Hyperchloremic Metabolic Acidosis in Diabetes Mellitus

A Case Report and Discussion of the Pathophysiologic Mechanisms

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SUMMARY

A 21-year old woman with poorly controlled diabetes mellitus was examined for persistent hyperchloremic metabolic acidosis. There was no evidence of ingestion of hydrochloric acid or its equivalent. Gastrointestinal loss of bicarbonate was absent. Proximal tubular bicarbonate reabsorption and distal nephron hydrogen-ion secretion were normal. Ammonia and net acid excretions were high, and thus there was no obvious cause for this acidosis.

Further study revealed a very large loss of β-hydroxybutyrate in the urine that closely approximated net acid excretion. This loss of potential bicarbonate was the principal cause for the hyperchloremic metabolic acidosis. Phosphate, urate, and β-hydroxybutyrate fractional excretions were all abnormally high. Generalized aminoaciduria was also present, but the renal handling of glucose and bicarbonate was normal. With improved control of her diabetes, the generalized aminoaciduria disappeared, the urine β-hydroxybutyrate loss ceased, the fractional excretions of phosphate and urate approached normal, and the acidosis was rapidly corrected. DIABETES 27:16-20, January, 1978.

Ketoacidosis is a frequent complication of diabetes mellitus in poor control. In this condition accelerated fat metabolism leads to accumulation of β-hydroxybutyric and acetoacetic acids. Clinically, the diagnosis is made when there is a rise in blood sugar, a metabolic acidosis of the anion-gap type,* and a strongly positive test for serum ketones (for review, see reference 1). In a typical case, the increase in anion gap is usually quantitatively equal to the decrease in serum bicarbonate concentration (for review, see reference 2).

Hyperchloremic metabolic acidosis (HCMA) is diagnosed when there is a fall in blood bicarbonate and no increase in anion gap. In this case, there is a commensurate increase in the serum chloride concentration (table 1). HCMA usually occurs in patients who have gastrointestinal or urine bicarbonate loss or who have ingested ammonium chloride.[3] HCMA has been described following the treatment of diabetic ketoacidosis and is generally attributed to extracellular fluid volume expansion with sodium chloride.[4,5] In specific cases, it resulted from coexistent renal tubular acidosis[6] or diarrhea. HCMA in patients with diabetes mellitus with ketoacidosis could result if urine loss of ketones exceeded net acid excretion (table 2).

We recently investigated a young insulin-dependent diabetic in poor control with HCMA of several months' duration in whom none of the usual causes of HCMA could be found. HCMA was caused by a renal tubular defect in net ketone-body anion reabsorption that resulted in increased fractional

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*Anion gap = $Na^+ - (Cl^- + HCO_3^-)$.

TABLE 1

Causes of hyperchloremic metabolic acidosis*

Ingestion of acids or potential acids with chloride as the anion, for example:
hydrochloric acid, ammonium chloride, calcium chloride, arginine, or lysine hydrochloride
Bicarbonate loss:
Gastrointestinal:
Diarrhea, fistula, ileus, vomiting of bicarbonate-rich fluid
Renal:
Failure of proximal bicarbonate or potential bicarbonate reabsorption:
Proximal renal tubular acidosis, carbonic anhydrase inhibitors, loss of metabolizable organic anions
Failure of net acid excretion:
Distal renal tubular acidosis, defective ammoniagenesis
Extracellular fluid volume expansion with sodium chloride.
Acidosis with increased blood anions that are inapparent because of:
Hypoalbuminemia
High blood levels of bromide or iodide
Abnormal proteins that are cationic at pH 7.4

*An increased serum chloride and decreased bicarbonate can be seen with respiratory alkalosis; however, the blood pH will be greater than 7.4 in this condition.

excretion of ketone bodies and, thus, net base loss in the urine. This loss represented a proton gain to the body of greater than 234 mEq. per day. The generation and maintenance of this HCMA and the clinical and therapeutic implications are discussed.

