REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES
Julie R. Ingelfinger, M.D., *Editor*

Acid–Base Problems in Diabetic Ketoacidosis

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THIS REVIEW FOCUSES ON THREE ISSUES FACING CLINICIANS WHO CARE FOR patients with diabetic ketoacidosis; all of the issues are related to acid–base disorders. The first issue is the use of the plasma anion gap and the calculation of the ratio of the change in this gap to the change in the concentration of plasma bicarbonate in these patients; the second concerns the administration of sodium bicarbonate; and the third is the possible contribution of intracellular acidosis to the development of cerebral edema, particularly in children with diabetic ketoacidosis. In this article, we examine the available data and attempt to integrate the data with principles of physiology and metabolic regulation and provide clinical guidance.

PLASMA BICARBONATE AND THE PLASMA ANION GAP

The accumulation of ketoacids in the extracellular fluid leads to a loss of bicarbonate anions and a gain of ketoacid anions. Because of hyperglycemia-induced osmotic diuresis and natriuresis, patients with diabetic ketoacidosis usually present with a marked contraction of the extracellular fluid volume. This factor affects the assessment of their acid–base status and in some cases their therapy.

Determination of the severity of metabolic acidemia is usually based on the extent of the decrease in the plasma bicarbonate concentration. Nevertheless, as shown in the equation below, the plasma bicarbonate concentration may be only moderately reduced when there is both a large deficit of bicarbonate in the extracellular fluid and a severe contraction of the volume of extracellular fluid. The bicarbonate deficit becomes evident during reexpansion of the volume of extracellular fluid when saline is administered:

$$\text{Extracellular fluid bicarbonate concentration } [HCO_3^-] = \text{extracellular fluid } HCO_3^- \text{ content} \div \text{extracellular fluid volume.}$$

The addition of new anions is reflected in an increase in the plasma anion gap,[1,2] which is the difference between the concentration of the major cation in plasma (sodium) and the major anions in plasma (chloride and bicarbonate). This difference is due largely to the net anionic valence on plasma proteins, principally albumin. A pitfall in using the plasma anion gap is the failure to correct for the net negative valence attributable to plasma albumin.[3] This correction must be made not only when the plasma albumin concentration decreases but also when it increases; the latter may occur in patients with diabetic ketoacidosis because of the marked contraction in the volume of extracellular fluid. For every decrease of 1 g per deciliter in the plasma albumin concentration from its normal value of 4 g per deciliter, one should add 2.5 mmol per liter to the calculated value of the plasma anion gap. For every increase of 1 g per deciliter in the plasma albumin level, one should subtract 2.5 mmol per liter from the calculated value of the plasma anion gap.[4,5] Even with this adjustment, it appears that the net negative valence on albumin is increased when there is an ap-

preciable decrease in the effective arterial blood volume, and hence there is a higher value for the plasma anion gap.[6]

The relation between the increase (Δ) in the plasma anion gap and the decrease (Δ) in the plasma bicarbonate concentration — which is commonly referred to as delta-delta (Δ-Δ) — is used to provide an estimate of the magnitude of the acid load and to detect the presence of coexisting metabolic acid–base disorders.[7,8] Some studies[9] indicate that in diabetic ketoacidosis, the ratio of the increase in the plasma anion gap to the decrease in the plasma bicarbonate concentration approximates 1. It is important to recognize that this ratio is based on "concentrations" and not "contents" and to take into account changes in the volume of extracellular fluid when using this ratio to gauge the magnitude of the acid load.[10] For example, consider a woman with type 1 diabetes whose weight is 50 kg and whose steady-state volume of extracellular fluid is 10 liters. She has a plasma bicarbonate concentration of 25 mmol per liter and a plasma anion gap of 12 mmol per liter. After the development of diabetic ketoacidosis, the plasma bicarbonate concentration decreases to 10 mmol per liter, and the plasma anion gap increases to 27 mmol per liter in this patient. Because of the hyperglycemia-induced osmotic diuresis and natriuresis associated with diabetic ketoacidosis, the current volume of extracellular fluid is only 7 liters. Although the ratio between the change in the plasma anion gap and the change in the plasma bicarbonate concentration is 1:1, the bicarbonate deficit and the amount of ketoacids retained in the extracellular fluid are not equal. The decrease in the content of bicarbonate ions is 180 mmol ([25 mmol per liter × 10 liters] − [10 mmol per liter × 7 liters]), whereas the gain of ketoacid anions is only 105 mmol ([approximately 0 mmol per liter × 10 liters] + [15 mmol per liter × 7 liters]).

