Diabetic Ketosis

Serial Plasma Growth Hormone Concentrations During Therapy

Philip E. Cryer, M.D., and William H. Daughaday, M.D., St. Louis

SUMMARY

Plasma growth hormone (GH) concentrations were measured serially during therapy in twelve cases of diabetic ketosis. The initial plasma GH levels varied widely, ranging from 2 to 215 ng./ml., and were not related to the clinical severity of the ketosis, the degree of depression of the serum bicarbonate, or the magnitude or the hyperglycemia. An increase in the plasma GH concentration followed the institution of insulin therapy in ten of twelve cases. This rise was associated with a fall in the plasma glucose concentration though the latter reached hypoglycemic levels in only one instance. There was no relationship between the total insulin administered during the first twelve hours of therapy and the area under the GH curve for the same period or the initial or peak plasma GH concentration. Thus, despite its known diabetogenic effect and the frequent occurrence of elevated plasma concentrations in ketotic diabetics, growth hormone cannot be a constant major determinant of the insulin resistance of diabetic ketosis. DIABETES *19*:519-23, July, 1970.

The antagonistic effect of growth hormone (GH) on glucose utilization has been well established in studies of acromegalic, normal, and hypopituitary patients.[1,2] Indeed, impaired glucose tolerance has been demonstrated less than two hours after the intravenous injection of 5 mg. of human growth hormone into normal subjects.[3] It is conceivable, therefore, that an acute increase in endogenous growth hormone secretion could contribute to the insulin resistance which typifies moderate to severe diabetic ketosis. The observation that the plasma GH concentration increases following the administration of 2-deoxyglucose[4] suggested that plasma GH concentrations might be elevated in other conditions characterized by impaired intracellular glucose utilization such as uncontrolled diabetes mellitus.

Roth and coworkers[5] found the initial plasma GH concentration to be normal in a patient with mild diabetic ketoacidosis. On the other hand, Unger[6] noted absolute elevations of the initial plasma GH concentration in three of six ketoacidotic subjects. Furthermore, the patient with the highest plasma GH concentration in Unger's series appeared to have the most severe ketoacidosis, as judged by depression of the serum bicarbonate and the initial insulin requirement, whereas the patient with the lowest GH concentration had relatively mild ketoacidosis. Therefore, it was concluded that growth hormone is an important anti-insulin factor in at least some patients with diabetic ketoacidosis.

In order to clarify the role of growth hormone in diabetic ketosis, and in the varying degrees of clinical insulin resistance which characterize this disorder, serial plasma GH concentrations were measured in ketotic diabetic patients.

METHODS

Twelve episodes of diabetic ketosis, occurring in nine patients, were studied on the ward medical service of Barnes Hospital over approximately a six-month period. Uncontrolled diabetes mellitus with a strongly positive serum nitroprusside test (Acetest, Ames) was the only requisite for inclusion. Therefore, patients were not selected for severe ketoacidosis. The clinical features are summarized in table 1.

Management of the patients was left entirely to the responsible physicians except, when mechanically feasible, a three-way stopcock was inserted into the intravenous apparatus so that blood for growth hormone determination could be obtained at frequent intervals without the imposition of additional venipunctures.

Plasma growth hormone (GH) was measured by the double antibody radioimmunoassay method of Schalch and Parker.[7] A highly purified preparation of human growth hormone (Hs 612A), kindly supplied by Dr. A. E. Wilhelmi, was used for standards. In one patient plasma insulin was measured, also by radioimmunoassay.[8] Glucose, bicarbonate, and urea nitrogen were measured in the clinical chemistry laboratory by routine technics. In five instances these determinations were initially performed on serum; in all other cases and on

From the Department of Medicine, Metabolism Division, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri.

TABLE 1

Clinical features of patients with diabetic ketosis

Patient	Age (yrs.)	Sex	Additional clinical diagnosis	Initial systolic pressure (mm. Hg)	Initial serum or plasma values CO_2 (mEq./L.)	Glucose (mg./100 ml.)	SUN (mg. %)
1. R. R.	15	M	None	120	22	213	14
2. N. C.	16	M	Diabetic hyperlipemia	120	18	360	9
3. B. H.	19	F	Pelvic infection	110	11	385	19
4. K. A.	48	M	Pneumococcal pneumonia	120	22	245	13
5. A. P.	43	F	Influenza	130	12	283	39
6. W. Z.	16	M	None	110	19	357	10
7. B. H.*	19	F	None	150	8	453	18
8. D.G.	16	F	Infected pilonidal cyst	118	9	285	15
9. W. Z.*	16	M	None	130	7	300	18
10. J. C.	45	M	None	180	14	584	80
11. R. R.*	16	M	None	120	8	408	14
12. R. T.	26	M	Oral moniliasis	158	4	340	14

*Three patients were studied on two separate occasions.

all repeat determinations plasma was used.

