Response of Growth Hormone (GH), FFA, Blood Sugar and Insulin to Exercise in Obese Patients and Normal Subjects

By F. SCHWARZ, D. J. TER HAAR, H. G. VAN RIET AND J. H. H. THIJSSEN

Ergometer tests with a constant workload of 600 Kg./min. during 30 minutes were done on eight normal subjects, eight severely obese patients, and two women who had formerly been obese. Arterial blood was sampled three times before, four times during and three times after exercise. The incidence and the height of the GH response were the same in the obese as in the normals. The results show that the obese are able to raise their plasma GH to very high levels if subjected to strenuous exercise. It could not be concluded, however, that they can do so to the same extent as normals, because the exercise was more exhausting for the obese, three of whom had to stop prematurely, than for the normal subjects. In eight of the 12 responders, the rise of GH began almost immediately at the start of bicycling. In all of them, GH valves decreased as soon as work was stopped, irrespective of the time it had lasted. There was no correlation between changes in GH and those on the other parameters measured. It is very probable that the elevation of GH was at least in two thirds of the cases triggered by stress rather than by the increase in energy expenditure. FFA levels were throughout the whole test higher in the obese, than in the normal subjects. No correlation with the GH levels could be found. Blood sugar remained stable in the normal subjects and in the majority of the obese. In three obese patients there was a rise of blood sugar during exercise followed by an elevation of plasma insulin. Two of these patients must be viewed as prediabetics on account of their family history. (Metabolism 18: No. 12, December, 1013-1020, 1969)

IT HAS BEEN DEMONSTRATED that long-term fasting causes an increase in plasma growth hormone (GH) in normal subjects but not in the majority of obese patients.[1,2] A diminished response of plasma GH in the obese has also been found after insulin-induced hypoglycemia[1,3] and during arginine-infusion.[4,5] As GH is a potent fat-mobilizer, it has been speculated that some intrinsic defect of GH production or secretion might be one of the causal factors in obesity.[6] Issekutz et al.[7] and Birkenhäger and Tjabbes[8] have shown since that the turnover of fatty acids in the obese is higher than in the normal so that a defect in fat mobilization in obesity is very improbable. Still the abnormality of the GH response in the obese remains intriguing.

In an earlier paper[2] we have reported that fat mobilization in long-term fasting

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obese is independent of the level of plasma GH. As an explanation for the lack of GH response, we suggested that in the severely adipose subject the abundance of available fatty acids prevents a real shortage of metabolic fuel. The secretion of GH was viewed as an emergency measure to obtain an additional supply of energy needed by the normal weight subject but not by the obese. This is in agreement with the findings of Hunter et al.[9] and Hartog et al.[10] These authors found a rise of plasma GH during exercise in normal subjects, which could be prevented by the administration of glucose.[9]

If our theory is correct, a rise of GH should occur also in the obese during bodily exercise. To test this hypothesis, the experiments to be described here were performed. FFA, blood sugar and insulin were determined simultaneously with GH. For comparison, a group of normal subjects and two formerly obese women were tested.

Material and Methods

Data about all subjects tested are summarized in Table 1. The normal controls were healthy students or laboratory technicians, some of them well trained and active in sports. In the two formerly obese women (Nos. 9 and 10), body weight had been stable for several months. The obese patients were hospitalized for weight reduction. The diet taken during the period preceding the tests is indicated in the table.

Tests were done after an overnight fast. The normal subjects were asked not to exert themselves in the morning of the experiment and to report at the laboratory at 8:30. The obese patients came there from the hospital wards. A 9:00 an arterial needle was inserted into the brachial artery and kept there until completion of the experiment.

Blood sampling was started about 30 minutes later. During the initial period the subjects rested in an easy chair, and blood was drawn at —40, —20 and 0 minutes. Exercise was done on a bicycle ergometer with a workload of 600 Kg/min during 30 minutes. At +5, +10, +20 and +30 minutes, blood samples were taken while the subjects was bicycling and at +40, +60 and +80 minutes with the subject again at rest in the chair.

