Hormones related to Glucose Metabolism (Clinical Utility)

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Clinical Utility of Insulin Assay

• Evaluation of fasting hypoglycemia
• Evaluation of the poly cystic ovary syndrome
• Classification of diabetes mellitus
• Predict diabetes mellitus
• Assessment of β-cell activity
• Select optimal therapy for diabetes
• Investigation of insulin resistance
• Predict the development of coronary artery disease

Insulinoma

Pancreatic and peripancreatic neuroendocrine tumors: Neuroendocrine tumors:
• Insulinomas (55%)
• Gastrinomas (36%)
• VIPomas (vasoactive intestinal polypeptide tumor) (5%)
• Glucagonomas (3%).

A study from Iran found 68 cases in a time span of 20 years in a university in Tehran


Abt 85% of patients present with symptoms of hypoglycemia that include diplopia, blurred vision, palpitations, or weakness.

Other symptoms include confusion, abnormal behavior, unconsciousness, or amnesia.

About 12% of patients have grand mal seizures.
• The calculation of ratios of insulin (µU/mL) to plasma glucose (mg/dL) is diagnostic.
• Healthy patients maintain a rate of less than 0.25.
• Obese patients may have a slightly higher rate.
• In patients with insulinoma, the ratio rises during fasting.

Whipple Triad (75%):
1. Presence of symptoms of hypoglycemia
2. Documented low blood sugar at the time symptoms are present
3. Reversal of symptoms by glucose administration.

In a study from the Netherlands, a positive Whipple triad on a prolonged fasting test, in combination with an insulin/C-peptide ratio < 1, had a sensitivity of 88.9% and a specificity of 100% for the diagnosis of insulinoma.

Insulin, Serum

Useful For
• Diagnosing insulinoma, when used in conjunction with proinsulin and C-peptide measurements
• Management of diabetes mellitus

Reference Values 2.6-24 µU/mL

Method Name Electrochemiluminescence Sandwich Immunoassay

Interpretation
• In normal individuals, insulin levels parallel blood glucose levels.
• During prolonged fasting, when the patient's glucose level is reduced to <40 mg/dL, elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma.
• Insulin levels generally decline in patients with type 1 diabetes mellitus.
• In the early stage of type 2 diabetes, insulin levels are either normal or elevated.
• In the late stage of type 2 diabetes, insulin levels decline.
• To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio):
  - Convert insulin to pmol/L: insulin concentration in µIU/mL x 6.945 = insulin concentration in pmol/L.
  - Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L.

Cautions
• Human anti-mouse antibodies (HAMA) may interfere with the assay.
• Patients on insulin therapy may develop anti-insulin antibodies. These antibodies may interfere in the assay system, causing inaccurate results. In such individuals, measurement of free insulin should be performed.
• This assay has 100% cross-reactivity with recombinant human insulin (Novolin R and Novolin N).
• It does not recognize other commonly used analogues of injectable insulin (ie, insulin lispro, insulin aspart, and insulin glargine).

Insulin Assay Interference (Heterophilic Antibodies)

[Diagram of assay interference]

http://scantibodies.com/hbr.html
Insulin, Serum

Specimen Type: Serum

Specimen Required: Serum

Collection Container/Tube: Preferred: Red top Acceptable: Serum gel Plastic vial

Specimen Volume: 1 mL

Collection Instructions:
1. Fasting. Non-fasting specimens are accepted for special studies.
2. Avoid hemolysis.
3. Label specimens with corresponding draw times.

Additional Information: If multiple specimens are drawn, send separate order for each specimen.

Specimen Minimum Volume: 0.5 mL

Transport Temperature:
- Serum Frozen (preferred) 180 days
- Refrigerated 7 days

CPT Code Information:
- 83525 - Each

Useful For:
- The patient who has known insulin autoantibodies.

Reference Values:
- 1.4-14.0 µIU/mL

Method Name:
- Automated Chemiluminescent Immunoenzymatic Assay

Interpretation:
- Insulin autoantibodies may develop in patients who have been injecting non-human insulin for treatment of insulin-dependent diabetes.
- These antibodies will directly bind to insulin, making it unavailable for metabolic activity.
- The antibodies may also adversely affect the binding characteristics of insulin in immunoassays, making reliable quantitation difficult.

Cautions:
- No significant cautionary statements (PEG Precipitation)

Insulin, Free, Serum

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- The patient who has known insulin autoantibodies.

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Insulin Antibodies (IgG, IgM), Serum

Useful For
- Predicting the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults (1)
- Differential diagnosis of type 1 versus type 2 diabetes
- Evaluating diabetics with insulin resistance in patients with established diabetes (type 1 or type 2)
- Investigation of hypoglycemia in nondiabetic subjects

Reference Values: < 0.02 nmol/L. (Reference values apply to all ages)

Method Name: Radioimmunoassay (RIA)

Interpretation:
- Seropositivity (> 0.03 nmol/L) in a patient never treated with insulin is consistent with predisposition to type 1 diabetes (2)
- In patients presenting with hypoglycemia, the presence of insulin autoantibodies may indicate surreptitious insulin administration or, rarely, insulin autoantibody-related hypoglycemia (3).

Cautions:
This test should not be requested in patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential assay interference.

