Influence of Exogenous Human Growth Hormone on the Metabolism of Fasting Obese Patients

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Three obese female patients were investigated during three courses of starvation. In two of them these periods lasted 12 days; in one 6 days. During the second starvation period HGH was administered on alternate days in a dosage of 10 mg. Plasma values of FFA, hydroxybutyric acid, insulin, electrolytes, glucose, HCO_3, and the pH were determined. In addition, a complete balance study of nitrogen, calcium, phosphate, Na, and K was done. In none of these cases HGH led to increased ketoacidosis. The rise of hydroxybutyric acid, as well as the decrease of HCO_3 and of the pH, was in one of the patients even less during HGH administration than during control periods. This patient showed an elevation of plasma insulin during HGH administration. The possibility is considered that growth hormone, by virtue of its stimulating action on pancreatic insulin secretion, might counteract the acidosis of starvation. The balance studies showed that during HGH there was less excretion of Na and K, but no other effects were demonstrable.

DURING PROLONGED FASTING obese patients are less prone to severe keto-acidosis than are normal subjects, although they metabolize at least as much fat.[1] In contrast to normal subjects they usually show no, or only a slight, rise in plasma growth hormone.[1,2] As administration of human growth hormone (HGH) has been shown to have a strong ketogenic action, at least in the juvenile hypophysectomized diabetic,[3] the possibility was considered that the fasting obese is protected against keto-acidosis by his lack of growth hormone response. If so, it might be expected that administration of HGH to starving obese might lead to enhanced keto-acidosis. The reports of Drenick et al.[4] and Felig et al.,[5] that were published after the conclusion of our experiments support the hypothesis. In our study, however, neither clinical nor laboratory signs of enhanced keto-acidosis were found.

Three obese patients were investigated during three starvation periods. In the second period 10 mg of HGH was administered on alternate days. Plasma values of FFA, hydroxybutyric acid (OHBA), insulin, growth hormone (GH), electrolytes, and pH were determined, and a complete balance study of nitrogen, calcium, phosphate, sodium, and potassium was done.

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Table 1. Personal Data and Loss of Body Weight During Treatment

Patient	Sex	Age (yr)	Height (m)	Body Weight (kg)
K-H	Female	49	1.56	112.2– 92.4
B-Z	Female	23	1.66	90.0– 74.5
K-W	Female	48	1.69	120.2–107.0

MATERIALS AND METHODS

The patients were admitted to the hospital for reduction of body weight. Treatment consisted of alternating periods in which a 600 kcal diet was given and starvation periods. During the whole observation the patients remained in a special ward; physical exercise was standardized as much as possible. During the starvation periods water intake was fixed at 1400, 1250, and 1200 ml/day, respectively. The 600 kcal diet consisted of 52.1–65.9 g of protein, 62–83 g of carbohydrate, and 8–11 g of fat. It was given in three meals a day. The food was prepared by a dietician, and its content calculated according to the Netherlands Table of Foodstuffs. As a check, duplicate meals were prepared and analyzed once in each period. During starvation only water was allowed, but supplements of the B vitamins and of vitamin C were given.

The data of the patients are listed in Table 1. Figure 2 shows the sequence of 6- and 12-day periods used. The HGH used was prepared by the N.V. Organon by the method of Raben and was tested immunologically and in balance studies. Its efficacy has been proved in the treatment of several children suffering from hypopituitary dwarfism.

Mrs. K-W did not feel well during the last few days of the first starvation period, and we were obliged to limit further starvation periods to 6 days. Notwithstanding the precautions taken, Mrs. B-Z failed to keep to her regimen during the third starvation period; she confessed to have taken some biscuits, but probably she had consumed other food too. The data obtained in this period were therefore disregarded.

