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Multicentre, retrospective cohort study protocol to identify racial and ethnic differences in acute kidney injuries in children and adolescents with diabetic ketoacidosis

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ABSTRACT

Introduction Approximately 40% of children with diabetic ketoacidosis (DKA) develop acute kidney injury (AKI), which increases the risk of chronic kidney damage. At present, there is limited knowledge of racial or ethnic differences in diabetes-related kidney injury in children with diabetes. Understanding whether such differences exist will provide a foundation for addressing disparities in diabetes care that may continue into adulthood. Further, it is currently unclear which children are at risk to develop worsening or sustained DKA-related AKI. The primary aim is to determine whether race and ethnicity are associated with DKA-related AKI. The secondary aim is to determine factors associated with sustained AKI in children with DKA.

Methods and analysis This retrospective, multicentre, cross-sectional study of children with type 1 or type 2 diabetes with DKA will be conducted through the Paediatric Emergency Medicine Collaborative Research Committee. Children aged 2–18 years who were treated in a participating emergency department between 1 January 2020 and 31 December 2023 will be included. Children with non-ketotic hyperglycaemic-hyperosmolar state or who were transferred from an outside facility will be excluded. The relevant predictor is race and ethnicity. The primary outcome is the presence of AKI, defined by Kidney Disease: Improving Global Outcomes criteria. The secondary outcome is 'sustained' AKI, defined as having AKI ≥48 hours, unresolved AKI at last creatinine measurement or need for renal replacement therapy. Statistical inference of the associations between predictors (ie, race and ethnicity) and outcomes (ie, AKI and sustained AKI) will use random effects regression models, accounting for hospital variation and clustering.

Ethics and dissemination The Institutional Review Board of Children's Minnesota approved this study. 12 additional sites have obtained institutional review board approval, and all sites will obtain local approval prior to participation. Results will be presented at local or national conferences and for publication in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large, geographically diverse study cohort will allow for adequate power to detect a difference between study groups.
⇒ Chart review overcomes the limitation of using only International Classification of Disease codes for identification of diabetic ketoacidosis and acute kidney injury.
⇒ Retrospective review introduces the potential for selection and classification bias by relying on the accuracy of data extraction.
⇒ Findings may not be generalisable to care centres other than children's hospitals.

INTRODUCTION

More than 3 000 000 children in the USA have type 1 diabetes (T1D)[1–3] and over 50% experience at least one episode of diabetic ketoacidosis (DKA).[4–7] Children with type 2 diabetes (T2D) are also at risk of developing DKA,[8 9] which has been increasing in this population.[10 11] Acute kidney injury (AKI) has been increasingly recognised as a complication in children with DKA, particularly children with severe DKA who require admission to a paediatric intensive care unit.[12 13] The true incidence of AKI during episodes of DKA is likely close to 40%, but estimates vary substantially from 25% to 78%.,[14–22] Moreover, renal tubular damage and acute tubular necrosis have been estimated to occur in 73% and 32% of children with DKA-related AKI, respectively.[22] However, the extent to which episodes of DKA-related AKI modify the risk of developing diabetic kidney disease (DKD) is unclear. Recent evidence suggests that the number of episodes of DKA-related AKI in childhood is associated with the development of persistent microalbuminuria, increasing the risk of chronic kidney damage.[23 24] Whereas transient microalbuminuria may regress,[25] persistent proteinuria signifies the onset of DKD, which progresses

to kidney failure in up to 27% of adults with T1D[26–29] and represents the leading cause of renal failure in the USA.[30]

