Review

Selected Aspects of the Pathophysiology of Metabolic Acidosis in Diabetes Mellitus

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Metabolic acidosis is the most common serious acid-base disorder complicating diabetes mellitus; typical values are shown in Table 1. In this review, we shall discuss the pathogenesis of certain types of metabolic acidosis that may develop in diabetic patients, emphasizing those areas in which new insights have been gained. A more complete classification of metabolic acidosis is shown in Table 2. Basic clinical concepts of acid-base physiology are not included; for these, readers are referred to recent reviews.[1,2]

INCREASED UNMEASURED ANION GAP METABOLIC ACIDOSIS

INTRODUCTION

Determination of the serum unmeasured anions, or anion gap, is an important step in the assessment of acid-base disorders. The anion gap is calculated by subtracting the sum of the serum concentrations of the major anions (chloride and bicarbonate) from the major cation (sodium); in the normal person, the value is 12 ± 2 meq/L. In certain forms of metabolic acidosis, including several associated with diabetes mellitus, the unmeasured anion fraction is found to be elevated. The degree of elevation in the anion gap in these situations is a reflection of the magnitude of the acid load and has been noted empirically to be almost quantitatively equal to the decrease in the serum bicarbonate concentration (for review, see refs. 3 and 4). Factors pertaining to this 1:1 relationship in diabetic ketoacidosis (DKA) will be detailed below as we discuss the separate fates of hydrogen ions and ketone body anions.

FACTORS INFLUENCING THE HYDROGEN ION CONCENTRATION OF BLOOD IN DKA

Hydrogen ion production. In DKA, hydrogen ions and ketone body anions are formed in the liver as a result of relative or absolute insulin deficiency and are released into the extracellular fluid (ECF) in equal quantities.

Distribution of hydrogen ions. When hydrochloric acid is administered to a nephrectomized dog, roughly 40% of this hydrogen ion load is buffered in the ECF compartment and 60% in the intracellular fluid (ICF) compartment.[5] In the ECF, the bicarbonate buffer system is by far the most abundant buffer and has a high affinity for hydrogen ions; thus, the decrease in bicarbonate content in the ECF is a quantitative reflection of the number of hydrogen ions buffered in this compartment. In the ICF compartment, the principal buffers appear to be intracellular proteins and the degree of buffering is a function of the quantity of the buffers and the pK of each buffer system; the specific pK values of ICF protein buffers and their quantity probably account for the fact that the number of hydrogen ions buffered in the ICF increases when acidemia is more severe.[6] In addition, hydrogen ions are also buffered by alkaline salts of bone.

On theoretical grounds, the proportion of hydrogen ions buffered in the ICF and ECF might be different in DKA as compared with other types of metabolic acidosis. For example, a loss of intracellular proteins, low insulin levels, or a net outward shift of potassium across the cell membrane could theoretically alter the proportion of hydrogen ions buffered in the ICF. Whether or not any of these potential aberrations are important has not been fully resolved.

Removal of hydrogen ions. Normal individuals remain in acid-base balance because they can excrete the daily acid load in the urine, principally in the form of ammonium (NH_4^+). In DKA, hydrogen ion production exceeds its excretion and metabolic acidosis ensues. There is an elevation in the anion gap because the rate of production of ketone body anions (B-hydroxybutyrate and acetoacetate) also exceeds the rate of disposal by metabolism and excretion. During the course of DKA, hydrogen ions and ketone body anions are produced (as acetoacetic and B-hydroxybutyric acids) and excreted (as ammonium acetoacetate and ammonium B-hydroxybutyrate) in roughly equal proportions. The excretion of ammonium salts of ketone body acids will not produce a net change in the acid balance nor alter the 1:1 relationship

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TABLE 1
Mean blood acid-base values in 83 patients presenting with diabetic ketoacidosis[34,35]

pH	7.10
Δ $[HCO_3^-]$* (meq/L)	15.5
B-Hydroxybutyrate† (meq/L)	10.6
Acetoacetate (meq/L)	3.0
Lactate (meq/L)	4.0
Total organic anions (meq/L)	17.6

* Δ $[HCO_3^-]$ = fall in plasma bicarbonate from the mean normal value of 24 meq/L. Hence, the mean bicarbonate concentration in these patients with DKA was 8.5 meq/L. This form of presentation permits the reader to compare directly the fall in bicarbonate concentration with the rise in organic anion concentration.
† Ketone body anions and lactate, and hence, total organic anions, were determined in 63 patients.

