NOTE

Deterioration of Glycemic Control during Octreotide LAR Treatment in an Acromegalic Japanese Patient with Type 2 Diabetes Mellitus

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Abstract. We report a case showing deterioration of glycemic control during octreotide long-acting release (LAR) treatment in an acromegalic Japanese patient with type 2 diabetes mellitus. The patient did not show much improvement of insulin sensitivity (QUICKI; 0.33 before treatment, 0.35 during octreotide LAR treatment), and showed a significant reduction in early insulin secretion (insulinogenic index; 0.28 before treatment, 0.08 during octreotide LAR treatment) on 75 g oral glucose tolerance test (75gOGTT), despite decreases in GH and IGF-I levels during the course of octreotide LAR treatment. Postoperatively, both insulin sensitivity and early insulin secretion on 75gOGTT were improved (QUICKI 0.59, insulinogenic index 0.35). There are some reports that insulinogenic index is lower in most Japanese patients with type 2 diabetes mellitus and that early insulin secretions are significantly suppressed after administration of octreotide LAR. Although the influence of octreotide LAR on glucose metabolism varies among individuals, it is necessary to manage the deterioration of glucose tolerance during octreotide LAR treatment in acromegalic Japanese patients with decreased insulinogenic index.

Key words: Acromegaly, Type 2 diabetes mellitus, Octreotide, QUICKI, Insulinogenic index

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CHRONIC growth hormone (GH) excess seems to induce a reduction of insulin sensitivity and worsening of glucose intolerance [1], and approximately 20% of acromegalic patients have diabetes mellitus [2]. Both marked improvements in insulin resistance and reduction of glycosylated hemoglobin (HbA1c) were reported to accompany postoperative decreases in GH level in these patients [3]. Although octreotide, which is the therapeutic agent used in the treatment of acromegaly, gradually reduces the GH level [4], it also inhibits the secretions of insulin, glucagon and other intestinal hormones. Furthermore, octreotide delays gastrointestinal movement, which leads to a decrease in glucose absorption [5]. Thus, these effects of octreotide are known

to influence glucose metabolism, and the changes in glucose tolerance in acromegalic patients receiving octreotide treatment vary with the individual. Here, we report an acromegalic patient showing deterioration of glucose tolerance during treatment with octreotide long-acting release (LAR), which was well tolerated and reduced mean 24-hour GH levels as effectively as multiple daily subcutaneous injections of octreotide [6], and glucose tolerance without octreotide improved following surgery for pituitary tumor.

Case Report

A 46-year-old woman was admitted to our hospital for a work-up for diabetes mellitus in July 2004. Her father also had diabetes mellitus. On physical examination, her body mass index (BMI) was 20.7 kg/m², blood pressure was 130/80 mmHg, and she showed acromegalic facies. Laboratory examinations were

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performed on admission, and the results were as follows: HbA1c, 7.0%; anti-glutamic acid decarboxylase (GAD) antibody <1.3 U/ml; and urinary excretion of C-peptide (u-CPR), 116 µg/day. There were no diabetic complications, such as neuropathy, retinopathy, or nephropathy. On endocrinological examination, basal GH level was 10.9 ng/ml (reference range: 0.6–3.7), and IGF-I level was 806 ng/ml (reference range: 121–436). On 75 g oral glucose tolerance test (75gOGTT), fasting plasma glucose level was 128 mg/dl, plasma glucose level at 120 min was 257 mg/dl, and the patient showed a diabetic pattern. The basal insulin level was 8 µU/ml, and the peak (99 µU/ml) was observed at 120 min. GH level was not suppressed by 75gOGTT. Brain magnetic resonance imaging (MRI) demonstrated a mass 4 mm in diameter at the left side of the adenohypophysis, and a diagnosis of acromegaly was made. Although we recommended transsphenoidal adenectomy for microadenoma, the patient refused surgery. Therefore, we began treatment with octreotide injection.

As the patient did not demonstrate the most common gastrointestinal side effects after subcutaneous octreotide treatment at 100 µg per day, it was changed to octreotide LAR at 20 mg per month. Although the IGF-I level decreased gradually with octreotide LAR treatment, HbA1c gradually worsened under 1600 kcal/

day diet therapy only (Fig. 1). The patient started to treatment with metformin hydrochloride from December, 2004; however, the medication was stopped due to gastrointestinal side effects after one month. There was no improvement in blood glucose despite repeated nutritional guidance, suggesting that octreotide LAR caused deterioration of the patient's diabetes mellitus. The patient eventually stopped octreotide LAR treatment in August, 2005, and underwent transsphenoidal adenectomy in September. Postoperatively, the patient was administered desmopressin acetate and hydrocortisone for about 6 weeks, at doses that were reduced gradually over time. After the medications were stopped, she did not show polyuria and the level of pituitary-adrenal hormone was normal (Table 1).

Table 1. Basal endocrine tests

	August, 2004	November, 2005
ACTH (pg/ml)	28.2	19.4
cortisol (µg/dl)	11.1	13.6
TSH (µIU/ml)	0.136	0.526
fT3 (pg/ml)	2.70	2.43
LH (mIU/ml)	20.5	24.2
FSH (mIU/ml)	7.2	8.6
PRL (ng/ml)	11.1	25.2
GH (ng/ml)	16.3	1.3

Fig. 1. The course of HbA1c and IGF-I levels during octreotide treatment. HbA1c gradually deteriorated despite normalization of the IGF-I level by octreotide LAR treatment.

On treatment with diet therapy only, IGF-I and HbA1c levels were 245 ng/ml and 5.4%, respectively, in February 2006.

