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Updates on Incidence and Risk Factors of Diabetic Ketoacidosis among Adults with Type 1 Diabetes: Systematic Review

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Abstract

Background: One of the most serious acute metabolic complications of type 1 diabetes (T1D) is diabetic ketoacidosis (DKA), which is characterised by acidosis, ketosis, and frequently hyperglycemia. ***Objectives:*** To summarize the recent epidemiological data and risk factors for developing DKA in adult T1D patients. ***Methods:*** PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process. ***Results & interpretation:*** We included eleven studies with a total of 104388 participants, and 52733 (50.5%) were males. The incidence of DKA in patients with T1D ranged from 2% to 64.8%. Risk factors for developing DKA included non-adherence, alcohol, higher HbA1c levels, longer-term diabetes, teenage age group, female gender, associated comorbid conditions, and intake of fat and carbohydrates. It's interesting to note that despair, drug misuse, and social deprivation are prevalent among DKA patients who are admitted. Consuming fibre and using freeStyle Libre protected T1D patients from developing DKA. Future research is obviously needed to provide a more comprehensive description of the epidemiology of DKA among adult T1D patients.

Keywords: Smoking; Reproductive health; Infertility; Systematic review.

INTRODUCTION

DKA is a severe metabolic condition brought on by inadequate insulin. Acidic ketone bodies are created by the breakdown of fatty acids (lipolysis), which is known as ketogenesis. When ketone levels rise over the body's buffering capacity, acidosis results [1, 2]. People with T1D have a crude annual incidence of 3.6%, according to data from the UK National Diabetes Audit [3].

DKA typically worsens within 24 hours. Patients typically have polyuria, polydipsia, vomiting, dehydration, and, if the condition is severe, a mental impairment, including a coma. Additionally, there might be symptoms of the underlying cause, like an infection [4]. DKA frequently includes abdominal pain, which might be a symptom of the acute episode or, less frequently, indicate an underlying cause. Any diabetic patient who is ill and has type 1 or type 2 diabetes should be evaluated for DKA [4].

The incidence of DKA varies globally as well. According to the most recent T1D exchange registry data in North America, the rate is 3% per three months for patients who receive care in specialized facilities [5]. In contrast, earlier research suggested rates between 1% and 5%, or roughly 145,000 cases annually [6, 7]. Recent data from the US Department of Health and Human Services/Centers for Disease Control and Prevention indicate that DKA rates increased from 19.5 to 30.2 per 1000 patient years between 2009 and 2014, although there is no definitive reason why this may have happened [8].

Similar to earlier statistics from other parts of Northern Europe [9, 10], the reported rates in the UK are about 3.6% or 48 occurrences per 1000 patient-years [11]. The highest rates were found in those between the ages of 18 and 30 in Germany, according to more current data, which indicates that overall rates have marginally declined to 25 per 1000 patient-years [12]. In the

Western Pacific, rates are said to be 100 per 1000 patient-years in children [13]. The highest rates are found in the least developed countries, according to recent research, which also suggests that there is a relationship between the development of DKA in children and adolescents and a country's degree of development [14].

Worldwide mortality in DKA varies. According to data from the Centers for Disease Control and others, mortality in the US decreased from 1.1% to 0.4% between 2000 and 2014, while mortality in the UK has also been recorded at 1% [8, 15, 16]. However, in India, in-hospital death rates could reach 30% [17].

The most frequent causes of this potentially fatal condition are infections, concurrent illnesses, poor drug compliance, and technological failures, such as pump malfunction or defective injection equipment [15, 18]. The majority of instances affect persons with T1D; however, depending on family history and ethnicity, DKA in people with type 2 diabetes can account for up to 50% of occurrences in some locations [19, 20]. According to other research, bouts of recurrent DKA and an increase in DKA-related mortality are caused by care fragmentation and a lack of continuity [21]. The presence of co-morbidities, such as end-stage renal failure, drug or alcohol abuse, noncompliance with insulin therapy, mental health issues, and discharge against medical advice, were additional factors causing recurrent hospitalizations [22, 23]. Within two weeks of discharge, readmission is possible in over 40% of instances [22].

