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WORD COUNT 3178
TIME SUBMITTED 18-JUL-2023 03:58PM
PAPER ID 101324865

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 86070

Manuscript Type: SYSTEMATIC REVIEWS

SGLT2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis in COVID-19-Infected Patients, A Systematic Review of Case Reports

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Abstract

BACKGROUND

Diabetic ketoacidosis (DKA) manifests as hyperglycemia, metabolic acidosis, and ketosis. However, euglycemic DKA (eu-DKA) conceals severe DKA with glucose levels below 200 mg/dL. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) can induce eu-DKA in diabetic patients. Notably, COVID-19-infected individuals with diabetes using SGLT2 inhibitors face an augmented risk of eu-DKA due to the direct toxic impact of the virus on pancreatic islets. This study aims to comprehensively investigate the association between SGLT2 inhibitors and eu-DKA in COVID-19 patients through meticulous case report analysis. Additionally, we endeavor to examine the outcomes and treatment approaches for COVID-19-infected diabetics receiving SGLT2 inhibitors, providing indispensable insights for healthcare professionals managing this specific patient population.

AIM

To investigate the connection between SGLT2 inhibitors and euglycemic DKA in COVID-19 patients through a meticulous analysis of case reports.

METHODS

We conducted an exhaustive search across prominent electronic databases, including PubMed, SCOPUS, Web of Science, and Google Scholar. This search encompassed the period from December 2019 to May 2022, incorporating published studies and pre-prints. The search terms employed encompassed "SGLT2 inhibitors," "euglycemic DKA," "COVID-19," and related variations. By incorporating these diverse sources, our objective was to ensure a thorough exploration of the existing literature on this subject, thereby augmenting the validity and robustness of our findings.

RESULTS

Our search yielded a total of seven case reports and one case series, collectively comprising a cohort of twelve patients. These reports detailed instances of euglycemic diabetic ketoacidosis (eu-DKA) in individuals with COVID-19. Crucially, all twelve patients were utilizing sodium-glucose cotransporter-2 inhibitors (SGLT2is) as their primary anti-diabetic medication. Upon admission, all oral medications were promptly discontinued, and the patients were initiated on intravenous insulin therapy to effectively manage the DKA. Encouragingly, eleven patients demonstrated a favorable outcome, while regrettably, one patient succumbed to the condition. Subsequently, SGLT2is were discontinued for all patients upon their discharge from the hospital. These findings provide valuable insights into the clinical management and outcomes of eu-DKA cases associated with COVID-19 and SGLT2is, underscoring the critical importance of prompt intervention and vigilant medication adjustments.

CONCLUSION

Our study sheds light on the possibility of diabetic patients developing both drug-related and unrelated DKA, as well as encountering adverse outcomes in the context of COVID-19, despite maintaining satisfactory glycemic control. The relationship between glycemic control and clinical outcomes in COVID-19 remains ambiguous. Consequently, this systematic review proposes that COVID-19-infected diabetic

patients using SGLT2is should contemplate alternative treatment protocols until their recovery from the disease.

INTRODUCTION

Understanding the signs, symptoms, risk factors, and outcomes of SARS-CoV-2 infection remains an ongoing endeavor for clinicians and scientists. While COVID-19 research progresses rapidly, recent discoveries call for rigorous investigation to establish new hypotheses and evidence-based conclusions. Patients with diabetes mellitus face a higher likelihood of developing severe COVID-19 and experiencing adverse outcomes [1]. Notably, SGLT2 inhibitors exhibit cardiovascular benefits that extend beyond glycemic control [2]. Diabetic ketoacidosis (DKA) represents a life-threatening complication of diabetes mellitus (DM) characterized by elevated serum glucose (> 250 mg/dL), high anion gap metabolic acidosis, and plasma ketone levels. However, DKA can occur even with mild to moderate serum glucose elevation, known as euglycemic DKA (eu-DKA) [3].

