

## APPROACH TO ORGANIC HYPERINSULINISM IN PATIENTS WITH DIABETES MELLITUS

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### SUMMARY

*In diabetic patients, the presence of hypoglycemia implies an inappropriate dosage of oral hypoglycemic agents or exogenous insulin, accompanied with excessive physical activity and poor diet. Hypoglycemia as the result of endogenous hyperinsulinemia due to an insulinoma is extremely rare in such patients. The criteria for diagnosing an insulinoma known as Whipple's triad include symptoms of hypoglycemia, documented low blood glucose concentration at the time of symptoms, and immediate relief of symptoms by glucose ingestion or infusion. Several options are available for localizing insulinomas including ultrasound, CT, MRI, and selective angiography. According to recent guidelines, intraoperative ultrasound and palpation of the pancreas show promise to localize small lesions not seen by other methods. In the management of diabetic patients with biochemical evidence of insulinoma, surgical enucleation or resection of insulinomas has*

*always been the treatment of choice. When tumors are not localized, medical management of hypoglycemia is recommended. As the causes of organic hyperinsulinism, nesidioblastosis and a combination of insulinoma and nesidioblastosis in addition to insulinoma should be considered.*

### INTRODUCTION

Hypoglycemia is one of the most common clinical entities, mainly due to its high prevalence as a complication of therapy for diabetes (1-3). However, it sometimes arises as a manifestation of other diseases. Insulinomas represent the most common cause of organic hypoglycemia (4). As a cause of hypoglycemia, especially in diabetic patients, nesidioblastosis in addition to insulinoma should be considered (5). Nesidioblastosis is hyperplasia of the islet cells of the pancreas causing hyperinsulinemic hypoglycemia. It is a predominantly neonatal disorder, although cases in adults have recently been reported (6). Although rare, insulinomas are the most common functioning islet cell tumor of the pancreas (7). The incidence is 4 cases *per million per year*. They are usually sporadic, solitary and less than 2 cm in diameter, only 5% of insulinomas are larger than 3 cm (8). Multiple insulinomas are observed in about 10% of cases, usually in patients with MEN 1 syndrome

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(multiple endocrine neoplasia) presenting with hyperparathyroidism and pituitary tumors (9). The malignant metastatic form of usually benign insulinoma is reported with an incidence rate from 5% to 15% of all insulinomas (10). These rare tumors appear at any age, but they are most common during the 5<sup>th</sup> to the 7<sup>th</sup> decade of life, median age 55 years (11). If one includes only patients with insulinoma and pre-existing diabetes mellitus, there are only ten to twenty cases described in the literature regarding functioning insulinoma suspected and diagnosed before operation. Among 313 patients with histologically confirmed insulinoma at Mayo Clinic in the period of 65 years, only one patient had pre-existing diabetes mellitus (12). At Vuk Vrhovac University Hospital, only one patient with non-insulin dependent diabetes mellitus with a clinical feature of organic hyperinsulinism due to insulinoma was treated over a 20-year period.

## ORGANIC HYPERINSULINISM

Patients with insulinoma are characterized by specific manifestation of clinical symptoms of hypoglycemia: anxiety, dizziness, lightheadedness, personality changes, unusual behavior, confusion, incoherence, blurred vision, seizures and coma. In addition to these neuroglycopenic symptoms, sympathoadrenal signs such as palpitations, diaphoresis and tachycardia may also be present (13).

Hypoglycemic episodes in patients with diabetes mellitus start to occur when multiple antihyperglycemic agents are used. Sulphonylureas, meglitinide derivatives and thiazolidinediones are extensively metabolized in the liver and may be subject to drug-drug metabolic interactions, resulting in hypoglycemia (14). Showing absence of these compounds in blood and urine by a sensitive method at the time of hypoglycemia is essential before starting diagnostic evaluation of insulinoma. In case of exogenous insulin administration causing hypoglycemia, endogenous hyperinsulinism is easy to distinguish. Laboratory findings will show inappropriately high insulin concentrations in the presence of low or suppressed C peptide values.