Since growth hormone production rates were not determined, the area under the GH curve for the first twelve hours of therapy was measured, and expressed in arbitrary units (ng.-min.-ml.$^{-1}$), as an index of total circulating plasma GH during that period. This manipulation required extrapolation of the GH curve in patients number 5 (two hours), number 7 (four hours), and number 11 (two hours).

RESULTS

The plasma growth hormone (GH) levels obtained during therapy of diabetic ketosis are listed in table 2. The initial plasma GH concentration, prior to the institution of insulin therapy, was elevated above normal resting levels (less than 10 ng./ml.) in seven of twelve cases of diabetic ketosis with values ranging from 13 to 215 ng./ml. Five patients had initial GH levels below 10 ng./ml. ranging from 2 to 6 ng./ml. Initial GH concentrations were not correlated with the clinical severity of the ketosis, the degree of depression of the serum bicarbonate, or the magnitude of the hyperglycemia. Furthermore, the initial plasma GH levels were not consistent in two of the three patients who were studied on two separate occasions; in patient R.R. the initial values were 215 and 13 ng./ml. and in patient B. H. they were 14 and 46 ng./ml. The three oldest patients (forty-three to forty-eight years of age) had initial GH concentrations of less than 10 ng./ml.

In view of the markedly elevated initial plasma GH concentration in case number 1, the measurement was repeated ten days later at a time when his diabetes was adequately controlled. The baseline GH level was 6 ng./ml. and the GH concentration suppressed to less than 2 ng./ml. after the ingestion of 100 gm. of glucose. This patient was a newly diagnosed diabetic and had not received previous insulin therapy. His initial plasma insulin concentration, while he was ketotic, was 16 μU./ml.

In ten of twelve instances the plasma GH concentration rose significantly during the course of therapy of the ketosis (table 2). In each case, the rise in plasma GH concentration was associated with a fall in plasma glucose concentration. Examples are shown in figure 1. In only one case (number 1) was the fall in plasma glucose concentration to hypoglycemic levels, however. In the remaining ten instances peak plasma GH levels were reached at a time when the plasma glucose concentration was greater than 150 mg./100 ml. The relationship between a falling plasma glucose concentration and the rise in plasma GH concentration was further illustrated in patient B. H. (number 3, figure 1) who received inadequate initial therapy with the result that the plasma glucose concentration had risen after three and one-half hours; the peak in plasma GH was delayed until five hours at which time the plasma glucose had fallen.

The total amount of regular insulin administered during the first twelve hours of therapy ranged from 70 to 625 U. and was not related to the area under the GH curve nor was it related to the initial or peak plasma GH concentration (figure 2).

DISCUSSION

The plasma GH concentration is the resultant of growth hormone secretion, distribution, and degradation. The latter has not been studied in ketotic diabetics, but Taylor, Finster, and Mintz[9] have noted a small

TABLE 2

Serial plasma growth hormone (GH) concentrations (ng./ml.) during therapy of diabetic ketosis

	Hour of therapy															
Patient	0	½	1	2	3	4	5	6	7	8	9	10	12	14	16	18
1. R. R.	215	106	110	250	98	15	56	38	—	—	56	—	—	—	—	8
2. N. C.	30	80	90	30	30	25	25	—	45	—	—	—	—	27	—	—
3. B. H.	14	—	40	40	70	—	190	—	30	—	—	20	—	—	30	—
4. K. A.	6	—	100	20	20	4	6	—	—	—	—	—	—	12	—	—
5. A. P.	4	—	130	80	20	8	—	12	—	19	—	6	—	—	—	—
6. W. Z.	4	—	11	36	30	38	—	27	—	6	—	—	6	—	—	—
7. B. H.*	46	—	43	10	13	10	6	—	11	9	—	—	—	—	—	7
8. D. G.	55	88	91	30	30	34	—	12	—	—	—	—	36	—	—	—
9. W. Z.*	13	—	100	44	5	18	—	14	—	5	—	—	10	—	—	—
10. J. C.	4	—	11	9	5	3	—	4	—	12	—	—	4	—	4	—
11. R. R.*	13	100	355	340	18	67	—	25	—	19	—	2	—	—	—	—
12. R. T.	2	—	2	3	5	2	—	2	—	2	—	3	2	—	—	—

*Three patients were studied on two separate occasions.

