Diabetes

C-peptide

Analyte Information

C-peptide

Introduction

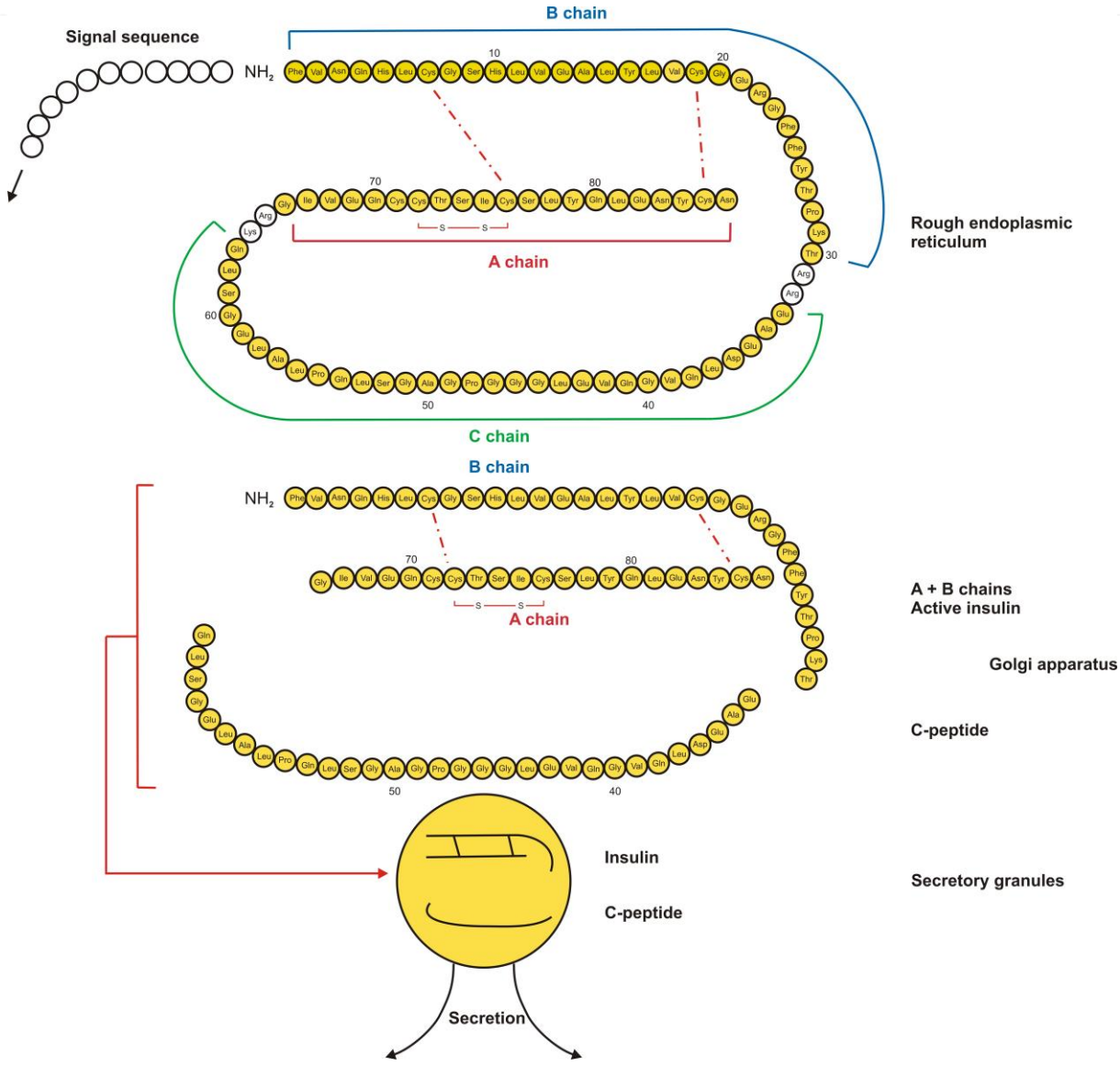
C-peptide (connecting peptide), a 31-amino-acid polypeptide, represents the mid-portion of the proinsulin molecule. Proinsulin resembles a hairpin structure, with the N-terminal and C-terminal, which correspond to the A and B chains of the mature insulin molecule, oriented parallel to each other and linked by disulfide bonds. The looped portion of the hairpin between the A and B chains is called **C-peptide** (see Fig.1).

During insulin secretion C-peptide is enzymatically cleaved off and co-secreted in equimolar proportion with mature insulin molecules.

Although insulin and C-peptide are secreted into portal circulation in equimolar amounts, fasting C-peptide concentrations are fivefold to tenfold higher than those of insulin owning to the longer half-life (about 35 min) of C-peptide.

C-peptide has molecular weight 3600 Da.

