Assessment of Insulin Resistance in Acromegaly Associated with Diabetes Mellitus before and after Transsphenoidal Adenomectomy

TARO WASADA, KAORI AOKI, AKIKO SATO, KOZO KATSUMORI, KAZUKO MUTO, OSAMU TOMONAGA, HIROKI YOKOYAMA, NAOKO IWASAKI, TETSUYA BABAZONO, CHIEKO TAKAHASHI, YASUHIKO IWAMOTO, YASUE OMORI, AND NAOMI HIZUKA*

Diabetes Center, *Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical College, Tokyo 162, Japan

Abstract. With a euglycemic hyperinsulinemic clamp method, whole-body insulin resistance was assessed in 6 cases with acromegaly associated with diabetes mellitus before and after transsphenoidal adenomectomy. The glucose infusion rate (GIR) correlated well with the plasma IGF-I level but poorly with that of GH. Further improvement in insulin sensitivity occurred 3-4 months after operation without substantial changes in plasma levels of both GH and IGF-I or glycemic control. These results indicate that GH excess can induce insulin resistance in association with plasma IGF-1 and also through undefined secondary effect.

Key words: Acromegaly, Adenomectomy, IGF-1, Insulin resistance

Received: October 25, 1996
Accepted: May 6, 1997

Correspondence to: Dr. Taro WASADA, Diabetes Center, Tokyo Women's Medical College, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan

IMPARED glucose tolerance or overt diabetes mellitus is frequently accompanied by acromegaly [1]. It is easy to suppose that insulin resistance plays a major role in the dysfunction of glucose homeostasis in this disorder, in which there coexists hyperinsulinemia or increased requirement of insulin, but there have been only a limited number of studies on the extent to which chronic GH excess actually causes insulin resistance [2, 3]. To understand the pathophysiology of diabetes secondary to acromegaly, it is necessary to assess how GH interfere with the action of insulin. Whole-body insulin resistance can be assessed by such quantitative methods as the euglycemic hyperinsulinemic clamp technique. Employing an identical clamp procedure helps in comparing the intensity of resistance to insulin-stimulated glucose uptake in various insulin-resistant conditions including excesses of other counterregulatory hormones and diabetes mellitus itself. We investigated the temporal relationship between the degree of insulin resistance and changes in plasma GH and IGF-I levels before and after transsphenoidal adenomectomy in 6 cases of acromegaly.

Patients and Methods

Patients

The present study population included six patients with acromegaly who initially presented with diabetes mellitus. All the patients underwent transsphenoidal adenomectomy (Hardy's operation). Four of 6 cases (Nos 1, 2, 5 and 6)
achieved total removal of the adenoma, but in two cases (Nos 3 and 4) there was only partial resection. No patients required any hormone replacement therapy postoperatively. The patients were given a detailed explanation of the purpose and protocol of the study, and their consent was obtained.

**Euglycemic hyperinsulinemic clamp study**

The euglycemic clamp study was performed with an artificial endocrine pancreas (Nikkiso STG-22, Nikkiso Co., Tokyo) as previously reported [4]. Briefly, after overnight fasting the subjects received primed-continuous infusion of insulin at the rate of 1.12 mU/kg/min, and the peripheral venous plasma glucose level was kept constant at 80 mg/dl by infusing 10% glucose solution according to the preprogrammed algorithm originally described by DeFronzo et al. [5]. The mean steady-state plasma insulin level was 68.5 ± 4.2 uU/ml (mean ± SEM). The clamp study was continued for 60 to 90 min after plasma glucose reached the plateau level. The average glucose infusion rate (GIR) was determined as an index of the whole-body insulin sensitivity during the last 30 min of steady-state euglycemia. No effort was made to reduce fasting plasma glucose level to near normal range during the preceding night of the experimental day. The clamp study was conducted before and around one month after surgery in all cases, and further clamp was repeated 3-4 months later in some cases.

**Assay of plasma IGF-I**

Plasma IGF-I levels were measured with an RIA kit (Nichols Institute Diagnostics, San Juan Capistrano, CA) and acid-ethanol extracted samples. In Case 1, several samples were also measured directly by using EDTA plasma with the same kit, and the values are expressed as U/ml instead of ng/ml. Plasma samples for determination of GH or IGF-1 concentrations were taken at the time close to the clamp study.

