Review

C-peptide in Precision Diabetes Care and Beyond: A Comprehensive Review

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Abstract

Impaired pancreatic β-cell function is a key feature in the pathophysiology of both type 1 and long-standing type 2 diabetes. C-peptide, produced in 1:1 ratio along with insulin, is secreted at a relatively steady rate over long duration, making it an effective biomarker for endogenous insulin secretion. Given the heterogeneity and complex pathophysiology of diabetes, C-peptide estimation plays an important role in the accurate classification of diabetes and in guiding treatment decisions, particularly for patients needing insulin therapy. In autoimmune diabetes, especially adult-onset forms, C-peptide has gained importance as a biomarker. However, its greatest utility is often observed 3 to 5 years post-diagnosis, when detectable C-peptide levels may help differentiate between MODY (Maturity-onset Diabetes of the Young) and type 2 diabetes. The clinical applications of C-peptide extend beyond diagnosis, including risk stratification for diabetes-related vascular complications, determining pharmacotherapy choices, evaluating hypoglycemia, and even in the context of bariatric surgery. Despite its usefulness, the role of C-peptide in type 2 diabetes remains limited, primarily due to insulin resistance, which may elevate C-peptide levels. Estimating C-peptide is a cost-effective and reliable method, but there is still considerable variation in its application. Factors such as sample collection, timing in relation to meals, and the lack of standardization in assay techniques raise issues regarding the consistency and repeatability of results among various laboratories. This review aims to explore the current evidence surrounding C-peptide estimation in diabetes care, as well as the limitations and uncertainties that continue to challenge its clinical application.

Plain Language Summary

Diabetes tends to develop when the body doesn't make enough insulin or can't use it properly. When the body makes insulin, it also releases a substance called C-peptide in equal amounts. Measuring C-peptide is a simple and helpful way to check how well the body is still making its own insulin. Testing C-peptide levels—either in the blood or urine—can show, still how active the insulin-producing cells are in the pancreas (called beta cells). This information can help medical professionals make a more accurate diagnosis and create a treatment plan that fits the person's specific needs. A random C-peptide estimation, along with a blood glucose test, can be useful when it's hard to tell what type of diabetes someone has or how best to treat it. However, C-peptide levels can vary depending on the duration of diabetes, whether the person is insulin resistant, has kidney problems, or has had weight loss surgery in the past. If someone with type 2 diabetes still has good C-peptide levels, it may mean they can manage their condition with non-insulin medications—even after having diabetes for many years. C-peptide tests can also help to tell the difference between autoimmune diabetes (especially when antibody tests are negative) and other types of diabetes caused by abnormal genes. In people with type 1 diabetes, having even a small amount of C-peptide in the normal range is linked to better outcomes, such as needing less insulin, having fewer low blood glucose episodes, and a lower risk of complications. C-peptide tests can also be useful in people who have repeated low blood glucose levels but are not using insulin. This article aims to explain when and why C-peptide tests are useful, what their benefits are, and what are the limitations of its use in clinical practice.

Keywords

precision diabetes, C-peptide, personalized medicine, diabetes diagnosis, diabetes management

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Introduction

C-peptide is an integral part of pro-insulin which is cleaved prior to co-secretion with insulin from the beta cells (β) of pancreas. It is produced in equimolar amounts to insulin from the β cells in response to glucose related stimulus. C-peptide exhibits a longer half-life compared to insulin and is eliminated at a steadier rate over an extended duration, resulting in plasma concentrations 5 times higher than insulin.[1,2]

Over the years, research on quantitative assessments of β cell function has demonstrated a predictive correlation between stimulated C-peptide levels and β cell activity. While approximately half of the insulin secreted by the pancreas undergoes first-pass metabolism in the liver, C-peptide remains unaffected by hepatic metabolism. C-peptide is essentially cleared in the peripheral circulation at a constant rate therefore direct measurement becomes more consistent than insulin which has a variable clearance rate.[3]

