Abnormal Serum Growth Hormone Response to Exercise in Juvenile Diabetics

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ABSTRACT Groups of male nonobese juvenile diabetics with recent onset, short term (1–8 yr), and long-term (12–30 yr) diabetes as well as comparable nondiabetic controls were studied during exercise experiments. The chosen exercise load, 450 kg/min for 20 min never induced changes in serum growth hormone in our nondiabetic control subjects.

The principal results of the study were as follows: (*a*) an immediate high rise in serum growth hormone followed the commencement of exercise in all diabetics. The increase and pattern of serum growth hormone was not related to the duration of the diabetes. (*b*) The abnormal growth hormone response to exercise in diabetics was observed when the patients were in poor control as well as when they were in clinically excellent control (fasting blood glucose level between 100 and 140 mg/100 ml). (*c*) However, the abnormal serum growth hormone response was significantly diminished when exceedingly strict control was achieved (fasting blood glucose level between 60 and 100 mg/100 ml). In two of these experiments an entirely normal growth hormone pattern was obtained. (*d*) The change in serum growth hormone pattern during regulation was totally unrelated to the changes in serum free fatty acid patterns. A normal free fatty acid level and exercise pattern was obtained much earlier during the improved control. (*e*) Fasting serum growth hormone levels were also significantly raised in the juvenile diabetics irrespective of the diabetes duration. (*f*) Fasting serum growth hormone levels were also significantly decreased during regulation. Furthermore, a significant *correlation* between blood glucose and fasting serum growth hormone concentration was established. (*g*) In the juvenile diabetics a significant increase in serum insulin was observed at the point of time when exercise was concluded.

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INTRODUCTION

Recently a few reports have indicated abnormalities of serum growth hormone in diabetes mellitus during fasting, throughout a 24 hr period of daily life, and in response to various stimuli (1–9). Strong exercise is a potent stimulus for growth hormone secretion in normal subjects (10–12). The present study was undertaken in order to investigate the fasting level of serum growth hormone and the response to exercise in juvenile diabetics. The significance of the duration of diabetes and the metabolic state during the experiments was also investigated.

METHODS

A control group and three groups of diabetics (group A, B, and C) with juvenile type diabetes of varying duration were selected for the study (Table I).

The control group consisted of eight young healthy nonobese male subjects with no family history of diabetes. Their total body fat content, measured with tritiated water (13), was 18.1 ±1.8% of their body weight.

Group A consisted of six young newly diagnosed untreated nonobese male patients with classic juvenile diabetes. In none of these patients was a rise of serum insulin observed during oral glucose tolerance tests, characterizing them as cases of classic juvenile diabetes. Only one of them had mild acidosis during the first experiment before treatment (patient 13). Their total body fat content was 14.8 ±1.2% of their body weight. The difference in body fat content between the control subjects and the newly diagnosed diabetics is not statistically significant.

Two experiments were performed in each patient. The first experiment was done before the patients were treated with insulin and the next experiment was done after 2–6 wk of intensive insulin treatment. Patients 12 and 13 were examined twice after institution of insulin treatment, once when the blood glucose level had fallen somewhat and again when it had become nearly normal. Patient 14 was examined on 2 successive days before insulin treatment, but not after insulin treatment.

Group B consisted of six young nonobese male juvenile diabetics who had had their disease for only a few years (1–8 yr). None of them had signs or symptoms of angiopathy. In two of the patients total CO_2 in plasma was

TABLE I

Clinical Data for All Subjects Investigated

Case No.	Age	Height/ weight	Diabetes duration	Diabetic angiopathy	Tota CO_2
	yr	*cm/kg*	*yr*		*mEq/liter*
Control subjects					
1	20	180/72			
2	38	177/71			
3	25	180/70			
4	25	178/65			
5	25	181/71			
6	25	174/62			
7	24	190/89			
8	23	174/71			
Mean	26	179/71			
Newly diagnosed juvenile diabetics (group A)					
9	38	182/81		0	23
10	17	174/63		0	21
11	16	176/52		0	27
12	22	181/64		0	22
13	20	178/64		0	14
14	20	181/69		0	25
Mean	22	179/66			22
Juvenile diabetics with few years duration of diabetes (group B)					
15	22	185/73	7	0	19
16	23	175/68	1	0	25
17	17	184/77	3	0	28
18	16	173/68	6	0	22
19	18	172/57	1	0	24
20	30	175/72	8	0	14
Mean	21	177/69	4	0	22
Juvenile diabetics with many years duration of diabetes (group C)					
21	24	168/70	12	0	11
22	22	176/59	18	Mild retinopathy	18
23	26	177/60	19	Mild retinopathy Mild nefropathy	20
24	31	168/67	30	Proliferative retinopathy Mild nefropathy	24
25	23	175/63	19	0	16
26	28	181/72	15	Mild retinopathy	26
27	26	178/64	13	Mild retinopathy Mild nefropathy	20
Mean	26	175/65	18		19

Serum total CO_2 at the end of the experiment in poor control.

found to be slightly or moderately reduced during the experiments in poor control.

Group C consisted of seven young nonobese male juvenile diabetics after many years of diabetes (12–30 yr). Five of the patients had angiopathy. However, serum creatinine was below 1.3 mg/100 ml in all of them. Total CO_2 in plasma was slightly to moderately reduced in five of the patients during the experiments in poor control. Total body fat content was not measured in all of the patients in group B and C. However, the height and weight of the subjects in the four groups were very similar.

