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DIABETIC KETOACIDOSIS: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, MANAGEMENT AND NEUROLOGICAL IMPACTS IN THE EMERGENCY SETTING

Maila Baracioli Catanozi
Universidade de Vassouras
Vassouras - Rio de Janeiro

Prof. Orientador
Universidade de Vassouras
Vassouras - Rio de Janeiro

Abstract: Diabetic ketoacidosis (DKA) is a critical medical emergency associated with diabetes mellitus, especially type 1, which requires immediate treatment to avoid serious complications. The condition results from insulin deficiency, leading to uncontrolled hyperglycemia, excessive production of ketone bodies and metabolic acidosis. Initial treatment focuses on rapid correction of dehydration with isotonic saline solutions, blood glucose control and insulin administration, followed by a switch to glucose-containing solutions. Studies indicate that DKA can cause significant cognitive decline, especially in children, and suggest that factors such as cerebral hypoperfusion and neuroinflammation may be more relevant to brain damage than the rate of fluid administration. The review also highlights the importance of biomarkers, such as metalloproteinases, in understanding blood-brain barrier dysfunction. Effective treatment must consider both metabolic and neurological aspects to improve clinical outcomes.
Keywords: Diabetes; ketoacidosis; emergency.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious and potentially fatal complication of diabetes mellitus, most commonly associated with type 1 diabetes, although it can also occur in patients with type 2 diabetes under conditions of extreme metabolic stress (Kitabchi et al., 2009). DKA results from a severe insulin deficiency, which leads to an uncontrolled hyperglycemic state, accompanied by the excessive production of ketone bodies and the development of metabolic acidosis (Pasquel & Umpierrez, 2014). This condition is a medical emergency and requires immediate treatment to prevent serious complications such as hypovolemic shock, acute renal failure and even death (Dhatariya et al., 2020).

The pathophysiology of DKA involves the interaction between absolute or relative insulin deficiency and the increased release of counter-regulatory hormones such as glucagon, cortisol, catecholamines and growth hormone (Chiasson et al., 2003). This situation generates a significant increase in lipolysis, leading to the release of free fatty acids, which are converted into ketone bodies in the liver, resulting in metabolic acidosis (Umpierrez & Korytkowski, 2016). The resulting hyperglycemia also promotes osmotic diuresis, which causes dehydration and electrolyte loss, further exacerbating the clinical picture (Kitabchi et al., 2009).

The most common causes of DKA include infections, which account for around 30% to 50% of cases, followed by omission or failure to administer insulin, myocardial infarction, trauma and other situations that increase the demand for insulin (Fadini et al., 2014). These situations contribute to increased metabolic stress, aggravating insulin deficiency and favoring the development of ketoacidosis (Umpierrez & Korytkowski, 2016). Therefore, early recognition and proper management of these underlying causes are crucial to prevent the progression of DKA.

The initial management of DKA in the emergency department involves rapid correction of dehydration, control of hyperglycemia and reversal of metabolic acidosis (Dhatariya et al., 2020). Hydration therapy is fundamental in this context, since most patients with DKA have a significant volume deficit, estimated at between 3 and 6 liters (Chiasson et al., 2003). Intravenous rehydration with isotonic saline solution (NaCl 0.9%) is the first therapeutic intervention and should be started immediately, with the infusion rate adjusted according to the degree of dehydration and the patient's cardiovascular function (Pasquel & Umpierrez, 2014).

As the patient's blood glucose approaches safer levels, the isotonic saline solution can be replaced by a solution containing glucose, such as 0.45% NaCl solution with 5% dextrose, to avoid hypoglycemia induced by insulin therapy, which will be administered concomitantly (Kitabchi et al., 2009). Hydration not only corrects the volume deficit, but also helps to reduce glycemia, improving renal perfusion and, consequently, the excretion of glucose and ketone bodies through the urine (Umpierrez & Korytkowski, 2016).

In summary, diabetic ketoacidosis is an acute complication of diabetes that requires a systematic approach in the emergency department. Early and adequate hydration is the cornerstone of treatment, complemented by insulin administration and correction of electrolyte and acid-base disturbances. Rapid recognition and effective management can prevent serious complications and significantly improve clinical outcomes for patients (Dhatariya et al., 2020).

The aim of this paper is to review and analyze diabetic ketoacidosis (DKA), highlighting its pathophysiology, emergency management and associated neurological impacts. By reviewing studies, the work aims to understand how DKA affects cognitive functioning, particularly in children with type 1 diabetes, and to evaluate the effectiveness of therapeutic interventions, including the administration of fluids and insulin.

