéz R, et al. (2018)	Acute complications of Diabetes Mellitus, practical vision for the physician in emergencies: Diabetic Ketoacidosis, Hyperosmolar State and Hypoglycemia.
5	DHATARIYA K, et al. (2017)	Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemia Hyperosmolar State (HHS): Advances in Hyperglycemic Crisis Management (UK vs. US)

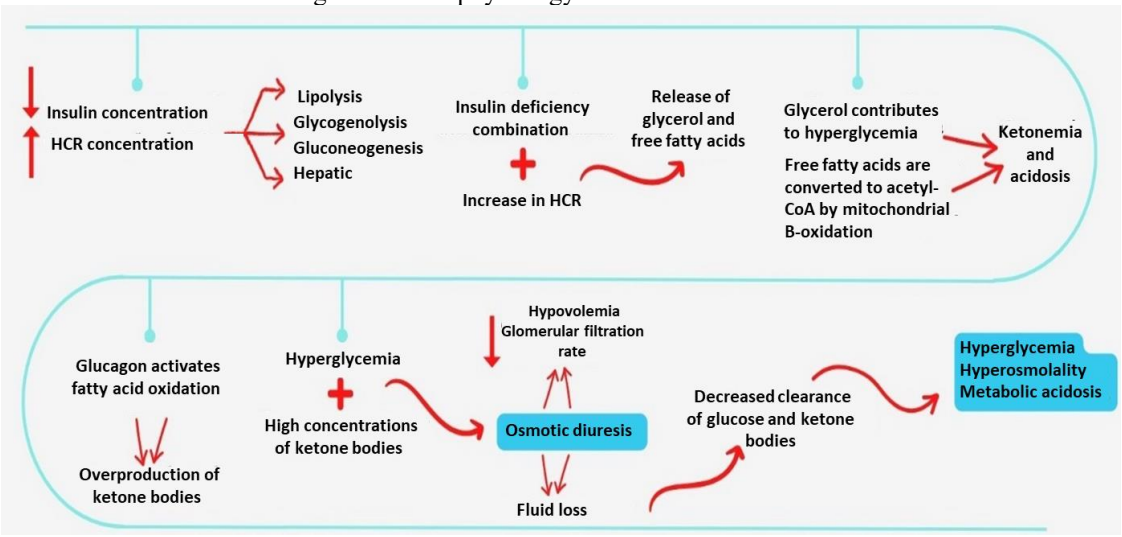
6	KARSLIOGLU F, et al. (2019)	Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients
7	ROMÁN-GONZALEZ, et al. (2018)	Inpatient management of patients with T2DM can become very difficult and complex if there are no clear guidelines for insulin initiation and titration.
8	KUTZ, et al. (2017)	In this large cohort of emergency medical department patients, admission hyperglycemia was strongly associated with adverse clinical course in people without diabetes
9	ALGHAMDI M, et al. (2021)	Administration of hyperosmolar hyperglycemic state in the emergency department; Literature review
10	JACOBI J (2019)	Management of endocrine emergencies in the ICU

5 DISCUSSION

5.1 METABOLIC EMERGENCIES ARISING FROM DIABETES

5.1.1 Diabetic Ketoacidosis

Figure 1- Pathophysiology of Diabetic Ketoacidosis



Source: Author's compilation

*The pathophysiology of DKA begins when low levels of insulin concentration associated with high concentrations of counterregulatory hormones, such as catecholamines, cortisol, glucagon, and growth hormone (GH) promote insulin-opposed metabolic pathways in both the liver and peripheral tissues. The increase in gluconeogenesis at the hepatic level due to the high availability of gluconeogenic precursors such as the amino acids alanine and glutamine (a result of accelerated proteolysis and decreased protein synthesis), lactate (due to increased muscle glycogenolysis) and glycerol (a result of increased lipolysis). Increased glycogenolysis and decreased utilization of glucose by peripheral tissues (MÉNDEZ et al, 2018, apud HIRSCH; EMMETT et al. 2017). *

According to Dhatariya et al (2016), the combination of insulin deficiency and increased counterregulatory hormones in DKA leads to uncontrolled release of glycerol and free fatty acids into the circulation from adipose tissue by increased lipolysis. Glycerol is used for gluconeogenesis, thus contributing to the maintenance of hyperglycemia, while free fatty acids are converted to acetyl-CoA by β-oxidation in mitochondria. In addition, hyperglycemia and DKA are also the result of an inflammatory state characterized by elevated pro-inflammatory cytokines, markers of oxidative stress (TNF-α, IL-6, IL-8, CRP), reactive oxygen species, lipid peroxidation, plasminogen-1 activator

inhibitor, and free fatty acids (MÉNDEZ et al, 2018, apud KENKATESH; PILCHER; PRINS et al. 2017).

