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Incidence of ketoacidosis in diabetic patients treated with sodium–glucose cotransporter-2 inhibitors: A prospective cohort study

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Abstract

Introduction: Sodium–glucose cotransporter 2 inhibitors (SGLT2is) have gained significant attention for their benefits in managing type 2 diabetes mellitus (T2DM), particularly in patients with chronic kidney disease (CKD) and heart failure. However, the potential for SGLT2is to increase the risk of ketoacidosis, particularly euglycemic diabetic ketoacidosis (EDKA), warrants further investigation. This prospective cohort study assesses the incidence of ketoacidosis among T2DM patients treated with SGLT2is and examines related risk factors.

Methods: This is a prospective study included 575 patients with T2DM. Patients over 18 years undergoing SGLT2i therapy were followed for six months. Baseline demographics, clinical history, glucose management practices, and medication use, with an emphasis on SGLT2is, were recorded. Blood gas analysis (BGA) and urine ketones were measured monthly. Ketoacidosis was defined by urine ketone positivity with pH <7.30, bicarbonate (HCO_3) ≤18 mEq/L, and an elevated anion gap.

Results: Out of 575 patients, 35.6% (205) had positive urine ketones at least once during the study, with 11 patients (0.7%) meeting ketoacidosis criteria. Patients with ketoacidosis had a mean hospital stay of 8.2 days compared to 5.4 days in non-ketoacidosis patients (p = 0.02). No in-hospital mortality occurred among ketoacidosis patients.

Conclusion: Ketoacidosis was rare but clinically relevant in T2DM patients on SGLT2is. The incidence of euglycemic ketoacidosis highlights the need for monitoring and identifying high-risk individuals early during SGLT2i treatment initiation.

Keywords: SGLT2 inhibitors; Euglycemic diabetic ketoacidosis; Type 2 diabetes mellitus

1. Introduction

Sodium–glucose cotransporter 2 inhibitors (SGLT2is) have emerged as a transformative therapy in managing type 2 diabetes mellitus (T2DM), with a range of metabolic benefits that extend beyond glycemic control [1]. Numerous clinical trials have demonstrated that SGLT2is reduce blood glucose levels, promote weight loss, lower blood pressure, and provide cardiovascular and renal protection in patients with T2DM, especially those with chronic kidney disease (CKD). Consequently, SGLT2is have become an essential component of treatment strategies for diabetic patients, particularly those with heart failure or CKD [2,3].

Despite these benefits, SGLT2is have been associated with a potentially life-threatening complication: ketoacidosis, specifically euglycemic diabetic ketoacidosis (EDKA) [2,3]. This condition, characterized by ketosis and acidosis without significant hyperglycemia, poses a diagnostic challenge as patients may present with nonspecific symptoms such as

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nausea, vomiting, and abdominal pain, with only mild elevations in blood glucose levels. The incidence of ketoacidosis in patients treated with SGLT2is has been reported to range from 1.4 to 8.8 events per 1,000 patient-years, though actual rates may vary based on patient population and clinical setting [4,5].

This study aims to quantify the incidence of ketoacidosis among T2DM patients treated with SGLT2is and to identify potential risk factors that may predispose certain patients to this complication.

2. Methods

2.1. Study Design

This prospective cohort study was conducted at two medical centers. Adult patients (≥18 years) with a confirmed diagnosis of T2DM and initiated on SGLT2i therapy were eligible. Exclusion criteria included previous episodes of ketoacidosis, liver disease, and other conditions that could interfere with participation. Institutional ethics committee approval was obtained, and informed consent was provided by all participants.

2.2. Data Collection

Baseline data were collected, including demographics (age, gender), body mass index (BMI), medical history (hypertension, CKD, dyslipidemia), glucose management practices (use of insulin, oral antidiabetics), and medication use. SGLT2i therapy specifics were recorded. Blood gas analyses (BGA) and urine ketone tests were performed at baseline and then monthly for six months (Table 1). The study was conducted with the approval of the Arab Renal Care Group Review Board, and informed consent was obtained from patients, although their identities were kept confidential.

Patients who tested positive for urine ketones underwent further evaluation, including arterial blood pH, bicarbonate (HCO3) levels, and electrolyte measurements to confirm ketoacidosis. Ketoacidosis was defined by urine ketones, blood pH <7.30, HCO3 ≤18 mEq/L, and an elevated anion gap.

Table 1 Baseline characteristics for 575 patients

Characteristic	Value
Age (years)	67 ± 11
Gender (Male)	49.5%
BMI (kg/m^2)	30.2 ± 4.8
Hypertension (%)	72.8
Dyslipidemia (%)	61.3
CKD Stage ≥3 (%)	41.6
Insulin Use (%)	25.1

2.3. Outcome Measures

The primary outcome was the incidence of ketoacidosis over the study period. Secondary outcomes included the incidence of positive urine ketones, low bicarbonate levels (bicarbonate level *less than* 22 mEq/L), and hospital admissions related to ketoacidosis or other diabetes-related complications.