METHODS

The search for scientific articles was carried out using the National Library of Medicine (PubMed) database. The descriptors were "*diabetic*"; *"ketoacidosis"; "emergency"*, using the Boolean operator "AND" between the respective words. The categories were: clinical trial and randomized clinical trial. The studies were selected from publications between 2013 and 2024, using articles in English and Portuguese as inclusion criteria. The exclusion criteria were articles that added other pathologies to the central theme, disconnected from the proposed subject. The academic papers were reviewed using the following steps, in the following order: defining the topic; establishing the study categories; proposing inclusion and exclusion criteria; checking and then analyzing the publications; organizing the information; and presenting the data.

RESULTS

By associating the descriptors used, a total of 1709 papers were obtained from the PubMed database. Using the inclusion criterion: articles published in the last 11 years (2013-2024), resulted in a total of 1215 articles. Next, clinical trials, randomized controlled trials or journal articles were added as inclusion criteria, giving a total of 33 articles. Articles in Portuguese or English were selected, resulting in 32 articles and then the free full text option was added, totaling 23 articles. After reading the abstracts, those that did not fit the topic or were duplicated were excluded, totaling 15 articles, as shown in Figure 1.

DISCUSSION

Diabetic ketoacidosis (DKA) is an acute and potentially fatal complication of diabetes, especially type 1 diabetes (TD1), which requires a systematic and well-coordinated approach in the emergency setting. A review of the texts discussed reveals a complex interrelationship between the treatment of DKA and its neurological and cognitive effects, as well as the importance of adequate hydration, insulin administration and correction of electrolyte and acidobase disturbances to prevent serious complications and improve patients' clinical outcomes (YAN ET AL., 2024).

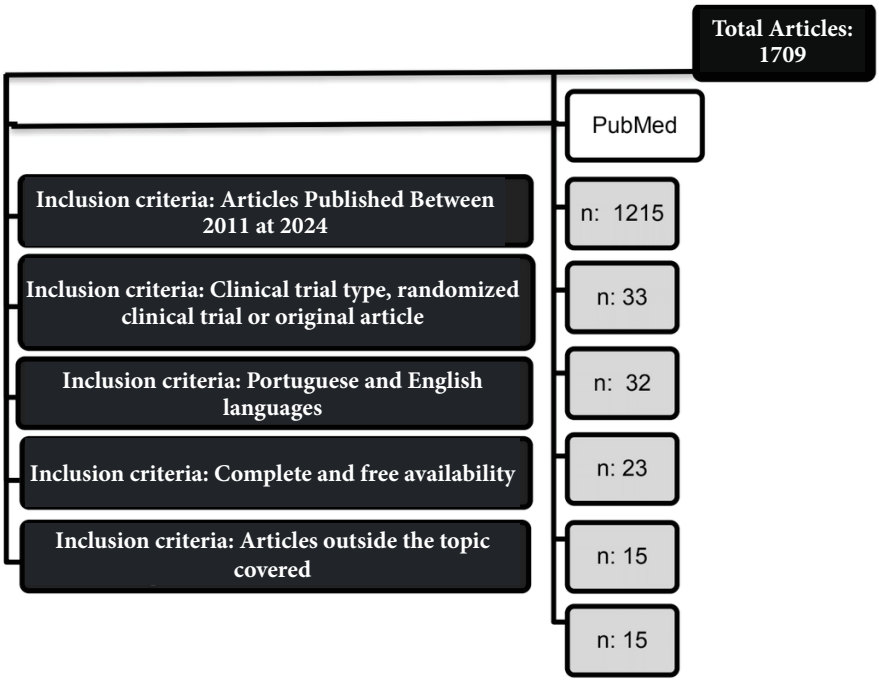

FIGURE 1: Flowchart for identifying articles in PubMed.

Source: Authors (2024)