All the patients in group B and C were examined during good as well as during poor control. Good control was defined as a condition in which blood glucose concentrations at 7 a.m., 1 p.m., and 5 p.m. were below 200 mg/100 ml for at least 2 days before the experiment. Most of the patients defined as being in good control received insulin in the evening as well as in the morning, but the evening injection was never given later than 5 p.m. the day before the experiment and no morning injection was given on the day of the experiment. Poor control was defined as a condition in which blood glucose concentrations at the same points of time were higher than 200 mg/100 ml for at least 2 days before the experiment. Usually it ranged between 250 and 350 mg/100 ml. In this experimental condition the patients were off insulin for at least 24 hr before the experiment.

In some of the patients the first experiment was performed in good control, and in others in poor control to avoid any one-sided influence on the serum growth hormone patterns caused by the possible greater stress of going through the investigation for the first time.

The procedure had been carefully explained to *all the subjects* and they had all tried the experimental apparatus the day before the study. They slept in the medical ward the night before the study and they were not allowed to rise from bed in the morning. 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 (Monark, 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. Arterial blood was not used as it had been reported (14) that insertion of arterial catheters may induce growth hormone release.

Oxygen consumption and respiratory quotient (RQ) were measured employing Noyons Diaferometer before, during, and after exercise. To exclude false RQ values no determinations were made during the first 15 min of exercise and during the first 15 min of rest after exercise.

The blood samples were immediately chilled in ice-water. After clotting they were centrifuged and stored at −20°C until analysis. Blood glucose was measured by a glucose oxidase method (15) and serum free fatty acids by a colorimetric method (16). Blood lactate was measured by Boehringers Lactate UV method. Serum insulin and serum growth hormone were determined by a single antibody radioimmunoassay employing wick chromatography (17). Serum insulin was measured only in group A of the diabetics. These patients were treated with comparatively large and frequent doses of insulin for 2–6 wk before "good control" was achieved. The serum samples obtained from the experiments during this period were therefore always examined for the presence of insulin antibodies. The results were negative in all cases except one in which the determination of serum insulin proved to be possible after dilution (18). In this case no binding of radioactive human insulin could be demonstrated employing a 1 10 dilution of serum before paper chromatography. Accordingly this dilution was used in the assay of that patient. Human insulin (NOVO, NOVO Industri A/S, Copenhagen, Denmark) was used for the preparation of insulin standards and a Wilhelmi preparation HS 968 C was used for growth hormone standard.

For statistical calculations Student's *t* tests were employed.

RESULTS

The blood glucose values in the control subjects and in the three groups of diabetics are seen in Fig. 1 and in Tables II, III, IV, and V. It appears from the average values that the patients in group A had not attained the

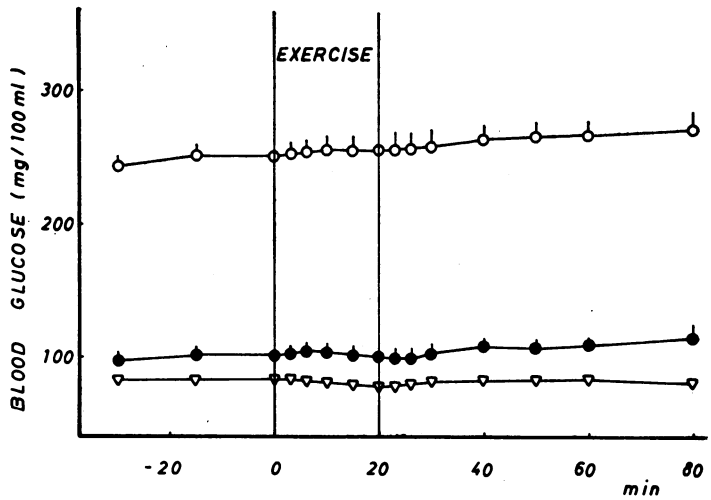

FIGURE 1 Blood glucose levels at rest and during exercise in the normal subjects ▽——▽, in all diabetics examined during poor control ○——○, and in all diabetics examined during good control ●——● (mean ±SEM, the SEM of the normal subjects were too small for illustration).

same degree of normalization as did the patients in group B and C. In the experiments in poor control the average blood glucose concentrations in group B and C were similar to the values in group A before insulin treatment. No significant variations in blood glucose were seen in any of the groups during exercise.

The average values and patterns of blood lactate, RQ, oxygen consumption, and serum free fatty acids during the experiments in good as well as during poor control were identical in the three groups of diabetics. Therefore, these three groups of diabetics are considered as one group in the further discussion of these parameters.

Fig. 2 shows the average blood lactate values in the control subjects and in the diabetics during experiments in poor and good control. The preexercise values and the rise during exercise were very similar in the control subjects and in the diabetics. The average rate of fall in the postexercise period was slower in the diabetics examined during poor control than during good control. However, the difference is not statistically significant.

