

Decrease in Growth Hormone and Insulin-like Growth Factor (IGF) - 1 Release and Amelioration of Acromegaly Features after Rosiglitazone Treatment of Type 2 Diabetes Mellitus in a Patient with Acromegaly

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A 28-year-old woman with clinical features of acromegaly and diabetes mellitus was admitted to our Reference Center for Clinical Neuroendocrinology and Pituitary Diseases at Sisters of Mercy University Hospital, Zagreb, Croatia. Magnetic resonance scan of the brain showed pituitary macroadenoma. After transsphenoidal resection, histological analysis confirmed it was a growth hormone (GH)-secreting pituitary adenoma. The tumor could not be completely removed, but the hormonal status normalized. A month after the surgery, octreotide was introduced because of a further increase in GH and insulin-like growth factor-I (IGF-I), but discontinued after a week due to intolerance. Alternative treatment with oral anti-diabetic agent, rosiglitazone, was introduced two weeks after octreotide was discontinued, and the fasting blood glucose concentration decreased from 8.4 mmol/L before the treatment to 6.7 mmol/L after 90 days of treatment. The concentration of GH and IGF-I in the week before rosiglitazone was introduced was 5.96 ng/mL and 990 ng/mL, respectively, and decreased to 2.92 ng/mL and 180.0 ng/mL, respectively, after 90 days of treatment. There was also a pronounced improvement in acromegalic features. It is possible that rosiglitazone induced the decrease in GH and IGF-I concentrations and its role in the long-term medical therapy of patients with pituitary tumors should be further investigated.

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Acromegaly is a disease characterized by excessive growth hormone (GH) secretion from pituitary adenomas, which in turn leads to overexpression of IGF-I, the main effector of GH action (1-3). Treatment of acromegaly is a therapeutic challenge (4). In most of these GH-secreting pituitary tumors, dopamine agonists or somatostatin analogues suppress the hypersecretion of GH and control tumor growth or induce tumor shrinkage (4,5). Nevertheless, a subset of patients with GH-secreting pituitary tumors do not respond to or do not tolerate these drugs (5,6). Pituitary microsurgery is usually the treatment of first choice, but is not always successful in achieving early remission. It is also associated with a significant incidence of late relapse. In spite of the combination of surgery, external x-ray therapy and medical therapy, many patients continue to have uncontrolled GH secretion and active disease (7). Excessive GH concentrations lead to insulin resistance in 80% of patients with acromegaly, with impaired glucose tolerance occurring in approximately 40% and diabetes mellitus in 10%-20% (8). These parameters improve with treatment, and complete resolution of diabetes mellitus occurs in two-thirds of these patients after successful surgery (2,8).

Rosiglitazone has been widely used in clinical practice as an oral antidiabetic agent for the treatment of diabetes mellitus and disturbed lipid metabolism in patients with type 2 diabetes mellitus and obesity (9). It also improves insulin sensitivity and glucose homeostasis in patients with impaired glucose tolerance (10). Rosiglitazone belongs to the class of thiazolidinediones, a group of compounds with high affinity for a nuclear hormone receptor pituitary peroxisome proliferator-activated receptor-gamma (PPAR- γ) (9). Activation of PPAR- γ is involved in adipocyte differentiation process (11), glucose metabolism (9), inhibition of inflammatory response (12), and anti-angiogenesis (13). Recently, abundant expression of this receptor was demonstrated in human PRL- and GH-secreting and non-func-

tioning pituitary tumors, as well as inhibition of tumor growth and hormonal activity in vivo and in vitro by PPAR- γ ligands (14). Bogazzi et al (15) demonstrated that PPAR- γ is expressed in all human GH-secreting adenomas and controlled GH transcription and secretion, as well as apoptosis and growth of GH-adenomas. In this case report, we describe the effects of rosiglitazone treatment of diabetes mellitus in a patient with acromegaly caused by a GH-secreting pituitary tumor.

Case Report

A 28-year-old woman, presenting with headache, bitemporal hemianopia, coarsening of the facial features and soft tissue, and swelling of the hands and feet was admitted to our Reference Center. These symptoms had been developing for four years before she was admitted. She was never treated before and was referred to the center by her general practitioner. The patient underwent physical examination, laboratory testing, and magnetic resonance imaging (MRI) of the head. Blood pressure was normal (120/80 mm Hg) and body mass index was 24.4 kg/m². Radioimmunoassay showed increased serum GH concentration of 28.31 ng/mL (normal values, <5 ng/mL). The concentration of IGF-I, determined with immunoradiometric assay, was also increased to >1300 ng/mL (normal range, 115-420 ng/mL) and there was a failure of adequate GH suppression after oral administration of 75 mg of glucose (appropriate suppression, after glucose load GH <1 ng/mL). Fasting plasma glucose was 8.4 mmol/L, postprandial plasma glucose 9.1 mmol/L, and HbA_{1c} 7.6%, confirming the diagnosis of type 2 diabetes mellitus. Renal and hepatic functions were normal, as well as electrolytes. The concentrations of thyroxine, triiodothyronine, thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH), cortisol, and prolactin (PRL) were normal, but the levels of gonadotropins were extremely low: luteinizing

hormone (LH) <1.0 IU/L (normal range, 1.9-8.0 IU/L), follicle-stimulating hormone (FSH) 1.2 IU/L (normal range, 2.4-9.3 IU/L) with resulting low levels of peripheral sex hormones estradiol 76 pmol/L (normal range, 92-367 pmol/L), progesterone <0.3 nmol/L (normal range, 0.3-3.8 nmol/L).