These calculations suggest that another component of bicarbonate loss occurred when ketoacids were added (i.e., some ketoacid anions were excreted in the urine along with sodium ions or potassium ions); this created an indirect form of loss of sodium bicarbonate (Fig. 1) that is not revealed by the increase in the plasma anion gap.[11] Once the volume of the extracellular fluid has been expanded with the administration of saline, the deficit in bicarbonate ions becomes evident to the clinician, since the decrease in the plasma anion gap will not be matched by a similar increase in the concentration of bicarbonate ions. This indirect loss of sodium bicarbonate may be the dominant (and occasionally the only) component of metabolic acidosis in some patients with diabetic ketoacidosis.[12,13]

TREATMENT WITH SODIUM BICARBONATE

The use of sodium bicarbonate to treat acute metabolic acidosis that is caused by the production of organic acids is controversial.[14-18] Severe acidemia may be associated with decreased cardiac contractility,[19,20] diminished responses to endogenous and administered catecholamines, and a predisposition to cardiac arrhythmias,[21,22] all of which may contribute to hemodynamic instability. In addition, severe acidemia may interfere with the binding of insulin to its receptor,[23] which may impair the capacity of insulin to slow the rate of ketoacid production.

In three randomized, controlled trials involving a combined total of 73 patients,[24-26] investigators examined the effect of the administration of sodium bicarbonate in adult patients with diabetic ketoacidosis.[27] Patients with serious concomitant illnesses (e.g., acute myocardial infarction, gastro-

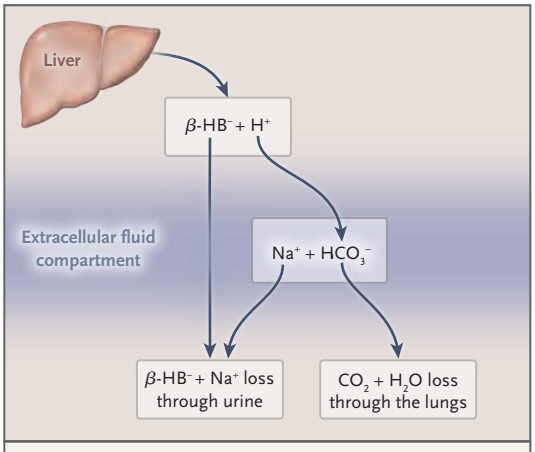

Figure 1. Indirect Loss of Sodium Bicarbonate Early in the Course of Diabetic Ketoacidosis.

β-hydroxybutyric acid is produced in the liver. It dissociates in the extracellular fluid into the β-hydroxybutyrate anion (β-HB⁻) and hydrogen ion (H^+). The loss of bicarbonate (HCO_3^-) and sodium ions (Na^+) occurs indirectly through two different routes. The loss of bicarbonate occurs after it reacts with H^+ producing carbon dioxide (CO_2) and water (H_2O); the CO_2 is lost through the lungs. The loss of sodium occurs during its excretion in the urine with β-hydroxybutyrate.

intestinal hemorrhage, chronic renal failure, or intraabdominal sepsis) were excluded from all three trials. On the basis of outcome measures such as the change in arterial pH, plasma bicarbonate concentration, and levels of metabolites measured, the administration of sodium bicarbonate was not beneficial. Mean arterial blood pressure was reported in only one study.[24] We have been unable to find published results from controlled trials that examined the effect of the administration of sodium bicarbonate on mortality, hemodynamic stability, or the incidence of complications such as acute myocardial infarction, acute kidney injury, or stroke in patients with severe acidemia.

In patients with a very low plasma bicarbonate concentration, a quantitatively small additional load of hydrogen ions will produce a proportionately larger decrease in both the plasma bicarbonate concentration and plasma pH. For instance, halving the plasma bicarbonate concentration will cause the arterial pH to decrease by 0.30 units if the arterial partial pressure of carbon dioxide ($Paco_2$) does not decrease (and in most cases, the $Paco_2$ will not decrease because the patient is in a state of maximum hyperventilation).

