Twenty-four-hour Serum Growth Hormone Levels in Maturity-onset Diabetics

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SUMMARY

Serum growth hormone, glucose, and insulin were studied every half hour during a twenty-four-hour period of "daily life" in four groups of subjects: nonobese normal subjects, obese normal subjects, nonobese maturity-onset diabetics, and obese maturity-onset diabetics.

It was found that (1) serum growth hormone was uniformly low without meal- and sleep-related peaks in obese normals and diabetics. The twenty-four-hour serum growth hormone level was significantly higher in nonobese subjects than in obese subjects, in both diabetics and normals; (2) the twenty-four-hour serum growth hormone level was more fluctuating and significantly higher in nonobese diabetics than in nonobese normals; (3) there was no difference in the twenty-four-hour serum growth hormone level between obese diabetics and obese normals. DIABETES *24*:977-82, November, 1975.

We earlier found high and fluctuating twenty-four-hour serum growth hormone levels and early and high serum growth hormone responses to exercise in male and female patients with juvenile diabetes compared with groups of control subjects.[1-8] In maturity-onset diabetics we found that nonobese patients showed elevated fasting serum growth hormone values and early and high serum growth hormone responses to exercise compared with those of controls. In the obese patients the average serum growth hormone response was also higher than in comparable nondiabetics, but the difference was not statistically significant.[9]

In the present study, serum growth hormone was measured every half hour during a twenty-four-hour period of normal life with three meals during the day and sleep during the night in four groups of subjects: nonobese normal subjects, obese normal subjects, nonobese maturity-onset diabetics, and obese maturity-onset diabetics.

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MATERIAL AND METHODS

The control subjects (table 1) consisted of seven nonobese male subjects with a mean age of fifty-five years (range 44-64) and a mean ideal body weight of 99 per cent (range 82-117) and of nine obese male subjects with a mean age of fifty-seven years (range 35-69) and a mean ideal body weight of 143 per cent (range 124-180).

All control subjects were in good health; in particular, none had signs or symptoms of cardiovascular disease, none had kidney or liver diseases, and none had endocrine disorders. Fasting serum glucose was within normal limits in all.

The maturity-onset diabetics (table 2) consisted of ten nonobese male subjects with a mean age of fifty-five years (range 41-65) and a mean ideal body weight of 97 per cent (range 86-107) and of seven obese male maturity-onset diabetics with a mean age of fifty-eight years (range 47-69) and a mean ideal body weight of 150 per cent (range 133-178). The mean known duration of diabetes was four years (range 1-12) in the nonobese patients and five years (range 1-10) in the obese patients.

In all cases the diagnosis of diabetes was made after the age of forty years. The diabetics were treated with either diet plus tolbutamide or with diet plus tolbutamide plus phenformin. All diabetics were in their usual clinical control when studied. The mean fasting serum glucose level was 165 mg./100 ml. (range 85-258) in the nonobese group and 137 mg./100 ml. (range 82-196) in the obese group. All the diabetics were in good health. None had signs or symptoms of diabetic angiopathy, cardiovascular diseases, kidney or liver diseases, or endocrine disorders.

All subjects came to the hospital before 7:30 on the day of the experiment after twelve hours' fasting. An indwelling venous catheter was inserted and the subjects rested for half an hour before blood sampling was started, at 8:00. Samples were drawn every half hour during the following twenty-four hours. The first 1 to 2 ml. of blood was drawn out by a syringe and dis-

TABLE 1

Clinical data for all control subjects investigated

Case no.	Age (yr.)	Ideal body weight (%)	24-hr. serum glucose (mg./100 ml.)	24-hr. serum growth hormone (ng./ml.)	24-hr. serum insulin (μU./ml.)
			Nonobese		
1	62	117	100	2.6	23
2	46	97	95	3.0	23
3	56	103	113	2.4	35
4	58	96	90	2.1	20
5	44	103	87	1.7	22
6	64	82	87	2.3	21
7	58	92	79	2.0	8
Mean	55.4	98.6	93.0	2.3	21.7
S.E.M.	2.9	4.1	4.2	0.2	3.0
			Obese		
8	64	154	119	2.0	46
9	35	180	104	0.7	57
10	57	156	96	1.6	69
11	63	128	96	1.7	28
12	69	128	90	2.5	42
13	63	128	103	2.1	36
14	41	124	95	1.5	33
15	59	139	110	1.3	28
16	63	154	104	2.1	55
Mean	57.1	143.4	101.9	1.7	43.8
S.E.M.	3.8	6.3	3.0	0.2	4.7

carded; it was not necessary, therefore, to prevent occlusion of the catheter by either saline or heparin. During the study the subjects were at leisure, sitting, talking, listening to the radio, and moving quietly around in their rooms. They all followed the program of "daily life" outlined in table 3. The diabetics received the usual dose of tolbutamide and/or phenformin on the day of the study; otherwise no medication