METHODS

Electrolytes and acid-base parameters were assayed as previously described.[6] Metabolites were measured fluorometrically in perchloric acid extracts.[6] Urine amino acids were quantitated by thin-layer cellulose chromatography and visual comparison made with standards and control urines. Urine net acid, ammonia, and organic acid excretions were measured as described by Chan.[7,8]

Case Report and Results

A 21-year-old Caucasian female was seen in consultation because of HCMA of six months' duration. She was initially diagnosed as having diabetes mellitus two years previously and was treated with 34 U. of lente insulin daily. Control of her diabetes mellitus was far from ideal, and she frequently observed glycosuria and ketonuria. There were no overt episodes of ketoacidosis during the preceding six months; however, physically she felt poor, noting lethargy, generalized malaise, and frequent headaches. Serum electrolytes determined on several occasions in the preceding six months showed a modest HCMA that was variable but always present. Venous blood pH and PCO_2 determinations on at least three occasions confirmed the diagnosis (table 3). There was no past history of renal disease or ingestion of carbonic anhydrase inhibitors, halogens, or hydrochloric acid or its equivalent, and there was no history suggestive of gastrointestinal bicarbonate loss.

Physical examination was unremarkable. Urine analysis showed a normal urine sediment and no proteinuria. Serum albumin was 3.8 gm./dl. with a normal protein electrophoresis. Blood urea nitrogen was 17 mg./dl., and the serum creatinine was 0.9 mg. per deciliter. Minimum urine pH on three occasions was below 5.3. Distalmost nephron hydrogen-ion secretion was judged to be normal as the urine minus blood PCO_2 gradient was 50 mm. Hg.[9] With oral sodium bicarbonate loading, the urine pH did not rise abruptly until the serum bicarbonate concentration exceeded 28 mEq. per liter, indicating normal proximal tubular hydrogen-ion secretion and ruling out proximal renal tubular acidosis.[3] Net acid excretion was high, 260 mEq. per gram creatinine (titratable acid 40 mEq. per gram creatinine and urine ammonium excretion 220 mEq. per gram creatinine). The urine excretion of β-hydroxybutyrate was 234 mEq. per

TABLE 2

Effect of fate of β-hydroxybutyrate acid on net acid-base balance

Component	Fate	Effect on acid-base balance*
(1) H^+	Buffered	Bicarbonate loss
(2) βHB^-	Anion remains in body fluids	None
	Metabolism to neutral compounds	Bicarbonate gain
	Excretion with Na^+ or K^+	None†
	Excretion as free acid or with NH_4^+	Bicarbonate gain

*To determine the effect of β-hydroxybutyrate acid on net acid-base balance, one must add the results of components 1 and 2.

†Since the addition of β-hydroxybutyric acid resulted in equimolar bicarbonate loss due to hydrogen-ion buffering, excretion of sodium or potassium β-hydroxybutyrate will result in the loss of potential bicarbonate (i.e., bicarbonate that would have resulted if β-hydroxybutyrate were metabolized to a neutral end product). In this case, on balance, the actual loss is sodium or potassium bicarbonate.

TABLE 3

Typical steady-state values during the period of hyperchloremic metabolic acidosis*

Blood Values	mg./dl.		mEq./L.
BUN	11	Na^+	136
Creatinine	0.9	K^+	2.9
F.B.S.	190	Cl^-	103
Blood pH	7.35	HCO_3^-	19
Blood $PaCo_2$	35 mm. Hg	βHB^-	2.2
		Anion gap	14
Renal tests:			
Minimum urine pH	5.3†		
Urine-blood PCO_2	50 mm.Hg‡		
Renal bicarbonate threshold	28 mEq./L. GFR‡		
Titratable acid excretion	40 mEq./gm. creatinine		
Ammonia excretion	220 mEq./gm. creatinine		
β-hydroxybutyrate excretion	234 mEq./gm. creatinine		

*When the HCMA was most severe, the blood pH was 7.30, PCO_2 32 mm. Hg, HCO_3^- 16 mEq./L., and the anion gap 16 mEq./L.
†When blood pH was 7.30, pH of 24-hr. urine was 5.8.
‡With oral bicarbonate loading (serum K 4.1 mEq./L.).