The average resting RQ (Fig. 3) was low in the diabetics examined during poor control, as was to be expected, and increased after intensive insulin treatment. The difference in resting RQ between the experiments in poor control and good control was statistically significant ($P < 0.001$). The resting RQ's of the diabetics in good control were identical with that of the control subjects. A rise of the same order of magnitude occurred during exercise in the control subjects and in

TABLE II

Serum Growth Hormone (ng/ml), Serum Insulin (μU/ml), and Blood Glucose (mg/100 ml) in the Control Subjects

	Preexercise			Exercise					Postexercise						
	−30	−15	0	3	6	10	15	20	3	6	10	20	30	40	60
		min				*min*						*min*			
Growth hormone															
Mean	0.34	0.68	0.63	0.56	0.49	0.42	0.64	0.32	0.59	0.83	1.04	0.94	1.42	2.06	3.10
SEM	0.20	0.27	0.34	0.18	0.33	0.21	0.27	0.20	0.26	0.33	0.41	0.60	0.96	1.44	2.73
Insulin															
Mean	15.1	13.8	15.0	15.0	12.5	12.9	13.4	11.6	12.1	15.4	14.8	17.8	18.3	16.4	15.6
SEM	2.9	2.5	3.0	3.6	2.8	3.6	3.0	3.0	3.4	2.6	3.6	3.9	4.8	3.4	3.7
Glucose															
Mean	82.8	83.1	84.0	84.1	82.9	81.6	79.4	78.0	79.0	80.6	82.3	82.9	82.4	83.8	81.4
SEM	2.0	1.6	1.9	2.5	2.2	2.5	2.2	1.8	2.1	1.8	2.7	2.2	2.2	2.5	2.1

The complete data for all of the subjects studied can be obtained from the National Auxiliary Publication Service.

TABLE III

Serum Growth Hormone (ng/ml), Serum Insulin (μU/ml), and Blood Glucose (mg/100 ml) in the Newly Diagnosed Juvenile Diabetics (Group A)

	Preexercise			Exercise					Postexercise						
	−30	−15	0	3	6	10	15	20	3	6	10	20	30	40	60
		min				*min*						*min*			
							Before treatment								
Growth hormone															
Mean	9.72	11.4	11.9	18.4	26.5	40.0	45.9	43.2	35.6	35.1	27.7	18.3	15.1	12.9	12.3
SEM	3.73	3.61	3.99	5.68	7.09	9.72	10.1	8.11	5.61	5.79	5.83	4.24	3.85	2.87	3.23
Insulin															
Mean	7.6	9.6	9.4	9.1	8.9	8.4	9.9	11.4	10.6	14.4	13.7	12.6	10.7	9.7	10.1
SEM	2.3	2.3	2.4	2.1	2.1	2.2	2.7	2.4	2.8	3.6	2.7	2.6	3.1	2.6	3.1
Glucose															
Mean	231.1	235.9	235.0	235.7	235.9	231.2	232.3	228.1	226.4	225.7	225.7	228.4	229.3	229.0	240.3
SEM	11.4	10.8	11.0	11.4	11.7	14.9	13.5	15.1	14.8	15.6	15.3	15.2	16.1	15.3	14.9
							After treatment								
Growth hormone															
Mean	5.13	5.37	4.30	5.90	5.90	12.3	17.8	24.5	30.9	30.6	24.3	17.9	17.9	16.7	9.38
SEM	3.98	3.94	2.39	1.74	2.01	4.97	6.58	6.26	8.19	8.90	6.66	4.51	5.69	5.36	2.79
Insulin															
Mean	13.2	9.5	9.7	8.8	8.2	8.2	10.5	9.3	6.0	10.2	10.2	9.3	9.0	8.7	8.4
SEM	1.7	1.6	1.5	0.8	0.8	1.4	2.3	1.7	1.5	1.4	1.9	1.3	1.9	1.6	2.2
Glucose															
Mean	111.7	114.0	113.7	113.2	113.5	112.5	110.7	108.5	106.8	107.0	108.8	111.0	113.0	112.8	112.5
SEM	5.2	5.1	4.8	5.6	5.8	5.3	5.2	5.5	6.4	5.9	6.3	6.9	6.9	7.2	7.6

The complete data for all of the subjects studied can be obtained from the National Auxiliary Publication Service.

the diabetics whether they were examined during good or poor control.

Table VI shows the oxygen consumption at rest and during exercise. The resting values and the rise during exercise are the same in the diabetics during good and poor control and identical to the values obtained in the control subjects.

The general pattern in serum free fatty acids obtained

TABLE IV

Serum Growth Hormone (ng/ml) and Blood Glucose (mg/100 ml) in the Juvenile Diabetics with Few Years Duration of Diabetes (Group B)

	Preexercise			Exercise					Postexercise						
	−30	−15	0	3	6	10	15	20	3	6	10	20	30	40	60
		min				*min*						*min*			
							Good control								
Growth hormone															
Mean	7.90	6.67	5.78	6.17	8.35	11.8	14.2	12.2	13.8	16.3	15.3	12.4	11.2	11.5	7.42
SEM	5.27	4.50	3.88	4.40	5.37	7.76	8.45	5.33	5.33	6.13	6.43	4.85	4.77	4.65	2.87
Glucose															
Mean	94.5	102.8	104.7	106.7	107.7	108.8	102.0	105.3	102.2	102.8	108.7	113.2	111.0	114.0	119.0
SEM	10.3	11.7	11.3	12.2	12.1	11.5	11.9	10.3	11.3	11.3	10.0	11.0	12.8	12.9	12.9
							Poor control								
Growth hormone															
Mean	7.68	7.67	11.2	12.1	15.7	20.7	24.6	28.3	31.6	25.9	27.8	15.4	12.4	14.0	11.0
SEM	3.90	3.98	4.15	4.55	5.77	7.57	6.47	6.83	9.96	6.10	8.83	4.50	3.83	5.68	3.25
Glucose															
Mean	239.7	247.3	253.0	247.0	248.5	254.3	253.8	256.3	256.0	254.4	260.5	264.8	268.8	268.0	264.8
SEM	19.7	21.0	19.9	19.5	20.3	20.7	22.8	23.5	24.3	29.9	24.6	24.7	25.0	25.0	25.1

The complete data for all of the subjects studied can be obtained from the National Auxiliary Publication Service.

