Diabetes Mellitus Following Hypophysectomy in Previously Normoglycaemic Patients with Acromegaly

B. Larijani, M.D.*, M. Nakhjavani, M.D.**

* Professor, **Associate Professor, Endocrine & Metabolism Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

Correspondence: Professor B. Larijani, Endocrine & Metabolism Research Center, Shariati Hospital, North Kargar Street, Tehran, 14114, Iran; E mail: emrc@sina.tums.ac.ir, Tel: +98 (21) 802-6902, Fax: +98 (21) 802-6903

Abstract:

Insulin resistance, impaired glucose tolerance and diabetes mellitus secondary to acromegaly generally improve following treatment of the underlying disease. In rare cases, in spite of normoglycaemia in the presence of active acromegaly, patients develop diabetes mellitus following hypophysectomy, to such an extent that insulin is required to control their diabetes. This article introduces the cases of 5 patients who underwent hypophysectomy between 1985 and 1996 at the Shariati and Imam Khomeiny hospitals in Tehran. In view of the above phenomenon, however, the regular measurement of blood glucose levels in post-hypophysectomy patients, even if normoglycaemic prior to surgery, seems to be a necessary step.

Key Words: Acromegaly, Diabetes Mellitus, Hypophysectomy, Growth Hormone.
Introduction:

Growth hormone has a biphasic effect, that is to say at low levels, it has an anti-insulin effect whereas moderate and high levels, it exhibits an insulin-like effect\(^1,2,3\). In the event of chronic exposure, the diabetogenic effects of growth hormone appear as reduced peripheral glucose uptake, a drop in adipocyte response to insulin, and increased blood glucose output by hepatocytes. Certain growth hormone by-products and metabolites also exert an influence on glucose metabolism, such as hGH1-43, which has an insulin-like hypoglycaemic effect, and hGH172-191, which has diabetogenic effects\(^5\). Impaired glucose tolerance is seen in 60-70 percent of patients with acromegaly, and in 10-20 percent of patients who are suitably predisposed, overt diabetes develops\(^1,2,3,4\). Following successful treatment of acromegaly, one expects growth hormone levels, as well as the response to glucose tolerance testing, to return to normal. In rare cases, however, through an unknown mechanism, patients have developed diabetes mellitus following treatment for acromegaly, whereas these patients had been normoglycaemic prior to treatment. This article introduces five such cases.

Case Summaries:

The five patients in question, aged between 17 and 65 years, all had acromegaly with normal blood glucose levels. Following hypophysectomy, which all five underwent between 1985 and 1996 at the Shariati or Imam Khomeiny hospitals in Tehran, the patients developed diabetes mellitus. Table 1 shows pre- and post-surgery growth hormone and blood glucose levels in these five patients.

Patient 1

Patient 1 was a 54 year-old woman who was diagnosed with acromegaly and admitted to hospital in 1985 with a five-year history of limb enlargement, weight gain, lethargy, paraesthesia and sleepiness. CT scan revealed a hypodense lesion in the sellar region. In addition to raised growth hormone levels, the patient also had hyper prolactinaemia (prolactin = 762 mu/ml). Growth hormone levels remained persistently high before and after glucose tolerance testing. The patient underwent Transsphenoidal Hypophysectomy. The pathology examination revealed an acidophilic pituitary adenoma. The patient also received a few sessions of radiation therapy. Seven months after surgery, the patient, having presented with polydipsia, polyuria and vaginal irritation and pruritus, was once again initiated on 20 units of insulin per day. Investigations at the time revealed normal levels of pituitary hormones and no evidence of tumor recurrence was discovered.

Patient 2

The second patient was a 35 year-old man who was admitted to hospital in 1988 with a diagnosis of acromegaly following a four-year history of headaches and progressive limb enlargement. His brain CT scan revealed a pituitary tumor. Fasting and postprandial blood glucose levels were normal. This patient, too, had hyperprolactinaemia in addition to elevated growth hormone levels (prolactin = 2000 mu/ml). The patient underwent hypophysectomy the same year, and received 25 sessions of radiation therapy because of residual symptoms. Two months later, the patient presented with polydipsia and polyuria and, following investigation, was diagnosed with diabetes mellitus and was initiated on 55 units of insulin per day.

Patient 3

Patient 3 was a 40 year-old man with an acromegalic appearance who, based on paraclinical findings, was diagnosed with a pituitary tumour and underwent craniotomy and hypophysectomy. The pathology report indicated a suprasellar pituitary adenoma with direct extension to the temporal region. Post-surgery, the patient developed polydipsia, polyuria and polyphagia, and presented one month later with a clinical picture of diabetic ketoacidosis (DKA), for which he was treated appropriately. This patient requires 150 units of NPH and 35 units of regular insulin per day in order to maintain blood glucose control.

