Risk of Diabetic Ketoacidosis Across Stages of Chronic Kidney Disease in Patients with Type 1 Diabetes in the U.S. Food and Drug Administration's Sentinel System

Presented at the 2025 ISPE Annual Meeting

Po-Yin Chang[1], Tae Hyun Jung[1], Joo-Yeon Lee[1], Yandong Qiang[1], Mari Suzuki[1], Justin Penzenstadler[1], Jamal T. Jones[1], Jillian Burk[2], Laura Hou[2], Katherine E. Round[2], Maria Lewis[2], Jennifer G. Lyons[3]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; [2] Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, MA, USA; [3] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

Background

Diabetic ketoacidosis (DKA) is a life-threatening complication of type 1 diabetes (T1D). There is a paucity of information in the literature describing the risk of DKA in patients with T1D with different chronic kidney disease (CKD) stages.

Objectives

To describe patient characteristics and estimate incidence rate of DKA in patients with T1D across CKD stages

Methods

Data Source (Study Period): Six Data Partners in the U.S. FDA Sentinel Distributed Database (March 1, 2013 - February 29, 2024)

Study Population: Insured patients who had dispensing records for short/rapid-acting insulin, with T1D identified by (1) >50% of diabetic diagnosis codes specific to T1D[a] and (2) no dispensing of noninsulin antidiabetic drug (except metformin) at baseline period (i.e., the 365 days before the index dispensing of the insulin)

DKA Events: Identified via diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 250.1x or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) E1x.1x) in any diagnosis position in inpatient or emergency department visits[b]

CKD Stage: Classified into three stages at baseline based on a code-based algorithm that was validated against estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2)[c]: Stages 1 or 2 (eGFR ≥60), 3 (eGFR 30-59), and 4 or 5 (eGFR <30, including dialysis)

Follow-Up: Began at the index dispensing of insulin; ended at the first occurrence of a DKA event, end of exposure, death, end of available data, switch to a different CKD stage, or day 365 since follow-up

Statistical Analysis: Estimated crude incidence rate for DKA across the CKD stages and crude hazard ratios (HR) along with 95% confidence intervals (CI) for DKA in CKD stage 3 and in CKD stage 4 or 5, using CKD stage 1 or 2 as reference

[a] Klompas, M, et al. 2013 https://pubmed.ncbi.nlm.nih.gov/23193215/
Schroeder EB et al. 2018 https://pubmed.ncbi.nlm.nih.gov/29292555/
[b] Bobo WV, et al. 2011 https://pubmed.ncbi.nlm.nih.gov/22112194/
[c] Friberg G, et al. 2018 https://pubmed.ncbi.nlm.nih.gov/29644067/

Results

Identified 683,436 patients with T1D, 50.2% were male

- 89.1% had CKD stage 1 or 2 (mean age 39 years), 5.6% had CKD stage 3 (mean age 62 years), and 5.3% had CKD stage 4 or 5 (mean age 54 years)
- **Insulin pump use** was observed in 22.0% of patients with CKD stage 1 or 2, 10.8% of patients with CKD stage 3, and 6.7% of patients with CKD stage 4 or 5
- 19.1% of patients with CKD stage 4 or 5 had a **history of DKA** at baseline, greater than the proportion of patients with CKD stage 1 or 2 (13.5%) and stage 3 (12.8%)
- 35.6% of patients with CKD stage 1 or 2 had **hypertension** at baseline, whereas >91% of patients with CKD stage 3 or above had hypertension

Table 1. Baseline Characteristics in 683,436 Patients with T1D Across CKD Stages

Characteristics of Patients with T1D	Stage 1 or 2[a]	Stage 3[a]	Stage 4 or 5[a]
N	608,462 (89.1%)[b]	38,583 (5.6%)[b]	36,391 (5.3%)[b]
Age (years), mean ±sd	39.1 ±16.1	62.2 ±14.0	53.8 ±15.2
<18	21.8%	0.4%	0.7%
19-24	10.0%	0.8%	0.9%
25-44	29.8%	15.4%	31.5%
45-64	21.8%	31.5%	38.8%
≥65	16.6%	51.9%	28.2%
Male	50.2%	48.5%	51.7%
Short/rapid-acting insulin[c]	87.5%	83.1%	79.9%
Long/intermediate-acting insulin	69.8%	70.0%	73.5%
Combination insulin	2.8%	4.7%	4.5%
Insulin pump	22.0%	10.8%	6.7%
Metformin	8.6%	7.9%	1.9%
Continuous glucose monitoring	23.5%	20.4%	14.3%
Overweight/obesity	10.8%	24.7%	25.7%
History of DKA	13.5%	12.8%	19.1%
Combined comorbidity score, mean ±sd	1.5 ±1.8	5.4 ±2.9	6.9 ±3.1
Hypertension	35.6%	91.8%	95.9%
Hyperlipidemia	39.1%	80.3%	77.0%
Alcohol use	3.6%	5.2%	5.1%

CKD, chronic kidney disease; DKA, diabetic ketoacidosis; sd, standard deviation; T1D, type 1 diabetes mellitus
[a] Stage 1 or 2: eGFR ≥60 mL/min/1.72 m^2; Stage 3: eGFR 30-59 mL/min/1.72 m^2, Stage 4 or 5: eGFR <30 mL/min/1.72 m^2
[b] Denominator is the 683,438 patients with T1D who received short/rapid-acting insulin
[C] Short/rapid-acting insulin use within 365 days before the index dispensing of the short/rapid-acting insulin

Table 2. Incidence Rate and HR (95% CI) for DKA among Patients with T1D Across CKD Stages

CKD Stage	T1D Patients, n	At-Risk PY	DKA Cases, n	Incidence of DKA, Cases per 100 PY	Crude HR (95% CI)
Stage 1 or 2	608,462	167,338	17,530	10.5	Reference
Stage 3	38,583	9,882	1,381	14.0	1.56 (1.47, 1.64)
Stage 4 or 5	36,391	8,687	2,384	27.4	2.84 (2.71, 2.97)

*Stage 1 or 2: eGFR ≥60 mL/min/1.72 m^2; Stage 3: eGFR 30-59 mL/min/1.72 m^2, Stage 4 or 5: eGFR <30 mL/min/1.72 m^2
CI, confidence interval; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; PY, person-years; T1D, type 1 diabetes mellitus

Conclusion

- Patients with T1D had different demographics and baseline characteristics (e.g., age, insulin pump use, DKA history) depending on their CKD stages
- Risk of DKA during a one-year follow-up increased numerically with advancing CKD stage
- Adjustment for potential confounding factors is needed for further investigation into the risk of DKA in patients with T1D with different CKD stages

Disclosure and Acknowledgements

- The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government
- This project was supported by Task Order 75F40124F19014 under Master Agreement 75F40119D10037 from the U.S. FDA
- J.B., L.H., K.E.R., M.L, and J.G.L. are employees of HPHCI, an organization which conducts work for government and private organizations, including pharmaceutical companies
- Many thanks are due to the Sentinel Data Partners who provided data used in the analysis