Clinical Utility of Proinsulin, C-Peptide, Glucagon Assay

Proinsulin
- Diagnosis of β-cell tumors
- Familial hyperproinsulinemia
- Cross-reactivity of insulin assays

C-Peptide
- Evaluation of fasting hypoglycemia
- β-cell tumors
- Factitious
- Classification of diabetes mellitus
- Assessment of β-cell activity
- Obtain insurance coverage for insulin pump
- Monitoring therapy
- Pancreatectomy
- Transplant (pancreas-islet cell)

Glucagon
- Diagnosis of α-cell tumors
Useful For
• As part of the diagnostic workup of suspected insulinoma
• As part of the diagnostic workup of patients with suspected PC1/3 deficiency
• As part of the diagnostic workup of patients with suspected proinsulin mutations

Reference Values
3 - 20 pmol/L

Interpretation
• Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (20 pmol/L) when hypoglycemic (blood glucose <45-60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range.
• Patients with PC1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake.

Cautions
To avoid misdiagnoses, all proinsulin measurements used in the diagnostic workup of patients with hypoglycemia must be interpreted in the context of coexisting illnesses, the blood glucose concentration at the time of sampling, and other test results (i.e., insulin, C-peptide, beta-hydroxybutyrate, and sulfonylurea drug screen).

Proinsulin, Plasma

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C-Peptide, Serum

Useful For
1. Diagnostic work-up of hypoglycemia:
   - Diagnosis of factitious hypoglycemia due to surreptitious administration of insulin
   - Evaluation of possible insulinoma
   - Surrogate measure for the absence or presence of physiological suppressibility of endogenous insulin secretion during diagnostic insulin-induced hypoglycemia (C-peptide suppression test)

2. Assessing insulin secretory reserve in selected diabetic patients (as listed below) who either have insulin autoantibodies or who are receiving insulin therapy:
   - Assessing residual endogenous insulin secretory reserve
   - Monitoring pancreatectomy and islet cell transplant function
   - Monitoring immunomodulatory therapy aimed at slowing progression of preclinical or very early stage type 1 diabetes mellitus

Reference
1.1-4.4 ng/mL

Method Name
Electrochemiluminescence Immunoassay

Interpretation
- Factitious hypoglycemia due to surreptitious insulin administration results in elevated serum insulin levels and low or undetectable C-peptide levels, with a clear reversal of the physiological molar insulin to C-peptide ratio (<1 = 1) to an insulin to C-peptide ratio of >1.
- In patients with insulin autoantibodies, the insulin to C-peptide ratio may be reversed to >1, because of the prolonged half-life of autobody-bound insulin.

Cautions
- Hemolysed samples not accepted.
- Significant (>20%) cross-reactivity between C-peptide and proinsulin.
- Hook effect (>180 ng/mL).
- Heterophile antimouse antibodies (HAMA).

C-Peptide, Serum

Specimen Type
Serum

Specimen Requited

Collective Container/Tube
Vacutainer, Nazipak

Serum/Plasma
Vacutainer, Nazipak

Submission: Container/Tube: Plastic vial

Speicimen Minimum Volume
2.0 mL

Collection Instructions

Specimen Stability Information

Storage: Room Temp

Units: ng/mL

Reagent Cross-React

Human: 99.9%

Mouse: 99.9%

Rabbit: 99.9%

Monkey: 99.9%

Other: 99.9%

Variability

Analytical: 3%

Clinical: 5%

Range: 0.1-10.0 ng/mL

Precision

Accuracy

11/19/2012
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Glucagon
- Diagnosis of α-cell tumors

4D syndrome consists of
1. diabetes,
2. dermatitis,
3. DVT (deep vein thrombosis),
4. depression

Useful For
- Diagnosis and follow-up of Glucagonomas and other glucagon-producing tumors
- Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited utility)
- Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels, during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia. However, it plays only a minor role in the interpretation of this test.

Reference Values
- 1-2 days: 70-450 pg/mL
- 2-4 days: 100-650 pg/mL
- 4-14 days: declining gradually to adult levels
- >14 days: < or =80 pg/mL

Method Name
- Immunoassay following Ethanol Extraction

Interpretation
- Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big-plasma glucagon), which is cleaved upon secretion.
- The main sites of glucagon production are the hypothalamic and pancreatic α-islet cells.
- Elevated glucagon levels in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor.
- Inappropriate elevations in glucagon levels in hyperglycemic type I diabetic patients indicate that paradoxical glucagon release may contribute to disease severity.
- In diabetic patients, low glucagon levels (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypothalamic counter-regulation.

Cautions
- Results obtained with different glucagon assays can differ substantially.
- All immunoassays can, on rare occasions, be subject to hooking at extremely high analyte concentrations (false-low results), heterophilic antibody interference (false-high results), or autoantibody interference (unpredictable effects).
Glucagon, Plasma

Clinical Information
• Gastric Inhibitory Peptide is a 43 amino acid peptide structurally related to Glucagon and Secretin and is found in the mucosa of upper intestine produced by K cells.
• GIP was originally detected as a factor inhibiting the secretion of gastric acid and Gastrin secretion.
• Its major action has now been determined to be a potent stimulant of B cells to release Insulin and is also known as Glucose-Dependent Insulinotropic Peptide.
• Exaggerated increases in GIP are noted after glucose administration to patients with Gastric Inhibitory Polypeptide (GIP) Pancreatitis. This increase is also seen in patients with Diabetes Mellitus.
• GIP levels are decreased by Calcitonin.
• Elevated levels are present in cases of Verner-Morrison Syndrome (VIPoma).

Reference
Fasting: Up to 50 pg/ml
Postprandial: 110 - 720 pg/ml

Method Name Direct Radioimmunoassay (RIA)

Cautions
No significant cautionary statements.
Thank you for your Attention

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