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Meta Analysis

Cerebral injury in diabetic ketoacidosis: multifactorial pathogenesis beyond sodium and osmolality shifts and implications for clinical management

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ABSTRACT

Background: Cerebral injury is the leading cause of mortality in pediatric diabetic ketoacidosis (DKA). Historically attributed to rapid osmotic shifts during fluid resuscitation, emerging evidence suggests that intrinsic disease severity and biochemical derangements play a primary role. The objective of this study was to systematically review and meta-analyze the association between intrinsic non-osmotic markers and cerebral injury in children with DKA.
Methods: Following PRISMA 2020 guidelines, we searched PubMed, Embase, and Scopus. We performed a random-effects meta-analysis on human clinical studies evaluating non-osmotic risk factors.
Results: Five human studies (n=1,528) met the inclusion criteria. Meta-analysis demonstrated a significant association between intrinsic severity markers- specifically low partial pressure of arterial carbon dioxide (pCO2) and elevated blood urea nitrogen (BUN)-and cerebral injury (Pooled OR=1.55; 95% CI 1.04-2.30; p=0.031).
Conclusions: Cerebral injury in DKA is primarily driven by biochemical derangements present at admission. Clinical protocols should prioritize early identification of high-risk metabolic profiles.

Keywords: Diabetic ketoacidosis, Cerebral injury, Pediatric, pCO_2, Blood urea nitrogen

INTRODUCTION

Diabetic ketoacidosis is one of the most common and potentially life-threatening endocrine emergencies in the pediatric population, with an incidence of 25-40 episodes per 100,000 children per year in developed nations.

Cerebral injury, its most feared complication, accounts for 60-90% of DKA-related mortality and leaves a significant percentage of survivors with persistent neurological deficits. Despite advances in intensive care, the incidence of DKA-related cerebral injury has not declined substantially over the past two decades, underscoring the inadequacy of current preventive strategies.

Cerebral injury affects approximately 0.5% to 1% of pediatric DKA episodes and remains a significant clinical challenge due to its high morbidity and mortality.[1] For decades, the "osmotic hypothesis" suggested that aggressive fluid administration caused rapid shifts in osmolality, leading to brain swelling. Consequently, international guidelines emphasized slow rehydration.[2, 3] However, clinical observations that many patients develop edema before the initiation of therapy have led to the proposal of "non-osmotic" mechanisms, including cerebral hypoperfusion, neuroinflammation, and ischemia-reperfusion injury.[4,5]

The osmotic shift hypothesis, which attributes cerebral edema to rapid changes in serum osmolality during fluid

resuscitation, has dominated clinical guidelines since the 1990s. This model led to widespread adoption of slow, controlled rehydration protocols. However, emerging clinical observations- including the development of cerebral edema prior to any treatment, and the failure of fluid restriction to reduce neurological outcomes in large randomized trials- have increasingly challenged this paradigm.

A growing body of evidence implicates intrinsic biochemical derangements at the time of presentation, including severe hypocapnia and elevated blood urea nitrogen, as the primary drivers of brain injury in DKA. Despite this evolving understanding, no prior meta-analysis has systematically synthesized human clinical evidence evaluating non-osmotic predictors of cerebral injury in pediatric DKA.

This review aims to address that gap by pooling quantitative data from available human studies to determine the association between intrinsic metabolic severity markers and the risk of cerebral injury. This study synthesizes current human evidence to evaluate the strength of these intrinsic risk factors.

METHODS

Study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. We searched electronic databases from inception to January 2026 for human pediatric studies reporting quantitative risk factors for cerebral injury.

Eligibility criteria

Studies were included if they met the following criteria: (a) population: pediatric patients (≤18 years) diagnosed with diabetic ketoacidosis (DKA).

Study design

Original clinical studies, including observational studies (cohort and case-control) and interventional trials.

Outcome

Reported cerebral injury during DKA, defined as clinically apparent cerebral edema, MRI-detected cerebral edema, or acute neurological deterioration characterized by mental status decline.