In diabetic patients, the precipitating events for DKA are lack of exogenous insulin due to poor adherence to treatment or subtherapeutic doses; infections such as urinary tract infections (UTIs), pneumonia, dental or skin abscesses, sepsis, viral syndromes, pelvic inflammatory disease and malignant otitis externa, and underlying medical conditions that cause release of hormones against regulators, such as appendicitis, pancreatitis, abdominal inflammation, trauma, pregnancy, cerebrovascular disease or acute myocardial infarction (AMI), as well as the use of some drugs and substances that cause metabolic decompensation, pancreatitis, abdominal inflammation, trauma, pregnancy, cerebrovascular disease or acute myocardial infarction), as well as the use of some drugs and substances that cause metabolic decompensation, such as cocaine, alcohol, sympathomimetic drugs, atypical antipsychotics, corticosteroids and thiazide diuretics, etc. (MÉNDEZ et al, 2018, apud UMPIERREZ; Korytkowski. 2016).

Euglycemic Diabetic Ketoacidosis (E-CAD) is an uncommon but potentially life-threatening condition and an emergency that can occur in people with T1D, T2D, or even in people without diabetes. It presents a diagnostic challenge because, as blood glucose is not very high, there may be delays in recognizing the diagnosis and initiating treatment. The E-DKA is defined by the presence of glycemia < 200 mg/dL, with pH < 7.3, bicarbonate < 18 mEq/L, anion gap 10-12 mEq/L and high concentrations of ketonemia. The measurement of ketonemia is preferred over ketonuria. Ketonemia indicates the serum level of β-hydroxybutyrate, which rises earlier and more markedly than aceto acetate, measured in the urine. Measurement of ketonemia is especially important if the patient is on SGLT2 inhibitors. In this situation, there may be a reduction in ketonuria by increased tubular reabsorption of aceto acetate, despite the increase in ketonemia (SANTOMAURO et al. 2022).

CAD-E results from absolute or relative insulin deficiency, associated with an increase in counterregulatory hormones (glucagon, cortisol, catecholamine, and growth hormone). In E-DKA, insulin deficiency and insulin resistance are milder, so glucose overproduction and underutilization are lower than in DKA, limiting the increase in blood glucose levels. The mechanism of ECAD-is due to the decrease in hepatic glucose production during the fasted state, and the urinary increase in glucose excretion induced by an excess of counterregulatory hormones, the former being the most common reason. In ISGLT2-induced E-CAD, renal glycosuria contributes to even lower plasma glucose levels (SANTOMAURO et al. 2022).

The American Diabetes Association (ADA) adopts, as a diagnostic criterion for DKA in adults, blood glucose > 250 mg/dL, pH < 7.3, bicarbonate (HCO3) < 18 and ketone bodies present in the urine. The clinical presentation of DKA begins with some or all of the following symptoms: polyuria, polydipsia, nausea, vomiting, abdominal pain, visual disturbances, lethargy, sensory alteration,

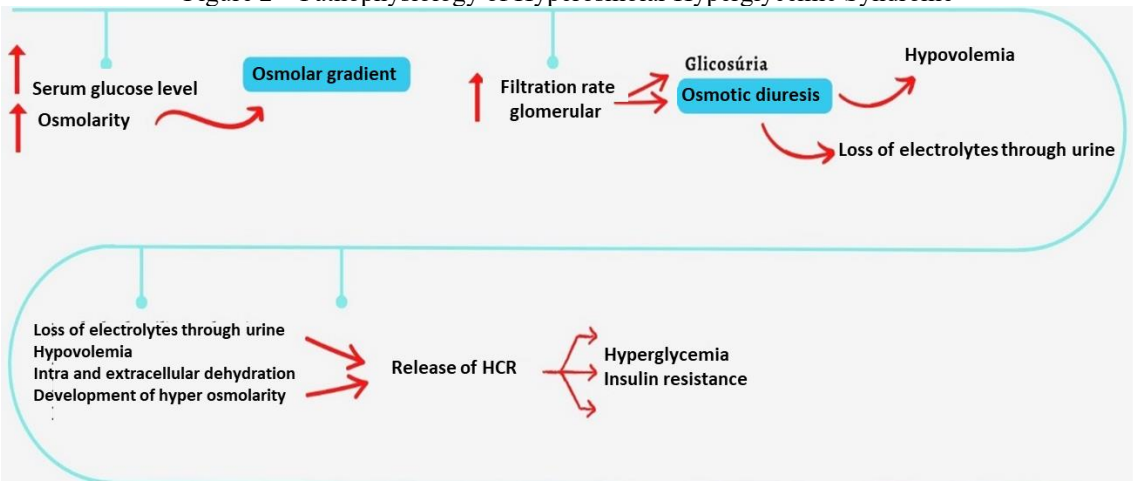
tachycardia, tachypnea, and Kussmaul breathing, with a fruity odor on the breath. Patients usually present with severe volume depletion with orthostatic hypotension. Patients with E-CAD secondary to treatment with an SGLT2 inhibitor may have less polyuria and polydipsia due to the milder degree of hyperglycemia and may present with malaise, anorexia, tachycardia, or tachypnea with or without fever (MODI; AGRAWAL; MORGAN. 2017).