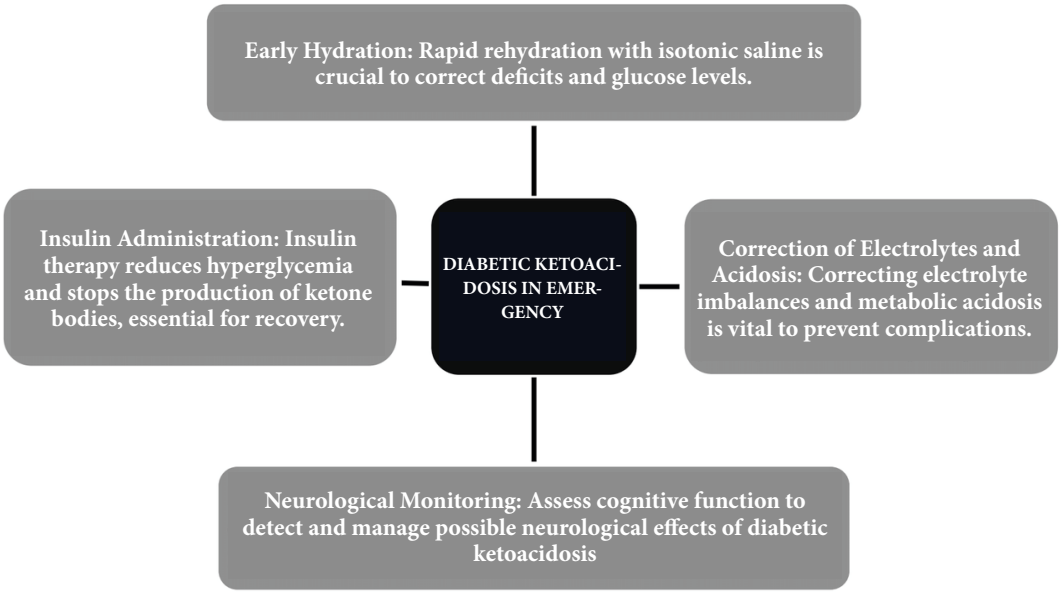

FIGURE 2: Summary of the most frequently found results according to the articles analyzed.

Source: Authors (2024)

The studies reviewed address different aspects of DKA, including the relationship between ketoacidosis and cognitive functioning in children, the influence of fluid administration rates on DKA treatment, and changes in circulating metalloproteinases (MMPs) levels that may reflect the severity of blood-brain barrier (BBB) dysfunction during DKA. These studies corroborate the assertion that a systematic and effective approach is crucial to preventing complications and improving the clinical outcomes of CAD patients (ZHANG & HE, 2023).

Diabetic ketoacidosis has been associated with significant cognitive decline in children with DT1. Studies show a robust association between DKA status and reduced IQ scores in young children within a few months of the onset of DT1. This finding is worrying, as it indicates that the impact of CAD on cognitive development may be more pronounced in young children than in older children, where no significant differences in IQ scores were found between children with and without exposure to CAD. This cognitive decline can occur rapidly after CAD and has important implications for the early and effective management of CAD to minimize adverse neurological impacts (TRAINOR ET AL., 2023).

Limitations of the studies include the relatively small sample size and the difficulty in controlling for all the variables that can influence cognitive function, such as acute kidney injury and socioeconomic factors. Therefore, future studies with larger samples and more rigorous methodologies are needed to better understand the factors that contribute to cognitive decline in children with TD1 and CAD. The fact that cognitive decline can be more pronounced in young children suggests that early and more intensive interventions may be needed to mitigate these effects (YIN ET AL., 2021).

Studies investigating fluid administration rates during the treatment of DKA found no significant differences in neurological outcomes between groups receiving fluids at different administration rates or with different sodium chloride contents. Although rapid fluid administration was associated with lower rates of mental status decline and clinically apparent brain damage, these differences were not statistically significant. These results indicate that rapid fluid administration may not be directly associated with CAD-related brain damage, challenging the hypothesis that rapid osmotic changes are the main cause of brain damage (REWERS ET AL., 2021).

Instead, factors such as cerebral hypoperfusion and neuroinflammation may play more important roles in CAD-related brain damage. The literature suggests that cerebral edema may be a consequence, rather than the cause, of brain injury, and that subtle brain injury may occur before treatment begins. These findings highlight the complexity of DKA and the need to consider multiple factors in managing the condition, beyond simply the rate of fluid administration (SELF ET AL., 2020).

Analysis of the levels of circulating metalloproteinases (MMPs) in children with CAD reveals a complex pattern. MMP-2, which is usually elevated in inflammatory conditions, was found to be reduced in children with CAD, while MMP-9 was elevated. This change in the expression of MMPs may reflect the dysfunction of the BBB and the vasogenic cerebral edema often observed during CAD. The reduction in MMP-2 levels may be associated with rapid degradation or redistribution to areas of tissue remodeling, while the increase in MMP-9 may be a reflection of the hyperglycemia and systemic inflammation associated with CAD (GHETTI ET AL., 2020).

