Insulin and Growth Hormone Responses to Glucose Loading in Treated Acromegalics* **

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Summary. The insulin and growth hormone responses to oral glucose load (100 g) in 23 acromegalic patients, previously treated by external irradiation, are described. Based on current clinical findings, sixteen acromegalics were considered "inactive" and seven patients "active". Two of the latter were treated diabetics. Thirteen healthy, non-obese subjects formed the control group. Five "inactive" acromegalics had blood glucose values exceeding the upper limits of normal after the glucose load. Both the "inactive" and "active" acromegalics had hyperinsulinemia in the fasting state and after glucose load. The observation of an exaggerated serum insulin response to glucose load in clinically "inactive" acromegalics suggested that chronically elevated levels of circulating growth hormone may have led to permanent changes in the responsiveness of the pancreatic islets to glucose stimulation. The mean fasting value of serum growth hormone was about the same in the controls and the "inactive" acromegalics; the latter did not show suppression in serum growth hormone levels after glucose load.

Taux d'insuline et d'hormone de croissance à la suite d'une charge en glucose chez des acromégaliques déjà traités

Résumé. Le taux d'insuline et d'hormone de croissance à la suite d'une charge en glucose (100 g) par voie orale fut mesuré chez 23 acromégaliques qui avaient été traités par radiothérapie. Seize de ces patients étaient considérés cliniquement en phase «inactive» et les sept autres en phase «active». Deux de ces derniers étaient diabétiques et sous traitement. Treize sujets normaux, non obèses, formaient le groupe témoin. Cinq acromégaliques en phase «inactive» ont présenté à la suite d'une charge en glucose des valeurs de la glycémie dépassant les limites supérieures de la normale. Tous les acromégaliques en phase «active» et «inactive» présentaient une hyperinsulinémie à l'état de jeûne et à la suite d'une charge en glucose. Cette observation d'une montée exagérée de l'insulinémie à la suite d'une charge en glucose chez des acromégaliques cliniquement «inactifs» suggère qu'un taux sérique d'hormone de croissance continuellement élevé peut avoir

amené des changements permanents de la réponse des îlots du pancréas à la suite d'une stimulation venant du glucose. Les valeurs moyennes du taux sérique de l'hormone de croissance étaient semblables à l'état de jeûne chez le groupe des témoins et chez les acromégaliques en phase «inactive». Ces derniers n'ont pas présenté une baisse du taux sérique d'hormone de croissance à la suite d'une charge en glucose.

Der Verlauf der Seruminsulin- und Wachstumshormonwerte nach Glucosebelastung bei behandelten Akromegalen

Zusammenfassung. Die vorliegende Arbeit beschreibt den Verlauf der Seruminsulin- und Wachstumshormonwerte nach oraler Verabreichung von 100 g Glucose bei 23 Patienten mit Akromegalie, die früher mit Bestrahlung behandelt worden waren. Auf Grund der klinischen Befunde zum Zeitpunkt der Untersuchungen wurden sechzehn Patienten als „inaktive“ und sieben Fälle als „aktive“ Akromegale eingestuft. Zwei von den „aktiven“ Akromegalen waren behandelte Diabetiker. Dreizehn gesunde, nicht fettsüchtige Personen bildeten die Kontrollgruppe. Fünf „inaktive“ Akromegale hatten nach der Glucosebelastung Blutglucosewerte über dem Normbereich. Sowohl die „inaktiven“ als auch die „aktiven“ Akromegalen zeigten Hyperinsulinämie nüchtern und nach Glucosezufuhr. Die gesteigerte Insulinsekretion der klinisch „inaktiven“ Akromegalen nach Glucosebelastung kann bedeuten, daß chronisch erhöhte Spiegel des zirkulierenden Wachstumshormons möglicherweise zu ständigen Veränderungen in der Reaktion der LANGERHANS'-SCHEN Inseln gegenüber Glucosestimulation geführt haben. Der durchschnittliche Serumwachstumshormonwert im Nüchternzustand war ungefähr der gleiche bei der Kontrollgruppe und bei „inaktiven“ Akromegalen; die letzteren wiesen keine Verminderung der Serumwachstumshormonwerte nach Glucoseverabreichung auf.

Key-words. Glucose load, insulin, growth hormone, acromegaly, pituitary irradiation, hyperinsulinism.