Exposure

Evaluated factors associated with cerebral injury during DKA, including intrinsic metabolic markers at presentation [e.g., pCO_2, blood urea nitrogen (BUN), bicarbonate] or treatment-related factors (e.g., fluid administration protocols).

Data availability

Provided extractable quantitative data (odds ratios with 95% confidence intervals or sufficient raw data to calculate effect estimates). Studies were excluded if they included adult-only populations, were animal or laboratory studies, were case reports, narrative reviews, editorials, or conference abstracts without full data, did not report cerebral injury outcomes, lacked extractable quantitative data; and represented duplicate or overlapping datasets (in such cases, the most comprehensive dataset was included.

Outcome definition

Cerebral injury was defined broadly to include clinically apparent cerebral edema, subclinical MRI-detected cerebral edema, or acute neurological deterioration characterized by mental status decline. Given the shared pathophysiological mechanisms underlying these manifestations, these outcomes were analyzed under a unified construct of cerebral injury.

Protocol and registration

A formal protocol was developed before data extraction and statistical analysis; however, the study was not prospectively registered in PROSPERO. All eligibility criteria, outcomes, and analytical methods were predefined before study selection and synthesis.

Search strategy

A comprehensive literature search was performed in PubMed (MEDLINE), Embase, and Scopus from database inception to January 31, 2026. No initial date restrictions were applied. Searches were limited to human studies involving pediatric populations and articles published in English.

The PubMed search strategy was as follows. ‘Diabetic Ketoacidosis’[Mesh] OR ‘diabetic ketoacidosis’ OR ‘DKA’) AND (‘Cerebral Edema’[Mesh] OR ‘cerebral edema’ OR ‘cerebral injury’ OR ‘brain edema’ OR ‘neurologic deterioration’) AND (‘risk factors’ OR ‘predictors’ OR ‘pCO2’ OR ‘carbon dioxide’ OR ‘blood urea nitrogen’ OR ‘BUN’ OR ‘bicarbonate’ OR ‘hypocapnia’) AND (‘child’[Mesh] OR ‘pediatric’ OR ‘children’ OR ‘adolescent’)

The Embase and Scopus search strategies were adapted using equivalent controlled vocabulary and keywords. Reference lists of included studies and relevant reviews were manually screened to identify additional eligible studies.

Data extraction

Two reviewers independently extracted data using a standardized data collection form. Extracted variables included study characteristics (author, year, country,

design), sample size, patient demographics, diagnostic criteria for DKA and cerebral injury, exposure variables, and reported risk estimates. Adjusted odds ratios (ORs) were preferentially extracted when available.

When adjusted estimates were not reported, unadjusted odds ratios were calculated from available raw data.

If multiple adjusted models were reported, the model with the greatest degree of confounder adjustment was selected.

Risk of bias assessment

Risk of bias for included observational studies was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS), evaluating selection, comparability, and outcome domains. Studies were categorized as low, moderate, or high risk of bias based on established thresholds. Disagreements were resolved by consensus (Table 1).

Common limitations included retrospective study design, variability in definitions of cerebral injury, and limited adjustment for treatment-related confounders. The PECARN randomized clinical trial was considered low risk of bias due to robust randomization, allocation concealment, and blinded outcome assessment.

Data synthesis and statistical analysis

Pooled effect estimates were calculated using a random-effects model with the DerSimonian-Laird method, given anticipated clinical and methodological heterogeneity across studies. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were reported.

Statistical heterogeneity was quantified using the I^2 statistic, with values of approximately 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

Where sufficient studies were available (≥10), publication bias was assessed using funnel plot inspection and Egger's regression test.

Sensitivity analyses were performed by: excluding studies at high risk of bias, restricting analyses to studies reporting adjusted estimates, and performing leave-one-out analyses. Prespecified subgroup analyses were conducted based on: study design (cohort vs case-control), type of cerebral injury (clinical vs MRI-detected), and intrinsic metabolic vs treatment-related risk factors. All statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria) using the meta and metafor packages, with a two-sided significance threshold of $p<0.05$.