The care of individuals with T1D is fraught with inequity.[31–33] Studies among adult populations have shown that DKD disproportionally affects people of colour, occurring in 13% of non-Hispanic black and Hispanic adults compared with 7% of non-Hispanic white adults.[34 35] Similarly, the probability of DKA-related AKI is significantly higher among non-Hispanic black children compared with non-Hispanic white and Hispanic children.[36] It is unclear why such disparities exist, although it has been suggested that differences in glycaemic control may contribute. Compared with non-Hispanic white and Hispanic children, non-Hispanic black children are more likely to have higher mean haemoglobin A1c levels,[37 38] emergency department (ED) visits, hospitalisations and mortality for diabetes-related conditions[36–39] and are less likely to use diabetes technology (insulin pumps, continuous glucose monitors)[37 38 40 41] or have routine outpatient diabetes care.[42] Measures of socioeconomic status have also been implicated as contributing factors. Non-Hispanic black children are more likely to be from families that have public insurance,[5 43–51] lower income or live in areas of poverty,[5 44 48 50 51] compared with non-Hispanic white or Hispanic children; all of which have been associated with higher risk and severity of DKA. At present, there is limited knowledge of racial and ethnic differences in diabetes-related kidney injury in children with T1D. Although recent studies have investigated risk factors for DKA-related AKI in children,[14–21] none have examined whether race and ethnicity are associated with differences in outcomes.

As a newly recognised complication in children with DKA, the mechanisms underlying DKA-related AKI are not well understood. Clinical and laboratory markers of volume depletion are associated with DKA-related AKI,[14–21] supporting the hypothesis that the underlying mechanism relates to prerenal azotaemia (eg, dehydration).[14–21] Although most children arrive at the ED with AKI already present, approximately 2%–7% develop worsening AKI during treatment, at a time when intravascular volume is being re-established.[15 20 21] This has led to the hypothesis that other mechanisms, such as reperfusion injury or inflammation, may contribute to DKA-related AKI.[21] Understanding factors associated with worsening or sustained AKI is important for early identification of at-risk children, allowing for targeted interventions that may reduce the risk of kidney damage and development of DKD. Current strategies to reduce the progression of DKD have centred on intensive glycaemic control[52–54] and optimisation of risk factors such as blood pressure and body weight.[55] Treatment with renin–angiotensin system blockers has also been shown to reduce DKD progression.[56–58] More recently, consideration has been given to novel therapies typically used for DKD in patients with T2D, such as sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists,[59 60] although it remains to be seen whether these medications are safe and effective for patient with T1D. At present, it is unclear which children will develop worsening or sustained DKA-related AKI and may benefit from more intensive interventions to reduce the risk of DKD.

We outline a multicentre, cross-sectional study of children and adolescents using a large, geographical and racially diverse sample in order to better understand racial and ethnic differences associated with DKA-related AKI. The objective of this study is to establish a national database of children with DKA and DKA-related AKI. The primary aim is to determine whether race and ethnicity are associated with DKA-related AKI. The secondary aim is to determine factors associated with sustained AKI in children with DKA. We hypothesise that non-Hispanic black children are more likely to develop DKA-related AKI compared with non-Hispanic white and Hispanic children. We hypothesise that we will identify distinct factors associated with sustained DKA-related AKI, defined as a composite measure of sustained AKI≥48 hours after identification of AKI (ie, increasing or persistently elevated creatinine), need for renal replacement therapy (RRT) or sustained AKI at last measurement in the hospital. Further, we hypothesise that race and ethnicity are independently associated with sustained AKI, where non-Hispanic black children are more likely to develop sustained AKI compared with non-Hispanic white or Hispanic children.

METHODS AND ANALYSIS

Study overview, design and population

We will conduct a retrospective, multicentre cross-sectional study of children and adolescents 2–18 years diagnosed with DKA and treated in a participating ED between 1 January 2020 and 31 December 2023. This study will be conducted in conjunction with the Paediatric Emergency Medicine Collaborative Research Committee (PEMCRC), which provides a framework for multicentre investigation. The PEMCRC is supported by the American Academy of Pediatrics Section on Emergency Medicine and facilitates the development of rigorous collaborative research in the field of paediatric emergency medicine. The PEMCRC is an unfunded volunteer effort that provides an important means of developing high-quality protocols and identifying interested coinvestigators at over 40 member sites. Site recruitment began in November 2023.