The Food and Drug Administration (FDA) has issued warnings about the increased risk of eu-DKA associated with sodium-glucose cotransporter-2 (SGLT2) inhibitors [4]. However, findings from the CANVAS trial suggest a low incidence of eu-DKA in patients using SGLT2 inhibitors (0.6 events per 1,000 patient years) [5]. It is important to note that COVID-19 infection may amplify this risk due to the potential pancreato-toxic effects of the virus. Although three studies have examined the relationship between SGLT2 inhibitors and eu-DKA, methodological variations exist [6-8]. The prevalence of eu-DKA among type 2 diabetes mellitus (T2DM) patients treated with SGLT2 inhibitors is less than 0.1% [9]. Eu-DKA is a critical crisis that often goes unnoticed due to the absence of evident hyperglycemic symptoms. Pathophysiological studies have elucidated the mechanisms underlying this effect [10]. SGLT2 inhibitors induce glucosuria by inhibiting the sodium-glucose cotransporter in the convoluted proximal tubule, leading to decreased serum glucose levels and subsequent

insulinopenia. Insulinopenia triggers an increase in counter-regulatory hormones (catecholamines and glucagon), which stimulates lipolysis and enhances fatty acid production, resulting in ketosis in the euglycemic state given the prior reduction in blood glucose by SGLT2 inhibitors.

The combined effect of COVID-19's pancreatic toxicity and SGLT2 inhibitors' glucosuria induces severe insulinopenia, potentially elevating the risk of eu-DKA in affected patients. However, the understanding of this mechanism and the management of eu-DKA in individuals with concurrent COVID-19 infection remains limited in the existing literature. In this systematic review, we have included a comprehensive analysis of relevant case report studies that provide important insights into the association between SGLT2 inhibitors, eu-DKA, and COVID-19 in patients with diabetes mellitus. These case reports shed light on the clinical manifestations, treatment approaches, and outcomes of eu-DKA in individuals with COVID-19 who are receiving SGLT2 inhibitor therapy.

MATERIALS AND METHODS

METHODS:

Data Sources and Search Strategy

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. A comprehensive electronic search was conducted from December 2019 to May 2022 using the SCOPUS, Web of Science, MEDLINE, and Google Scholar databases. The search was limited to English language publications, and the detailed search string employed is provided in the supplementary file. In addition, we included the pharmaceutical, generic, and trade names of SGLT2 inhibitors in our search. To ensure thoroughness, we manually examined the reference lists of the included studies to identify any potentially relevant articles that might have been overlooked. Detailed search strategies used for all databases are available in the Supplementary material. The research protocol for this

review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022341562.

Study Selection

We included published case reports, case series, and pre-print articles. The selection of studies was based on specific eligibility criteria, which included the following: (a) reports describing patients with euglycemic diabetic ketoacidosis (eu-DKA) who were admitted and treated following the guidelines set by the Association of British Clinical Diabetologists [12]; (b) inclusion of adult patients with either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM); (c) utilization of SGLT2 inhibitors as the primary intervention for glucose control; and (d) confirmation of eu-DKA cases. Exclusion criteria were as follows: (a) studies that did not focus on the association between SGLT2 inhibitors and eu-DKA in COVID-19 patients; (b) studies involving pediatric patients; (c) non-English language publications; (d) studies without clear documentation of eu-DKA cases or treatment approaches; and (e) review articles, editorials, and conference abstracts. The study selection process followed specific eligibility criteria based on the PICO framework:

Participants (P): Adult patients with either T1DM or T2DM diagnosed with eu-DKA.

Intervention (I): Utilization of SGLT2 inhibitors as the primary intervention for glucose control.

Comparator (C): Not applicable as this review focused on the association between SGLT2 inhibitors and eu-DKA in COVID-19 patients.

Outcomes (O): Clinical manifestations, treatment approaches, and outcomes of eu-DKA in patients with concurrent COVID-19 infection. The favorable outcome was defined as survival and hospital discharge.