TABLE V

Serum Growth Hormone (ng/ml) and Blood Glucose (mg/100 ml) in the Juvenile Diabetics with Many Years Duration of Diabetes (Group C)

	Preexercise			Exercise					Postexercise						
	−30	−15	0	3	6	10	15	20	3	6	10	20	30	40	60
		min				*min*						*min*			
						Good control									
Growth hormone															
Mean	3.80	8.17	13.0	14.8	22.4	26.4	29.6	29.0	31.4	29.7	18.3	18.8	19.2	17.8	14.9
SEM	1.55	3.47	5.55	6.54	10.6	12.5	12.1	10.8	11.3	11.2	6.40	6.28	6.27	6.51	6.28
Glucose															
Mean	79.4	84.7	93.2	88.4	90.3	89.3	87.6	85.1	85.6	85.3	86.9	93.7	92.4	96.7	109.2
SEM	8.0	10.0	12.2	11.8	12.1	11.3	11.1	10.2	10.6	10.4	10.5	12.7	12.0	13.7	18.7
						Poor control									
Growth hormone															
Mean	19.3	11.5	11.4	11.5	15.4	24.0	29.3	32.9	28.6	27.0	22.8	14.3	12.4	11.3	14.5
SEM	6.49	2.41	1.09	1.06	1.65	5.52	7.15	9.21	6.10	6.47	5.77	3.10	2.14	2.66	4.2
Glucose															
Mean	256.6	270.0	273.0	273.7	276.0	280.3	279.7	285.9	288.1	288.1	291.9	300.4	301.0	301.3	305.1
SEM	12.2	14.1	12.9	11.6	12.7	12.0	10.4	12.0	11.6	10.9	11.9	11.9	9.9	9.9	10.8

The complete data for all of the subjects studied can be obtained from the National Auxiliary Publication Service.

in the control subjects and in the diabetics was the same (Fig. 4). There was a fall immediately after start 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. However, in the experiments during poor control the preexercise values were significantly increased ($P < 0.001$) and the exercise-induced rise was very pronounced compared with the rise during good control. The average serum free fatty acid values in the control subjects and the values in the diabetics examined during good control were identical.

The serum growth hormone values in the control subjects and in the three groups of diabetics are seen in Tables II, III, IV, and V. Fig. 5 shows the average growth hormone values in the control subjects and in the three groups of diabetics examined during poor control. In the *control subjects* the average preexercise serum growth hormone value was 0.6 ng/ml and *no increase* was observed during exercise. The growth hormone pattern in the diabetics was strikingly different. The average preexercise serum growth hormone value in *group A* was 11 ng/ml. Immediately after start of exercise, it increased and then reached a mean maximum value of 46 ng/ml 15 min later. Basal values were

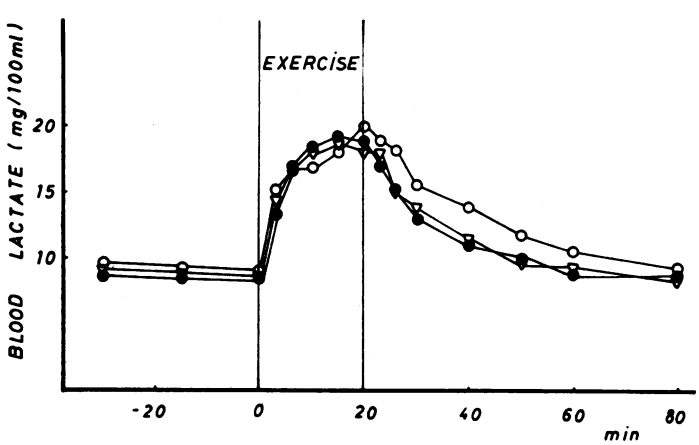

FIGURE 2 Average blood lactate values at rest and during exercise in the normal subjects ▽——▽, in all diabetics examined during poor control ○——○, and in all diabetics examined during good control ●——●.

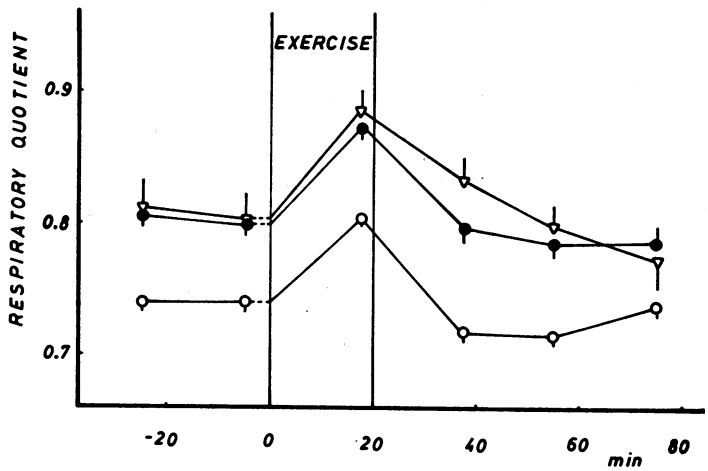

FIGURE 3 Respiratory quotient (RQ) at rest and during exercise in the normal subjects ▽——▽, in all diabetics examined during poor control ○——○, and in all diabetics examined during good control ●——● (mean ±SEM).

