Uric Acid Excretion in Diabetic Ketoacidosis

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SUMMARY

Renal clearance studies in five patients during and after an episode of diabetic ketosis showed that there was decreased uric acid excretion and consequent elevation of the serum level. This was due to altered tubular handling of urate. Similar renal changes were produced by the infusion of beta-hydroxybutyrate in three normal subjects. DIABETES *15*:357-59, May, 1966.

Elevation of the serum uric acid has been reported in patients with diabetic ketoacidosis by Padova and Bendersky,[1] who observed that the uric acid level paralleled ketosis and decreased as ketonemia and ketonuria cleared. The mechanism responsible for this hyperuricemia was not explained.

In the present study, clearance studies were performed in five patients during an episode of diabetic ketoacidosis and repeated several days later when the ketosis had cleared and the diabetes was controlled. In all of the subjects studied, there was a decreased uric acid excretion and consequent elevation of the serum level during the period of ketosis as compared to the control period.

Experimentally, ketosis was produced in three normal subjects by the infusion of beta-hydroxybutyrate, and again a fall in uric acid clearance was noted. A similar reduction in uric acid clearance has been noted by others.[2-4]

MATERIALS AND METHODS

The five patients were admitted to the wards of the Presbyterian Hospital because of diabetic ketoacidosis. No infection or other precipitating illness was present, and none of the patients had been taking salicylates, thiazides, or phenformin. All were acidotic (CO_2 combining power ranging from 4 to 9 mEq./L.), and ketotic (both serum and urine giving strongly positive test for ketones) at the time of the initial study.

Therapy consisted of the standard measures of insulin, large volumes of intravenous saline and sodium bicarbonate, plus glucose and potassium supplements when indicated. Sodium lactate solutions were not used. The clearance studies were performed within three hours after therapy was instituted. For study purposes inulin was given as a priming dose and added to the intravenous infusion in amounts sufficient to maintain a plasma level of approximately 25 mg. per 100 ml. After thirty minutes equilibration, urine was collected by an indwelling catheter, and the bladder was emptied by air washout at ten-minute intervals. Blood samples were collected at appropriate times. The repeat clearance studies employing the same technics were performed four to eight days later when ketosis was no longer present.

In the three subjects studied subsequently, cobalt 57-vitamin B_{12} was given intravenously in a sustaining solution and its clearance of low specific activity used to measure glomerular filtration rate.[5] The subjects voided spontaneously at the close of each twenty-minute period. After three control periods, beta-hydroxybutyrate was added to the infusion and the study continued for three additional periods of twenty minutes each. Twenty-five grams of DL-beta-hydroxybutyric acid sodium, hydrate* were dissolved in 50 ml. of distilled water, sterilized by passing through a millipore bacteria-excluding filter and stored in sterile 10-ml. vials at 4° C. until used.

Ketones were detected with a nitroprusside reagent tablet.† Inulin was measured in plasma and urine by the alkali-stable method.[6] Uric acid was measured by the enzymatic spectrophotometric method of Praetorius.[7] Clearances were calculated in standard fashion and not corrected for body surface area.

RESULTS

The studies in the diabetic patients are shown in table 1. The figures represent the means of four ten-minute periods. In each patient, the renal clearance of uric acid was lower during ketoacidosis than in the later control study and, correspondingly, the serum level of

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†Acetest tablet, Ames Laboratories.

uric acid was higher.

As measured by inulin clearance, the glomerular filtration rate (GFR) was not decreased during ketoacidosis; rather it was equal to or slightly greater than the GFR in the repeat study in each instance.

Table 2 summarizes the results in the three subjects who received beta-hydroxybutyrate intravenously during acute clearance studies as described. A fall in uric acid clearance and the urate clearance/GFR ratio was demonstrable within forty minutes and paralleled the appearance of ketones in the urine.

DISCUSSION

The clearance studies in the five patients with ketoacidosis show that the elevated serum uric acid levels were the result of impairment of renal excretion. The decrease in the urate clearance/GFR ratio (see table 1) demonstrates that this was due to a change in glomerular flow. In fact, there was no fall in glomerular flow. It is not possible to be certain of the nature of such a tubular alteration, but we believe it represents an inhibition of uric acid secretion as has been postulated previously in such situations as lactate infusion[8] or salicylate[9] or chlorothiazide[10] administration.

Despite the fact that glycosuria itself tends to increase uric acid excretion,[11] the net result in diabetic ketoacidosis is the reverse, indicating that the inhibiting effect of the ketones is greater than the augmenting effect of glucose.

A number of factors could conceivably produce the observed decrease in uric acid excretion.

