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Original Article

Risk Factors for Cerebral Edema in Pediatric Diabetic Ketoacidosis: a Systematic Review and Meta-Analysis of Observational Studies

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Abstract
Background: Cerebral edema is a rare but serious complication of pediatric diabetic ketoacidosis, and risk factors remain uncertain.
Objective: To synthesize current evidence on risk factors associated with the development of cerebral edema (CE) in pediatric patients with diabetic ketoacidosis (DKA).
Methods: A systematic search was conducted in MEDLINE, EMBASE, LILACS, and the Cochrane Library through January 2025. Observational studies were included. Risk of bias was assessed with Joanna Briggs Institute tools, and evidence certainty was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
Results: Eleven studies (n=2,545) were included. Bicarbonate administration may be associated with CE (OR 4.21; 95% CI: 2.37, 7.46; low certainty). The evidence is very uncertain about the associations between CE and younger age (MD −1.60 years; 95% CI: −2.38, −0.82), newly diagnosed type 1 diabetes (OR 1.54; 95% CI: 1.01, 2.35), and a more severe presentation phenotype characterized by greater acidosis and elevated urea (very low certainty). The evidence is also very uncertain about the association between higher early fluid volume and CE (MD 9.86 mL/kg; 95% CI: 5.06, 14.66; very low certainty).
Conclusion: Bicarbonate administration may be associated with CE, which is consistent with current recommendations against its routine use in pediatric DKA. The evidence is very uncertain about the associations of younger age, new-onset diabetes, and a severe metabolic phenotype with CE; these findings may indicate increased risk but should be interpreted with caution. Prospective studies with standardized definitions and confounder adjustment are needed.
Keywords: Diabetic ketoacidosis, brain edema, risk factors, bicarbonates, systematic review

What is already known on this topic?
Cerebral edema is an uncommon but life-threatening complication of pediatric diabetic ketoacidosis. Reported risk factors, mostly from observational studies, include severe acidosis, elevated urea, hypocapnia, and treatment-related factors such as bicarbonate use and higher early fluid volumes, but findings are not consistently confirmed.

What this study adds?
In this systematic review and meta-analysis of observational studies, bicarbonate administration may be associated with approximately four-fold higher odds of CE in pediatric DKA (low certainty). The evidence is very uncertain about the associations of younger age, newly diagnosed type 1 diabetes, and a more severe presentation phenotype (characterized by greater acidosis, hypocapnia, and elevated urea and glucose) with CE. A possible association with higher early fluid volume is supported by very low certainty evidence and should be interpreted with caution. Prospective studies with standardized CE definitions and pre-specified confounder adjustment are needed to clarify the magnitude and clinical relevance of these associations.

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Introduction

Diabetic ketoacidosis (DKA) is a frequent acute complication of type 1 diabetes mellitus (T1DM) and a significant cause of morbidity and mortality in the pediatric population (1,2). Among the acute complications of DKA, cerebral edema (CE) is the most severe and potentially fatal (3). Although rare, occurring in approximately 0.5%–1% of pediatric DKA episodes (4), CE is associated with high mortality (20%–40%) and long-term neurological sequelae in up to 26% of survivors (5,6). Diagnosing CE remains clinically challenging because symptoms typically develop 3–12 hours after treatment initiation (7). Neuroimaging is not always reliable in the early stages; edema may develop hours to days after neurological deterioration, and approximately 40% of patients exhibit normal brain imaging findings at the onset of symptoms (8,9).

The pathophysiology of CE remains incompletely understood. Current evidence suggests that CE may reflect an interplay between pre-treatment metabolic derangements and treatment-related exposures (10). Observational studies have reported associations between CE and several patient and disease characteristics, including younger age, new onset T1DM, higher blood urea nitrogen (BUN), and greater acidosis severity at presentation. Treatment-related exposures, particularly early fluid volume and bicarbonate administration, have also been evaluated. However, findings have been inconsistent across studies, and the strength and independence of these associations remain uncertain (11). Given the high morbidity and mortality associated with this complication, identifying robust predictors is crucial for stratifying high-risk patients and implementing preventive measures. This systematic review and meta-analysis aimed to synthesize the available evidence on risk factors for CE in pediatric patients with DKA.

Methods

We conducted this review following the Joanna Briggs Institute (JBI) methodology for systematic reviews of etiology and risk factors (12) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13). The protocol was prospectively registered in PROSPERO (CRD42021233073).

Search strategy

We conducted a comprehensive systematic search in January 2025, across the MEDLINE, EMBASE, LILACS, and Cochrane Library databases. The search strategy combined indexed terms (MeSH, DeCS, and Emtree) with free-text keywords. We considered studies published in English or Spanish, with no restrictions on publication date (Supplementary Data S1). To minimize publication bias and identify grey literature, we searched Google Scholar and screened the reference lists of all included studies.

Eligibility criteria

The study population comprised pediatric patients of either sex, aged 1 month to 18 years, with a confirmed diagnosis of DKA according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria (14). We excluded patients with pre-existing neurological, genetic, autoimmune, endocrine, or infectious conditions, as well as those meeting diagnostic criteria for a hyperglycemic hyperosmolar state. Potential risk factors for CE considered in this review included intrinsic patient characteristics, metabolic parameters at admission and treatment-related factors.

The primary outcome was the development of CE. We accepted the diagnostic criteria established by ISPAD (14), as well as other validated definitions including: sudden deterioration of consciousness associated with pH < 7.35 and/or low bicarbonate; or altered consciousness accompanied by signs of increased intracranial pressure (e.g., hypertension with bradycardia, abnormal respiratory patterns, pupillary changes, or posturing) or radiological confirmation. We included epidemiological study designs, specifically prospective and retrospective cohorts, case-control studies, and analytical cross-sectional studies.

Study selection

Records identified through database searches were imported into EndNote X7®, and duplicates were removed. Two reviewers (LR and KC) independently screened records and performed eligibility assessments using Rayyan®. Titles and abstracts were screened first, followed by a full-text assessment of potentially relevant reports. Disagreements were resolved by consensus or consultation with a third reviewer (RK).