Plasma levels of growth hormone (GH) were estimated by the radioimmunoassay method

Table 1

Subject	Sex	Age	Weight (Kg.)	Height (m)		
1.	M	31	82.3	1.80	normal	
2.	M	27	93.0	1.93	normal	
3.	M	28	72.1	1.81	normal	
4.	M	28	95.2	1.96	normal	
5.	M	39	87.3	1.85	normal	
6.	M	23	73.0	1.83	normal	
7.	F	24	53.0	1.65	normal	
8.	F	28	67.0	1.80	normal	
9.	F	40	67.3	1.63	formerly obese	
10.	F	44	73.0	1.70	formerly obese	
						Reducing Diet
11.	M	52	144.8	1.79	obese	900 cal/day
12.	M	24	106.0	1.78	obese	600 cal/day
13.	F	20	110.0	1.65	obese	600 cal/day
14.	F	19	108.0	1.64	obese	600 cal/day
15.	F	18	93.8	1.78	obese	1000 cal/day
16.	F	31	77.0	1.67	obese	1200 cal/day
17.	F	40	77.4	1.62	obese	600 cal/day
18.	F	47	86.5	1.68	obese	600 cal/day

of Glick at al.[11] Plasma insulin levels were measured by the immunoassay of Yalow and Berson,[12] iodination done by a method analogous to that of Hunter et al.,[13] and plasma FFA determined using the method of Dole, as modified by Dole and Meinert.[14] Blood glucose was measured in a Technicon Auto-Analyzer. The radioimmunoassays were done by Dr. W. Schopman, Bergweg Municipal Hospital (Rotterdam).

RESULTS

The results of all experiments are shown in Figs. 1 and 2. The numbers of the right upper corners of the graphs correspond to those in Table 1. Number 13, a girl of 20 years, has been tested twice, with an interval of one week. The first time she stopped after 20 minutes of cycling; the second time she was able to continue for 30 minutes (No. 13A). Obese subjects 11 and 14 got exhausted after only 10 minutes of work.

Elevation of GH during exercise is seen in normal subjects 5, 6, 7 and 8, in one of the formerly obese women (No. 10), and in six of the obese patients (Nos. 11, 13, 14, 16, 17 and 18). In the cases of Number 5 and 6 (both normal con-

