

C-peptide in Stage 3 Type 1 Diabetes

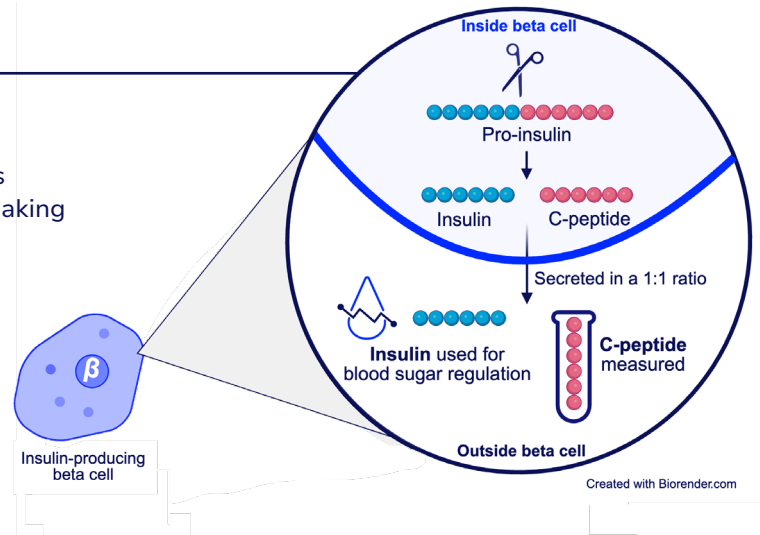
A Guide for Healthcare Providers

Background

Type 1 diabetes (T1D) is an autoimmune disease in which the immune system destroys the beta cells in the pancreas. While treatment has centered on lifelong insulin replacement, disease-modifying therapies (DMTs) intended to delay or prevent progression of T1D are being studied as promising treatment options. Measuring C-peptide is important for guiding care in the evolving treatment landscape.

What Is C-peptide?

Insulin and C-peptide are produced by pancreatic beta cells in equimolar amounts from the cleavage of proinsulin. C-peptide is produced only during endogenous insulin synthesis and has a longer half-life than insulin, making it a reliable biomarker of endogenous insulin production and beta cell function. C-peptide levels decline over the months to years before Stage 3 T1D diagnosis, and continue to fall in the period immediately after.



Measuring C-peptide for DMTs

- Consider measuring C-peptide at or shortly after Stage 3 T1D diagnosis to determine eligibility for a clinically available DMT or clinical trial.
- C-peptide must be measured with a paired glucose to assist in interpretation. C-peptide secretion is appropriately decreased in the setting of hypoglycemia and rises with increasing glucose concentrations.
- When determining DMT eligibility, stimulated C-peptide levels should be measured after a meal or as part of a mixed meal tolerance test.
 - Fasting C-peptide levels should not be measured to assess endogenous insulin production when considering eligibility for DMTs as less endogenous insulin is produced while fasting.
- C-peptide **should not** be measured within 2 weeks of an episode of DKA, as levels may be transiently suppressed and may not accurately reflect beta-cell function. Hypoglycemia in the 3-4 hours preceding the test can also lead to transient decreases in C-peptide. Consider rescheduling if a person is hypoglycemic on the morning of a scheduled test.
 - In stage 3 T1D, a C-peptide of ≥ 0.2 pmol/mL (0.6 ng/mL) is needed to be eligible for teplizumab and most DMT clinical trials.
 - For people ages 8-17 years with recent-onset stage 3 T1D, the window for eligibility for teplizumab is 8 weeks from diagnosis.
 - For DMT trials that aim to preserve C-peptide in stage 3 T1D, the window of eligibility is usually <100 days from diagnosis.
 - For people ages ≥ 1 year with Stage 2 T1D, C-peptide levels are not required to be eligible for teplizumab.

Disclaimer: This resource is provided by Breakthrough T1D for educational purposes for qualified healthcare providers. It is not intended for medical advice, or substitute for the independent clinical judgment of the treating provider. Providers are solely responsible for all diagnostic and treatment decisions. Breakthrough T1D assumes no liability for treatment decisions made based on this material.