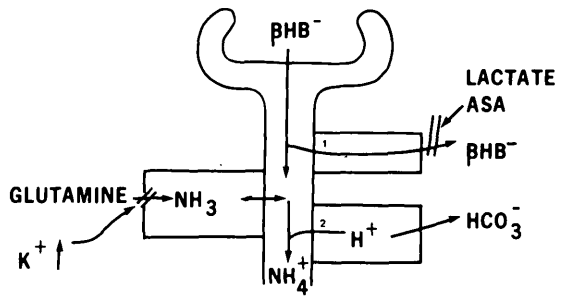


FIGURE 1. Renal excretions influencing ECF bicarbonate and the A/G. For details, see text. Ammonium excretion results in a gain of bicarbonate. This requires NH_3 synthesis plus H^+ secretion. Ketonuria will cause a decrease in the anion gap without a change in bicarbonate. Disease 1 is a proximal tubular defect in ketone body reabsorption and defect 2 is distal renal tubular acidosis, where a favorable pH gradient to trap NH_3 as ammonium cannot be generated. Hyperkalemia may inhibit ammoniagenesis and ASA or lactate may inhibit B-hydroxybutyrate reabsorption.

between the plasma bicarbonate concentration and the anion gap. It should be stressed that there is no mandatory link between the renal excretion of ammonium and ketone body anions, as their excretions are controlled by different factors (Figure 1). As will be detailed in a later section, should a discrepancy in their excretion rates occur, a disproportion between the decrease in the plasma bicarbonate concentration and the elevation in the anion gap will be seen. Although ketone bodies can decrease the rate of ammoniagenesis,[7] this does not seem to be clinically important as the rate of ammonium excretion in DKA is high.

Significant removal of hydrogen ions also occurs as a consequence of the nonenzymatic conversion of acetoacetic acid to acetone and carbon dioxide. This pathway results in almost as much acid loss per day as does maximal renal net acid excretion.[8] Should the NADH/NAD ratio increase, as a result of poor oxygenation, for example, both pyruvic and acetoacetic acids will be converted into their corresponding hydroxy-acids (lactate and B-hydroxybutyrate). The resultant fall in acetoacetic acid concentration will lead to a marked reduction in the rate of hydrogen ion removal via the acetone pathway, since the rate of nonenzymatic conversion of acetoacetic acid to acetone and carbon dioxide is proportional to the acetoacetic acid concentration.

TABLE 2
Classification of metabolic acidosis based on the unmeasured anion gap

1. Metabolic acidosis with increased anion gap
   (i) Ketoacidosis
   (ii) Lactic acidosis
   (iii) Renal failure
   (iv) Ingestion of toxins (salicylate, methanol, paraldehyde, ethylene glycol)
   (v) Combined disorders
2. Metabolic acidosis with a normal unmeasured anion gap
   (i) HCl intake (or NH_4Cl, arginine or lysine HCl, $CaCl_2$)
   (ii) Direct bicarbonate loss
      (a) Gastrointestinal tract (diarrhea, fistula, ileus)
      (b) Renal
         —proximal RTA
         —carbonic anhydrase inhibition
   (iii) Indirect bicarbonate loss
      (a) Reduction in acid excretion
         —distal RTA
         —ammonia excretion defects (including hyperkalemia)
      (b) Acid gain with loss of the anion* but not the accompanying hydrogen ions in
         —urine—profound ketonuria
         —gastrointestinal tract
   (iv) Rare problems
      (a) dilutional acidosis
      (b) H^+ shifts from ICF
      (c) loss of bicarbonate in the GI tract due to carbonate precipitation (e.g., $CaCl_2$ intake)

* See text for a more detailed discussion.

FACTORS INFLUENCING THE KETONE BODY ANION CONCENTRATION IN DKA

Production of ketone body anions. Ketone body anions and hydrogen ions are produced by the same biochemical process.

