Acromegaly and insulin resistance: a case study


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Abstract. Elevated levels of growth hormone (GH) alter both the glucose tolerance and the sensitivity of peripheral tissue to insulin. We have studied the relationship between impaired glucose metabolism and its variations with different plasma levels of endogenous GH in one patient with acromegaly. To do so, we studied the decline in blood glucose concentration, as induced by iv insulin infusion, from a given hyperglycaemic level. With high levels of GH (GH = 120 µg/l), the slope of the straight line representing the decrease in blood glucose after insulin infusion was -0.71, the time required to achieve normoglycaemic levels, 270 min, and the corrected area under the curve representing blood glucose 26070 units². After 10 months’ bromocriptine treatment, GH plasma concentration fell to 8 µg/l, at which point the slope of the straight line was -1.40, the time required to achieve normoglycaemic levels 115 min, and the area under the curve 8956 units². There was a greater total clearance of glucose when GH levels were lower (1.90 vs 1.00 ml/min/kg), as well as greater elimination of glucose from the extracellular glucose pool (4.02 vs 1.67 mg/min/kg). In conclusion, in this patient the elevated plasma levels of endogenous GH induced insulin resistance. Once GH levels were reduced by the administration of bromocriptine, glucose metabolism improved.

The initial studies of Houssay et al. (1932) and Young (1937) demonstrated a relationship between acromegaly and diabetes. Later works have attempted to study the mechanism by which GH induces changes in the glucose metabolism. Thus, some investigators have proposed that insulin resistance induced by GH could be explained by increased splanchnic release of glucose (Bratusch-Marrain et al. 1980). Others believe that such resistance is due to lack of sensitivity to endogenous insulin in peripheral tissue. Recently, Bratusch-Marrain et al. (1984) demonstrated that elevated GH plasma levels caused insulin resistance by a double mechanism: lack of sensitivity of peripheral tissue to insulin, and greater splanchnic release of glucose.

Studies of insulin receptor alterations in experimental animals (Kahn et al. 1978) and in acromegalic patients (Muggle et al. 1979) have demonstrated the existence of decreased binding in the presence of elevated concentrations of insulin. Maloff et al. (1980) showed, in in vitro studies, that deficient carbohydrate metabolism was due to a disturbance in glucose transport. Rizza et al. (1982), using the euglycaemic clamp technique, later showed that GH-determined insulin resistance in both hepatic and extrahepatic tissue was due to a postreceptor defect.

It has been suggested that the biochemical mechanism of resistance is an increase in fatty acid oxidation, which causes inhibition of glycolysis and subsequent inhibition of glucose phosphorylation (Kostyo & Reagan 1976). Most recently, this hypothesis has been put forward by Sherwin et al. (1983). Finally, Wade et al. (1982) identified and synthesized the C-terminal fragment of the GH molecule, which included the amino acid residue...
Nos. 178–191, where the insulin antagonitic activity resides.

In the present study we attempted to confirm, for the first time, the relationship between deficient glucose metabolism in one patient with acromegaly and the change of this metabolism with different plasma GH levels.

Material and Methods

Case history

On a 49 year old acromegalic woman, weighing 78 kg and 1.57 m tall, an oral glucose tolerance test was performed (100 g of glucose in a 20% water solution) in order to study the suppression of plasma GH. The results are shown in Table 1. A lateral X-ray of the skull demonstrated enlargement of the sella turcica, with a calculated volume (DiChiro & Nelson 1962) of 3.78 cm³.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose (mmol/l)</th>
<th>GH (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.8</td>
<td>27</td>
</tr>
<tr>
<td>30</td>
<td>7.8</td>
<td>23</td>
</tr>
<tr>
<td>60</td>
<td>10.4</td>
<td>27</td>
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<tr>
<td>90</td>
<td>—</td>
<td>23</td>
</tr>
<tr>
<td>120</td>
<td>10.9</td>
<td>21</td>
</tr>
<tr>
<td>150</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>180</td>
<td>9.3</td>
<td>22</td>
</tr>
</tbody>
</table>

A CAT scan confirmed the presence of a pituitary tumour (1.28 × 1.52 cm³) with no suprasellar extension (Fig. 1). The tumour, on removal, proved to be an

Fig. 1.

