Cancer Association of South Africa (CANSA)

Research • Educate • Support

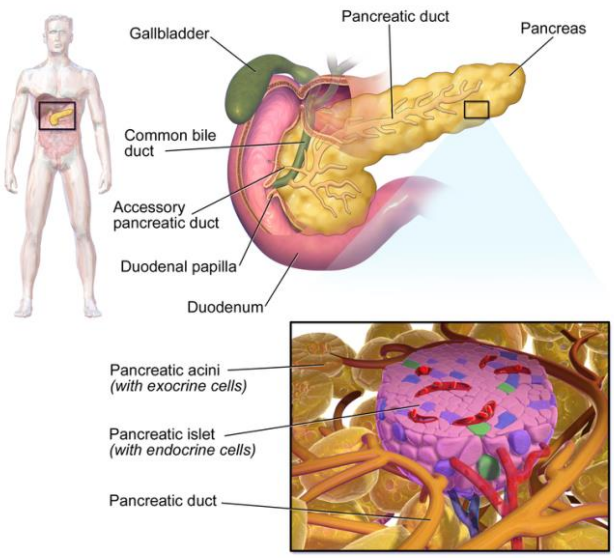
Fact Sheet on Insulinoma

Introduction

The pancreas is about 15 centimetres long and lies across the back of the abdomen, behind the stomach. The head of the pancreas is on the right side of the abdomen and is connected to the duodenum (the first section of the small intestine) through a small tube called the pancreatic duct. The narrow end of the pancreas, called the tail, extends to the left side of the body.

The pancreas is made up of exocrine cells and endocrine cells. These cells have different functions.

[Picture Credit: Pancreas]



Pancreatic Tissue

Most of the cells in the pancreas are exocrine cells. Exocrine cells make and release pancreatic juice. The juice travels through the pancreatic duct into the duodenum. Enzymes in the pancreatic juice help digest fat, carbohydrates and protein in food.

A small number of the cells in the pancreas are endocrine cells. They are arranged in clusters called islets, or islets of Langerhans. The islets make, and release, insulin and glucacon into the blood. These hormones help control the level of sugar, or glucose, in the blood.

Insulin lowers the amount of sugar in the blood when the blood sugar is high. It also stimulates the liver, muscles and fatty tissues to absorb and store the extra blood sugar.

Glucagon increases the amount of sugar in the blood when the blood sugar is low. It stimulates the liver and other body tissues to release stored sugar into the blood.

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Insulinoma

An insulinoma is a tumour of the pancreas that is derived from beta cells and secretes insulin. It is a rare form of a neuroendocrine tumour. Most insulinomas are benign in that they grow exclusively at their origin within the pancreas, but a minority metastasise. Insulinomas are one of the functional PanNET group ("functional" because it increases production of insulin; "PanNET" as an abbreviation of pancreatic neuroendocrine tumour).

Beta cells secrete insulin in response to increases in blood glucose. The resulting increase in insulin acts to lower blood glucose back to normal levels at which point further secretion of insulin is stopped. In contrast, the secretion of insulin by insulinomas is not properly regulated by glucose and the tumours will continue to secrete insulin causing glucose levels to fall further than normal.

As a result patients present symptoms of low blood glucose (hypoglycaemia), which are improved by eating. The diagnosis of an insulinoma is usually made biochemically with low blood glucose, elevated insulin, proinsulin and C-peptide levels and confirmed by localising the tumour with medical imaging or angiography. The definitive treatment is surgery.

Zhou, F. & Anastasopoulou, C. 2020.

"Insulinoma is a type of functional neuroendocrine tumor (NET) which manifests with hypoglycemia caused by inappropriately high secretion of insulin. It more commonly presents as a solitary benign tumor, but it can sometimes be associated with multiple endocrine neoplasia type 1 (MEN1). Patients with insulinoma have hypoglycemic episodes, more characteristically as fasting hypoglycemia. Insulinoma is usually diagnosed by biochemical testing when there is high clinical suspicion. Surgical resection is the preferred treatment choice. Localization with imaging studies is fundamental to characterize the tumor better before surgical resection. There are also other treatment options available depending on the stage and grade of the tumor."