Elevated levels of circulating insulin in acromegalics in the fasting state [7] and after glucose loading [16, 20, 1] are well documented. However, few reports are available on the effect of radiation treatment on the metabolic derangements found in acromegaly.

The usual assessment of activity or inactivity depends mainly on clinical and radiological findings. We have attempted to determine the value of insulin

and growth hormone response to glucose loading as a further index of activity. For this purpose, we studied 23 patients treated for acromegaly by external irradiation.

Patients and Methods

Twenty-three acromegalic patients were subjected to a clinical and biochemical assessment as outpatients. They had been treated by external irradiation (^{60}Co in 22 and X-ray in 1 patient) with a mean dose of 3860 rads (range 3490—5600 rads) to the pituitary area from one and a half to 21 years earlier. One patient had also had a partial hypophysectomy. For the study, the acromegalics were separated into two groups. One group consisted of 16 patients, who had shown some

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improvement of their acromegaly after treatment. They are referred to as "inactive". The remaining seven had had little or no improvement after treatment, and are referred to as "active". The classification was based on current clinical findings; which included overall assessment of headache, acral enlargement, visual fields, heel pad and skin thickness, size and shape of the sella turcica; and on a comparison between earlier and present blood glucose values in glucose tolerance tests, and between earlier and present values of serum inorganic phosphorus. The clinical aspects of the study will be reported separately.

Some clinical data, necessary as a background for our studies, are summarized in Table 1. The mean weight of the "inactive" acromegalics was $104.2 \pm 3.9\%$ and that of the "active" acromegalics $118.8 \pm 4.1\%$ of the average weights for men and women, according to Metropolitan Life Insurance Company table (1960). All patients were euthyroid.

Thirteen young and middle-aged, healthy, non-obese subjects (four females, nine males) were studied as a control group. The acromegalic subjects had taken

180 min after glucose administration. Sampling at 180 min was omitted in the controls.

Blood glucose was determined by the method of HOFFMAN [9] as adapted for autoanalyzer. The remaining blood, allowed to stand at room temperature until clot retraction, was centrifuged; the serum was frozen until the radioimmunoassays of serum insulin and growth hormone could be made. We measured serum insulin by the immunoassay method of HERBERT [8], using coated charcoal-dextran. Human insulin standards were used and the results are expressed in $\mu\text{U/ml}$. Growth hormone was determined by the MORGAN technique [14] of double-antibody immunoassay and the results are given as $\text{m}\mu\text{g/ml}$ (ng/ml).

Student's *t*-test was applied to the differences. They were considered significant at the 5 per cent level.

Results

Blood glucose (BG). The "active" acromegalics had significantly higher BG values at 60 and 90 min after loading compared with the controls ($P < 0.02$ in both

Table 1. *Clinical Data on Acromegalic Patients*

Case No.	Sex	Present Age yrs.	Weight kg	Time at study in yrs.		Remarks
				from 1st symptom	from radio-therapy	
<i>"Inactive"</i>						
1	M	48	67	7	7	
2	F	36	83	7-10	6	
3	F	39	54	9-10	7	
4	F	49	74	12-14	6	
5	M	54	61	6-8	6	
6	M	40	86	10-14	4	
7	F	55	64	15-25	6	
8	M	57	91	17	12	
9	F	55	66	6	2	Partial hypophysectomy, then ⁶⁰ Co
10	F	53	65	6	4	
11	F	36	62	10	8	
12	M	35	107	6	3	Heavily muscled, not obese
13	M	51	75	> 3	3	
14	F	60	77	> 4	4	
15	F	73	65	> 6	6	
16	M	38	95	1½	1½	
<i>"Active"</i>						
17	M	36	98	12	5	
18	F	70	73	23	4	
19	M	53	91	10-17	2	
20	M	43	110	22	21-18	Treated by external X-ray
21	M	35	107	7	5	
22	M	48	97	17	6	Diabetes diagnosed 1958. NPH 40 I.U.
23	M	59	86	> 2	2	Diabetes diagnosed 1965. Tolbutamide

at least 300 g carbohydrate/day for three days before the test and the controls had taken adequate carbohydrates for a corresponding time. After an overnight fasting period and a one hour rest in the sitting position the subjects were given 100 g of glucose orally. Venous blood was drawn fasting and at 30, 60, 90, 120 and

instances), and also at 90 min compared with the "inactive" acromegalics ($P < 0.05$) (Fig. 1).