Misclassification of diabetes is seen in up-to 15% of the cases and this is often an underestimated rate owing to the use of clinical judgment as a reference.[4] But accurate classification of the type of diabetes is crucial as it allows a better understanding of etiology of the disease and helps to formulate appropriate treatment strategies. When combined with factors such as clinical presentation, autoantibodies, genetic testing, family history, and environmental influences, C-peptide measurement can aid in accurately diagnosing the type of diabetes.[5] As disease modifying therapy to preserve β cell function is now being considered as an alternative and adjunctive therapy to insulin in early/stage 2 type 1 diabetes, the role of C-peptide as a reliable surrogate outcome marker is being increasingly recognized to predict the responses to such pharmacotherapies.[6] Moreover, C-peptide assay helps to determine the need for initiating insulin therapy when the type of diabetes is unclear. Additionally, C-peptide is the cornerstone of the assessment of non-diabetes associated hypoglycemia, factitious hypoglycemia, diagnosing insulinoma and to explore reasons for hypoglycemia in post bariatric patients.[3]

C-peptide is a specific, sensitive, feasible and reliable biomarker that provide insights into the underlying pathophysiology of disease and its progression, but its expansive role has now been utilized in exploring monogenic diabetes, and diabetes related complications.[7] This article reviews current evidence surrounding the utility of measurement of C-peptide in the clinical management of patients with and without diabetes.

C-Peptide – Physiology

Human proinsulin is an 86-amino acid polypeptide in which the N-terminus of the insulin A-chain is connected to the C-terminus of the B-chain through a 35-amino acid linking segment.[8] Proinsulin is produced by ribosomes attached to the rough endoplasmic reticulum and subsequently transported to the Golgi apparatus for further processing.[9,10] Proinsulin is packaged into beta cell granules, where it undergoes cleavage by proteolytic enzymes as the granules mature and move toward the plasma membrane of pancreatic beta cells.[11] After cleavage of proinsulin, insulin and C-peptide (31 amino-acid peptide) are produced in equal amounts.[2,12]

Although equimolar amounts of insulin and C-peptide are secreted in the portal vein, the serum ratio is between 1:5 to 1:15 due to removal of approximately 50% of the insulin from the blood during initial passage through the liver (first pass metabolism).[13] C-peptide has negligible extraction by the liver but is principally metabolized by the kidney; 69% of the total metabolic clearance. Whereas, the insulin renal extraction accounts for only 33% of the total clearance.[14,15] As the half-life of C-peptide is longer (20-30 vs 3-5 minutes), the concentration of C-peptide in the systemic circulation is five times higher than the portal circulation.[16] Peripheral C-peptide levels reflect the portal insulin secretion more appropriately and accurately. The key differences of metabolism between insulin and C-peptide are listed in the Table 1.[17,18]

C-Peptide Assay

C-peptide assay is preferred to insulin measurement while assessing β cell function in clinical practice. Earlier assays of C-peptide were done by time consuming radio-immunoassays which were often inaccurate. Modern day techniques involve non-isotopic methods (chemiluminescence, fluorescence etc.) which are more standardized, sensitive and specific. C-peptide can also be assessed using less invasive methods, such as transdermal capillary blood sampling (TBS), which has demonstrated sensitivity, specificity, and acceptability comparable to venous sampling. This method is less intrusive and may be particularly advantageous for infants and children.[19] C-peptide measurement lacks standardization among different assay methods which interferes with result comparability and precision. Optimal standardization of C-peptide measurements has not been achieved yet therefore different laboratories may produce different results despite using the same methods for estimation. Modern assays can detect C-peptide values as low as 0.0015 to 0.0025 nmol/L[20] but it is important to be aware that cross reactivity with pro-insulin and presence of anti-insulin antibodies can give falsely elevated values.[21,22] It is commonly expressed as nmol/L, pmol/L, and ng/mL. In healthy individuals, plasma concentrations can vary between 0.3-0.6 nmol/L (Fasting) and 1-2 nmol/L (Post meal); (1 nmol/L = 1000 pmol/L = 3 ng/mL).[2]

In persons with diabetes, the C-peptide levels can have wide variation depending on the type of diabetes and residual beta cell dysfunction. A person with recent diagnosis of type 2 diabetes may show higher fasting C-peptide levels owing to insulin resistance as opposed to long standing Type 2 diabetes with declining beta cell function. Similarly, the serum levels of C-peptide can be variable in a person with type 1 diabetes depending on the stage at presentation. The Table 2[23-25] provides the typical fasting and stimulated reference ranges for both insulin and C-peptide in healthy adults and individuals with diabetes.[26]

Table 1. Hepatic and Renal Metabolism of Insulin and C-peptide.[17,18]

