Insulinoma in a Patient with Non-Insulin-Dependent Diabetes Mellitus

AKIHIRO SAKURAI, TORU AIZAWA, MASAFUMI KATAKURA**, YOSHIHIKO SATO, GENGO KANEKO*, KUNIO YOSHIZAWA**, AND KIYOSHI HASHIZUME

Department of Geriatrics, Endocrinology and Metabolism, and *Department of Surgery II, Shinshu University School of Medicine, Matsumoto 390, and **Asama General Hospital, Saku 385, Japan

Abstract. Insulinoma in a patient with pre-existing diabetes is exceedingly rare. Only a small number of well-documented cases have been reported in the world during the last 40 years. We describe a case with non-insulin-dependent diabetes mellitus who after seven years of sulfonylurea treatment experienced recurrent episodes of hypoglycemia. Endogenous hyperinsulinism was found and radiographical examination and transhepatic venous sampling confirmed an insulin secreting pancreatic tumor. After surgical excision of the tumor, patient was relieved from hypoglycemic attacks but required to initiate insulin injection for the treatment of hyperglycemia.

Key words: Insulinoma, Diabetes, Pancreas tumor

(Endocrine Journal 44: 473–477, 1997)
Case Report

A 70-year-old male was referred to Shinshu University Hospital because of frequent hypoglycemic attacks. He was discovered having positive urine glucose at the age of 46. Diagnosis of diabetes was subsequently made and treatment with gliclazide was instituted in 1985 when he was 62 years old (Fig. 1). Until 1990, he had been treated with gliclazide (80 mg/day) and his hemoglobin A1 level gradually lowered. Note that this happened despite increase in the body weight from 52 kg (body mass index; 22.5 kg/m²) to 62 kg (27.6 kg/m²) during the same period. In 1990, he experienced the initial hypoglycemic attack before lunch, and the dose of gliclazide was reduced to 60 mg/day. In 1992, he experienced recurrent preprandial hypoglycemic attacks before almost every meal, progressive forgetfulness and lethargy. Dose of gliclazide was further reduced and the medication was finally discontinued. In December, 1992, 3 weeks after discontinuation of gliclazide, his fasting plasma glucose was 3.1 mmol/l (55 mg/dl) and plasma insulin (IRI) and C-peptide levels were 264 pmol/l (44 μU/μl) and 5.1 ng/ml, respectively. Hypoglycemia and endogenous hyperinsulinism was thus confirmed. Hemoglobin A1c level was 4.1% (normal: 3.5–5.5%).

On admission in January, 1993, the body weight was 65.0 kg, and the height was 150 cm (body mass index; 28.9 kg/m²). Results of routine laboratory tests including blood chemistry, hemogram and serology were unremarkable. Function of the pituitary, thyroid and adrenal glands were normal. Urinary C-peptide was elevated to 164 μg/day. Anti-insulin antibody was negative. As shown in Fig. 2, 75 g oral glucose tolerance test showed a diabetic pattern with plasma glucose being 12.1 mmol/l (217 mg/dl) at 120 min despite high level of plasma IRI. Computed tomography and digital subtraction angiography revealed a single hypervascular mass (25 × 25 mm) at the body of the pancreas (Fig. 3). A sharp step-up of IRI level immediately distal to the tumor in splenic vein was noted by the percutaneous transhepatic venous sampling (Fig. 4).
Diagnosis of insulin-producing pancreatic tumor in a patient with NIDDM was thus made, and enucleation of the tumor was performed in March, 1993. Histopathological examination confirmed an islet cell adenoma, and with immunostaining, tumor was positive for insulin and chromogranin A, but negative for glucagon and somatostatin.

After surgery, urinary C-peptide excretion decreased to 24.4 µg/day, and insulin injection was started for the treatment of hyperglycemia. In September, 1996, hemoglobin A1c level was 8.6% with 42 U/day of insulin injection. The body weight had been 56–57 kg after operation.

**Discussion**

Etiology of insulinoma has been mostly unknown. Because the incidence of insulinoma in general population is about 4/million/year [1] and the prevalence of NIDDM in adults is 5–10% in industrial countries [18], insulinoma in a patient with NIDDM should have been observed more commonly in those countries. However, coincidence of these two disorders are exceedingly rare as to warrant individual case reports. The incidence and prevalence of insulinoma in Japanese is unknown. Among 443 cases reported from 1976 to 1990, coincidence of diabetes was noted in only one case with malignant insulinoma, of which the detail was not described [19]. Since the prevalence of NIDDM in Japan is similar to that in other industrial countries [18], it seems that, regardless of ethnic origin, the presence of diabetes prevents occurrence of insulinoma and/or manifestation of clinical symptoms caused by insulinoma. Several possibilities could be considered for this negative correlation between two disorders. The number of β cells is decreased in patients with IDDM and non-obese NIDDM [20, 21], which means the decrease of the cellular basis for tumor formation. However in the majority of diabetic patients, who are usually obese and non-insulin dependent, the number of β cells may not be decreased. It is also possible that β cell regeneration capability is depressed in patients with diabetes leading to low incidence of insulinoma. Alternatively, insulinoma may occur in diabetic patients with the same incidence as in non-diabetic subjects, but not readily be diagnosed because of insulin resistance [16]. In our case, gradual increase in body weight (Fig. 1) suggests that hyperinsulinism, probably due to insulinoma, had existed for long time. This may have caused insulin resistance, thus preventing clinical symptoms to appear until hyperinsulinism becomes severe. Insulin resistance in our case was confirmed by hyperinsulinemic-isoglycemic clamp method (data not shown) [22]. Also, hypoglycemia due to insulinoma occurred in diabetic patients could be mistakenly considered as the over-dose of hypoglycemic agents or insulin, either iatrogenic or factitious. Consequently, the delay of diagnosis may occur for milder cases: iatrogenic or factitious hyperinsulinism could easily be distinguished from insulinoma by measuring plasma C-peptide.
Recent progress in understanding of the molecular mechanism of insulin secretion and tumorigenesis in islet cells should be helpful to elucidate the preventive effect of diabetes on the formation of insulinoma.

References


113: 1714–1717 (In German).