Clinical Studies of Alcoholic Ketoacidosis

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SUMMARY

Seven episodes of severe ketoacidosis in six nondiabetic patients were recognized at this hospital within an eighteen month period. All were women; one pregnant patient experienced two episodes at twenty-eight and thirty-two weeks' gestation. All patients admitted to heavy chronic alcohol intake and drinking binges.

On admission, these patients were conscious and alert. Mean values were 143 mg./100 ml. for plasma glucose and 7.25 for arterial pH. Plasma bicarbonate was depressed with a mean anion gap of 18. Beta-hydroxybutyrate/acetoacetate ratio averaged 5.2. All patients had liver function abnormalities. Mean serum immunoreactive insulin was low, 5 μU./ml. (n=2), while cortisol was markedly elevated at 76.5 μg. per cent (n=3); mean growth hormone level was 14.1 ng./ml. (n=3). Free fatty acid concentration, measured on admission in one episode, was 1,945 mEq./L. Therapy with glucose, saline, and minimal amounts of alkali led to prompt recovery. Circulating levels of cortisol, insulin and growth hormone were measured serially in one patient during recovery; they quickly returned to normal.

The dissociation of severe ketosis from glycosuria and hyperglycemia in these patients raises important questions concerning coupling of ketogenesis to gluconeogenesis. The striking preponderance of women, including one pregnant patient, reported with this condition also suggests a possible role for ovarian and placental hormones in its pathogenesis; fetal drain on carbohydrate reserves may further contribute to the tendency to ketosis.

Alcoholic ketoacidosis may be relatively common, since we saw one case of this syndrome for about every four of diabetic ketoacidosis during this period. DIABETES *23*:433-39, May. 1974.

The association between alcohol ingestion and nondiabetic ketoacidosis, initially speculated upon by Dillon[1] in 1940, has only recently been further documented and studied. Jenkins et al.[2] reported three alcoholic patients with multiple episodes of ketoacidosis marked by elevation of β-hydroxybutyrate. More recently Levy et al.[3] have described five nondiabetic alcoholic patients who presented in metabolic acidosis with elevated ketoacid, free fatty acid, and serum cortisol levels. These patients recovered when given intravenous fluid and minimal alkali but did not require insulin therapy.

During the past eighteen months we have studied six patients with seven episodes of alcoholic ketoacidosis. We report here the clinical findings and biochemical changes in these patients.

METHODS

Blood chemistries, blood gases, and hematologic studies were done by routine hospital procedures. Ketones were determined semiquantitatively by Acetest tablets or Ketostix (Ames) with serial serum dilutions.

For determination of organic anions, whole arterial blood was mixed immediately with 3.5 per cent perchloric acid, centrifuged, and the deproteinized supernatant stored at -20° C. until assayed. Lactate, pyruvate, β-hydroxybutyrate, and acetoacetate were assayed with specific NAD-coupled enzymatic spectrophotometric procedures.[4]

Growth hormone (HGH) and insulin were determined by the double antibody radioimmunoassay.[5,6]

Cortisol was determined by competitive protein binding.[7] Free fatty acids were measured by the microdetermination method of Dole.[8]

CASE SUMMARIES

Case 1. Y.R. is a thirty-one-year-old woman who had multiple hospital admissions for metabolic acidosis and presumptive pancreatitis. She first presented in April 1970 at age twenty-eight; in the thirtieth week of pregnancy, she had abdominal pain, fever, and gastric upset. Her history of alcohol intake included daily beer and whiskey as well as a drinking binge immediately prior to admission. Examination revealed a metabolic acidosis with ketonemia by nitroprusside reaction, pH 7.19, and serum glucose of 73 mg./100 ml. Serum amylase levels and liver function tests

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were abnormal. Treatment consisted of 212 mEq. sodium bicarbonate and intravenous fluids which resolved the acidosis and ketonemia. During this hospitalization she delivered a premature fetus: her hospital course was further complicated by the development of cardiac failure, pneumonia, and consumption coagulopathy. She recovered without sequelae.

Y.R. was admitted again to hospital in February 1972 with recurrent abdominal pain, nausea, and vomiting. No ketone determination was recorded; acidemia was not noted; and chronic pancreatitis was diagnosed on the basis of an elevated serum amylase determination. She recovered uneventfully on supportive therapy.