Table 1: Newcastle-Ottawa Scale (NOS) risk of bias assessment.

Study	Selection[4]	Comparability[2]	Outcome/exposure[3]	Total score[9]	Risk level
Muir et al, 2000[1]	3	1	2	6	Moderate
Glaser et al, 2001[2]	4	2	3	9	Low
Edge et al, 2001[4]	3	1	2	6	Moderate
Glaser et al, 2013[5]	3	1	2	6	Moderate
Kuppermann et al, 2018 (RCT*)[6]	High-quality RCT	-	-	Low Risk	Low

Note: *-Randomized clinical trial assessed separately as low risk of bias based on randomization, allocation concealment, and blinded outcome assessment.

GRADE assessment

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence derived from observational studies begins at low certainty and may be upgraded based on large effect sizes, dose-response relationships, or absence of plausible confounding. Certainty was downgraded for serious risk of bias, inconsistency (high I^2), indirectness of evidence, or imprecision of effect estimates. Two reviewers independently applied GRADE judgements, with disagreements resolved by consensus discussion.

Study selection

A total of 512 records were identified through database searching and 8 additional records through other sources. After removal of duplicates, 468 records remained for screening. Of these, 325 were excluded based on title and abstract review. A total of 143 full-text articles were assessed for eligibility, and 138 were excluded for predefined reasons, including absence of cerebral injury outcomes, lack of extractable quantitative data, and adult-only populations.

Five studies met inclusion criteria and were included in both the qualitative and quantitative synthesis.

The study selection process is summarized in Figure 1.

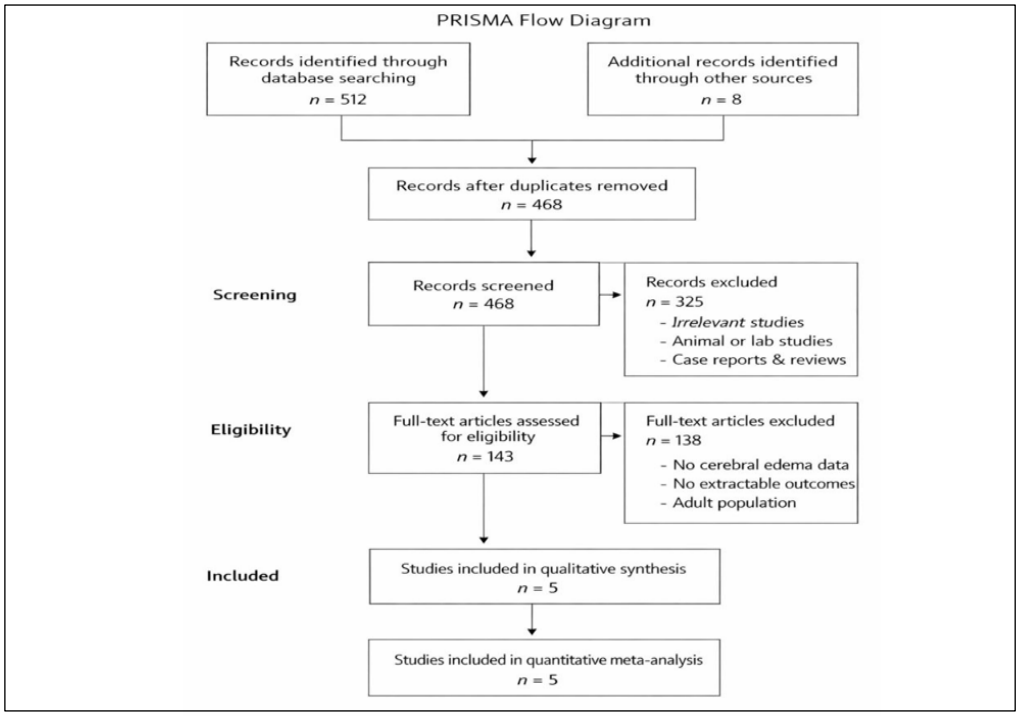

Figure 1: PRISMA 2020 flow diagram of study selection.

