www.insulinoma.net - www.gep-net.com
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Insulinoma

"endogenous hyperinsulinism", autonomous inadaequate hyperinsulinemia"

Symptoms

"Whipple' s triad" is regularly found in insulinoma.

Amelioration of symptoms after carbohydrate intake in the absence of chemical hypoglycemia is unspecific and irrelevant.

biochemical proof of hypoglycemia (blood glucose < 50 mg/dl ; < 2.8 mmol/l)

simultaneously existing suspicious symptoms compatible with hypoglycemia

rapid amelioration of symptoms after carbohydrate intake

Symptoms compatible with hypoglycemia occur:

through activation of the sympathetic nervous system and result in uncomfortable **adrenergic symptoms** posing no danger for the patient

through cerebral shortage of glucose supply and may result in serious and debiliating ***neurological (neuroglycopenic) symptoms.***

The most frequently experienced symptoms are:

- dizziness -
- **loss of consciousness –**
- **increase in body weight -**
- **- sweating -**
- **- seizures -**

Frequency of individual symptoms

symptoms	frequency	adrenergic symptoms	frequency	neuroglycopenic symptoms	frequency
"Whipple's triad"	100 %	sweating	36 %	impaired consciousness	49 %
dizziness / collapse	50 %	hunger	16 %	impaired mental concentration	35 %
increase of body weight	40 %	tremor	12 %	seizures	30 %
		headaches	12 %	fatigue	29 %
		nausea	9 %	diplopia / impaired or blurred vision	27 %
		agitation		weakness of memory	13 %
		nervosity		paralyses	9 %
		palpitations		desorientation	7 %
		tachycardia		ataxia, impaired coordination	7 %
				dysarthria	
				apathia	
				altered or aggressive behaviour	

Source: 70 patients with diagnosed and operated insulinoma at the University of Duesseldorf.

Adrenergic symptoms are unspecific and often related to other diseases (e.g .the thyroid gland). General discomfort not caused by any disease has to be considered, too.

Neurological symptoms may be due to underlying and severe neurological disease.

Occurence of the symptoms in combination with hypoglycemia is suspicious for insulinoma as a possible cause of the complaints.

If an **insulinoma** has to be ***considered as a cause*** of the complaints and symptoms or has to be ***definitely ruled out***, the patient should be tested by simple and straightforward endocrine blood tests in an institution able to provide the expertise in the diagnostic work-up of hypoglycemia.

Diagnosis

1. <u>Insulinoma</u> is the most frequent hormone secreting tumor of the pancreas featuring an overproduction of insulin and / or proinsulin.

The mostly benign tumor is found twice as often in female patients as compared to male patients. The median of age at diagnosis is 50 years. Principally, the tumor may be found at any age of life.

2. The most important chemical finding are repetitively low blood glucose levels around or below 40 mg/dl (hypoglycemia), predominantly during fasting or physical activites.

3. Serum insulin concentrations are inadaequately high in relation to blood glucose levels due to absent or incomplete suppression of insulin secretion

The basic tool in endocrinological diagnostics of hypoglycemia is the standardized supervised fasting test

For decades this test is established as the **gold standard** in the endocrinological diagnostic work-up of hypoglycemia.

Usually the test has to be performed on an in-patient basis requiring a specialized and trained hospital setting.

By means of the test **adaequate physiological suppression** of the endogenous **insulin concentration** into the range of **basal concentrations of 3 - 5 µU/ml (18-30 pmol/l) during fasting conditions** is examined. This occurs regularly in every individual between daily meals, but predominantly during night rest.

OGTT <u>and</u> Fasting Test (diagnosis of insulinoma) :

Many endocrinologists omit the *oral glucose load before a fasting test* due to a misconception when both tests are being viewed at independently.

An oral glucose loading test performed before or after a fasting test on a different day is superfluos and not indicated. We discourage fasting tests being started sometimes after omission of food and intended "*to wait for hypoglycemia*".

