Normalization of Growth Hormone Hyperresponse to Exercise in Juvenile Diabetics after "Normalization" of Blood Sugar

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ABSTRACT The serum-growth hormone response to exercise is greater and occurs earlier in juvenile diabetics than in nondiabetics. A simple exercise test has been devised which unequivocally reveals the growth hormone hypersecretion of juvenile diabetics. Using this procedure we have shown that after a period of exceedingly strict metabolic control of the diabetes, complete normalization of growth hormone secretion is attained. It is concluded that the abnormalities in serum growth hormone found in juvenile diabetics are of a metabolic origin.

INTRODUCTION

In an earlier report (1) we demonstrated a striking difference in the serum-growth hormone response to exercise between juvenile diabetics and normal subjects. We found that a certain moderate work load (450 kg/min for 20 min) would induce a high rise in serum growth hormone in diabetics, while no rise occurs in normal subjects. The abnormal growth hormone response to exercise in the diabetics was observed when the patients were in poor control as well as when they were in clinically very good control (fasting blood glucose level on the day of the experiment between 100 and 140 mg/100 ml). However, the abnormal serum-growth hormone response was significantly diminished when exceedingly strict control was achieved (fasting blood glucose level on the day of the experiment between 60 and 100 mg/100 ml). In two of these experiments, an entirely normal growth hormone pattern was observed. The diurnal blood sugar level in these exceedingly strictly controlled diabetics had been below 200 mg/100 ml at least 2 days before the experiments.

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The present study was undertaken in order to elucidate whether the growth hormone hyperresponse to exercise could be totally normalized in diabetics after longer periods with diurnal blood sugar levels in the normal range from 80 to 120 mg/100 ml.

METHODS

Six young, newly diagnosed, untreated nonobese male patients with classic juvenile diabetes were selected for the study. The general data of the diabetics are given in Table I.

The patients were studied with an exercise test before insulin treatment, and with two to four exercise tests during a period of increasingly strict insulin treatment, where insulin (regular and NPH [neutral protamin Hagedorn])[1] was given two to four times a day in order to obtain a diurnal blood sugar level as close to normal levels as possible, without inducing hypoglycemic episodes. Levels of blood sugar were measured at least three times a day: 7 a.m. (in fasting state), 1 p.m. (1 hr after lunch), and 5 p.m. (just before dinner). After a period of 7–13 mon where the patients had been followed in the outpatient clinic, five of them were admitted to the department again for another exercise test. The day before this test, insulin was withdrawn in order to obtain less rigid metabolic control. Total CO_2 in serum on the day of the experiment in these patients was 22–28 mEq/liter.

The experimental procedure was identical to that described in the earlier paper (1). The procedure had been carefully explained to all of the diabetics and they had tried the experimental apparatus before the first experiment was done. They were not allowed to rise from bed during the night before the exercise experiments. Before the start of the experiment, between 7 and 8 a.m., after 12 hr fasting, they were transported in their beds to the laboratory and placed on a couch with an attached bicycle ergometer (AB Cykelfabrikken Monark, Varberg, Sweden). The subjects were supine during the entire experimental period. The exercise load was 450 kg/min for 20 min. Blood was taken through an indwelling catheter inserted into an antecubital vein.

[1] *Abbreviations used in this paper:* FFA, free fatty acids; NPH, neutral protamin Hagedorn insulin.

The blood samples were immediately chilled in ice water. After clotting they were centrifuged and serum was stored at −20°C until analysis. Blood glucose was measured by a glucose oxidase method (2) with exception of the blood sugars taken at 7 a.m., 1 p.m., and 5 p.m. each day; these were determined by the standard o-toluidine method of the Clinic (3). This method gives in our hands, results which are 10–30 mg/100 ml higher than values obtained with the glucose oxidase method. Serum free fatty acids were determined by a colorimetric method (4). Serum growth hormone was determined by a single antibody radioimmunoassay employing wick chromatography (5). For growth hormone standard a Wilhelmi preparation (HS 968 C) was used.

RESULTS

Figs. 1 and 2 show the average daily blood sugar values, i.e. the average of the three determinations at 7 a.m., 1 p.m., and 5 p.m. in patient 1–4 during their hospitalization and the growth hormone results from the individual exercise experiments in the same patients. Tables II and III show the growth hormone, glucose, and free fatty acid values during the individual experiments in patients 5 and 6.

