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FACTORS ASSOCIATED WITH THE SEVERITY OF DIABETIC KETOACIDOSIS IN CHILDREN AND ADOLESCENTS

FATORES ASSOCIADOS À GRAVIDADE DA CETOACIDOSE DIABÉTICA EM CRIANÇAS E ADOLESCENTES

FACTORES ASOCIADOS A LA GRAVEDAD DE LA CETOACIDOSIS DIABÉTICA EN NIÑOS Y ADOLESCENTES

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ABSTRACT

Introduction: Diabetic ketoacidosis (DKA) is one of the most serious acute complications of diabetes in childhood. Its severity reflects the interaction between biological vulnerability, duration of insulin deficiency, diagnostic delay, intercurrent illness, treatment interruption, psychosocial conditions, and access to health care. Factors associated with DKA at the initial diagnosis of diabetes differ from those responsible for episodes in patients with established disease.

Objective: To identify and critically evaluate the factors associated with DKA severity in children and adolescents, distinguishing predisposing factors, precipitating events, admission markers, and predictors of acute complications.

Methods: A structured integrative review was conducted using PubMed/MEDLINE and reference chaining. Pediatric guidelines, systematic reviews, meta-analyses, registry studies, cohort studies, and clinically relevant trials published through September 2026 were considered. Evidence was organized according to DKA at diabetes onset, DKA in established diabetes, biochemical severity, recurrence, and adverse outcomes. Because definitions, populations, and effect measures were heterogeneous, the findings were synthesized narratively.

Results and Discussion: Young age, particularly younger than 2 years, delayed or missed diagnosis, low residual beta-cell function, infection, socioeconomic deprivation, rural residence, and limited health care access were consistently associated with DKA at type 1 diabetes onset. In a systematic review, age younger than 2 years was associated with an odds ratio (OR) of 3.51 for DKA, while delayed or incorrect diagnosis was associated with an

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OR of 2.27. During the coronavirus disease 2019 pandemic, the relative risk of severe DKA increased by 76%. In established diabetes, insulin omission or interruption, previous DKA, chronic hyperglycemia, psychosocial difficulties, and barriers to diabetes technology or specialist follow-up were predominant. A 2026 meta-analysis found that previous DKA increased recurrence risk almost eightfold (OR 7.97; 95% confidence interval [CI] 4.33–14.67). At admission, profound acidosis, hypocapnia, elevated blood urea nitrogen, hyperosmolality, and altered mental status identified patients at greater risk of cerebral or renal injury, but these variables are primarily markers of established severity rather than upstream causes.

Conclusion: Severe pediatric DKA results from a multilevel process rather than a single risk factor. Prevention requires earlier recognition of diabetes symptoms, rapid ketone-based sick-day management, uninterrupted insulin access, structured post-DKA follow-up, psychosocial assessment, and interventions directed toward socially vulnerable families. Severity should be classified by acid-base status, while the risk of complications should be assessed separately using clinical, biochemical, and neurologic findings.

Keywords: Diabetic Ketoacidosis. Type 1 Diabetes Mellitus. Child. Adolescent. Risk Factors. Disease Severity.

RESUMO

Introdução: A cetoacidose diabética (CAD) é uma das complicações agudas mais graves do diabetes na infância. Sua gravidade reflete a interação entre vulnerabilidade biológica, duração da deficiência de insulina, atraso diagnóstico, doenças intercorrentes, interrupção do tratamento, condições psicossociais e acesso aos serviços de saúde. Os fatores associados à CAD no diagnóstico inicial do diabetes diferem daqueles responsáveis pelos episódios em pacientes com doença já estabelecida.

Objetivo: Identificar e avaliar criticamente os fatores associados à gravidade da CAD em crianças e adolescentes, distinguindo fatores predisponentes, eventos precipitantes, marcadores na admissão e preditores de complicações agudas.

Métodos: Foi realizada uma revisão integrativa estruturada utilizando as bases PubMed/MEDLINE e o encadeamento de referências. Foram considerados diretrizes pediátricas, revisões sistemáticas, metanálises, estudos de registros, estudos de coorte e ensaios clinicamente relevantes publicados até setembro de 2026. As evidências foram organizadas de acordo com a CAD no início do diabetes, a CAD em pacientes com diabetes já estabelecido, a gravidade bioquímica, a recorrência e os desfechos adversos. Como as definições, populações e medidas de efeito foram heterogêneas, os achados foram sintetizados de forma narrativa.

Resultados E Discussão: A baixa idade, particularmente inferior a 2 anos, o diagnóstico tardio ou perdido, a baixa função residual das células beta, as infecções, a vulnerabilidade socioeconômica, a residência em áreas rurais e o acesso limitado aos serviços de saúde estiveram consistentemente associados à CAD no início do diabetes tipo 1. Em uma revisão sistemática, a idade inferior a 2 anos esteve associada a uma razão de chances (OR) de 3,51 para CAD, enquanto o diagnóstico tardio ou incorreto esteve associado a uma OR de 2,27. Durante a pandemia da doença pelo coronavírus de 2019 (COVID-19), o risco relativo de CAD grave aumentou 76%. Em pacientes com diabetes já estabelecido, a omissão ou

interrupção da insulina, episódios prévios de CAD, hiperglicemia crônica, dificuldades psicossociais e barreiras ao acesso a tecnologias para o diabetes ou ao acompanhamento especializado foram predominantes. Uma metanálise de 2026 constatou que episódios prévios de CAD aumentaram o risco de recorrência em quase oito vezes (OR 7,97; intervalo de confiança de 95% [IC] 4,33–14,67). Na admissão, acidose profunda, hipocapnia, níveis elevados de nitrogênio ureico no sangue, hiperosmolalidade e alteração do estado mental identificaram pacientes com maior risco de lesão cerebral ou renal, mas essas variáveis são principalmente marcadores de gravidade já estabelecida, e não causas antecedentes.

Conclusão: A CAD pediátrica grave resulta de um processo multifatorial e multinível, e não de um único fator de risco. A prevenção requer reconhecimento precoce dos sintomas do diabetes, manejo rápido dos dias de doença baseado em cetonas, acesso ininterrupto à insulina, acompanhamento estruturado após a CAD, avaliação psicossocial e intervenções direcionadas às famílias socialmente vulneráveis. A gravidade deve ser classificada com base no estado ácido-base, enquanto o risco de complicações deve ser avaliado separadamente por meio de achados clínicos, bioquímicos e neurológicos.

Palavras-chave: Cetoacidose Diabética. Diabetes Mellitus Tipo 1. Criança. Adolescente. Fatores de Risco. Gravidade da Doença.

RESUMEN

Introducción: La cetoacidosis diabética (CAD) es una de las complicaciones agudas más graves de la diabetes durante la infancia. Su gravedad refleja la interacción entre la vulnerabilidad biológica, la duración de la deficiencia de insulina, el retraso diagnóstico, las enfermedades intercurrentes, la interrupción del tratamiento, las condiciones psicosociales y el acceso a los servicios de salud. Los factores asociados con la CAD en el diagnóstico inicial de la diabetes difieren de aquellos responsables de los episodios en pacientes con enfermedad ya establecida.