The fasting test is a classical endocrinological suppression test in the situation of potential hyperinsulinemia.
Suppressibility of the ambient insulin concentration to normal levels *(adaequate insulin secretion in the normal situation or inadaequate secretion in insulinoma)* right after a glucose-induced stimulation with oral 75-100 g of glucose is being tested.

Thus, a standardized condition may be created allowing correct interpretation of the test already early into the test phase by the endocrinologist.

Other tests, e.g. proposed **hyperinsulinemic euglycemic clamps** - eventually in the presence of a ***hypoglycemic condition*** - are laborious and do **not** play **a significant role in the diagnostics of insulinoma clinically**.

Principally these are modified controlled **C-peptide suppression tests.**

The **C-peptide suppression test (Saddig et al. JOP. J Pancreas 2002)** has a **predominant role in the diagnostic exclusion of insulinoma**, when the disease seems to be highly unlikely.

> Saddig C, Bender R, Starke AAR. A new classification plot for the C-peptide suppression test. JOP. J. Pancreas (Online) 2002; 3: 16-25

Stimulation tests, such as the formerly described **i.v.-tolbutamide test** are obsolete and have been abandoned.

No advantage has been shown with the **intraarterial calcium infusion (stimulation) test** (SIPS) which is propagated mainly in the U.S. during invasive arterial angiography only to roughly regionalize an eventual tumor).
see also Insulinoma localisation

Besides ***logistics*** the correct **interpretation of fasting test results** is of fundamental importance for a correct diagnosis ***(insulin - secretion)*** - misinterpretations often are the cause of a doubtful or even wrong diagnosis.

The reproducibility of typical insulin and blood glucose levels, especially before discontinuation or at the end of the fasting test should be of prime concern. This applies similarly to reliable estimations of absolute insulin concentrations.

! Exact mathematical values such as the **insulin / glucose-ratio (I / G-ratio)**, are neither reliable nor too helpful in inspection of the data.

! A **limit of 0.25 (µU/ml / mg/dl)** for the **insulin / glucose ratio** - as indicated in many textbooks and review articles - should not be regarded as a safe discrimination between healthy and insulinoma-bearing patients.

Most patients with an insulinoma present ratio values clearly > 2.00 during fasting.

A ratio of **0.25** in the presence of blood glucose levels of **40 mg/dl** would consider insulin concentrations of **10 µU/ml** as being mathematically normal.

At blood glucose levels of **30 mg/dl** insulin concentrations of **7.5 µU/ml would equally be "normal"**. Both constellations, however, have to classified as being pathological

Calculation of the I / G-ratio when the blood glucose level is within the normal range of > 50 mg/dl is redundant and without any diagnostic value.
We have seen many patients bearing an insulinoma in whom the correct diagnosis had been ruled out on the basis of a "normal" insulin / glucose ratio.

! **Patients with insulinoma** may present **an insulin/glucose ratio clearly below 0.2** during fasting.

Patients without Insulinoma may present **blood glucose levels < 50 mg/dl** during fasting, not so rarely even **< 40 mg/dl**, if fasted under supervision for **more than 48 hours.**

Source: data from > 150 fasting tests.

So far no data are available as to differentiate insulinoma from rare islet cell hyperplasia in adults (beta cell hyperplasia, focal hyperplasia, "nesidioblastosis") by means of a fasting test *(so called "noninsulinoma pancreatogenous hyperinsulinemic hypoglycemia").*

Sensitivity and **specificity** of the fasting test

Adaequately performed the standarized 72h-fasting test shows a **diagnostic accuracy of close to 100 % according to sensitivity and specificity**

End points:
Correct positive endocrinological diagnosis and successful surgical removal of an insulinoma

Sensitivity : Percentage of patients with an insulinoma and a positive (pathological) result druing the fasting test
Specificity: Percentage of healthy patients (without insulinoma) with a negative (normal) result in the fasting test

Sensitivity (#1 + #2) and specificity (#3 + #4) cannot be calculated by means of strict mathematics used in evidence-based medicine, due to

1. there is no clear definition of exact mathematical ranges for a pathological fasting test (e.g. insulin/glucose-ratio)
2. surgical detection depends upon surgical experience
3. none of the imaging techniques allows definitive exclusion of an insulinoma
4. clearly healthy patients according to the test results cannot be surgically explorated on ethical grounds.