The average daily blood sugar values during the period before treatment ranged between 200 and 550 mg/100 ml and there was considerable day to day variations in most of the patients. Successful normalization of the average daily blood sugar level for several days was obtained during insulin treatment in all patients. In the five patients who were reexamined after 7–13 months of treatment in the outpatient clinic, four showed average daily blood sugar values between 230 and 380 mg/100 ml. However, one patient (patient 4) showed a normal daily blood sugar level, although he received no insulin on the day preceeding the experiment.

There was an immediate and high serum-growth hormone response to exercise in all the six patients, when the experiments were performed before insulin treatment. With progressive lowering of the mean blood glucose level during treatment the growth hormone response to exercise became more delayed and showed lower maximum values, until finally no rise occurred. This general pattern of growth hormone normalization was evident in patients 1–5. In patient 6, however, there

TABLE I

The General Data of the Six Diabetics Examined

Case No.	Age	Height	Weight	Total CO_2§	Average insulin dose during good control
	yr	*cm*	*kg*	*mEq/liter*	*Units*
1	22	183	69*–72‡	22	32 NPH 20 regular
2	25	170	65*–69‡	20	52 NPH
3	19	178	53*–59‡	25	48 NPH 8 regular
4	29	158	56*–60‡	16	44 NPH 8 regular
5	31	174	62*–62‡	25	20 NPH 12 regular
6	25	167	53*–63‡	27	44 NPH 8 regular

* Body weight before insulin treatment.

‡ Body weight after "normalization" of the daily blood sugar level.

§ Serum total CO_2 at the time of the first exercise experiment.

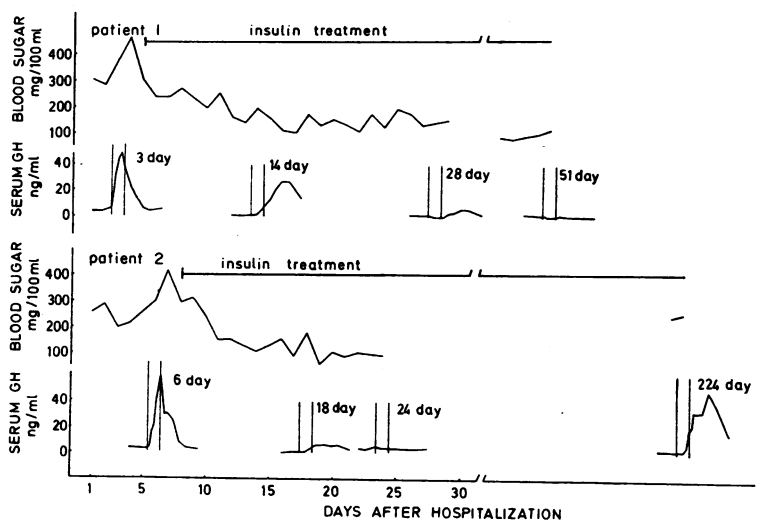

FIGURE 1 The patterns of normalization during hospitalization of diurnal blood sugar levels and serum-growth hormone responses to exercise in patients 1 and 2.