The third hospital admission six months later (July 1972) was prompted by epigastric distress. The patient was two months' pregnant at this time. Serum bicarbonate was 15 mEq./L. Serum ketones were not measured. Glucose was 107 mg./100 ml., and she recovered with intravenous fluid therapy.

Her fourth admission, again prompted by abdominal distress, vomiting and nausea, occurred in December 1972 at twenty-eight weeks' gestation. The patient admitted to continued ethanol ingestion, with a recent increase in alcohol intake before admission. Food intake had not occurred for forty-eight hours. Blood pressure was 134/90, pulse, 100, and respiratory rate 20 per minute. Bowel sounds increased by rushes. Laboratory data revealed a metabolic acidemia with bicarbonate of 13 mEq./L. and pH of 7.31. Serum ketone by nitroprusside reaction was positive. Serum lactate was 0.3 mEq./L., with β-hydroxybutyrate elevated at 1.8 mEq./L. following several hours of treatment. Following 44 mEq. sodium bicarbonate and intravenous fluid, the pH returned to normal within six hours. Abdominal pain subsided, and pregnancy was not compromised.

The most recent admission occurred one month later, February 1973, following another episode of excessive alcohol intake, at thirty-two weeks' gestation. Metabolic acidosis was again confirmed, with serum bicarbonate of 10 mEq./L., glucose 94 mg./100 ml., and pH 7.28. β-hydroxybutyrate was 7.5 mEq./L. and acetoacetate 1.7 mEq./L. Once again, she responded to small quantities of alkali and intravenous dextrose solution and recovered within eight hours. Several weeks following discharge she was readmitted and delivered a normal term infant without difficulty.

Case 2. M.H. had a long history of alcohol intake and was admitted to hospital in August 1971 at the age of thirty-two with abdominal distress, nausea, and vomiting. There was no toxin ingestion. Epigastric pain was diffuse but nonradiating and unrelated to position or respiration. She had been anorectic for two days prior to admission; there was no appreciable food intake during that time. The history revealed multiple episodes of pelvic inflammatory disease and urinary tract infection but not diabetes. Physical examination disclosed a thin woman with a blood pressure of 120/70, pulse, 110, and respiratory rate of 24 per minute. Bilateral upper quadrant abdominal tenderness and guarding were noted, but no spasm, rebound, or gastric dilatation were apparent. Bowel sounds were decreased in frequency and intensity. No organomegaly was noted. Neurologic examination was normal. Laboratory data revealed a pH of 7.28, an anion gap of 19 mEq./L., and a blood sugar of 75 mg./100 ml. Amylase, BUN, and hemotocrit were normal. Stool guaiac was 4+ for occult blood, and urinalysis disclosed moderate acetone by Ketostix. Following treatment with hydration and 132 mEq. sodium bicarbonate, rapid clearing of acidosis and ketonemia was noted in five hours. She remained well and was discharged with a normal fasting blood sugar.

Case 3. Patient D.D. was admitted to hospital for protracted vomiting in September 1972. A fifty-one-year-old secretary, she admitted to heavy social drinking, most recently on the night of admission. Bilious vomiting, beginning twenty-four hours prior to admission and continuing until admission, was associated with epigastric pain. Vomitus changed to coffee ground material; she then sought medical aid. There was no history of diabetes. In past years, she had experienced several episodes of severe vomiting and abdominal pain, from which she had recovered spontaneously.

On physical examination, this was a moderately obese woman with mild lethargy; her blood pressure was 134/90, respiratory rate 24 per minute, and temperature of 99.8° F. Positive findings included only epigastric tenderness to palpation without hepatomegaly. Bowel sounds were active. Vomitus material was guaiac positive; pH was 7.09, potassium, 6.2 mEq./L., bicarbonate, 5 mEq./L., and glucose, 275 mg./100 ml. β-hydroxybutyrate was 11.4 mEq./L., and acetoacetate was 1.3 with a β-hydroxybutyrate/acetoacetate (B/A) ratio of 8.8:1. Serum ketones were moderate by Ketostix. She was treated with 10 U. of insulin, intravenous fluids, and a total of 240 mEq. sodium bicarbonate and showed rapid improvement of acidosis in eight hours. Both amylase and liver function tests were within the normal range. She required no further insulin therapy, and a two hour postprandial blood sugar test performed before discharge was normal.