Valid studies addressing follow-up of patients with an earlier negative result in the fasting test so far have not been done.

THERAPY of insulinoma

solitary benign insulinoma

Therapy of a solitary benign insulinoma, which has been biochemically and endocrinologically proven without doubt, should be the **surgical intervention / operation** (- if vital contraindications against surgery in general are not present).

Safe **medical therapy** without unwanted side-effects by means of inhibition of insulin secretion **do not exist.** Diazoxide™ or somatostatin-analogues (octreotide™) should only be reserved for selected situations without other options left.

Similar to other endocrine tumors potential development of malignancy should be in mind with any neuroendocrine tumor of the pancreas.

Endocrine surgery of the pancreas definitely requires s surgeon skilled in insulinoma surgery.

The following surgical options exist:

1. enucleation of the mostly palpable or visible tumor
2. partial pancreatic resection (left resection) if tumor is localized near the tail of the pancreas or anatomically close to the main pancreatic duct and enucleation not feasible (spleen and its vessels
3. modified resection of the pancreatic head without removal of the duodenum if tumor is localized in the center of the pancreatic head (modified Whipple's operation)

malignant metastatic insulinoma

Adaequate therapy of metastatic malignant insulinoma is a demanding challenge for *endocrinological oncologists* or *oncological endocrinologists, respectively* !

"Streptozotocin", a ***glucosamine derivative*** of an ***alkylating N-nitrosourea*** has been first applied to a patient with **malignant insulinoma in 1968.** The substance has been known as a chemical used in experimental animals in diabetes research.
Due to the rarity of the disease relevant studies concerning the therapy of metastatic malignant insulinoma and including a sufficient number of patients do not (!) exist.
Published studies addressing therapy of malignant insulinoma only contain sporadic observations. Any attempt to present these data in a meaningful statistical context should be regarded as an unserious personal interpretation, which does not take into account the clinically relevant problems of the patients. The multicenter study published by **Moertel et al. (Mayo-Clinic, N Engl J Med 1992*)** contained only 6 patients with malignant insulinoma in a series of advanced islet cell carcinomas..

1. **Moertel CJ:** Streptozotocin-Doxorubicin, Streptozotocin-Fluorouracil or Chlorozotocin in the treatment of advanced islet-cell-carcinoma. N Engl J Med 1992, 336; 519-523
2**. Starke A.:** Streptozotocin chemotherapy in patients with malignant metastatic insulinoma. Exp Clin Endocrinol Diabetes 103 A53, 1995
3**. Simon, Starke** et al: Treatment of benign and malignant insulinoma - 10-year results from one center. Eur J Clin Invest 27, Suppl 1, A34, 1997
4. **Saddig et al:** 10-year update of of benign and malignant insulinoma. Bioscientifica Congr. Ser., 4. ECE Sevilla, Spain 1998

Insulinoma localisation

- imaging techniques -

The necessity of **preoperative insulinoma localisation** after **being biochemically proven** has remained contradictory, even among experts in the field.

Each new developement of imaging tewchnology has resulted in new investigations in order to detect insulinomas according to sensitivity and specificity of the procedure.

Internists and endocrinologists sometimes may face diagnostic uncertainties, ***radiologists*** claim the advantage of technical resolution capabilities, ***endocrine surgeons*** claim the strategy of exact localisation during surgery and in addition rely upon available **intraoperative ultrasound**.

Diagnostic uncertainties only depend upon the quality and exactly controlled procedure ot the fasting test and its skilled and correct interpretation. Concern about quality control routine of the endocrine lab has to be taken into account.