Data extraction

Two researchers (LR and KC) independently extracted data using a standardized form. Collected variables included: study details (metadata and design), population characteristics, exposure specifics (frequency, intensity, duration), outcomes, and statistical methods (effect measures, confidence intervals).

Risk of bias assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for analytical cross-sectional and case–control studies (15). Two reviewers (LR and KC) independently appraised the studies. Following recent JBI methodological updates (16), we emphasized key domains of internal validity. For cross-sectional studies, items 1–2 were mapped to selection bias, items 3–4 to measurement bias, and items 5–6 to confounding. For case–control studies, items 1–2 captured selection bias, items 4–5 measurement bias, and items 7–8 confounding. Overall risk of bias was classified as high (any "no" or >2 "unclear"), unclear (one "unclear"), or low (all "yes"). Small-study effects and publication bias were assessed using funnel plots and Egger's test for outcomes reported in at least 10 studies (17).

Certainty of evidence assessment

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, adhering to specific guidelines for prognostic factor research (18). In this framework, evidence from observational studies starts as high certainty and may be downgraded based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. In contrast, certainty may be upgraded in the presence of a large effect size, a dose–response gradient, or if plausible confounding would be expected to underestimate the effect.

Data synthesis

Quantitative data were pooled in a statistical meta-analysis using Review Manager 5 (RevMan 5) software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark), with a random-effects model (DerSimonian and Laird). Effect sizes were reported as odds ratios (OR) for categorical data and mean differences (MD) for continuous data, with 95% confidence intervals. Statistical heterogeneity was assessed via visual inspection of forest plots, the χ^2 test, and the I^2 statistic, interpreted as low (0–49%), moderate (50–74%), or high (≥75%) (19). For factors with considerable heterogeneity ($I^2 \geq 75\%$), quantitative pooling was not performed and findings are presented narratively. We conducted subgroup analyses based on study design and performed sensitivity analyses by excluding studies at high or unclear risk of bias to test the robustness of the results.

Results

Study selection

A total of 1,572 records were identified through the four-database search. Following duplicate removal, 1,035 records were screened by title and abstract, of which 967 were excluded. The remaining 68 full-text reports were assessed for eligibility; 57 were excluded primarily due to incorrect study population, absence of cerebral edema as an outcome, or inappropriate study design (Supplementary Table S1). Eleven studies met the inclusion criteria and were included in the final synthesis. The complete selection process is illustrated in the PRISMA flow diagram (**Figure 1**).

Study characteristics

Eleven studies were included in this review: seven analytical cross-sectional studies (20–26) and four case–control studies (7,11,27,28). The studies were published between 2001 and 2022 and involved a total of 2,545 participants, with sample sizes ranging from 48 to 1,275 and mean ages ranging from 6 to 12 years. A detailed description of each study is provided in Table 1. The risk of bias was generally low for most analytical cross-sectional studies; however, González et al. (20) were classified as unclear risk, Hoorn et al. (25) and Yaneva et al. (24) as high risk. Among the case–control studies, Glaser et al. (28) and Lawrence et al. (11) were rated as high risk, while the remaining studies were assessed as low risk (Supplementary Tables S2 and S3). A complete mapping of each analyzed risk factor to the contributing studies, the number of studies, the type of effect estimate, the nature of the contributing data, and the type of evidence synthesis is provided in Supplementary Table S4**.**

Demographic and clinical factors

Age

Data pooled from nine studies revealed a statistically significant association between younger age and CE. Children who developed CE were, on average, 1.60 years younger than those who did not (MD −1.60 years; 95% CI −2.38, −0.82, $p < 0.001$; $I^2 = 55\%$) (**Figure 2A**).

Sex

Based on eight studies, sex was not significantly associated with CE (OR 1.08; 95% CI 0.72, 1.63, $p = 0.70$; $I^2 = 36\%$) (**Figure 2B**).

New diagnosis of T1DM

Ten studies compared CE events in patients with new onset T1DM versus established disease. The pooled analysis indicated higher odds of CE among newly diagnosed patients (OR 1.54; 95% CI 1.01, 2.35, $p = 0.05$; $I^2 = 47\%$) (**Figure 2C**).

Biochemical factors at admission

pH and $PaCO_2$

Severe metabolic acidosis and hypocapnia at admission showed a consistent association with the development of CE. Across the 11 studies that evaluated arterial/venous pH, lower values were observed in the CE group in 9 of 11 studies (range of mean differences: −0.23 to +0.02), three studies did not reach statistical significance (Figure 3A). In nine studies, $PaCO_2$ was lower in the CE group, with a pooled mean difference of −2.99 mmHg (95% CI −4.94, −1.05, p=0.003; I^2=72%) **(Figure 3B).**

Bicarbonate

Across the 11 studies that evaluated admission serum bicarbonate, lower values were observed in the CE group in 9 of 11 studies (range of mean differences: −4.80 to +0.85 mmol/L); two studies did not reach statistical significance (Figure 3C).

Glucose and urea

Admission serum glucose was higher in the CE group, with a pooled mean difference of 96.56 mg/dL (95% CI 56.35, 136.78, $p < 0.001$; $I^2 = 65\%$) across ten studies (**Figure 3D**). Across the 9 studies that evaluated admission urea, the direction of effect was consistent toward higher values in the CE group, with individual mean differences ranging from 0.50 to 6.30 mmol/L; three studies did not reach statistical significance (**Figure 3E**).

Electrolytes and osmolarity

Admission serum osmolarity, sodium, and potassium showed inconsistent directions of effect across contributing studies, with no clear pattern favoring either the CE or the control group. Individual mean differences ranged from -17.50 to 26.30 mOsm/kg, -9.00 to 9.40 mmol/L, and -0.54 to 0.60 mmol/L, respectively, and a substantial proportion of studies did not reach statistical significance for any of these parameters **(Figures 3F–H).**

Factors Related to DKA Treatment

Bicarbonate treatment

Bicarbonate administration during hospital management was associated with CE. Pooling data from six studies showed that children who received bicarbonate had higher odds of developing CE than those who did not (OR 4.21; 95% CI 2.37, 7.46, $p < 0.001$; $I^2 = 16\%$) (**Figure 4A**).