approached again after 40 min rest. The average preexercise serum growth hormone value in *group B* was 8.8 ng/ml and the mean maximum value during exercise was 32 ng/ml. The average preexercise serum growth hormone value in *group C* was 14 ng/ml and the mean maximum value during exercise was 33 ng/ml. The fact that the three average preexercise values were so different in this particular group was due to the presence of "spontaneous" peaks in some of the patients. Such abnormal peaks are known to occur more often in juvenile diabetics than in normals (9). It so happened that in group A and B very few peaks occurred. The average preexercise values were not significantly different in the three groups of diabetics. The average rise during exercise was higher in the untreated diabetics than in the other two groups of diabetics during the whole exericse period. However, this difference could not be shown to be statistically significant. The difference in preexercise values between diabetics and normals was, however, highly significant ($P < 0.001$).

The preexercise blood glucose levels achieved in the diabetics during the experiments in good control varied between 60 and 140 mg/100 ml. Eight patients had blood glucose levels below 100 mg/100 ml throughout the experimental period (patients 12, 15, 16, 21, 23, 25, 26, and 27). The serum growth hormone patterns of the remaining 11 diabetics (12 experiments) who had higher blood glucose levels than 100 mg/100 ml were not significantly altered after the attempt to obtain good control (Fig. 6). On the other hand, in the group with blood glucose levels below 100 mg/100 ml, the average serum growth hormone values before, during, and after exercise were lower during the experiments in good control than during the experiments in poor control (Fig. 7). This difference was statistically significant in the preexercise period ($P < 0.05$) employing the method of paired comparisons on the results. The difference was also statistically significant in the remaining experimental period in seven of the eight patients when the areas of the curves in good and poor control in the individual patients were compared with Student's t test, excluding the values 40 and 60 min after stop of work, where preexercise values had been obtained again. The seven patients in which the growth hormone values during and after exercise were lower during good than during poor control were patient 12 ($P < 0.001$), patient 15 ($P < 0.05$), patient 16 ($P < 0.05$), patient 21 ($P < 0.025$), patient 23 ($P < 0.001$), patient 25 (P

TABLE VI

The Cxygen Consumption (ml/min) in the Control Subjects and in the Diabetics during Good and Poor Control

	Pre-exercise	Exercise	Postexercise		
Control subjects					
Mean 234	231	1288	246	252	152
SEM 6.5	10.7	43.3	9.2	8.1	6.9
Diabetics in good control					
Mean 233	227	1201	244	233	228
SEM 5.9	6.3	27.9	6.7	5.9	7.9
Diabetics in poor control					
Mean 249	249	1251	275	258	259
SEM 6.0	6.1	42.0	8.5	6.5	6.2

The results are expressed as mean and SEM.

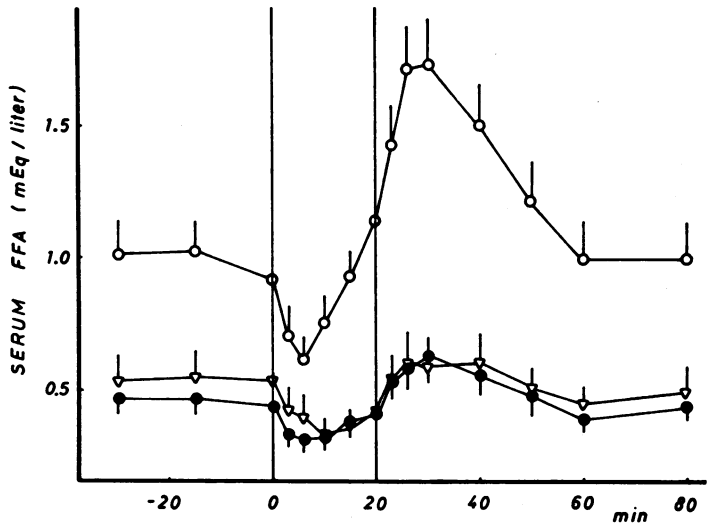

FIGURE 4 Serum free fatty acid (FFA) levels at rest and during exercise in the normal subjects ▽——▽, in all diabetics examined during poor control ○——○, and in all diabetics examined during good control ●——● (mean ±SEM).

< 0.005), and patient 26 ($P < 0.02$). In the remaining patient (No. 27) the opposite finding occurred with high significance ($P < 0.001$). The obtained changes, seven out of eight patients showing improvement, would occur by chance with a probability less than 0.035. This group of exceedingly well controlled diabetics contained the only two patients with entirely normal growth hormone pattern during the whole experimental period.

It is of course arbitrary to divide the patients who were examined during good control into the two groups with blood glucose levels higher and lower than 100 mg/100 ml. On the other hand, by dividing the patients into two groups of *equal* size on the basis of blood glucose concentrations, it was found that the areas below the growth hormone curves during and after exercise were significantly lower ($P > 0.05$) in the group with the lowest blood glucose values compared with the group with the highest blood glucose values.