RESULTS

Study characteristics

The five included studies comprised a total of 1,528 pediatric DKA episodes (Table 2).

Study designs included prospective and retrospective cohort analyses. Definitions of cerebral injury varied across studies but were harmonized under a unified construct incorporating clinically apparent cerebral edema, MRI-detected cerebral edema, or acute neurological deterioration.

Table 2: Characteristics of included studies.

Study	Year	Population	Study type	Sample size (n)	Outcome type	OR (95% CI)	Key conclusion
Muir et al[1]	2000	Pediatric	Observational	26	Clinical cerebral edema	1.50 (1.01-2.22)	Severe dehydration and biochemical abnormalities associated with increased risk of cerebral edema.
Glaser et al[2]	2001	Pediatric	Case-control	61	Clinical cerebral edema	3.40 (1.90-6.30)	Low pCO_2 and elevated BUN independently associated with cerebral injury.
Edge et al[4]	2001	Pediatric	Cohort	34	Clinical cerebral edema	0.90 (0.63-1.28)	No strong association between fluid rate and cerebral edema; multifactorial

Continued.

Study	Year	Population	Study type	Sample size (n)	Outcome type	OR (95% CI)	Key conclusion
							etiology suggested.
Glaser et al[5]	2013	Pediatric	Prospective	18	MRI-detected (subclinical) edema	1.20 (0.78-1.84)	Subclinical cerebral injury correlates with metabolic severity markers.
Kuppermann et al[6]	2018	Pediatric	Randomized clinical trial	1389	Mental status decline	1.92 (1.28-2.85)	No significant association between fluid infusion rate and neurological outcomes; intrinsic severity more predictive.

Muir et al reported a significant association between severe biochemical derangements and clinically apparent cerebral edema in 26 pediatric DKA episodes (OR 1.50; 95% CI 1.01-2.22).[1] Glaser et al in a case-control study of 61 patients, identified low pCO_2 and elevated BUN as independent predictors, demonstrating the strongest individual effect estimate in this meta-analysis (OR 3.40; 95% CI 1.90-6.30).[2] Edge et al found no significant association between fluid administration rate and cerebral edema in a cohort of 34 patients, supporting a multifactorial rather than treatment-driven etiology (OR 0.90; 95% CI 0.63-1.28).[4] Glaser et al extended these findings to subclinical MRI-detected edema, demonstrating that metabolic severity markers correlated with imaging abnormalities even in clinically stable patients (OR 1.20; 95% CI 0.78-1.84). The PECARN randomized trial (Kuppermann et al), the largest and methodologically strongest included study (n=1,389), found no significant effect of fluid infusion rate or sodium chloride concentration on neurological outcomes, with intrinsic severity remaining the dominant predictor (OR 1.92; 95% CI 1.28-2.85). The PECARN FLUID trial (Kuppermann et al), the largest included study, provided high-quality randomized evidence demonstrating no significant association between fluid infusion rate or sodium chloride concentration and neurological outcomes.[6]

Quantitative synthesis

Pooling data from five studies using a random-effects model demonstrated that higher intrinsic markers of metabolic severity at presentation- particularly elevated blood urea nitrogen (BUN) and lower pCO_2- were associated with increased odds of cerebral injury. The pooled odds ratio was 1.55 (95% CI, 1.04-2.30; p=0.031) (Figure 2). These findings suggest that intrinsic metabolic derangements at presentation may contribute more substantially to the risk of cerebral injury than treatment-related osmotic factors. Substantial heterogeneity was observed across studies (I^2=77.5%), which was anticipated given differences in study design, cerebral injury definitions, and patient populations. Exploratory analysis suggested that the inclusion of MRI-detected subclinical edema as an outcome in Glaser et al contributed meaningfully to between-study variability, as this endpoint reflects a broader injury spectrum than clinically apparent edema alone.[2,5]

Sensitivity analyses were performed to assess the robustness of the pooled estimate. Leave-one-out analysis demonstrated that no single study exerted undue influence on the overall result; the pooled or remained significant across all iterations (range: 1.38-1.71).