Fluid therapy

Higher fluid volumes administered during the first 4 hours were associated with CE. The pooled MD from two studies indicated that patients with CE received 9.86 mL/kg more fluid than controls (95% CI 5.06, 14.66, $p < 0.001$; $I^2 = 0\%$) (**Figure 4B**). Additionally, Tiwari et al. (23) reported that CE cases received a higher mean number of fluid boluses (2.1 vs. 1.4; $p = 0.001$).

Electrolyte composition and replacement

In studies evaluating electrolyte management during pediatric DKA, early sodium/potassium administration, timing of potassium replacement, and infused sodium concentration were not statistically significantly associated with CE (24,25,27).

Insulin therapy

Statistical pooling for insulin-related exposures was not feasible due to methodological heterogeneity. However, Hoorn et al. (25) reported a higher frequency of insulin boluses among patients who developed CE ($p = 0.001$), and Edge et al. (27) found that CE cases were more likely to receive insulin within the first hour of treatment (OR 4.7; 95% CI 1.5, 13.9; $p = 0.007$). In contrast, other insulin parameters, including dose and infusion rate, were not significantly associated with CE.

Subgroup and sensitivity analyses

Subgroup analyses stratified by study design did not identify statistically significant differences between designs for any factor (Supplementary Figure S1–S3). Sensitivity analyses excluding studies with high or unclear risk of bias generally confirmed the direction of the main findings (Supplementary Figure S4–S6).

Certainty of evidence assessment

According to the GRADE framework, the certainty of evidence for most factors was rated as very low, primarily due to risk of bias, heterogeneity, and indirectness related to variable CE definitions. For the association between bicarbonate treatment and CE, the certainty of evidence was rated as low. Although the evidence was upgraded by one level due to a large effect size (OR 4.21; 95% CI: 2.37, 7.46), this was offset by very serious risk of bias concerns, as only two studies adjusted for confounding factors, using different variables and methods (7,27), while the remaining studies did not identify or address them (Supplementary Table S5).

Publication bias

We assessed small-study effects and publication bias for outcomes reported in at least 10 studies (new diagnosis of T1DM, pH, bicarbonate, and glucose). Although some funnel plots appeared visually asymmetric, Egger's test was not significant. (Supplementary Figure **S7**).

Discussion

CE is a relatively uncommon yet potentially fatal complication of DKA in children and adolescents. In this systematic review and meta-analysis, we synthesized evidence from 11 observational studies to identify factors associated with CE in pediatric DKA.

CE has frequently been reported to be more common in younger children, particularly those under 5 years of age, possibly reflecting the increased vulnerability of the developing brain to the metabolic and vascular disturbances associated with DKA (29). Age was one of the most consistently reported variables across the included studies. Our meta-analysis showed that patients who developed CE were, on average, 1.6 years younger than those who did not. Between-study heterogeneity for this association was moderate. Part of this heterogeneity may reflect the increased frequency of moderate-to-severe DKA in younger populations, which itself is a risk factor for CE (30); studies enrolling more severe phenotypes may therefore show a stronger age effect. Variability in the operational definition of CE across the contributing studies may also have contributed, particularly in young children, where assessment of mental status may be more difficult (31).

Previous studies have identified a new diagnosis of T1DM as a potential risk factor for the development of CE (32). This finding is consistent with the results of our meta-analysis, in which a new diagnosis of T1DM was associated with 54% higher odds of CE compared with previously established disease. However, this finding was characterized by moderate heterogeneity, potentially attributable to variations in DKA severity at

presentation across the contributing studies. The proportion of severe DKA tends to be higher among patients with new-onset T1DM (33), and clinical severity may act as a confounding factor in the observed association.

Regarding biochemical parameters at hospital admission, the severity of acidosis has been frequently associated with an increased risk of CE. In our review, patients who developed CE presented with greater acidosis at admission across contributing studies, consistent with the hypothesis that more severe metabolic acidosis may be involved in the pathogenesis of this neurological complication (28).

Among the proposed pathophysiological mechanisms of CE, an osmotic hypothesis has been advanced whereby the accumulation of osmotically active solutes increases brain effective osmolality and predisposes to cerebral swelling (34). However, this explanation remains controversial, as markers of serum osmolality and their short-term changes have not been consistently associated with CE across studies (35). In our review, admission serum osmolality did not show a consistent direction of effect across the contributing studies; nevertheless, patients who developed CE presented with higher serum glucose levels at admission.

Markers of dehydration and prerenal compromise have been implicated in the pathophysiology of CE in pediatric DKA. Elevated serum urea, as a surrogate of more severe dehydration and hemodynamic impairment, has been repeatedly reported as a risk marker for CE (5); consistent with this, patients who developed CE in the contributing studies tended to present with higher admission serum urea levels. Electrolyte abnormalities are common in pediatric DKA and have been proposed as contributors to CE. Hyperkalemia may result from impaired renal perfusion due to hypovolemia, whereas hyponatremia can reflect substantial sodium loss through osmotic diuresis (36). Nevertheless, in our review, admission serum sodium and potassium levels did not show a consistent direction of effect across the contributing studies.

Treatment-related factors in the management of DKA have been extensively examined as potential contributors to the development of CE. Among these, bicarbonate administration has received particular attention owing to ongoing debate regarding its efficacy and potential risks. The underlying mechanisms by which bicarbonate therapy may contribute to CE are complex and multifactorial (37). Experimental data suggest that the rapid systemic alkalinization induced by bicarbonate therapy, particularly when combined with insulin, may increase the affinity of hemoglobin for oxygen, thereby reducing its availability to neurons and exacerbating cerebral hypoxia (38). Consistent with this, our meta-analysis identified an association between bicarbonate administration and CE (OR 4.21; 95% CI: 2.37, 7.46), which is consistent with current clinical recommendations against the routine use of bicarbonate in the management of pediatric DKA (39). However, this association should be interpreted with caution, as the certainty of the evidence was rated as low. The pooled estimate is derived from crude, unadjusted data, and confounding by indication is a key concern: patients who receive bicarbonate are typically those with the most severe metabolic derangements including lower pH and higher serum urea which are themselves associated with increased CE risk. Among the contributing studies, only two provided estimates adjusted for disease severity (7,27), and these yielded discordant results depending on the variables and methods used to control for confounding; the remaining studies did not identify or adjust for potential confounders. Therefore, the observed association may partly reflect underlying disease severity rather than a direct treatment effect.