Plasma growth hormone was measured by the method of Glick et al.,[6] (lower limit of sensitivity 2 ng/ml), plasma insulin by the method of Yalow and Berson,[7] (lower limit of sensitivity 5 μU/ml), FFA by the method of Dole and Meinertz,[8] hydroxybutyric acid (OHBA) by the method of Bergmeyer and Bernt,[9] the electrolytes by flame photometry, and the pH and bicarbonate by the method of Astrup. Urinary and fecal nitrogen was determined by Kjeldahl titration, calcium by EDTA titration, and phosphate by the method of Fiske Subbarov.[10] The completeness of urine collection was checked by creatinine determination.

RESULTS

Figure 1 shows the effect of HGH administration on the plasma levels of FFA, OHBA, insulin, and GH. Blood was drawn in patients K-H and K-W immediately before the HGH injections; in patient B-Z blood was drawn three times on the days between injections. Therefore, most values in K-H and K-W were obtained 48 hr after HGH; in B-Z 24 hr after the injection. In patient K-H there is little difference in FFA and OHBA values between the three starvation periods. In none of these periods could insulin be detected, and GH levels were always very low. In patient B-Z the FFA values are higher and the OHBA levels lower during the period of HGH administration than in the preceding period. Moderately high insulin values were found in the control period, which rose to very high levels during HGH administration. GH was

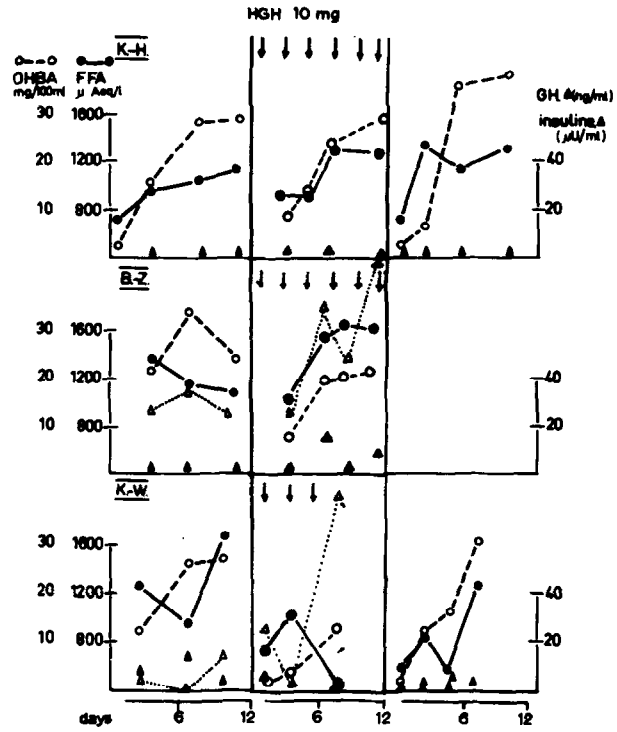

Fig. 1

elevated twice. As the rate of resorption from an intramuscular depot is unknown, one cannot be certain whether this was endogenous or exogenous GH. Patient K-W showed lower FFA and OHBA values in the second and third period than in the first period. The very low FFA value after 6 days of fasting in the HGH period coincided with a high insulin level. In none of these patients did the OHBA values, obtained during HGH administration, exceed those of the control periods. The data on pH and bicarbonate shown in Table 2 are in good agreement with those findings. The values obtained during HGH administration are certainly not lower than before or thereafter. During HGH the patients showed no clinical signs of keto-acidosis. In Table 2 the morning blood sugar values are listed. Data on serum electrolytes are not shown as they give no further information.

Table 3 summarizes the mean balance data per period expressed in grams or milliequivalents per day, respectively. As has been explained in the preceding section, the third balance period of patient B-Z is omitted. In patient K-W severe constipation during fasting caused difficulties in the collection of feces within the 6-day periods. For this reason the data on calcium and phosphorus balance must be regarded as unreliable and are left out.