Patient 4

Patient 4 was a 65 year-old man who was admitted to hospital in 1993 with acromegaly. Clinical symptoms
had first appeared 20 years earlier, in the form of gradual limb enlargement and changing appearance. Brain CT scanning revealed enlargement of the sella turcica and the presence of a mass within it. That same year, the patient underwent transsphenoidal hypophysectomy. The pathology report pointed to an chromophobe-acidophilic pituitary tumour. The patient developed symptoms of hyperglycaemia following surgery. Laboratory investigation pointed to the presence of diabetes mellitus. During his stay in hospital, the patient was treated with insulin but, following discharge, treatment was discontinued because his hyperglycaemia had been resolved.

**Patient 5**

Patient 5 was a 17 year-old woman who was admitted for the second time to hospital in 1996 with a diagnosis of pituitary tumor. Three years before, with a clinical picture indicating elevated growth hormone levels and following laboratory evaluation, a diagnosis of acromegaly had been confirmed, and the patient had undergone transsphenoidal hypophysectomy. The patient's last referral was for limb enlargement, headache and amenorrhea. A brain CT scan revealed enlargement of the sella turcica together with the presence of a macroadenoma. The patient once again underwent surgery (craniotomy, this time). One month later, the patient developed symptoms of hyperglycaemia and subsequent laboratory investigations confirmed the diagnosis of diabetes mellitus. To maintain blood glucose control, the patient requires a mixture of NPH and regular insulin (135 units in total).

**Discussion**

The goal of therapy in acromegaly is to reduce or eliminate its clinical and paraclinical manifestations. There are different methods of treatment for this disease. The most prevalent forms are surgical, radiation and medical therapies. The first step in the treatment of acromegaly is invariably surgery. Patients with post-surgical recurrence, or those who are not suitable surgical candidates, may be treated with radiation or pharmacological agents. In the event of success, these treatment modalities can also eliminate the secondary manifestations of disease, such as diabetes mellitus\(^{(1,2,3)}\). Against expectations, however, diabetes mellitus emerges post-operatively in rare cases, such as the five patients introduced in this article. Similar cases have been reported by other investigators, such as Bunick et al, who in 1977 described a 32 year-old woman with acromegaly, who was normoglycaemic before undergoing transsphenoidal hypophysectomy, but thereafter developed elevated blood sugar levels. The patient's blood sugar went from 334 mg/dl during surgery to 506 mg/dl on the third post-operative day; she was initiated on 30 units of NPH insulin per day in order to achieve glycaemic control. This report does not describe any particular correlation between growth hormone levels, duration of acromegaly, and the incidence of diabetes\(^{(6)}\). In another study in 1978, Maruyamo et al investigated five acromegalic patients with diabetes and impaired glucose tolerance, three acromegalic patients without diabetes or impaired glucose tolerance, and six patients with prolactinoma. Patients were administered steroids pre-operatively in this study, which caused an elevation in blood sugar in the first group but no glycaemic changes in the second and third groups. Upon induction of anesthesia and surgery, fasting blood glucose in all three groups rose in similar fashion. According to the results of this study, manipulation of the tumor during surgical procedure did not lead to an elevation in growth hormone levels compared to pre-operatively\(^{(7)}\). Lindhop et al also reported on two acromegalic patients in 1975, both of whom required repeat operations as part of their treatment. One of the patients developed diabetes mellitus, Cushing's and thyrotoxicosis following the initial surgical intervention\(^{(8)}\).

Conventionally, treatment of acromegaly leads to a reduction in growth hormone levels, which should therefore reduce or eliminate the symptoms and secondary manifestations of the disease.

The above reports, however, point to the occurrence of diabetes mellitus in previously normoglycaemic patients following surgery. Anesthesia and surgery both activate the hypothalamic-pituitary-adrenal axis. On the other hand, stimulation of the hypothalamus activates the sympathetic nervous system, thereby increasing circulating catecholamine levels. The latter also lead to elevated blood glucose
levels. Intra-operative manipulation of the tumor can lead to a sudden surge in circulating growth hormone, and consequently blood glucose levels (Figure 1, below).

Figure 1: Glycaemic Influence of Surgery and Anaesthesia

All the mechanisms referred to above cause transient diabetes mellitus. According to the aforementioned reports, however, diabetes persists in certain patients and requires insulin therapy. This phenomenon may be due to a disturbance in tissue glucose metabolism, which leads to an impaired glucose tolerance test (1,2). The bi-phasic effect of growth hormone in different quantities - exhibiting anti-insulin effects at low levels and pro-insulin effects at intermediate and high levels - may also possibly play a determining role in the occurrence of this phenomenon (1,2,3). In any case, the principal mechanism underlying this phenomenon remains unknown.

Given that this phenomenon indeed occurs, regular blood glucose determinations after hypophysectomy, even in patients who are normoglycaemic prior to surgery, seem to be indicated.

### Table 1: Blood Glucose and Growth Hormone levels Before and After Hypophysectomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Growth Hormone (ng/ml)</th>
<th>Blood Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Surgery</td>
<td>After Surgery</td>
</tr>
<tr>
<td>1</td>
<td>17</td>
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<tr>
<td>2</td>
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<td>-</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>7.3</td>
</tr>
</tbody>
</table>

FBS = Fasting Blood Sugar
BS = Postprandial Blood Glucose

### References