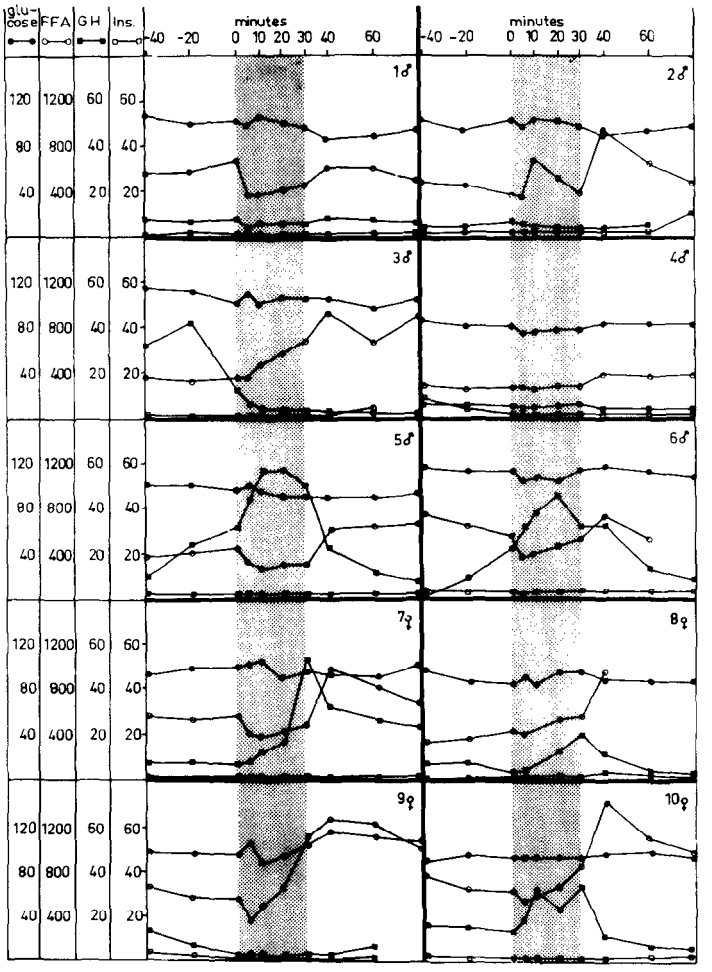

Fig. 1.—Response of GH, insulin, FFA and blood sugar of eight normal subjects and two formerly obese women (Nos. 9 and 10) to ergometer test. Shaded areas represent working period.

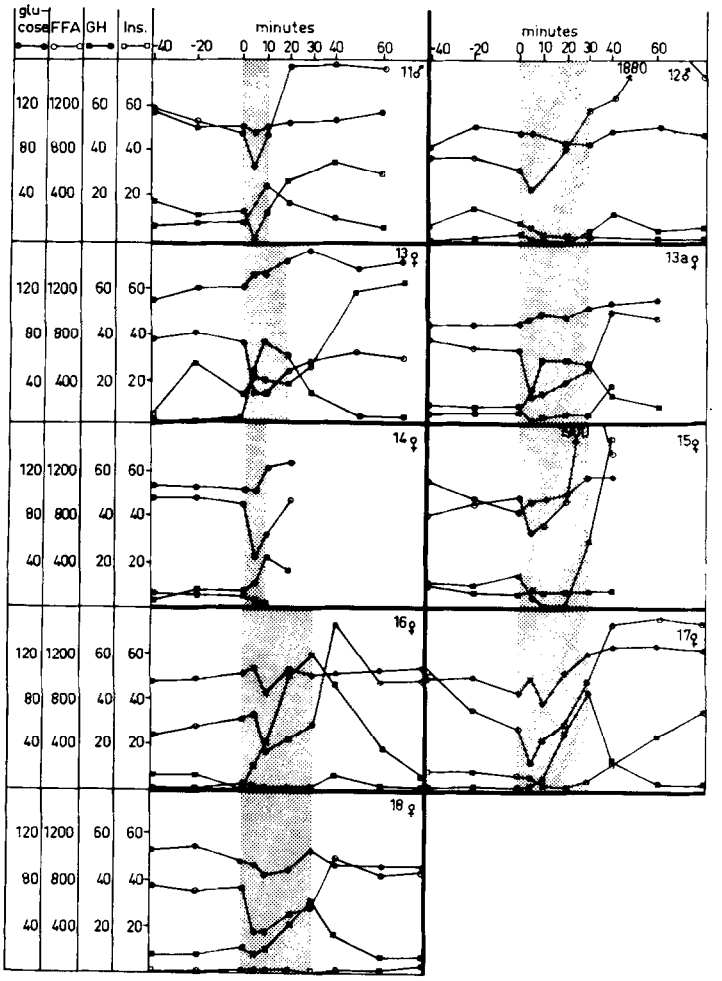

Fig. 2.—Response of GH, insulin, FFA and blood sugar of eight obese patients to ergometer test. Shaded areas represent working period.

trols), the rise of GH seems to be brought about by some event before the start of the ergometer test (possibly by the stress of the whole experimental procedure) but is clearly enhanced by the exercise. Case 3 shows an elevation of GH which subsides before the ergometer test is started.

In interpretating the GH data, the sex of the subjects must be taken into consideration. It has been shown by several authors [4,15] that under various conditions GH responses are elicited more easily in the female than in the male. This is also true for our material. Only three of the eight male subjects showed a GH response against eight of the 10 females (Table 2). Although our groups are badly matched with respect to sex, it is clear from the table that in neither incidence nor height of GH response is there a difference between the obese and the normal subjects.