The optimal fluid treatment protocol for children with DKA remains controversial. Historically, CE has been linked to higher intravenous fluid infusion rates, prompting recommendations for more conservative rehydration regimens with slower infusion rates to reduce the risk of this complication (40). In our review, a possible association between higher early fluid volume and CE was observed, with patients who developed CE receiving on average an additional 9.9 mL/kg during the first 4 hours of treatment; however, the certainty of the evidence for this finding was very low, and confidence in this estimate is limited, as it is based on only two studies reporting unadjusted data.

Although the pathophysiology of DKA-associated CE remains incompletely understood, contemporary evidence supports a prominent role for cerebral hypoperfusion and the DKA-related hyperinflammatory state, whereas variability in fluid administration likely has a smaller contribution (41). This is consistent with the PECARN FLUID Trial, which found no significant differences in neurological outcomes between slower and more rapid fluid administration protocols in children with DKA (42), and with current ISPAD guidelines, which indicate that variations in fluid treatment likely have minimal effects on the risk of cerebral injury (39). Similarly, a systematic review of randomized controlled trials by Patiño-Galarza et al. (43) found no differences in cerebral edema across fluid protocols including comparisons of volume, tonicity, and administration systems although substantial heterogeneity across trials prevented statistical pooling, underscoring the uncertainty that remains regarding the optimal fluid strategy for pediatric DKA.

Study Limitations

The main limitations of this review reflect challenges inherent to observational evidence, including design-related risk of bias and between-study variability. High heterogeneity ($I^2 \geq 75\%$) was observed for several biochemical parameters at admission, including pH, serum bicarbonate, serum urea, serum osmolality, serum sodium, and serum potassium, for which results are presented narratively. We explored heterogeneity through subgroup analyses stratified by study design; effect estimates remained largely unchanged across study designs.

The observed heterogeneity may be partly explained by the substantial variability in the operational definition of CE used by the contributing studies, which spans purely clinical criteria, mixed clinical and imaging-based definitions, and stricter outcome-based definitions limited to overt neurological deterioration before treatment. Stricter outcome-based definitions tend to capture only severe and clinically overt CE, which may amplify the apparent associations with markers of disease severity and with treatment-related exposures, whereas broader clinical definitions also include milder or subclinical cases and may attenuate these associations. Conversely, definitions limited to CE present at admission do not capture cases that develop during DKA treatment, which is particularly relevant for the interpretation of treatment-related associations such as bicarbonate administration and early fluid volume.

Furthermore, all pooled estimates for treatment-related exposures are derived from crude, unadjusted data. Confounding by indication is a particularly important concern: patients receiving bicarbonate or higher fluid volumes are typically those with more severe disease, which is itself a risk factor for cerebral edema, and most contributing studies did not identify or implement strategies to address potential confounders.

Conclusion

In this systematic review and meta-analysis, the evidence is very uncertain about the associations of younger age, newly diagnosed type 1 diabetes, and a more severe presentation phenotype (characterized by greater acidosis, hypocapnia, and elevated urea and glucose) with CE in pediatric DKA. Bicarbonate administration may be associated with CE (low certainty), which is consistent with current recommendations against its routine use; however, this association should be interpreted with caution given the potential for confounding by disease severity. The evidence is very uncertain about the association between higher early fluid volumes and CE, and should be interpreted with caution. The overall certainty of evidence was low to very low, driven primarily by risk of bias, heterogeneity, and the lack of confounder adjustment in most contributing studies. Prospective studies with standardized CE definitions and pre-specified confounder adjustment are needed to clarify the magnitude and clinical relevance of these associations.

Statements and Declarations

Author contributions: L.G.R., K.C. and R.K.C. conceived and designed the study. L.G.R. and K.C. conducted the study selection and data extraction. L.G.R., K.C. and L.A.V. analyzed and interpreted the data. L.G.R. drafted the manuscript, and all authors contributed to the discussion, critically revised and edited the manuscript, and approved the final version for submission. L.G.R. is the guarantor of this paper.