Sada, A., Glasgow, A.E., Vella, A., Thompson, G.B., McKenzie, T.J. & Habermann, E.B. 2020.

Introduction: Due to the rarity of malignant insulinoma, a lack of the literature describing factors affecting outcomes exists. Our aim was to review malignant insulinoma incidence, characteristics and survival trends.

Methods: We identified all patients with malignant insulinoma in the SEER registries from 1973 to 2015. Incidence, neoplasm characteristics and factors affecting cancer-specific survival (CSS) were described.

Results: A total of 121 patients were identified. The crude annual overall incidence was low (range 0.0-0.27 cases per million person years). The largest proportion had localized disease (40%), while 16% had regional disease, 39% distant metastatic disease, and stage was unreported in 5%. Most neoplasms were in the body/tail of the pancreas, followed by the head of the pancreas. Grade was reported in 40% of patients; only a single patient reported as having grade IV with the remainder all grades I/II. Surgical resection was performed in 64% of patients. Within surgical patients, the median primary neoplasm size was 1.8 cm. Regional lymph nodes were examined in 57.1% of surgical patients, while 34% of examined nodes were positive. The median CSS was 183 months. On multivariable analysis, surgical resection, male sex and absence of metastatic disease were associated with superior survival.

Conclusion: While the greatest proportion of patients with malignant insulinoma present with localized disease, regional lymph node involvement was found in 34% of whose nodes were tested. Further studies are needed to assess the role of lymph node dissection in improving survival and preventing recurrence given the observed frequency of lymph node involvement.

Incidence of Insulinoma in South Africa

The National Cancer Registry (2017) does not provide any information regarding the incidence of Insulinoma.

Signs and symptoms of Insulinoma

- Insulinomas are characterised clinically by the Whipple triad, as follows:
  - Presence of symptoms of hypoglycaemia [low blood sugar] (about 85% of patients)
  - Documented low blood sugar at the time of symptoms
  - Reversal of symptoms by glucose administration

- About 85% of patients with insulinoma present with one of the following symptoms of hypoglycaemia:
  - Diplopia (double vision)
  - Blurred vision
  - Palpitations
  - Weakness

- Hypoglycaemia can also result in the following:
  - Confusion
  - Abnormal behaviour
  - Unconsciousness
  - Amnesia (memory loss)

- Clinical Picture
  - Adrenergic symptoms (from hypoglycaemia-related adrenalin release): Weakness, sweating, tachycardia (rapid pulse), palpitations, and hunger
  - Seizures
  - About 85% of patients present with symptoms of hypoglycaemia (low blood sugar) that include diplopia, blurred vision, palpitations, or weakness
  - Other symptoms include confusion, abnormal behaviour, unconsciousness, or amnesia
  - About 12% of patients have grand mal (major) seizures
  - Adrenergic symptoms (hypoglycaemia causes adrenalin release) include weakness, sweating, tachycardia (rapid pulse rate), palpitations, and hunger
  - Symptoms may be present from 1 week to as long as several decades prior to the diagnosis (1 month to 30 years, median 24 months, as found in a large series of 59 patients). Symptoms may occur most frequently at night or in the early morning hours
  - Hypoglycaemia usually occurs several hours after a meal
  - In severe cases, symptoms may develop in the postprandial period (occurring after a meal). Symptoms can be aggravated by exercise, alcohol, hypocaloric diet, and treatment with sulfonylureas
  - Weight gain occurs in 20-40% of patients. Because of hyperinsulinism, many patients may be overweight

Diagnosis of Insulinoma
The biochemical diagnosis is established in 95% of patients during prolonged fasting (up to 72 hours) when the following parameters are found:

- Serum insulin levels of 10 µU/mL or more (normal <6 µU/mL)
- Glucose levels of less than 40 mg/dL
- C-peptide levels exceeding 2.5 ng/mL (normal <2 ng/mL)
- Proinsulin levels ≥22 pmol/L, or greater than 25% (or up to 90%) that of immunoreactive insulin
- Screening for sulfonylurea negative