Objetivo: Identificar y evaluar críticamente los factores asociados con la gravedad de la CAD en niños y adolescentes, distinguiendo los factores predisponentes, los eventos precipitantes, los marcadores al ingreso y los predictores de complicaciones agudas.

Métodos: Se realizó una revisión integradora estructurada utilizando PubMed/MEDLINE y el encadenamiento de referencias. Se consideraron guías pediátricas, revisiones sistemáticas, metanálisis, estudios de registros, estudios de cohortes y ensayos clínicamente relevantes publicados hasta septiembre de 2026. La evidencia se organizó de acuerdo con la CAD al inicio de la diabetes, la CAD en pacientes con diabetes establecida, la gravedad bioquímica, la recurrencia y los resultados adversos. Debido a la heterogeneidad de las definiciones, las poblaciones y las medidas de efecto, los hallazgos se sintetizaron de forma narrativa.

RESULTADOS Y DISCUSIÓN: La corta edad, particularmente inferior a 2 años, el diagnóstico tardío o no realizado, la baja función residual de las células beta, las infecciones, la vulnerabilidad socioeconómica, la residencia en zonas rurales y el acceso limitado a los servicios de salud se asociaron de manera consistente con la CAD al inicio de la diabetes tipo 1. En una revisión sistemática, la edad inferior a 2 años se asoció con una razón de probabilidades (OR) de 3,51 para CAD, mientras que el diagnóstico tardío o incorrecto se asoció con una OR de 2,27. Durante la pandemia de la enfermedad por coronavirus de 2019

(COVID-19), el riesgo relativo de CAD grave aumentó un 76%. En pacientes con diabetes establecida, la omisión o interrupción de la insulina, los episodios previos de CAD, la hiperglucemia crónica, las dificultades psicosociales y las barreras para acceder a tecnologías para la diabetes o al seguimiento especializado fueron predominantes. Un metanálisis de 2026 encontró que los episodios previos de CAD aumentaron el riesgo de recurrencia casi ocho veces (OR 7,97; intervalo de confianza del 95% [IC] 4,33–14,67). Al ingreso, la acidosis profunda, la hipocapnia, los niveles elevados de nitrógeno ureico en sangre, la hiperosmolalidad y la alteración del estado mental identificaron a los pacientes con mayor riesgo de lesión cerebral o renal, pero estas variables son principalmente marcadores de una gravedad ya establecida y no causas subyacentes.

Conclusión: La CAD pediátrica grave resulta de un proceso multifactorial y multinivel, más que de un único factor de riesgo. La prevención requiere el reconocimiento temprano de los síntomas de la diabetes, un manejo rápido de los días de enfermedad basado en la medición de cetonas, acceso ininterrumpido a la insulina, seguimiento estructurado después de la CAD, evaluación psicosocial e intervenciones dirigidas a las familias socialmente vulnerables. La gravedad debe clasificarse según el estado ácido-base, mientras que el riesgo de complicaciones debe evaluarse por separado mediante hallazgos clínicos, bioquímicos y neurológicos.

Palabras clave: Cetoacidosis Diabética. Diabetes Mellitus Tipo 1. Niño. Adolescente. Factores de Riesgo. Gravedad de la Enfermedad.

1 INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute metabolic emergency caused by absolute or marked relative insulin deficiency in combination with increased concentrations of counter-regulatory hormones. Reduced insulin activity stimulates hepatic glucose production, impairs peripheral glucose utilization, and accelerates lipolysis. The resulting free fatty acids are converted into ketone bodies, principally beta-hydroxybutyrate and acetoacetate, producing high-anion-gap metabolic acidosis. Hyperglycemia causes osmotic diuresis, electrolyte loss, dehydration, and progressive circulatory compromise.[1],[2]

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), DKA is diagnosed by the combination of hyperglycemia, metabolic acidosis, and ketosis. The biochemical criteria include plasma glucose greater than 11 mmol/L or approximately 200 mg/dL, venous pH below 7.30 or serum bicarbonate below 18 mmol/L, and blood beta-hydroxybutyrate of at least 3 mmol/L or moderate-to-large ketonuria.[1] Although marked hyperglycemia is common, glucose concentration alone does not determine DKA severity. A child with moderate hyperglycemia may have profound acidosis, whereas an adolescent with severe hyperglycemia may have a hyperosmolar or mixed DKA–hyperglycemic hyperosmolar state phenotype.

Pediatric DKA is classified as mild, moderate, or severe according to the degree of acidosis.[1] This classification is clinically useful, but it should not be confused with the probability of complications. A child with moderate acidosis and deteriorating consciousness may require more intensive monitoring than an alert child with a slightly lower pH. Similarly, biochemical severity at admission is not equivalent to the factors that caused the episode. Low pH, elevated blood urea nitrogen, and hypocapnia are markers of advanced metabolic decompensation, whereas diagnostic delay, insulin omission, infection, and barriers to care are upstream determinants.

DKA occurs in two substantially different clinical contexts. At the initial presentation of type 1 diabetes, the principal determinants include age, rate of beta-cell loss, recognition of polyuria and polydipsia, diagnostic accuracy, parental knowledge, socioeconomic circumstances, and access to laboratory testing. A recent systematic review identified 38 factors associated with DKA at pediatric type 1 diabetes onset and demonstrated particularly strong associations with age younger than 2 years and delayed or incorrect diagnosis.[3]

International registry data show that DKA at diagnosis remains frequent despite advances in pediatric diabetes care. An analysis of 59,000 children from 13 countries found

an adjusted prevalence of 29.9%, with substantial variation between countries. Preschool-aged children, adolescents, and children from ethnic minority populations were frequently at greater risk.[4] In the United States SEARCH for Diabetes in Youth Study, DKA prevalence increased from 35.3% in 2010 to 40.6% in 2016, corresponding to an adjusted relative increase of approximately 2% per year.[5]

In children with established diabetes, the causal pathway is different. DKA usually results from insufficient insulin delivery during illness, intentional or unintentional insulin omission, failure to respond to persistent hyperglycemia or ketosis, infusion-set failure, inability to obtain insulin or supplies, or difficulties with family and psychosocial functioning. Previous DKA is one of the strongest predictors of another episode, suggesting that recurrence reflects persistent vulnerabilities rather than independent isolated events.

The distinction between the occurrence of DKA, the biochemical severity of an episode, and the development of complications is essential. Factors that increase the probability of presenting with DKA may not necessarily predict severe acidosis. Likewise, severe acidosis increases the risk of organ injury but does not invariably produce cerebral injury, acute kidney injury, or death. This review therefore evaluates DKA severity as a continuum extending from prehospital determinants to acid-base derangement, recurrence, and acute adverse outcomes.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To identify the demographic, clinical, biological, socioeconomic, behavioral, and health-system factors associated with the severity of DKA in children and adolescents.

2.2 SECONDARY OBJECTIVES

1. To distinguish factors associated with DKA at the initial diagnosis of diabetes from those associated with DKA in established diabetes.
2. To describe the biochemical criteria used to classify mild, moderate, and severe pediatric DKA.
3. To examine the roles of age, diagnostic delay, infection, residual beta-cell function, socioeconomic deprivation, insulin omission, previous DKA, and diabetes technology.
4. To differentiate upstream determinants of severe DKA from admission markers of already established metabolic severity.