Data extraction and assessment of study quality

The systematic search yielded articles that were imported into the Endnote Reference Library software, where duplicates were identified and removed. Initially, two independent reviewers (Author 1 and 2) screened the articles based on titles and abstracts. Subsequently, two additional independent reviewers (Author 5 and 6)

performed full-text screening of the filtered articles. The entire content of each article was thoroughly reviewed, with two authors (Authors 3 and 4) ensuring its relevance and piloting the process with one report. In case of any discrepancies, a third investigator (Author 7) was consulted for resolution. Information extracted from the articles included demographic background, comorbidities, disease onset, initial symptoms, laboratory tests, diabetes mellitus type, SGLT2 inhibitor type, study date, study design, treatment intervention, and case outcomes. The quality of the included studies was assessed using the CARE (CAse REport) guidelines [13].

Synthesis of results

The extracted information was qualitatively synthesized using a narrative approach due to the limitations of the included case reports, which presented small effect sizes and precluded quantitative analysis for calculating effect estimates.

RESULTS

RESULTS

Study results, study characteristics, and baseline demographics

The study selection process was summarized using the PRISMA flow chart (Figure 1), which illustrates the search and selection of studies. Initially, a total of 3,370 studies were identified from the databases, and after removing duplicates (n = 1823), eight studies met the inclusion criteria and were included in this review. These studies consisted of seven case reports and one case series that investigated the incidence of euglycemic diabetic ketoacidosis (eu-DKA) in COVID-19 patients receiving SGLT2 inhibitors [14-19, 28,29]. The combined study population across these studies comprised 12 patients.

Quality Assessment

All the included case reports adhered to the CARE guidelines, ensuring a standardized reporting of case details. A comprehensive quality assessment table can be found in Supplementary Table 1, providing a detailed evaluation of the methodological quality of each included study.

Evidence Synthesis

The patients included in the studies were from various countries, including the United States (n = 3) [14,18,19], United Kingdom (n = 5) [15], Brazil (n = 1) [16], Malaysia (n = 1) [28], and Belgium (n = 2) [17,29]. The reported cases of type 1 diabetes mellitus (T1DM) were observed in the studies conducted in the UK and Belgium [17,29].

The age range of the patients included in the studies varied from 40 to 79 years, with a higher proportion of male patients (75%) compared to female patients. Among the patients, type 2 diabetes mellitus (T2DM) was the most prevalent form, accounting for 83.33% of the cases. The most commonly observed comorbidities among the patients were hypertension (50%), hypothyroidism (16.66%), obstructive sleep apnea (16.7%), and hyperlipidemia (8.3%). Empagliflozin was the predominant SGLT2 inhibitor used by the patients, accounting for 83.3% of the cases.

Common symptoms reported by the patients included tachypnea, dyspnea, and tachycardia. The diagnostic criteria for eu-DKA frequently involved a combination of arterial blood gas (ABG) analysis, serum tests, and urine analysis. Serum glucose levels ranged from 113 to 286 mg/dL. ABG analysis revealed deviations from normal levels, with pCO2 ranging from 13 to 43 mmHg, bicarbonate ranging from 3 to 20 mEq/L, and pH ranging from 6.94 to 7.48.

COVID-19 was primarily diagnosed using reverse transcription-polymerase chain reaction (RT-PCR), and the symptoms of eu-DKA appeared 2 to 9 days after the identification of COVID-19. Treatment for COVID-19 included intubation and oxygen therapy for the majority of patients, except for one patient with T1DM who also required invasive mechanical ventilation. Another patient received High Flow Nasal Cannula (HFNC). Empagliflozin use was associated with a shorter duration between COVID-19 infection and the onset of eu-DKA symptoms. All patients received intravenous fluids and intravenous insulin as part of the eu-DKA treatment protocol.

Out of the 12 patients included in the studies, 11 patients successfully survived, recovered, and were discharged from the hospital, while unfortunately, one patient died. A favorable outcome was defined as not requiring oxygen or life support and

having blood pH within the normal range of 7.35-7.45. The patients with T1DM also experienced successful recoveries. SGLT2 inhibitors were discontinued until the resolution of COVID-19, and subcutaneous insulin was initiated after recovery from eu-DKA. A summary of the results can be found in Table 1.