The findings on 75gOGTT during the clinical course are shown in Table 2. On 75gOGTT before octreotide treatment, the minimum GH level was 11.2 ng/ml, quantitative insulin sensitivity check index (QUICKI = $1/[\log(\text{glucose}) + \log(\text{insulin})]$) was 0.33, insulinogenic index (I.I. = $[\text{insulin level at 30 min} - \text{basal insulin}] / [\text{glucose level at 30 min} - \text{basal glucose}]$), which reflects the function of early insulin secretion from the pancreatic β -cells in response to glucose intake, was 0.28 (August, 2004). Minimum GH level, QUICKI, and I.I. were 1.7 ng/ml, 0.35, and 0.08, respectively, on 75gOGTT during treatment with octreotide LAR (April, 2005). Minimum GH level, QUICKI, and I.I. were 0.4 ng/ml, 0.59, and 0.35, respectively, on 75gOGTT postoperatively (November, 2005). The patient did not show much improvement of insulin sensitivity, and showed a significant reduction of early insulin secretion on 75gOGTT, despite the decreases in GH and IGF-I levels during the course of octreotide LAR treatment. Postoperatively, both insulin sensitivity and early insulin secretion on 75gOGTT were improved by diet therapy only.

Discussion

The influence of octreotide treatment on glucose metabolism appears complex. Some reports have shown that octreotide treatment in acromegalic patients worsens glucose tolerance, whereas other reports have shown remarkable improvement of hyperglycemia after octreotide treatment [7]. Hypoglycemia and hyperglycemia are observed as side effects of octreotide treatment in 2% and 7–15% of cases, respectively [8], and most cases do not show abnormalities in glucose metabolism during octreotide treatment. On the other hand, there was a report that HbA1c worsened significantly after octreotide treatment in most Japanese diabetic patients [9]. Sato *et al.* reported that plasma insulin responses to 75gOGTT in Japanese patients with glucose intolerance were lowered after the administration of octreotide although plasma insulin responses to 75gOGTT in Japanese patients with normal glucose tolerance were increased after the administration of octreotide [10]. In acromegalic Japanese patients with diabetes mellitus, glucose tolerance may worsen by octreotide treatment.

Octreotide LAR treatment may affect glucose metabolism more than that with conventional subcutaneous octreotide, because fasting GH, which correlated strongly with free IGF-I, was significantly reduced in patients receiving octreotide LAR compared with that during subcutaneous octreotide administration [6].

Table 2. Findings on 75gOGTT during clinical course

75gOGTT(August, 2004)					
time (minutes)	0	30	60	120	180
PG (mg/dl)	128	218	281	257	137
IRI (μ U/ml)	8.0	33.0	58.0	99.0	68.0
GH (ng/ml)	16.3		14.1		11.2
75gOGTT (April, 2005)					
time (minutes)	0	30	60	120	180
PG (mg/dl)	192	279	298	340	300
IRI (μ U/ml)	3.6	10.6	10.4	15.0	11.9
GH (ng/ml)	2.0	1.7	2.5	6.1	4.6
75gOGTT (November, 2005)					
time (minutes)	0	30	60	120	180
PG (mg/dl)	97	213	209	243	115
IRI (μ U/ml)	0.5	41.3	11.4	84.9	17.3
GH (ng/ml)	1.3	0.6	0.9	0.4	1.3
QUICKI					0.33
insulinogenic index					0.28
QUICKI					0.35
insulinogenic index					0.08
QUICKI					0.59
insulinogenic index					0.35

Octreotide LAR has high binding affinity for the somatostatin receptor subtype SSTR2, and SSTR2 was constantly detected in many pancreatic β -cells [11]. Baldelli *et al.* also reported that insulin levels 30 min after OGTT were significantly suppressed after the administration of octreotide LAR [12], and it is suggested that the decrease in early insulin secretion by OGTT during treatment with octreotide LAR is involved in worsening of glucose tolerance.

I.I. was reported to be lower in most Japanese patients with type 2 diabetes mellitus [13, 14], and it seems that insulin secretion ability is genetically weak in Japanese type 2 diabetic patients compared with Westerners. This patient had type 2 diabetes mellitus with acromegaly; she had a family history of diabetes mellitus and also showed a diabetic pattern with 75gOGTT postoperatively. Although u-CPR and the peak level of insulin with 75gOGTT in the present patient were sufficient at the beginning of treatment, the I.I. was reduced during octreotide LAR treatment. It is suspected that repeated administration of octreotide LAR suppressed early insulin secretion, and caused gradual deterioration of diabetes mellitus.

A recent study showed that QUICKI is a more accu-

rate index of insulin sensitivity than HOMA (homeostasis model assessment) across a broad range of insulin sensitivities [15]. QUICKI is also useful for monitoring improvements in insulin sensitivity in response to therapy in patients not only with normal glucose tolerance but also with type 2 diabetes mellitus [16, 17]. This present case did not show significant change on QUICKI despite decreases in GH and IGF-I levels during octreotide LAR treatment. Based on these findings, deterioration of glycemic control during octreotide LAR treatment is associated with reduced insulin secretion rather than changes in insulin resistance due to decreases in GH and IGF-I levels.

In conclusion, we had an acromegalic Japanese patient with type 2 diabetes mellitus with reduced I.I. after the administration of octreotide LAR. Insulin secretion ability is genetically weak in Japanese type 2 diabetic patients compared with Westerners, and the influences on glucose metabolism by octreotide LAR in Japanese type 2 diabetic patients may be different from that in Westerners. It is necessary to manage the deterioration of glucose tolerance in Japanese patients with acromegaly accompanied by type 2 diabetes mellitus during prolonged octreotide LAR treatment.

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