5. To evaluate the relationship between DKA severity and cerebral injury, acute kidney injury, hyperosmolarity, neurocognitive outcomes, intensive care use, and mortality.
6. To identify clinically applicable strategies for preventing severe and recurrent DKA.

3 METHODOLOGY

3.1 STUDY DESIGN

This study was developed as a structured integrative review. The review question was: Which factors are associated with greater biochemical severity or adverse outcomes of DKA in children and adolescents?

The review was designed to include evidence addressing three related but distinct outcomes: DKA at the diagnosis of diabetes, severe DKA defined by acid-base criteria, and recurrent DKA in patients with established diabetes. Studies limited to treatment efficacy were included only when they contributed to the interpretation of complications or prognostic markers.

3.2 SEARCH STRATEGY

Structured searches were performed in PubMed/MEDLINE, supplemented by backward and forward reference tracing. Search terms included combinations of “diabetic ketoacidosis,” “severe diabetic ketoacidosis,” “children,” “adolescents,” “type 1 diabetes,” “type 2 diabetes,” “risk factors,” “diagnostic delay,” “misdiagnosis,” “socioeconomic deprivation,” “insulin omission,” “recurrent ketoacidosis,” “cerebral injury,” “acute kidney injury,” and “COVID-19.”

The evidence base was updated through September 4, 2026. Recent pediatric guidelines, systematic reviews, meta-analyses, multicenter registries, population-based studies, and large clinical cohorts were prioritized. Earlier studies were retained when they established definitions or provided foundational evidence on cerebral injury and DKA complications.

3.3 ELIGIBILITY CRITERIA

Eligible studies included children, adolescents, or predominantly pediatric populations with biochemically confirmed DKA. Studies were required to evaluate at least one demographic, biological, clinical, socioeconomic, behavioral, treatment-related, or health-

system factor associated with DKA occurrence, severity, recurrence, complications, or mortality.

Adult-only studies, isolated case reports, studies without an identifiable DKA definition, and publications reporting only treatment protocols without risk-factor or outcome information were excluded from the principal synthesis.

3.4 DEFINITIONS AND OUTCOME CLASSIFICATION

DKA severity was interpreted according to ISPAD acid-base criteria.[1] When pH and bicarbonate indicated different categories, the more severe acid-base abnormality was considered clinically relevant, although individual studies varied in their classification rules.

"Factors associated with severity" were divided into four categories:

- Predisposing factors: characteristics present before metabolic decompensation, such as age, socioeconomic vulnerability, and limited access to care.
- Precipitating factors: events directly preceding DKA, including infection, insulin omission, vomiting, and insulin-delivery failure.
- Severity markers: findings reflecting the magnitude of established metabolic injury, such as low pH, low bicarbonate, elevated blood urea nitrogen, hypocapnia, and hyperosmolality.
- Prognostic factors: variables associated with cerebral injury, acute kidney injury, prolonged intensive care, recurrence, or death.

3.5 EVIDENCE SYNTHESIS

The results were synthesized narratively because the studies differed substantially in DKA definitions, age groups, health systems, statistical adjustment, and outcome selection. Effect estimates reported by systematic reviews and large cohorts were preserved whenever possible. No new meta-analysis was performed.

Risk of bias was considered according to study design, sample size, adjustment for confounding, outcome definition, missing data, and the possibility of selection or information bias. Particular caution was applied to retrospective single-center studies, administrative databases, and analyses treating race or ethnicity as biological rather than structural variables.

4 RESULTS

The available evidence demonstrates that severe DKA is produced by the accumulation of biological, diagnostic, social, and treatment-related disadvantages. The relative importance of each factor varies according to whether the episode represents the first manifestation of diabetes or occurs after diagnosis.

4.1 BIOCHEMICAL CLASSIFICATION OF PEDIATRIC DKA

Table 1

Classification of DKA severity in children and adolescents[1]

Classification	Venous pH	Serum bicarbonate	Clinical interpretation
Mild DKA	7.20–7.29	10 to <18 mmol/L	Established ketoacidosis with relatively preserved acid-base compensation
Moderate DKA	7.10–7.19	5–9 mmol/L	Greater ketone accumulation and reduced buffering capacity
Severe DKA	<7.10	<5 mmol/L	Profound metabolic acidosis and increased risk of circulatory, neurologic, and renal complications

This classification is based on acidosis rather than glucose concentration. Severe hyperglycemia, calculated effective osmolality, dehydration, electrolyte disturbances, hemodynamic status, and neurologic findings must be evaluated separately.[1,2]

4.2 QUANTITATIVE EVIDENCE FROM MAJOR PEDIATRIC STUDIES

Table 2

Principal studies evaluating factors associated with pediatric DKA, severe presentation, recurrence, or adverse outcomes

Study	Population	Main outcome	Quantitative findings
Rugg-Gunn et al.[3]	Systematic review; 195 articles	DKA at type 1 diabetes onset	Age <2 years: OR 3.51 (95% CI 2.85–4.32); delayed or incorrect diagnosis: OR 2.27 (1.72–3.01); family history of type 1 diabetes: OR 0.46 (0.37–0.57); screening participation: OR 0.35 (0.21–0.59)
Cherubini et al.[4]	59,000 children from 13 countries	DKA at diagnosis	Adjusted prevalence 29.9%; marked variation among countries; preschool age, adolescence, and minority status were frequent risk indicators
Jensen et al.[5]	7,612 youths with incident type 1 diabetes	DKA at diagnosis	Overall prevalence 38.5%; increased from 35.3% in 2010 to 40.6% in 2016; adjusted RR 1.02 per year
Auzanneau et al.[6]	10,598 German children and adolescents	DKA at diagnosis	DKA increased from 20.6% in the least deprived regions to 26.9% in the most deprived; rural areas 27.6% versus 22.7% in towns/suburbs

Study	Population	Main outcome	Quantitative findings
Alonso et al.[7]	21,020 children from six countries	DKA at diagnosis	Overall DKA prevalence 36.5%; deprivation associated with DKA at ages 0.5–<6 years: OR 1.16 (95% CI 1.10–1.23)
Lee et al.[8]	163 Korean patients with classifiable DKA severity	Severe DKA at diagnosis	Low parental education and preceding infection were independently associated with severe DKA; lower C-peptide was also associated with greater severity
Mavinkurve et al.[9]	127 Malaysian children	DKA and severe DKA at diagnosis	DKA prevalence 73.2%; 54.9% of DKA was severe; misdiagnosis predicted DKA: OR 3.73 (95% CI 1.36–10.24)
Alfayez et al.[10]	Meta-analysis of 20 observational studies	DKA during the COVID-19 pandemic	DKA: RR 1.35 (95% CI 1.20–1.53); severe DKA: RR 1.76 (1.33–2.33)
Hammersen et al.[12]	29,325 pediatric patients with type 1 diabetes	Recurrent DKA	DKA in the preceding year: OR 10.0 (95% CI 8.6–11.8); risk remained elevated 4 years later: OR 2.3 (1.6–3.1)
Alsabri et al.[13]	Meta-analysis; 12 studies and 58,911 patients	Recurrent DKA	Previous DKA: OR 7.97 (95% CI 4.33–14.67); diabetes duration of 12–15 years: OR 1.94 (1.21–3.11)
Bergmann et al.[15]	72,726 pediatric DKA encounters	Readmission and acute complications	Black children had higher 365-day readmission probabilities than Hispanic or White children at comparable neighborhood-opportunity levels; AKI probability 6.8%, 4.2%, and 4.8%, respectively
Myers et al.[18]	1,359 pediatric DKA episodes	Acute kidney injury	AKI occurred in 43% (95% CI 40%–46%); 43% of AKI episodes met stage 2 or 3 criteria
Yousif et al.[22]	4,565 admissions with DKA or hyperosmolar crises	Death or intensive care >48 hours	Type 2 diabetes, maximum glucose, and initial pH were the strongest predictors; mortality was 0.18%; prediction-model AUC ranged from 0.873 to 0.960 in validation periods