The fasting BG was 112 mg/100 ml in one "inactive" and in one "active" acromegalic patient. In addition, five other "inactive" patients and four "active" acromegalics had one or two BG values ex-

ceeding the upper limits of normal for venous blood: 170 mg/100 ml at 60 minutes, 120 mg/100 ml at 120 min, and/or 110 mg/100 ml at 180 min [12].

Fig. 1. Blood glucose response to 100 g glucose given orally, mean $\pm$ SE, in controls and "inactive" and "active" acromegalics

Serum insulin (IRI). The fasting level of serum IRI and the response of serum IRI to oral glucose load are shown in Fig. 2. The data on the two diabetics (cases # 22 and # 23) with active acromegaly, who received treatment for their diabetes, are not included. The fasting level of serum IRI in the "inactive" acromegalics was significantly higher than in the controls ($P < 0.05$). The hyperresponsiveness of serum IRI to glucose load in the "inactive" acromegalics was most pronounced at 90 min, the mean value of IRI being significantly higher than in the controls ($P < 0.05$). The six "inactive" acromegalics with impaired glucose tolerance had hyperinsulinism both fasting and after glucose load, and their mean serum IRI values fasting

The ratio of serum IRI to BG. The ratio of serum IRI to BG ($\frac{\mu\text{U/ml}}{\text{mg/100 ml}}$), indicating the responsiveness

Fig. 2. Serum insulin ($\mu\text{U/ml}$), mean $\pm$ SE, before and after administration of 100 g glucose orally in controls and "inactive" and "active" acromegalics. Two "active" acromegalics who received treatment for their diabetes are not included

of the islets to stimulation by glucose, is presented in Table 2. The IRI/BG ratio was higher in the fasting state in the "inactive" acromegalics than in the controls ($P < 0.05$), although BG was higher in the latter. Comparison between the ratio of "inactive" acromegalics and controls after glucose administration and at times when the BG was about the same in both groups, did not show significant differences. However, the ratio tended to be higher in the "inactive" acromegalics. The six "inactive" acromegalics with impaired glucose tolerance had a higher mean fasting IRI/BG ratio than the controls ($P < 0.05$), the BG values being in both groups about equal.

Table 2. The ratio of serum insulin, $\mu\text{U/ml}$, to blood glucose, mg/100 ml, in oral glucose tolerance test in control and acromegalic subjects, mean $\pm$ SE

	0	30 min.	60 min.	90 min.	120 min.	180 min.
Controls (13)	0.16 ± 0.05	0.89 ± 0.13	1.24 ± 0.18	1.03 ± 0.12	1.06 ± 0.15	
"Inactive" acromegalics (16)	0.34 ± 0.06	1.23 ± 0.20	1.27 ± 0.17	1.49 ± 0.26	1.37 ± 0.26	1.26 ± 0.23
"Active" acromegalics (5) ^a	0.53 ± 0.18	1.67 ± 0.42	1.78 ± 0.38	1.35 ± 0.22	2.01 ± 0.54	1.84 ± 0.49

^a Two diabetics receiving treatment omitted

and at 120 min were significantly higher than in the controls ($P < 0.02$ and < 0.005 respectively). The "active" acromegalics had significantly higher serum IRI values compared with the controls at 60 minutes ($P < 0.025$) and 90 min ($P < 0.05$).

Correlation of Δ BG to Δ IRI. A positive correlation existed between the changes in BG (Δ BG) and the changes in serum IRI (Δ IRI) from the fasting level both in the controls and the "inactive" acromegalics at 30 min (correlation coefficient $r = 0.56$, $P < 0.05$,

and $r = 0.57$, $P < 0.01$ respectively). At 90 min and at 120 min a correlation between Δ BG and Δ IRI was found only in the "inactive" acromegalics ($r = 0.60$, $P < 0.02$, and $r = 0.63$, $P < 0.005$ respectively). On the other hand, a positive correlation existed in the controls between the maximal increase in the BG over the fasting level and the increase in serum IRI at the same moment over the fasting level ($r = 0.57$, $P < 0.025$). This did not hold for the "inactive" acromegalics.