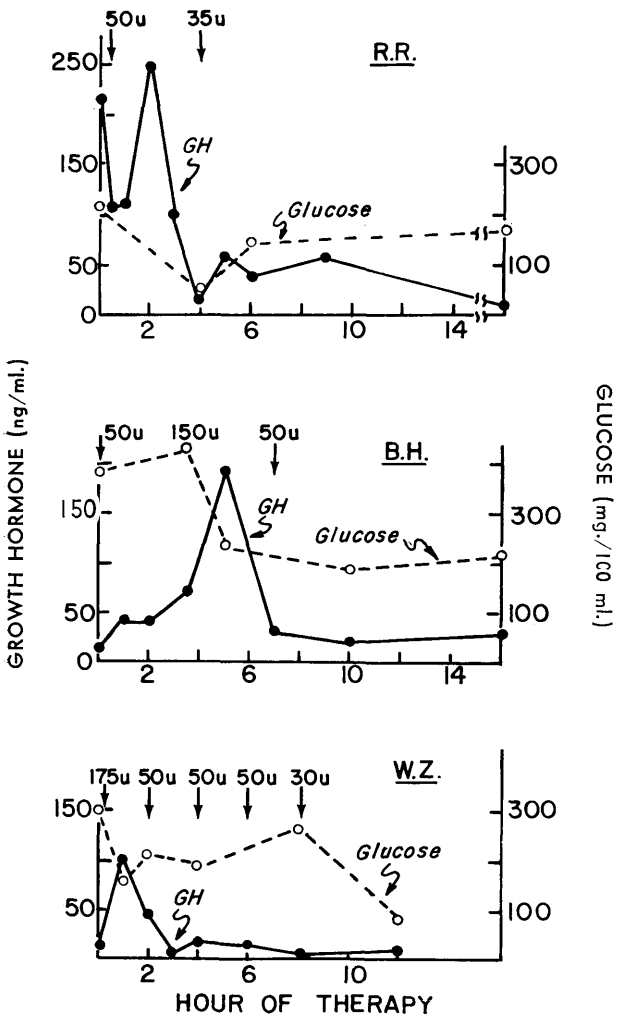

FIG. 1. Plasma growth hormone (GH) and glucose concentrations during therapy of diabetic ketosis in cases number 1 (R. R.), 3 (B. H.), and 9 (W. Z.). The doses of regular insulin administered are shown at the top of each panel.

but significant decrease in the metabolic clearance rate of growth hormone in insulin-dependent diabetics. Quantitatively, these changes would not explain the marked increases in plasma GH concentration which occurred in the majority of the patients in the present series. These increments are therefore assumed to reflect changes in growth hormone secretion.

The initial plasma GH concentration varied widely in patients with diabetic ketosis, ranging from 2 to 215 ng./ml., and was not correlated with the severity of the clinical illness or with simple biochemical changes such as the degree of depression of the serum bicarbonate or the magnitude of the hyperglycemia. Variation in the initial value was apparent not only among the entire group of patients but also in the same patient studied on more than one occasion. Elevations occurred despite the presence of hyperglycemia which would normally be expected to suppress GH secretion.[4]

Since 2-deoxyglucose administration impairs intracellular glucose utilization and produces a rise in the plasma GH concentration,[4] Unger suggested that elevation of the initial plasma GH concentration in some patients with diabetic ketosis may also be due to decreased glucose utilization, in this instance due to insulin deficiency.[6] This explanation does not seem likely for two reasons, however. First, it may be assumed that all of the patients in the present series had an absolute or relative deficiency of insulin, yet the initial plasma GH concentration varied from normal-resting values to markedly elevated values. In fact, the highest initial plasma GH concentration encountered was in case number 1 who had mild ketosis and easily measurable plasma insulin (16 μU./ml.). Patients number 5 and 10, on the other hand, had initial GH concentrations