Distribution of ketone body anions. It is generally accepted that undissociated B-hydroxybutyric acid, but not the B-hydroxybutyrate anion, crosses the cell membrane with ease and achieves an equal concentration in the ECF and the ICF. However, in animals with moderately severe DKA, the concentration of B-hydroxybutyrate in the ICF is about one-half that in the ECF.[9] Since the pK of this acid is less than 5, it will be almost completely dissociated in body fluids. By the law of mass action:

$$[H^+]_{ICF}\ [\beta HB^-]_{ICF} = K[H\beta HB]_{ICF}$$

and

$$[H^+]_{ECF}\ [\beta HB^-]_{ECF} = K[H\beta HB]_{ECF}$$

Therefore if $[H\beta HB]_{ICF} = [H\beta HB]_{ECF}$, it follows that

$$[H^+]_{ICF}/[H^+]_{ECF} = [\beta HB^-]_{ECF}/[\beta HB^-]_{ICF}$$

Thus, the observed lower concentration of B-hydroxybutyrate in the ICF[9] requires a higher hydrogen ion concentration (lower pH) in the ICF. This is consistent with published data using weak acid indicators to reflect a mean pH of the ICF.[10]

In summary, although ketoacids enter the ICF in the undissociated form, the eventual distribution of the B-hydroxybutyrate anion and the hydrogen ion will depend on separate factors. For the ketone body anion, its concentration in the ICF will depend on the concentration of free acid and the pH of the ICF. In contrast, the quantity of hydrogen ions distributed in the ICF is a function of the quantity of ICF buffers, their pKs, and the ICF pH.

Removal of ketone body anions. The renal handling of ketone body anions occurs by mechanisms independent of those for hydrogen ions (Figure 1). During the ketosis of fast-

ing, ketone bodies are freely filtered at the glomerulus and the vast majority of the anions are reabsorbed during transit through the nephron regardless of their concentrations.[11] The renal handling of ketone bodies has not been extensively studied in DKA but, in theory, may be influenced by the degree of osmotic diuresis, ECF volume contraction, potassium deficiency, and metabolic acidosis, which are also present. For example, since the glomerular filtration rate is markedly reduced in DKA, the filtered load and hence the urinary excretion of ketone bodies should be much lower in DKA than in the ketosis of fasting for any given plasma ketone body concentration.

On the other hand, excessive ketonuria has been reported to occur under several circumstances, such as when the filtered load of lactate or acetosalicylate is elevated[12] or if there is a primary defect in proximal tubular function.[13] As will be discussed, excessive ketonuria may result in diagnostic confusion by markedly altering the 1:1 proportion between the fall in the plasma bicarbonate concentration and the rise in the anion gap.

When the metabolic defect of DKA is corrected, ketone body anions are metabolized to neutral end products. This results in the production of an amount of bicarbonate that is identical to the quantity of ketone body anions consumed.

Bicarbonate can be generated by the nonenzymatic, spontaneous decarboxylation of acetoacetic acid to acetone and CO_2.

SUMMARY

In DKA, ketone body anions and hydrogen ions are produced in the liver and removed by metabolism in a 1:1 ratio. Hydrogen ions are either buffered in bone and the ICF, excreted as ammonium or titratable acid in the urine, or eliminated indirectly via the lungs. It is conceivable that in DKA, the proportion of ICF versus ECF hydrogen ion buffering may be different from that in the experimental model, in which metabolic acidosis was produced by hydrochloric acid administration.

In severe DKA, it appears that more hydrogen ions than ketone body anions enter the ICF. Three implications may be drawn from these observations: first, the rise in the anion gap should be greater than the fall in the plasma bicarbonate concentration when patients with DKA are admitted. The failure to observe this change (Table 1) is probably the result of the renal excretion of ketone body anions that exceeds that of ammonium. Second, on reversal of the DKA, more hydrogen ions than ketone body anions (or bicarbonate) would return to the ECF and lead to a lesser rise in the plasma bicarbonate concentration than the fall in the anion gap. Oh et al.[14] have recently described such a fall in the ECF bicarbonate plus ketone body anion contents following recovery from DKA. Third, for electroneutrality, some hydrogen ions must exchange across the cell membrane with cations such as potassium or sodium.

From the foregoing, it should be appreciated that multiple factors influence the fate of hydrogen ions and ketone body anions independently. Therefore, the 1:1 relationship between reduced serum bicarbonate and increased ketone body anions (anion-gap) is either fortuitous or based on mechanisms that are incompletely understood.