**Results**

Table 1 shows plasma GH and IGF-1 concentrations as well as the corresponding data for GIR and clinical parameters before and after the operation. The postoperative GIR was determined three to five weeks after selective adenomectomy in all cases. GIR values before surgery seemed to correlate well with IGF-1 concentrations (Fig. 1) rather than those of GH (Fig. 2). After surgery, GIR values improved in all cases, four of them returning to within the normal range. As shown in Fig. 2, the second GIR in Case 1 was determined after three-weeks' treatment with octreotide (50 µg, twice a day for the first 2 weeks, followed by 50 µg three times a day for a further week). This treatment had a minimal effect on GIR (from 0.77 to 1.9 mg/kg/min), despite substantial decreases in GH from 90.1 to 28.4 ng/ml, IGF-I from 7.9 to 1.14 U/ml (normal range: 0.4-1.6), FPG from 220 to 121 mg/dl, and HbA1c from 12.6 to 8.3%. Cases 1 and 2 showed further improvement in GIR (from 3.00 to 7.36 in Case 1, and from 4.81 to 6.95 in Case 2, respectively) over the 3-4 months after the operation, although there were no apparent changes in HbA1c (from 7.6 to 6.9% in Case 1, from 7.0 to 7.1% in Case 2) or the IGF-1 level (from 0.48 to 0.51 U/ml in Case 1, from 150 to 120 ng/ml in Case 2).

<table>
<thead>
<tr>
<th>Case No</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
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<td>54/M</td>
<td>38/M</td>
<td>48/M</td>
<td>53/M</td>
<td>56/F</td>
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<tr>
<td>GH (ng/ml) before</td>
<td>90.1</td>
<td>41.8</td>
<td>127.5</td>
<td>30.3</td>
<td>30.9</td>
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<td>3.3</td>
<td>24.2</td>
<td>23.0</td>
<td>1.8</td>
<td>2.9</td>
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<td>IGF-1 (ng/ml) before</td>
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<td>547</td>
<td>773</td>
<td>1100</td>
<td>691</td>
<td>1405</td>
</tr>
<tr>
<td>after</td>
<td>312</td>
<td>150</td>
<td>530</td>
<td>–</td>
<td>309</td>
<td>294</td>
</tr>
<tr>
<td>FPG (mg/dl) before</td>
<td>220</td>
<td>102</td>
<td>178</td>
<td>115</td>
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<td>116</td>
<td>71</td>
<td>98</td>
<td>100</td>
<td>113</td>
<td>128</td>
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<tr>
<td>HbA1c (%) before</td>
<td>12.6</td>
<td>11.5</td>
<td>10.6</td>
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<td>0*</td>
<td>46</td>
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</tbody>
</table>

GIR (mg/kg/min) before, after surgery: Normal range for IGF-1, 106–398 ng/ml (male); 121–436 ng/ml (female). *; diet alone.
Discussion

Lowering plasma GH levels after removal of a pituitary adenoma resulted in normalization of the GIR value in all the patients except one in which only partial removal was achieved. These observations indicate that a chronic increase in the plasma GH concentration is a major cause of insulin resistance in acromegaly, but the plasma levels of GH and GIR value showed poor correlations among individual patients (Fig. 2), suggesting that other factors are also involved. IGF-I appears to be more directly related to insulin resistance (Fig. 1). For example, the subnormal GIR values in Cases 2 and 3 (3.15 and 4.16 mg/kg/min, respectively) despite of much increased GH levels (41.8 and 127.5 ng/ml, respectively) may be explained in part by only slightly increased IGF-I concentrations (547 and 773 ng/ml, respectively) (Table 1). In contrast, Cases 4 and 6 had lower GIR values (2.21 and 0.57 mg/kg/min, respectively), which may be attributed to higher IGF-1 levels (1405 and 1100 ng/ml, respectively), despite of moderately increased GH levels (20.4 and 23.0 ng/ml, respectively). The dissociation between plasma GH and IGF-I levels is not a rare occurrence in acromegaly. Previous studies [6, 7] demonstrated that there was weak correlation between serum GH and IGF-I concentrations with an r value of 0.31, and suggested that IGF-I measurements correlated better with the clinical manifestations of disease activity than did random serum GH measurements. Therefore, it is reasonable to consider that insulin-mediated glucose uptake is more directly affected by the plasma level of IGF-1 than that of GH.

Another point of interest is the continued improvement in insulin resistance over 3-4 months after pituitary adenomectomy as observed in Cases 1 and 2 (Fig. 2). This occurred despite comparable plasma levels of GH, IGF-1, and glycemic condition. Furthermore, in Case 1 short-term suppression of plasma GH and IGF-I with octreotide treatment resulted in a minimal improvement in GIR. These findings suggest that a delayed process may be involved during complete restoration of insulin...
sensitivity.

In previous studies, the administration of pharmacological and physiological amounts of GH increased glucose production and decreased insulin-stimulated glucose uptake [2, 3, 8]. Since GH excess has not been shown to impair insulin binding in any of the tissues studied [9, 10], GH seems to interfere with the actions of insulin through post-receptor mechanisms in both the liver and peripheral tissues including the muscle. In conclusion, whole-body insulin resistance was reduced along with lowering plasma IGF-I concentrations in acromegaly, and complete restoration of insulin resistance took several months after normalization of the hormone levels.

References