Measuring C-peptide for DMTs

TEST	PROCEDURE	CONSIDERATIONS
Mixed-Meal Tolerance Test (MMTT)—Gold standard, often used in clinical trials	- Fast 10-12h overnight - Glucose of 70-200 mg/dL (3.8-11.1 mmol/L) at start of test¹ - Measure C-peptide & glucose 10 min before and immediately (0min) prior to liquid meal¹ - Drink Boost High Protein within 5min¹ 6 mL/kg, max 360 mL - Measure C-peptide & glucose at 15, 30, 60, 90, and 120 min¹	- Managing insulin before the MMTT: - Continue long-acting or pump/ AID basal insulin. - Hold rapid acting insulin boluses ≥ 2 h and short acting insulin ≥ 6 h prior to the start of the test¹ - C-peptide & glucose levels are used to measure AUC* 90-min paired glucose and C-peptide levels may be an alternative to full MMTT²
Random Non-fasting C-peptide — Clinical Use	Single sample obtained ~90 min postprandially for optimal beta cell stimulation^{3,4}	- Consider similar insulin management as in MMTT. - No clear glucose threshold has been established for measuring C-peptide when assessing candidacy for DMTs. - A glucose level >144mg/dL (8mmol/L) is often considered to reflect stimulated insulin and C-peptide secretion.⁵ - Individuals with more robust residual beta cell function may have difficulty reaching glucose levels > 144 mg/dL (8 mmol/L). - If C-peptide is <0.2 pmol/mL (0.6 ng/mL) with a postprandial glucose levels <144 mg/dL (8 mmol/L), consider repeating a random C-peptide level or obtaining an MMTT.

*AUC=area under the curve; h=hour; min=minutes;

Factors that can influence C-peptide results?

FACTOR	EFFECT ON C-PEPTIDE	CONSIDERATIONS
Fasted State	↓	Stimulated C-peptide should be used to assess for DMT eligibility
Fed State	↑	Stimulated C-peptide should be used to assess for DMT eligibility
Recent DKA	↓	Should not be tested within 2 weeks of DKA resolution
Hypoglycemia	↓	Rescheduled if glucose is <70 mg/dL (3.9 mmol/L)
Impaired Renal function	↑	Decreased renal clearance of C-peptide
Insulin Resistance	variable	Numerous causes: puberty, T2D, hypothyroidism, obesity, and more

Benefits of Residual C-peptide in T1D

Evidence from multiple studies, including the landmark Diabetes Control and Complications Trial (DCCT), show that residual beta cell function, measured by C-peptide, is associated with:

- Lower HbA1c
- Lower risk of severe hypoglycemia
- Lower risk of retinopathy development and progression

If a person with newly diagnosed Stage 3 T1D has a stimulated C-peptide, ≥ 0.2 pmol/mL (>0.6 ng/mL), assess their eligibility for clinically available DMT therapies or consider referral for a DMT clinical trial.

References: 1. Bogun MM, Bundy BN, Goland RS, Greenbaum CJ. C-peptide levels in subjects followed longitudinally before and after type 1 diabetes diagnosis in TrialNet. Diabetes Care. 2020;43(8):1836-1842. PMID: 32457058. 2. Mayo Clinic Laboratories. C-peptide, Serum (Test ID: CPR). Mayo Clinic Endocrinology Catalog. Available at: ndocrinology.testcatalog.org/show/CPR. CPT Code: 84681. 3. Breakthrough T1D. C-peptide: Everything You Need to Know. April 28, 2026. Available at: breakthrough1d.org/news-and-updates/C-peptide-everything-you-need-to-know. 4. Ramos EL, Dayan CM, Chatenoud L, et al.; PROTECT Study Investigators. Teplizumab and B-cell function in newly diagnosed type 1 diabetes. N Engl J Med. 2023;389(23):2151-2161. doi:10.1056/NEJMoa2308743. 5. Lachin JM, McGee P, Palmer JP; DCCT/EDIC Research Group. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. Diabetes. 2014;63(2):739-748.