Growth hormone (GH). The mean values $\pm$ SE in the fasting state and after glucose load are shown in Fig. 3. One of the four female controls had a high fasting GH level of 31 ng/ml, which fell after glucose administration to 5 ng/ml at 60 minutes and 3.3 ng/ml at 120 min. The mean fasting GH value of the nine female "inactive" acromegalics was 8.6 ± 1.0 ng/ml and of the seven male "inactive" acromegalics 11.3 ± 1.6 ng/ml. The "inactive" acromegalics did not show marked changes in serum GH values after the glucose load, in contrast to the significant drop from the fasting level in the controls. GH levels in the "active" acromegalics were significantly higher than in the controls throughout the test, and usually higher than the levels in the "inactives".

Fig. 3. Serum growth hormone (ng/ml), mean $\pm$ SE before and after oral glucose load (100 g) in controls and "inactive" and "active" acromegalics.

Correlation of GH to IRI. A significant correlation existed between fasting GH level and fasting serum IRI value in the controls ($r = 0.61$, $P < 0.01$), but not in the two groups of patients with acromegaly. No correlation was found between fasting GH level and the maximal increase in serum IRI over the fasting level in any of the three groups.

Discussion

KARAM and co-workers [11] found the serum insulin response to glucose load normal in inactive acromegal-

ics, and increased in active acromegalics. The elevated serum insulin levels of the active acromegalics corresponded with the clinical criteria of activity regardless of the presence of diabetes. Some authors report an increased insulin response to glucose load after radiation treatment for acromegaly [1], others a decrease after radioactive yttrium (^{90}Y) implantation [15], and after treatment by hypophysectomy or X-rays [19].

LUFT and co-workers [13] described a normalization of the insulin response to glucose infusion after treatment of acromegaly with surgical hypophysectomy or ^{90}Y implantation in patients with normal pre-treatment k-values. In a group of three patients with impaired glucose tolerance before treatment, the glucose tolerance became normal postoperatively in two cases. However, the insulin response remained low in this group. The authors suggested that diabetes develops in acromegaly only in pre-diabetic individuals.

BODEN et al. [3], in their recent report on the GH response to intravenous glucose load in 17 acromegalics, 15 of whom had received conventional X-ray therapy, considered that their findings indicated a peripheral insensitivity to circulating endogenous insulin. The authors did not comment on the degree of activity of their patients' acromegaly, but the mean fasting GH value was 36.8 ± 5.2 $\mu\text{g/ml}$ and all individual fasting values exceeded the mean fasting values of normal subjects.

Our results indicate hyperinsulinism in both "inactive" and "active" acromegalic patients in the fasting state and after an oral glucose load. The sustained hyperresponsiveness in serum IRI to glucose load in the "inactive" acromegalics was reflected also in the longer-lasting correlation between changes in BG and changes in serum IRI compared with the controls. On the other hand, the "inactive" acromegalic group showed a lack of correlation between the maximal increase in BG and the corresponding increase in serum IRI over the fasting value. Furthermore, the "inactive" acromegalics had higher IRI/BG ratios than the controls. These two observations may indicate an excessive insulin secretion in the "inactive" acromegalics in response to a given glucose stimulation.

The hyperresponsiveness in serum IRI to glucose load in clinically and radiologically "inactive" acromegalics was observed one and a half to 12 years after treatment, suggesting that chronically elevated levels of circulating GH may have led to permanent changes in the responsiveness of the pancreatic islets to glucose stimulation. On the other hand, external irradiation may not arrest acromegaly totally, and therefore GH stimulation of the pancreatic islets might continue after treatment; this would be in keeping with the lack of suppression by oral glucose of GH levels in the "inactive" group. Our findings differ from those of KARAM et al. [11], who did not find insulin hyperresponsiveness in "inactive" acromegalics. The patients in our series were not clinically obese. Two "inactive" acromegalics were 135% of the average weights for age

and sex and two "active" acromegalics were 131% and 136% of average weights respectively. This increase over the average might be due to acromegaly itself.

The non-suppression or rise in serum GH levels after glucose load in the "active" acromegalics in our series correspond well with data reported earlier [18, 2, 4, 10, 17, and 5]. The question of the suppression of GH by glucose load in inactive acromegalics remains controversial: GREENWOOD et al. [6] did not find it after a meal in "burnt-out" acromegaly, nor did they find differences in postcibal serum GH values in acromegalics of varying clinical activity. SÖNKSEN and co-workers [19] described a patient whose posthypophysectomy serum GH dropped after a glucose load. In our series, the fasting GH levels in the controls were about equal to those in the "inactive" acromegalics, but glucose did not suppress serum GH in the latter.

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