Parameters	Insulin	C-peptide
Clearance	Liver (primary), Kidney (secondary)	Kidneys (primary)
Liver metabolism	Yes (50%-60%, first pass)	No
Kidney metabolism	Yes (minor unless exogenous)	Yes (major route)
Half life	5 min	30 min
Stability in blood	Less stable	More stable

Table 2. The Typical Fasting and Stimulated Reference Ranges for Insulin and C-Peptide in Healthy Adults and in Persons With Diabetes.[23-25]

Fasting	Healthy adults	Type 1 diabetes	Type 2 diabetes
Insulin	2-20 µU/mL (14-140 pmol/L)	Low or undetectable	Often elevated (>25 µU/mL)
C-peptide	0.5-2.0 ng/mL (0.17-0.66 nmol/L)	0.3- 0.6 ng/mL (0.1-0.2 nmol/L) or undetectable	Normal or elevated
Stimulated (GST/MMT/OGT)			
Insulin	Peaks: 30-100 µU/mL (210-700 pmol/L) within 60 min	Minimal or no increase	Often delayed or blunted
C-peptide	Peaks: 2-6 ng/mL (0.66-2.0 nmol/L)	<0.6 ng/mL (or undetectable)	Blunted peak but still often > 1.5 ng/mL

Reference Range: Insulin: 2-20 µU/mL (14-140 pmol/L); C-peptide: 0.5-2.0 ng/mL (0.17-0.66 nmol/L).

Table 3. C-peptide Reference Range Based on Estimated Glomerular Filtration Rate (eGFR).[17,28,29]

Stage of CKD	eGFR (mL/min/1.73m^2)	Expected C-peptide elevation	Clinical consideration
Stage 1	⩾90	Normal or slightly elevated	Standard interpretation
Stage 2	60-89	Up to 1.5 × normal	Minor adjustment
Stage 3	30-59	1.5-3 × normal	Significant adjustment
Stage 4	15-29	3-5 × normal	Major interpretation changes
Stage 5	<15	>5 × normal	Interpretation unreliable

C-peptide levels must be interpreted with caution in patients with renal failure. As majority of C-peptide is metabolized by the kidneys with 5-10% excreted unchanged in the urine, the levels can be falsely elevated in patients with chronic kidney disease and in renal impairment.[1,27] C-peptide levels can increase by 2-5 times in patients with moderate to severe kidney disease compared to those with normal kidney function. This elevation occurs even when insulin production remains unchanged, making it challenging to interpret C-peptide results in the context of kidney disease. Standard reference ranges may not apply, and adjustments based on estimated glomerular filtration rate (eGFR) or creatinine levels are often necessary (Table 3).[17,28,29]

Collection of Samples for C-Peptide

Blood Sample (Fasting, Post-Prandial or Stimulated)

A random non-fasting sample for serum C-peptide estimation is the simplest and easily performed test which allows flexibility in an outpatient setting. Random samples can be taken at any time of the day whereas a fasting sample should be collected after an 8 to 10 hour fast. Formal stimulation tests can be carried out by using a mixed meal or using intravenous glucagon, intravenous/oral glucose, sulfonylureas, glucose like peptides and amino acids.[21,27,30] Random C-peptide levels have been shown to correlate with fasting C-peptide and glucagon stimulated C-peptide levels in patients with defined type 1 and type 2 diabetes.[31] Moreover, random levels also appear to be superior to fasting C-peptide levels in classifying diabetes based on auto-antibody status.[32] Non-fasting C-peptide levels are primarily affected by elevation of plasma glucose following ingestion of a meal whereas the fasting C-peptide levels reflects static β-cell response to ambient plasma glucose concentration. A mixed meal tolerance test (C-peptide measured 90-120 minutes after meal) has been recognized to be the "gold standard" owing to its excellent sensitivity and detecting residual insulin secretion.[21,33] The glucagon stimulated C-peptide estimation is the gold standard in research setting (measured 6 minutes after 1 mg of intravenous glucagon in fasting state).[33,34] Glucagon stimulates insulin secretion acutely and this is independent of glucose and incretin hormones thereby producing a short-lived response. Some studies have demonstrated that C-peptide levels following glucagon stimulation are a consistently sensitive measures of β cell function which may be associated with type of diabetes and future use of insulin,[33,35,36] whereas others have concluded that in early part of type 1 diabetes the levels at 90 minutes after a mixed-meal is more reproducible than glucagon stimulated C-peptide levels.[33] Fasting samples are more relevant while assessing insulin resistance in insulin naïve patients but

while assessing β cell function, estimation of C-peptide after stimulation appears to be more advantageous.[37] Comparatively, as opposed to stimulation tests, fasting and random measurements are much user friendly, less time consuming and less invasive.