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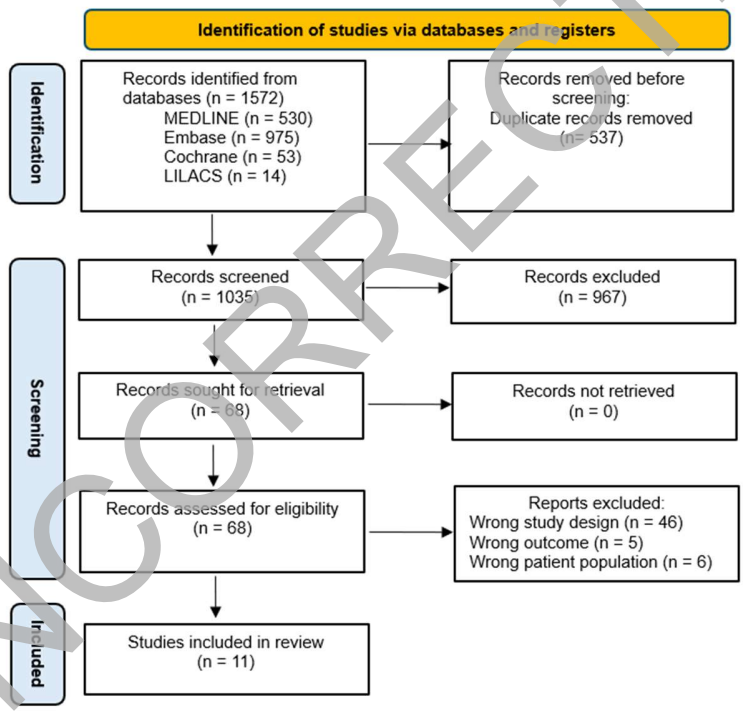
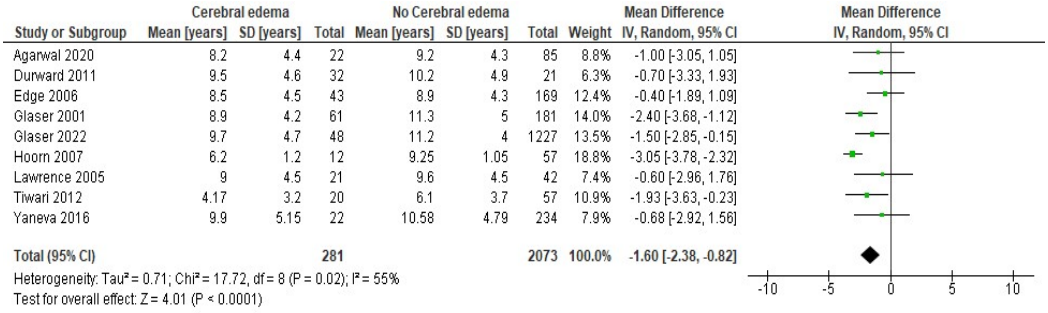
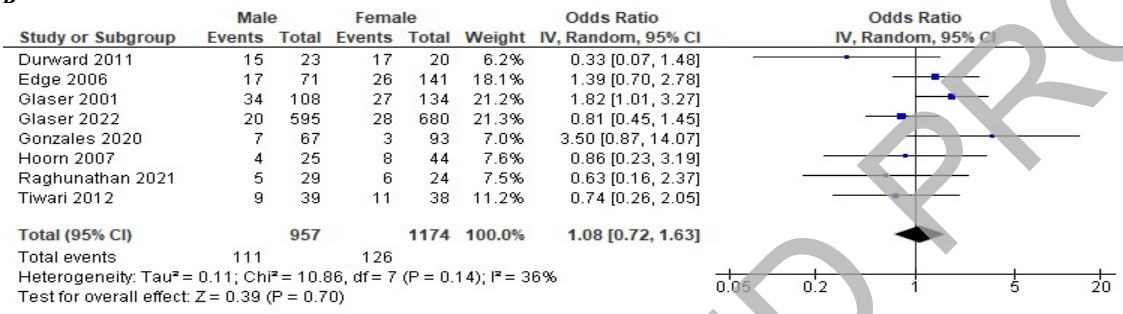


Figure 1. PRISMA flow diagram of selected studies

A



B



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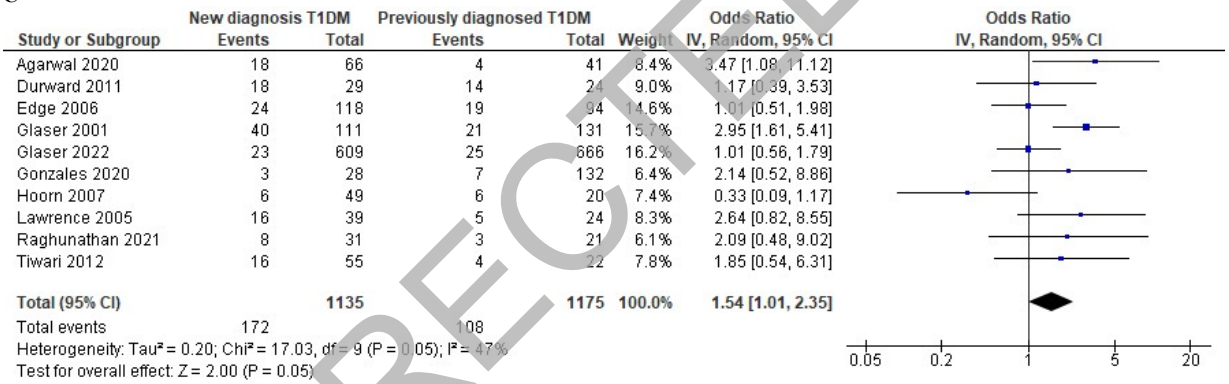
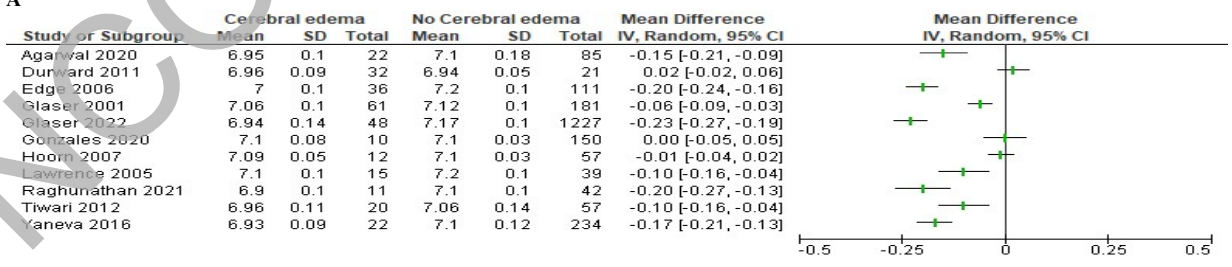


Figure 2. Forest plot of demographic and clinical factors: (A) Age (B) Sex (C) New diagnosis of type 1 diabetes mellitus