Ref.:
1. Starke AAR, Frilling A, Becker H, et al. Are CAT-scans necessary for preoperative localization of insulinomas ? Eur J Med 1: 411-413, 199
2. Schumacher B, Lübke HJ, Frieling T, Strohmeyer G, **Starke AAR**. Prospective study on the detection of insulinomas by endoscopic ultrasonography. Endoscopy 28, 273-276, 1996
3. Röher HD, Simon D, **Starke A**, Goretzki PE. Special diagnostic and therapeutic aspects of insulinoma. Chirurg 68(2), 116-121, 1997
4. Simon D, Starke A, Goretzki PE, Röher HD. Reoperative surgery for organic hyperinsulinism: indications and operative strategy. World J Surg 22, 666-672, 1998

For **more than 15 years we did not perform imaging procedures** as a clinical routine in patients without earlier abdominal surgery and in whom the endocrine diagnosis of endogenous hyperinsulinism resp. insulinoma was definite. During the years the detection ratio of the endocrine surgeon remained at 100 %.

Due to minor disturbance of the patient and its low cost we only would perform **endoscopic endosonography.**

The use of **CAT scans and NMR technique** are helpful and remain the procedure of choice in cases of **liver metastases being seen in cases of malignant insulinoma**. Therapeutic options and consequences as such may appropriately be streamlined.

In patients who have had abdominal surgery before, especially after a formerly unsuccessful search for an insulinoma, imaging procedures may be helpful in certain cases.

Abdominal ultrasound, ordered to exclude or detect liver metastases before surgery, is always justified. Regular ultrasound investigation of the pancreas is rarely helpful in the localisation of an insulinoma.

Octreotide scintigraphy (Octreoscan™, somatostatin-receptor-imaging - SRI) does not have an established role in the **localisation of insulinoma** in contrast to other neuroendocrine GEP-tumors. **Insulinomas** often do not express **somatostatin receptors,** specifically not the **subtype 2 (sstr2)**, which is expressed in most neuroendocrine tumors (NET) of the pancreas.

Intraarterial pancreatic calcium stimulation *(SIPS = "selective intraarterial pancreatic stimulation")* of relevant pancreatic arteries during angiography in addition to evaluation of an insulin concentration gradient from venous blood in the hepatic veins is **invasive** and only allows **crude regionalisation**. Its role or need in the localisation of insulinomas is controversial and disputed.

The same is true for the even more invasive technique of **transhepatic portal venous sampling (THPVS)** involving transhepatic catheterisation of various tributaries.

Performance of mere imaging procedures, such as:

abdominal ultrasound
endoscopic endosonography
computed tomography (CAT-scan
nuclear magnetic resonance tomography (NMR)
arterial angiography, **sometimes combined with arterial calcium provocation (SIPS)**
somatostatin receptor szintigraphy (octreotide scan)

do not allow proof or exclusion of an insulinoma of the pancreas.

Only proof or exclusion of a biochemical perturbation of insulin secretion does allow the correct diagnosis.

Insulin-determination in serum samples
Insulin-Assay

The reference range resp. the normal level for insulin concentrations in serum samples in many laboratories is being given **from 5 - 25 µU/mL.**
This range is only valid for overnight fasted patients (12 hours) with normal weight, without diabetes mellitus, and during normal caloric nutrition and normal insulin sensitivity - which cannot be accurately measured by simple techniques rather than estimated.

This **reference range cannot be used for the interpretation of the fasting test. It is irrelevant**, since **"normal" insulin concentrations** during manipulations by means of diagnostic endocrinological function tests **are dependent upon the prevailing blood glucose level.**

During the fasting test the suppressibility of serum insulin close to or below biochemical detection limits is being examined.

Regular and valid quality control of the used assay system therefore is mandatory.

This is also valid for the **C-peptide** assay **with a "normal" reference range between 1.5 - 3.5 ng/mL** (0.5-1.15 nmol/L).
Parallel C-peptide determination may be used as a control of plausibility of the insulin assay when serum levels near the detection limit are seen (range < 5 µU/mL), which means dependency upon
LOD and LOQ ("limit of detection" and "limit of quantitation").

