Understanding the Prevalence and Burden of Diabetic Ketoacidosis (DKA) in People with T1DM at High Risk for DKA: A Structured Literature Review

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PURPOSE

- Diabetic ketoacidosis (DKA) is a serious complication for people with diabetes (PwD) – it is more often experienced with type 1 diabetes mellitus (T1DM) but can also occur with type 2 diabetes mellitus (T2DM).[1,2]
- DKA is characterised by a triad of hyperglycaemia (or a history of diabetes), ketosis, and metabolic acidosis, with rapid symptom onset.[2] Symptoms include increased thirst, excessive urine production, weight loss, excessive tiredness, nausea, vomiting, dehydration, abdominal pain, hyperventilation, and reduced consciousness.[1-3]
- If left untreated, DKA can be life-threatening.[3]
- DKA is particularly prevalent with T1DM in paediatrics and adolescents, resulting in increased incidence of hospitalizations, recurrence, and mortality.[4]
- Furthermore, poor glycaemic control in paediatrics and adolescents, especially for those with a haemoglobin A1c (HbA1c) level of more than 9%, is a known risk factor for developing DKA.[5]
- DKA in insulin pump-users is also a concern, particularly as device-related malfunctions can result in a failure of required insulin delivery.[6] Use of SGLT2 inhibitors (SGL2i) is also associated with DKA.
- This structured literature review investigated the published burden of DKA and associated unmet needs, with a particular focus on paediatric and adolescent, and people managed with an insulin pump or SGLT2i.

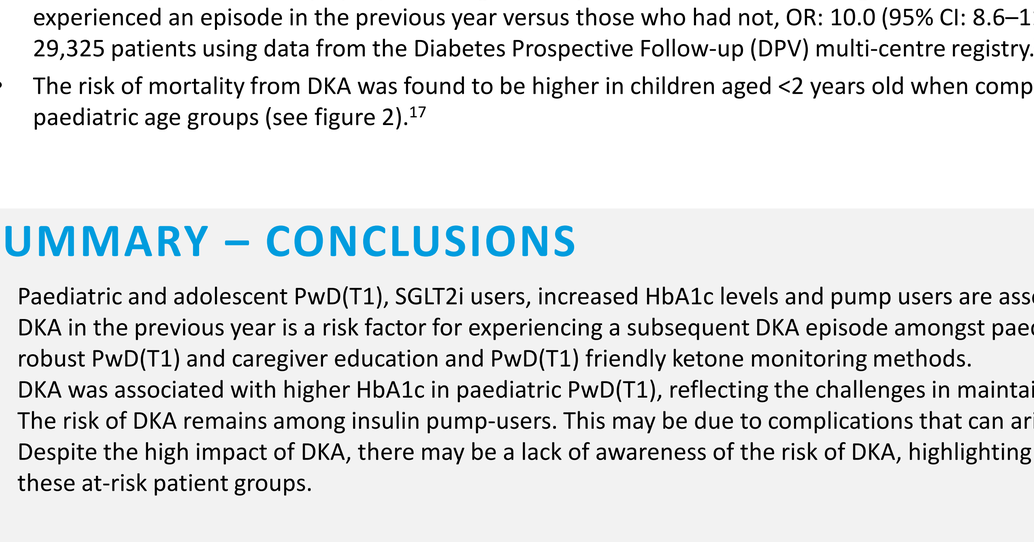
METHODS

- A literature search was conducted in MEDLINE and Embase via the Ovid platform, using terms for burden of DKA in T1DM.
- Publication dates were limited to a 10-year period from 2011–2021, plus conference proceedings from 2020 and 2021.
- Results underwent title, abstract and full text screening stages using pre-specified PICOS criteria for burden of DKA in paediatric and adolescent PwD(T1) , insulin pump-users and people undergoing treatment with SGLT2i.
- A quality check of selected records was performed by a second reviewer and any disagreements were resolved via a consensus between the reviewers.

RESULTS

- 43 articles were included in the final review (see figure 1)[6-48]:
  - 19 – burden and unmet need in paediatric and adolescent PwD(T1)
  - 5 – unmet need associated with ketone testing
  - 8 – burden and unmet need in pump users
  - 11 – burden in people treated with SGLT2i.
- The findings presented from this review were exploratory in nature due to the highly variable evidence base which differed greatly in terms of study design, sample size and geography. Also, over half of studies identified (n=22) did not report how DKA was defined within the methods. The results should therefore be interpreted with caution.

Figure 1. PRISMA Diagram



Burden and unmet need of DKA in paediatric and adolescent PwD(T1)

- Literature identified was from over 22 countries with the most common study designs being observational studies, retrospective cohort studies, retrospective chart studies and literature reviews.
- DKA frequency is higher in paediatric and adolescent patients with T1DM, with a greater incidence of DKA per 1,000 compared to the overall T1DM population, (108 DKA events per 1,000 patients versus 55.5 per 1,000 patients respectively, based on matched populations).[7]
- Studies reporting the prevalence of DKA in paediatric PwD(T1) were highly heterogenous and the prevalence reported varied across all age groups and between the studies.[8-19] DKA percentage prevalence varied from 4.0%–47.2%.[11,14]
- The risk of paediatric PwD(T1) experiencing a DKA episode was reported to be greater in those who had experienced an episode in the previous year versus those who had not, OR: 10.0 (95% CI: 8.6–11.8) among 29,325 patients using data from the Diabetes Prospective Follow-up (DPV) multi-centre registry.[20]
- The risk of mortality from DKA was found to be higher in children aged <2 years old when compared to older paediatric age groups (see figure 2).[17]
- Poor adherence or non-compliance to insulin therapy and not regularly monitoring glucose have been reported to be substantial precipitating factors of DKA events across paediatric PwD(T1) (68.1% and 78.7% respectively) in a trial of 47 patients with a history of DKA episodes.[21] Furthermore, people have been reported to mistake DKA symptoms, e.g. nausea and fever, for influenza and thus may not check ketone levels while experiencing DKA episodes.[1]
- A multi-centre, retrospective observational study of paediatric PwD(T1) in Italy (n=2,025, 43 experienced DKA), found that DKA was more prevalent in individuals with higher HbA1c levels(see figure 3).[12]