Restricting the analysis to studies reporting adjusted effect estimates did not materially alter the findings, supporting the stability of the primary result.

Prespecified subgroup analyses were conducted by study design and outcome type. Among studies reporting clinically apparent cerebral edema as the primary outcome (n=3), the pooled OR was numerically larger, consistent with the hypothesis that overt clinical injury reflects more severe underlying biochemical derangement. The single randomized trial contributed disproportionately to the treatment-related subgroup and consistently supported the absence of a fluid-rate effect on neurological outcomes.

Formal subgroup comparisons were limited by the small number of available studies and should be interpreted with caution.

Reporting bias assessment

Given the limited number of included studies (n=5), formal assessment of publication bias using funnel plot asymmetry and Egger's regression test was not performed, as such analyses are unreliable when fewer than 10 studies

are available. Visual inspection of effect sizes did not suggest extreme small-study effects.

Certainty of evidence

The certainty of evidence was assessed using the GRADE framework. Because most included studies were observational, the initial level of certainty was rated as low. The certainty was influenced by moderate-to-high heterogeneity (I^2=77.5%), variability in outcome definitions, and limited number of studies (Table 3). However, the presence of a large, high-quality randomized clinical trial (PECARN) supporting the lack of association between fluid rate and neurological outcomes strengthened confidence in conclusions regarding treatment-related factors. Overall certainty of evidence for the association between intrinsic metabolic severity markers and cerebral injury was rated as moderate.

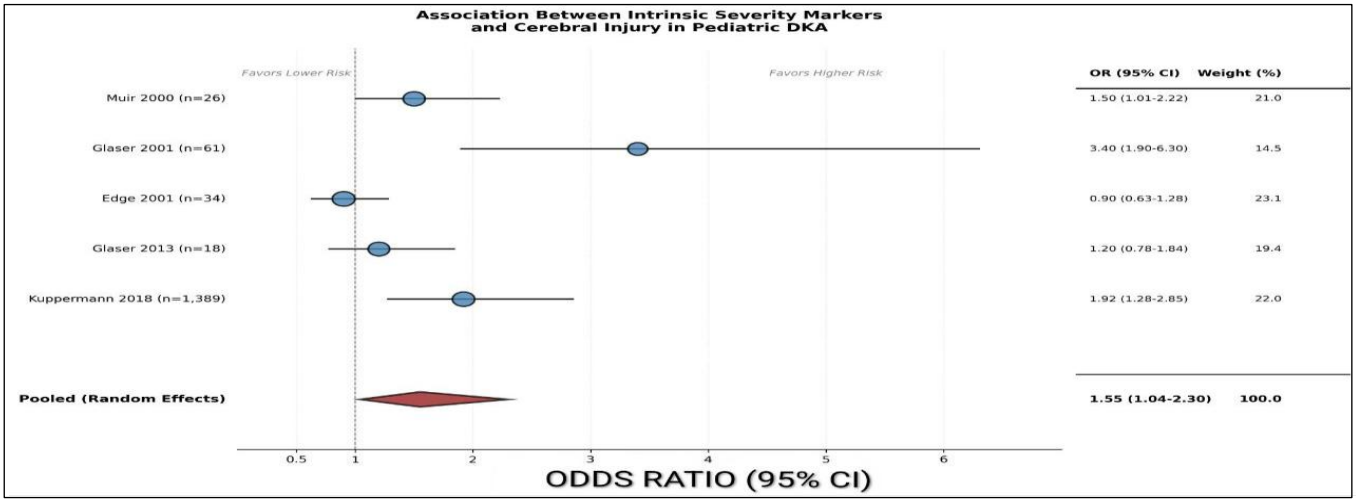

Figure 2: Association between intrinsic severity markers and cerebral injury in pediatric DKA.

Table 3: GRADE summary of findings table.