To anticipate which patients with diabetic ketoacidosis may have a more severe degree of acidemia, one must understand the factors that influence the rates of production and removal of ketoacids. The oxidation of long-chain fatty acids (e.g., palmitic acid) in hepatic mitochondria yields acetyl coenzyme A (the precursor of ketoacid formation); meanwhile, nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH and flavin adenine dinucleotide (FAD) is reduced to its hydroquinone form, $FADH_2$.[28] Since these critical cofactors are present in only tiny concentrations in mitochondria, NADH must be converted to NAD^+ and $FADH_2$ must be converted to FAD if ketoacid production is to continue. This conversion occurs during coupled oxidative phosphorylation (Fig. 2), in which adenosine triphosphate (ATP) is regenerated from adenosine diphosphate (ADP). In turn, the hydrolysis of ATP (to perform biologic work) results in the formation of ADP. Therefore, the rate of performance of biologic work and hence the availability of ADP set a limit on the rate of oxidative phosphorylation.[30-32] In patients with diabetic ketoacidosis who are ingesting little protein, the supply of amino acids that is available is insufficient to permit high rates of hepatic protein synthesis, a process that utilizes ATP.[33] Accordingly, the liver cannot work hard enough to produce an adequate amount of ADP or, consequently, to convert enough NADH to NAD^+ (and $FADH_2$ to FAD), thereby setting a limit on the rate of ketoacid production.[32]

The observed rate of production of ketoacids during prolonged starvation (approximately 1500 mmol per day)[34,35] suggests that there are ways in which the liver can bypass the limit on ketoacid production created by an insufficient supply of ADP. One possibility is uncoupled oxidative phosphorylation, in which hydrogen ions reenter mitochondria by means of hydrogen ion channels that are not linked to the conversion of ADP to ATP (Fig. 2).[29,36,37]

Unless oxidative phosphorylation is markedly uncoupled during diabetic ketoacidosis, it is likely that the rate of ketoacid production will not be substantially higher than it is in people with ketosis caused by prolonged starvation. Thus, a severe degree of acidemia may develop in patients with diabetic ketoacidosis because of the diminished metabolic removal of ketoacids.

Ketoacids are oxidized primarily in the brain and kidneys.[34] The same principles of metabolic regulation apply to their removal (i.e., the rate of ATP utilization sets an upper limit on the rate of fuel oxidation, in the absence of an appreciable rate of uncoupled oxidative phosphorylation). Patients with ketosis resulting from prolonged starvation have only a mild degree of acidemia, since the rate of ketoacid removal by the brain and kidney matches the rate of hepatic ketoacid production.[34,35,38] During the ketosis of prolonged starvation, the brain can oxidize approximately 800 mmol of ketoacids daily.[38] If reabsorption of sodium by the kidneys occurs at its usual rate, the kidneys will oxidize approximately 250 mmol of ketoacids and excrete approximately 150 mmol of ketoacid anions (largely with ammonium) daily.[35] In such cases, the acid–base balance is preserved; the metabolism of ketoacid anions or their excretion in the urine with ammonium is equal, since new bicarbonate ions are generated when ammonium ions are excreted.[39]

Most patients with diabetic ketoacidosis do not require the administration of sodium bicarbonate, since infused insulin will slow the rate of ketoacid production, and bicarbonate ions will be produced when ketoacid anions are oxidized. However, after insulin is administered, the rate of ketoacid production may not decrease for several hours. In addition, the production of bicarbonate ions will