DISCUSSION

The use of SGLT2 inhibitors in adults with COVID-19 infection remains a controversial topic, and this systematic review represents the first attempt to define the outcomes of this particular patient cohort. However, the availability of data is unfortunately limited. Nonetheless, the available data suggest that SGLT2 inhibitors may contribute to the development of eu-DKA in COVID-19-infected patients.

We included 8 studies comprising a total of 12 patients. The survival rate among these patients exceeded 90%. Most patients presented with symptoms of COVID-19 within 2-3 days before the onset of eu-DKA. Significant deviations in arterial blood pH levels were observed, with the lowest reported pH being 6.87. In response, all patients had their SGLT2 inhibitors immediately discontinued and received treatment with fluids and intravenous insulin.

The term "eu-DKA" was first defined by Munro *et al* in 1973 [20]. It is distinct from classic DKA in that it is characterized by severe metabolic acidosis despite normal blood glucose levels. Diagnosis of eu-DKA is confirmed through direct measurement of beta-hydroxybutyrate levels in the blood and assessment of arterial blood pH levels [21].

The occurrence of eu-DKA due to SGLT2 inhibitors involves decreased insulin production (insulinopenia) and increased glucagon secretion. Multiple factors influence increased glucagon secretion, which occurs through both direct and indirect mechanisms. The inhibitory effects of SGLT2 inhibitors on the SGLT2 transporters in the glucagon-secreting pancreatic alpha cells of the Langerhans islets directly contribute to increased glucagon secretion. Indirectly, increased glucose excretion leads to lower insulin levels and decreased insulin to glucagon ratio. The resultant decrease in insulin stimulates the synthesis of free fatty acids and ketone bodies, leading to excessive

catabolism of fatty acids and subsequent ketosis [22]. Ketosis is further exacerbated in the presence of SGLT2 inhibitors, as these medications inhibit the reabsorption of glucose in the proximal renal tubules, leading to glucosuria and promoting a state of starvation [23].

Eu-DKA has emerged as a prevalent condition observed in diabetic patients with COVID-19 who are also using SGLT2 inhibitors. The higher incidence of eu-DKA in male diabetic patients with COVID-19 aligns with reports indicating a greater propensity for presentation in this subgroup. The clinical manifestation of eu-DKA in COVID-19-infected diabetic patients taking SGLT2 inhibitors is diverse, including tachypnea and tachycardia during clinical examination, along with an anion gap metabolic acidosis and normal serum glucose levels observed in laboratory investigations.

In patients infected with COVID-19, eu-DKA differs from the non-infected population due to the pancreatic toxicity induced by the virus, leading to severe insulinopenia. Consequently, infected patients require insulin therapy in addition to the discontinuation of SGLT2 inhibitors to prevent the recurrence of eu-DKA. Conversely, in patients without COVID-19 infection, resolution and prevention of eu-DKA can typically be achieved by discontinuing SGLT2 inhibitors, allowing insulin levels to return to normal [18]. Unlike individual case reports, the accumulation of evidence from multiple cases supports the occurrence of eu-DKA in diabetic patients following the onset of COVID-19 and concurrent use of SGLT2 inhibitors.

The severe toxic effects of COVID-19 on the pancreas have been well-documented. When these toxic effects combine with the dehydrating and glycosuric effects of SGLT2 inhibitors, it can lead to the development of eu-DKA. Recent studies have discussed the occurrence of pancreatic injury in patients with COVID-19, highlighting the link between COVID-19-related pancreatic toxicity, enzyme elevation, and insulinopenia [24,25]. The ACE2 receptor, which is expressed in the beta cells of Langerhans islets, plays a role in both COVID-19 and SARS-CoV-1 infections. These viruses utilize the ACE2 receptor to enter the cell, triggering immune system activation and the release of cytokines and chemokines that lead to cell death [26,27]. The destructive

effect on beta cells results in insulinopenia and subsequent ketoacidosis. Moreover, the acidic environment of eu-DKA is known to facilitate the growth of COVID-19.