The time between the onset of symptoms of hypoglycemia and the diagnosis of insulinoma is often prolonged. According to literature data, the median is 24 months (15). Hyperinsulinemia due to pancreatic cell tumors leads to insulin resistance. Thus, typical hypoglycemic symptoms can even be absent because of insulin resistance associated with obesity (16).

## BIOCHEMICAL DIAGNOSIS

The clinical diagnosis of insulinoma in patients with diabetes should be based on modified Whipple's triad: development of fasting hypoglycemia; evidence that hypoglycemia is not caused by administration of excess exogenous insulin or oral hypoglycemic agents; exclusion of other reasons for fasting hypoglycemia; presence of endogenous hyperinsulinemia and amelioration of hypoglycemia by removal of the neuroendocrine pancreatic tumor (17).

In most patients with insulinoma, the diagnosis is established by monitoring the insulin/glucose ratio, plasma glucose, insulin and C peptide concentrations in the 72-hour fasting test. A ratio  $>0.3$  is suggestive of insulinoma. Insulinoma is characterized by inappropriately high insulin and/or proinsulin, high C peptide, and suppressed low  $\beta$  hydroxybutyrate serum concentrations (18). The 72-hour fasting test is the oldest, best established and most reliable test for evaluation of hypoglycemia disorders. The fast is conducted at hospital under medical supervision and the patient is allowed to drink only non-caloric and caffeine-free beverages (18). Blood samples are collected in the beginning of the test, every six hours during the test, and in the end. Regular plasma glucose, insulin, C peptide and proinsulin concentrations are measured. Usually serum cortisol, adrenocorticotropic hormone (ACTH) and growth hormone (GH) are also measured to rule out hypoglycemia due to suppression of the hypothalamic-pituitary-adrenal axis. The fast is terminated when the plasma glucose concentration falls below 2.5 mmol/L and the patient has neuroglycopenic symptoms. In the absence of symptoms and hypoglycemia, the test is terminated at 72 hours. Current studies show that the 48-h fast should replace the 72-h fast in textbooks and hospital protocols as a new diagnostic standard. Now that

insulin and proinsulin measurements are widely available, all of the necessary information from the fast can be derived in the first 48 h. Furthermore, of 127 patients with insulinoma included in the study over a 30-year period, in 120 (94.5%) fast was terminated due to hypoglycemia by 48 h (19).

## DIAGNOSTIC APPROACH

The major problem with insulinoma is to localize the tumor. A variety of procedures have been advocated for detecting insulinomas, but there is little consensus about the best method or combination of methods (20). The imaging techniques used include computed tomography (CT), ultrasonography, truncus coeliacus angiography and intra-arterial calcium stimulation with venous sampling. CT scan of the abdomen is suboptimal in sensitivity, ranging from 20% to 80%, with possible false positive results (21).

CT and magnetic resonance (MR) imaging of the pancreas are accurate as the size of the tumor increases from less than 1 cm to around 2 cm. False negative results are present in 70% of cases. Preoperative MR identifies insulinomas with 50% sensitivity (20). According to some authors, the diagnostic localization procedure of choice for insulinomas is selective angiography. This technique is very sensitive in localizing insulinomas, and has been reported to be positive in up to 75% of cases (8,22). Yet, the detection of the tumor by angiography depends on both tumor vascularity and tumor size, and is therefore useful only in selected patients (23).

Many small previously overlooked tumors were diagnosed by intra-arterial calcium stimulation with pancreatic venous sampling (21). The use of THPVS (transhepatic portal venous sampling) detects around 60% of the tumors less than 1 cm in diameter. The drawback of the THPVS is that it is invasive, uncomfortable for the patient, and may potentially result in complications (20).

Intraoperative ultrasonography in one series correctly identified all tumors that could not be palpated (15). Intraoperative ultrasonography in combination with intraoperative palpation after careful

mobilization of the pancreas gives best results and is recommended for patients who have not had previous pancreatic operations (20).