Figure 2. DKA mortality by paediatric age group (n=297)[17]

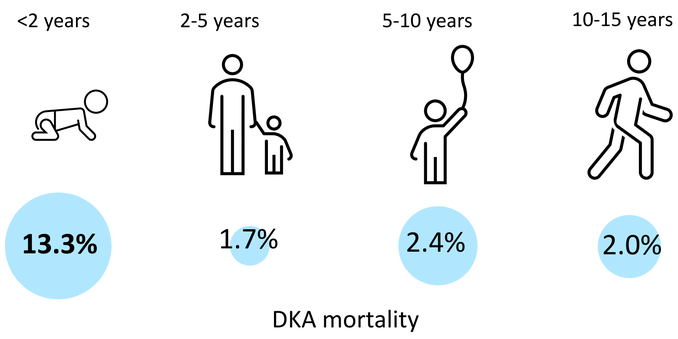
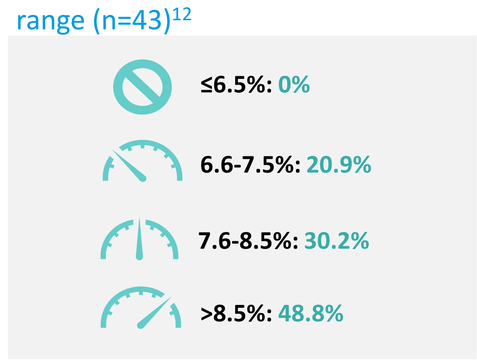


Figure 3. DKA episodes by HbAc1 range (n=43)[12]



Burden and unmet need of DKA in insulin pump-users

- Data regarding frequency of DKA with insulin pump use vs non-pump users was varied and inconclusive across the studies identified (8-59% for non-pump vs 2% to 41% pump users).[30-35] Although, the findings suggested a trend for lower frequency of DKA with pump use across the studies, DKA still remains a concern with use of these devices.
- The frequency of DKA episodes was reduced in insulin pump-users by 4.9% when compared to MDI (multiple daily injection) users.[37] However, DKA is still a serious complication among insulin pump-users due to device-related issues.[47]

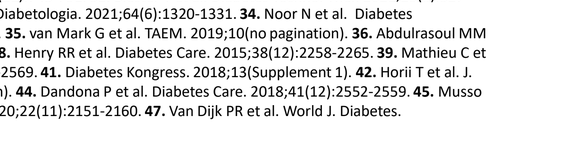
The unmet need associated with ketone testing

- A questionnaire study (n=2,995) reported that 45% of paediatric and adult participants with T1DM claimed to "never" check ketones when they detected a fever and 38% reported "never" checking ketones when experiencing vomiting.[25]
- Only about 20% of PwD(T1) reported having a blood ketone meter according to a 2019 registry study carried out in the US.[26]
- Three studies reported on methods of ketone monitoring of T1DM in paediatric and adolescent PwD(T1) experiencing DKA. Ketone monitoring methods included testing urine and blood ketone levels, and monitoring changes in β-hydroxybutyrate (BHB).[27,28,29]

Association between DKA and patients undergoing treatment with SGLT2i

- Overall, an increased risk of DKA was reported in PwD(T1) treated with SGLT2i (see figure 4).[29,37-46]
- A meta-regression study including 7,396 PwD(T1), reported an increased risk of DKA in people treated with SGLT2i (risk ratio: 2.81, 95% CI 1.97–4.01, p<0.001).[45]
- DKA associated with SGLT2i use is euglycemic and not accompanied by spikes in glucose level as in classic DKA symptoms, thus making it harder to detect.[48]

Figure 4. Frequency of DKA with and without SGLT2i in people with T1DM[42–44]



*n= 11,475[42], n= 3,238[43], n=708[44]

SUMMARY – CONCLUSIONS

- Paediatric and adolescent PwD(T1), SGLT2i users, increased HbA1c levels and pump users are associated with an increased risk for DKA, despite heterogeneity and inconsistency in reporting across studies.
- DKA in the previous year is a risk factor for experiencing a subsequent DKA episode amongst paediatric and adolescent PwD, making it important to prioritise methods of detection and prevention of DKA events, including robust PwD(T1) and caregiver education and PwD(T1) friendly ketone monitoring methods.
- DKA was associated with higher HbA1c in paediatric PwD(T1), reflecting the challenges in maintaining glucose control in this population.
- The risk of DKA remains among insulin pump-users. This may be due to complications that can arise with pump use such as device malfunction or infusion-related issues.
- Despite the high impact of DKA, there may be a lack of awareness of the risk of DKA, highlighting the need for more education and improvements in ketone monitoring to reduce the occurrence and overall burden of DKA in these at-risk patient groups.

DECLARATION OF INTEREST

- Biju Varughese was an employee of Abbott Diabetes Care during the time this research was conducted.
- Ben Rousseau, Rikal Bhaila and Louisa Oliver are employees of Adelphi Values PROVE.
- Adelphi Values PROVE conducted the research, with funding from Abbott Diabetes Care.
- Abbott Diabetes Care provided financial support for this poster.

Poster EPH138 presented at ISPOR Europe 2022 conference, November 6-9, 2022 in Vienna, Austria

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