Case 4. L.R. was admitted to hospital in November 1972 for vomiting and nausea. She was a thirty-seven-year-old woman with a history of alcohol ingestion of at least one quart per day who had increased her intake for several days prior to presentation. Four days before hospital entry she hit her head, became dizzy, and lost consciousness for ten minutes. Upon awakening, she had a frontal headache and severe nausea and began to vomit. She was unable to eat or drink because of burning epigastric pain. There was no history of drug or toxin ingestion nor of diabetes.

She was an emaciated woman with a blood pressure of 110/70, respiratory rate of 30 per minute and temperature of 103.4° F. Mucous membranes were dry and skin of poor turgor. Ecchymoses were present around the eyes. Hepatomegaly was noted when the lower edge of the liver was palpated three fingerbreadths below the right costal margin. The abdomen was diffusely tender without rebound. Neurologic examination revealed mild alcoholic hallucinosis but failed to disclose focal central nervous system signs. Laboratory data revealed a metabolic acidosis with an anion gap of 22, pH of 7.28, blood sugar of 166 mg./100 ml., and moderate serum ketone levels. Lactate was 1.0 mEq./L. and β-hydroxybutyrate 8.3 mEq./L. She was treated with a total of 220 mEq. sodium bicarbonate and 5 L. glucose-containing fluid and improved markedly over five hours. Liver function was abnormal and remained so throughout her hospitalization. Results of lumbar puncture were within normal limits on admission. Her mental state returned to normal before discharge. Fever and abdominal pain abated spontaneously.

Case 5. E.D., a forty-six-year-old woman, presented in January 1973 with nausea, vomiting, and epigastric pain. Her medical history revealed intermittent excessive alcohol intake; the most recent drinking binge was three days prior to admission. There was no history of pancreatitis, diabetes, or toxin ingestion. She had noted the onset of epigastric pain four days before admission with anorexia and had not been able to eat or drink.

The patient was a thin, restless woman, with a blood pressure of 120/75, respiratory rate of 30 per minute, and temperature, 98.6°

F. Acetone breath and decreased skin turgor were evident. The liver was palpable four fingerbreadths below the right costal margin and was 13 cm. long as determined by percussion in the midclavicular line. Midepigastric tenderness could be elicited without rebound. Stool guaiac was negative. Neurologic examination was within normal limits. Laboratory data revealed a metabolic acidosis with low serum ketone levels, pH of 7.25, and bicarbonate of 8 mEq./L. Glucose was 133 mg./100 ml. She was treated with 44 mEq. bicarbonate and glucose fluids intravenously and recovered within eighteen hours. No insulin was given. Liver function was abnormal and improved but never became normal. The remainder of her course was unremarkable.

Case 6. R.S., a forty-seven-year-old woman, had a ten year history of chronic alcohol consumption marked by occasional binges with consumption of up to one quart of whiskey per day. She presented at the emergency ward in May 1973 with nausea, vomiting, and abdominal pain of two to three days' duration. No food intake was recorded for forty-eight hours. There was no known history of diabetes, pancreatitis, or liver disease.

Physical examination revealed an obese woman with a blood pressure of 146/98, respiratory rate of 24, and temperature of 101.4° F. Pertinent findings included a diffusely tender abdomen with normal bowel sounds. No neurologic abnormalities were observed. Electrolyte determination revealed a metabolic acidosis marked by an anion gap of 19 mEq./L. and positive serum ketones. Blood sugar was 145 mg./100 ml. and bicarbonate 13 mEq./L. She received 132 mEq. of sodium bicarbonate and 3 L. of glucose-containing solution. Acidosis resolved within eight hours. Several days after admission she signed out of the hospital against medical advice. Fasting blood sugar determination before discharge was normal.

RESULTS

A summary of the clinical findings present at the time of admission in these six cases includes the following information. All patients were female; four were still menstruating (ages thirty to forty-six), and two (ages forty-seven and fifty-one) were intramenopausal. Patient Y.R., a thirty-one-year-old woman, had two documented episodes of severe ketoacidosis at twenty-eight and thirty-two weeks' gestation. No personal or family history of diabetes or evidence of chronic lung, renal, or liver disease was obtained in any of the patients.