Although elevated MMP-9 levels may be related to inflammatory processes and leukocytosis, the elevation of MMP-3 was difficult to interpret due to the low circulating levels observed in both groups. MMP-3 may play a role in the pathophysiology of CAD-related brain damage, but its production may be more localized in the brain without significant increases in plasma levels. The interpretation of these data suggests that BBB dysfunction during CAD is multifaceted and involves a complex interaction between different inflammatory mediators and tissue remodeling processes (DEPIERO ET AL., 2020).

The studies discussed confirm that effective treatment of diabetic ketoacidosis is fundamental to preventing serious complications and improving clinical outcomes. Early and adequate hydration, along with insulin administration and correction of electrolyte and acidobase disturbances, remains the cornerstone of DKA management. Evidence indicates that, in addition to conventional treatment, it is crucial to consider the potential neurological impacts of DKA, such as cognitive decline and brain damage, especially in children (WILLIAMS ET AL., 2020).

In addition, the data suggest that the approach to fluid administration should be carefully considered and adjusted based on the individual needs of patients and the severity of CAD. Understanding changes in metalloproteinases and other biomarkers can offer valuable insights into optimizing treatment and preventing CAD-related brain damage. The combination of a systematic approach to treating CAD and consideration of the associated neurological and cognitive aspects can significantly improve outcomes for patients and contribute to evidence-based clinical practice (DOSHI ET AL., 2015).

Finally, the need for future studies is evident to further improve management strategies and to explore the complex interactions between CAD, inflammatory factors and neurological effects. With ongoing research and a focus on the specific needs of patients, it is possible to advance the treatment of CAD and improve the quality of life of affected individuals (GHETTI ET AL., 2023).

CONCLUSION

Diabetic ketoacidosis (DKA) is a critical medical emergency associated with diabetes mellitus, predominantly type 1 diabetes, and which requires an immediate and well-coordinated treatment approach to minimize complications and optimize clinical outcomes. This review addressed the complex pathophysiology of DKA, the therapeutic interventions and the neurological and cognitive effects associated with this condition. A detailed understanding of these aspects is crucial to improving the management of CAD and patients' quality of life. The treatment of DKA is based on rapid correction of dehydration, control of hyperglycemia and reversal of metabolic acidosis. Adequate hydration, with initial administration of isotonic saline solutions and subsequent switching to glucose-containing solutions as blood glucose improves, is the cornerstone of treatment (Dhatariya et al., 2020). This approach not only corrects the volume deficit, but also helps to reduce blood glucose and improves renal perfusion, facilitating the excretion of glucose and ketone bodies. The administration of insulin is also fundamental, acting to reduce blood glucose and stop the production of ketone bodies. Correction of electrolyte and acid-base disorders completes the management, preventing further complications and promoting the patient's recovery. In addition to conventional therapeutic strategies, the review revealed the

importance of considering the neurological impacts of DKA. Studies indicate that CAD can be associated with significant cognitive decline, particularly in children with type 1 diabetes. The evidence that exposure to CAD can lead to a reduction in IQ scores highlights the need for early and effective interventions to mitigate possible adverse effects on cognitive development. These findings suggest that the treatment of DKA should include strategies to monitor and address potential neurological impacts, as well as focusing on metabolic and fluid corrections. Analysis of fluid administration rates and their effects on neurological function revealed that although rapid fluid administration can reduce mental status decline and overt brain damage, the statistical differences were not significant. This suggests that the rate of fluid administration may not be the main factor in CAD-related brain damage. Factors such as cerebral hypoperfusion and neuroinflammation appear to play more substantial roles, indicating that brain damage may be a complex and multifaceted consequence of CAD. A review of changes in circulating metalloproteinase (MMP) levels offers new insights into blood-brain barrier (BBB) dysfunction and cerebral edema associated with CAD. The reduction in MMP-2 levels and the increase in MMP-9 suggest an inflammatory response and complex tissue remodeling processes. These biomarkers may provide additional insights to adjust treatment and prevent neurological complications. In conclusion, effective management of DKA requires a multifaceted approach that includes prompt treatment for dehydration and hyperglycemia, insulin administration, and correction of electrolyte and acidobase disturbances. Consideration of potential neurological effects, such as cognitive decline and brain damage, is equally important. Personalization of treatment based on individual patient needs, consideration of inflammatory biomarkers and ongoing research into the effects of CAD can contribute to evidence-based clinical practice and significantly improve outcomes for affected patients. Future studies are needed to refine management strategies, explore the complex interactions between CAD and inflammatory factors, and advance understanding of the neurological impacts associated with the condition. With a careful approach grounded in ongoing research, it is possible to improve the treatment of CAD and promote a better quality of life for affected individuals.

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