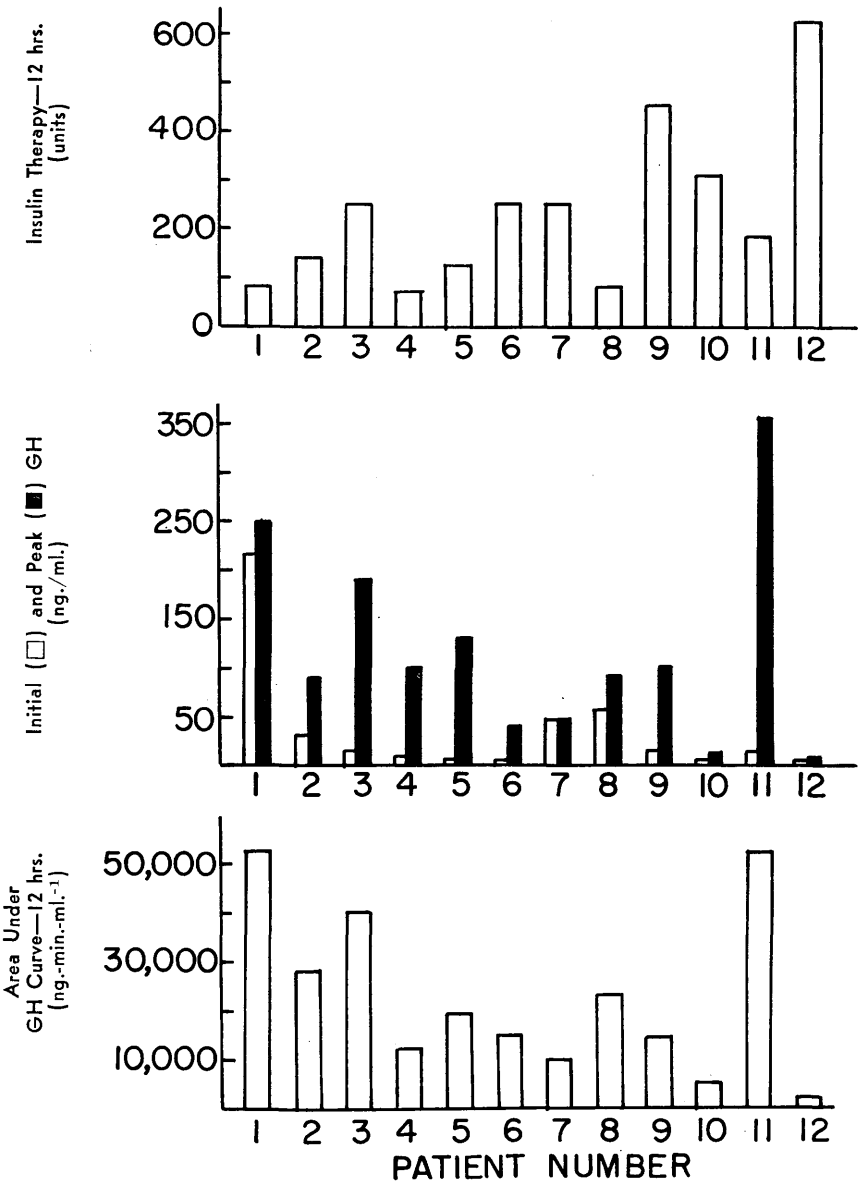

FIG. 2. Area under the plasma growth hormone (GH) curve for the initial twelve hours of therapy of diabetic ketosis (lower panel) and initial and peak plasma GH concentrations (middle panel) compared with the total dose of regular insulin administered during the first twelve hours of therapy (upper panel).

of 4 ng./ml. with serum bicarbonate values of 12 and 14 mEq./L. respectively and the initial GH level was 2 ng./ml. in patient number 12 who had a serum bicarbonate of 4 mEq./L. Second, the experimental findings of Glick,[10] who found no increase in the plasma GH concentration in squirrel monkeys in which acute insulin deficiency was produced by the infusion of anti-insulin serum, do not support the hypothesis that insulin deficiency causes GH secretion in ketotic diabetics.

The elevated initial plasma GH concentrations in the presence of hyperglycemia require explanation. Several recognized stimuli to growth hormone secretion are not suppressed by hyperglycemia. These include surgical stress,[11-13] pyrogen administration,[14] and arginine infusion.[15] Only two of the patients in the present series were febrile (numbers 4 and 12) and the initial plasma GH concentrations were 6 and 2 ng./ml. respectively. Since elevated plasma amino nitrogen concentrations in patients with diabetic ketoacidosis have been reported,[16] it is conceivable that the elevated initial GH levels in the present series were due to

endogenous elevation of the plasma amino acid levels. The plasma amino nitrogen concentrations appear to be a function of the severity of the ketosis;[17] if this were the case and if the GH elevations were due to hyperaminoacidemia, an association between the initial plasma GH concentration and the severity of the ketosis, not found in the present series, would be expected.

In addition to that associated with surgical stress, elevation of the plasma GH concentration has been reported in some patients subjected to emotional stress[14,18] and in occasional patients, especially children, undergoing the relatively innocuous physical stress of venipuncture.[19] Perhaps the variable elevations of the initial plasma GH concentration in the young ketotic diabetic patients in the present series were due to the emotional and/or physical stresses of their acute illness.