During the whole experiment, the level of FFA was higher in the obese patients than in normal controls. This is shown in Fig. 3 in which the FFA data of those obese patients who completed the working period of 30 minutes are plotted

Table 2.—Incidence and Height of GH Response

	Male		Female	
	Incidence of GH Response	Maximum Values Found (ng./ml.)	Incidence of GH Response	Maximum Values Found (ng./ml.)
				31
				29
Obese	1 (2)*	25	5 (6)*	60
				44
				24
Formerly obese	—		1 (2)*	34
Normals	2 (6)*	58	2 (2)*	54
		23		20

* Total number of subjects in group.

with those of the normal subjects. The differences between the values found in both groups are statistically significant at the 5 per cent level (Wilcoxon's test) at all points except at +5 and +10 minutes. In both groups the difference between the basal values and those obtained during the recovery period is significant. Blood sugar levels did not show any marked change in the normal subjects and insulin remained low or undetectable in all of them. One of the formerly obese (No. 9) exhibited a rise of blood sugar without change in insulin levels. A rise of blood sugar during exercise was seen in four of the obese (Numbers 13, 14, 15 and 17). A drop of the insulin level was seen in all cases in which this was measurable at the beginning of the test except in case 13. A rise in blood sugar followed by a marked rise in insulin was seen in cases 13, 15 and 17. It is remarkable that two of these patients were the only ones with a positive family history for diabetes mellitus.

Discussion

In the discussion of the data presented here, it must be kept in mind that our groups were in several respects not comparable. The difference in sex ratio

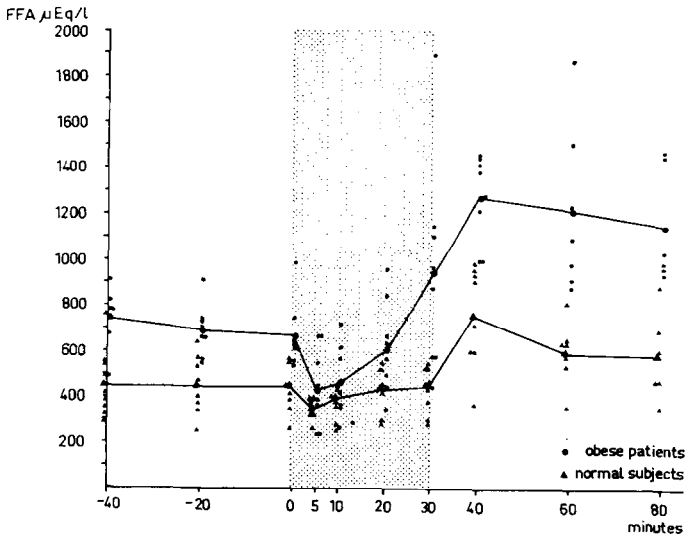

Fig. 3.—Response of FFA in normal subjects and in obese patients to ergometer test. Shaded area represents working period. Lines connect mean values of normals and obese, respectively.

has already been dealt with (Table 2). There was a difference in food intake during the period before the tests; the obese had been on reducing schemes while the normal subjects and the formerly obese women were not restricted in their diet. It should be emphasized that although the workload was the same for all subjects, the test was much more exerting for the obese, three of whom had to stop prematurely while others were barely able to complete the entire working period of 30 minutes.

The results show clearly that obese patients are able to raise their plasma GH levels considerably. The maximum values found were in the same range as those found in the normal subjects, although it is by no means sure that these would not have shown even higher values if tested to an equal degree of exhaustion as the obese. Nevertheless we believe that the high values we found in the obese exclude the possibility of an intrinsic defect in GH secretion. If the GH response during exercise were due to the increased need for energy, one would expect it to occur only some time after the beginning of the work. Such a time relation has been found by Hunter et al.[9] and by Hartog et al.[10] The workload they imposed on their subjects was considerably less than that used in our study. It appears from Figs 1 and 2 that in eight of the 12 subjects of our experiments the GH rise started almost immediately at the beginning of the exercise. This occured in the obese as well as in the normal weight group, in men and in women, and there was no correlation between the timing of the rise and the maximum GH value attained. In all the responders the GH values decreased as soon as work was stopped, although the changes in the other parameters measured were at this time by no means normalized. This decrease was seen irrespective of the time the exercise had lasted: in cases 11 and 14, ten minutes; in case 13, the first time 20 minutes and the second time 30 minutes.