CAT scan of the sella turcica: enlargement of the sella caused by a pituitary tumour is demonstrated.
eosinophilic cell pituitary adenoma. Four months later a second OGTT was performed (see Table 2). A second CAT scan revealed that the adenoma had reappeared. A TRH test (Fig. 2) showed GH response, and therefore treatment with progressively increasing doses of bromocriptine was initiated. The patient discontinued treatment after a few days because of adverse reactions. Nine month postoperatively, she consulted us because of polyuria, polydipsia and polyphagia. Fasting glucose at this time was 20.2 mmol/l. She was treated with diet and NPH insulin, 10 units before breakfast and 5 units in later afternoon. Two weeks later she was taken to the emergency room and admitted to the hospital for ketoacidosis, which was corrected. Insulin was increased progressively without achieving adequate control (fasting glucose 18.3 ± 3.5 mmol/l).

**Table 2.** Postoperative GH response to oral glucose tolerance test (100 g).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose (mmol/l)</th>
<th>GH (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.1</td>
<td>24</td>
</tr>
<tr>
<td>30</td>
<td>9.7</td>
<td>26</td>
</tr>
<tr>
<td>60</td>
<td>12.5</td>
<td>34</td>
</tr>
<tr>
<td>90</td>
<td>14.6</td>
<td>35</td>
</tr>
<tr>
<td>120</td>
<td>14.5</td>
<td>31</td>
</tr>
<tr>
<td>150</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>

**Fig. 2.**

Four months after surgery, an abnormal response of GH levels (- - - -) to stimulation with TRH is noted. The response of prolactin (Prl) (Δ---Δ) is normal.

**Method**

A two step protocol was designed to follow the capacity for the elimination of glucose from the extracellular pool after insulin infusion, and to observe its relationship to GH levels.

**Step I.** One week after correction of her ketoacidosis, the patient was connected to the BIOSTATOR (GCIIS) (Miles), and her hyperglycaemia (16.8 mmol/l) was corrected according to a 3:1 static-dynamic mode of operation: maximum insulin infusion of 300 mU/min (FI), and insulin infusion of 24 mU/min (RI) when the blood glucose reached a predetermined level (B1) of 5.5 mmol/l. When normoglycaemia was achieved, basal GH, glucagon and C-peptide levels were determined. These were again noted after iv infusion of arginine hydrochloride (30 g) for 30 min; blood was taken at 5, 15, 30 and 60 min after the infusion was initiated. Bromocriptine treatment was then started, with a dose that was slowly increased to a maximum of 18.75 mg/day.

**Step II.** Bromocriptine (18.75 mg/day) was continued for 10 months, after which step I was repeated. At this point a bolus of 28 g of glucose followed by infusion of 40% glucose via BIOSTATOR, 7:1 mode of operation (static infusion of glucose) was needed to achieve a hyperglycaemia of 16.6 mmol/l. One blood glucose reached a steady state concentration of 16.6 mmol/l, it was corrected as in step I; in this case FI = 306 mU/min; RI = 24 mU/min; and B1 = 5.5 mmol/l. Plasma insulin and C-peptide levels were measured in the basal period (blood glucose = 5.6 mmol/l), at the hyperglycaemic peak (blood glucose = 16.6 mmol/l), and during iv insulin infusion. Basal GH was also measured. Blood glucose was measured by the analyzer in the BIOSTATOR (GCIIS) (Fogt et al. 1978). The Tandem kit was used for GH determinations (normal values < 7 µg/l), and the Gammacon kit was used for insulin (normal values < 20 µU/ml). C-peptide levels were determined with the Immunex kit, the normal values of which for non-diabetics are 1.79 ng/ml (normal range between 0 and 5.4 ng/ml). Glucagon was measured with the Radioassays System Laboratories kit (normal range between 50 and 125 pg/ml).

**Calculations**

The following were calculated: 1) the slope and corresponding angle of the straight line representing the best approximation of the fall in blood glucose from 16.6 to 5.5 mmol/l, using a least-square fit, 2) time course (in min) of decline in blood glucose from 16.6 to 5.5 mmol/l, 3) corrected area under the curve of decline in blood glucose, in units², 4) insulin infusion (units) necessary to correct the initial hyperglycaemia, 5) fractional turnover of glucose (K), defined as the time necessary for glucose to fall to half its highest concentration (K = 0.693/t½ · min⁻¹), 6) total clearance of glucose, expressed as the product of the fractional turnover (K).