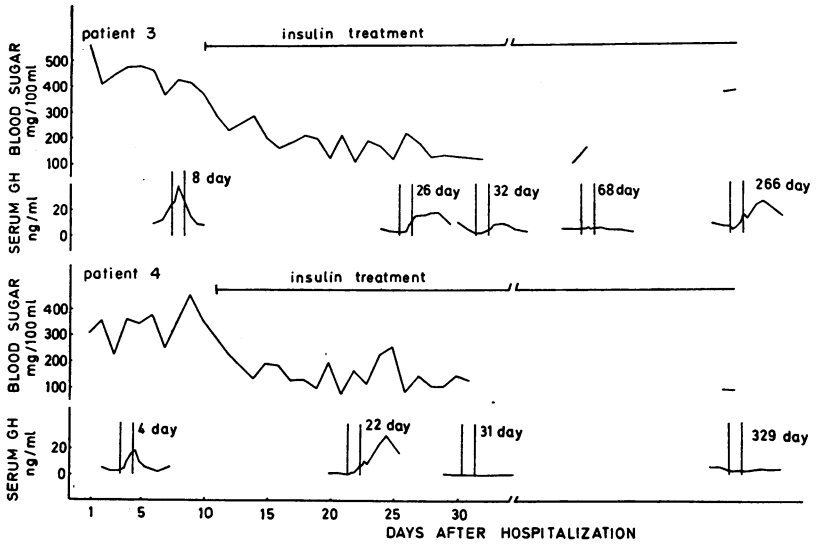

FIGURE 2 The patterns of normalization during hospitalization of diurnal blood sugar levels and serum-growth hormone responses to exercise in patients 3 and 4.

was no tendency to lowered and delayed responses during the first part of the normalization period. In four of the five patients retested in less rigid control, the growth hormone responses to exercise were abnormal again, showing immediate and high rises; on two occasions the rises were even higher than observed in the pretreatment experiments. In the patient who showed a normal daily blood sugar level when retested, no rise in growth hormone during exercise was observed.

When the areas of the growth hormone curves during the 20 min of exercise and during the first 30 min after exercise are used as an expression of the exercise-induced growth hormone "production," significant correlations were found between growth hormone production and average daily blood sugar levels 1, 2, and 3 days before the experiments ($r = 0.4819$ $P = 0.01$, $r = 0.4633$ $P < 0.05$ and $r = 0.4571$ $P < 0.05$). Fig. 3 shows the correlation between the areas of the growth hormone curves and the average daily blood sugar concentration 1 day before the exercise experiments. There

TABLE II

Serum Growth Hormone (ng/ml), Blood Glucose (mg/100 ml), and Serum Free Fatty Acids (μEq/liter) in Patient 5

	Preexercise			Exercise					Postexercise					
	min				*min*					*min*				
	− 30	− 15	0	3	6	10	15	20	3	6	10	20	30	40	60
Experiment (6 days after admission)															
GH	2.4	0.5	1.1		1.7	14	3.5	5.0			7.0	6.5	5.2		
BS	226	235	239		248	236	236	231			248	230	226		
FFA	1170	870	590		680	360	1020	1410			1110	940	620		
Experiment (27 days after admission)															
GH	0.5	0	0.6	0.2	0.4	1.9	5.4	7.8	9.6	11	10	6.2	4.2	2.3	1.2
BS	133	138	130	136	135	131	140	133	138	142	142	136	149	149	132
FFA	540	500	480	530	470	540	650	720	1020	1120	1250	710	660	580	580
Experiment (33 days after admission)															
GH	1.8	0.5	0	0	0	0.3	0.7	1.2	1.6	2.8	2.0	1.2	0.6	0.8	1.0
BS	70	71	70	69	70	71	71	73	70	71	73	73	72	71	71
FFA		760	750	510	450	430	520	440	580	910	1040	790	640	560	540
Experiment (264 days after admission)															
GH	2.1	0.7	2.8	2.6	3.0	4.2	9.2	17	28	41	55	51	34	23	9.6
BS	235	237	219	221	233	225	215	217	220	214	215	210	204	202	202
FFA	790	750	810	490	630	570	360	510	680	1030	900	740	400	460	550

TABLE III

Serum Growth Hormone (ng/ml), Blood Glucose (mg/100 ml), and Serum Free Fatty Acids (μEq/liter) in Patient 6