Interpretation of random C-peptide values depend on the time and composition of last meal whereas samples collected in fasting state are less affected by the confounders. A practical approach would be to correct C-peptide results for concurrent glucose levels and consider the time and composition of last meal and ensure the patients renal function are normal. Concurrent glucose measurement helps to exclude hypoglycemia which would otherwise suppress secretion of insulin and C-peptide. A random serum C-peptide level below 200 pmol/L (0.2 nmol/L or 0.6 ng/mL) when the corresponding plasma glucose is above 8 mmol/L (144 mg/dL) suggests an absolute insulin deficiency state.[31,38]

Urine Sample

C-peptide is primarily metabolized by the kidneys, with approximately 5% to 10% of it being excreted unchanged in the urine.[39] The urinary C-peptide to creatinine ratio (UCPCR) serves as a practical alternative for assessing C-peptide levels, with the creatinine ratio compensating for variations in urine concentration. C-peptide concentration in urine is 10 to 20 times higher than in plasma, largely because it is not degraded by proteolytic enzymes. The collection of 24-hour sample for C-peptide estimation is inconvenient and cumbersome, therefore its estimation in a spot urine sample is non-invasive and more attractive option for patients. The boric acid primed container which is easily available in most health care settings can be used to collect the mid-stream urine sample and transported to laboratory for C-peptide assay. It will remain stable at room temperature for up to 72 hours in boric acid primed container and up to 24 hours in a plain container.[40] Ideally the urine C-peptide should be collected 2 hour post the largest meal of the day, and the values correlate well to the serum C-peptide levels post mixed meal tolerance test. In patient with normal glucose tolerance UCPCR has been shown to correlate well with 24-hour urinary C-peptide[40] but the clearance is more in patients with diabetes as hyperglycemia may induce hyperfiltration.[41] Studies have shown that UCPCR correlates well with serum C-peptide levels after a mixed meal tolerance test in patients with insulin treated diabetes[42] and in persons with diabetes who are not insulin dependent.[43] UCPCR is higher in women owing to women having less muscle mass resulting in less urinary creatinine but no correction for gender differences have been suggested in clinical practice. A UCPCR < 0.2 nmol/mmol is equivalent to < 0.2 nmol/L or < 200 pmol/L or 0.6 ng/mL of serum C-peptide and signifies absolute insulin deficiency.[1,2] UCPCR > 1.1 nmol/mmol after 3 to 5 years of diabetes diagnosis, confirms favorable beta cell function.

Table 4. Clinical Areas Where C-Peptide Measurement Is Beneficial.

Indications for estimation of C-peptide
Distinguishing between different types of diabetes [Type 1, Type 2, MODY]
Evaluating for endogenous insulin secretion
Differentiating between exogenous insulin use and endogenous insulin production
Investigation of autoimmune diabetes
Prediction of need for insulin
Prediction of response to non-insulin based therapies
Prediction of diabetes related complications (Macrovascular and Microvascular)
Evaluation of hypoglycemia
Assessment of β-cell function after pancreatic transplantation
Monitoring insulinoma
Evaluation of renal function in diabetic nephropathy
Monitoring metabolic outcomes after bariatric surgery

Utility of C-Peptide in Clinical Practice

Measurement of circulating C-peptide has vastly contributed to our understanding of the natural history and pathophysiology of diabetes and the insulin feedback mechanisms that are involved during hypoglycemia but over the years its clinically utility have expanded significantly beyond these settings. In clinical practice, estimation of C-peptide is comparatively a low-cost tool which appears to have allowed us to disentangle uncertain diagnoses of diabetes when presentations are complex and helped us to determine the type of treatment that is needed for patients. Moreover, growing research evidence have shown the benefit of estimating C-peptide in a wide range of scenarios which are listed in Table 4.