Inclusion criteria

The study population will first be identified using International Classification of Disease, 10th revision (ICD-10) codes, which include children with T1D with DKA and T2D with DKA. Encounters will be reviewed at each site to confirm the presence of DKA using laboratory criteria.[20 61]

- Children and adolescents 2–18 years.
- Treated in a participating ED between 1 January 2020 and 31 December 2023.

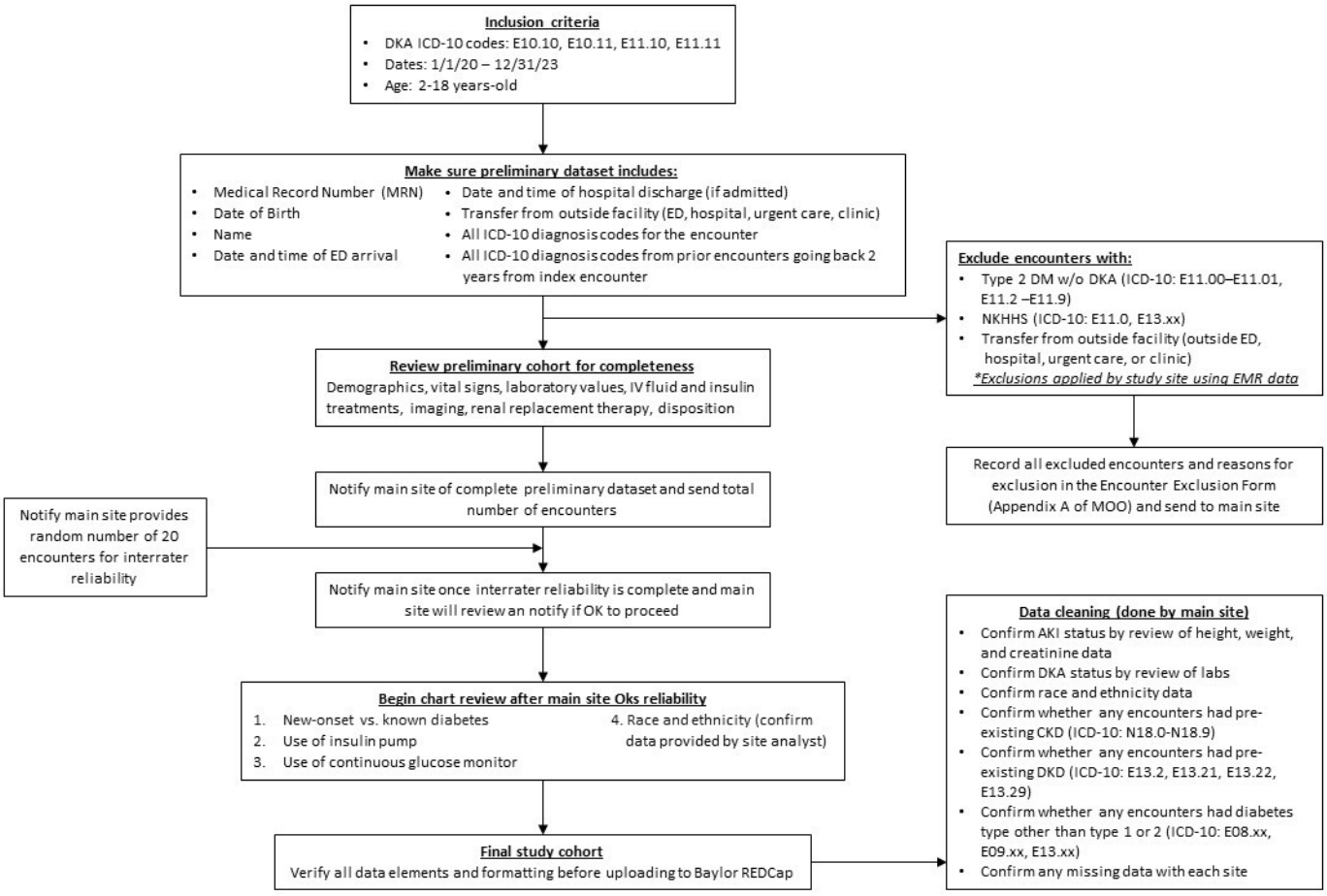

Figure 1 Study cohort identification strategy. DKA, diabetic ketoacidosis; ED, emergency department; ICD-10, International Classification of Disease, 10th revision; CKD, chronic kidney disease; DKD, diabetic kidney disease.