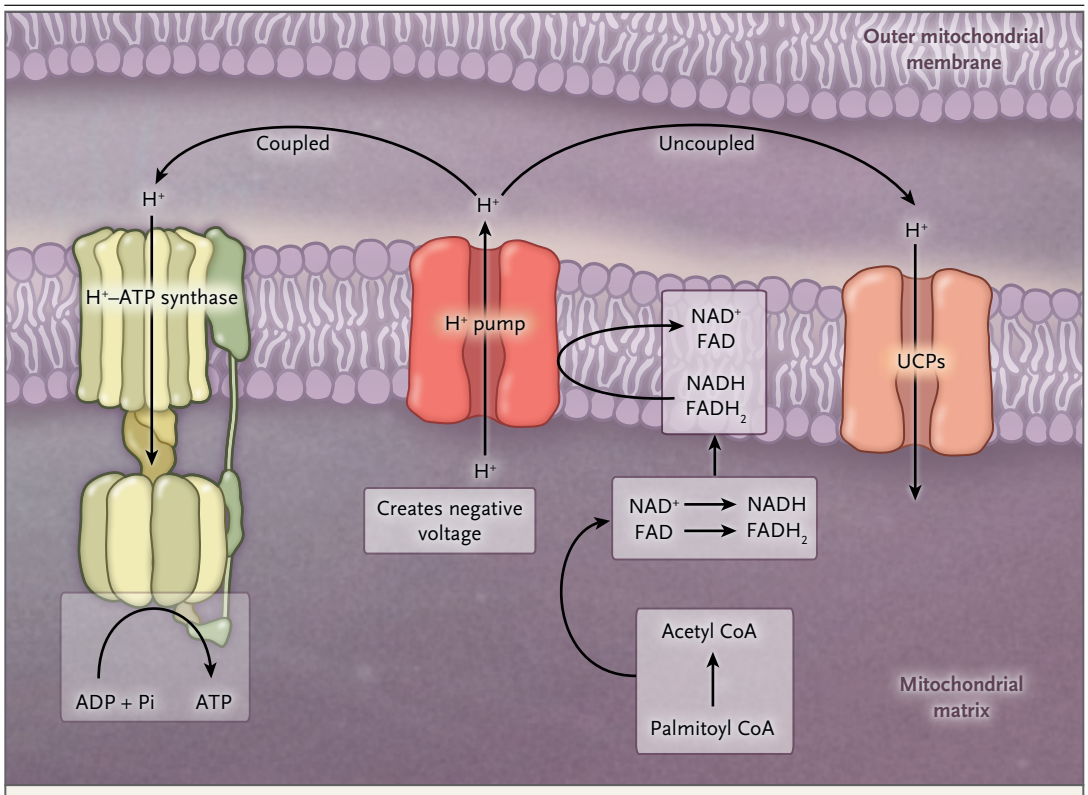

Figure 2. Coupled and Uncoupled Oxidation of Fatty Acids in Mitochondria.

The inner mitochondrial membrane with its outer layer and inner layer is shown. Oxidation of palmitoyl coenzyme A (CoA) in hepatic mitochondria produces acetyl CoA and converts mitochondrial nicotinamide adenine dinucleotide (NAD^+) to its reduced form, NADH, and flavin adenine dinucleotide (FAD) to its hydroquinone form, $FADH_2$. Oxidation of NADH and $FADH_2$ produces electrons. Flow of these electrons through the electron transport chain releases energy that is used to pump hydrogen ions (H^+) from the mitochondrial matrix through the inner mitochondrial membrane. This creates a huge electrochemical driving force for the reentry of H^+. The energy is recaptured as H^+ ions flow through the H^+ channel portion of the H^+–ATP synthase in the inner mitochondrial membrane, which is coupled to the conversion of adenosine diphosphate (ADP) plus inorganic phosphate (Pi) to adenosine triphosphate (ATP). In uncoupled oxidative phosphorylation, H^+ ions reenter mitochondria through uncoupling protein channels (UCPs); these H^+ channels are not linked to the regeneration of ATP,[29] which permits a higher rate of conversion of NADH to NAD^+ and $FADH_2$ to FAD when little ADP is present.

be diminished if the brain and kidneys oxidize fewer ketoacids. The rate of utilization of ATP decreases in the brain during coma[40] and during sedation with drugs or ethanol, since both of these conditions may cause decreases in the rate of cerebral metabolism. In patients who have a very low glomerular filtration rate (GFR) that is caused by the marked decrease in effective arterial blood volume, the removal of ketoacids by the kidneys decreases because the rates of both β-hydroxybutyrate oxidation and ammonium excretion decrease.[41] Furthermore, the expansion of the effective arterial blood volume that occurs with rapid administration of saline may lead to a further decrease in the plasma bicarbonate concentration, first because of dilution and second because bicarbonate ions are removed by hydrogen ions that were bound to intracellular proteins in muscles. These hydrogen ions are released as the level of $Paco_2$ in blood in muscle capillaries decreases when the blood flow to muscles is improved, and hence their bicarbonate buffer system works more effectively to remove the hydrogen load.[42] In addition, as the GFR increases, the urinary excretion of ketoacid anions results in a loss of anions that could have been metabolized to produce bicarbonate ions.[10]