2.4. Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics. Categorical variables were expressed as percentages, while continuous variables were reported as means ± standard deviation (SD). Incidence rates of ketoacidosis were calculated per patient-year and 95% confidence intervals (CIs) were calculated for each outcome. Student's t-test was used to compare hospital length of stay between patients with and without ketoacidosis.

2.5. Ketoacidosis Management and Outcomes

Patients who developed ketoacidosis were treated with standard care, including intravenous hydration, insulin administration, and electrolyte replacement, resulting in symptom resolution in all cases. The incidence of ketoacidosis

was low, affecting only 0.7% of patients. However, 35.6% of patients demonstrated positive urine ketones, which could signal metabolic stress or subclinical ketoacidosis, warranting closer observation.

In addition, 9.4% of patients showed low bicarbonate levels (below 22 mEq/L), which may be indicative of a risk for metabolic acidosis, emphasizing the need for regular monitoring of bicarbonate levels. Urinary tract infections (UTIs) were reported in 14.4% of patients.

Hospital admissions due to diabetes-related complications were seen in 4.5% of patients, highlighting the need for continuous monitoring and preventive care. Patients with ketoacidosis had an average hospital stay of 8.2 days, significantly longer than the 5.4-day average for patients without ketoacidosis ($p = 0.02$), underscoring the impact of this condition on healthcare utilization and the importance of proactive management. (Figure 1,2)