- Diagnosed with T1D or T2D and DKA based on ICD-10 coding:
  - E10.10, E10.11, E11.10, E11.11.
- The presence of DKA is confirmed by having all of the following laboratory criteria[62]:
  - Venous pH<7.3 or bicarbonate <18 mmol/L.
  - Positive urine or serum ketones.
  - Glucose >200 mg/dL.

Exclusion criteria

- T2D without DKA (ICD-10: E11.00–E11.01; E11.2–E11.9).
- Nonketotic hyperglycaemic-hyperosmolar state (ICD-10: E11.00, E13.0x, E13.1x).
- Transferred from an outside ED, hospital, urgent care or clinic, as such children are likely to receive IV fluids prior to transfer, which would impact the presence of AKI.
- Missing laboratory values that would preclude confirmation of DKA (exclusion to be applied by the main site during data cleaning).

Data abstraction

We will use retrospective data collected by a combination of local electronic medical record (EMR) data extraction and chart review at all participating sites (figure 1). A detailed manual of operations has been developed, which outlines case ascertainment procedures. A dataset will be maintained at each site per institutional research standards. Each site's dataset will contain the minimum necessary protected health information and identifiers, so that site coinvestigators are able to identify research subjects included from their institution (eg, medical record number, name). Each child will be assigned a unique identification number, which will be used when sharing data with Baylor College of Medicine, the data coordinating centre (DCC). Deidentified data collected at individual sites will then be submitted electronically via REDCap,[63] a secure data collection tool housed at the DCC.

Site recruitment has already taken place, and we have conducted a 'kick-off' meeting to review the study aims and the protocol. In the spring of 2024, we will host two data entry training sessions in order to ensure the accuracy of data entry. Further, we will have quarterly meetings with the main study team to keep the project moving forward, and ad hoc meetings to address any pressing issues that may arise. We anticipate that data collection will begin in July 2024, with study completion by September 2025.

Outcomes and study variables

The primary outcome is the presence of AKI, which is defined by Kidney Disease: Improving Global Outcomes

Table 1 Q values for FAS

Age, years	Height, cm	Q mg/dL
Boys and girls		
1	75.0	0.26
2	87.0	0.29
3	95.5	0.31
4	102.5	0.34
5	110.0	0.38
6	116.7	0.41
7	123.5	0.44
8	129.5	0.46
9	135.0	0.49
10	140.0	0.51
11	146.0	0.53
12	152.5	0.59
13	159.0	0.59
14	165.0	0.61
Male adolescents		
15	172.0	0.72
16	176.0	0.78
17	178.0	0.82
18	179.0	0.85
Female adolescents		
15	164.5	0.64
16	166.0	0.64
17	166.5	0.69
18	167.0	0.69

FAS, full age spectrum.

(KDIGO) criteria and is based on presenting serum creatinine and a baseline creatinine value.[64] The KDIGO criteria define AKI in stages as follows: stage 1 is 1.5–1.9 times baseline creatinine, stage 2 is 2.0–2.9 times baseline creatinine and stage 3 is ≥3.0 times baseline creatinine or the initiation of RRT.[64] Most children are unlikely to have baseline creatinine values, or if they do, likely had values obtained during times of previous illness. As such, we will use an estimated baseline creatinine (EBC) based on an estimated glomerular filtration rate (GFR) of 120 mL/min/1.73 m^2.[65] The child's height and first creatinine measurement in the ED are all that is needed to calculate an EBC and determine the presence of AKI. We will then determine the presence of AKI via both the (1) Schwartz estimating equation,[65] consistent with recent studies[15 21] and (2) full age spectrum (FAS) GFR equation, which has recently been shown to be more accurate.[66–70] Notably, FAS is based on a normalised ratio of the serum creatinine to a constant 'Q', where Q is the median serum creatinine from healthy children based on sex, and either age or height (table 1).[66–70] Thus, the FAS can be calculated with either a 'Q age extension' or 'Q height extension', depending on whether age or height is used for the constant Q. The equations, and variables required, are as follows:

