Response to Comments on Hyperglycemic Crises in Adults With Diabetes: A Consensus Report. Diabetes Care 2024;47:1257–1275

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We appreciate the insights of Cao and Cao (1) as well as Gosmanov (2) regarding the recent international consensus update on managing diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) in adults (3). Both stressed the importance of an elevated anion gap in diagnosing DKA and raised concerns about the exclusion of the anion gap from the revised diagnostic criteria of DKA. Cao and Cao further noted that measured osmolality should be considered a diagnostic criterion for HHS. They queried the role of 0.45% sodium chloride in correcting the free water deficit in the setting of hypernatremia.

The diagnosis of DKA is based on three criteria: hyperglycemia, elevated ketones, and metabolic acidosis. Of these, the main diagnostic indicator of DKA is the rise in circulating ketone body concentration, which can be assessed by directly measuring β-hydroxybutyrate in the blood or by the nitroprusside reaction in urine or serum. Most individuals with DKA present with a high-anion-gap metabolic acidosis (4). An anion gap >12 mmol/L indicates DKA, as stated in the consensus report; however, over one-third of patients with DKA display mixed acid-base disorders characterized by metabolic acidosis and metabolic alkalosis resulting from hyperglycemia-induced osmotic diuresis and natriuresis as well as nausea and vomiting that can lead to volume contraction and metabolic alkalosis alongside compensatory respiratory alkalosis (5). Additionally, hyperchloremic normal anion gap metabolic acidosis occurs in 10% of patients admitted with DKA and is almost invariably present after ketonemia resolves following normal saline administration (6). Using the anion gap as the primary diagnostic indicator of elevated ketones or requiring normalization of the gap to confirm the resolution of ketoacidosis may be misleading and delay appropriate care (7). Nevertheless, the anion gap remains an informative adjunctive tool in cases of mixed acid-base disorders (which are not the focus of the consensus report) or in resource-limited settings where ketone measurement is unavailable.

HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration without ketoacidosis. The diagnostic criteria for HHS, derived from case series reported by Gerich et al. and Arieff and Carroll in 1971, have remained unchanged (for a review of the diagnostic criteria and treatment of HHS, see Pasquel and Umpierrez [8]). Osmolarity is defined as the number of milliosmoles of solute per unit volume of solution, while osmolality represents the milliosmoles of solutes per unit mass. Serum osmolality can be directly measured using an osmometer (in milliosmoles per kilogram), while osmolarity can be estimated using calculations based on the levels of the major plasma osmoles. The difference between the measured and calculated osmolarity is known as the osmolar gap (9). An osmolar gap is elevated when it exceeds 10 mOsm/kg H_2O. A high osmolar gap can result from various causes, including ingesting toxic alcohols, such as methanol, ethanol, ethylene glycol, diethylene glycol, propylene glycol, or isopropanol (10). Other potential causes include shock, kidney failure,

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electrolyte imbalances, and contrast dye. Taking a thorough history is crucial, and as suggested by Cao and Cao, incorporating alcohol into the calculation may be warranted in the presence of a high anion gap. However, in most institutions, serum alcohol measurement is not readily available and may lead to delays in diagnosis. A euglycemic hyperosmolar hypernatremia state and HHS are managed similarly, beginning with an infusion of a relatively hypotonic solution, such as 0.9% sodium chloride solution (4). We do not recommend 0.45% sodium chloride as the initial fluid of choice because of the potential danger of reducing the serum osmolality too rapidly, which could lead to neurological compromise.

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References

1. Cao S, Cao S. Comment on Umpierrez et al. Hyperglycemic crises in adults with diabetes: a consensus report. 2024;47:1257–1275 (Letter). Diabetes Care 48:e40–e41
2. Gosmanov A. Comment on Umpierrez et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47:1257–1275 (Letter). Diabetes Care 48:e38–e39
3. Umpierrez GE, Davis GM, ElSayed NA, et al. Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024;47:1257–1275
4. Dhatariya KK, Joint British Diabetes Societies for Inpatient Care. The management of diabetic ketoacidosis in adults–an updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabet Med 2022;39:e14788
5. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. N Engl J Med 2015;372:546–554
6. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care 2001;24:131–153
7. Dhatariya K. Blood ketones: measurement, interpretation, limitations, and utility in the management of diabetic ketoacidosis. Rev Diabet Stud 2016;13:217–225
8. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care 2014;37:3124–3131
9. Choy KW, Wijeratne N, Lu ZX, Doery JC. Harmonisation of osmolal gap–can we use a common formula? Clin Biochem Rev 2016;37:113–119
10. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers 2020;6:40