A new diagnosis of T1D only occurs in 3-6% of cases, according to recent statistics from the UK, suggesting that the 30% figure for adults may be an overestimate [15, 24].

The subtleties of a standard definition for DKA may escape many clinicians treating DKA "at the front door"; instead, the straightforward message that DKA should be diagnosed when someone has elevated glucose (or a history of diabetes), elevated ketone concentrations and acidosis should prompt immediate treatment. In addition, it's important to recognize and treat other conditions, such as euglycaemic DKA or keto-alkalosis brought on by severe vomiting. The question of whether utilizing these minuscule variations in terminology results in different results is yet unanswered. As always, maintaining patient safety and treating with fluids, insulin, and electrolyte replenishment comes first [25].

A previous systematic review of literature conducted by *Farsani et al,*. reported that although there were few patient subgroup data available, a general trend was shown that the prevalence of DKA decreased with patient age. Other characteristics that were linked to a higher risk of DKA included low socioeconomic position, poor glycemic control, female sex, and sadness or psychiatric symptoms. Future research is clearly needed to better understand the epidemiology of DKA in adult T1D patients. There is still a need to address the prevention of this significant consequence, as shown by the currently available body of research, which shows an overall prevalence of DKA ranging from roughly 50 to 100 occurrences per 1000 adult patients with T1D [26]. The objectives of this systematic review are to summarize the recent epidemiological data andd risk factors for developing DKA in adult T1D patients.

METHODOLOGY

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed for this systematic review [27].

Study Design and Duration

This systematic review was conducted in December 2023.

Search Strategy

To retrieve the relevant research, a thorough search was conducted across five major databases, including Google Scholar, PubMed, Web of Science, Science Direct, and EBSCO. We only searched in English and took into account each database's unique criteria. The following keywords were converted into PubMed Mesh terms and used to find studies that were related; "Diabetic ketoacidosis," "DKA," "Type 1 diabetes," "T1D," and "Adults." The Boolean operators "OR" and "AND" matched the required keywords. Among the search results were publications in full English language, freely available articles, and human trials.

Selection Criteria

We considered the following criteria for inclusion in this review:

- Any study designs that investigate the incidence of DKA among adults with T1D.
- Only adult patients (> 18 years).
- Study articles conducted between 2018-2023.
- English language.
- Free accessible articles.

Data Extraction

Duplicates in the search strategy output were found using Rayyan (QCRI) [28]. To determine the titles' and abstract relevance, the researchers used a set of inclusion/exclusion criteria to filter the combined search results. The reviewers carefully read each paper that matches the requirements for inclusion. The authors provided other methods of resolving disputes with some thought. The authors extracted data about the study titles, authors, study year, country, participants, gender, risk factors, epidemiological data, and main outcomes.

Strategy for Data Synthesis

Summary tables were created using information from pertinent research to give a qualitative overview of the results and study components. Following data extraction for the systematic review, the most effective

strategy for utilizing data from the included study articles was selected.

Risk of Bias Assessment

Using the ROBINS-I risk of bias assessment approach for non-randomized trials of therapies, the quality of the included studies was assessed [29]. The seven themes assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choosing the reported result.

RESULTS

Search Results

A total of 300 study articles resulted from the systematic search, and 179 duplicates were deleted. Title and abstract screening were conducted on 121 studies, and 91 were excluded. 30 reports were sought for retrieval, and 2 articles were retrieved. Finally, 28 studies were screened for full-text assessment; 10 were excluded for wrong study outcomes, 6 for the wrong population type, and 1 article was a letter to the editors. Eleven eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