Christ, E., Antwi, K., Fani, M. & Wild, D. 2020.
"Receptors for the incretin glucagon-like peptide-1 (GLP-1R) have been found overexpressed in selected types of human tumors and may, therefore, play an increasingly important role in endocrine gastrointestinal tumor management. In particular, virtually all benign insulinomas express GLP-1R in high density. Targeting GLP-1R with indium-111, technetium-99m or gallium-68-labeled exendin-4 offers a new approach that permits the successful localization of small benign insulinomas. It is likely that this new non-invasive technique has the potential to replace the invasive localization of insulinomas by selective arterial stimulation and venous sampling. In contrast to benign insulinomas, malignant insulin-secreting neuroendocrine tumors express GLP-1R in only one-third of the cases, while they more often express the somatostatin subtype 2 receptors. Importantly, one of the two receptors appears to be always overexpressed. In special cases of endogenous hyperinsulinemic hypoglycemia (EHH), that is, in the context of MEN-1 or adult nesidioblastosis GLP-1R imaging is useful whereas in postprandial hypoglycemia in the context of bariatric surgery, GLP-1R imaging is probably not helpful. This review focuses on the potential use of GLP-1R imaging in the differential diagnosis of EHH."

Treatment of Insulinoma
The main treatment for insulinomas is surgery. This cures most insulinomas. But surgery is not always possible. Some cancerous insulinomas have already spread when they are diagnosed. If one cannot have surgery one will have drug treatment to control blood sugar levels and other symptoms.

The treatment depends on:
- Whether one has one or more tumours
- Whether the tumour is benign or malignant
- Whether the tumour has spread to other parts of the body
- Where in the pancreas the tumours are
- General health of the patient
- Whether the patient has a familial cancer syndrome

Other treatments may include:
- Treatment to control symptoms
- Chemotherapy

Surgery - the type of surgery the patient has will depend on:
- Whether he/she has one or more tumours
- Where in the pancreas the tumour is

- The size of the tumour

Treating symptoms of insulinoma - some cancerous (malignant) insulinomas are diagnosed when they are already advanced. And some come back after treatment. The most common place for malignant insulinoma to spread to is the liver.

Radiofrequency ablation – This procedure uses heat made by radio waves to kill cancer cells.

Cryotherapy – This procedure uses a cold probe to destroy cells and tissue by freezing.

Transcatheter arterial chemoembolisation (it is also sometimes referred to as transarterial chemoembolisation or TACE) - is a minimally invasive procedure performed in interventional radiology to restrict a tumour's blood supply. Small embolic particles coated with chemotherapeutic agents are injected selectively into an artery directly supplying a tumour. The substance may also be a gel or tiny plastic beads and helps to keep the chemotherapy around the tumour.

Selective internal radiation therapy (SIRT) - is a form of radiation therapy used in interventional radiology to treat cancer. It is generally for selected patients with unresectable cancers, those that cannot be treated surgically, especially hepatic cell carcinoma or metastasis to the liver. SIRT - is when microscopic beads that are coated with a radioactive substance called Yttrium-90 and is a type of targeted radiotherapy.

Drugs and diet to control blood sugar - the symptoms of an insulinoma can be difficult to cope with. To help to control blood sugar, the patient may need to have a high glucose diet. Being aware of the symptoms of a low blood sugar will help the patient correct it quickly by eating something that contains glucose.

Chemotherapy - may also help to control symptoms of a malignant insulinoma that cannot be removed with surgery. The drugs used may include doxorubicin and streptozocin.
(Cancer Research UK).

Matej, A., Bujwid, H. & Wroński, J. 2016.
"Insulinoma is the most common neuroendocrine tumor of the pancreas. Surgical management of insulinomas is considered to be the only curative method. However, effective glycemic control preoperatively and in unresectable insulinomas remains a significant issue. Hyperinsulinism, occurring as a result of the hormone-secreting tumor, leads to life-threatening hypoglycemia episodes which require urgent medical treatment. This article discusses current management of hypoglycemia in insulinomapatients, including: education and lifestyle modifications, pharmacotherapy (diazoxide, somatostatin analogs, mTOR inhibitor - everolimus), cytoreductive methods and continuous glucose monitoring systems."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments

- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

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