Although the current consensus opinion[43,44] is that sodium bicarbonate should not be administered in patients with diabetic ketoacidosis unless the arterial plasma pH falls below 6.90, we suggest that this decision in adult patients with dia-

betic ketoacidosis should be individualized and not based solely on an arbitrary blood pH value. Therapy with sodium bicarbonate may be required in patients in whom a large component of the acidemia is due to hyperchloremic metabolic acidosis, since they may have insufficient circulating anions to metabolize and produce bicarbonate ions, and acidemia may worsen quickly with a rapid infusion of saline, as detailed above.

Therapy with sodium bicarbonate may also be considered in the initial treatment of a subgroup of patients who are expected to have a low rate of ketoacid removal (i.e., patients who have a marked decrease in their level of consciousness or those with preexisting advanced renal dysfunction [estimated GFR, <30 ml per minute]), to avoid a dangerous decrease in plasma pH and possible deterioration of hemodynamic status. For these patients, sodium bicarbonate should be infused at a rate that matches the rate of hepatic ketoacid production, which is approximately 60 mmol per hour, on the basis of data from a study involving adult patients with starvation ketosis.[35] Data on the benefit of this approach are lacking from a clinical trial in which outcome measures that include the restoration of hemodynamic stability and the incidence of complications such as acute kidney injury, myocardial infarction, and stroke are evaluated in this subgroup of adult patients who have moderately severe acidemia (pH, <7.20; and plasma bicarbonate level, <12 mmol per liter) and who are in a hemodynamically unstable condition.

In a multicenter, case-controlled, retrospective study involving pediatric patients with diabetic ketoacidosis, Glaser et al.[45] observed that the risk of cerebral edema was significantly increased among patients who had a low $Paco_2$ or a high level of blood urea nitrogen at presentation or who received sodium bicarbonate. These associations neither prove causation nor rule out other confounding factors that were not analyzed and that may have influenced the associations, particularly with regard to the administration of sodium bicarbonate.[45] Furthermore, the risk of cerebral edema with the administration of sodium bicarbonate may have been increased if the patients also received a bolus of insulin (Fig. 3). Nevertheless, in view of the possible harm, we concur that sodium bicarbonate should not be administered in children with diabetic ketoacidosis unless acidemia is marked (pH, <6.90; and plasma bicarbonate concentration, <5 mmol per liter)[46] and they have not had a response to standard maneuvers to restore hemodynamic stability.

CEREBRAL EDEMA DURING TREATMENT

The incidence of cerebral edema during therapy for diabetic ketoacidosis in children remains unacceptably high.[47] Brown[48] emphasized that this dreaded complication occurred most often after therapy began. Why does cerebral edema occur after the initiation of treatment? It has been suggested that cerebral hypoperfusion that is already present before treatment of diabetic ketoacidosis may confer a predisposition to cerebral edema when reperfusion occurs.[49] A case–control study of cerebral edema complicating diabetic ketoacidosis in children in the United Kingdom showed that children in whom cerebral edema developed had a more severe degree of acidemia than those in whom cerebral edema did not develop.[50] In that study, both the administration of insulin in the first hour after the initiation of therapy and the administration of a large volume of fluid over the first 4 hours (adjusted for the severity of acidemia) were associated with an increased risk of cerebral edema.

Cerebral edema occurs when cells within the brain swell, when there is an increase in extracellular fluid volume in the brain, or both. Brain cells swell when there is a large osmotic force favoring an intracellular shift of water, owing to a higher effective osmolality in brain cells than the effective osmolality in plasma in capillaries near the blood–brain barrier. The equations below show the difference between the calculation of the total plasma osmolality and the calculation of the effective plasma osmolality. Both calculations are expressed in milliosmoles per liter. To convert from milligrams per deciliter to millimoles per liter, the concentration of glucose in plasma in milligrams per deciliter should be divided by 18 and the concentration of the blood urea nitrogen in milligrams per deciliter should be divided by 2.8.