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and the volume of distribution of glucose (25% body weight) (ml/min/kg) (Reichard et al. 1961; Manocigian et al. 1964). 7) total rate of removal of glucose from the extracellular pool, calculated as the product of the volume of distribution and the decline in blood glucose, divided by the time course of the decline, according to the following formula: glucose removal (mg/min/kg) = glucose(initial) – glucose(final) (mg/ml) × 250 ml/kg time(final) – time(initial) (min).

\[ \text{Corrected area under the curve of blood glucose (units²)} \]

\[ \text{Time needed to reach normoglycaemia (min)} \]

\[ \text{Insulin infusion (units)} \]

\[ \text{Fractional turnover of glucose (\% \cdot min}^{-1}) \]

\[ \text{Total glucose clearance (ml/min/kg)} \]

\[ \text{Total rate of removal of glucose from the extracellular glucose pool (mg/min/kg)} \]

Table 3.

Parameters for the study of the decline in blood glucose to normoglycaemic levels after iv insulin infusion.

<table>
<thead>
<tr>
<th></th>
<th>Step I</th>
<th>Step II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope of the decline in blood glucose</td>
<td>-0.71</td>
<td>-1.40</td>
</tr>
<tr>
<td>Corrected area under the curve of blood glucose (units²)</td>
<td>26070</td>
<td>8956</td>
</tr>
<tr>
<td>Time needed to reach normoglycaemia (min)</td>
<td>270</td>
<td>115</td>
</tr>
<tr>
<td>Insulin infusion (units)</td>
<td>45.38</td>
<td>13.52</td>
</tr>
<tr>
<td>Fractional turnover of glucose (% \cdot min}^{-1})</td>
<td>0.40</td>
<td>0.76</td>
</tr>
<tr>
<td>Total glucose clearance (ml/min/kg)</td>
<td>1.00</td>
<td>1.90</td>
</tr>
<tr>
<td>Total rate of removal of glucose from the extracellular glucose pool (mg/min/kg)</td>
<td>1.67</td>
<td>4.02</td>
</tr>
</tbody>
</table>

Results

The equation for the straight line representing the glucose fall after insulin infusion in the presence of active acromegaly (GH = 120 µg/l) was

\[ Y = -0.741X + 314.982, \]

with a slope of -0.71.

---

**Fig. 3.**

Upper: curve of blood glucose decrease in step I and in step II after iv insulin infusion. The fall in blood glucose was more marked in step II (step I: O--O) (step II: Δ---Δ). Lower: insulin infusion necessary to obtain normoglycaemia in steps I and II. The corrected area under the curve of insulin infusion is less when GH levels are lower (step II).

**Fig. 4.**

Response of glucagon (Δ---Δ) and C-peptide (O--O) levels to iv infusion of 30 g of arginine hydrochloride (0.5 g/kg body weight).
This represents an angle of decline of 145°. The time from maximum glucose concentration to normoglycaemia was 270 min, and the corrected area under the curve of glucose decline was 26,070 units² (Fig. 3). The amount of insulin necessary to obtain normoglycaemia was 45 units. In the step I study, the fractional turnover of glucose and the total clearance of glucose were 0.40% · min⁻¹ and 1.00 ml/min/kg, respectively. The total rate of removal of glucose from the extracellular glucose pool was 1.67 mg/min/kg (Table 3).

Glucagon and C-peptide levels were normal under basal conditions and after arginine infusion (Fig. 4).

Once treatment with bromocriptine was started, insulin needs were drastically reduced. As the bromocriptine dose was slowly increased, daily insulin requirements decreased inversely (day 5–15) (Fig. 5). This coincided with a decline in plasma GH levels from 120 to 8 µg/l.

In the step I study, the equation for the best approximation of the straight line representing the fall in blood glucose was \( Y = -1.430X + 280.56 \), with a slope of \(-1.40\), representing an angle decline of 125°. The corrected area under the curve of glucose decline was 8956 units² (Fig. 3). The time from maximum glucose levels to normoglycaemia was 115 min, and the amount of infused insulin to obtain normoglycaemia 14 units. The fractional turnover of glucose and the total clearance were 0.76% · min and 1.90 ml/min/kg, respectively. The total rate of removal of glucose from the extracellular glucose pool was 4.02 mg/min/kg (Table 3). Basal plasma GH, determined after this study was 8 µg/l.