Fig.1: C-peptide and Insulin synthesis



Biosynthesis

C-peptide or connecting peptide is a side product of insulin production.

Insulin is secreted primarily in response to elevated blood concentrations of glucose. Insulin is "in charge" of facilitating glucose entry into cells. Some neural stimuli (e.g. sight and taste of food) and increased blood concentrations of other fuel molecules, including amino acids and fatty acids, also promote insulin secretion.

Pre-proinsulin is synthesized in the β-cells of the pancreatic islets. It is made up of a signal sequence (approximately 23 amino acids that are rapidly cleaved after hormone synthesis), and B chain, connecting (or C) peptide and A chain. After cleavage of signal sequence Proinsulin is created. A and B chains are joined together by two disulfide bonds between common cysteine amino-acid residues. The connecting peptide is essential to the formation of these disulfide bonds and is split off in the Golgi apparatus leaving the active insulin molecule composed of joined A and B chains. The cleaved C-peptide is co-secreted with insulin and both are released into blood stream in equimolar quantity.

Metabolism

Insulin and C-peptide enter the portal circulation and are routed through the liver, where at least 50% of the insulin binds to receptors, initiates specific hepatic actions (stimulation of hepatic glucose uptake and suppression of glycogenolysis, gluconeogenesis, and ketogenesis) and is subsequently degraded. Most of the insulin molecules that pass through the liver into the main circulation bind to peripheral insulin receptors, promoting glucose uptake, while the remaining molecules undergo renal elimination. **Unlike insulin, C-peptide** is subject to neither significant hepatic nor peripheral degradation, but it is mainly removed by the kidneys. As a result, C-peptide has a longer half-life than insulin (30 - 35 minutes versus 4 - 5 minutes) and therefore, a normal molar ratio C-peptide/Insulin is > 5 in the peripheral circulation. As mentioned above, hepatic extraction of C-peptide is small and constant when compared with insulin. Only about 12% of C-peptide is extracted by the liver. Most of circulated C-peptide is extracted unchanged into urine through the kidney.

Physiological function

Previously considered to have no physiological role, C-peptide is now recognized to have G-protein-coupled cellular receptors and it is likely to have some function in regulation of blood flow and renal function. C-peptide has significant protective effects on development of diabetic neuro-, nephro- and retinopathy.

Levels

Typical C-peptide levels are given in table 1.

For each assay, relevant reference values are given in the appropriate Instructions for Use (IFU).

Tab.2: Typical C-peptide levels

Specimen (serum, fasting)	**Reference range** (nmol/L)
	0.26 – 0.63
Specimen (urine, 24 hours)	**Reference range** (µg/day)
	64.6 ± 20.5

Equation for the conversion of units for C-peptide: 1 nmol/L x 3= ng/mL

Diagnostic utility – prospects and possibilities

C-peptide measurement usually provides more reliable information about the endogenic insulin secretion than measurement of insulin itself. In most disease conditions associated with abnormal serum insulin levels, the changes in serum C-peptide levels parallel insulin-related alterations. Both serum C-peptide and insulin levels are elevated in renal failure and in disease states that lead to increased primary endogenous insulin secretion (e.g., insulinoma, sulfonylurea intoxication). Both also may be raised in any disease states that cause secondary increases in endogenous insulin secretion mediated through insulin resistance, primarily obesity, metabolic syndrome, glucose intolerance, and early diabetes mellitus (DM) type 2, as well as endocrine disorders associated with hypersecretion of insulin-antagonistic hormones (e.g., Cushing syndrome, acromegaly). Failing insulin secretion in DM type 1 and longstanding DM type 2 is associated with corresponding reductions in serum C-peptide levels.

Discordant serum insulin and serum C-peptide abnormalities are mainly observed in two situations: in exogenous insulin administration and in the presence of anti-insulin autoantibodies. Factitious hypoglycemia due to surreptitious insulin administration results in appropriate suppression of endogenous insulin and C-peptide secretion. At the same time, the peripherally administered insulin bypasses the hepatic first-pass metabolism. In these situations, insulin levels are elevated and C-peptide levels are decreased.

In patients with insulin antibodies, insulin levels are increased because of the prolonged half-life of autoantibody-bound insulin. In these patients, the proper insulin compensation may be very difficult.

DM type 1 (former IDDM Insulin Dependent Diabetes Mellitus, juvenile diabetes) is characterized by a highly reduced secretion of insulin and C-peptide and non-responsiveness to the main stimuli, glucose and glucagon. Fasting and stimulated C-peptide levels reflect the damage of β-cells by autoimmune inflammation of islets (insulitis).

DM type 2 (former NIDDM Non-Insulin Dependent Diabetes Mellitus, diabetes of adults) is characterized by hyperinsulinism and insulin resistance of tissues in the beginning. Consequently, C-peptide levels are increased as well. Nevertheless, after several years the levels of insulin and C-peptide decrease.