The initial MRI of the pituitary region, performed on a Siemens 1T instrument (Siemens, Erlangen, Germany), with 2-mm thick sections, showed a 40×30×40 mm macroadenoma of the pituitary gland (Figure 1A). The patient underwent transsphenoidal surgery, but the tumor could not be completely removed (Figure 1B). The residual tumor mass of 16×19×12 mm was located in the left cavernous sinus, adjacent to the cavernous segment of the internal carotid artery. Postoperative histological analysis of the resected tumor tissue confirmed the diagnosis of GH-secreting pituitary adenoma. A week after the operation, the patient's hormonal status was normal, with a decrease in the concentration of growth hormone to 4.20 ng/mL and IGF-I to 486 ng/mL. Since the concentrations of growth hormone and IGF-I increased again to 6.15 ng/mL and 637 ng/mL, respectively, one month after the operation, octreotide treatment was introduced.

Treatment with octreotide (Sandostatin, Sandoz Pharma Ltd, Basel, Switzerland) in a subcutaneous daily dose of 0.5 mg, which was commenced 30 days after the surgery, had to be discontinued after one week due to intolerance. The evaluation of patient's hormonal status two weeks after the discontinuation of octreotide treatment revealed increased concentrations of both growth hormone (5.96 ng/mL) and IGF-I (990 ng/mL). In addition, the patient complained of visual disturbances and headaches, while the swelling of the lips and enlargement of the hands and feet were still present. Treatment with oral PPAR- γ agonist rosiglitazone (Avandia, Glaxo Wellcome Production, Mayenne, France) in a dose of 8 mg once per day was introduced for

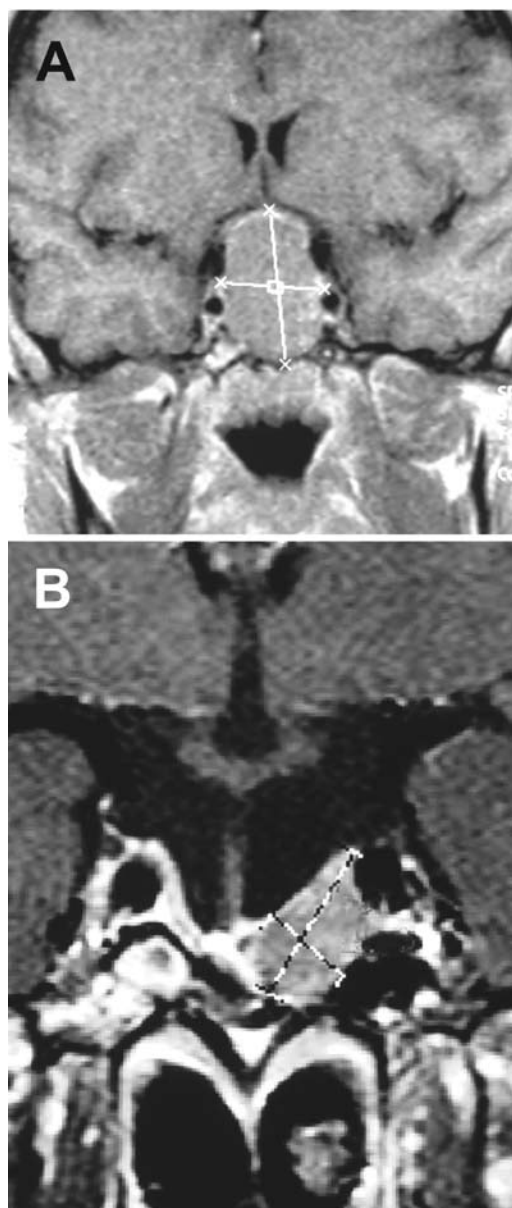


Figure 1. Magnetic resonance imaging (MRI) brain scan in the 28-year-old patient with acromegaly. (A) Preoperative MRI coronal scans revealed a tumor mass in the sellar and parasellar region. The largest size of tumor mass at the baseline was 40×30×40 mm. (B) Coronal MRI brain scans after transsphenoidal surgery of pituitary adenoma showed residual tumor mass. The largest size of tumor mass was 16×19×18 mm.

the treatment of diabetes mellitus, which was still present in the patient, two weeks after octreotide was discontinued. The patient tolerated rosiglitazone well and was discharged from the hospital, but remained under regular medical supervision.

