Test Definition: PINS

Proinsulin, Plasma

Overview

Useful For

As part of the diagnostic workup of suspected insulinoma

As part of the diagnostic workup of patients with suspected prohormone convertase 1/3 deficiency

As part of the diagnostic workup of patients with suspected proinsulin variations

Method Name

Electrochemiluminescent Immunoassay (ECLIA)

NY State Available

Yes

Specimen

Specimen Type

Plasma EDTA

Specimen Required

Patient Preparation:

Fasting: 8 hours, required; Infants younger than 2 years should fast a maximum of 6 hours

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)

Collection Container/Tube: Ice-cooled, lavender top (EDTA)

Submission Container/Tube: Plastic vial

Specimen Volume: 0.5 mL Plasma

Collection Instructions:

1. Immediately after draw, place the whole blood on ice for at least 10 minutes.
2. Centrifuge at refrigerated temperature, aliquot plasma into a plastic vial, and freeze specimen.

Specimen Minimum Volume

Plasma: 0.25 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma EDTA	Frozen	30 days	

Clinical & Interpretive

Clinical Information

Proinsulin is the precursor of insulin and C-peptide (connecting peptide). Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin.

Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis rests primarily on demonstrating nonsuppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). Diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. Insulin injections or hypoglycemic drugs can also mimic insulinoma. Evaluation of these patients frequently requires a prolonged fast (72 hours) as well as supplementary tests in addition to insulin and glucose measurements, including a sulfonylurea screen and measurement of C-peptide, proinsulin, and beta-hydroxybutyrate. The inappropriate oversecretion of insulin by insulinomas causes the release of an increased numbers of secretory granules with incompletely processed insulin, resulting in elevated serum/plasma proinsulin concentrations. This oversecretion of proinsulin in insulinomas is accentuated during fasting, when proinsulin normally does not account for more than 5% of the insulin concentrations.

Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Variants in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These variants can also lead to markedly elevated proinsulin levels but are usually not accompanied by diabetes or any other hormonal abnormalities.

Reference Values

3.6-22 pmol/L

Interpretation

Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (22 pmol/L) when hypoglycemic (blood glucose <60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 22 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, which is recommended by Mayo Clinic's highly-experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis.

Patients with prohormone convertase 1/3 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. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotropic hormone and other peptides), infertility, and, often, obesity.

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, blood glucose concentration at the time of sampling, and other tests, namely, insulin, C-peptide, beta-hydroxybutyrate measurements, and a sulfonylurea drug screen.

Patients with chronic kidney failure and type 2 diabetes mellitus can have increased proinsulin, C-peptide, and insulin values but usually without suppressed (<45 mg/dL) blood glucose concentrations.

Clinical Reference

1. Murtha TD, Lupsa BC, Majumdar S, Jain D, Salem RR. A systematic review of proinsulin-secreting pancreatic neuroendocrine tumors. J Gastrointest Surg. 2017;21(8):1335-1341
2. Placzkowski KA, Vella A, Thompson GB, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab. 2009;94(4):1069-1073
3. Vezzosi D, Bennet A, Fauvel J, Caron P. Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. Eur J Endocrinol. 2007;157(1):75-83
4. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995;332(17):1144-1152
5. Steiner DF. The proprotein convertases. Curr Opin Chem Biol. 1998;2(1):31-39

Performance

Method Description

Sequential 2-site electrochemiluminescent immunoassay performed on the MesoScale Discovery instrument. The assay uses a monoclonal biotinylated anti-insulin capture antibody and an anti-C-peptide detection antibody labeled with SULFO-TAG. The signal is directly proportional to the amount of proinsulin in the sample. Assay calibration is traceable to the World Health Organization 1st International Standard for human proinsulin, NIBSC code: 09/296. This assay demonstrates no cross-reactivity with insulin or C-peptide.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Tuesday, Friday

Report Available

2 to 5 days

Specimen Retention Time

2 weeks

Test Definition: PINS

Proinsulin, Plasma

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

84206

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PINS	Proinsulin, P	27882-0

Result ID	Test Result Name	Result LOINC® Value
80908	Proinsulin, P	27882-0