Categorization and Classification of Diabetes (Table 5)

C-peptide denotes endogenous insulin production, and the levels correlates well with the type of diabetes and duration of diabetes but its usefulness in classifying different types of diabetes must be interpreted in the clinical context of individual patient. Therefore, duration of disease, family history and presence of co-morbidities should be considered simultaneously.[3]

In current practise, a substantial overlap is found amongst patients at presentation with type 1 and type 2 diabetes. Adults are being diagnosed with type 1 diabetes at higher age group (often > 40 years old) and a significant proportion of patients with T1 diabetes and latent autoimmune diabetes in adults (LADA) are found to be overweight or obese.[5,47] Traditionally, type 2 diabetes is usually diagnosed in middle age or older age group especially with features of raised body mass index (BMI) and insulin resistance, but a significant proportion of patients are now diagnosed with type 2 diabetes in the pediatric and adolescent

Table 5. Quantitative Comparison of C-Peptide Level in healthy adults, LADA, Type 1 and Type 2 Diabetes.[26,44-46]

Group	Fasting C-peptide	Stimulated C-peptide	Comments
Healthy adults	0.5-2.0 ng/mL (0.17-0.66 nmol/L)	2.0-6.0 ng/mL (0.66-2.0 nmol/L)	Normal insulin production
Type 2 diabetes	1.0-5.0 ng/mL (0.33-1.66 nmol/L)	Often > 3.0 ng/mL (>1.0 nmol/L)	Frequently elevated due to insulin resistance
LADA (Early)	0.3-1.2 ng/mL (0.10-0.40 nmol/L)	<3.0 ng/mL, often 1.0-2.5 ng/mL (~0.33-0.83 nmol/L)	Initially preserved but declining beta-cell function; intermediate values
LADA (late/Insulin dependent)	<0.3 ng/mL (<0.10 nmol/L)	Often < 0.6 ng/mL (<0.20 nmol/L)	Declines progressively, mimicking Type 1 diabetes
Type 1 Diabetes	Undetectable to <0.3 ng/mL (<0.10 nmol/L)	Undetectable to <0.6 ng/mL (<0.20 nmol/L)	Reflects near-total beta-cell failure

population. Additionally, a lean variant of type 2 diabetes may be encountered in people of South Asians and sub-Saharan heritage which may be misclassified as type 1 diabetes in the absence of defined specific features.[48,49]

Type 1 diabetes is typically characterized by autoimmune destruction of pancreatic β cells and consequent development of absolute insulin deficiency over a period. After clinical onset of type 1 diabetes, some patients lose endogenous insulin secretory capacity within a few weeks or months whereas others may retain some secretory capacity for 3 to 5 years form onset of disease.[21] Majority of patients with type 1 diabetes will have positive autoantibodies (anti-islet cell antigen – IA2, anti-glutamic acid decarboxylase – anti GAD65 or Zinc transporter 8 – ZnT8 antibodies), either alone or in combination but a negative auto-antibody status should not discount the diagnosis of type 1 diabetes or need for insulin. Age and mode of presentation, duration of illness and other biochemical parameters should be considered before an alternative diagnosis is considered.

There is considerable overlap of C-peptide levels in early phase of type 1 and type 2 diabetes especially when patients are obese and older, and it is often clinically difficult to classify these patients into different subsets of diabetes. It is estimated that 15%-40% of patients with type 1 diabetes will become overweight or obese and some of these individuals will develop features of metabolic syndrome with high insulin requirement in the years to come.[50,51] C-peptide level appears to be more conclusively discriminatory when the duration of diabetes is longer. Unmeasurable C-peptide or levels less than 0.05-0.10 nmol/L indicate absolute insulin deficiency and confirms diagnosis of type 1 diabetes if samples were obtained within the first few years of diagnosis, but higher levels should be interpreted with caution especially in patients with obese phenotype or it may also represent a continued "honeymoon" phase of type 1 diabetes.[52] C-peptide concentration declines with duration of diabetes. The DCCT data has shown at least 48% of type 1 diabetes population had a mixed meal stimulated C-peptide level of 0.2 nmol/L 5 years after diagnosis whereas only 8% persisted with such levels when diabetes duration exceeded between 5 and 15 years.[21,53] Interestingly, it has been observed that patients with type 1 diabetes who maintain C-peptide concentrations above 0.1-0.2 nmol/L exhibit improved glycemic control, reduced glucose variability, and a lower risk of hypoglycemia. This suggests that even minimal residual endogenous insulin secretion provides a buffering effect on glucose homeostasis.[54]