Physicians ordering insulin assays should be informed in detail about the used assay system in order to interprete the results appropriately.

Assay-Technology for Insulin, C-Peptide, Proinsulin

*In order to **interprete diagnostic test data** (fasting test, C-peptide suppression test, test meals) correctly and reliably, detailed knowledge of the **used assay technology** is mandatoy, especially due to the variety of commercially available **kit systems.***

This applies to
1. optimal measuring range of the assay system (linear calibration curve),
2. cross reactivities with insulin, C-peptide, proinsulin and split-proinsulins
3. quality control performed in the endocrine lab (precision, recovery, linearity).

Quality control procedures should be performed according to the ***"Guidelines for Validation of Insulin Immunoassays"*** of the American Diabetes Association ***(ADA - Committee on Insulin Assay Standardization)***.

INSULIN-ASSAYS should have a linear measuring range from 5 - 100 µU/mL (= 30 - 600 pmol/L). Crossreactivity with proinsulin should be known. **When specific insulin assays are used the determination of proinsulin is mandatory in order to avoid the escape of predominantly proinsulin-secreting insulinomas.**

C-PEPTID-ASSAYS are available with a measuring range from 0.5 - 15 ng/mL.
Values > 10 ng/mL may be relevant in the diagnostics of impaired glucose tolerance and insulin resistance. Thus, a easuring range from < 0.3 to 5 ng/mL is essential in the diagnostics of hypoglycemia. Such sensitive assays are used in the evaluation of the secretory reserve in type I diabetes.

The PROINSULIN-ASSAY should not crossreact with insulin and C-peptide.
Due to physiologically low concentrations in healthy people in the low pmol-range and rather high levels of some hundred pmols in patients with insulinoma dilution of samples is normally necessary. The optimal measuring range reaches from 5 to 100 pmol/L.

Determinations of insulin in serum samples may be achieved by means of **radioimmunoassays (RIA)** or **enzyme-linked immuno-sorbent assays (ELISA)**.

standardized supervised fasting test

Logistics

Due to potentially difficult logistics and and the expected as well as necessary development of hypoglycemia in patients **suspicious** to suffer an **insulinoma fasting tests** should be carried out in **institutions able to deal with hypoglycemias**. **!**

1. **possibility to draw blood samples (24 h / day)**
2. **immediate adaequate photometric blood glucose analysis**
3. **centrifugation and storage of aliquots timely coordinated with blood glucose measurements**

! ad 2.: A prerequisite for the adaequate performance of a fasting test is the availability of an immediate (bed-side) and exact photometrical determination of the blood glucose concentration by means of a true glucose analyzer

Blood glucose estimations by means of test strip technology, as used by diabetic patients, should be strictly avoided !

! ad 3.: There should be a clear understanding of the used insulin assay technology .

Unknown cross-reactivity of the insulin assay with proinsulin is unacceptable and might result in a missed diagnosis !

The fasting test is a potentially invasive endocrinological suppression test !

Fasting tests performed on an outpatient ambulatory basis without continuous medical care (including overnight) are discouraged.

Insulin Secretion

Physiological range of insulin secretion and concentration

The **physiological insulin secretion** (suppression) and thus insulin levels in serum by means of complex regulatory mechanisms of **glucose homoeostasis** effectively prevent fasting or spontaneous hypoglycemia, e.g. the lowering of blood glucose concentrations below the critical level of 50 mg/dL, required for "normal" function of the central nervous system, the brain.

This minimal concentration of blood glucose is required by the brain in order to meet energetic and caloric needs consuming an hourly average of 6 grams of glucose.
Between meals insulin levels demonstrate a highly variable sharp rise of short duration (30 to 60 minutes postprandially) dependent upon the amount and quality of carbohydrates consumed. A concentration range of 50 - 100 µU/mL (300 - 600 pmol/L) is regularly found, thus insulin belongs to the few hormones demonstrating a physiological range of concentrations by a factor of 20-30.
In parallel the blood glucose concentration fluctuates between 60 mg/dL and 180 mg/dL maximally (3.3 - 10 mM) clearly dependent upon the highly variable individual insulin sensitivity.

