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Original article

# A severe but reversible reduction in insulin sensitivity is observed in patients with insulinoma

## *Une réduction sévère, mais réversible, de la sensibilité à l'insuline est observée chez les patients souffrant d'insulinome*

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**Abstract**

*Background.* – Hypoglycemic manifestations are highly variable in patients with an insulinoma and largely independent of tumour size and severity of insulin hypersecretion. *Objectives.* – We investigated the clinical, biological and tumoral characteristics of insulinomas in a large monocentric series of patients and we evaluated their insulin sensitivity before and after successful pancreatic surgery. *Patients and methods.* – This was a retrospective analysis of 40 patients treated for an insulinoma between 1982 and 2012 in our academic hospital. Insulin sensitivity and beta cell function were evaluated by a HOMA test outside hypoglycaemic episodes in a large subset of these patients. *Results.* – The mean age at onset of symptoms was 48.8 ± 20.1 years and the mean age at diagnosis was 50.7 ± 19.9 years. Neuroglycopenic symptoms were observed in 90% of patients. The most effective preoperative imaging technique to localize the tumour was endoscopic ultrasound. Insulin sensitivity was greatly reduced in patients with insulinoma (38.9% ± 22.3%), while beta cells function was increased (359.0 ± 171.5%), but to a variable extent (range: 110.6–678.6%). After complete resection of the tumour and remission of hypoglycemic episodes, insulin sensitivity increased in all evaluated subjects (72.8 ± 36.7%) and normalized in the majority. *Conclusion.* – Although neuroglycopenic symptoms are present in most patients, diagnosis of insulinoma is often delayed. Endoscopic ultrasound remains the most sensitive preoperative technique to localize the tumour. We also show that in response to chronic hyperinsulinemia, patients with insulinoma develop protective mechanisms responsible for a marked insulin resistance, which is reversible after complete resection of the tumour.


*Keywords:* Insulinoma; HOMA test; Insulin sensitivity; Hypoglycemia; Endoscopic ultrasound

**Résumé**

*Objectifs.* – Les manifestations hypoglycémiques sont variables chez les patients souffrant d'un insulinome, et indépendantes de la taille de la tumeur et de l'importance de l'hypersécrétion en insuline. Cette étude revoit les caractéristiques des insulinomes et vise à évaluer la sensibilité des tissus périphériques à l'insuline en cas d'insulinome et son évolution après chirurgie. *Patients et méthodes.* – Quarante patients suivis aux cliniques universitaires Saint-Luc entre 1982 et 2012 ont été inclus dans cette étude rétrospective. La sensibilité à l'insuline et la fonction des cellules bêta ont été évaluées par un test HOMA, ce en dehors des épisodes hypoglycémiques. *Résultats.* – L'âge moyen d'apparition des premiers symptômes est de 48,8 ans, tandis que le diagnostic de l'insulinome est posé vers 50,7 ans. Des symptômes neuroglucopéniques sont observés chez 90 % des patients. La technique d'imagerie la plus efficace est l'écho-endoscopie. La sensibilité à l'insuline mesurée en dehors d'une hypoglycémie est fortement diminuée en cas d'insulinome (38,9 % ± 22,3 %), alors que la fonction bêta est logiquement augmentée (359,0 ± 171,5 %), mais de manière très variable (110,6 – 678,6 %). Après exérèse complète de la tumeur et disparition des hypoglycémies, la sensibilité à l'insuline augmente chez tous les sujets évalués (72,8 ± 36,7 %), tout en se normalisant pour la majorité. *Conclusion.* – Bien que les symptômes neuroglycopiques soient

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présents chez la plupart des patients, le diagnostic d'insulinome est souvent retardé. L'échographie endoscopique reste la technique préopératoire la plus sensible pour localiser la tumeur. Nous montrons aussi qu'en réponse à l'hyperinsulinisme chronique, les patients porteurs d'un insulinome développent des mécanismes de défense responsables d'une résistance à l'insuline, qui sont réversibles après l'exérèse complète de la tumeur.


*Mots clés :* Insulinome ; Test de HOMA ; Sensibilité à l'insuline ; Hypoglycémie ; Echographie endoscopique

## 1. Introduction

Insulinomas are rare neuroendocrine tumours of the pancreas, which are often misdiagnosed for a long period of time. Their incidence is estimated to be 1–4 cases per million in the general population but is likely underestimated, as such tumours are found in 0.8–10% of cases in autopsy reports [1,2].