While the eight patients who attained the lowest blood glucose values during good control differed from the other patients with respect to their *serum growth*

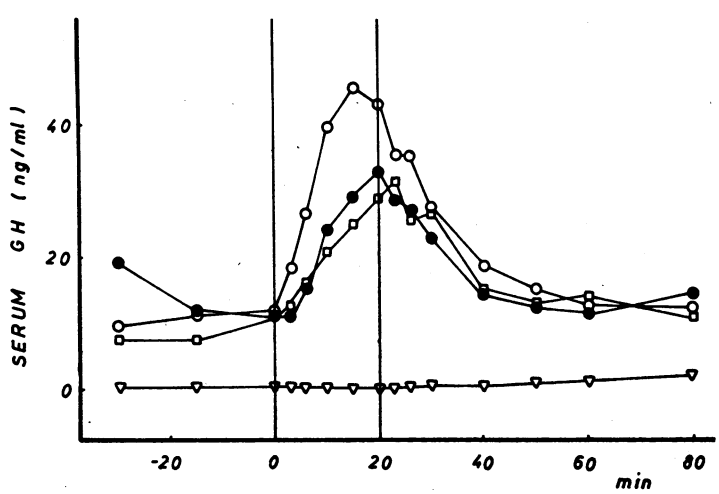

FIGURE 5 Average serum growth hormone (GH) values at rest and during exercise in the normal subjects ▽——▽ and in the three groups of diabetics examined during poor control. Group A, ○——○; group B, □——□; and group C, ●——●.

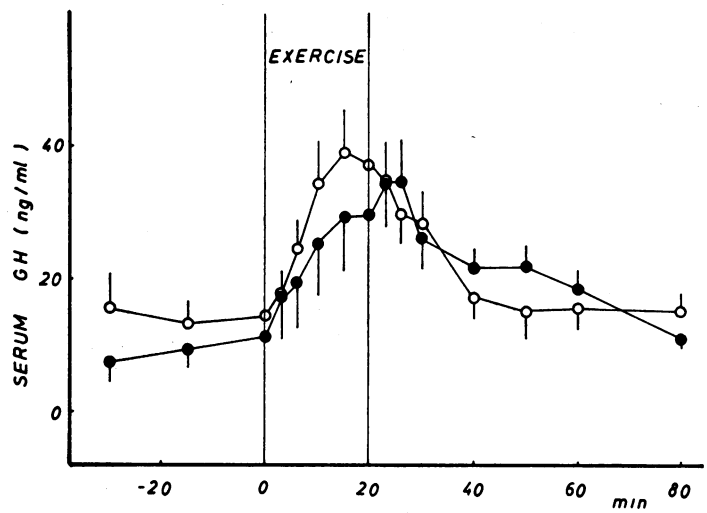

FIGURE 6 Serum growth hormone (GH) values at rest and during exercise in the 11 diabetics who had fasting blood glucose levels between 100 and 140 mg/100 ml after the attempt to obtain good control. The experiments in poor control ○——○; the experiments in good control ●——● (mean ±SEM).

hormone, their changes in *serum free fatty acids* and their absolute values before and after control (Fig. 8) were identical with those obtained in the total group of diabetics (Fig. 4), i.e., all the diabetics obtained a normal free fatty acid level and response during good control.

The preexercise serum insulin values in the control subjects and in the diabetics in group A examined before and after insulin treatment did not differ significantly (Fig. 9 and Tables II and III). No significant change was observed during exercise in the control subjects or in the diabetics examined after insulin treatment. However, in these diabetics during the period when they were not yet treated, an increase in serum insulin occurred after exercise. This increase was statistically significant ($P < 0.05$) when the three preexercise values were compared with the values 6, 10, and 20 min after cessation or work.

Correlation analyses in the diabetics. A highly significant correlation could be demonstrated between fasting blood glucose values and fasting serum free fatty acids ($r = 0.548$; $P < 0.001$). A significant correlation

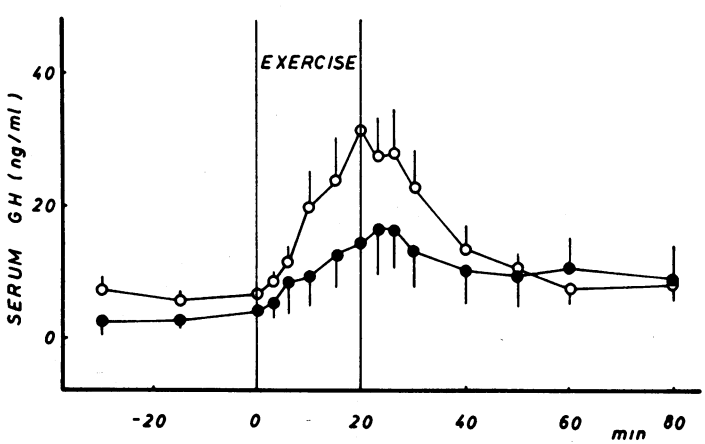

FIGURE 7 Serum growth hormone (GH) values at rest and during exercise in the eight diabetics who had obtained fasting blood glucose values between 60 and 100 mg/100 ml during treatment. The experiments in poor control ○——○; the experiments in good control ●——● (mean ±SEM).