4.3 SUMMARY OF ASSOCIATED FACTORS

Table 3

Clinical interpretation of factors associated with DKA severity

Domain	Factors	Predominant clinical context	Interpretation
Age and development	Age <2 years; preschool age; adolescence	Mainly diabetes onset; recurrence during adolescence	Limited symptom communication in young children; rapid metabolic deterioration; increasing autonomy and treatment burden in adolescents
Diagnostic pathway	Misdiagnosis; delayed glucose testing; delayed referral	Diabetes onset	Modifiable determinant that permits prolonged insulin deficiency and progressive acidosis
Biological reserve	Low C-peptide; lower body mass index; extensive weight loss	Diabetes onset	Suggests greater beta-cell loss and longer or more intense catabolism
Intercurrent illness	Infection; fever; vomiting; gastroenteritis-like symptoms	Both contexts	Increases counter-regulatory hormones and may conceal classic diabetes symptoms

Domain	Factors	Predominant clinical context	Interpretation
Socioeconomic conditions	Deprivation; rural residence; public or absent insurance; transportation and supply barriers	Both contexts	Reflects structural barriers to recognition, specialist care, insulin access, and follow-up
Treatment-related factors	Insulin omission; infusion-set failure; delayed ketone testing; inadequate sick-day response	Established diabetes	Produces absolute or functionally severe insulin deficiency
Psychosocial factors	Depression; diabetes distress; family conflict; disordered eating; unstable housing	Predominantly recurrent DKA	May impair insulin administration, communication, supervision, and access to urgent care
Previous DKA	One or more prior episodes	Established diabetes	Strongest reproducible marker of recurrence and persistent vulnerability
Admission markers	Low pH and bicarbonate; high blood urea nitrogen; hypocapnia; hyperosmolality; altered consciousness	Established DKA	Reflects severity already present and predicts need for intensive monitoring
Diabetes phenotype	Type 2 diabetes with ketosis; mixed DKA–hyperosmolar state	Mainly adolescents	Greater hyperglycemia and hyperosmolality may increase risk beyond acid-base classification

5 RESULTS AND DISCUSSION

5.1 DKA SEVERITY IS A MULTISTAGE OUTCOME

Severe DKA should be understood as the final expression of a causal sequence. The sequence begins with inadequate effective insulin activity and continues through ketogenesis, hyperglycemia, osmotic diuresis, volume depletion, reduced renal clearance of glucose and ketones, and progressive acidosis.[2] The duration and intensity of each stage determine how far the child progresses before treatment begins.

This model explains why associated factors should not be interpreted as equivalent. A diagnostic error may prolong untreated insulin deficiency and therefore contribute causally to severe acidosis. By contrast, a low pH measured at admission defines severity but does not explain why the child became acidotic. Similarly, elevated blood urea nitrogen may indicate dehydration and reduced renal perfusion, but it is principally an intermediate marker of the established episode.

Studies combining DKA occurrence, biochemical severity, intensive care admission, and mortality into a single outcome may consequently obscure clinically important differences. Intensive care admission is also influenced by institutional protocols and available resources. Acid-base classification is more standardized, although neurologic status, perfusion, and hyperosmolality provide essential additional information.

5.2 AGE AND DEVELOPMENTAL STAGE

Young age is one of the most reproducible risk factors for DKA at type 1 diabetes diagnosis. In the 2022 systematic review, children younger than 2 years had more than three times the odds of presenting with DKA compared with older children.[3] Several mechanisms may contribute. Infants and toddlers cannot reliably describe thirst, polyuria, fatigue, or visual symptoms. Increased urination may be overlooked in children wearing diapers, while weight loss can be attributed to feeding difficulties or infection.

Young children have lower glycogen reserves, greater proportional fluid requirements, and a potentially more rapid decline in beta-cell function. Their clinical condition can therefore deteriorate quickly after nonspecific symptoms such as vomiting, tachypnea, irritability, or lethargy appear. Low C-peptide concentrations in young children presenting with DKA support the contribution of limited endogenous insulin reserve.[3],[8]

Adolescence represents a second period of vulnerability, especially in established diabetes. Pubertal insulin resistance increases insulin requirements, while progressive transfer of responsibility from caregivers to adolescents may create gaps in treatment. School activities, fear of hypoglycemia, diabetes distress, body-image concerns, substance use, family conflict, and inconsistent routines may further compromise insulin administration.

Age associations are nevertheless context-dependent. International registries have identified increased risk at both the youngest ages and adolescence, whereas a small Malaysian study found age of at least 5 years to be associated with DKA.[4],[9] The very wide confidence interval in the Malaysian estimate indicates imprecision and demonstrates why local age associations should not replace the broader international evidence.

5.3 DIAGNOSTIC DELAY AND MISDIAGNOSIS

Delayed or incorrect diagnosis is among the most important modifiable factors associated with DKA at diabetes onset. The pooled OR of 2.27 identified by Rugg-Gunn et al. indicates that a missed diagnostic opportunity substantially increases the likelihood that insulin deficiency will progress to ketoacidosis.[3] An earlier systematic review similarly showed that many children presenting with DKA had been evaluated by a health professional before the diabetes diagnosis was established.

The earliest manifestations of diabetes are often nonspecific. Polyuria may be interpreted as urinary infection, polydipsia as a behavioral habit, weight loss as dietary variation, and fatigue as a viral illness. When vomiting, abdominal pain, and tachypnea

develop, children may be diagnosed with gastroenteritis, appendicitis, pneumonia, or asthma. The deep respiratory pattern of metabolic acidosis can be mistaken for primary respiratory disease.

In the Malaysian cohort, misdiagnosis was associated with a 3.73-fold increase in the odds of DKA.[9] A large United States administrative cohort of 11,716 children presenting with new-onset diabetes and DKA found evidence of a recent missed emergency-department diagnosis in 2.9%. Children with delayed diagnosis had more complications than those without delay, 4.4% versus 2.2%, and required intensive care and mechanical ventilation more frequently.[26]

A normal or minimally abnormal physical examination does not exclude evolving diabetes. Point-of-care capillary glucose and urine or blood ketone testing are rapid and inexpensive when diabetes is clinically plausible. Diagnostic interventions should therefore focus on making glucose testing routine in children with unexplained polyuria, polydipsia, weight loss, nocturia, dehydration, recurrent candidiasis, persistent vomiting, or unexplained tachypnea.