Basal insulin concentration prior to administration of the glucose bolus was 20 µU/ml (5.6 mmol/l blood glucose). During peak hyperglycaemia (16.6 mmol/l), which reached a steady state 54 min after bolus administration, the insulin concentration was 40 µU/ml. During iv insulin infusion, insulin values were 111 and 62 µU/ml, with blood glucose values of 11.6 and 6.4 mmol/l, respectively.

**Discussion**

This study demonstrates the existence of insulin resistance in the presence of elevated GH levels. Thus, when the patient's acromegaly was in the active phase (GH = 120 µg/l), the capacity for glucose turnover was notably less than that found 10 months later, when the patient was receiving bromocriptine and had lower GH levels. Deficient glucose turnover was also demonstrated by the amount of infused insulin needed to obtain a decline in blood glucose: much greater during active acromegaly than during administration of bromocriptine. Therefore, in the presence of elevated levels of GH there is decreased sensitivity of peripheral tissue to insulin. This had been seen prior
to the initiation of the study since the patient’s insulin needs rose 72 units over her initial dose after correction of ketoacidosis. Basal GH levels coinciding with the highest insulin needs were 120 μg/l. It should also be pointed out that the fractional turnover, clearance and total rate of removal of glucose from the extracellular glucose pool were lower than those found when the GH hypersecretion was controlled.

Support for these observations comes from the work of Marek et al. (1976), who noted that patients with acromegaly and high GH levels had a greater probability of developing diabetes than those whose GH levels were lower, despite the fact that 23% of those with elevated GH levels showed normal insulin secretion and glucose tolerance. Other investigators have found no relationship between basal GH levels and tissue sensitivity to iv insulin (Harrison & Flier 1980). Still others have failed to note any relationship between the levels of glucose, insulin and GH, offering as an explanation the absence of an integrated level of GH and the discrepancy between the bioactive and immunoreactive forms of the hormones (Herrington et al. 1974). Nonetheless, Rizza et al. (1982) and Bratusch-Marrain et al. (1982), using the glucose clamp, have clearly shown that GH infusion produces insulin resistance in peripheral tissue as well as resistance to insulin-mediated hepatic glucose production.

Various possible causative factors have been ruled out: the possibility of a pancreatic lesion by the finding of normal basal levels of C-peptide, which responded adequately to arginine infusion; hyperglycaemia by the demonstration of normal basal levels of this substance; and increased hepatic gluconeogenesis by the induced hyperglycaemia and hyperinsulinaemia, which are known to inhibit hepatic production of glucose (Liljenquist et al. 1979; Sacca et al. 1981). Notwithstanding, Bratusch-Marrain et al. (1984) observed, in the presence of elevated GH levels, an increased release of glucose from the splanchnic area after oral glucose ingestion, despite the existence of hyperglycaemia and hyperinsulinaemia. Therefore, the ‘anti-insulin’ activity of GH could theoretically act at both hepatic and extrahepatic sites.

Although, theoretically, the reduced tissue response to insulin in this patient could be explained by her obesity (53% overweight), there was a notable improvement of the metabolic capacity for glucose in the second step of the study, when the patient was even more overweight (63%). In normal weight controls, Barret et al. (1982) found the fractional turnover and time of glycæmic decline to be 1.95–3.7% · min⁻¹ and 0.31 ± 0.03 h, respectively, indicating an insulin sensitivity significantly greater than that presented by our patient during step II.

Another indication of the effect of GH levels on peripheral tissue sensitivity to insulin was the decrease in daily insulin needs during bromocriptine treatment. Schwinn et al. (1977) and Demura et al. (1978) also reported improved glucose tolerance and insulin secretion following bromocriptine treatment in many - though not all - cases.

In conclusion, the elevated GH levels in this patient produced insulin resistance. Bromocriptine treatment decreased GH and improved the glucose metabolism.

Acknowledgment

We are grateful to Miss Rosa Ares and Miss Luisa Igle

References


Received on February 13th, 1985.