Given the widespread use of SGLT2 inhibitors for their cardiovascular and renal benefits, clinicians must familiarize themselves with eu-DKA to enable timely diagnosis and treatment, particularly in the context of the ongoing COVID-19 pandemic.

Limitations

This study has limitations, including a small number of studies with small effect sizes, all of which were case reports or case series. The non-randomized allocation of interventions and the absence of a standardized protocol for diagnosing eu-DKA in COVID-19 patients introduce selection and bias risks. The diverse treatment settings and limited data availability further hinder comprehensive analysis. Further research is needed to address these limitations and provide more robust evidence on the topic.

CONCLUSION

Our systematic review suggests that SGLT2 inhibitors may increase the risk of euglycemic diabetic ketoacidosis in COVID-19-infected diabetic patients. The pancreatic toxicity associated with SARS-CoV-2 infection may contribute to this effect. While this narrative synthesis of case reports provides valuable insights, further research with larger sample sizes and rigorous designs, such as retrospective cohorts, is needed to investigate the association between eu-DKA development in COVID-19 patients and SGLT2 inhibitors. Studies with larger effect sizes and randomization would help elucidate clinically relevant endpoints and enable more effective management of individuals at higher risk.

ARTICLE HIGHLIGHTS

Research background

The coexistence of COVID-19 infection and the use of SGLT2 inhibitors have generated debate due to the potential risk of euglycemic diabetic ketoacidosis (eu-DKA)

development. Limited information regarding this specific patient population is available, necessitating a systematic review to investigate the outcomes and characteristics associated with eu-DKA in COVID-19-infected diabetic patients treated with SGLT2 inhibitors.

Research motivation

Given the controversy and limited data surrounding the association between SGLT2 inhibitors, COVID-19 infection, and eu-DKA, there is a pressing need to investigate this topic to enhance our understanding of the potential risks and outcomes.

Research objectives

The primary objectives of this study are to examine the association between SGLT2 inhibitors and the development of eu-DKA in COVID-19-infected diabetic patients, explore the potential mechanisms underlying this relationship, and assess the clinical outcomes and management strategies for this patient population.

Research methods

We conducted a comprehensive search of relevant databases to identify studies reporting on the association between SGLT2 inhibitors and eu-DKA in COVID-19-infected diabetic patients. We followed the PRISMA guidelines for study selection and data extraction. The extracted data were qualitatively synthesized to provide a narrative overview of the findings.

Research results

The systematic review included eight studies comprising 12 patients, investigating the association between SGLT2 inhibitors and eu-DKA in COVID-19-infected diabetic patients. The majority of patients presented with eu-DKA symptoms 2-3 days after the onset of COVID-19 symptoms. The survival rate was over 90%, with one reported fatality. Significant pH deviations were observed, with the lowest reported pH being

6.87. All patients discontinued SGLT2 inhibitors and received treatment with fluids and IV insulin. The results highlight the potential risk of developing eu-DKA in this patient population.

Research conclusions

This systematic review concludes that the use of SGLT2 inhibitors in COVID-19-infected diabetic patients may increase the risk of euglycemic diabetic ketoacidosis (eu-DKA). The pancreatic toxicity induced by the SARS-CoV-2 virus is believed to contribute to this phenomenon. The analysis of case reports provides evidence supporting the association between SGLT2 inhibitors and eu-DKA in this patient population. Further studies with larger sample sizes and robust designs are necessary to enhance our understanding and inform clinical decision-making for high-risk individuals.

Research perspectives

Further research is needed to investigate the mechanisms of eu-DKA in COVID-19 patients on SGLT2 inhibitors. Larger randomized studies are necessary to establish a causal relationship and identify risk factors. Standardized protocols for diagnosis and management should be developed to improve patient outcomes. These research perspectives will enhance understanding and guide evidence-based approaches in the future.

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