METABOLIC ACIDOSIS WITH A NORMAL UNMEASURED ANION GAP IN DIABETICS

This topic will be discussed under two major headings, hyperchloremic metabolic acidosis in patients with DKA and hyperchloremic metabolic acidosis in the diabetic but independent of DKA. In the first group, this type of metabolic acidosis is present in virtually every case of DKA on admission and is due to an "indirect" loss of sodium bicarbonate (Tables 3 and 4). In addition, on recovery from DKA, hydrogen ions reenter the ECF from the ICF and thereby result in a further loss of ECF bicarbonate. For the above two reasons, a hyperchloremic metabolic acidosis should be expected with the usual successful initial therapy for DKA. In the second major group, patients with diabetes mellitus may develop RTA independent of DKA. The pathogenesis of these disorders is discussed and emphasis is given to the acidification disorder associated with aldosterone deficiency (type IV RTA).

PATIENTS WITH DKA

It is important to recall that the bicarbonate content in the ECF is the product of the bicarbonate concentration (amount/volume) and the total ECF volume. Therefore, 360 meq of bicarbonate is present in the ECF in a typical patient (24 meq/L + 15 L, see Table 3). For every meq of ketoacid added to the ECF, 1 meq of bicarbonate is lost, 1 meq of ketone body anion is gained, and the sum of bicarbonate

TABLE 3
Relationship of bicarbonate and organic anion concentrations and content in the ECF during the course of DKA

	ECF				
	Bicarbonate		Organic anion		Bicarbonate + organic acid
	meq/L	Total meq	meq/L	Total meq	(Total meq)
1. Normal	24	360*	1	15	375
2. Admission*	8.5	102	17.5	210	312†
3. Therapy					
12–24 h	18	270	1	15	285‡
>48 h	24	360	1	15	375

* We assumed the ECF volume has fallen from 15 L to 12 L; the ECF has been returned to 15 L by 12–24 h.
† Despite the fact that the fall in bicarbonate concentration was equal to the rise in the organic anion concentration (data from Table 1), their contents are very different because of the change in the ECF volume.
‡ The further reduction in bicarbonate plus organic anion content probably reflects ICF hydrogen ion buffering in excess of ICF ketone body anion content.

TABLE 4
Indirect loss of sodium bicarbonate* in the diabetic

Process	Result	
	Gain to ECF	Loss from ECF
1. Gain of acid	$H^+ + KB^-$	
2. Buffering (loss of HCO_3^-) in ECF		$H^+ + HCO_3^- \rightarrow CO_2 \uparrow$
3. Anion excretion (loss of Na^+)†		$KB^- + Na^+ \rightarrow$ urine
Sum of 1 + 2 + 3		$Na^+ + HCO_3^-$ loss

* DKA involves the addition of organic acids to the ECF. The hydrogen ion is buffered and the ketone body anion may be retained, metabolized, or excreted. In the cycle described in this table, hydrogen ions and ketone body anions are produced and lost in equal quantities. Indirect loss of sodium bicarbonate occurs when there is a net loss of bicarbonate via the lungs and sodium in the urine to balance the electrical charge of the ketone body anions. Sodium loss in the urine is normally minimized because of ammonium excretion. The excretion of ammonium may be reduced in the diabetic because of either a primary renal disease, hyperkalemia, insufficient time for the adaptive changes in ammoniagenesis, or by defects in hydrogen ion secretion.
† Should process (3) not happen, then an indirect loss of sodium bicarbonate would not occur. Two major alternatives can replace process (3): first, the ketone body anions may be completely reabsorbed by the kidney resulting in a simple anion gap type of metabolic acidosis; second, the excretion of the ammonium salt of B-hydroxybutyrate would cause the blood bicarbonate concentration to rise because the excretion of ammonium results in bicarbonate generation.

plus ketone body anions remains constant. If we assume for the moment that the quantity of hydrogen ions and ketone body anions added to the ECF is equal at steady state, then the number of meq of bicarbonate that are lost must be equal to the number of meq of ketone body anions gained. It then follows that 360 meq of bicarbonate plus ketone body anions should be contained in the ECF at steady state during DKA. However, due principally to an osmotic diuresis, patients with DKA lose between 5 and 10 meq of sodium per kg body weight.[15] As a round figure, we shall assume a 20% decline in the ECF volume (or a 3-L deficit). This contraction of ECF volume should lead to an increase in the sum of the bicarbonate plus ketone body anion concentration during DKA (i.e., 360 meq ÷ 12 L, or 30 meq/L). However, as shown in Table 1, the mean sum of the bicarbonate and ketone body anion concentrations in patients with DKA is only 26 meq/L, a value significantly less than would be predicted by the degree of ECF volume depletion. In other words, the fall in bicarbonate is greater than can be explained by the rise in unmeasured anions (i.e., ketone body anions). These observations suggest that a loss of ECF bicarbonate and/or ketone body anions has occurred during the development of DKA. Therefore, at presentation, patients with DKA have two factors contributing to the metabolic acidosis: first, increased production of ketoacids, and second, the loss of bicarbonate or potential bicarbonate* (the latter will become more obvious after insulin therapy).