5.4 RESIDUAL BETA-CELL FUNCTION AND CLINICAL PHENOTYPE

Lower C-peptide concentrations are consistently associated with DKA at diabetes diagnosis and may be related to greater severity.[3,8] C-peptide is not a practical emergency risk score by itself, but it reflects residual endogenous insulin production. Children with less residual secretion have a lower physiological buffer against ketogenesis and may deteriorate more rapidly once symptomatic hyperglycemia develops.

Low body mass index and substantial weight loss have also been associated with DKA at diagnosis. These findings may reflect prolonged catabolism rather than an independent causal characteristic. Similarly, elevated glycated hemoglobin indicates that dysglycemia has been present for weeks or months but does not reliably classify the immediate severity of acidosis.

Glucose concentration must be interpreted in the same way. Higher glucose generally indicates more severe insulin deficiency and osmotic diuresis, but it does not define DKA severity. Children with partially treated or euglycemic DKA may have marked ketonemia despite less impressive glucose values. Conversely, adolescents with type 2 diabetes may develop extreme hyperglycemia and hyperosmolality with only moderate acidosis.

5.5 INFECTION AND OTHER ACUTE PHYSIOLOGICAL STRESSORS

Infection can contribute to DKA by increasing catecholamines, cortisol, glucagon, and growth hormone, thereby increasing hepatic glucose production, lipolysis, and insulin requirements. Preceding infection was associated with both DKA occurrence and severe DKA in the Korean multicenter study.[8]

Infection may also contribute indirectly by obscuring the diagnosis. Fever, anorexia, vomiting, tachypnea, and lethargy may be attributed entirely to an infectious process, delaying glucose testing. Conversely, leukocytosis is common during DKA because of physiological stress and does not independently establish bacterial infection.

In children with established diabetes, gastrointestinal illness creates a particularly dangerous combination of reduced food intake, vomiting, dehydration, and caregiver concern about administering insulin. Basal insulin should not be discontinued during illness. Families require explicit instructions that insulin deficiency, not food intake alone, determines the need for basal insulin and ketone monitoring.

The coronavirus disease 2019 pandemic provided a natural example of the interaction between health-system disruption and DKA severity. The meta-analysis by Alfayez et al. found a 35% increase in overall DKA risk and a 76% increase in severe DKA during the pandemic compared with prepandemic periods.[10] A second meta-analysis reported increases in new-onset type 1 diabetes, DKA, and severe DKA of approximately 9.5%, 25%, and 19.5%, respectively.[11]

The larger increase in severe DKA than in overall DKA supports the role of delayed presentation, reduced primary care access, fear of health care exposure, and interruptions in routine services. These studies do not prove that severe acute respiratory syndrome coronavirus 2 directly caused the metabolic deterioration in every case.

5.6 SOCIOECONOMIC DEPRIVATION AND HEALTH CARE ACCESS

Socioeconomic conditions influence nearly every stage of the DKA pathway. Families experiencing deprivation may have reduced access to transportation, primary care, pediatric endocrinology, glucose or ketone testing, refrigeration, stable housing, health literacy resources, and uninterrupted insulin supplies. Work constraints may limit caregiver availability, while the cost of emergency evaluation may delay presentation.

In the German DPV Registry, DKA prevalence increased progressively from 20.6% in the least deprived regions to 26.9% in the most deprived. Rural residence was also

associated with greater DKA prevalence than residence in towns, suburbs, or cities.[6] These findings are important because they were observed in a health system with broad insurance coverage, indicating that universal coverage alone does not eliminate geographic and socioeconomic barriers.

A 2026 international comparison of 21,020 children from six countries found an overall DKA prevalence of 36.5%. Regional deprivation was associated with DKA in children younger than 6 years, with an OR of 1.16 per standardized increase in deprivation. The association was weaker among older children, suggesting that families of younger children may be particularly dependent on local diagnostic capacity and caregiver resources.[7]

Race and ethnicity should not be interpreted as biological causes of DKA. They may represent exposure to structural discrimination, differences in insurance, unequal access to technology, language barriers, neighborhood resources, and variation in the quality or continuity of care. In more than 72,000 pediatric DKA encounters, Black children had higher probabilities of readmission than Hispanic or White children at similar neighborhood-opportunity levels.[15] This persistence after neighborhood adjustment suggests that area-level indices do not capture every relevant structural or health-system mechanism.

5.7 DKA IN ESTABLISHED DIABETES: INSULIN INTERRUPTION AND OMISSION

In established type 1 diabetes, DKA nearly always reflects insufficient effective insulin delivery. The immediate mechanism may be missed injections, failure to administer correction doses, infusion-set displacement, pump occlusion, degraded insulin, vomiting without appropriate sick-day management, or inability to obtain insulin and supplies.

The term “nonadherence” should be used cautiously because it may conceal heterogeneous and remediable causes. An omitted dose can result from depression, fear of hypoglycemia, cognitive overload, unstable housing, inadequate family supervision, medication cost, school restrictions, disordered eating, or misunderstanding of dose adjustments. A clinically useful assessment therefore asks how and why insulin delivery failed rather than merely assigning responsibility to the patient.

Intentional insulin restriction for weight control is particularly concerning in adolescents. Other relevant psychosocial factors include anxiety, depressive symptoms, diabetes burnout, family conflict, substance use, fear of weight gain, and limited caregiver engagement. Recurrent DKA should trigger a private adolescent interview, family

assessment, screening for depression and eating disorders, and evaluation of access to food, insulin, housing, transportation, and communication technology.

Intercurrent illness remains a frequent precipitant in established diabetes, but infection alone does not explain why some children develop severe DKA. The progression frequently involves failure to increase monitoring, inability to measure blood ketones, delayed supplemental insulin, or delayed contact with the diabetes team.

5.8 PREVIOUS DKA AND RECURRENCE

Previous DKA is the strongest reproducible predictor of another episode. In the DPV cohort of 29,325 pediatric patients, DKA during the preceding year increased the odds of DKA in the most recent year tenfold. Although the association weakened over time, risk remained elevated four years after an episode.[12]

A 2026 systematic review and meta-analysis of 12 observational studies and 58,911 patients confirmed this relationship. Previous DKA increased recurrence risk almost eightfold, while a diabetes duration of 12–15 years was associated with an OR of 1.94. Female sex was not significantly associated with recurrence in the primary pooled analysis, and the estimate was sensitive to heterogeneity.[13]

A 2025 cohort examining severe and recurrent DKA found a strong correlation between the number of previous DKA events and subsequent severe episodes. Black and female patients were overrepresented among patients with multiple recurrent and repeated severe episodes, while pump use was protective in the recurrence model.[14] These associations require contextual interpretation and should be used to identify unmet care needs rather than to assume intrinsic susceptibility.

Every pediatric DKA admission should consequently be treated as a sentinel event. Discharge after biochemical resolution without investigation of the precipitating mechanism leaves the strongest predictor of recurrence unaddressed. Follow-up should occur promptly and include review of insulin access, dosing knowledge, ketone testing, school arrangements, technology data, caregiver responsibilities, and mental health.