Recognizing Patients With Maturity Onset Diabetes of the Young (MODY) and Latent Auto-Immune Diabetes of Adult (LADA, Figure 1)

Genetic diabetes encompasses a group of inherited forms of diabetes, where mutations in specific genes affect beta cell function or insulin action. One of the well-known types of genetic diabetes is MODY, a monogenic form characterized by early-onset diabetes typically before the age of 25 years. MODY is mostly caused by mutations of HNF1A and HNF4A (>60%) genes which responds to sulfonylurea treatment[55] whereas others are caused by mutations of glucokinase (GCK) and HNF1B genes which often don't require glucose lowering treatment. MODY may be often difficult to diagnose as it may have overlapping features with type 1 and type 2 diabetes. Clinical criteria such as age of onset, family history, and treatment response can help to differentiate MODY from other forms of diabetes. Additionally, MODY probability calculators and genetic testing can aid in confirming the diagnosis.[56]

MODY is often misdiagnosed and misclassified as type 1 diabetes. Persons diagnosed as type 1 diabetes but with atypical phenotype, negative autoantibodies and requiring low or very low total daily dose of insulin after several years of the type 1 diabetes diagnosis should be offered C-peptide testing. It would facilitate to differentiate between type 1 diabetes and MODY. Patients with MODY will persist to produce C-peptide long after their diagnosis which would not be the case in patients with type 1 diabetes outside the "honeymoon" phase. A post meal urine C-peptide: creatinine ratio of ⩾0.2 nmol/mmol > 5 years post diagnosis has 97% sensitivity and 96% specificity for differentiating MODY from Type 1 diabetes.[57] The Figure 1 will depict the pathway of C-peptide testing to help to differentiate between MODY and Type 1 diabetes.

Individuals with adult-onset autoimmune diabetes typically retain varying degrees of beta cell function at the time of diagnosis. The age of onset of the autoimmune disease is frequently linked to distinct clinical, demographic, and