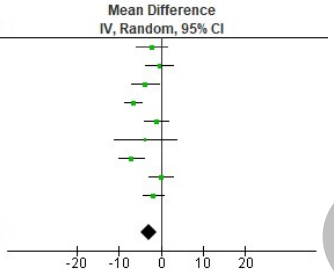
A



B

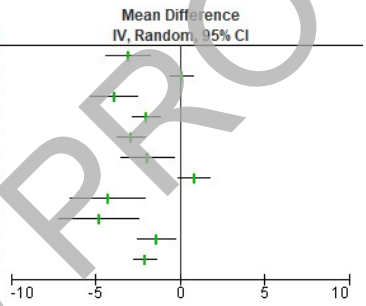
Study or Subgroup	Cerebral edema Mean [mmHg]	SD [mmHg]	Total	No Cerebral edema Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI
Agarwal 2020	18.7	7.9	22	20.9	8.2	87	10.2%	-2.20 [-5.92, 1.52]
Durward 2011	11.63	6.75	32	12	5.25	21	11.2%	-0.37 [-3.61, 2.87]
Edge 2006	16.9	8.2	31	20.7	8	96	11.1%	-3.80 [-7.10, -0.50]
Glaser 2001	11.3	6.5	61	17.9	7.8	181	14.0%	-6.60 [-8.59, -4.61]
Glaser 2022	25	9.8	48	26.1	7.2	1227	12.2%	-1.10 [-3.90, 1.70]
Lawrence 2005	21.7	12.7	14	25.5	9.7	34	4.8%	-3.80 [-11.21, 3.61]
Raghunathan 2021	13	3.8	11	20.1	6.7	42	11.7%	-7.10 [-10.12, -4.08]
Tiwari 2012	15.7	5.8	20	15.7	6.05	57	11.8%	0.00 [-2.99, 2.99]
Yaneva 2016	14.7	5.71	22	16.5	5.29	231	12.9%	-1.80 [-4.28, 0.68]
Total (95% CI)			**261**			**1976**	**100.0%**	**-2.99 [-4.94, -1.05]**

Heterogeneity: Tau² = 6.02; Chi² = 28.67, df = 8 (P = 0.0004); I² = 72%
Test for overall effect: Z = 3.02 (P = 0.003)



C

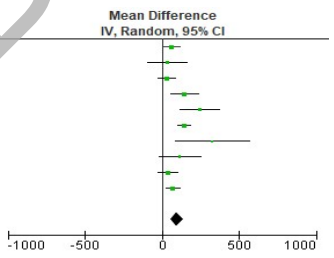
Study or Subgroup	Cerebral edema Mean [mmol/L]	SD [mmol/L]	Total	No Cerebral edema Mean [mmol/L]	SD [mmol/L]	Total	Mean Difference IV, Random, 95% CI
Agarwal 2020	5.2	2.2	22	8.3	4.4	85	-3.10 [-4.41, -1.79]
Durward 2011	2.6	1.45	32	2.5	1.1	21	0.10 [-0.59, 0.79]
Edge 2006	5.7	3.7	39	9.6	4.4	140	-3.90 [-5.27, -2.53]
Glaser 2001	5.9	2.7	61	7.9	3.6	181	-2.00 [-2.86, -1.14]
Glaser 2022	6.1	2.9	48	9	3.2	1227	-2.90 [-3.74, -2.06]
Gonzales 2020	7.5	2.3	10	9.4	4.2	150	-1.90 [-3.48, -0.32]
Hoorn 2007	8	1.6	12	7.15	0.8	57	0.85 [-0.08, 1.78]
Lawrence 2005	5.9	2.7	16	10.2	5.5	37	-4.30 [-6.51, -2.09]
Raghunathan 2021	4.4	3	11	9.2	5.2	42	-4.80 [-7.17, -2.43]
Tiwari 2012	4.09	1.8	20	5.47	3.03	57	-1.38 [-2.49, -0.27]
Yaneva 2016	3.29	1.32	21	5.35	2.64	231	-2.06 [-2.72, -1.40]



D

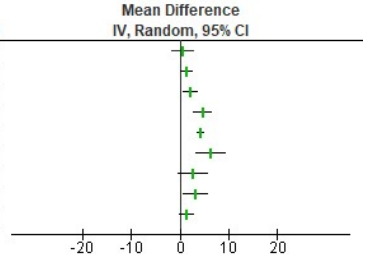
Study or Subgroup	Cerebral edema Mean [mg/dl]	SD [mg/dl]	Total	No Cerebral edema Mean [mg/dl]	SD [mg/dl]	Total	Weight	Mean Difference IV, Random, 95% CI
Agarwal 2020	538.68	113.5	22	473.82	117.1	85	13.7%	64.86 [11.30, 118.42]
Durward 2011	657.58	259.43	21	623.42	190.99	32	6.3%	34.16 [-95.03, 163.35]
Edge 2006	554.89	149.53	37	522.46	185.56	146	13.3%	32.43 [-24.38, 89.24]
Glaser 2001	758	330	61	614	244	181	9.5%	144.00 [53.88, 234.12]
Glaser 2022	759	445	48	514	146	1227	6.5%	245.00 [118.85, 371.15]
Hoorn 2007	684	72	12	540	45	57	15.1%	144.00 [101.62, 186.38]
Lawrence 2005	931	515	20	607	277	42	2.4%	324.00 [83.25, 564.75]
Raghunathan 2021	576.6	218.3	11	462	133.7	42	5.9%	114.60 [-20.59, 249.79]
Tiwari 2012	537	119	20	497	142	57	12.4%	40.00 [-23.87, 103.87]
Yaneva 2016	473.82	103.77	22	404.64	103.59	232	14.7%	69.18 [23.82, 114.54]
Total (95% CI)			**274**			**2101**	**100.0%**	**96.56 [56.35, 136.78]**

Heterogeneity: Tau² = 2321.41; Chi² = 25.84, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 4.71 (P < 0.00001)



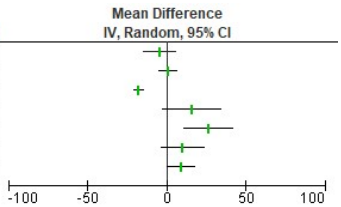
E

Study or Subgroup	Cerebral edema Mean [mmol/L]	SD [mmol/L]	Total	No Cerebral edema Mean [mmol/L]	SD [mmol/L]	Total	Mean Difference IV, Random, 95% CI
Durward 2011	8.7	4.7	32	8.2	3.8	21	0.50 [-1.80, 2.80]
Edge 2006	7.8	3	36	6.5	2.7	142	1.30 [0.22, 2.38]
Glaser 2001	9.62	5	61	7.48	3.92	174	2.14 [0.76, 3.52]
Glaser 2022	10.54	6.45	48	5.88	2.57	1227	4.66 [2.83, 6.49]
Hoorn 2007	11.6	1.2	12	7.4	0.7	57	4.20 [3.50, 4.90]
Lawrence 2005	13.29	5.38	13	6.99	2.89	32	6.30 [3.21, 9.39]
Raghunathan 2021	6.49	4.9	11	3.85	2.13	42	2.64 [-0.33, 5.61]
Tiwari 2012	9.59	5.13	20	6.46	3.93	57	3.13 [0.66, 5.60]
Yaneva 2016	6.51	2.49	13	5.2	2.44	135	1.31 [-0.10, 2.72]