A number of mechanisms could explain this bicarbonate and/or ketone body anion deficit. Direct bicarbonate loss may occur via the gastrointestinal tract or the urine; the former is usually obvious to the clinician, although bicarbonate sequestration in the small intestine during an ileus may be more difficult to recognize. This complication can occur in diabetics who have marked potassium deficits or abdominal pathology. Direct loss of bicarbonate in the urine occurs when there is a defect in proximal tubular reabsorption of bicarbonate (proximal rTA); when uncompliated, this disorder is characterized by the excretion of large quantities of bicarbonate in the urine (urine pH greater than 6.3). Proximal RTA is rare in diabetic patients, although it may be seen in association with severe hypophosphatemia[16] or the intake of carbonic anhydrase inhibitors.

Ketonuria could lead to a decrease in the bicarbonate plus ketone body anion content provided that the excretion of ketone body anions exceeds that of ammonium plus hydrogen ions. This might occur due to the presence, either singly or in combination, of four different circumstances (because ammonium excretion requires both NH_3 production and hydrogen ion secretion in the distal nephron): (1) reduced ammoniagenesis in the renal cortex due to kidney disease or hyperkalemia (for review, see ref. 17); (2) reduced medullary transfer of NH_3 from the loop of Henle to the collecting duct,[18] for example, due to interstitial nephritis; (3) reduced hydrogen ion secretion in the distal nephron; and (4) presentation of a filtered load of ketones that is so large that even with the normal reabsorptive rate, ketonuria would exceed the augmented renal capacity for ammonium excretion.

When ketone body excretion exceeds that of net acid (NH_4 + titratable acid), the excess ketone body anions are excreted with sodium and potassium ions and the net result is an indirect loss of sodium bicarbonate. To understand the sequence of events resulting in the indirect loss of sodium bicarbonate, consider the following three steps (summarized in Table 4). First, there is the addition of B-hydroxybutyric and acetoacetic acids to the ECF; second, there is buffering of the hydrogen ions by bicarbonate with the resultant removal of carbon dioxide via the lungs; third, there is a loss of the ketone body anion in the urine along with sodium or potassium. Taken together, the above result in a net "indirect" loss of sodium bicarbonate from the ECF.

Following successful therapy for DKA, the plasma bicarbonate concentration is approximately 20 meq/L.[19,20] As discussed previously, the mean bicarbonate plus potential bicarbonate content of the ECF is lower than anticipated in typical patients with DKA before therapy, despite the fact that the sum of their concentrations is 26 meq/L (Table 1). If the ECF volume is then reexpanded to normal with a bicarbonate-free solution (sodium plus potassium chloride), and all the excess ketone body anions oxidized to produce bicarbonate, the plasma bicarbonate concentration will be

* Potential bicarbonate is defined as organic anions such as ketone body anions or lactate that can be metabolized to produce bicarbonate.

20% below normal. In addition, hydrogen ion reentry into the ECF in excess of ketone body anions will lower this value even further (these hydrogen ions probably entered the ECF in exchange for sodium or potassium, Table 3). This bicarbonate deficit will be repaired by the renal excretion of ammonium chloride over the next 24–48 h, provided there is no primary renal defect.

HYPERCHLOREMIC ACIDOSIS IN THE DIABETIC INDEPENDENT OF DKA

Physiology of hydrogen ion secretion in the distal nephron. Metabolic acidosis with a normal anion gap (hyperchloremic acidosis) may occur in diabetic patients as a consequence of various disorders of distal nephron hydrogen ion secretion. Since hydrogen ion secretion in the distal nephron occurs via a hydrogen ion pump, the activity of which is increased by a lumen-negative transepithelial electrical gradient or a low lumenal hydrogen ion concentration (Figure 2), disorders of hydrogen ion secretion will be discussed within this context (for review, see ref. 21).