In calculating total plasma osmolality, one includes the contributions of the major osmoles — sodium and its accompanying anions as well as glucose and urea. Since urea is transported across most cell membranes and achieves equal concentrations in the extracellular fluid and the intracellular fluid, urea is not an effective osmole. This

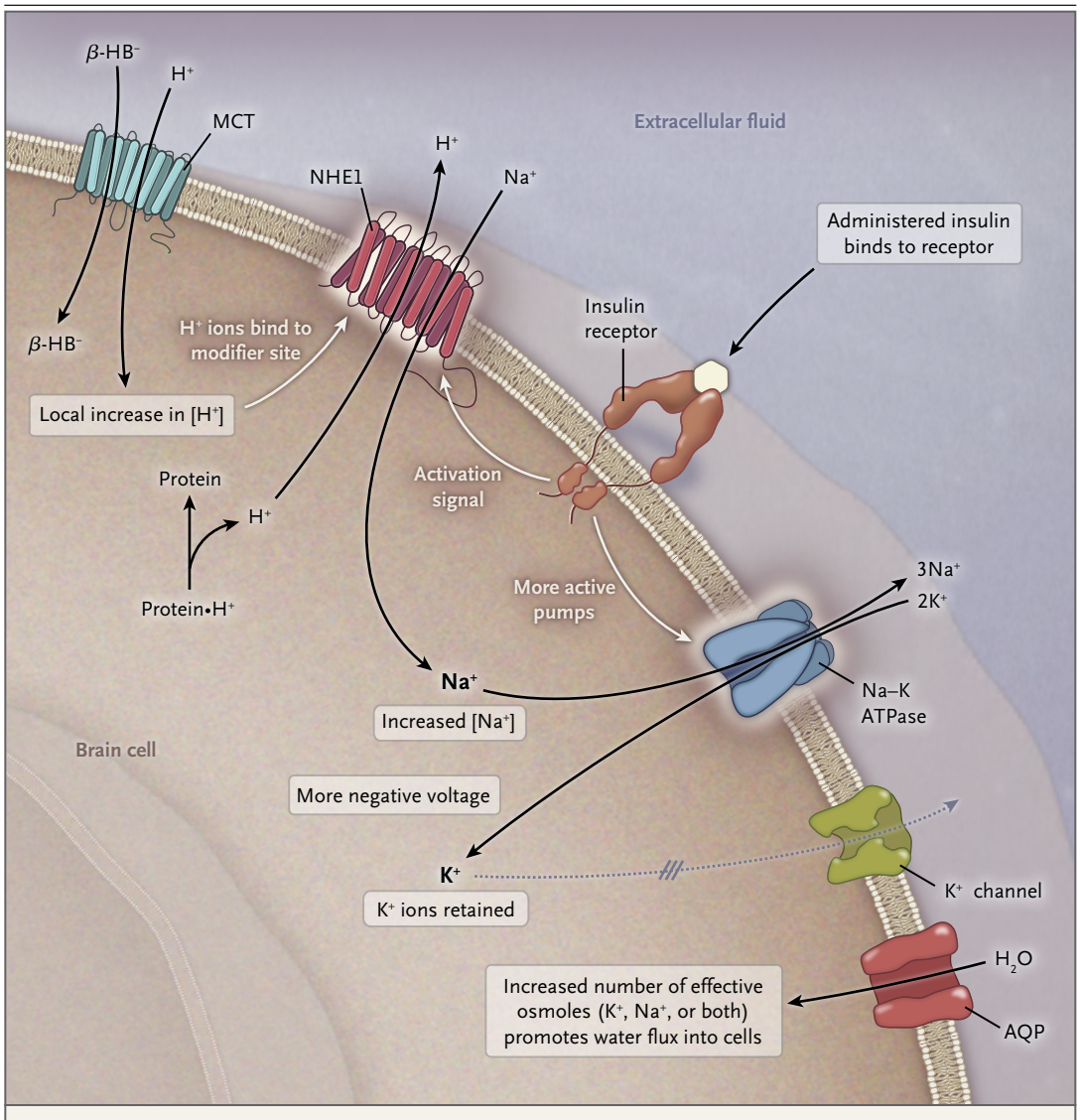

Figure 3. Increased Flux through the Sodium–Hydrogen Exchanger 1 Leading to an Increase in the Number of Effective Osmoles in Brain Cells.