After the initiation of insulin therapy the plasma GH concentration increased in ten of the twelve cases of diabetic ketosis. This rise was associated with a fall in the plasma glucose concentration, though hypoglycemic levels were reached in only one instance, and reaffirms the observation, first made by Roth and coworkers,[4] that a fall in plasma glucose may stimulate GH secretion without reaching hypoglycemic levels.

Despite its recognized diabetogenic effect,[1-3] growth hormone does not appear to be a major determinant of the insulin resistance of diabetic ketosis. In the present series there was no correlation between the total amount of regular insulin administered during the first twelve hours of therapy and the total circulating GH, as reflected by the area under the GH curve, or the initial or peak plasma GH concentration. This was well illustrated by patient number 1 who, despite marked elevation of the plasma GH concentration, became hypoglycemic after only 50 U. of regular insulin and by patient number 12 who required a total of 625 U. of insulin in the first twelve hours though his plasma GH levels were not elevated.

ACKNOWLEDGMENT

The authors wish to thank the house-staff of the ward medical service, Barnes Hospital, for assisting in the study of their patients and Miss Mary Comfort for performance of the growth hormone assays.

Dr. Cryer is a Fellow in Metabolism supported by Training Grant AM 05027. Research support was provided by NIH Research Grant AM 5105.

REFERENCES

1 Daughaday, W. H., and Kipnis, D. M.: The growth-promoting and anti-insulin actions of somatotropin. Recent Progr. Hormone Res. *22*:49, 1966.

2 Luft, R., and Cerasi, E.: Human growth hormone as a regulator of blood glucose concentration and as a diabetogenic substance. Acta Endocr. Suppl. *124*:9, 1967.

3 Schalch, D. S., and Kipnis, D. M.: Abnormalities in carbohydrate metabolism associated with elevated plasma nonesterified fatty acids. J. Clin. Invest. *44*:2010, 1965.

4 Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Secretion of human growth hormone: Physiologic and experimental modification. Metabolism *12*:577, 1963.

5 Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Influence of blood glucose on the plasma concentration of growth hormone. Diabetes *13*:355, 1964.

6 Unger, R. R.: High growth-hormone levels in diabetic ketoacidosis. JAMA *191*:945, 1965.

7 Schalch, D. S., and Parker, M. L.: A sensitive double immunoassay for human growth hormone in plasma. Nature *203*:1141, 1964.

8 Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: Two antibody system. Diabetes *12*:115, 1963.

9 Taylor, A. L., Finster, J. L., and Mintz, D. H.: Metabolic clearance and production rates of human growth hormone (abstract). Clin. Res. *16*:444, 1968.

10 Glick, S. M.: Normal and abnormal secretion of growth hormone. Ann. N. Y. Acad. Sci. *148*:471, 1968.

11 Glick, S. M., Roth, J., Yalow, R. S., and Berson, S. A.: The regulation of growth hormone secretion. Recent Progr. Hormone Res. *21*:241, 1965.

12 Ross, H., Johnston, I. D. A., Welborn, T. A., and Wright, A. D.: Effect of abdominal operation on glucose tolerance and serum levels of insulin, growth hormone and hydrocortisone. Lancet *2*:563, 1966.

13 Charters, A. C., Odell, W. D., and Thompson, J. C.: Anterior pituitary function during surgical stress and convalescence. Radioimmunoassay of blood TSH, LH, FSH, and growth hormone. J. Clin. Endocr. *29*:63, 1969.

14 Greenwood, F. C., and Landon, J.: Growth hormone secretion in response to stress in man. Nature *210*:540, 1966.

15 Rabinowitz, D., Merimee, T. J., Burgess, J. A., and Riggs, L.: Growth hormone and insulin release after arginine: Indifference to hyperglycemia and epinephrine. J. Clin. Endocr. *26*:1170, 1966.

16 Luetscher, J. A., Jr.: The metabolism of amino acids in diabetes mellitus. J. Clin. Invest. *21*:275, 1942.

17 Gray, C. H., and Illing, E. K. B.: Plasma and urinary amino acids in diabetes. J. Endocr. *8*:44, 1952.

18 Schalch, D. S.: The influence of physical stress and exercise on growth hormone and insulin secretion in man. J. Lab. Clin. Med. *69*:256, 1967.

19 Helge, H., Weber, B., and Quabbe, H. J.: Growth hormone release and venipuncture. Lancet *1*:204, 1969.