Clinical assessment of distal nephron hydrogen ion secretion. There are several ways to assess hydrogen ion secretion by the distal nephron. Before the use of the urine minus blood PCO_2 difference in alkaline urine (U-B PCO_2) to reflect this parameter,[22] clinicians evaluated the urine pH when acidemia was present. However, as the pH represents only the free hydrogen ion concentration, a low urine pH may indicate either a high rate of hydrogen ion secretion, a decreased rate of hydrogen ion buffering, or a combination of the two. In fact, a patient with a renal medullary disease might well have a low urine pH despite a reduced rate of distal nephron hydrogen ion secretion because of a relatively greater reduction in the rate of ammonia addition to the urine, ammonia being the major urine buffer. The low urine pH in such a case would not indicate normal urine acidification, but rather, deficiency of buffer.

The U-B PCO_2 reflects the rate of distal nephron hydrogen ion secretion in vivo. The general principle of the test is that when a large load of bicarbonate is given, bicarbonate is virtually the only hydrogen ion acceptor in the urine. Hydrogen ions secreted in the distal nephron combine with lumenal bicarbonate and the end result is an elevation of the bladder urine PCO_2 (see refs. 22 and 23 for details). Thus, the PCO_2 difference between blood and urine is approximately 30 mm Hg due to hydrogen ion secretion into alkaline urine in the distal nephron. If there is impaired distal nephron hydrogen ion secretion, the U-B PCO_2 will be reduced; in 10 patients with distal RTA, the U-B PCO_2 was 2 ± 2 mm Hg.[22] By combining data from the minimum urine pH, ammonium excretion, the U-B PCO_2, and the maximum rate of bicarbonate reabsorption, the clinician can readily separate the various subtypes of disorders of hydrogen ion secretion.[23]

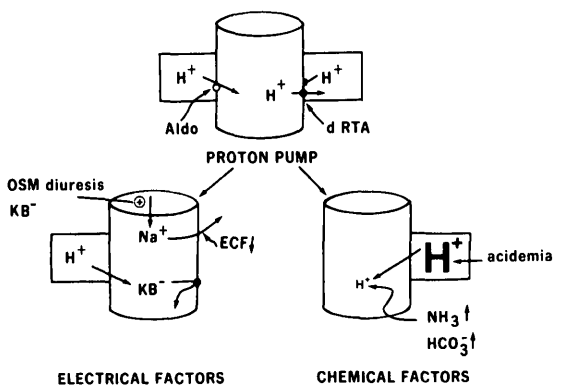
Distal RTA. A defect in the proton pump can occur in patients with diabetes mellitus and chronic interstitial nephritis (e.g., chronic pyelonephritis). This latter defect can destroy the collecting duct cells that contain the hydrogen ion pump. This abnormality can be diagnosed in patients who have a low U-B PCO_2 and a urine pH that is not maximally reduced during acute metabolic acidosis (pH 5.5–6.0).

Electrical augmentation of hydrogen ion secretion is produced when sodium, but not its accompanying anion, is actively reabsorbed in the distal nephron. Both osmotic diuresis and ketonuria in patients with DKA may lead to a large electrical stimulus to hydrogen ion secretion due to increased distal sodium delivery in the presence of ECF volume contraction. A defect in this area may be seen in those patients with a lower aldosterone bioactivity. The diagnostic features of this clinical syndrome are summarized in a later section.

Steinmetz and Lawson[24] have shown that hydrogen ion secretion in in vitro models of the collecting duct is inhibited when the transepithelial hydrogen ion concentration gradient opposing hydrogen ion secretion rises. Such a rise will occur in the collecting duct if there is a decreased quantity of the principal urine hydrogen ion buffer (or trap), NH_3. Therefore, a fall in NH_3 will result in a high free lumenal hydrogen ion concentration (low urine pH) and a decreased rate of hydrogen ion secretion. In the diabetic, two factors can theoretically produce this syndrome: first, a low rate of ammonia synthesis due to the hyperkalemia of hypoaldosteronism and second, the presence of interstitial nephritis (it has recently been shown that medullary structures play an important role in the generation of ammonia in the medulla.[18] This type of disorder may be diagnosed by observing a rate of ammonium excretion in the urine that is much lower than in patients with other types of metabolic acidosis.