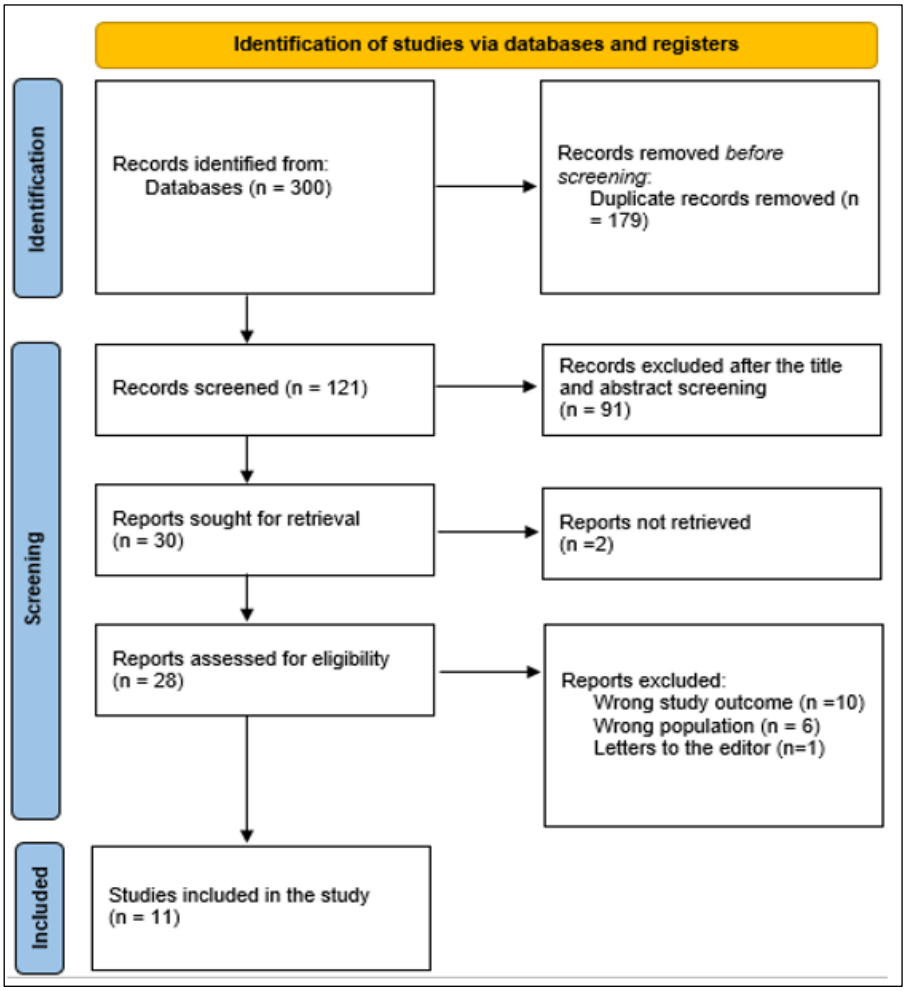

Figure (1): PRISMA flowchart summarizes the study selection process

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included eleven studies with a total of 104388 participants, and 52733 (50.5%) were males. Six studies were retrospective in nature [32-34, 36-38], two were cross-sectional studies [31, 35], one was a cohort study [31], and one was a case-control study [39].

Table (2) presents the clinical characteristics. The incidence of DKA in patients with T1D ranged from 2% [31] to 64.8% [36]. The included studies reported that non-adherence, alcohol, greater HbA1c levels, longer-term diabetes, teenage age group, female gender, associated comorbid diseases, and fat and carbohydrate intake were risk factors for developing DKA [31-33, 35, 36]. Interstingly, people with DKA who are admitted have significant rates of depression, drug abuse, and social deprivation [38, 39]. Fibre intake and freeStyle Libre were protective factors for developing DKA in T1D [31, 33].