Patients with an insulinoma are at variable risk of severe hypoglycemia due to the wide ranges of both tumoral insulin secretion and peripheral tissue sensitivity to chronic endogenous hyperinsulinemia. Furthermore, hypoglycemic manifestations are heterogeneous and largely independent of tumour size and degree of insulin hypersecretion. This differential susceptibility to exhibit symptomatic hypoglycemic episodes makes the diagnostic challenging, despite improvements in both biological and imaging techniques.

In this context, the aims of our study were to investigate the clinical, biological and tumoral characteristics of a large series of patients with insulinoma treated in our institution, and to better understand the pathophysiology of insulinoma-related symptoms by evaluating the sensitivity of peripheral tissues to insulin, before and after successful surgery.

## 2. Materials and methods

We retrospectively analyzed the data from 40 patients with an immunohistochemically confirmed insulinoma who elected to undergo a surgical resection of the tumour(s) in our academic centre between 1982 and 2012. Variables such as patient's characteristics, clinical presentation, results of biochemical investigations as well as those of various invasive and noninvasive imaging techniques used to localize the tumour were retrieved from the medical records. Biochemical diagnostic was based on the combined observations of a plasma glucose below 50 mg/dL (2.7 mmol/L) together with concentrations of insulin of at least 18 pmol/L (3.0 μU/mL) and of C-peptide of at least 0.20 nmol/L (0.6 μg/L), as recommended by the most recent guidelines [3]. A 72 h fasting test was performed in 27 patients who did not have spontaneous hypoglycemia. A screen for urinary sulfonylurea was also done at the time of a hypoglycemic event and was negative in all cases.

To be considered malignant, these tumours had to show evidence of either local invasion into surrounding soft tissues, lymph node extension or the presence at diagnosis or subsequent development of metastases. In a subset of tumours, the Ki67 proliferative index was calculated and expressed as a percentage based on the count of Ki67-positive cells among 2000 tumour cells in areas of the highest immunostaining using a MIB-1 monoclonal antibody at a dilution of 0.5 mg/L (Dako, Agilent Technologies, Santa Clara, CA).

Several techniques had been used to localize the tumour, including pancreatic ultrasonography (US), computed tomography scan (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), intraoperative ultrasonography (IOUS), positron emission tomography CT (PET-CT), somatostatin receptor scintigraphy (Octreoscan®) and selective intra-arterial calcium stimulation with hepatic venous sampling.

We assessed insulin sensitivity (HOMA-S) and beta cell function (HOMA-B) using the Homeostasis Model Assessment (HOMA) test and express them as percentages of mean values obtained in normal young adults when using similar assays for paired fasting plasma glucose and insulin or C-peptide steady-state concentrations [4]. This test has been validated for a range of 20–400 pmol/L for insulin and of 3–25 mmol/L for glucose. A plasma glucose less than 3 mmol/L, which is a non-steady-state situation, should not be used in the model and therefore insulin sensitivity and beta cell function were always evaluated in a fasting state with no concurrent hypoglycemia. Furthermore, whenever available, we used the mean of three HOMA-S and HOMA-B determinations derived from different samples in the same individuals.

Plasma glucose was measured by the glucose oxidase method. Since 1982, different types of insulin assays were used in our department. An in-house developed radio-immuno-assay (RIA) for nonspecific insulin was used until December 1999, the Elecsys Roche® insulin specific assay between January 2000 and June 2006, the Immulite DPC® insulin assay between July 2006 and June 2008, and thereafter until now, the method was shifted to the Liaison Diasorin® assay. We adjusted the equations used in the HOMA computer model as a function of the immunoassay type [5,6]. Despite adjustment, differences were observed between the HOMA values calculated using nonspecific insulin in comparison with the specific insulin assays, but they did not affect the results of our study which remained similar when only considering data obtained with the most recent specific immunoassays.

Statistical analyses were performed with the SPSS 23 software (SPSS Inc., Chicago, IL). For normally distributed variables, we used unpaired *t*-tests to compare the different subgroups of patients and paired *t*-tests to compare values observed at two different times in the same subjects (i.e. HOMA index before and after surgery). When variables had a non-normal distribution, we used non-parametric tests (Mann–Whitney U test or Kruskal–Wallis test). Proportions were compared by $Chi^2$ tests. Survival analysis was based on the Kaplan–Meier method. Patients lost for follow-up were censored at the date of the latest

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