The criteria for the diagnosis of DKA begin on physical examination, when in the presence of acidosis, hyperpnea can be observed and, in more severe situations, Kussmaul's breathing. Dehydration with dry and cold skin, dry tongue, hypotonia of the eyeballs, cold extremities, agitation, hyperemic face, muscle hypotonia, rapid pulse, and blood pressure ranging from normal to hypovolemic shock may occur. Initial laboratory evaluation of patients with DKA should include determination of plasma glucose, phosphorus, urea, creatinine, ketonemia, electrolytes, including anion-gap calculation, urinary analysis, ketonuria, blood gas analysis, blood count, and electrocardiogram. When necessary, chest X-rays and blood and urine cultures are ordered. The last ADA recommendation, dated 2009, adopts, as a diagnostic criterion for DKA, blood glucose ≥ 250 mg/dL,1 but some patients have smaller increases in blood glucose concentration values after retention or decrease of insulin dose in the presence of diseases that decrease food intake (SOCIEDADE BRASILEIRA DE DIABETES, 2019-2020).

5.2 HYPEROSMOLAR HYPERGLYCEMIC SYNDROME

HHS is defined by severe hyperglycemia, elevated serum osmolarity and dehydration, the pathogenesis of HHS differs from DKA in that a more severe degree of dehydration is present due to osmotic diuresis and an absence of significant ketosis/ketone.

Figure 2 – Pathophysiology of Hyperosmolar Hyperglycemic Syndrome



Source: Author's compilation

* The pathophysiology of SHH begins when there is an extreme elevation in serum glucose level and hyperosmolarity with significant absence of ketosis. After an increase in the level of serum glucose and extracellular osmolarity, an osmolar gradient is formed, which draws water from the cells. Initially, the glomerular filtration rate (GFR) increases, which leads to glycosuria and osmotic diuresis, consequently, this glycosuria prevents the progression of severe hyperglycemia,

provided that the GFR is normal. Eventually, when osmotic diuresis continues and hypovolemia develops, it results in a progressive decline in GFR and worsening of hyperglycemia (KARSLIOGLU et al. 2019; ALGHAMDI et al. 2021). *

Unlike what occurs in DKA, in HHS there is a higher concentration of hepatic and circulating insulin with low levels of glucagon, preventing the development of ketogenesis and ketoacidosis, especially because patients with HHS have some functional pancreatic β cells. The passage of intracellular to extracellular fluid resulting from osmotic gradients can cause hyponatremia (reduction in plasma sodium concentration) in the early stage of HHS. Osmotic diuresis can lead to the loss of potassium, sodium, magnesium, and phosphate through the urine. The consequences of the loss of electrolytes in the urine, hypovolemia, intra and extracellular dehydration and the development of hyper osmolarity, leads to the release of counterregulatory hormones, which exacerbates hyperglycemia and contributes to insulin resistance. The total body water deficit is estimated at 7 to 12L in the SHH, representing a loss of 10% to 10% of the total body weight. Elderly patients with HHS usually have enough insulin to protect them from lipolysis and the consequent abundance of ketoacidosis, but do not have enough insulin to protect them from hyperglycemia (ALGHAMDI et al. 2021).

The laboratory diagnoses for HHS according to the ADA are blood glucose greater than 600 mg/dL, effective serum osmolarity greater than 320 mOsm/L, and absence of ketoacidosis (pH > 7.3 and bicarbonate > 18 mEq/L). HHS has an insidious onset, the clinical picture is related to hyperglycemia and increased serum osmolarity, causing signs and symptoms of dehydration and changes in the level of consciousness. In general, patients report a history of polyuria, polydipsia, weakness, blurred vision, and progressive decline in the level of consciousness. In more severe cases, there may be focal neurological symptoms, seizures, hypotension, shock, and/or acute renal failure. Nausea and vomiting are uncommon in HHS. Infection can occur without the presence of fever due to peripheral vasodilation (BRAZILIAN DIABETES SOCIETY, 2019-2020).