	Preexercise				Excerise					Postexercise					
	min				*min*							*min*			
	− 30	− 15	0	3	6	10	15	20	3	6	10	20	30	40	60
Experiment (3 days after admisssion)															
GH	7.0	8.4	8.7	8.4	12	12	12	9.2	6.7	5.9	4.9	3.5	2.5	3.0	8.4
BS	220	234	229	230	232	232	236	236	237	234		240	240	239	238
FFA	920	870	850	900	840	860	1130	1350	1660	1890	1750	1260	960	670	740
Experiment (18 days after admission)															
GH	13	6.4	4.5	4.0	6.0	12	14	17	15		14	10	7.4	6.5	5.5
BS	84	98	111	116		120	124	121	125		125	131	135	137	148
FFA	320	500	540	360	520	510	420	440	480		670	570	530	430	250
Experiment (33 days after admission)															
GH	6.1	6.0	7.3	7.4	7.4	11	17	21	22	19	22	16	12	11	8.1
BS	76	82	85	84	84	86	85	85	83	82	84	83	83	85	89
FFA	170	150	220	180		170	170	160	210	200	220	200	260	230	260
Experiment (41 days after admission)															
GH	5.6	6.1	5.9	5.9	7.4	10	20	23	24	24	22	13	9.7	7.0	3.6
BS	78	81	84	86	83	84	84	88	92	91	92	94	94	95	98
FFA	360	390	320	270	280	270	240	270	320	380	420	360	370	390	450
Experiment (103 days after admission)															
GH	5.8	4.4	4.1	3.2	2.8	3.0	3.1	2.2	2.4	2.5	2.9	2.1	1.7	1.5	2.1
BS	67	70	73	69	68	69	67	69	75	66	69	78	74	73	75
FFA	710	780	760	540	660	660	750	710	1260	1410	1270	1070	870		480
Experiment (399 days after admission)															
GH	5.3	3.9	5.4	5.6	8.9	14	36	77	80	78	78	72	57	44	21
BS	225	226	223	226	225	225	231	220	223	225	220	221	220	225	217
FFA	1270	910	830	340	620	680	740	630	1190	1190	1280	970	820	820	1040

was also a significant correlation between growth hormone areas and the actual fasting blood glucose level on the day of the experiments ($r = 0.4921$ $P < 0.01$).

The average preexercise serum-growth hormone value in the six diabetics was significantly higher in the pretreatment experiments than in the experiments where no serum-growth hormone response to exercise was observed, 5.90 ±1.30 ng/ml as compared to 2.82 ±0.47 ng/ml (Mean ±SEM), ($P < 0.05$). There was a significant correlation between the preexercise serum-growth hormone values and the actual fasting blood glucose level on the day of the experiments ($r = 0.3805$ $P = 0.05$). However, no statistically significant correlation could be demonstrated in this series of experiments between the preexercise serum-growth hormone values and the average daily blood sugar levels 1, 2, and 3 days before the experiments.

The serum FFA values from the individual exercise experiments in patients 5 and 6 are seen in Table II and III. The general pattern of serum FFA was the same in all exercise experiments in all patients. There was a fall immediately after beginning of exercise followed by an increase, reaching a maximum value which was higher than the fasting value a few minutes after the cessation of work. The average preexercise serum

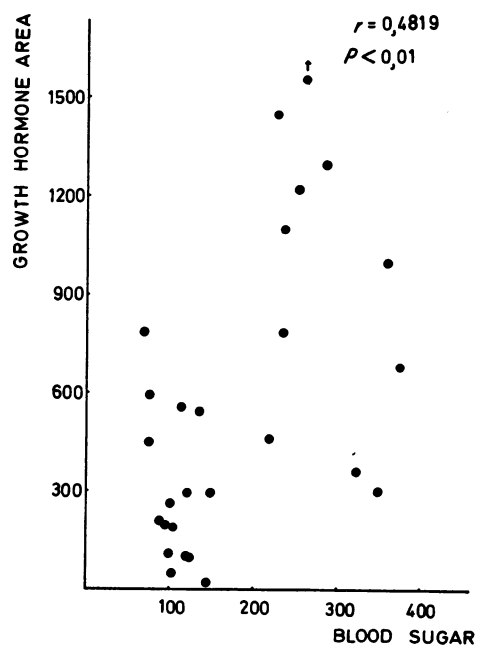

FIGURE 3 The correlation between the areas of the growth hormone curves (arbitrary units) and the average daily blood sugar concentration (in mg/100 ml) 1 day before the exercise experiments.

FFA value was significantly higher in the pretreatment experiments than in the experiments where no serum-growth hormone response to exercise was observed, 974 ±60 μEq/liter as compared to 563 ±53 μEq/liter (Mean ±SEM) ($P < 0.01$). This was also the case with the average maximum serum FFA values obtained a few minutes after the cessation of work, 2122 ±174 μEq/liter as compared to 872 ±163 μEq/liter ($P < 0.01$). As could be expected, there was a correlation between preexercise serum FFA values and preexercise blood glucose values ($r = 0.5769$ $P < 0.01$). However, no statistically significant correlation could be demonstrated between preexercise serum FFA values and the serum-growth hormone areas. Nor was there any significant correlation between preexercise serum FFA values and preexercise serum-growth hormone values.