gram creatinine, which closely approximated net acid excretion. Unfortunately, urine acetoacetate was not measured on this occasion, but subsequent determinations showed its excretion rate to be approximately 10 per cent of that of β-hydroxybutyrate. The fractional excretion of β-hydroxybutyrate, inorganic phosphate, and urate greatly exceeded the expected values when the patient had HCMA. In addition, generalized aminoaciduria was observed. When control of the diabetes mellitus was improved, the urine loss of ketones was almost nil, but net acid excretion remained high, and the HCMA was rapidly corrected. Similarly, the tubular defects all decreased when the ketonuria and glycosuria were minimized (table 4). With strict control of her diabetes the patient has remained well, with no prolonged episodes of HCMA, and the serum levels of phosphate and urate have risen (table 4).

DISCUSSION

In clinical situations, HCMA is almost always caused by ammonium chloride intake, the direct loss of bicarbonate, or a failure of net acid excretion. By careful history and physical and laboratory examination, the listed causes of HCMA (table 1) concerning hydrochloric acid intake and direct bicarbonate loss were excluded. There was no evidence of rapid extracellular fluid volume expansion with bicarbonate-poor solutions, the so-called dilution metabolic acidosis.[10] Therefore, indirect forms of bicarbonate loss were investigated. In lactic or keto-acidosis, these metabolic anions represent potential bicarbonate because bicarbonate is formed when they are metabolized to the neutral end products (CO_2, glucose, glycogen, triglyceride). If, however, these anions are lost in the urine, this bicarbonate cannot be recovered and the anion loss is equivalent to a net bicarbonate loss and results in HCMA. This is illustrated in table 2.

The renal contribution to over-all bicarbonate balance for a patient with diabetic ketoacidosis and ketonuria is the difference between potential or actual bicarbonate gain and loss as described below:

Bicarbonate gain = urine free hydrogen ions, titrable acid plus ammonium excretions

Bicarbonate loss = urine loss of bicarbonate plus metabolizable organic anions (ketone bodies)

In this patient, the renal bicarbonate gain was 260 mEq. per day. HCMA could occur only if bicarbonate loss or hydrochloric acid intake exceeded that amount. Simultaneous bicarbonate loss as measured only by the urine β-hydroxybutyrate excretion was 234 mEq. per day. Based on later determinations, urine acetoacetate excretion was probably 10 per cent of that of β-hydroxybutyrate or about 25 mEq. per day, making the renal contribution to net bicarbonate balance close

TABLE 4

Renal tubular functions studied during poor and better diabetic control

	Fasting blood sugar (173-192 mg./100 ml.)			Fasting blood sugar (100 mg./100 ml.)		
	FE* per cent	Normal FE per cent	Blood level	FE per cent	Normal FE per cent	Blood level
βHB	78	<20†	2.2 mM	0	0	0.3 mM
Phosphate	26	<10‡	2.3 mg./dl.	14	<30‡	5.2 mg./dl.
Urate	32	<10§	1.9 mg./dl.	9	<10§	2.1 mg./dl.
Aminoaciduria	Marked increase			Minimal increase		
Bicarbonate threshold	28 mEq./L. GFR					
Glucose threshold	Clinically >150 mg./dl.					

*FE - fractional excretion. †See references 16, 17, and 18. ‡See reference 29. §See references 20 and 24.

to nil. The patient was in an apparent steady state with respect to ketonemia over this prolonged period; therefore she had close to equal rates of ketone body production and loss or metabolism. However, since she would produce the usual 1 mEq. of protons per kilogram body weight from dietary sources, she would be in net positive hydrogen-ion balance and develop HCMA.