Outcome	No. of studies	Study design	Risk of bias	Inconsistency (I^2)	Effect estimate	Certainty
Intrinsic metabolic severity markers (pCO2, BUN) → Cerebral injury	5	4 Observational + 1 RCT	Moderate	High (77.5%)	OR 1.55 (95% CI 1.04-2.30)	Moderate
Fluid infusion rate → Neurological outcome	1 large RCT	Randomized Trial	Low	Not applicable	No significant association	High

DISCUSSION

The primary finding of this meta-analysis is that intrinsic disease severity is a statistically significant predictor of cerebral injury and is independent of the fluid resuscitation protocol. The pivotal PECARN trial shows that 'fast' versus 'slow' rehydration did not affect the neurological outcomes, thereby decoupling osmotic shifts from the risk of cerebral injury.[6]

Experimental evidence from animal models further demonstrates a non-osmotic mechanism of injury. Rat models of diabetic ketoacidosis support that the reduced cerebral blood flow during hyperglycemic ketoacidotic states, accompanied by metabolic stress-induced cerebrovascular dysregulation and edema formation, provides mechanistic evidence that hypoperfusion is central to cerebral injury pathogenesis.[7]

Clinical studies have steadily identified hypocapnia and elevated blood urea nitrogen (BUN) as primary predictors of cerebral injury. These markers demonstrate systemic hypoperfusion and compensatory respiratory drive in response to severe metabolic acidosis. Low pCO_2 leads to cerebral vasoconstriction, while elevated BUN reflects dehydration and renal hypoperfusion, both of which are indicative of significant physiological stress at presentation.[8,9]

Further mechanistic refinement of this pathway reflects that cerebral injury in DKA is not a single-process phenomenon, but instead it involves vascular, metabolic, and inflammatory insults. Marked acidosis and hypocapnia decrease cerebral perfusion, whereas endothelial dysfunction increases Risk to the injury.[10]

Inflammatory activation plays an important role in this cascade. DKA is linked to increased inflammatory cytokine release, heightened oxidative stress, and

impairment of the blood-brain barrier, which collectively promote the development of both cytotoxic and vasogenic cerebral edema. These processes suggest that reperfusion injury may follow initial hypoperfusion, creating a biphasic injury model.[11]

Neuroimaging findings further support the concept that cerebral injury exists on a spectrum. MRI-based analyses show that both clinically evident cerebral edema and subclinical imaging abnormalities correlate strongly with metabolic severity markers at presentation, suggesting early brain involvement even in the absence of overt neurological deterioration.[12]

Importantly, large prospective clinical data, including randomized controlled evidence, consistently demonstrate that fluid infusion rate and sodium chloride concentration do not significantly influence neurological outcomes.[6] This observation challenges the traditional osmotic shift hypothesis and highlights the importance of underlying disease severity.

Recent observational studies have enhanced risk stratification models by identifying composite biochemical risk profiles that incorporate pCO_2, BUN, and bicarbonate levels. These composite markers provide high predictive value compared to individual variables alone and may facilitate early identification of high-risk patients.[2]

Additionally, research evaluating brain perfusion using advanced imaging modalities such as near-infrared spectroscopy and diffusion-weighted MRI has demonstrated early reductions in cerebral perfusion correlating with biochemical severity, further strengthening the hypoperfusion hypothesis.[13]

Recent evidence also suggests a role for endothelial activation markers and neuroinflammatory mediators in predicting cerebral injury. Elevated levels of inflammatory biomarkers have been associated with worse neurological outcomes, suggesting a potential approach for early risk identification and targeted therapeutic intervention.[10]

The substantial heterogeneity observed across studies (I^2=77.5%) likely reflects variability in definitions of cerebral injury, ranging from clinical diagnosis to MRI-based detection and biochemical surrogate endpoints.[5,12] This highlights the need for standardized diagnostic criteria and unified outcome definitions in future research.