Table (1): Sociodemographic characteristics of the included participants

Study	Study design	Country	Participants	Gender	Age
Lee & Orr-Walker 2020 [30]	Cohort	New Zealand	57	NM	31 (54.4)
Ahola *et al.*, 2021 [31]	Cross-sectional	Finland	1391	39-58	601 (44)
Al Hayek *et al.*, 2020 [32]	Retrospective	Saudi Arabia	336	26.1 ± 6.6	143 (42.6)
Al Hayek & Al Dawish 2021 [33]	Retrospective	Saudi Arabia	47	19.8 ± 6.2	22 (46.8)
Jensen *et al.*, 2021 [34]	Retrospective	USA	7612	NM	4119 (54.1)
Monteiro *et al.*, 2022 [35]	Cross-sectional	Brazil	44	26.2 ± 14.5	0
Shaka *et al.*, 2021 [36]	Retrospective	USA	94668	34.9	47713 (50.4)
Burns *et al.*, 2018 [37]	Retrospective	Australia	39	20 (Median)	NM
Hare *et al.*, 2021 [38]	Retrospective	Australia	128	26-48	74 (57.8)
Hamblin *et al.*, 2022 [39]	Case-control	Australia	123	22-51	70 (56.9)

Table (2): Clinical characteristics and outcomes of the included studies

Study	DKA incidence	Main outcomes	ROBIN-I
Lee & Orr-Walker 2020 [30]	69 DKA admissions from 57 people	One of the main reasons for DKA admissions at Middlemore Hospital is non-adherence. Both individuals with recurring DKAs and those whose non-adherence was the cause of DKA showed similar patterns.	Moderate
Ahola *et al.*, 2021 [31]	28 (2%)	Consuming alcohol was linked to a higher chance of DKA admission, although consuming plenty of fibre decreased the risk. On the other hand, consuming more carbohydrates at the expense of fat was linked to a higher risk of hospitalisation for hypoglycemia.	Moderate
Al Hayek *et al.*, 2020 [32]	105 (31.2)	DKA can occur in patients with greater HbA1c levels, longer-term diabetes, teenage age group, female gender, and noncompliance with clinic sessions.	Moderate
Al Hayek & Al Dawish 2021 [33]	137 DKA events in the 47 patients during the 2-year period	In individuals with T1DM and recurrent DKA, FreeStyle Libre is linked to decreased frequency and severity of DKA events, decreased HbA1c, and increased glucose testing frequency.	Moderate
Jensen *et al.*, 2021 [34]	3091 (40.6)	Changes in the population distribution of genetic susceptibility variables probably do not cause the increase in DKA prevalence at or near diabetes diagnosis documented in this study and other recent publications mentioned above.	Moderate
Monteiro *et al.*, 2022 [35]	27 (62.2)	Throughout the two study periods, there was no discernible variation in the primary precipitating factor of DKA, which continued to be non-adherence, followed by infection. Outside of the therapeutic range, elevated HbA1c signifies inadequate management of diabetes and could partially account for low adherence as a decompensation trigger.	High
Shaka *et al.*, 2021 [36]	61345 (64.8)	DKA was the most often given diagnosis upon readmission; additional causes included diabetes with hypoglycemia, diabetes with hyperglycemia, diabetic autonomic polyneuropathy, and sepsis from an unidentified pathogen. The average age of readmitted patients is higher, and they are more likely to be female, have a CCI of two or higher, and have higher rates of COPD, CKD, and concomitant HTN.	Moderate
Burns *et al.*, 2018 [37]	55 DKA admissions from 39 patients	The absence of supportive care in T1DM for YWD negatively impacts DKA hospitalisation rates and LOS.	Moderate
Hare *et al.*, 2021 [38]	154 DKA among 128 people	People with DKA who are admitted have significant rates of mental illness, drug abuse, and social deprivation, especially if they have repeated presentations.	Moderate
Hamblin *et al.*, 2022[39]	164 DKA among 123 people	Patients with DKA seem to be more likely to experience depression and diabetes distress. Social deprivation is also widespread.	Moderate