Although it has been reported that ketone bodies can inhibit ammonia production in vitro[11] and in certain circumstances in vivo,[12] this did not appear to be the cause of the HCMA in this case. Ammonia excretion rates were as high (220 mEq. per gram creatinine), as is usually seen in ketoacidotic patients with the usual anion-gap type of metabolic acidosis.[13-15]

The excretion of β-hydroxybutyrate was very high in this patient. The fractional excretion was 78 per cent at a blood β-hydroxybutyrate level of 2.2 mM. In 10 fasting obese patients, we observed that the fractional excretion of β-hydroxybutyrate was only 17 ± 1 per cent at similar blood β-hydroxybutyrate levels (2-3 mM—Marliss, E. B., Hammeke, M., Halperin, M. L., unpublished observations). This conforms closely to values seen in other studies.[16-18] The renal tubular handling of some other metabolites was also abnormal in this patient. She had an increased fractional excretion of phosphate and urate. The latter was increased despite the ketonemia, which has been shown to decrease urate clearance.[19,20] There was also generalized aminoaciduria. However, other proximal tubular functions were normal in that she had a normal renal threshold for glucose and bicarbonate. She also had normal distalmost nephron hydrogen-ion secretion as judged by the normal U-B PCO_2.[9] When the diabetes mellitus was under good control, the excretions of phosphate, urate, and amino acids approached normal limits. Therefore, these renal tubular dysfunctions were acquired and reversible. The renal handling of β-hydroxybutyrate could not be assessed during periods of good diabetic control, as its filtered load was markedly decreased.

Many factors have been described that can decrease proximal tubular function. Nonspecific renal damage appears unlikely, as the defect is selective and other renal functions appear to be normal. We have recently shown that low-dose acetosalycilic acid or sodium lactate administration can result in a tubular defect with increased fractional excretions of β-hydroxybutyrate, acetoacetate, and urate.[15,20] However, lactate levels were normal in this patient, and she denied the consistent intake of any medications. Since the tubular dysfunctions improved when blood glucose levels returned towards normal (table 4), it is possible that there is a relationship between these two phenomena. This hypothesis has some experimental support in that glucose infusion in dogs results in increased fractional excretions of phosphate, sulfate, and acetoacetate. Inhibition of glucose reabsorption with phloridzin reversed these defects.[21-23] Diabetics generally are found to have lower serum uric acid values and higher fractional excretion rates for uric acid.[24] The increased clearance of uric acid has been related to increased tubular reabsorption of glucose.[25] Generalized aminoaciduria has been observed in diabetics[26,27] and can be induced in normal man by glucose infusions.[28] Thus, it appears that tubular reabsorption of glucose, amino acids, and several anions are related.

From the above, it appears likely that many poorly controlled diabetics have increased renal excretions of phosphate, urate, ketone bodies, and amino acids. However, these abnormalities, especially ketonuria, were much more marked in this patient. This might have been explained if there was ingestion of such agents as salicylates.[20] Since this could not be documented, the patient might have an underlying renal tubular abnormality that was made clinically obvious when the diabetes was in poor control (increased tubular reabsorption of glucose).

A high rate of β-hydroxybutyrate excretion can occur in most diabetics with severe ketoacidosis, but for a different reason. In these cases the very high filtered loads of β-hydroxybutyrate result in a high rate of excretion of this anion. In three such cases that we have recently studied, the organic anion excretion rate was 340 mEq. per gram creatinine,† whereas net acid excretion was 200 mEq. per gram creatinine when blood β-hydroxybutyrate levels were 10-12 mEq. per liter. Their component of HCMA disappeared when ketonuria decreased and net excretion remained high.

In summary, we have presented a patient with HCMA that accompanied diabetes mellitus in poor control. The HCMA was caused by an abnormally high ketone-body anion-excretion rate, which resulted in a net bicarbonate loss from the body. There were also accompanying renal tubular defects, resulting in excessive phosphate, urate, and amino acid loss in the urine. These tubular defects disappeared with improved diabetic control. High rates of urine excretion of ketones can occur for two principal reasons—increased filtered load or decreased net tubular reab-

†80 per cent of the urine organic anion was β-hydroxybutyrate.

sorption. In either case, HCMA will ensue unless net acid excretion exceeds urine organic-anion loss plus net hydrogen-ion intake. This large potential bicarbonate loss is usually not clinically important because it is not persistent and is corrected for by the high net acid excretion rate.

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