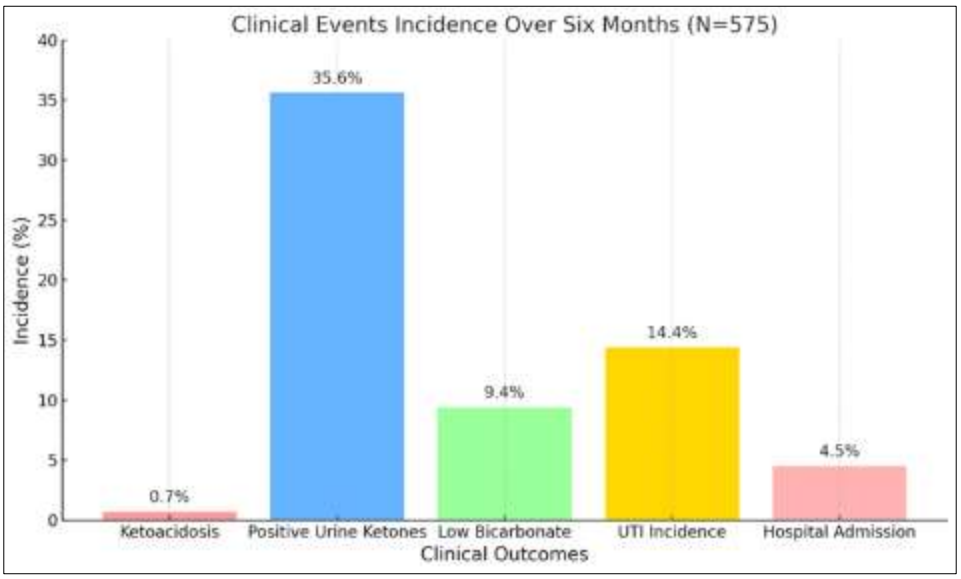

Figure 1 Clinical events incidence over six months

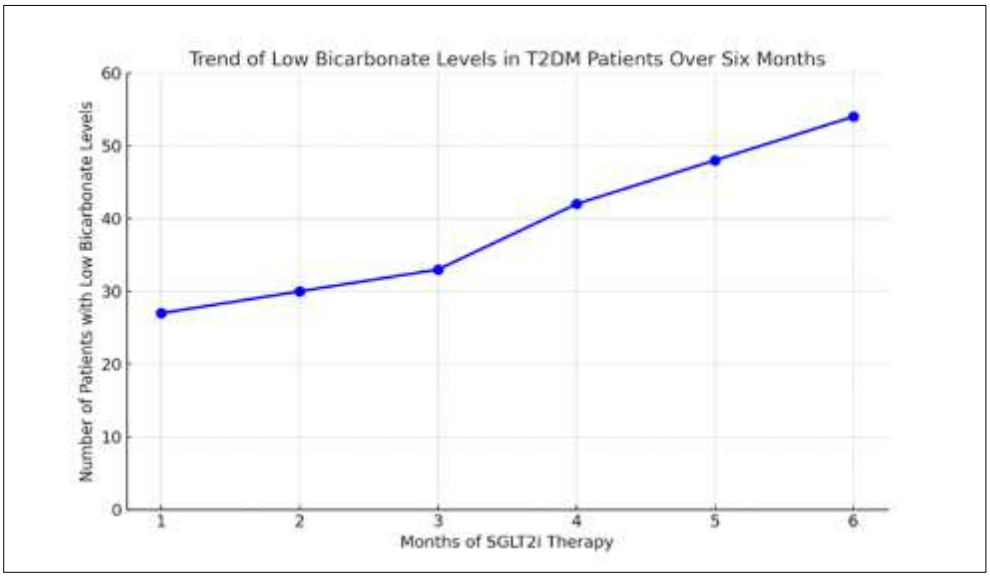

Figure 2 Trend of law bicarbonate levels in T2DM patients over six months

3. Discussion

This study presents a low but clinically meaningful incidence of ketoacidosis in type 2 diabetes mellitus (T2DM) patients treated with sodium–glucose cotransporter-2 inhibitors (SGLT2is) over a six-month period. The incidence rate of 0.7% is consistent with existing literature suggesting that ketoacidosis, particularly euglycemic diabetic ketoacidosis (EDKA), is an infrequent but critical risk in SGLT2i therapy [1][4][5]. Notably, all cases of ketoacidosis in our cohort were euglycemic, reinforcing that these metabolic complications can arise without the hallmark high blood glucose levels typically associated with diabetic ketoacidosis (DKA) [7]. This finding emphasizes the importance of monitoring ketone bodies and acid-base status in patients undergoing SGLT2i therapy, as relying on blood glucose levels alone may delay diagnosis and treatment [8].

The study's demographic data, including the mean age of 67 years and high prevalence of comorbidities such as hypertension (72.8%), dyslipidemia (61.3%), and chronic kidney disease (CKD) (41.6%), aligns with the profiles of patients who are often prescribed SGLT2is for cardioprotective and renoprotective benefits [9][10][11]. These comorbidities, particularly CKD, appear to influence the risk of ketoacidosis. CKD can exacerbate metabolic disturbances due to impaired acid clearance and increased risk of fluid-electrolyte imbalances, which may contribute to a heightened ketoacidosis risk in this population [12]. This association underscores the need for careful patient selection and monitoring strategies, especially in older patients with renal impairment [13].

The observed relationship between insulin use and ketoacidosis occurrence further adds to the discussion of potential risk factors. In our cohort, approximately 25.1% of patients were receiving insulin in conjunction with SGLT2is, and a subset of these developed ketoacidosis [14]. The combined use of insulin and SGLT2is can lead to altered metabolic dynamics, where a reduction in exogenous insulin requirements (due to SGLT2is' glucose-lowering effects) may inadvertently precipitate ketosis [15][16]. This situation is particularly challenging in clinical practice as insulin requirements are highly individualized, and inadvertent reductions in dosing may increase the risk of ketone accumulation without evident hyperglycemia [17]. Hence, a multidisciplinary approach involving endocrinologists, nephrologists, and pharmacists may be beneficial for optimizing medication regimens and monitoring in high-risk patients [18].

Our data also indicate that the number of patients with low bicarbonate levels increased from 27 in the first month to 54 by the sixth month of SGLT2i therapy. This trend may suggest a progressive risk of metabolic acidosis over time, which could be linked to accumulated effects of SGLT2is on renal gluconeogenesis and ketogenesis [19,20,21]. Identifying this early decline in bicarbonate levels may serve as a potential marker for preemptive interventions, such as closer ketone monitoring and adjustments in concurrent glucose-lowering therapies.

The extended hospital stay for patients who developed ketoacidosis (8.2 days compared to 5.4 days for non-ketoacidosis patients) highlights the economic and clinical burden associated with this complication [22]. Lengthier stays correlate with increased healthcare costs and reflect the intensity of care required for managing ketoacidosis, which typically involves intravenous fluids, insulin, and electrolyte replacement [23]. Given the low mortality observed, effective treatment protocols appear to be in place, yet the potential for prolonged recovery emphasizes the need for preventive strategies to reduce incidence and hospital resource utilization.

Our findings support the view that while SGLT2is confer numerous benefits for glucose control and cardiometabolic health, their association with ketoacidosis necessitates vigilant patient selection, particularly in populations with multiple comorbidities and concurrent insulin therapy. This study contributes to the broader understanding of SGLT2i-associated risks in real-world clinical settings and suggests that further research on personalized risk assessment and monitoring protocols is warranted [23]. Randomized controlled trials focusing on high-risk subgroups could also provide deeper insights into minimizing ketoacidosis risk while maximizing the therapeutic benefits of SGLT2i therapy in diabetic patients.

4. Conclusion

In conclusion, the data underscore the importance of routine monitoring for metabolic disturbances in patients prescribed SGLT2is, with an emphasis on early ketone and bicarbonate screening. Preventive strategies, including patient education and interdisciplinary care coordination, are essential for ensuring patient safety and optimizing clinical outcomes in this patient population.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest related to this study.

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