5.9 GLYCEMIC CONTROL AND DIABETES DURATION

High glycated hemoglobin is commonly associated with recurrent DKA. It reflects prolonged insufficient insulin exposure, missed doses, ineffective dose adjustment, or difficulty sustaining diabetes-management behaviors. However, glycated hemoglobin is also

influenced by social and treatment-related circumstances and should not be interpreted as a behavioral judgment.

Longer diabetes duration increases the period during which treatment fatigue, transitions in responsibility, and changes in family structure can develop. The association between 12–15 years of disease duration and recurrent DKA in the 2026 meta-analysis probably reflects a combination of adolescence or young adulthood, complete loss of residual insulin secretion, and accumulated psychosocial burden.[13]

DKA at the initial diagnosis of diabetes may also identify a less favorable subsequent glycemic trajectory. In the SEARCH cohort, children presenting with DKA had higher glycated hemoglobin over follow-up than those without DKA at diagnosis.[23] This association may reflect biological differences in residual beta-cell function, but social and health-system factors present at diagnosis may persist during long-term care.

5.10 INSULIN PUMPS AND CONTINUOUS GLUCOSE MONITORING

Insulin pumps deliver rapid-acting insulin continuously and do not provide a depot of long-acting insulin. Interruption of infusion can therefore lead to ketosis within hours. Families using pumps need specific instructions for recognizing unexplained hyperglycemia, checking blood ketones, changing the infusion set, and administering correction insulin by injection when pump failure is suspected.

At a population level, however, pump therapy should not be characterized simply as a DKA risk factor. In a propensity-matched cohort of 30,579 children, adolescents, and young adults, pump therapy was associated with a lower DKA rate than injection therapy: 3.64 versus 4.26 events per 100 patient-years. Pump users also had lower glycated hemoglobin.[17]

This apparent contrast can be reconciled clinically. Pump therapy may improve overall glycemic control and reduce DKA frequency when the device, supplies, training, and follow-up are reliable. Nevertheless, an individual episode of infusion failure may progress rapidly if it is not detected. The relevant factors are therefore not pump use alone but access to supplies, alarm response, continuous glucose monitoring, ketone availability, backup insulin, and the ability to troubleshoot the device.

Continuous glucose monitoring can identify persistent hyperglycemia earlier, but glucose data alone cannot confirm or exclude DKA. Blood ketone measurement remains essential during illness, prolonged hyperglycemia, vomiting, or suspected infusion failure.

Technology may also widen disparities if access, connectivity, training, or ongoing technical support are unequal.

5.11 ADMISSION MARKERS OF SEVERE METABOLIC COMPROMISE

Venous pH and serum bicarbonate remain the central biochemical measurements for severity classification. Beta-hydroxybutyrate confirms and quantifies ketosis, while serial measurement may help evaluate resolution. Anion gap is useful when direct ketone measurement is unavailable, but it is affected by chloride administration and other unmeasured anions.

A low partial pressure of carbon dioxide reflects respiratory compensation for metabolic acidosis. An extremely low carbon dioxide concentration relative to the degree of acidosis may indicate prolonged or severe metabolic stress. Elevated blood urea nitrogen reflects dehydration, reduced renal perfusion, and increased protein catabolism. Both lower carbon dioxide and higher urea nitrogen were associated with cerebral edema in a foundational multicenter case-control study.[19]

Serum sodium must be interpreted in relation to glucose concentration. Measured sodium may be reduced by glucose-related water shifts, while corrected sodium provides additional information about water deficit. Failure of corrected sodium to increase as glucose falls may accompany severe water imbalance, but no single sodium trajectory should replace serial clinical and neurologic assessment.

Effective serum osmolality is particularly important in adolescents with extreme hyperglycemia, type 2 diabetes, or mixed DKA–hyperglycemic hyperosmolar state. Profound hyperosmolality can produce neurologic dysfunction and circulatory instability even when pH does not meet the threshold for severe DKA.

5.12 CEREBRAL INJURY

Clinically apparent cerebral injury is uncommon but remains one of the most feared pediatric DKA complications. Its pathophysiology is multifactorial and probably includes cerebral hypoperfusion, reperfusion, inflammation, blood–brain barrier dysfunction, osmotic changes, and individual susceptibility.

Severe acidosis, marked hypocapnia, elevated blood urea nitrogen, and altered mental status at presentation identify patients at increased risk.[19] These findings support the

concept that cerebral injury often begins before treatment or reflects the severity and duration of the underlying DKA process.

Historically, rapid fluid administration was considered a principal cause of cerebral edema. The Pediatric Emergency Care Applied Research Network (PECARN) randomized trial compared four combinations of faster or slower fluid administration and sodium chloride concentration. Neurologic outcomes did not differ significantly among treatment groups.[20] The results indicate that clinically appropriate fluid replacement within the tested ranges is not the sole determinant of cerebral injury.

Continuous neurologic observation remains essential. Headache, irritability, slowing heart rate, altered consciousness, cranial nerve abnormalities, oxygen desaturation, incontinence, or abnormal respiratory patterns should prompt immediate treatment for suspected cerebral injury. Neuroimaging should not delay therapy when clinical suspicion is high.

5.13 ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is common during pediatric DKA and reflects more than simple dehydration. In the PECARN cohort, AKI occurred in 584 of 1,359 episodes, corresponding to 43%. Of these events, 43% were classified as stage 2 or 3.[18]

Greater acidosis, dehydration, and circulatory compromise were associated with AKI. Renal hypoperfusion, osmotic stress, inflammation, rhabdomyolysis, and hyperchloremia may contribute. Serum creatinine must be interpreted against age and expected baseline values, which are often unavailable at admission.

AKI should be viewed as an indicator of systemic DKA severity and not merely as an incidental laboratory abnormality. Monitoring urine output, renal function, potassium, phosphate, chloride, and fluid balance is especially important in severe DKA. The presence of AKI may also influence the rate of electrolyte correction and the safety of potassium replacement.

5.14 NEUROCOGNITIVE CONSEQUENCES

DKA was previously regarded as completely reversible once metabolic abnormalities were corrected. Evidence now suggests that even without clinically apparent cerebral edema, DKA may be associated with subtle neurocognitive effects.

In a prospective study of 758 children with DKA and 376 children with type 1 diabetes without DKA exposure, moderate or severe DKA was associated with lower intelligence quotient, item-color recall, and forward digit span. Among children with previously diagnosed diabetes, repeated DKA exposure and higher glycated hemoglobin were independently associated with lower intelligence quotient.[21]

These findings do not mean that every DKA episode produces clinically detectable permanent impairment. The observed average differences were subtle, and residual confounding is possible. Nevertheless, they reinforce the importance of preventing severe and recurrent episodes, particularly during periods of active brain development.

5.15 TYPE 2 DIABETES AND MIXED HYPERGLYCEMIC CRISES

DKA increasingly occurs in adolescents with type 2 diabetes, particularly in the presence of severe insulin deficiency, infection, or ketosis-prone diabetes phenotypes. These patients may also have marked obesity, extreme hyperglycemia, greater effective osmolality, and features of hyperglycemic hyperosmolar state.