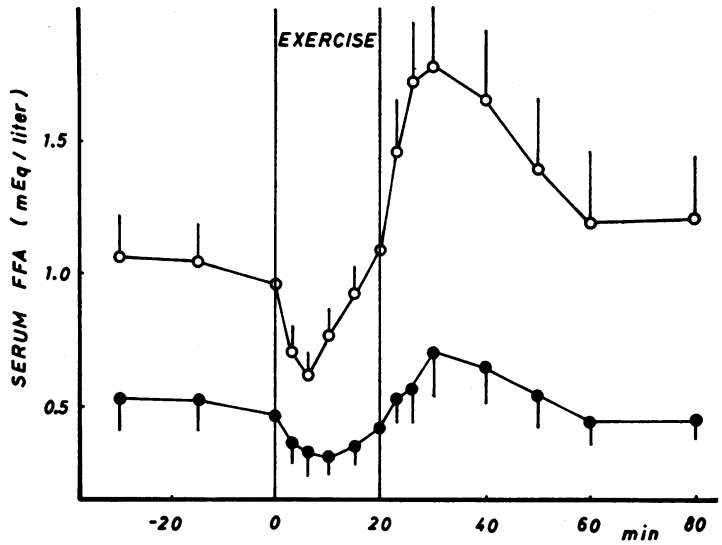

FIGURE 8 Serum free fatty acid (FFA) values at rest and during exercise in the eight diabetics who had obtained fasting blood glucose values between 60 and 100 mg/100 ml during treatment. The experiments in poor control ○——○; the experiments in good control ●——● (mean ±SEM).

could also be demonstrated between fasting blood glucose values and fasting serum growth hormone values ($r = 0.360$; $P < 0.05$). On the other hand, no significant correlation was found between fasting blood glucose values and areas of growth hormone curves, or between fasting serum free fatty acid values and fasting serum growth hormone values, or between fasting serum free fatty acid values and areas of growth hormone curves. Neither was there any association between maximal free fatty acid values and areas of growth hormone curves.

DISCUSSION

In the present study a work load of 450 kg/min for 20 min was used, resulting in a 5- to 6-fold increase in

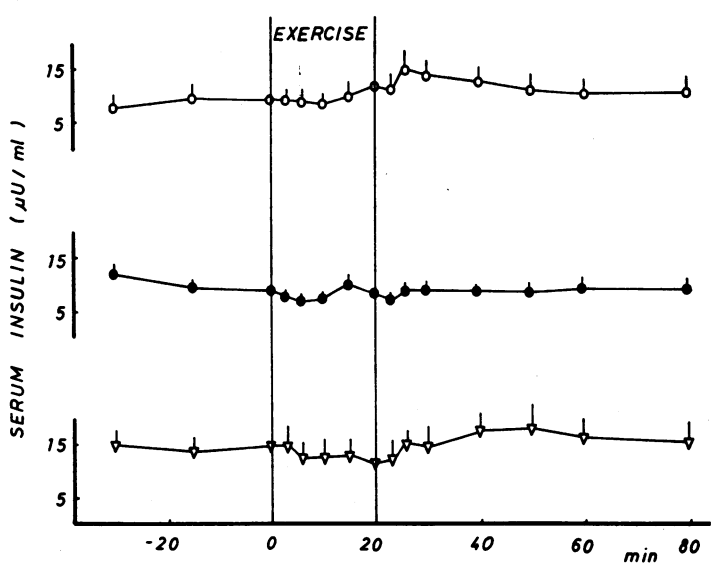

FIGURE 9 Serum insulin values at rest and during exercise in the normal subjects ▽——▽ and in the diabetics in group A examined before insulin treatment ○——○ and after insulin treatment ●——● (mean ±SEM).

oxygen uptake. The increase was the same in each of the experimental groups, controls and diabetics, whether they were in good or poor control. This work load did not lead to any rise in serum growth hormone in our normal subjects. In other experiments in progress in this laboratory dealing with intravenous glucose infusion with the aim of blocking the exercise-induced growth hormone rise in normals and diabetics, we have, however, observed that a rise in serum growth hormone occur in normal subjects with larger work loads, or when the working period is prolonged.[1] These findings confirm earlier reports demonstrating a rise in serum growth hormone in normal subjects when a certain amount of work is exceeded (10–12).

The two results which have interested us most in the present study were (*a*) that fasting serum growth hormone levels in male nonobese patients with classic juvenile diabetes were much higher than in comparable nondiabetics, and (*b*) that juvenile diabetics showed a 3- to 4-fold increase in serum growth hormone in response to a work load which never induced any change in the control subjects. These two growth hormone abnormalities were present not only at the clinical onset of diabetes mellitus, but also after a few years of diabetes duration and even after many years of diabetes. However, the average growth hormone values during the exercise period were somewhat higher in the newly diagnosed untreated diabetics than in the diabetics with few and many years duration of diabetes. This finding could suggest a connection between the duration of the metabolic disturbance and severity of the growth hormone abnormality, because the period of metabolic disturbance was much longer before the experiment in the newly diagnosed, untreated diabetics than in the other two groups of diabetics.

After intensive insulin treatment of all the three groups of diabetics, average fasting serum growth hormone and growth hormone response to exercise declined, but the change was statistically significant only in the group where blood glucose values had been reduced to *normal fasting levels,* i.e., between 60 and 100 mg/100 ml. In the remaining group of diabetics in whom the attempt at blood sugar normalization resulted in glucose values between 100 and 140 mg/100 ml, which in clinical terms indicates a very good diabetes control, no significant diminution was observed. Even in the group with the best control of blood glucose values only two of the eight patients showed a completely normal growth pattern, i.e., normal fasting values and no response to exercise.

[1] Hansen, Aa. P. The effect of i.v. glucose infusion on the exercise induced serum growth hormone rise in normals and juvenile diabetics. To be published.

In some of the patients slight ketoacidosis was present during the experiments in poor control. It is clear, however, that ketosis or acidosis cannot be an important cause of the serum growth hormone rise during exercise, as an identical rise was achieved in the patients after moderately good control.

