

# Insulinoma in a patient with long lasting type 2 diabetes

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## Abstract

Insulinoma in a patient with pre-existing diabetes is rare. We describe a case of 68-year-old type 2 diabetic patient who after 20 years of disease experienced recurrent episodes of hypoglycaemia. Insulinoma was confirmed by elevated plasma insulin and C-peptide levels in fasting test and identification of pancreatic tumor in computer tomography. After surgical excision of the tumor, no further hypoglycaemic attacks occurred. However, the patient required insulin injections for satisfactory control of hyperglycaemia. In conclusion, insulinoma must be taken into consideration as a reason for hypoglycaemia in type 2 diabetes, however the coincidence of these two diseases is extremely rare.

**Key words:** insulinoma, hypoglycaemia, type 2 diabetes.

## Introduction

Insulinoma belongs to the commonest pancreatic islet cell tumors, occurring in general population in four per million per year [1]. It is usually a small, solitary tumor, arising from  $\beta$  cells of the pancreas, although up to 16% insulinomas are malignant [2]. The highest incidence of insulinoma is in the age of 40 to 60 years. Typical clinical features of insulinoma are deep hypoglycaemic episodes in the state of food deprivation [1]. However, hypoglycaemia is more common in patients with diabetes as an adverse event of the hypoglycaemic treatment. The prevalence of type 2 diabetes is 5-10% in industrial countries. However, the coincidence of these two disorders is exceedingly rare [3]. Here, we report a case of insulinoma in a patient with long history of type 2 diabetes.

## Case report

A 68-year-old woman was admitted to our Department because of recurrent hypoglycaemia for five months. She had a 20-year history of type 2 diabetes treated for first five years with sulphonylureas and then with insulin (the conventional insulin therapy using mixtures of insulin). The diabetes was complicated by diabetic nephropathy in the stage of renal insufficiency and diabetic retinopathy after laser therapy. The family history for type 2 diabetes was positive. The patient has had also hypertension for three years. She complains about recurrent episodes of hypoglycaemia for the last five months despite gradual withdrawing of insulin (on admission the patient was without insulin treatment). The attacks were mostly before meals and during the night. During this time she put on weight three kilograms (body weight: 89.5 kg).

On admission in physical examination the blood pressure was 180/90 mm Hg and body mass index (BMI) 39 kg/m<sup>2</sup>. The routine laboratory tests revealed renal insufficiency (creatinin level: 168.8 µmol/l, GFR: 27.8 ml/min) and atherogenic dyslipidaemia (total cholesterol: 6.8 mmol/l, LDL cholesterol: 4.9 mmol/l, HDL cholesterol: 1.1 mmol/l, triglycerides: 3.0 mmol/l). The patient underwent a fasting test. After 28 h of starvation she had symptoms of hypoglycaemia. Two paired plasma glucose, C-peptide and insulin levels were taken. The results are presented in Table I.

Abdominal computer tomography revealed a single hypervascular mass (15 mm diameter) in the tail of the pancreas (Figure 1). Diagnosis of insulinoma in a patient with type 2 diabetes was thus made and the tumor was removed. Histopathological examination confirmed an islet cell adenoma, and in immunostaining tumor was positive for chromogranin.

The patient returned to our Department two months later because of high levels of glycaemia. Directly after surgery she was treated with insulin but the metabolic control was not satisfactory (HbA<sub>1c</sub> 7.9%). She lost 7 kg weight (body weight 82.5 kg). The patient was released from the hospital 8 days later. During hospitalization insulin therapy was modified and afterwards her diabetes was well controlled with mixtures of insulin (the demand for insulin was 0.6 U/kg).

## Discussion

Overdosing of hypoglycaemic agents and mistakes in insulin therapy are the commonest reasons for hypoglycaemia in type 2 diabetes. However, insulinoma should be considered in these patients if hypoglycaemia persists despite lowering doses or discontinuing of treatment for diabetes. Patients experience symptoms of hypoglycaemia usually in a fasting state. Diagnosis of insulinoma is based on the exclusion of the most common causes of hypoglycaemia and demonstration of raised both plasma insulin and C-peptide levels in the presence of low level of glycaemia [2]. In our patient we have found these laboratory results after 28 h starvation. The tumor was revealed in computer tomography, but in some cases it may be problematic because of small size of insulinoma. Only approximately 66% of insulin-secreting tumors may be localized using the imagine techniques [1].

Insulinoma in a patient with type 2 diabetes is relatively rare [2]. Only a small number of well-documented cases have been reported [3-5]. Previous reports suggested that hyperplasia and even adenomatous transformation of the β cells of the pancreas might be induced by chronic therapy of diabetes with sulphonylureas or insulin resistance due to long lasting type 2 diabetes [6].

**Table I.** Plasma glucose, serum insulin and C-peptide concentrations in the fasting test

	Sample 1	Sample 2	Normal range
Plasma glucose [mmol/l]	1.9	2.1	3.9-5.5
Insulin [µU/ml]	83.96	60.65	2.6-24.9
C-peptide [ng/ml]	12.99	12.13	1.1-4.4



**Figure 1.** Abdominal computer tomography presenting insulinoma

It is now clear that insulin plays an important role in the regulation of adult β-cell mass. It seems to be that long lasting stimulation insulin secretion by sulphonylureas and overdose of exogenous insulin therapy might lead to uncontrolled β-cell proliferation via intracellular “insulin signaling” pathway. Recently, Beith *et al.* have demonstrated that insulin directly stimulates β-cell proliferation and that Raf-1 kinase is involved in this process [7]. Despite the progress in identifying regulators of β-cell expansion the mechanisms linking type 2 diabetes and insulinoma are not fully explained.

In conclusion, insulinoma must be taken into consideration as a reason for hypoglycaemia in type 2 diabetes, however the coincidence of these two diseases is extremely rare. Although the removal of tumor is usually curative we must reconsider insulin injection requirement after surgery.

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