This course of the GH curves can be more readily explained by the effect of the stress of bicycling (enhanced by the discomfort of the arterial needle) than by the increased energy expenditure. The fact that various forms of stress may give rise to an elevation of plasma GH has been amply documented by Schalch and Reichlin[16] and by Baylis et al.[17]

Our conclusion must therefore be that obese patients under the conditions of the experiments performed are able to raise their plasma GH to very high levels, but that in at least two-thirds of the cases, this rise has probably been caused by the experimental stress and not by the increased energy expenditure.

The difference in FFA level beween the normal-weight group and the obese (Fig. 3) can possibly be explained by the nutritional conditions. The obese had been on reducing diets for some time. This is sufficient reason for the elevated resting levels. It may also be assumed that their tissues had been adopted to the preferential utilization of the fatty acids, which may explain the sharp decrease of the FFA levels at the beginning of the exercise. Fat mobilization appears to lag somewhat behind the FFA utilization but leads to considerable overshooting of the plasma FFA levels during the recovery period. This overshooting proves that the obese is able to mobilize fatty acids in excess of his needs. There is no correlation between the maximal FFA levels attained during the recovery period and the height of the preceding GH peak. The highest FFA level (1990

μEq./1.) was seen in subject 15 who did not show any elevation of GH. It is apparent that in this situation fat mobilization was independent of the plasma GH titer.

In the majority of the subjects, the blood sugar did not show any significant change. In contrast to the FFA levels, there was no initial decrease. It is very probable that sugar utilization is increased during work, but the regulatory mechanisms apparently are able to stabilize the blood level. Possibly the decrease of the insulin titer during exercise may be of importance in this respect. This decrease of insulin can be seen in Figs. 1 and in all subjects with a measurable insulin titer with the exception of case 13. In this young woman two tests could be done with a one-week interval. In the first test, the blood sugar started at a slightly elevated level of 110 mg. per 100 ml. and rose during the exercise to 142 mg. per 100 ml. The insulin titer was 14 μU. per milliliter at the beginning of the exercise, did not decrease during the working period, and rose during the recovery period to 95 μU. per milliliter. The work had to be stopped after 20 minutes because of exhaustion. In the second test (No. 13A), which could be completed, the blood sugar was initially normal. It rose slightly during the exercise while the insulintiter declined. Unfortunately one insulin value is missing so that we do not know whether there occurred a late increase.

Because of her family history, this girl has to be viewed as prediabetic. Although her glucose tolerance curve was entirely normal, we wonder whether the abnormalities of the blood sugar and insulin response must not be taken as a sign of latent diabetes mellitus. The same holds for case 15, a young girl whose mother had diabetes mellitus, which occurred also in the family of her father. There was a rise of the blood sugar during exercise followed by a very strong elevation of insulin. From the third subject who showed this pattern (No. 17), no positive family history of diabetes mellitus could be elicited. It may be of significance that the two other subjects who could not complete the test (Nos. 11 and 14) had slightly elevated blood-sugar levels at the beginning of the experiment. Subject 11 also had a somewhat high insulin titer. The initial FFA and GH values were not remarkable in these cases. One wonders if it may be a difference in the state of carbohydrate metabolism which determines whether severe bodily exertion can be sustained.

The two formerly obese women were included in the experiments to find out whether they would react like the normals or the obese. As there was no difference between both groups with respect to GH, it can only be said that in one of them there was a rise of plasma GH and in the other there was none. During the recovery period, both subjects showed an overshooting of the FFA levels, which was clearly in the range of the obese group. We are not entirely certain that these women have not been dieting during the time before the test. Apparently they were still conditioned to a strong release of FFA from their fat depots.

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