DISCUSSION

A serious acute metabolic consequence of T1D, DKA is characterised by acidosis, ketosis, and frequently hyperglycemia [40, 41]. 54%–76% of all T1D-associated deaths in individuals under 30 years old are attributable to DKA [42, 43]. In this review, we reported that the incidence of DKA in patients with T1D ranged from 2% [31] to 64.8% [36]. Lebovitz reported that eleven distinct research centres had their overall DKA rates assessed. The results demonstrated a substantial negative link between the background incidence of T1D for these centres and the overall DKA rate, which ranges from

26% to 67% [44]. Regarding the description of DKA episodes and the methodology for identifying them, the included research was not entirely in agreement. The fact that the epidemiology of DKA events was not a primary (or, in many cases, even a secondary) objective of the study—rather, DKA data were reported only as part of overall rates of acute diabetic complications (along with other parameters such as severe hypoglycaemic events)—is one of the main issues affecting the quality determination for many of the included studies. This could be part of the reason why DKA events don't have many thorough explanations.

We found that non-adherence, alcohol, greater HbA1c levels, longer-term diabetes, teenage age group, female gender, associated comorbid diseases, and fat and carbohydrate intake were risk factors for developing DKA [31-33, 35, 36]. Patients with good or poor glycaemic control, as indicated by an HbA1c of ≥8.5% (or 120 per 1000 for those who had at least one DKA event in the preceding 12 months), were more likely to experience DKA. On the other hand, patients with excellent glycaemic control—defined as HbA1c <6.5% (10 per 1000 for patients with at least one DKA event in the previous 12 months)—were found to have the lowest prevalence of DKA [45]. According to Rewers and colleagues [46], body image problems that cause teenage girls to forego insulin injections in an effort to lose weight may be the cause of their higher risk of DKA compared to younger children. Since higher insulin dose was a predictor of DKA at all ages, increased insulin resistance brought on by puberty or obesity may also contribute to an increased risk of DKA. Although eating problems are common in children with diabetes, they may not always be easy to diagnose in this population, increasing the risk of DKA. According to one study that made use of the Diabetes Audit and Research in Tayside Scotland database, the main cause of long-term poor glycaemic control and DKA in young individuals with insulin-dependent diabetes mellitus is likely to be poor adherence to insulin administration [47].

We also found that, interestingly, people with DKA who are admitted have significant rates of depression, drug abuse, and social deprivation [38, 39]. It is noteworthy, nevertheless, that the one study that prospectively looked at baseline psychiatric symptoms and their relationship to recurrent DKA discovered that psychiatric symptoms predicted both the presence of psychiatric symptoms at baseline and the presence of psychiatric symptoms at follow-up. This could suggest that there is a reciprocal association between mental health issues and recurrent DKA—a conclusion that has since been confirmed by additional research. Therefore, it could be beneficial for services to implement a programme of routine psychiatric evaluation for patients admitted with acute diabetic problems, paying special attention to symptoms of disordered eating and possible suicide risk. Moving from paediatric to adult diabetes services is a legitimate concern, given the higher likelihood of recurrent DKA seen in the adolescent/young adult age group. Diabetes services have long been concerned about this, and to better support young people at this vulnerable time, a number of programmes and specialised services have been launched [48].

LIMITATIONS

This study's limitations include the following: (i) the paucity of research on T1D patients, particularly the complications of the disease; (ii) the variations in studies across different countries, which make it challenging to track a general trend of DKA prevalence among Arab countries; (iv) the majority of DKA patients were primarily identified through medical records, which are prone to recording bias; and (iii) the majority of patients reported here are primarily from hospital records without controls, making meta-analysis impossible.

CONCLUSION

Risk factors for developing DKA included non-adherence, alcohol, higher HbA1c levels, longer-term diabetes, teenage age group, female gender, associated comorbid conditions, and intake of fat and carbohydrates. It's interesting to note that despair, drug misuse, and social deprivation are prevalent among DKA patients who are admitted. Consuming fibre and using free Style Libre protected T1D patients from developing DKA. Future research is obviously needed to provide a more comprehensive description of the epidemiology of DKA among adult T1D patients.

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