F

Study or Subgroup	Cerebral edema Mean [mOsm/kg]	SD [mOsm/kg]	Total	No Cerebral edema Mean [mOsm/kg]	SD [mOsm/kg]	Total	Mean Difference IV, Random, 95% CI
Durward 2011	297.5	18.5	32	302	18	21	-4.50 [-14.52, 5.52]
Edge 2006	305	15	32	304	14	139	1.00 [-4.69, 6.69]
Hoorn 2007	304	5	12	321.5	3	57	-17.50 [-20.43, -14.57]
Lawrence 2005	335.6	38.1	19	319.5	20.4	36	16.10 [-2.28, 34.48]
Raghunathan 2021	330.7	25	11	304.4	12.3	42	26.30 [11.07, 41.53]
Tiwari 2012	326	28	20	316	23	57	10.00 [-3.65, 23.65]
Yaneva 2016	331.59	15.45	13	322.48	16.23	134	9.11 [0.27, 17.95]



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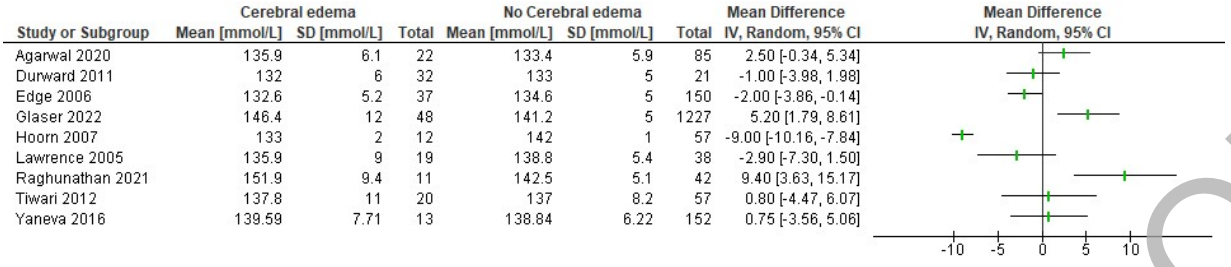

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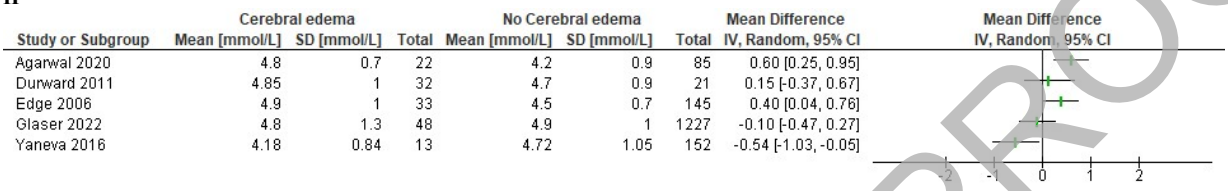
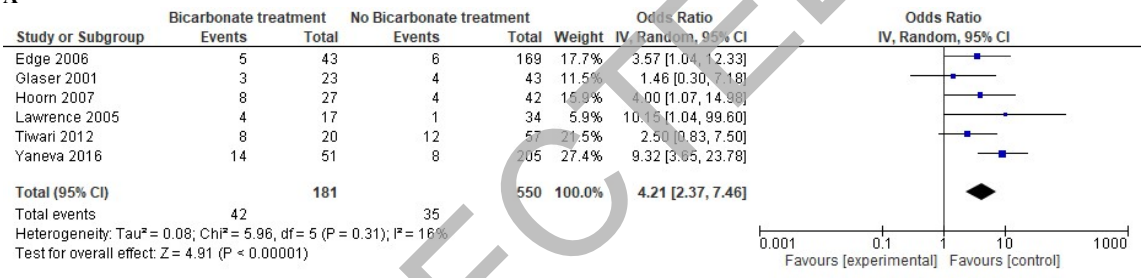


Figure 3. Forest plot of biochemical factors at hospital admission: (A) pH †, (B) $PaCO_2$ (C) Bicarbonate † (D) Glucose (E) Urea † (F) Osmolarity † (G) Sodium † (H) Potassium †
†Pooled estimates are not reported due to considerable heterogeneity ($I^2 \geq 75\%$).

A



B

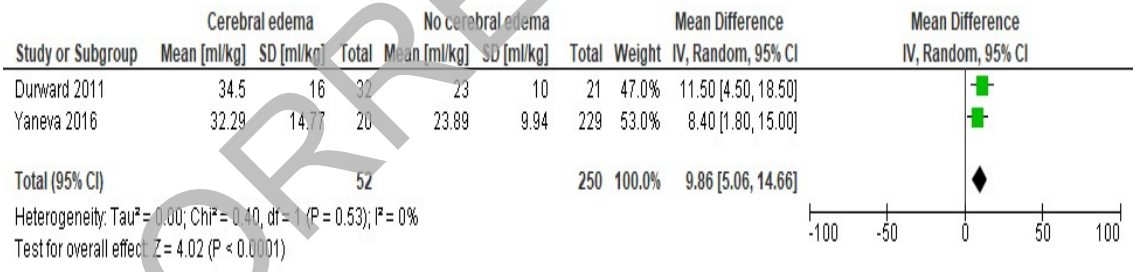


Figure 4. Forest plot of treatment-related factors:(A) Treatment with bicarbonate (B) Volume of fluids used during the first 4 hours

Table 1. Characteristics of the included studies

Study	Year, Country	Design	Sample Size	Participant Characteristics	Diagnostic Method for Cerebral Edema	Definition of Cerebral Edema	Risk Factors for Cerebral Edema and Time of Measurement
Agarwal (21)	2020, India	Analytical cross-sectional	107	DKA: glucose >200 mg/dL, venous pH <7.30 or HCO_3 <15mmol/L, ketonemia. Mean age	Clinical criteria	ISPAD criteria	At admission: age, glucose, pH, HCO_3, $PaCO_2$, sodium, potassium, new diagnosis of T1DM, prior fluid therapy.