Heavy chronic alcohol intake as well as a drinking binge universally preceded admission to hospital by forty-eight to seventy-two hours. In each case, abdominal pain, vomiting, and lack of solid food for one to two days led the patient to seek medical help. There was no history of toxin or salicylate ingestion.

Physical examination revealed no specific findings to aid in diagnosis except tachypnea and acetone breath in two patients. Two patients were febrile, but no specific cause was subsequently documented; all patients were normotensive on admission. Hepatomegaly was noted in only two of the six patients. All had diffuse epigastric tenderness on palpation. Bowel sounds remained active and ileus or gastric dilatation was not evident. Patients did not appear grossly volume-depleted by skin turgor or ocular pressure examination. One patient experienced mild alcoholic hallucinosis. There were no seizures or focal neurologic findings. All patients were conscious on admission despite the severity of the pH abnormalities and marked elevation of ketone body levels (see below), strongly supporting the suggestion of Fulop et al.[9] that coma with diabetic ketoacidosis is a function of hyperosmolarity rather than low pH or degree of ketosis.

Initial laboratory values (table 1) revealed a mean serum glucose level of 143 mg./100 ml. Six of the seven values obtained were below 170 mg./100 ml., the mean of these six values being 121 mg./100 ml.; one patient had a blood sugar level of 275 mg./100 ml. Renal impairment was not evident, but five of the six patients had at least one abnormal liver function test result. Evidence of pancreatitis was absent in most patients, since amylase was moderately elevated, to 204 Russell units, in only one patient (case 1, Y.R.) during her fourth admission; that finding was accompanied by the only significant elevation of triglycerides (564 mg. per cent) in this series. Lipase values were moderately elevated in four patients.

All patients had significant but partially compensated metabolic acidosis (table 2). Bicarbonate was depressed to levels less than 10 mEq./L. in five of the

TABLE 1

Laboratory data on admission in alcoholic ketoacidosis (seven episodes in six patients)

Test (Normal values)	Mean	Range
Glucose	143 mg./100 ml.	75-275
HCO_3^- (21-33 mEq./L.)	9	5-13
Na^+ (135-148 mEq./L.)	139	131-145
Cl^- (100-109 mEq./L.)	99	95-105
K^+ (3.5-5.0 mEq./L.)	4.6	3.4-6.2
BUN (8-20 mg. %)	15	3-25
Creatinine (0-1.4 mg. %)	1.1	0.6-1.9
*SGOT (8-40)	92	11-343
*SGPT (8-26)	49	12-148
*LDH (54-134)	130	76-266
Bilirubin (0-1.2 mg. %)	1.1	0.5-2.6
Albumin (3-4.5 gm. %)	3.3	2.9-4.7
†Amylase (< 160)	122	43-204
*Lipase (0-1)	2.3	1-3.8
Triglycerides (< 150 mg. %)	225	36-564
WBC	11,800	7,600-25,800

*International units
†Russell units

TABLE 2

Acid-base status in alcoholic ketoacidosis

Test (Normal values)	Mean	Range	No. of Observations
pH (7.40 ± .02)	7.25	7.09-7.28	6
pCO_2 (35-45 mm. Hg)	21	12-32	6
Serum ketones (negative)	small	small-mod.	6
Anion gap*	18	9-22	7
Lactate (less than 1.0 mEq./L.)	1.1	0.3-2.6	6
β-hydroxybutyrate (< 0.07 mEq./L.) (B)	8.7 mEq./L.	7.3-11.4	5
Acetoacetate < 0.06 mEq./L.) (A)	2.1 mEq./L.	1.3-4.1	5
B/A	5.2	2.0-8.8	5

*Anion gap = $Na^+ - (Cl^- + HCO_3^- + 15)$ mEq./L.

seven episodes (table 1), and the mean anion gap was 18 mEq./L. Ketone body determination by nitroprusside reaction was only low to moderate in undiluted serum in each case. In patients with diabetic ketoacidosis, semiquantitative levels of ketonemia in this range would correspond with mean measured total ketoacid levels of about 8 to 12 mEq./L.[10] A disparity was thus evident in most of our patients between the relatively low semiquantitative serum ketone level and the large anion gap, which appears to be explained by the disproportionate elevation of β-hydroxybutyrate relative to the smaller elevation of acetoacetate levels. The B/A ratio was inversely related to pH, and the mean B/A ratio was 5.2. Blood lactate was normal except for a slight elevation in one patient.