TABLE 2

Clinical data for all diabetic subjects investigated

Case no.	Age (yr.)	Ideal body weight (%)	Diabetes duration (yr.)	Treatment	24-hr. serum glucose (mg./100 ml.)	24-hr. serum growth hormone (ng./ml.)	24-hr. serum insulin (μU./ml.)
				Nonobese			
17	43	93	1	D + T*	173	7.3	15
18	41	86	1	D + T + P	286	6.3	11
19	52	104	2	D + T + P	194	5.1	11
20	54	97	8	D + T	115	5.0	8
21	60	107	12	D + T	104	6.2	46
22	56	97	5	D + T + P	190	4.4	11
23	63	86	1	D + T	117	5.1	29
24	52	93	1	D + T	129	3.6	29
25	65	102	1	D + T + P	240	5.1	32
26	62	105	5	D + T	195	3.6	22
Mean	54.8	97.0	3.7		174.3	5.2	21.4
S.E.M.	2.6	2.4	1.2		18.8	0.4	3.9
				Obese			
27	60	137	1	D + T	135	1.2	85
28	69	133	4	D + T	130	1.3	24
29	62	147	10	D + T	164	1.0	35
30	54	178	6	D + T	169	1.7	65
31	63	139	7	D + T	105	2.1	42
32	47	153	1	D + T	138	2.4	55
33	48	162	6	D + T	134	1.2	60
Mean	57.6	149.9	5.0		139.3	1.6	52.3
S.E.M.	3.1	6.0	1.2		8.2	0.2	7.7

*D = diet; T = tolbutamide; P = phenformin.

TABLE 3

Timetable for the twenty-four-hour period of "daily life"

8.00- 8.30	Breakfast containing	
	protein	6 gm.
	carbohydrate	65 gm.
	lipid	17 gm.
	calories	453
10.30-11.00	Two cups of coffee without sugar, cream, or milk.	
12.00-12.30	Lunch containing	
	protein	24 gm.
	carbohydrate	44 gm.
	lipid	28 gm.
	calories	538
15.00-15.30	Two cups of coffee without sugar, cream, or milk.	
17.30-18.00	Dinner containing	
	protein	16 gm.
	carbohydrate	123 gm.
	lipid	28 gm.
	calories	*830*
	One beer containing	
	carbohydrate	9 gm.
	alcohol	12 gm.
	Calories	130
22.00-22.30	One beer	
24.00-	Sleep period	

was given to any of the subjects.

The blood samples were centrifuged at 4° C. and stored at minus 20° until analysis. Serum growth hormone and insulin were measured by a single antibody radioimmunoassay employing wick chromatography.[10] The standards were Wilhelmi HGH (HS 1216C) and Novo human insulin. Serum glucose was measured by a glucose oxidase method.[11]

For statistical analysis two tests were used. Comparison of sample means were performed by Student's test and correlation analyses were performed by Spearman's rank correlation test.

RESULTS

Normal Subjects

Figure 1 shows the average values of serum growth hormone, glucose, and insulin during the twenty-four-hour period of "daily life" in the seven nonobese and the nine obese normals.

Serum growth hormone was uniformly low without meal- and sleep-related peaks in the obese group. The average level was more unstable in the nonobese group, showing several postprandial peaks and a few sleep-onset peaks on the individual curves. The average twenty-four-hour serum growth hormone value was significantly higher in the nonobese group than in the obese group (2.3 ng./ml. as against 1.7 ng./ml.; $p < 0.05$).