Entry of β-hydroxybutyric acid into cells through the monocarboxylic acid cotransporter (MCT), and its subsequent dissociation into β-HB^- anions and + H^+ ions may lead to a large increase in the concentration of H^+ ions in the local submembrane area where the sodium–hydrogen exchanger 1 (NHE-1) is located. NHE-1 is activated by a high concentration of H^+ ions in the cell interior as H^+ ions bind to a modifier site of NHE-1. NHE-1 is also activated by a high insulin concentration in interstitial fluid. Flux through NHE-1 will lead to a gain of effective osmoles because sodium ions (Na^+) enter, whereas the bulk of H^+ ions exported from these cells are not effective osmoles; most of these H^+ ions are bound to intracellular proteins (shown as protein•H^+). If a bolus of insulin was administered during therapy, Na^+ that entered these cells through NHE-1 may be exported by the electrogenic Na-K–ATPase, which is activated by insulin. The increased intracellular negative voltage can cause retention of potassium ions (K^+) in these cells, which promotes water flux through aquaporin water channels (AQP) in these cells. Whether this process leads to a gain of K^+, Na^+, or both, the net effect is an increase in the number of effective osmoles in brain cells.

means that urea is incapable of creating an osmotic gradient across cell membranes to affect the distribution of water between the extracellular fluid volume and the intracellular fluid volume, which includes brain cells. Thus, blood urea nitrogen is not included in the calculation of effective plasma osmolality in patients with diabetic ketoacidosis.

$$\text{Total osmolality in plasma} = 2 \times [\text{plasma sodium}] + [\text{plasma glucose}]/18 + [\text{blood urea nitrogen}]/2.8$$

and

$$\text{Effective osmolality in plasma} = 2 \times [\text{plasma sodium}] + [\text{plasma glucose}]/18$$

An increased number of intracellular brain osmoles may occur with an increased influx of sodium ion into brain cells (Fig. 3). A high concentration of hydrogen ions in brain cells may activate mechanisms of sodium ion transport in cell membranes, primarily the sodium–hydrogen exchanger 1. The concentration of hydrogen ions in brain cells could increase when β-hydroxybutyric acid enters cells on the monocarboxylic acid cotransporter. This cation exchanger is also activated by a high insulin concentration in interstitial fluid. We speculate that after a patient with severe acidemia receives an intravenous bolus of insulin, the sodium–hydrogen exchanger 1 in brain-cell membranes may be activated. This would increase the number of effective osmoles in cells, since sodium ions enter them, whereas the bulk of hydrogen ions exported are osmotically inactive, because they are bound to intracellular proteins. An insulin bolus administered as part of early therapy could have a more dramatic effect on activation of this cation exchanger 1, when the blood–brain barrier may be more permeable to insulin. Current guidelines for the treatment of diabetic ketoacidosis recommend against the administration of an intravenous insulin bolus.[46,51] If cation exchange through this sodium–hydrogen ion exchanger 1 increases further when the pH in the extracellular fluid increases, that could explain, at least in part, the increased risk of cerebral edema among children with diabetic ketoacidosis when sodium bicarbonate is administered.

A decrease in the effective osmolality in plasma could be due to a rapid decrease in the plasma glucose concentration, a gain of electrolyte-free water, or both.[52] A rapid decrease in the plasma glucose concentration occurs when a large amount of glucose is metabolized, excreted in the urine (owing to an increase in the GFR after reexpansion of the effective arterial blood volume), or both.

A gain of electrolyte-free water could be attributable to several possible sources, including the administration of hypotonic saline or of 5% dextrose in water to prevent neuroglycopenia when the plasma glucose concentration decreases. After the glucose is metabolized, a large volume of electrolyte-free water may be retained in the body. Other sources of electrolyte-free water are less obvious. Patients with diabetic ketoacidosis often consume large volumes of fluids containing glucose (or sucrose) or water to quench thirst. This ingested fluid may be retained in the stomach because hyperglycemia slows gastric emptying.[53] If gastric emptying occurs during the course of treatment, this fluid will be absorbed in the small intestine and lead to a gain of a potentially large quantity of electrolyte-free water.[54] The usual clinical practice is to administer large volumes of saline in patients with diabetic ketoacidosis; electrolyte-free water may be generated in the body through desalination.[55] If vasopressin is released (owing to nonosmotic stimuli that may be present), water reabsorption will increase in the distal portions of the nephron. As the concentration of glucose in the urine decreases, the concentration of sodium will increase, and the excess saline that was administered may be excreted in the urine as a hypertonic (to the patient) solution.