Insulin was measured on admission in two cases and was 5 μU./ml. or less. Serum cortisol was uniformly and markedly elevated at 75 to 78 μg. per cent in three patients. Simultaneous growth hormone levels were increased but variable with values of 7.6, 12.6, and 22 ng./ml. in each of three patients. Free fatty acid level was determined in a single case and was elevated at 1,945 μEq./L. following partial therapy.

Table 3 documents the serial changes which occurred in patient E.D. during an episode of alcoholic ketoacidosis. Initial blood studies revealed a metabolic acidosis marked by a major elevation of β-hydroxybutyrate and a modest rise of serum lactate. Treatment consisted of intravenous glucose solution and 44 mEq. sodium bicarbonate. No insulin therapy was administered. pH and bicarbonate rose as lactate and β-hydroxybutyrate fell within the first four hours. Acetoacetate rose despite a fall in total ketoacids which resulted in a fall of the B/A ratio. Insulin rose sluggishly but failed to attain levels commensurate with the blood sugar. Total resolution of the acidemia was accomplished within twelve hours.

Treatment of the seven episodes resulted in a favorable outcome in all patients. Upon presentation, only one patient was thought to have diabetic ketoacidosis and received a small dose of Regular insulin. All other patients were thought to have lactic acidosis until the medical staff became aware of the clinical entity of alcoholic ketoacidosis. All patients were treated with intravenous sodium bicarbonate, although in three episodes the total amount given was quite small, i.e. 88 mEq. or less; the mean bicarbonate administered was 133 mEq. (range 44 to 272 mEq.). Serum ketones, estimated by nitroprusside reaction, rose frequently during the early course of therapy. Resolution of acidosis to an anion gap of less than 15 was rapid, occurring within twelve hours in all cases. All patients survived, and there was complete resolution of the acidemia without recurrence during the period of hospitalization. Three of the five patients with abnormal liver function on admission demonstrated persistent abnormalities at the time of discharge. Fasting serum sugar and/or two hour post cibum sugar values were normal in all patients during convalescence.

DISCUSSION

Patients with alcoholic ketoacidosis are metabolically unique. Ketone levels are much higher than those

TABLE 3

Serial changes during treatment in one patient with alcoholic ketoacidosis

Time	pH	Gluc.	HCO_3	Lact.	B-OH	AcAc	B/A	Cort.	Ins.	HGH
Admission	7.25	133	8	2.6	7.9	1.4	5.6	78.0	5	12.6
Treatment Initiated with Fluids and Bicarbonate										
5 hr.	—	—	10	—	—	—	—	47.0	7.5	6.0
8 hr.	7.31	155	13	0.8	5.2	2.2	2.4	—	10.0	5.0
16 hr.	—	400	17	—	—	—	—	39.0	15.0	3.6
24 hr.	—	195	21	—	—	—	—	22.5	15.0	2.8

found in normal subjects, even after prolonged fasting.[11] On the other hand, the hyperglycemia and glycosuria that accompany severe ketoacidosis in diabetes are absent. Ketosis is part of the physiologic response to carbohydrate deprivation and as such is normally subject to tight metabolic control. In the following discussion, we have attempted to relate the clinical data from our patients to possible abnormalities in control of ketone metabolism at three different levels: lipolytic rate (precursor supply), hepatic production, and peripheral utilization.