None of the therapeutic measures used in treating diabetic ketoacidosis in these patients is known to produce this effect. Metabolic acidosis was present, but since it has been observed that considerable changes in urine *p*H have little influence on uric acid excretion,[12] it is unlikely that the acidosis is responsible for the observed decrease in this study. Yü and Gutman[9] found that acidosis decreased the clearance of uric acid by a maximum of 37 per cent, whereas four of these five patients showed falls of 50 per cent to 75 per cent. Elevation of the serum lactate has been demonstrated to reduce uric acid excretion as mentioned.[8] Lactate was not measured in these patients and conceivably may have been a factor, but Huckabee[13] found the serum lactate to be only slightly elevated in his patients with ketoacidosis.

Similar impairment of uric acid excretion has been observed in other clinical states marked by ketosis such as the ingestion of a high fat diet[14] and total starvation.[2,3,15,16] It seems likely that the mechanism responsible for the decreased uric acid excretion in these states and in experimental ketosis is the same: the presence of ketones in the serum and urine. It is postulated that the ketone bodies, as weak acids, are secreted by the same renal tubular mechanism as uric acid and may competitively inhibit its transport.

TABLE 1

Uric acid clearance in diabetic ketoacidosis and in recovery

Patient's age and sex	Day	Serum uric acid (mg./100 ml.)	Clearance uric acid (ml./min.)	Clearance inulin (ml./min.)	Cu/GFR
47 M	1	11.3	3	134	0.02
	7	4.5	12	100	0.12
30 F	1	6.0	13	135	0.09
	8	4.0	16	110	0.14
16 F	1	6.0	12	200	0.06
	6	2.0	22	158	0.14
33 M	1	8.6	9	150	0.06
	9	3.9	18	155	0.11
28 F	1	6.7	9	170	0.05
	5	2.0	30	160	0.18

Values each represent the mean of four ten-minute periods.

TABLE 2

Uric acid clearance following ketone infusion

Patient's age and sex	Serum uric acid (mg./100 ml.)	Urine ketones	Clearance uric acid (ml./min.)	Clearance B_{12} (ml./min.)	Cu/GFR
36 M	5.8	0	10.8	97	0.11
	Beta-hydroxybutyrate 0.5 gm., intravenous				
	5.6	+	5.7	94	0.06
55 F	2.8	0	12.9	66	0.19
	Beta-hydroxybutyrate 2 gm., intravenous				
	2.4	+	8.3	87	0.09
43 M	6.6	0	6.3	109	0.06
	Beta-hydroxybutyrate 10 gm., intravenous				
	6.5	+	3.5	117	0.03

Values each represent the mean of four ten-minute periods.

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BRIEF NOTES AND COMMENTS

The State of Insulin in Human Plasma

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SUMMARY

In plasma obtained from normal fasting subjects insulin was precipitated by anti-insulin serum. Both the precipitate and the supernatant were extracted with acid-alcohol. Insulin or insulin-like activity was measured in the extracts by immunoassay, glucose uptake by the rat hemidiaphragm and CO_2 production by the rat epididymal fat pad. The amount of insulin found in plasma before extraction was quantitatively recovered from the insulin-anti-insulin precipitate extracted with acid-alcohol as measured by the immunoassay. No insulin was detected in the extracted supernatant. In close agreement were the results obtained with the diaphragm. Only the adipose tissue was able to demonstrate ILA in the extracted supernatant. This ILA was present even in control samples (buffer with known amounts of Crystalline Insulin added) in spite of the fact that all the added insulin had been recovered in the precipitate.

These results suggest that in normal human plasma all the insulin is readily available to react with insulin antibodies. Results with the epididymal fat pad method strongly suggest the possibility that factors other than insulin stimulate the production of CO_2 from glucose. DIABETES *15*:359-62, May, 1966.

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The nature of circulating insulin is controversial and unresolved. Two prevailing concepts are: (a) that the form of insulin that reacts with anti-insulin accounts for all the endogenous hormone that circulates in plasma; or (b) that insulin is present in more than one form, part of which is available to react with specific anti-serum, and part which is detected only by biological assays or after special treatment of plasma.

Moloney[1] reported that in a sample of equine serum, following precipitation of insulin by anti-insulin serum, it was possible to recover 2,000 μU. of insulin from the supernatant, after extraction with acid-alcohol. The biological activity of this extracted insulin was neutralizable by anti-insulin serum. Moloney's experimental design seemed to be useful to explore this problem in other species. The present report is part of an investigation in which Moloney's methodology—with the modification described below—has been applied to human plasma. Thus far, samples from fasting normal subjects were examined, while studies on plasma of diabetic patients are in progress.

METHOD

Blood samples from fasting normal subjects were obtained in heparinized syringes. As control, 100 or 250 μU. of crystalline beef insulin was added to borate buffer (*p*H 6.8) with 1 per cent beef serum albumin and treated in the same way as the plasma samples. Five milliliters of freshly obtained plasma or buffer control were incubated for twenty-four hours at 4° C. with 0.1 ml. of guinea pig anti-beef insulin serum. The guinea pig anti-insulin serum was obtained from animals immunized with crystalline beef insulin according to the procedure of Moloney and Coval[2] and had