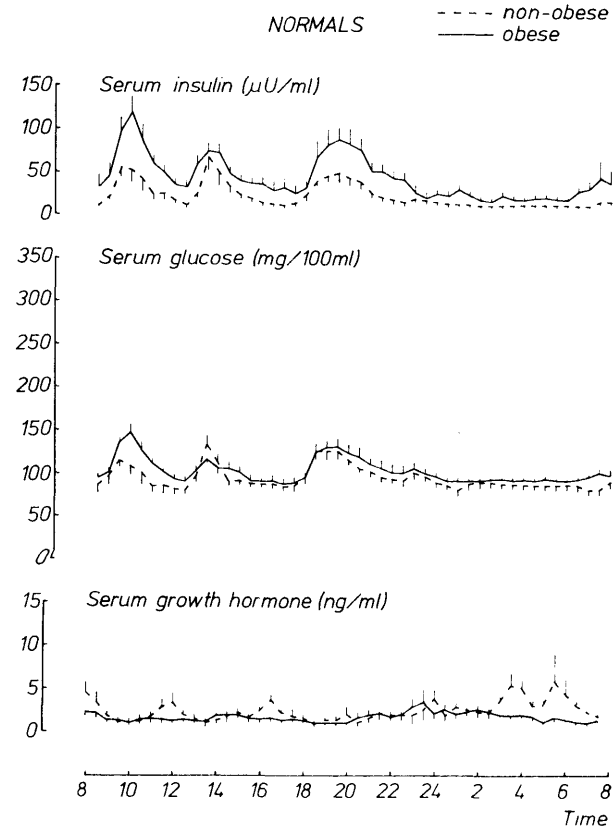

FIG. 1. Serum growth hormone, glucose, and insulin values during a twenty-four-hour period of "daily life" in seven nonobese normals and nine obese normals (mean ± S.E.M.).

Serum glucose rose after the meals in both groups. The average twenty-four-hour value was insignificantly higher in the obese than in the nonobese group (102 mg./100 ml. as against 93 mg./100 ml.).

Serum insulin also rose after meals, and in this case the average twenty-four-hour value was significantly higher in the obese than in the nonobese group (44 μU./ml. as against 22 μU./ml.; $p < 0.005$).

Diabetics

Figure 2 shows the average values of serum growth hormone, glucose, and insulin during the twenty-four-hour period of "daily life" in the ten nonobese and the seven obese patients.

Serum growth hormone behaved similarly in these obese diabetics as in the obese normals; the level was low, without any peaks. In the nonobese patients the level fluctuated with many meal- and sleep-related peaks and also peaks unrelated to these events. The average twenty-four-hour serum growth hormone value was significantly higher in the nonobese group than in the obese group (5.2 ng./ml. as against 1.6 ng./ml.; $p < 0.001$).

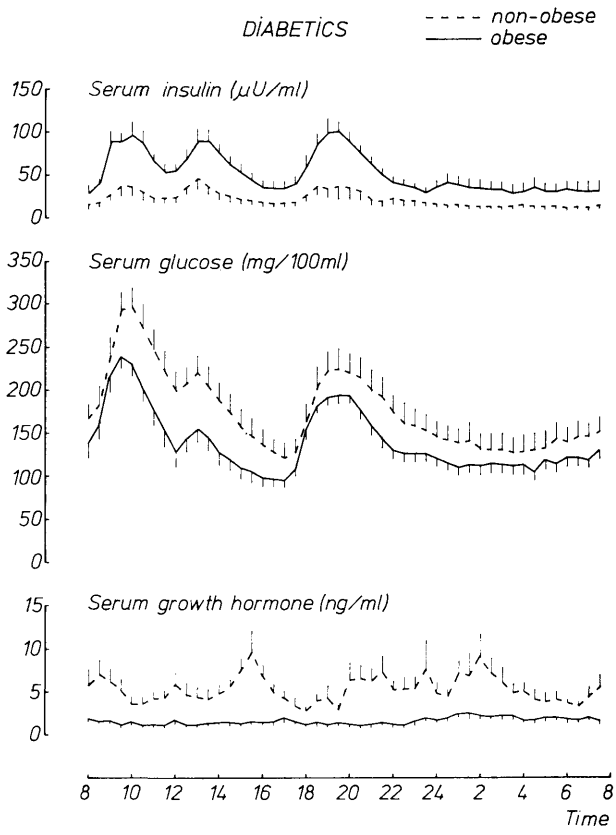

FIG. 2. Serum growth hormone, glucose, and insulin values during a twenty-four-hour period of "daily life" in ten nonobese maturity-onset diabetics and seven obese maturity-onset diabetics (mean ± S.E.M.).