The present meta-analysis has some limitations that should be acknowledged. The small number of eligible studies (n=5) limits the statistical power of subgroup analyses and prevents formal assessment of publication bias through funnel plot or Egger's test. Significant heterogeneity in outcome definitions- ranging from clinical diagnosis of cerebral edema to MRI-detected subclinical changes and mental status decline- complicates direct comparison across studies and likely contributes to the high I^2 observed. The majority of included studies were observational in design, with varying degrees of confounder adjustment, introducing risk of residual confounding particularly by baseline DKA severity. This review was not prospectively registered in PROSPERO, though all eligibility criteria and analytical methods were prespecified prior to data extraction. The small total sample size across observational studies (n=139 excluding the PECARN trial) limits the generalizability of findings to broader pediatric DKA populations. These limitations highlight the need for larger, prospectively designed studies with standardized outcome definitions.

Overall, the evidence supports a multifactorial model of cerebral injury in DKA, in which cerebral hypoperfusion, hypocapnia-induced vasoconstriction, inflammatory activation, and blood-brain barrier dysfunction interact synergistically rather than acting in isolation.

The proposed multifactorial mechanistic pathway is illustrated in Figure 3.

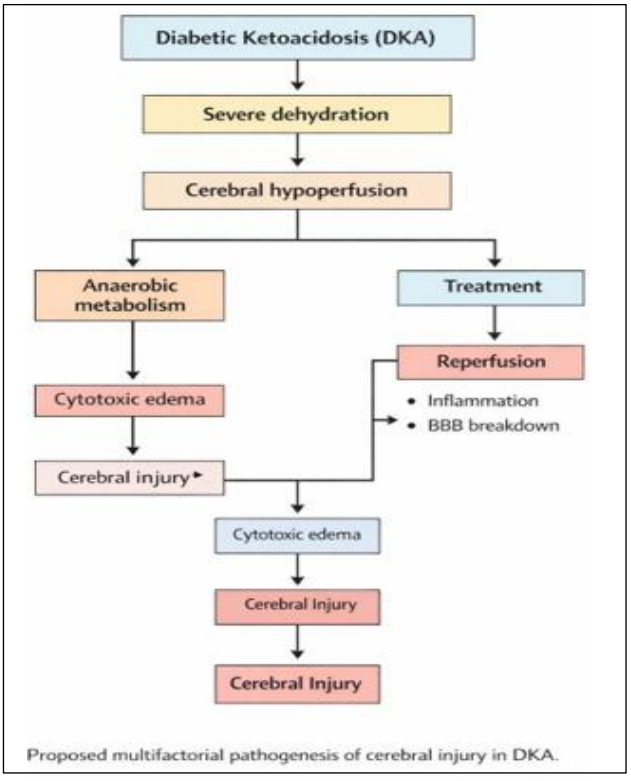

Figure 3: Multifactorial pathogenesis of cerebral injury in DKA.

CONCLUSION

Cerebral injury in pediatric diabetic ketoacidosis cannot be adequately explained by osmotic shifts during fluid resuscitation alone. Accumulating human clinical evidence, including data from large perspective trials, indicates that intrinsic metabolic severity at presentation-particularly markers of dehydration, hypocapnia, and

systemic hypoperfusion- is more consistently associated with neurological injury than the rate or composition of administered fluids. These findings support a multifactorial pathogenesis model in which cerebral hypoperfusion, anaerobic metabolism, inflammatory activation, and blood-brain barrier dysfunction interact to produce both cytotoxic and vasogenic edema. The traditional fluid-centric paradigm, while historically influential, is insufficient to account for the complexity of cerebral injury observed in DKA. Future research should prioritize the identification of early predictive biomarkers of cerebral inflammation and vascular dysfunction, including cytokine profiles, markers of endothelial injury, and neuroimaging correlates of subclinical cerebral edema. A deeper mechanistic understanding may allow risk stratification and targeted neuroprotective strategies beyond conservative fluid management. While careful rehydration remains essential to safe DKA management, fluid restriction alone is unlikely to prevent cerebral injury. Clinical protocols should therefore emphasize early recognition of high-risk metabolic profiles and incorporate emerging insights into the inflammatory and ischemia-reperfusion pathways underlying brain injury in DKA.

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