The interstitial compartment of the extracellular fluid volume in the brain will expand if there is an increase in capillary hydrostatic pressure, a decrease in plasma colloid osmotic pressure, an increase in capillary permeability, or all these factors. Since administered saline is distributed initially in plasma and reaches the blood–brain barrier before equilibrating with the entire extracellular fluid volume, a large bolus of saline may increase capillary hydrostatic pressure, lower the plasma albumin concentration, and hence decrease the capillary colloid osmotic pressure. Moreover, there is evidence to suggest that the blood–brain barrier may already be leaky at the time patients with diabetic ketoacidosis are admitted to the hospital.[56,57]

Given the above analysis, a number of focused measures might be considered in the treatment of patients with diabetic ketoacidosis.[58] To reduce the risk of cerebral edema, we suggest that the effective osmolality in plasma must not be permitted to decrease during the first 15 hours of treatment, the time period in which most cases of cerebral edema occur.[45] Of note, in the study by Glaser et al.,[45] a lack of increase in the plasma sodium concentration during therapy was associated with an

increased probability of cerebral edema. When potassium ions are needed, this goal can be achieved if potassium chloride is added to 0.9% saline, at a concentration of 30 to 40 mmol per liter. This solution has an effective osmolality that is reasonably close to that of the urine in these patients at that time.[52] Since children with diabetic ketoacidosis often have near-normal plasma sodium concentrations, a degree of hypernatremia would develop with this infusion, but that would be an important trade-off to prevent a decrease in the effective osmolality in plasma. If glucose is to be administered to prevent neuroglycopenia when the plasma glucose concentration decreases, it seems prudent to administer it in a solution that has the smallest possible volume of electrolyte-free water.

The clinician should take a detailed history of fluid ingestion and look for signs that indicate recent gastric emptying,[54] with its attendant risk of intestinal absorption of electrolyte-free water. Such signs include the absence of a large decrease in the plasma glucose concentration when there is a high rate of excretion of glucose in the urine or a sudden decrease in the effective osmolality in plasma, which will happen if water was ingested without sugar. Rapid absorption of a large volume of ingested water may result in an appreciable decrease in effective osmolality in arterial blood, which may not be detected by measurements in venous blood.[59]

A large bolus of saline should be administered only if there is a hemodynamic emergency. The goal of saline therapy should be to maintain hemodynamic stability. The use of hematocrit and the plasma sodium concentration may provide a means for a quantitative estimate of the extracellular fluid volume and the magnitude of the deficit of sodium ions in the individual patient with diabetic ketoacidosis.[60]

SUMMARY

We reviewed three issues related to the acid–base disturbance and the clinical implications of these issues in patients with diabetic ketoacidosis. Acidemia in most patients with this condition is due in part to an indirect loss of sodium bicarbonate. This process is not revealed from the 1:1 ratio of the increase in the plasma anion gap to the decrease in the plasma bicarbonate concentration because this calculation is based on "concentrations" and not "contents." Severe acidemia in a patient with diabetic ketoacidosis is probably due to a decreased rate of removal of ketoacids by the brain and kidneys rather than solely an increased rate of production of ketoacids by the liver. Activation of the sodium–hydrogen exchanger 1 in brain cells as a result of intracellular acidosis may lead to a net gain of effective osmoles and thereby contribute to the development of cerebral edema in children with diabetic ketoacidosis.

Dr. Halperin reports holding a patent on the use of sodium-linked glucose transporter 2 inhibitors to increase the excretion of water in patients with hyponatremia (US 8,518,895,B2) and a pending patent application on the use of sodium-linked glucose transporter 2 inhibitors to increase urine volume and lower solute concentration in the urine (08578 11286 PSP). No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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