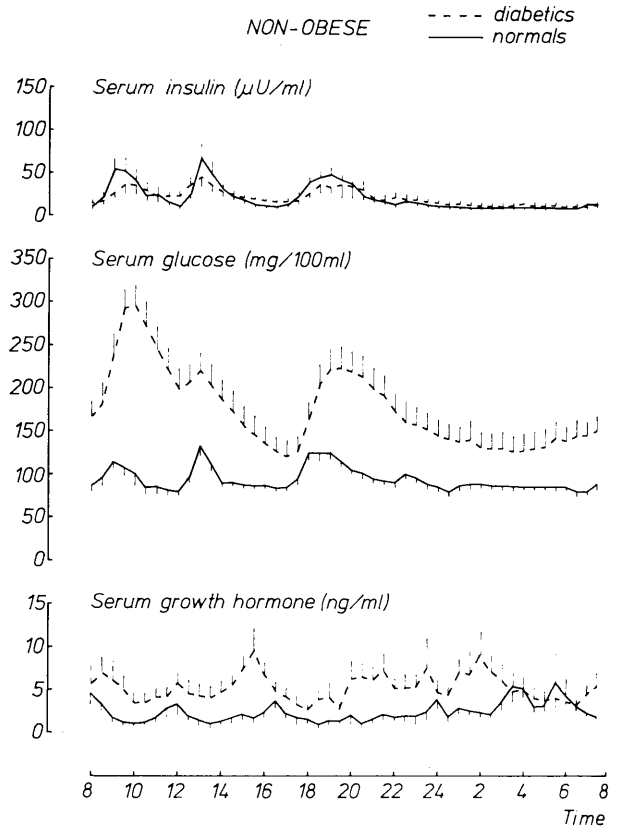

FIG. 3. Serum growth hormone, glucose, and insulin values during a twenty-four-hour period of "daily life" in ten nonobese maturity-onset diabetics and seven nonobese normals (mean ± S.E.M.).

Serum glucose rose after the meals in both groups. The average fasting value (165 mg./100 ml. as against 137 mg./100 ml.) and the average twenty-four-hour value (174 mg./100 ml. as against 139 mg./100 ml.) were insignificantly higher in the nonobese group than in the obese group.

The rises in serum insulin after meals were much higher in the obese than in the nonobese group, and the average twenty-four-hour value was also highest in the obese group (52 μU./ml. as against 21 μU./ml.; $p < 0.005$).

Nonobese Subjects

Figure 3 shows the average values of serum growth hormone, glucose, and insulin during the twenty-four-hour period of "daily life" in the seven nonobese normals and the ten nonobese diabetics. This figure and the next one appear after rearrangement of the curves in figures 1 and 2.

Serum growth hormone fluctuated more in the diabetics than in the normals, and the average twenty-four-hour value was significantly higher in diabetics than in normals (5.2 ng./ml. as against 2.3 ng./ml.; $p < 0.001$). The fasting serum glucose value, the glucose rises during meals, and the twenty-four-hour glucose value were much higher in diabetics than in normals. The rises in serum insulin after meals were more sluggish in diabetics than in normals, but the average twenty-four-hour values in the two groups were not significantly different.

Obese Subjects

Figure 4 shows the average values of serum growth hormone, glucose, and insulin during the twenty-four-hour period of "daily life" in the nine obese normals and the seven obese diabetics.