$$\text{Schwartz estimating equation (2009)} : \text{eGFR} = \frac{0.413 \times height\ (cm)}{serum\ creatinine\ \left(\frac{mg}{dL}\right)}$$

$$\text{FAS equation} : \text{eGFR} = \frac{107.3}{serum\ creatinine\ \left(\frac{mg}{dL}\right) \div Q}$$

Using this method, an EBC can be determined using either of the above equations. The EBC will then be compared with the creatinine at the time of the ED encounter, namely the ratio of ED creatinine to EBC, similar to recent studies.[15 20 21]

The secondary outcome is 'sustained' AKI, which will be determined during the data cleaning process. Sustained AKI will be defined as having at least one of the following:

- AKI ≥48 hours after the first creatinine value obtained in the ED (ie, persistently increased ratio of creatinine to EBC). This is consistent with the consensus definition of persistent AKI.[71]
- Unresolved AKI is defined as the ratio of last measured creatinine to EBC (ie, using the last creatinine measurement in the hospital).
- Need for RRT (haemodialysis, peritoneal dialysis or continuous RRT).

We will examine variables known to be associated with DKA-related AKI,[15 17 18 21] including demographics, aspects of the medical history, laboratory studies and clinical interventions during the ED encounter and hospital stay.

Predictors and exposures

Race and ethnicity will be collected as they are recorded in the child's chart. We will categorise race and ethnicity using, at a minimum, the following groups: non-Hispanic black, non-Hispanic white, Hispanic and Asian. This approach is consistent with recent studies[72] and the US Census Bureau approach to categorising racial and ethnic groups.[73] To address limitations with reporting race and ethnicity, each participating site will be asked to provide reporting practices at their institution. The relevant exposure is the presence of DKA.

Data reliability

We will ask investigators from each site to enter the first 20 cases and then pause data entry. The principal investigator will review the submitted data for data entry errors and confirmation of appropriate case ascertainment, and site coinvestigators will then be allowed to continue entering data so long as no errors exist. In the event that case ascertainment or data entry is significantly incorrect, the principal investigator will meet with the site coinvestigator to review the study protocol.

To minimise bias, a second independent reviewer at each site will be asked to review a random sample of 20 charts from their institution. Based on sample size estimates, this would reflect approximately 5%–10% of

encounters. The second independent reviewer will review the five variables that we are seeking for chart review (race, ethnicity, known or new-onset T1D, use of a continuous glucose monitor and use of an insulin pump). Race and ethnicity will be abstracted from the EMR initially, and secondary reviewers will confirm that the EMR data pull race and ethnicity are correct. A weighted kappa will be calculated. Sites with poor agreement will meet with the principal investigator to review data abstraction concerns and complete further training.

Missing data

We anticipate that sites will generally have complete data. However, research staff from the main site will review all data for completeness and will communicate with site coinvestigators about missing data or correcting errors. After review and confirmation of data with site coinvestigators, variables with only a small amount of missing data (eg, <5%–10% of the sample) will be included in the analysis, and variables with more substantial missing data may be excluded. Options for handling missing data include complete case analysis (ie, including only children with no missing data values) or multiple imputation. Specific variables of particular importance are weight during the encounter, height within 3 months of the encounter and initial creatinine value within 4 hours of ED arrival time, all of which are required for the determination of an EBC. As such, we will summarise the degree of missing values for these variables among the entire cohort in order to ensure children with EBC are representative of ED encounters with DKA.

