C-peptide (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
C-peptide

1.2 Alternative names
None

1.3 Description of analyte
C-peptide is the amino acid sequence that links the A and B peptide chains of insulin in its precursor, proinsulin. C-peptide is excised to leave insulin, which consists of two separate peptide chains joined only by disulphide bonds.

1.4 Function of analyte
C-peptide has a longer half-life in the circulation than insulin itself, which is why it is used as a surrogate marker of β-cell function. C-peptide was long believed to be merely a by-product of insulin secretion with no intrinsic function. However, evidence is now emerging that C-peptide deficiency in type 1 diabetes plays a role in the development of microvascular complications. The excess circulating C-peptide that is seen in insulin resistance may also contribute to macrovascular disease. However, at present these functions remain in the domain of research rather than current clinical practice.

2 Sample requirements and precautions

2.1 Medium in which measured
Serum or plasma

2.2 Precautions re sampling, handling etc.
Limited data are available on *in vitro* stability. Serum should be separated from cells as soon as possible and the sample either be analysed within 24 h (ideally 2–3 h) or frozen. Once thawed, frozen samples should not be refrozen.

3 Summary of clinical uses and limitations of measurements

3.1 Uses
1. Differentiation between endogenous and exogenous hyperinsulinism.
2. Differentiation between type 1 and type 2 diabetes mellitus (though such differentiation is not routinely required).

3.2 Limitations
A C-peptide measurement for distinguishing the source of hyperinsulinism is of value only if the sample is taken when the patient is actually hypoglycaemic.
C-peptide discriminates poorly between type 1 and type 2 diabetes in patients with kidney disease as it accumulates in renal failure.

4. Analytical considerations

4.1. Analytical methods
Several immunoassays are available commercially.

4.2. Reference method
Isotope-dilution liquid chromatography–mass spectrometry.

4.3. Reference materials
WHO International Reference Reagent, C-peptide of human insulin, NIBSC code 84/150. One ampoule contains 10 μg by definition. (1 μg = 0.333 nmol).

4.4. Interfering substances
Possible cross-reactivity with proinsulin (positive).

4.5. Sources of error
Icterus has been reported to give negative interference with the Immulite 2500 method.

5 Reference intervals and variance

5.1.1 Reference interval (adults)
There is no single accepted reference interval in the conventional sense. However it is agreed that in the presence of hypoglycaemia, C-peptide should be suppressed below 0.2 nmol/L (see section 9.2).

5.1.2 Reference intervals (others)
Not applicable

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 23.2%

5.1.3.2 Intraindividual CV: 16.6%

5.1.3.3 Index of individuality: 1.4

5.1.3.4 CV of method: generally ≤6%

5.1.3.5 Critical difference: 118% (if assay CV 6%)

5.1.4 Sources of variation
Recent food intake, insulin resistance, kidney disease all increase plasma [C-peptide].

6. Clinical uses of measurement and interpretation of results

6.1. Indications for measurement
1. Hypoglycaemia
The main indication for measurement is differentiation between endogenous and exogenous hyperinsulinism as a cause of hypoglycaemia. In general, hypoglycaemia accompanied by raised insulin and raised C-peptide is caused by endogenous insulin secretion, whereas hypoglycaemia accompanied by raised insulin and low C-peptide suggests exogenous insulin administration. However such results are not absolute proof of insulin administration: the combination of raised insulin with low or relatively low C-peptide has been described in the presence of autoantibodies to insulin or its receptor.
2. Distinguishing between type1 and type 2 diabetes.

Measurement of C-peptide may be used to distinguish type 1 from type 2 diabetes, although in practice this should only be required in a small number of ambiguous cases.
3. C-peptide used as a marker of β-cell function in research settings.

6.2 Confounding factors
Taking blood for C-peptide measurement during or after treatment for hypoglycaemia rather than while hypoglycaemia is still present can cause problems in interpretation, since raising blood [glucose] will lead to insulin and C-peptide secretion.
Kidney disease (see 3.2)

7. Causes of abnormal results

7.1 High values
7.1.1 Causes
1. Raised plasma [C-peptide] accompanying endogenous hyperinsulinism may be seen in:

- insulin resistance or type 2 diabetes
- infants of diabetic mothers
- persistent hyperinsulinaemic hypoglycaemia of infancy
- Beckwith syndrome
- sulphonylurea overdose
- insulinoma
- insulin autoimmune syndrome (though *free* C-peptide is typically low).

2. Kidney disease also results in raised C-peptide, owing to impaired excretion.
7.1.1 Investigation
Further tests may include measurement of urinary sulphonylureas and pancreatic imaging.

7.2 Low values
7.2.1 Causes:

- fasting state
- type 1 diabetes
- exogenous insulin administration.

7.2.2 Investigation
Not usually required

8. Performance

8.1 Sensitivity, specificity etc. for individual conditions
Not applicable.

9. Systematic reviews and guidelines

9.1 Systematic reviews
None identified.

9.2 Guidelines

1. Cryer PE, Axelrod L, Grossmann AB *et al.* Evaluation and management of adult hypoglycaemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009;94:709-728.
This identifies 0.2 nmol/L (0.6 μg/L) as the critical concentration below which C-peptide should be suppressed during hypoglycaemia.
2. Sacks DB, Arnold M, Bakris GL *et al.* Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011;34:e61-e99.
This detailed guidance gives measurement of C-peptide only a small role in the investigation of the minority of diabetic patients in whom the distinction between type 1 and type 2 diabetes is unclear.

9.3 Recommendations
See section 9.2.

10. Links

10.1 Related analytes
Insulin

10.2 Related tests
None

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