Currently available imaging modalities sometimes fail to detect some small insulinomas, therefore scintigraphic imaging with Octreoscan has been introduced in an attempt to improve topographic assessment. The results were disappointing, since Octreoscan scintigraphy with planar imaging led to detection of only 20%-50% of insulinomas (24-26). The use of single-photon emission computed tomography (SPECT) has recently been reported to improve detection of insulinomas by Octreoscan scintigraphy (26). In agreement with previous findings in infants, preoperative <sup>18</sup>F-DOPA positron emission tomography (PET) seems to be the method of choice for the detection of beta cell hyperplasia or insulinoma in adult patients with confirmed hyperinsulinemic hypoglycemia when other diagnostic work-up is negative, according to some authors (27). Other experts used whole-body (WB) PET with (11)C-5-hydroxytryptophan (5-HTP) as a universal imaging technique for neuroendocrine tumors and compared this technique with established imaging methods (WB-CT and somatostatin receptor scintigraphy (SRS)). The results showed that the tumor lesions were imaged with PET in 95% of the patients. In 58% of the patients, PET could detect more lesions than SRS and CT, and equal numbers in 34%, indicating that WB-(11)C-5-HTP-PET can be used as a universal imaging method for detection of neuroendocrine tumors. This study also showed the WB-(11)C-5-HTP-PET to be sensitive in imaging small neuroendocrine tumor lesions such as primary tumors, and can in the majority of cases image significantly more tumor lesions than SRS and CT. However, further studies are necessary to validate these results because only 42 patients with neuroendocrine tumors were involved in the study and only one of them had insulinoma (28). We conclude that there is no ideal imaging technique for insulinoma. Despite many attempts aimed at localizing insulinomas, the tumors remain undetected in 3% to 10% of cases, even after intraoperative palpation and use of intraoperative ultrasound (8,20).

## THERAPEUTIC APPROACH

The goal of treatment of a patient with an insulinoma is to identify and excise the tumor (8). Surgical treatment is the only curative method accomplished with enucleation or partial pancreatic resection (13). When no tumor can be identified, the dilemma is whether to perform partial pancreatectomy or refrain from further surgical intervention. It is recommended not to perform partial pancreatectomy if the tumor cannot be identified at operation (21). In view of the lack of sensitivity and specificity of current imaging techniques, additional treatment of occult insulinomas should be considered.

Diazoxide treatment of insulinoma is the method of choice for tumors that are not localized, including failed previous surgery. Treatment is effective according to literature data. In a series of patients with insulinoma in the UK, 59% of the patients receiving diazoxide had no symptoms of hypoglycemia and 38% had only occasional symptoms (29). Side effects as notably fluid retention and hirsutism are common, and some authors recommend conjunction with a thiazide diuretic (chlorothiazide) that both potentiates its hyperglycemic action and inhibits the associated fluid

retention (30). Diazoxide is a nonselective opener of ATP sensitive potassium (K ATP) channels Kir6.2/SUR1 resulting in inhibition of insulin secretion from  $\beta$  cells of the pancreas. Because of its lack of potency and selectivity giving rise to side effects, new selective openers of Kir6.2/SUR1 channels are pursuing (31).

Inhibition of tumor secretion by the synthetic somatostatin analogue octreotide can help improve hypoglycemic symptoms in only about 50% of patients. The reason is the lack of somatostatin receptors.

After the excision of the insulin producing tumors in previously diabetic patients, the carbohydrate metabolism usually returns to a mild type 2 diabetic state and requires diet therapy or medical treatment of diabetes (32,33).

In conclusion, this review points to the significance of diagnostic evaluation of hypoglycemia in diabetic patients and the possibility of coexisting diabetes mellitus and insulinoma. It also emphasizes some features of insulinoma of which a clinician should be aware, including diagnostic difficulties in imaging and treatment modalities.

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