Data analysis

Simple summary statistics and χ^2 tests will be used for unadjusted and descriptive analysis of AKI by race and ethnicity. Statistical inference of the associations between predictors (ie, race and ethnicity) and outcomes (ie, AKI and sustained AKI) will use random effects regression models, which account for hospital variation and clustering and also will adjust for a priori defined confounders (age, sex, insurance status, new vs known T1D, a history of DKA episodes, use of an insulin pump or continuous glucose monitor). For the secondary aim, a stability analysis will be performed excluding those with unresolved AKI at the last measurement in the hospital if the hospital stay was <48 hours (ie, unable to meet the definition of persistent AKI). We will conduct a sensitivity analysis excluding encounters with coding for chronic kidney disease (ICD-10: N18.0–N18.9) and coding for diabetes-related kidney disease, including 'other specified diabetes mellitus with kidney complications' (ICD-10: E13.2), 'other specified diabetes mellitus with diabetic nephropathy' (ICD-10: E13.21), 'other specified diabetes mellitus with chronic kidney disease' (ICD-10: E13.22), 'other specified diabetes mellitus with diabetic kidney complication' (ICD-10: E13.29). We will conduct a second sensitivity analysis excluding diabetes types other than type 1 or type 2, including 'diabetes mellitus due to underlying condition' (ICD-10: E08.xx), 'drug or chemical induced diabetes mellitus' (ICD-10: E09.xx) and 'other specified diabetes mellitus' (ICD-10: E13.xx).

Sample size and power analysis

42 sites are planning to participate in this study (figure 2). Results from a survey of sites indicated that there will be at least 2500 total DKA encounters per year—or equivalently, 60 DKA encounters per site, per year. Over a 4-year period, this equates to 10 000 DKA encounters. However, we anticipate approximately 20% site attrition. Therefore, we conservatively expect at least 7500 DKA encounters to be included. Based on US Census Bureau estimates,[73] as well as incidence rates of T1D and T2D across racial and ethnic groups,[3 74] we anticipate that approximately 4500

Figure 2 PEMCRC study sites planning for study participation. PEMCRC, Paediatric Emergency Medicine Collaborative Research Committee.

(60%) will be non-Hispanic white children, 1350 (18%) will be Hispanic children, 975 (13%) will be non-Hispanic black children and 675 (9%) will be reported as other race and ethnicity.

For the primary aim, comparing the proportion of encounters with DKA-related AKI,[20] the anticipated sample size has at least 89% power to detect a 5 percentage point difference when comparing non-Hispanic white to Hispanic children, and at least 81% power when comparing non-Hispanic white to non-Hispanic black children. For the secondary aim, comparing the proportion of encounters with sustained DKA-related AKI, we consider a binary risk factor that is prevalent in 20% of the sample and the high and low-risk rates of sustained AKI are 5% and 3%, respectively; under these assumptions, this sample size has 95% power to detect this difference at the 5% significance level. If the risk factor is race and ethnicity (primary aim) and the proportion of sustained AKI is 3% among non-Hispanic white children and 5% among Hispanic children and non-Hispanic black children, respectively, then this sample has 92% and 84% power for the comparison of non-Hispanic white children compared with Hispanic children and non-Hispanic black children, respectively. These calculations do not account for additional adjustment of other factors; however, a regression analysis will typically be more powerful than unadjusted comparisons.

Ethics and dissemination

Each coinvestigator will be required to obtain local institutional review board approval at their respective sites prior to local data collection and study participation. This study has been approved by the Institutional Review Board of Children's Minnesota (2023-086), as well as the following 11 institutions: Baylor College of Medicine (H-54867), Boston Children's Hospital (P00047688), Emory University and Children's Healthcare of Atlanta (00002147), John's Hopkin's University (00430237), Lincoln Medical Center (24-003), Medical College of Wisconsin (000050577), Rady Children's Hospital (810070), Rainbow Babies and Children's Hospital (20231591), Seattle Children's Hospital (00004813), Washington University in St. Louis/St. Louis Children's Hospital (202402114) and Yale New Haven Hospital (2000037110). All institutional review board approval letters will be sent to and stored at the main site—Children's Minnesota—to ensure compliance. The results of this study will be presented at local, regional and/or national conferences in the form of abstracts/poster or oral platform presentations. Additionally, Strengthening the Reporting of Observational Studies in Epidemiology[75] will be used for reporting in peer-review journals.