Plasma glucose, GH, and IGF-I were determined before and on the day 1, 2, 7, 30, 60, and 90 of the rosiglitazone treatment. During the 90 days of rosiglitazone treatment, fasting plasma glucose concentration ranged between 8.4 and 6.7 mmol/L (normal range, 4.1-6.1 mmol/L), and postprandial plasma glucose was 8.2 mmol/L (normal range, <7.8 mmol/L). Plasma GH and IGF-I values in the week before the surgery were 5.96 ng/mL and 990 ng/mL, respectively, and decreased to 2.92 ng/mL and 180 ng/mL, respectively, after 90 days of rosiglitazone treatment (Figure 2). There was also a noticeable improvement in acromegalic features, the headache and swellings resolved, and the patient made a good recovery.

Discussion

A 28-year-old woman with residual pituitary tumor, clinical features of acromegaly and diabetes mellitus was treated with PPAR- γ agonist, rosiglitazone, to improve blood glucose level. She did not tolerate octreotide treatment so it was discontinued. Blood glucose levels normalized in our patient over the 90 days of rosiglitazone treatment. The octreotide treatment was discontinued and blood glucose levels normalized over the 90 days of rosiglitazone treatment. Serum GH and IGF-I concentrations also decreased to normal values, and acromegalic features remarkably improved.

The reduction of the tumor mass as well as postoperative decrease in growth hormone and IGF-I blood concentrations was the result of surgical removal of the tumor. However, in our patient, IGF-I levels steadily rose during the 30 days of postoperative period. Octreotide therapy that lasted 7 days could not significantly influence the reduction of the residual tumor mass due to short duration of administration. Also, octreotide could influence the secretion of growth hormone and IGF-I only during the 7 days of administration. Given the short half-life of Sandostatin

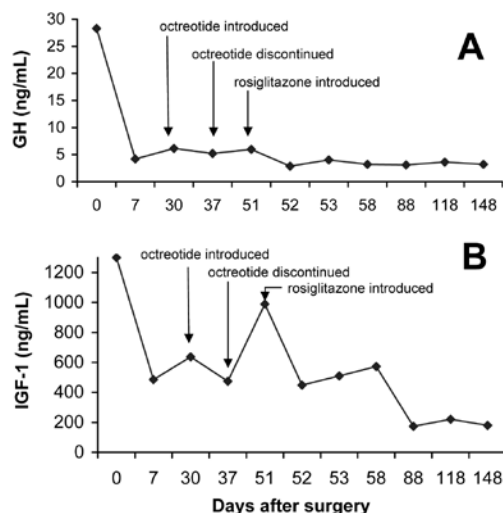


Figure 2. Decrease in growth hormone (GH) (A) and insulin-like growth factor I (IGF-I) (B) secretion in the patient with acromegaly during 90 days of rosiglitazone treatment after hypophyseal surgery.

(τ = 100 minutes), longer influence on the secretion of the hormones could not be expected after the treatment was discontinued. Therefore, it seemed plausible to conclude that the further decrease in hormone concentrations was the result of rosiglitazone treatment. Finally, it is possible that the long term effectiveness of rosiglitazone on hormone secretion might also be due to the induction of G0-G1 cell-cycle arrest and apoptosis by PPAR- γ agonist, as shown in secreting and non-functioning pituitary adenomas (14).

Rosiglitazone is indicated primarily for the treatment of diabetes mellitus and has only recently emerged as a potential therapy for pituitary tumors (14). Heaney et al (14) found that PPAR- γ was abundantly present in PRL-, GH-, and LH-secreting, as well as non-functioning pituitary tumors and that exposure of the tumor tissue to rosiglitazone inhibited both the proliferation of tumor cells in vitro and in vivo and secretion of PRL-, GH-, and LH in vivo. Thus, PPAR- γ could become a novel molecular target in the treatment of patients with non-functioning and hormone-secreting pituitary tumors that are unresponsive to current dopamine ago-

nist and/or somatostatin analogues (16). There are few reports on the effects of rosiglitazone in the treatment of patients with pituitary tumor-related conditions. A recent report on the results of rosiglitazone treatment in two patients with Cushing disease showed that the drug, administered for a few weeks at a dose of 8 mg/d, significantly decreased urinary levels of free cortisol and led to a modest clinical improvement in both cases (17). On the other hand, rosiglitazone showed no effects in lowering ACTH levels in patients with Nelson syndrome (18).

The primary indication for rosiglitazone treatment in our patient was diabetes mellitus. However, during the postoperative follow-up of the patient's hormonal status, we observed an unexpected decrease in the GH and IGF-I secretion and remarkable improvement in acromegalic features. There is a reasonable assumption that rosiglitazone was responsible for the normalization of GH and IGF-I secretion, in addition to blood glucose concentration. Since this is the first report on the outcome of rosiglitazone treatment in a patient with GH-secreting pituitary tumor and consequent acromegaly and diabetes mellitus, further research is needed to establish and confirm the possible role of this drug in the treatment of patients with pituitary tumors. Since we were only able to use the maximum dose licensed for use in diabetes (8 mg), further carefully designed studies of both dose and duration are required to confirm and define its possible role.

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