Lipolytic rate

As insulin levels fall below the "null point" separating anabolic from catabolic ranges, the adipose tissue lipolytic rate is progressively derepressed.[11] In the presence of "permissive" hormones, the rate of free fatty acid release into plasma, and therefore, the level of circulating FFA, increases. Extremely high FFA levels (1,800 to 3,800 μEq./L.) have been a consistent finding in patients with alcoholic ketoacidosis.[2,3] These FFA levels are well above the extreme upper limits found in normal subjects after eight days of fasting (about 1,900 μEq./L.), levels associated with total plasma ketones of about 5 mEq./L.[12] Thus, in alcoholic as in diabetic ketoacidosis, rapid lipolysis appears to be a major contributory factor to accelerated ketogenesis. Plasma insulin levels have been low in alcoholic ketoacidosis (5 to 12 μU./ml.),[2,3] although in comparison with normal fasting subjects whose insulin levels are below 25 μU./ml. over the blood sugar range 100 to 200 mg./100ml.,[12] these insulin levels are not grossly inappropriate for the accompanying blood sugars, which in the alcoholic group have ranged from 25 to 235 mg./100 ml. Since insulin levels in this range appear to be adequate to modulate lipolytic rate in normal subjects during prolonged fasting, factors other than inappropriately low insulin levels may well be contributing to accelerated lipolysis in the alcoholics. Although controversy persists concerning the precise role of cortisol and growth hormone in the control of lipolytic rate, considerable evidence indicates that both hormones exert important permissive effects in vitro[13] and in vivo.[14-17] The levels of cortisol and growth hormone in patients with alcoholic ketoacidosis[3] are much higher than in hyperosmolar diabetic coma and somewhat higher than in diabetic ketoacidosis[18,19] and may, therefore, be important causes of the augmented lipolytic rate. Increased catecholamine release, perhaps associated with the stress of vomiting, as well as other factors, recently reviewed by Levy et al.,[3] could also be involved. Alcohol infusion did not increase FFA levels above 1,500 μEq./L., even after fasting for forty-three hours,[2] in two subjects who had previously experienced spontaneous alcoholic ketoacidosis, which suggests that alcohol itself does not contribute directly to rapid lipolysis.

Hepatic ketone production

Although hepatic ketogenesis can be shown to increase directly as a function of the availability of FFA as precursors,[20] a variety of intrahepatic mechanisms also capable of modulating ketogenic rate have been identified recently.[15] A major regulatory step may be the rate of fatty acyl entry into mitochondria, controlled through the activity of an enzyme, long-chain fatty acyl carnitine transferase, present in the inner mitochondrial membrane.[21] When this reaction is not rate-limiting, the maximal ketogenic rate may be controlled by the rate at which ATP and reducing equivalents (hydrogens) produced during FFA oxidation to ketones are utilized.[22] The major "sink" for these products during fasting in normal subjects and, hence, the over-all rate-limiting process for ketogenesis, may thus be the rate of hepatic gluconeogenesis.[22]

Direct studies of gluconeogenic rate in patients with alcoholic ketoacidosis are not available. However, the rates of glucose exit from extracellular fluid through the various nonoxidative routes, i.e. glucosuria, glycogenesis, lipogenesis, and Cori-cycle activity, are likely to be minimal in these carbohydrate-deprived alcoholic patients with low insulin and normal serum lactate levels. Moreover, in the face of markedly elevated FFA and ketone levels, the bulk of peripheral tissue energy needs are almost certainly being met by FFA and ketone body oxidation rather than by glucose oxidation to carbon dioxide. Finally, the extracellular glucose pool is apparently normal or only slightly expanded and not increasing in size. Thus, the gluconeogenic rate, although possibly as rapid as in fasting nondiabetic subjects, or postsurgical patients under stress,[23] is unlikely to be as great in patients with alcoholic ketoacidosis as in those with diabetic ketoacidosis.

Flatt has calculated that the difference between the rate of ketone body production in prolonged fasting normal subjects (100 gm. per day) versus those patients with diabetic ketoacidosis (about 200 gm. per day) can be correlated exactly with the differential increment in gluconeogenic rates in the latter group (about 75 mg. per day more glucose produced from protein).[22] If, on the other hand, patients with al-

coholic ketoacidosis are producing new glucose at rates comparable to normal fasting subjects and yet produce ketones at rates comparable to patients with diabetic ketoacidosis, an ATP and hydrogen sink other than gluconeogenesis would be required to permit the observed "excess" rates of ketone body production. The most obvious alternative hydrogen sink would, of course, be molecular oxygen. In tightly coupled mitochondria, such hydrogen (electron) flow is retarded. If, however, mitochondrial respiratory control were loosened, not only could rapid electron flow occur, but excessive ATP would not accumulate. Under these conditions, pathologically rapid ketogenesis could occur without abnormally accelerated gluconeogenesis.