5.3 HYPOGLYCEMIA

Acute hypoglycemia is a common consequence of treatment with insulin or oral hypoglycemic agent with reduced glucose intake, but may arise from errors in insulin dosing, liver failure (reduced gluconeogenesis), decreased insulin levels, or changes in corticosteroid therapy without changes in insulin regimen. Severe hypoglycemia can lead to seizures, brain or heart injuries, early recognition of signs and symptoms (sympathetic stimulation, sweating, anxiety, confusion of visual changes, aphasia, etc.) leads to earlier therapy. However, recognition of hypoglycemia may be difficult in patients who are sedated or who have a blunted hypoglycemic response with chronic diabetes and autonomic failure or with concurrent therapy with β-blockers. Hypoglycemia can be classified as mild 55 to 69 mg/dL, moderate 50 to 54 mg/dL, or severe (less than 40 mg/dL), and all are associated with a mortality in the

Intensive Care Unit (ICU) 2 to 3 times higher than normoglycemia, and any value lower than 70 mg/dL should be a warning value for the treatment of the patient and evaluation of the insulin and nutritional regimen (JACOBI, 2019).

According to Román-Gonzalez et al 2018, hypoglycemia is a complication with a wide spectrum of manifestations, as it can be asymptomatic or can be accompanied by autonomic symptoms, pallor, blurred vision, sweating, dizziness, asthenia, adynamia, tachycardia and nervousness, asthenia, adynamia, tachycardia and nervousness; it can also manifest with loss of consciousness, and even death if it is not identified in time. The main risk factors for the development of hypoglycemia are advanced age, chronic kidney disease, malnutrition, medication and diabetes without adequate control. The annual prevalence of severe hypoglycemia is approximately 30% in individuals with T1DM. It is higher in those with risk factors, including strict glycemic control, impaired awareness of hypoglycemia, and increased duration of DM. It is also common during sleep, i.e. nocturnal hypoglycemia. The diagnosis of hypoglycemia is based on three criteria (Whipple's triad): symptoms and signs suggestive of hypoglycemia (feeling faint, dizzy and sweating); low blood sugar levels during seizures (<70 mg/dl); and resolution of symptoms after glucose administration (FORTOFOIU M, et al. 2022).

5.4 HYPERGLYCEMIA

Hyperglycemia is considered as a condition that has an important prognosis, since it affects normal physiology in multiple systems; It is also an independent risk factor for mortality in both diabetics and non-diabetics, especially in acute coronary patients with acute coronary syndrome of any kind. The acute effects of hyperglycemia are not so decisive for the establishment of the hospitalization of diabetics, unless the cause of hospitalization is the acute decompensation of diabetics due to hyperosmolar hyperglycemia, that is, HHS or DKA, conditions in which dehydration is an important factor (ROMÁN-GONZALEZ et al. 2018).

Hyperglycemia leads to certain chronic metabolic changes, such as direct involvement of the entire endothelium, procoagulant tendency, peripheral axonal damage, loss of self-regulation of autonomic functions over time and activation of pro-inflammatory signaling pathways, among the latter are increased oxidative stress, deficiency of platelets and erythrocytes, protein glycation, debilitated phagocytosis, change to the polyol pathway, increased TNF alpha and other cytokines. Taking into account all this, it is to be expected that diabetic patients are prone to infections, which affect them much more markedly, and that, management is sometimes more difficult due to hypoperfusion, endothelial involvement and immune dysfunction (ROMÁN-GONZALEZ et al. 2018).

Hyperglycemia leads to impaired performance of the polymorphonuclear neutrophil cell, a key factor in innate immunity. Reduced levels of neutrophilic degranulation and exaggerated coagulation

were also found during human hyperglycemia, with decreased lipopolysaccharide-stimulated messenger ribonucleic acid (mRNA) of different pro-inflammatory cytokines compared to normoglycemic people. Diabetes also affects the adaptive immune system, with decreased T-cell function and decreased antibody production (KUTZ et al. 2017). Insocomial hyperglycemia is defined by blood glucose values greater than 140 mg/dL.

6 CONCLUSION

The present study on hyperglycemic emergencies revealed a wide range of information essential for the understanding and management of these conditions. The literature review addressed the main characteristics, causes and diagnostic criteria related to diabetic ketoacidosis, hyperosmolar state syndrome and hyperhypoglycemia.

Through the analysis of the selected studies, it was possible to understand the complications and potential sequelae of these conditions. In addition, recent advances in the diagnosis and treatment of these conditions were discussed, aiming to improve clinical outcomes and quality of life of patients.

In short, research on diabetic emergencies provides a solid knowledge base for health professionals and researchers, contributing to improve the early identification, appropriate treatment and prevention of these complications, aiming to improve the quality of life of individuals with DM.

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