In a study of 4,565 pediatric admissions, type 2 diabetes, maximum glucose concentration, and initial pH were the strongest predictors of death or intensive care lasting longer than 48 hours.[22] The model achieved an area under the receiver operating characteristic curve of 0.948 in the training cohort and between 0.873 and 0.960 in validation periods.

These findings demonstrate that acid-base severity should be combined with diabetes phenotype and hyperosmolarity when estimating prognosis. A pH-based DKA category alone may underestimate risk in a patient with severe hyperglycemia, circulatory compromise, and hyperosmolality.

5.16 PREVENTION OF SEVERE DKA AT DIABETES DIAGNOSIS

Public and professional recognition of polyuria, polydipsia, nocturia, weight loss, and fatigue remains central to prevention. Campaigns should emphasize that vomiting, abdominal pain, or tachypnea may represent advanced diabetes rather than isolated gastrointestinal or respiratory illness.

Presymptomatic type 1 diabetes screening provides a different preventive pathway. In the systematic review by Rugg-Gunn et al., participation in screening was associated with an

OR of 0.35 for DKA at clinical onset.[3] Children identified through the Fr1da public health screening program had milder metabolic manifestations when stage 3 diabetes developed.[24]

Screening cannot yet replace clinical awareness because its availability remains limited and optimal population strategies are still evolving. Nevertheless, identification of islet autoimmunity permits education, glucose surveillance, and planned initiation of insulin before severe metabolic decompensation.

Interventions directed toward primary care have included educational sessions, diagnostic reminders, referral pathways, direct communication, and provision of glucose or ketone meters. A 2024 systematic review found that the number and methodological quality of such studies were insufficient to determine which isolated intervention is most effective.[25] Multifaceted strategies are therefore more defensible than reliance on a single campaign.

5.17 PREVENTION OF SEVERE AND RECURRENT DKA AFTER DIAGNOSIS

Effective prevention begins with written sick-day instructions that are understandable to the child and caregivers. The plan should specify when to measure glucose and blood ketones, how to administer supplemental rapid-acting insulin, when to change an infusion set, how to maintain hydration, and when to seek urgent evaluation.

Families must have uninterrupted access to basal and rapid-acting insulin, syringes or pens, ketone strips, glucose monitoring, pump supplies, and emergency contact information. Prescribing instructions without ensuring that supplies are affordable and physically available is insufficient.

After any DKA admission, the clinical team should reconstruct the sequence of events. This review should include insulin administration, device data, preceding symptoms, school or family circumstances, access barriers, mental health, eating behavior, and the timing of contact with health professionals. Because recurrence risk is highest in the year after an episode, follow-up should be intensified during this period.[12]

High-risk patients may benefit from case management, social work, psychological support, telehealth, pharmacy coordination, school-based planning, remote glucose-data review, and proactive contact after missed appointments. The objective is not only to improve knowledge but to reduce the practical and psychological conditions that repeatedly interrupt insulin delivery.

6 LIMITATIONS

The evidence base is dominated by observational and retrospective studies, which limits causal inference. Associations between deprivation, race, insurance, rural residence, and DKA may be influenced by unmeasured differences in health care access, family resources, treatment availability, and local diagnostic practices.

Definitions of DKA and severe DKA varied across studies. Some studies used different pH or bicarbonate thresholds, administrative codes, clinician documentation, or combined outcomes. This heterogeneity limits direct comparison of prevalence and effect estimates.

Several large registry studies evaluated the occurrence of DKA rather than biochemical severity specifically. Factors associated with presenting in DKA may overlap with those associated with severe acidosis, but they are not necessarily identical. Evidence specifically comparing severe with mild or moderate pediatric DKA remains more limited.

Insulin omission, psychosocial vulnerability, eating disorders, and family conflict were inconsistently measured. These factors are often identified after hospitalization through nonstandardized interviews and may be underestimated because of stigma, incomplete documentation, or fear of judgment.

Finally, the review did not conduct a new quantitative meta-analysis. The numerical estimates presented were derived from published systematic reviews and primary studies with different populations and analytical methods. They should therefore be interpreted as indicators of the magnitude and consistency of associations rather than as a universal pediatric prediction model.

7 CONCLUSION

Severe DKA in children and adolescents results from the interaction of biological vulnerability, prolonged insulin deficiency, diagnostic delay, acute illness, treatment interruption, psychosocial difficulties, and structural barriers to health care. No single demographic or laboratory variable adequately explains the entire pathway.

At the onset of type 1 diabetes, the most consistent factors are very young age, delayed or incorrect diagnosis, lower endogenous insulin secretion, preceding infection, socioeconomic deprivation, rural residence, and limited access to timely assessment. Polyuria, polydipsia, nocturia, weight loss, vomiting, and unexplained tachypnea should prompt immediate glucose and ketone testing.

In established diabetes, insulin omission or interruption is the central proximal mechanism, but its underlying causes must be investigated. Previous DKA is the strongest marker of recurrence, while chronic hyperglycemia, longer disease duration, diabetes distress, disordered eating, supply insecurity, family conflict, and inconsistent specialist follow-up identify additional opportunities for intervention.

Biochemical severity should be classified using venous pH and serum bicarbonate. Neurologic status, perfusion, blood urea nitrogen, carbon dioxide concentration, renal function, corrected sodium, and effective osmolality provide complementary prognostic information. These admission findings reflect established metabolic compromise and should not be confused with the upstream causes of DKA.

Prevention requires a coordinated strategy involving symptom awareness, presymptomatic screening where available, reliable insulin and ketone-supply access, individualized sick-day education, technology support, psychosocial assessment, and intensive follow-up after every DKA episode. The transition from generalized education to risk-stratified, family-centered, and socially responsive care offers the greatest potential to reduce severe and recurrent pediatric DKA.

REFERENCES

1 Alfayez, O. M., Aldmasi, K. S., Alruwais, N. H., Bin Awad, N. M., Al Yami, M. S., & Almohammed, O. A. (2022). Incidence of diabetic ketoacidosis among pediatrics with type 1 diabetes prior to and during COVID-19 pandemic: A meta-analysis of observational studies. Frontiers in Endocrinology, 13, 856958. https://doi.org/10.3389/fendo.2022.856958

2 Alonso, G. T., Reinauer, C., Williams, G. M., Gesuita, R., Jefferies, C., Dovc, K., et al. (2026). Regional deprivation and diabetic ketoacidosis at type 1 diabetes diagnosis in children and adolescents: International comparison among 6 countries. Hormone Research in Paediatrics, 99(4), 591–598. https://doi.org/10.1159/000543139

3 Alsabri, M., Aboali, A. A., Rath, S., Hasan, M. T., Alhaddad, J., Aziz, M. M., et al. (2026). Risk factors for recurrent DKA in children and adolescents with established diabetes: A systematic review and meta-analysis. Current Emergency and Hospital Medicine Reports, 14, 8. https://doi.org/10.1007/s40138-026-00340-6