Back-leak of hydrogen ions across the distal nephron lumenal membrane rarely occurs in the diabetic. It is diagnosed when patients have a high urine pH during metabolic acidosis and a normal U-B PCO_2 with bicarbonate loading. This is the lesion seen in distal RTA associated with Amphotericin B therapy.[24,25]

FIGURE 2. For description, see text. As shown on the left side of the upper panel, the proton pump actively secretes H^+ and the activity of this pump can be increased by mineralocorticoids. On the right side, the pathophysiology of type I distal RTA is depicted as either a defect in the proton pump or to back-leak of hydrogen ions through a permeable membrane. In the left-hand panel, electrical factors should normally augment distal nephron hydrogen ion secretion in DKA because there is a high rate of sodium delivery (caused by the osmotic diuresis and the ketonuria), a stimulus for sodium reabsorption (ECF volume contraction and high mineralocorticoids), and a high delivery rate of nonresorbable anions (ketone bodies). Furthermore, agents which decrease the electrical gradient (amiloride and lithium) are not usual medications for these patients. Defects in this parameter might occur with a profound fall in sodium delivery or when there is decreased aldosterone bioactivity. Lastly, the chemical gradient for hydrogen ion secretion should be augmented because acidemia presumably increases the ICF hydrogen ion concentration. Should there be a reduction in PNH_3 in the renal medulla (hyperkalemia, medullary disease),[18] the rate of hydrogen ion secretion would decrease due to the unfavorable chemical gradient for hydrogen ions.



From the above discussion of the pathogenesis of distal RTA, one can readily see how the lower bioactivity of aldosterone can lead to distal RTA due to several mechanisms: first, the hydrogen ion pump activity may be reduced, due either to aldosterone deficiency or interstitial renal disease; second, the electrical augmentation of hydrogen ion secretion may also be diminished due to the mineralocorticoid deficiency; third, the hyperkalemia induced by aldosterone deficiency can decrease ammonia synthesis and thereby inhibit hydrogen ion secretion due to decreased chemical stimulation of the proton pump. The constellation of findings of hyporeninemia, hypoaldosteronism, hyperkalemia, and non-anion-gap metabolic acidosis has been termed "type IV RTA" and is not uncommonly found in diabetics. This subject has been discussed in several recent review articles.[26–29] The hyporeninemia may be due to an expanded ECF volume possibly related to increased chloride permeability,[30–32] a sympathetic neuropathy, or structural damage to the juxtaglomerular apparatus. In a smaller group of cases, interstitial nephritis may lead to decreased renal responsiveness to normal or even elevated levels of aldosterone. The diagnosis of type IV RTA is confirmed by the demonstration of a defect in net acid excretion together with a high serum potassium concentration and a relatively low rate of potassium and ammonium excretion in the urine. If reduced ammonium excretion is present, ammoniagenesis may be increased by the correction of the hyperkalemia. It is important to evaluate the plasma and urine potassium concentrations to help differentiate between type IV and the other types of distal RTA. In the type IV RTA patients, the plasma potassium concentration is elevated, whereas the converse is true in the other types of distal RTA. This difference in plasma potassium concentration is most likely the result of the low rate of potassium excretion in the former group whereas renal potassium wasting occurs commonly in the latter group of patients.

It is important to identify diabetic patients with hypoaldosteronism, since they are very prone to develop hyperkalemia with hyperglycemia.[33] In such patients, aldosterone antagonists should be avoided, as they will exacerbate both the acidosis and the tendency to hyperkalemia. Patients should be placed on a low potassium diet and be given sodium bicarbonate to correct the acidosis and decrease the hyperkalemia. Diuretics, such as furosemide, may be required to maintain sodium balance and, if necessary, oral mineralocorticoid therapy may be given to correct the hyperkalemia and the metabolic acidosis.

SUMMARY

Metabolic acidosis with a normal anion gap results from either bicarbonate loss or a urine acidification defect. The bicarbonate loss may be via the gastrointestinal tract or the urine, or may be indirect due to excretion of the sodium and potassium as opposed to the ammonium salts of ketone body anions. Defects in urine acidification in the diabetic have several etiologies: first, hydrogen ion secretion may be decreased because of an intrinsic defect in the hydrogen ion pump (i.e., diseases of the renal medulla); second, there may be a failure to augment hydrogen ion secretion by a favorable electrical gradient (e.g., reduced mineralocorticoids); and third, there may be a failure to generate a favorable chemical gradient to augment hydrogen ion secretion (e.g., reduced urine ammonia). Reduced levels of aldosterone associated with hyporeninemia has been termed type IV RTA, and these patients have specific therapeutic needs.

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