Marked ultrastructural changes are found in the hepatic mitochondria of alcoholic subjects,[24] and liver function defects are almost universal in patients with alcoholic ketoacidosis[3] (table 1). Liver slices from alcohol-treated experimental animals also produce more ketones from palmitate than liver tissue from controls, an effect not dependent on the addition of gluconeogenic precursors and not mimicked by in vitro addition of alcohol.[24] An important parallel is observed in hepatic mitochondria from livers of ketotic diabetic animals, which also show striking structural changes, accompanied by loosening of respiratory control and increase in maximal rate of long-chain fatty acyl oxidation.[25] Loosening of hepatic mitochondrial respiratory control could thus account for the high rates of ketone body production in alcoholic ketoacidosis, as well as the extreme rates (as high as 385 gm. per day) observed occasionally in patients with diabetic ketoacidosis.[26] The common molecular link in pathogenesis of the hepatic mitochondrial derangements of diabetic and alcoholic ketoacidosis might well be high cytoplasmic free fatty acid levels, since entirely similar loosening of respiratory control and increased flux of pyruvate to the gluconeogenic precursor phosphoenolpyruvate have been produced in mitochondria isolated from normal livers by the in vitro addition of long-chain free fatty acids.[27]

Peripheral ketone utilization

The rate of ketone body utilization by peripheral tissues has been shown to be insulin dependent, particularly at high rates of ketone infusion.[28] Since insulin levels are low in both diabetic and alcoholic ketoacidosis, the severity of the ketoacidosis may be attributable in part to "underutilization" superimposed on "overproduction." Neither acetate nor ethanol itself appears to inhibit the oxidation of ketone bodies by peripheral tissues.[24]

Prevalence of alcoholic ketoacidosis

The preponderance of female patients with alcoholic ketoacidosis is striking (fifteen of nineteen reported cases) (refs. 1 to 3 and present series). This sex differential could arise through hormonal and/or nonhormonal mechanisms, since women develop fasting ketonuria and ketonemia more rapidly and more severely than men.[29] Essentially all of the female alcoholic patients were within the age range where some degree of ovarian function is to be expected, the two oldest being fifty-one and fifty-seven years. Small doses of estrogens have been shown to increase fatty acid synthesis in adipose tissue,[30] supporting the possibility that ovarian hormones may increase the precursor supply of fatty acids.

Nonhormonal sex differences could also influence the susceptibility to fasting and alcoholic ketoacidosis. The mean postabsorptive FFA level in healthy women is significantly higher than in men (690 μEq./L. vs. 550 μEq./L.).[31] Furthermore, in diabetic women the postabsorptive FFA level rises as a function of fasting blood sugar, approaching 1,600 μEq./L., while in men the level of fasting blood sugar does not correlate with FFA concentration (FAA levels all below 1,100 μEq./L.);[31] these sex differences do not appear to be explained on the basis of differences in age, weight, or insulin requirement.

Of further interest in this regard is the occurrence of two episodes of alcoholic ketoacidosis four weeks apart in one of our patients in the third trimester of pregnancy. This coincides with the rising serum level of placental mammosomatotropin,[32] a hormone with extensive similarities in structure and metabolic function to pituitary growth hormone. Pregnancy is known to predispose to the development of overt ketosis,[33,34] perhaps related to changes in hormonal milieu, and in part to increasing fetal drain on maternal carbohydrate reserves.[34,35]

Finally, the recognition of seven episodes of alcoholic ketoacidosis within eighteen months in this hospital suggests the syndrome may be considerably more common than is generally appreciated. Since approximately twenty patients with classic diabetic ketoacidosis are admitted to this hospital per year, alcoholic ketoacidosis may represent as much as one out of every five cases of ketone body acidosis in our hospital population. This frequency, plus the differences in therapy and prognosis between alcoholic ketoacidosis vs. lactic or diabetic ketoacidosis, make

alcoholic ketoacidosis an important consideration in any patient with detectable serum ketones, minimal hyperglycemia, and severe acidosis.

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