4 Auzanneau, M., Rosenbauer, J., Warncke, K., Maier, W., Kamrath, C., Hofmann, T., et al. (2022). Frequency of ketoacidosis at diagnosis of pediatric type 1 diabetes associated with socioeconomic deprivation and urbanization: Results from the German multicenter DPV Registry. Diabetes Care, 45(8), 1807–1813. https://doi.org/10.2337/dc21-2227

5 Beccia, C., McMorrow, R., Rodrigues, F., Kilov, G., Atlas, G., Craig, M. E., et al. (2024). Have interventions aimed at assisting general practitioners in facilitating earlier diagnosis of type 1 diabetes in children been successful? A systematic review. BMJ Open, 14, e085635. https://doi.org/10.1136/bmjopen-2024-085635

6 Bergmann, K. R., Nickel, A., Hall, M., Cutler, G., Abuzzahab, M. J., Bretscher, B., et al. (2022). Association of neighborhood resources and race and ethnicity with readmissions for diabetic ketoacidosis at US children's hospitals. JAMA Network Open, 5(5), e2210456. https://doi.org/10.1001/jamanetworkopen.2022.10456

7 Cherubini, V., Grimsmann, J. M., Åkesson, K., Birkebæk, N. H., Cinek, O., Dovč, K., et al. (2020). Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: Results from 13 countries in three continents. Diabetologia, 63(8), 1530–1541. https://doi.org/10.1007/s00125-020-05152-1

8 Dhatariya, K. K., Glaser, N. S., Codner, E., & Umpierrez, G. E. (2020). Diabetic ketoacidosis. Nature Reviews Disease Primers, 6(1), 40. https://doi.org/10.1038/s41572-020-0165-1

9 Duca, L. M., Reboussin, B. A., Pihoker, C., Imperatore, G., Saydah, S., Mayer-Davis, E., et al. (2019). Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: The SEARCH for Diabetes in Youth Study. Pediatric Diabetes, 20(2), 172–179. https://doi.org/10.1111/pedi.12809

10 Everett, E., & Mathioudakis, N. (2019). Association of area deprivation and diabetic ketoacidosis readmissions: Comparative risk analysis of adults versus children with type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism, 104(8), 3473–3480. https://doi.org/10.1210/jc.2018-02232

11 Glaser, N., Barnett, P., McCaslin, I., Nelson, D., Trainor, J., Louie, J., et al. (2001). Risk factors for cerebral edema in children with diabetic ketoacidosis. The New England Journal of Medicine, 344(4), 264–269. https://doi.org/10.1056/NEJM200101253440404

12 Glaser, N., Fritsch, M., Priyambada, L., Rewers, A., Cherubini, V., Estrada, S., et al. (2022). ISPAD clinical practice consensus guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric Diabetes, 23(7), 835–856. https://doi.org/10.1111/pedi.13406

13 Ghetti, S., Kuppermann, N., Rewers, A., Myers, S. R., Schunk, J. E., Stoner, M. J., et al. (2020). Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. Diabetes Care, 43(11), 2768–2775. https://doi.org/10.2337/dc20-0187

14 Hadley, S. M., & Michelson, K. A. (2024). Delayed diagnosis of new onset pediatric diabetes leading to diabetic ketoacidosis: A retrospective cohort study. Diagnosis, 11(4), 416–421. https://doi.org/10.1515/dx-2024-0024

15 Hammersen, J., Tittel, S. R., Warncke, K., Pacaud, D., de Beaufort, C., Kordonouri, O., et al. (2021). Previous diabetic ketoacidosis as a risk factor for recurrence in a large

prospective contemporary pediatric cohort: Results from the DPV initiative. Pediatric Diabetes, 22(3), 455–462. https://doi.org/10.1111/pedi.13185

16 Hummel, S., Carl, J., Friedl, N., Winkler, C., Kick, K., Stock, J., et al. (2023). Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation. Diabetologia, 66(9), 1633–1642. https://doi.org/10.1007/s00125-023-05953-0

17 Jensen, E. T., Stafford, J. M., Saydah, S., D'Agostino, R. B., Jr., Dolan, L. M., Lawrence, J. M., et al. (2021). Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: The SEARCH for Diabetes in Youth Study. Diabetes Care, 44(7), 1573–1578. https://doi.org/10.2337/dc20-0389

18 Karges, B., Schwandt, A., Heidtmann, B., Kordonouri, O., Binder, E., Schierloh, U., et al. (2017). Association of insulin pump therapy versus insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA, 318(14), 1358–1366. https://doi.org/10.1001/jama.2017.13994

19 Kuppermann, N., Ghetti, S., Schunk, J. E., Stoner, M. J., Rewers, A., McManemy, J. K., et al. (2018). Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. The New England Journal of Medicine, 378(24), 2275–2287. https://doi.org/10.1056/NEJMoa1716816

20 Lee, H. J., Yu, H. W., Jung, H. W., Lee, Y. A., Kim, J. H., Chung, H. R., et al. (2017). Factors associated with the presence and severity of diabetic ketoacidosis at diagnosis of type 1 diabetes in Korean children and adolescents. Journal of Korean Medical Science, 32(2), 303–309. https://doi.org/10.3346/jkms.2017.32.2.303

21 Mavinkurve, M., Ramzi, N. H., Jalaludin, M. Y. B., Samingan, N., & Zaini, A. A. (2024). Predictors and trends of diabetic ketoacidosis at diagnosis of type 1 diabetes mellitus in Malaysian children. Journal of Clinical Research in Pediatric Endocrinology, 16(4), 411–418. https://doi.org/10.4274/jcrpe.galenos.2024.2024-1-8

22 Myers, S. R., Glaser, N. S., Trainor, J. L., Nigrovic, L. E., Garro, A., Tzimenatos, L., et al. (2020). Frequency and risk factors of acute kidney injury during diabetic ketoacidosis in children and association with neurocognitive outcomes. JAMA Network Open, 3(12), e2025481. https://doi.org/10.1001/jamanetworkopen.2020.25481

23 Rahmati, M., Keshvari, M., Mirnasuri, S., Yon, D. K., Lee, S. W., Il Shin, J., et al. (2022). The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis. Journal of Medical Virology, 94(11), 5112–5127. https://doi.org/10.1002/jmv.27996

24 Rugg-Gunn, C. E. M., Dixon, E., Jorgensen, A. L., Usher-Smith, J. A., Marcovecchio, M. L., Deakin, M., et al. (2022). Factors associated with diabetic ketoacidosis at onset of type 1 diabetes among pediatric patients: A systematic review. JAMA Pediatrics, 176(12), 1248–1259. https://doi.org/10.1001/jamapediatrics.2022.3586

25 Schwartz, D. D., Erraguntla, M., DeSalvo, D. J., Buckingham, D., Dave, D., Sonabend, R., et al. (2025). Severe and recurrent diabetic ketoacidosis in children and youth with type 1 diabetes: Risk and protective factors. Diabetes Technology & Therapeutics, 27(10), 801–811. https://doi.org/10.1089/dia.2025.0128

26 Yousif, M. F., Dolak, K. D., Adhikari, S., & White, P. C. (2025). Risk factors for adverse outcomes in children with diabetic ketoacidosis. The Journal of Clinical Endocrinology & Metabolism, 110(5), e1609–e1618. https://doi.org/10.1210/clinem/dgae500