Risks and benefits of study participation

Risks to this retrospective, observational study are minimal. Because data from participating sites will be deidentified and will not contain protected health information, the risk of breach of confidentiality is minimal. Deidentified data will be stored in the REDCap system at the Baylor College of Medicine DCC. The DCC will facilitate the deposit of collected data in a secure and curated repository. Only trained and delegated team members will have access to the data. Any computers used to access study data will be password protected and encrypted. Obtaining a HIPAA (Health Insurance Portability and Acountability Act) authorisation is not practical as this is a retrospective, observational study of previously collected information. A waiver of consent will be requested as the protocol involves minimal risk to the parent and minor child. In addition, a data use agreement will be in place between all participating sites and Baylor College of Medicine. This includes a data use agreement between Children's Minnesota and Baylor College of Medicine. The principal investigator and senior research coordinator at Children's Minnesota will have access to the REDCap database and will be able to download data in a secure manner so that analysis can be conducted at Children's Minnesota.

There are no anticipated direct benefits to children in this study as it is retrospective and observational in nature. The medical community will benefit from further understanding of disparities in the care of children with diabetes, and individuals may benefit from the identification of modifiable risk factors for AKI development.

Patient and public involvement

This research study was designed without patient or public involvement.

DISCUSSION

Strengths

There is limited knowledge regarding which populations with DKA are most at risk for AKI, despite recent literature identifying AKI as a common complication of DKA. Achieving our study aims will allow us to address two specific gaps in knowledge: (1) whether racial differences exist in this population, which is particularly important given the known disparities in diabetes care and (2) whether there are distinct factors associated with sustained AKI, which will allow for identification of children most at risk of renal complications. One of the main strengths of our study is the large, geographically diverse sample, which will represent the largest number of children with DKA and AKI reported to date. Another strength is reporting on racial and ethnic differences in diabetic-related kidney disease. Despite the fact that racial and ethnic differences in kidney disease exist among adults with diabetes, only one study has investigated whether such differences exist in childhood or adolescence.[36] However, this study was limited by using ICD codes to identify the presence of AKI, which likely accounts for the lower prevalence of AKI in this study[36] (4.9%) compared with other studies using laboratory data to identify AKI (25%–78%).[14–21] Results from our study will help to inform prospective investigation focused on

confirmation of racial and ethnic disparities, if found, and will inform studies concentrating on strategies to mitigate health disparities.

Limitations

Our study will be limited by chart review of retrospective data and reliance on documentation within the EMR, which may lead to classification bias. For example, it is unlikely that clinical information will be documented in the same manner across all sites. To overcome this limitation, we developed a detailed manual of operations, which outlines all study variable definitions and methods for data abstraction. Additionally, we will conduct a training session to review data entry and answer questions that may arise from site coinvestigators. This session will be recorded for all site investigators to review. Second, our definition of DKA will rely on ICD-10 coding, which may introduce inaccuracy with case ascertainment. However, we will attempt to overcome this by having coinvestigators also abstract laboratory values to confirm the presence of DKA at the time of the ED encounter. In addition, the use of ICD-10 coding will limit our ability to confirm diabetes diagnosis via the presence of autoantibodies, which may be obtained with varying frequency across sites or from a primary care provider's office. Third, documentation of race and ethnicity will rely on local reporting practices at each participating site, which may lead to misclassification of a child's race and/or ethnicity. To minimise misclassification, we will have a second investigator from each site independently review race and ethnicity data from a random sample of 20 charts. Fourth, since most participating sites are large, tertiary care children's hospitals, our sample will be subject to selection bias. For example, we may not capture children with diabetes who are managed at community hospitals or facilities other than children's hospitals. Therefore, our findings may not be generalisable to these care settings.

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