The only clearly visible effect of HGH to be seen is a smaller excretion of electrolytes during its administration. As reported by other authors[11,12] and also observed in our patients, potassium loss is higher than could be theoretically expected from nitrogen and phosphorus excretion. During the 600 kcal period after HGH administration calcium and phosphorus retention is en-

Table 2. pH and Standard Bicarbonate Values During Starvation, With and Without HGH Administration

	Starvation				Starvation + HGH				Starvation			
K-H												
pH	7.409	7.403	7.274	7.291	7.481	7.421	7.423	7.375	7.430	7.435	7.385	7.349
Standard bicarbonate (meq/liter)	17.3	19.0	15.3	14.6	29.5	26.0	24.8	20.3	25.0	25.0	23.8	17.7
Morning blood sugar (mg/liter)	94	—	—	94	110	113	98	99	113	96	80	75
Day of starvation	1	4	8	11	3	5	7	11	1	3	7	10
B-Z												
pH	—	7.344	7.305	7.317	7.371	—	7.315	7.310				
Standard bicarbonate (meq/liter)	—	20.0	17.0	16.0	—	—	16.7	17.6	Data disregarded as			
Morning blood sugar (mg/liter)	—	82	77	75	71	82	104	82	not reliable.			
Day of starvation	—	4	7	11	3	6	8	10				
K-W												
pH	—	7.380	7.320	7.319	7.460	7.415	—	—	7.400	7.446	7.329	—
Standard bicarbonate (meq/liter)	—	15.0	13.2	17.0					26.2	24.1	22.2	—
Morning blood sugar (mg/liter)	—	56	94	92	98	110	—	—	96	89	—	—
Day of starvation	—	3	6	11	3	7	—	—	1	3	5	—

Table 3. Mean Balance Data per Period

	Starvation	600 kcal	Starvation + HGH	600 kcal	Starvation	600 kcal
Weight (g/day)						
K-H	—717	+ 33	—540	+400	—530	+166
B-Z	—483	+133	—450	+200		
K-W	—820	+418	—418	+230	—470	+ 50
Mean	—670	+195	—469	+277	—500	+108
N (g/day)						
K-H	— 5.8	+ 1.8	— 3.1	+ 4.2	— 3.4	+ 4.2
B-Z	— 5.2	+ 2.3	— 4.0	+ 3.3		
K-W	— 7.7	+ 4.2	— 3.3	+ 5.9	— 3.9	+ 5.5
Mean	— 6.2	+ 2.8	— 3.5	+ 4.5	— 3.6	+ 4.8
Ca (g/day)						
K-H	— 0.20	+ 0.25	— 0.16	+ 0.73	— 0.20	+ 0.65
B-Z	— 0.12	+ 0.66	— 0.25	+ 0.84		
K-W						
Mean	— 0.16	+ 0.46	— 0.21	+ 0.79	— 0.20	+ 0.65
P (g/day)						
K-H	— 0.58	+ 0.46	— 0.48	+ 0.68	— 0.43	+ 0.65
B-Z	— 0.77	+ 0.40	— 0.50	+ 0.57		
K-W						
Mean	— 0.68	+ 0.43	— 0.49	+ 0.63	— 0.43	+ 0.65
Na (meq/day)						
K-H	—34.8	+24.8	—12.9	+35.2	—16.5	+31.4
B-Z	—20.0	+31.8	—25.4	+40.0		
K-W	—37.6	+19.1	— 7.0	+17.6	—21.7	+ 3.7
Mean	—30.8	+25.2	—15.1	+30.9	—19.1	+17.5
K (meq/day)						
K-H	—29.2	+18.3	—22.5	+39.0	—23.9	+33.5
B-Z	—33.3	+48.0	—24.0	+48.0		
K-W	—53.5	+46.0	—10.0	+21.4	—40.7	+17.4
Mean	—38.7	+37.4	—18.8	+36.1	—32.3	+25.4

hanced. It cannot be judged whether this is a rebound phenomenon or a continued action of the HGH injections.

The mean nitrogen loss during the HGH period is less than in the first period and equal to that in the third period. Usually there is a gradual decline in nitrogen excretion in consecutive periods of starvation.[13] Our findings could therefore be explained as an indication of a slight nitrogen-sparing action of HGH.