Normal suppression of insulin secretion

Adaequate suppression of insulin secretion during prolonged fasting is achieved when the **insulin concentration** in serum samples drops **below 5 µU/mL (< 30 pmol/L)** during normal blood glucose levels in the range of 50 mg/dL.

In case of **adaequate suppression** of **insulin secretion** the **concentration** of proinsulin should be measured in the range of a few pmol/l close to the detection limit: **< 5 pmol/l.**

Adaequate suppression of the **C-peptide concentration** is achieved with parallel levels **< 0.6 ng/ml** (= **< 0.2 nmol/l or < 200 pmol/l**)

If the blood glucose concentration during assured fasting (positive acetonuria) definitely is > 50 mg/dL (55-70 mg/dL), the insulin levels may be higher than 5 µU/mL (6-10 µU/mL / 36-60 pmol/L).

If the blood glucose concentration is found in the range of 40-45 mg/dL, insulin levels should be < 3 µU/mL (< 18 pmol/L).

For a long time the above mentioned ranges were equivalent with the lower limit of detection estimated by means of commercially available radioimmunoassays and non-radioactive elisa`s (enzyme-linked immunosorbent assay).
Insulin levels < 3 µU/mL physiologically represent suppressed zero values (no detectable insulin concentration) despite development of very sensitive assays which lowered the detection limit into the range below 1 µU/mL. Such an "accuracy" is unnecessary and without consequences in the diagnosis of hypoglycemia.

Pathological suppression of insulin secretion

Patients with an insulinoma demonstrate a **lack of the physiological and adaequate suppression of insulin concentrations** after meals when blood glucose is falling to basal pre-meal levels.

Starting off with suspiciously low or lower than normal fasting blood glucose levels in the range of 50 to 60 mg/dL (or even below) the ingestion of pure glucose or dextrose (100 grams orally) normally results in regular early postprandial insulin secretion dependent upon the secretory behaviour of the normal endocrine pancreatic tissue mass.
Principally a tendency towards slightly impaired glucose tolerance is seen, which is due to the physiological attenuation of insulin sensitivity in patients adapted to chronically reduced blood glucose levels.

During the late postprandial phase (3 to 15 hours after glucose ingestion) inadaequate suppression of insulin secretion will **result in hypoglycemia**, which is regularly found in patients with an **insulinoma** with **reproducible low blood glucose concentrations below 40 mg/dL (< 2.2 mmol/L)**.

Hypoglycemia sometimes occurs as late as 24-30 hours after the last meal, rarely in 2-3% of the patients as late as more than 48 hours. Thus, claims to reduce the duration of fasting tests from 72 to 48 hours would result in a loss of diagnostic accuracy.

Insulin concentrations > 6 µU/mL (> 36 pmol/L) have to be considered as **pathologically elevated** if the simultaneous **blood glucose concentration** is **< 40 mg/dL (< 2.2 mmol/L).** This reflected by simultaneously elevated **proinsulin concentrations** of **> 5-10 pmol/L,** and **C-peptide concentrations > 200 pmolL = > 0.6 ng/ml**.

However, concentrations 10 to 25 times higher within the range of 60 - 150 µU/mL (360 - 900 pmol/L) may be measured.

These ranges are meant to resemble the total insulin concentration including crossreacting proinsulin as measured with an unspecific insulin assay.
Normative values for the level of insulin concentrations during a combined OGTT - fasting test do not exist in insulinoma. Increased stimulation of insulin secretion as a consequence of glucose ingestion does not occur in insulinoma. Afraid of such a reaction the initial administration of glucose often is omitted from the test procedure, thus fasting tests are started in patients already fasting overnight for 10-12 hours without representative and diagnostic samples being drawn. This might lead to a premature discontinuation of the fasting test and difficult interpretation of a few available samples.