It is well known that the growth hormone response to various stimuli is blunted or absent in obese patients (10). A difference in total body fat content in groups of subjects might therefore explain the observed difference in growth hormone response. In the present study the average value of body fat was somewhat lower in the diabetics in group A than in the controls, but the difference was not significant. Total body fat content was not measured in all of the patients in group B and C. However, no significant difference in height and weight could be found between these patients and the controls. The significance of serum growth hormone rise during exercise is not clear. Hunter, Fonseka, and Passmore (11) suggested that the rise in growth hormone during exercise in normal subjects was of importance in initiating and maintaining the mobilization of depot fat. However, Hartog, Havel, Copinschi, Erll, and Ritchie (12) felt that this could not be so because in their experiments the rise in plasma glycerol and plasma free fatty acids during exercise occurred before the rise in growth hormone. In our study the rise in free fatty acids in the diabetics appeared after the rise in growth hormone, thus supporting the hypothesis of Hunter et al (11). However, the idea of a causal relationship between rise in serum growth hormone and release of free fatty acids from depots is somewhat weakened by our finding of complete normalization of free fatty acid response in 11 patients in whom unsatisfactory blood sugar normalization and unchanged growth hormone responses were obtained.

The principal finding in the present study, the very pronounced rise of serum growth hormone in diabetics exposed to a work load which will induce no change in serum growth hormone in normal subjects, is not explained by the study of the other parameters examined here. Blood lactate followed the expected patterns in normals as well as in diabetics. In agreement with previous reports (19, 20) free fatty acid values were found to be elevated in the diabetics in poor control. The free fatty acid pattern during exercise in the diabetics was similar to that described by Carlstrøm (21), except that no initial fall was observed by Carlstrøm whose measurements were made on arterial blood. However, in exercise studies in normal subjects Friedberg, Harlan, Trout, and Estes (22) found an initial fall in serum free fatty acids in arterial blood. In the present study the serum free fatty acids showed the same normal pattern in the 8 experiments performed during exceed-

ingly strict control and in the 12 experiments where a less excellent control was achieved. This is in contrast to the lesser and more variable "improvement" in serum growth hormone. This contrast indicates that the normalization of the serum free fatty acids during fasting and in response to exercise occurs at a higher blood glucose level than the normalization of serum growth hormone.

In the newly diagnosed untreated diabetics, serum insulin rose after the cessation of work. This postexercise rise cannot readily be explained. It does not occur in normals, and the long-term treated diabetics could not be investigated for technical reasons. However, it could in some way be connected to a sudden disappearance of high blood catecholamine level during exercise in diabetics.

Growth hormone abnormalities have been reported in juvenile diabetics in other situations than during exercise. Juvenile diabetic children show a hyperresponse to arginine infusion and glucagon injection (3). We have studied the 24 hr pattern of serum growth hormone in normals and diabetics (9) and have found that the blood of male nonobese patients with recently discovered untreated classic juvenile diabetes contains much more growth hormone than that of nondiabetics and that the level fluctuates much more wildly. High and fluctuating serum growth hormone values in unstable diabetics have also been reported by Molnar, Ackerman, Rosevear, Gatewood, and Moxness (4). While hyperglycemia blocks growth hormone release in response to arginine infusion in normals, Burday, Fine, and Schalch (2) found that the high blood sugar of insulin-dependent diabetics had no such blocking effect. Yde (6) has found an abnormal early rise in serum growth hormone in juvenile diabetics after oral glucose ingestion; and quite recently Sabeh, Mendelsohn, Corredor, Sunder, Friedman, Morgan, and Danowski (7) reported elevated serum growth hormone level before and during disposal of an oral glucose load. On the other hand, in diabetic children Parker, Pildes, Chao, Cornblath, and Kipnis (23) and Baker, Root, Haque, and Kaye (24) found a normal growth hormone response to oral and intravenous glucose as well as to intravenous tolbutamide.

The findings presented here clearly show that growth hormone is secreted in excess during fasting and during exercise in juvenile diabetics with recent onset, with few years, and with many years duration of diabetes. The hypersecretion of growth hormone in juvenile diabetics now demonstrated by several authors may be of metabolic origin solely, or it may be an inborn error of metabolism playing a role for the development of diabetes. The significant decrease in fasting serum growth hormone values and in serum growth hormone response to exercise after only a few days of exceedingly well controlled diabetes found in this study show that the hypersecretion of growth hormone in juvenile diabetics for a major part is of metabolic origin. However, only two patients out of the eight exceedingly well controlled diabetics showed a quite normal growth hormone pattern. A metabolic component in the growth hormone abnormality in diabetes mellitus is also supported by the finding of Unger (1) and Jacobs and Nabarro (8) that the elevated serum growth hormone values in ketoacidotic diabetics decreased to normal values after insulin treatment. The possibility exists, however, that the growth hormone hypersecretion in juvenile diabetics is caused in part by a genetic defect in growth hormone release. This defect could be a factor in the production of diabetes mellitus. This hypothesis is supported by the work of Boden, Soeldner, Gleason, and Marble (25) who found elevated fasting serum growth hormone values, and increased growth hormone response to intravenous tolbutamide and intravenous glucose in prediabetic males.

Further studies in exceedingly well controlled juvenile diabetics, in juvenile diabetics in remission, and in prediabetics are necessary in order to elucidate this problem.

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