				8.2 years (SD 4.4); 62% male.			
Durward (22)	2010, UK	Analytical cross-sectional	53	DKA: glucose >200 mg/dL, venous pH <7.30 or bicarbonate <15 mmol/L, ketonemia/ketonuria. Mean age 9.7 years (SD 4.7); 44% male.	Clinical criteria, neuroimaging or response to CE treatment	Marcin scale ≥3 without other causes, or improvement after osmotherapy, or radiological evidence of edema (28).	At admission: age, sex, new diagnosis of T1DM, glucose, sodium, potassium, urea, effective osmolality, pH, $PaCO_2$, HCO_3. DKA treatment: insulin infusion rate, fluid volume in first 4 h.
Edge (27)	2006, UK	Case-control	212	CE cases: 43 (5 at admission), 70.5% female, mean age 8.5 years (SD 4.5). Controls: 169, 68.1% female, mean age 8.9 years (SD 4.3).	Clinical criteria or neuroimaging	Altered consciousness with ≥1 signs of intracranial hypertension or moderate/severe radiological CE.	At admission: age, sex, new diagnosis of T1DM, sodium, potassium, urea, HCO_3, osmolarity, corrected sodium, glucose, pH, $PaCO_2$. DKA treatment: fluid volume in first 4 h, sodium concentration in fluids, potassium replacement, bicarbonate use, insulin administration.
Glaser (7)	2001, USA	Case-control	235	CE cases: 61, mean age 8.9 years (SD 4.2), 57% male. Controls: 181, mean age 11.3 years (SD 5.0), 41% male.	Clinical criteria with neuroimaging or response to CE treatment	Altered mental status plus radiographic/pathological confirmation or rapid clinical improvement after CE treatment.	At admission: age, sex, white race, new diagnosis of T1DM, HCO_3, BUN, creatinine, glucose, arterial pH, $PaCO_2$. DKA treatment: insulin bolus, bicarbonate use, fluid, sodium, and insulin infusion rates.
Glaser (28)	2022 USA	Case-control	1275	CE: 48 children. Controls (uncomplicated DKA): 1,227 children.	Clinical criteria	Altered mental status before DKA treatment: GCS <14 at admission or clinical documentation of marked somnolence, coma, or severe confusion in the ED.	At admission: age, sex, new diagnosis of T1DM, pH, BUN, glucose, creatinine, bicarbonate, corrected sodium, potassium.
González (20)	2020, Argentina	Analytical cross-sectional	160	DKA: glucose >200 mg/dL, pH <7.30 and/or bicarbonate <15 mmol/L, glucosuria, ketonuria. Median age 11.5 years (IQR 2.0–18.8); 70% male.	Clinical criteria	ISPAD criteria	At admission: age, sex, new diagnosis of T1DM, serum sodium, BUN, $PaCO_2$, pH, HCO_3.
Hoorn (25)	2007, Brazil	Analytical cross-sectional	69	DKA: glucose >200 mg/dL, venous pH <7.30 or HCO_3 <15 mmol/L. Mean age 8.2 years (SD 1.1); 37% male.	Clinical criteria with neuroimaging or response to CE treatment	Altered mental state confirmed radiologically/pathologically, or rapid improvement after specific CE treatment.	At admission: age, weight, sex, sodium, osmolality, glucose, pH, HCO_3, creatinine, new diagnosis of T1DM. DKA treatment: fluid bolus, insulin bolus, bicarbonate use, fluid volume at 6 h, Na^+ and K^+ administered at 6 h.
Lawrence (11)	2005, Canada	Case-control	53	CE cases: 21, mean age 9.0 years (SD 4.5), 62% male. Controls: 42 with DKA, mean age 9.6 years (SD 4.5).	Clinical criteria with neuroimaging	Sudden/unexpected consciousness deterioration with pH <7.35 and/or low HCO_3, diabetes and ketonuria. Neuroimaging required before DKA treatment to exclude DKA-related altered consciousness.	At admission: age, pH, glucose, osmolality, new diagnosis of T1DM, $PaCO_2$, HCO_3, sodium, BUN. DKA treatment: fluid and sodium infusion rates, bicarbonate use.

Raghunathan (26)	2021 India	Analytical cross-sectional	48	DKA: defined by 2014/2018 ISPAD guidelines. n = 48.	Clinical criteria	CE defined per Muir et al. clinical criteria.	At admission: age, sex, new diagnosis of T1DM, infections, glucose, bicarbonate, PCO_2, sodium, urea, osmolality. At 12/24 h: bicarbonate, chloride. DKA treatment: fluid rate (mL/kg/24 h), rate of blood glucose decline (mg/dL/h).
Tiwari (23)	2012, India	Analytical cross-sectional	77	DKA: glucose ≥250 mg/dL, positive urinary ketones, venous pH <7.30 or arterial pH <7.25. Mean age 6.1 years (SD 3.7); 52.6% male.	Clinical criteria	Persistent altered consciousness despite pH improvement to 7.3 and glucose to 300 mg/dL, or altered consciousness + signs of intracranial pressure.	At admission, 6–12 h, 24 h: age, sex, new diagnosis of T1DM, pH, $PaCO_2$, HCO_3, glucose, osmolality, urea, creatinine, sodium. DKA treatment: number of fluid boluses, bicarbonate therapy.
Yaneva (24)	2016, Bulgaria	Analytical cross-sectional	256	DKA: glucose >200 mg/dL, venous pH <7.30, HCO_3 <15 mmol/L, ketonemia/ketonuria. n = 256; mean age 10.2 years (SD 4.9).	Clinical criteria	ISPAD criteria	At admission: age, $PvCO_2$, pH, HCO_3, urea, osmolality, sodium, potassium, phosphate. DKA treatment: bicarbonate use, timing of insulin therapy, insulin dose (first 4 h), start of hypotonic solution, fluid volume (first 4 h), timing of potassium replacement.

Abbreviations: DKA: diabetic ketoacidosis; ISPAD: International Society for Pediatric and Adolescent Diabetes; T1DM: type 1 diabetes mellitus; CE: cerebral edema; BUN: blood urea nitrogen; GCS: Glasgow Coma Scale.