Obesity is associated with markedly elevated insulin and C-peptide secretion, in terms of both basal secretion and the respond to stimuli. Normalization of body weight in usually associated with C-peptide level normalization.

Insulinoma is characterized by attacks of hypoglycemia with high insulin and C-peptide levels. Adenomas frequently show exaggerated responses to any stimuli. Insulin producing tumours secrete proinsulin in a higher proportion than the normal β-cells does.

In diabetic patients who are under treatment with insulin, the serum C-peptide levels reflect the secretory capacity of β-cells.

Elevated C-peptide levels

- insulinoma (pancreatic islet cell tumor)
- DM type 2
- pancreas or β-cell transplants
- renal failure
- Cushing´s syndrome
- obesity (patients with body mass index (BMI)> 25)
- metabolic syndrome
- ingestion of oral hypoglycemic drugs

Diminished C-peptide levels

- DM type 1
- late phase of DM type 2
- factitious hypoglycemia due to insulin administration

Diagnostic utility – practical applications

C-peptide examination under basal conditions (fasting and postprandial), and after glucagon stimulation, or in the course of OGTT, is recommended in the following cases:

Differential diagnosis of some cases of DM type 1 and 2 and LADA (Latent Autoimmune Diabetes of Adults)

Prediction, diagnosis, and follow-up of the course of remission in DM type 1

Evaluation of residual insulin secretion as a prevention of diabetic microanginopathy progression in diabetic patients type 1

Prediction of insulin–dependence development in LADA type DM

Prediction of insulin–dependence development in type 2 DM

Therapeutic transfer to insulin in type 2 diabetes patients

C-peptide immeasurable fasting levels and values < 20 pmol/L after stimulation are unambiguous indications for DM type 1. However, in the period after DM type 1 manifestation and in DM type 1 remission, C-peptide values are often found in normal range (or even higher if the basal values are followed-up only), and the diagnosis is based on the proof of autoimmune process to islet cells by means of specific autoantibodies determination. As C-peptide level reflects residual insulin secretion its higher levels are associated with higher possibility of disease remission. Even minimal residual C-peptide secretion prevents from development of diabetic microangiopathy, therefore, its monitoring by means of C-peptide has high clinical significance. The C-peptide decreased levels along with positive findings of autoantibodies (anti-GAD and anti-IA2 in particular) are considered to be the crucial indicators of early insulin-dependence in type LADA diabetes.

Normal and increased C-peptide levels at diabetic syndrome manifestation support rather the DM type 2 diagnosis. Nevertheless, the C-peptide (and insulin) levels may drop after several years of type 2 DM duration. Once it happens, patient becomes insulin-dependent, and exogenous insulin therapy must be applied.

In states characterized by insulin-resistance, as obesity, PCOs, metabolic syndrome, thyrotoxicosis, Cushing syndrome, acromegaly, pheochromocytoma, hypokalaemia, pregnancy, renal insufficiency, glucocorticoid therapy, hormonal contraceptives, and in some other situations, β-cells increase their compensatory basal and stimulated secretion of both C-peptide and insulin in the extent keeping the glucose tolerance within normal range.
Nevertheless, extremely elevated C-peptide levels and delayed secretion curve peak (120 to 180 minutes after secretory stimulus) may be found. Following insulin-resistance adjustment i.e. after remarkable weight loss, decreasing or omitting prednison dose, after the stress or infection trailing away, adjustment of both Insulin and C-peptide secretion may occur. In long-lasting insulin-resistance β-cells may get exhausted, which is manifested by subsequent drop of initially stimulated secretion, and later also by drop of basal secretion and by development of glucose-tolerance disorder or diabetes.

Differential diagnostics of hypoglycemic states (organic versus iatrogenic origin)

C-peptide examinations play the most important role in differential diagnostics of hypoglycaemia of iatrogenic origin (by exogenous insulin application) from organic origin hyperinsulinism. Insulinoma produces excessive amount of insulin, C-peptide, as well as proinsulin. On the other hand, the insulin artificially increased level is not accompanied with proinsulin increased values, and C-peptide level is, as a rule, remarkably decreased as a result of endogenous insulin secretion suppression. Insulin and C-peptide secretion in insulinoma is autonomous and is not under regulation. Therefore the extended fasting (72 hours) does not usually lead to suppression of C-peptide and insulin secretion.

Measurement of C-peptide in urine

Determination of C-peptide waste in 24 hours urine is used as a monitoring marker of residual secretory capacity of ß-cells. The 24-hours urine C-peptide content (in the absence of renal failure, which produces increased levels) correlates well with fasting serum C-peptide concentration. It can be used when blood sampling is not practical.

References

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