Serum growth hormone was low and stable in both diabetics and normals, and the average twenty-four-hour value in the two groups was not significantly different (1.6 ng./ml. as against 1.7 ng./ml.). The fasting serum glucose value, the glucose rises during meals, and the twenty-four-hour glucose value in these obese subjects were also much higher in diabetics than in normals. The rises in serum insulin after meals occurred rapidly in both diabetics and normals, and the average twenty-four-hour values in the two

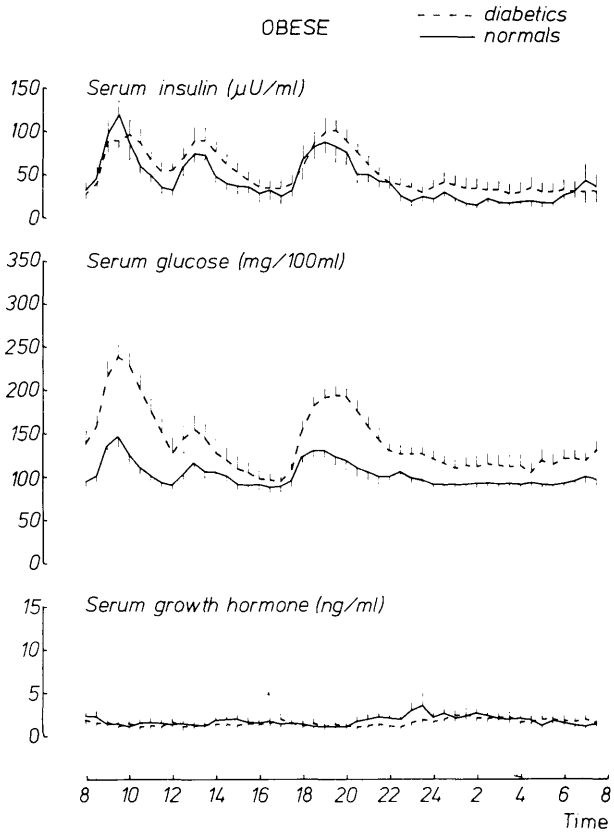

FIG. 4. Serum growth hormone, glucose, and insulin values during a twenty-four-hour period of "daily life" in seven obese maturity-onset diabetics and nine obese normals (mean ± S.E.M.).

groups were not significantly different.

Significance of Body Weight and Serum Glucose

A significant negative correlation was demonstrated between the twenty-four-hour serum growth hormone values and body weights in the total group of normal subjects ($r = 0.506$; $2\alpha = 0.05$) and also in the total group of diabetics ($r = 0.644$; $2\alpha = 0.01$). There was no positive correlation between the twenty-four-hour serum growth hormone values and the twenty-four-hour serum glucose values in the total group of diabetics.

DISCUSSION

The results obtained in the present study are in accordance with those obtained in a previous study of serum growth hormone during exercise in nonobese and obese elderly persons.[9]

In the twenty-four-hour study the nonobese diabetics showed the same abnormally high serum growth hormone values as in the exercise experiments. The obese diabetics responded to exercise by an increase in serum growth hormone that was higher on the average but statistically insignificant. In the unstimulated condition of the twenty-four-hour study no elevation of the serum growth hormone plateau was observed.

It is well known that obesity is associated with low basal levels of serum growth hormone and blunted responses to various stimuli; it is low in the fasting state,[12-14] during prolonged fasting,[15,16] in the late phase of glucose injection,[14,15,17] after insulin and tolbutamide-induced hypoglycemia,[14,18-21] during a twenty-four-hour period of "normal life,"[22] during infusion of arginine,[13,23,24] 2-deoxy-D-glucose,[21], or propranolol,[25] after injection of nicotinic acid,[26] and during exercise.[27]

The mechanisms by which obesity suppresses growth hormone secretion are unknown.

The absence of the serum growth hormone abnormality in obese diabetics under the conditions of the twenty-four-hour study is probably an expression of the obese state in itself. The fact that the diabetes of the obese patients was somewhat milder than that of the nonobese may also play a role, although no statistically significant correlation could be demonstrated between the serum growth hormone and the serum glucose in the course of the period of study.

We have put forward the hypothesis that overproduction of growth hormone is a causal factor in the development of diabetic angiopathy.[28,29] This hypothesis was based on the inhibition of the development of retinopathy after hypophysectomy, shown in a controlled clinical trial,[30] and on the finding of high serum growth hormone in young diabetic patients.

Elderly obese diabetic patients do develop diabetic angiopathy, although the relative prevalences in obese and nonobese are not known.

The present results do not exclude, of course, the possibility that elderly obese diabetics may have inappropriately elevated plasma growth hormone in the course of their life, e.g. during periods of mental stress, infections, or trauma. At the moment, however, it seems reasonable to accept that other causal factors may be more important for the development of diabetic vascular disease in elderly obese diabetics.

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