DISCUSSION

This study demonstrates that the exercise induced serum-growth hormone hypersecretion as well as the elevated fasting serum-growth hormone in juvenile diabetics can be totally normalized after some days of very strict diabetic control with diurnal blood sugar levels in the normal range from 80 to 120 mg/100 ml.

Progressive lowering of the mean blood sugar level resulted in growth hormone responses to exercise that were more delayed and showed lower maximum values, until finally no rise in serum growth hormone occurred when the blood sugar level was completely normal. This pattern cannot be caused by a decreasing degree of what is usually called "stress" during the period of progressive lowering of the mean blood sugar level. Firstly, great care was taken to familiarize the patients with the procedure before the experiments were started. Secondly, abnormal growth hormone responses were again observed in the four patients reexamined at a later time in less rigid control.

All diabetics, except one, showed an increase in body weight during insulin treatment as could be expected (Table I). Malnutrition is known to produce elevated serum-growth hormone values (6). However, the changes in body weight from low values to normal values during treatment could not explain the growth hormone normalization pattern, because the growth hormone hyperresponse to exercise was observed again in the four patients after they had been well treated with insulin in the outpatient clinic for 7–13 months. During this period they had maintained normal weight.

We therefore believe that the growth hormone hypersecretion in juvenile diabetics is caused by the diabetic metabolic state.

In our 24-hr studies (7) we found that the elevated and wildly fluctuating serum-growth hormone levels observed during day and night in untreated and poorly controlled juvenile diabetics became significantly less elevated and less fluctuating after strict insulin treatment. However, total normalization of the diurnal blood glucose and diurnal growth hormone pattern was not achieved in these experiments.

A normal diurnal blood sugar level on the days preceeding the experiment may be more important in producing a normal growth hormone response to exercise, than a normal fasting blood glucose level on the day of the experiment. Statistical correlations of the same order of magnitude were calculated between growth hormone production and fasting blood glucose on the day of the experiment, and between growth hormone production and average diurnal blood sugar levels on the days preceeding the experiments. Nevertheless, it was found that on five occasions, fasting blood glucose levels on the day of the experiments were in the normal range whereas diurnal blood sugar levels and growth hormone responses to exercise were elevated. On one occasion, fasting blood glucose level was elevated whereas diurnal blood sugar levels and growth hormone response to exercise were normal (data not shown). This conclusion is further strengthened by reexamining the results from an earlier study (1). In the exceedingly strictly controlled diabetics described in that paper, the fasting blood glucose level was between 60 and 100 mg/100 ml on the day of the experiments but the diurnal blood sugar levels were about 200 mg/100 ml on the days preceding the experiments. Only two out of eight diabetics in this series showed a normal growth hormone response to exercise.

The two most characteristic changes in the serum FFA pattern during the normalization period were the decrease in preexercise values as well as the decrease in the maximum values obtained few minutes after the cessation of work. Both had reached normal values in all diabetics before normalization of the serum-growth hormone pattern had occurred. This indicates that the normalization of the serum FFA during fasting and in response to exercise takes place at a higher blood glucose level than the normalization of serum growth hormone. The same conclusion has been drawn from results published earlier (1). It seems unlikely, therefore, that the rise in serum FFA during exercise should be initiated by a rise in serum growth hormone.

It appears from the series of exercise experiments before the state of complete normalization that high rises in serum growth hormone occur during exercise even when the diabetics are in good clinical control. The growth hormone abnormality does not disappear until after a period of exceedingly strict diabetic control, a degree of normalization which is not obtainable

in clinical practice. This means that diabetic patients, at least male juvenile diabetics as studied here, are exposed throughout their daily life to markedly elevated and rapidly changing levels of growth hormone and that very moderate work performances as required of all young diabetics will increase serum growth hormone to very high levels.

The increased growth hormone level in diabetics may well be of considerable clinical importance. Elsewhere we have presented evidence for the hypothesis that growth hormone hypersecretion may be responsible, at least partly, for the vessel abnormalities found in nearly all diabetics after many years of diabetes (8).

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