In Fig. 2 the complete nitrogen balance is shown for all cases. As the urine has been sampled in 2-day periods, it is possible that an acute effect of the HGH injections might have escaped our attention, but the figure proves that there is no cumulative effect. As the patients had been on a 600 kcal diet for about a week before the investigation started, the nitrogen balance is in equilibrium or slightly positive during the first 12-day period. The successive 600 kcal periods after starvation show an increasingly positive nitrogen bal-

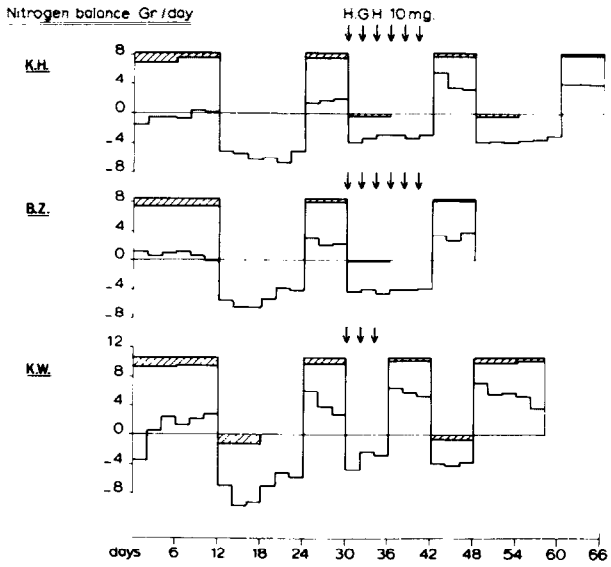

Fig. 2

ance, indicating that protein loss is limited considerably by intermittent starvation, but no influence of HGH can be seen.

DISCUSSION

In our study remarkably little effect of HGH administration was seen. The biological activity of the preparation used cannot be doubted, as it gave good therapeutic results in children with pituitary infantilism. Felig et al. gave 5 mg twice daily during 3 days; Drenick et al. 12–18 mg of a less active preparation (1 mg approximating 1 USP unit, whereas ours equalled 1½ USP unit), but the effects were already visible in both studies on the first day of administration. Although we did not aim at the detection of acute changes, similar effects could not have been missed in our study, neither can the differences in dosage explain the discrepancy of the results.

The most likely explanation for the difference in results is the fact that we started HGH during the first days of starvation while the other authors gave it after withholding food for at least 26 days. It is conceivable that the effect of HGH depends on the stage of depletion at which it is applied. For our problem the results obtained in an experiment of relatively short duration seem appropriate, as the metabolic differences between the normal subjects and the obese manifest themselves already during the first days of starvation.

From our results HGH appears not to be ketogenic but rather to induce higher values of pH and bicarbonate and lower levels of OHBA. The observations in patient B-Z might give a clue to the mechanism. In this patient, the only one in whom blood was drawn 24 hr after HGH, very high insulin levels were found during the HGH period; OHBA levels were then lower, although those of FFA surpassed those of the preceding period. It is well known that HGH stimulates pancreatic insulin secretion, and there is evidence that it might inhibit ketone body formation at the level of acetylcoenzyme A.[14] The findings in patient B-Z might be interpreted as the results of FFA mobilization and

simultaneously an antiketotic effect through stimulation of insulin release.

It is remarkable that these high insulin values did not cause hypoglycemia. The blood sugar level was apparently sustained by the anti-insulin action of HGH.

Drenick et al. found increased nitrogen loss during HGH.[4] Felig et al. found no change in the nitrogen balance.[5] They showed that retention of urea nitrogen was compensated by enhanced excretion of ammonia. In our study, urinary ammonia was not determined. As there was no increase in keto-acidosis, higher output of ammonia is improbable. The balance data are in agreement with a slight nitrogen sparing action of HGH. The diminished excretion of potassium points in the same direction.

Bray[15] has reported on a calorigenic action of HGH in fasting obese. In our study oxygen consumption was not measured. The weight changes found in our patients (Table 3) do not indicate that administration of HGH led to an increased calorie expenditure, even if the masking effect of fluid retention is taken into account.

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