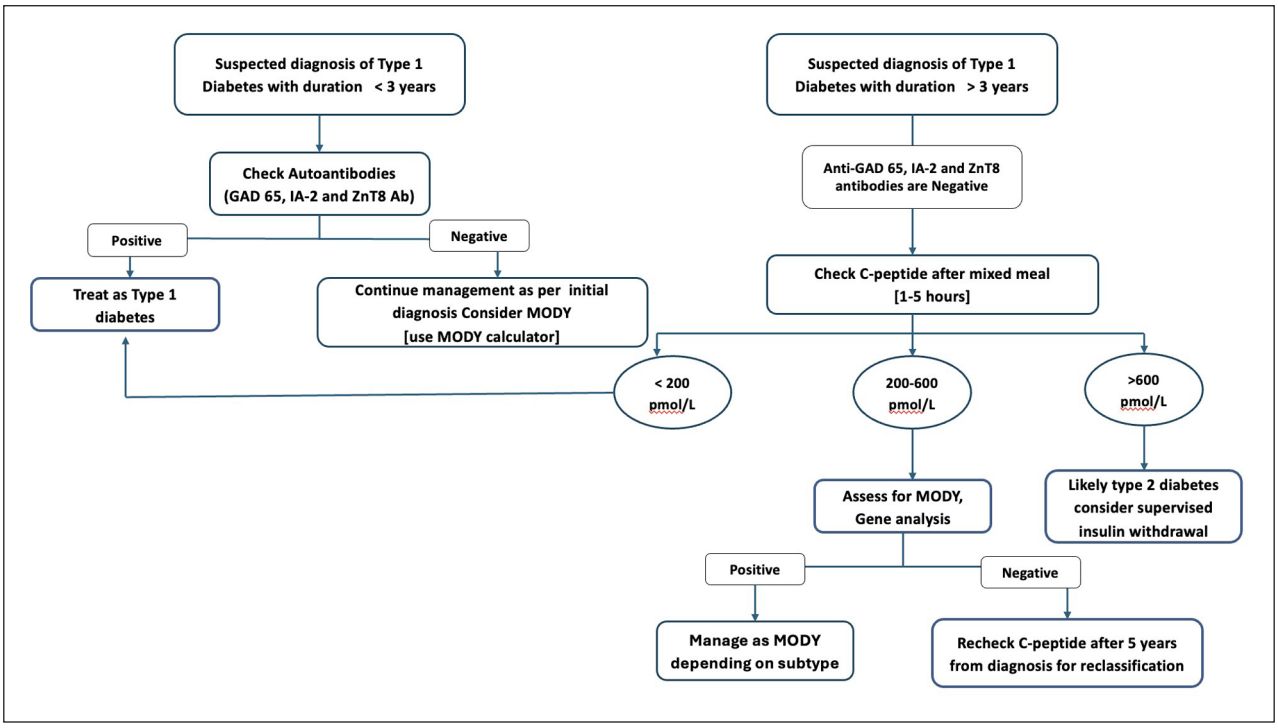

Figure 1. C-peptide testing for distinguishing Autoimmune diabetes and MODY.
C-peptide levels : <200pmol/L = <0.2nmol/L, 200-600pmol/L = 0.2 – 0.6nmol/L, >600pmol/L = >0.6nmol/L.

immunogenic characteristics.[58-60] In patients with LADA, C-peptide can play a crucial role in diagnosis, as these individuals are often misdiagnosed with type 2 diabetes. At the onset of LADA, fasting C-peptide levels are typically lower than those in healthy non-diabetic individuals but higher compared to persons with type 2 diabetes, strongly indicating an insulin secretory defect in the pathogenesis of LADA. The extent of beta cell reserve varies among LADA patients, reflecting differences in the severity of the autoimmune process. Those with high levels of autoantibodies, particularly when multiple autoantibodies are present, tend to experience an earlier and more aggressive disease progression. In such cases, beta cell function and C-peptide secretion decline rapidly.[61,62] Patients with low auto-antibody levels may have similar C-peptide levels and similar rates of changes like those with type 2 diabetes. C-peptide sampling may be an effective initial screening tool for LADA but auto-antibody screen (anti GAD65, IA-2 and ZnT8) should be considered to confirm diagnosis. Taken in isolation, serum C-peptide may not distinguish type 1 from type 2 diabetes in gray cases as there is no definitive biomarker for type 2 diabetes. Therefore, a diagnostic model which integrates clinical features of diabetes, associated auto-antibodies and type 1 diabetes gene risk score is essential before a diagnosis of autoimmune diabetes (type 1 or LADA) is entirely dismissed. The joint ADA/EASD consensus report[52] on the management of type 1 diabetes in adults recommended the evaluation of C-peptide beyond 3 years after diabetes diagnosis in auto-antibody negative adults receiving insulin treatment. C-peptide levels < 0.2 nmol/L is suggestive of a diagnosis of type 1 diabetes and values > 0.6 nmol/L indicating likelihood of type 2 diabetes. They also suggested that levels of C-peptide between 0.2 and 0.6 nmol/L should be interpreted with caution as no absolute value in this range can be discriminatory between autoimmune, monogenic or type 2 diabetes.[63]

Predicting the Need for Insulin and Response to Treatment

Patients with absolute insulin deficiency depicted as having fasting C-peptide level < 0.08 nmol/L or < 0.2 nmol/L after mixed meal stimulation will need insulin irrespective of the etiology of diabetes.[64,65] They will have poor response with sulfonylurea or incretin-based therapies and should be managed with multiple daily injections of insulin or by continuous insulin infusion via pumps to ensure glycemic stability and prevent ketoacidosis. There is limited evidence to suggest whether C-peptide levels alone can predict the need for insulin in the future, but studies have shown that a peak glucagon stimulated C-peptide level of < 0.6 nmol/L is usually associated with insulin treatment later.[35] Likewise, a fasting C-peptide level of < 0.25 nmol/L at diagnosis as an independent factor for predicting need for insulin treatment during follow up had a sensitivity of 60% and specificity of 96%.[66] The chances of insulin requirement in the future rises most significantly if patient has 1 or more positive autoantibodies in the early phase of disease. C-peptide levels may also help to identify patients in whom insulin can be safely replaced with other glucose lowering agents if they have sufficient beta cell reserve. A stimulated C-peptide level of 0.3 to 0.8 nmol/L usually differentiates between patients requiring insulin or non-insulin requiring diabetes.[67,68] These ranges are relevant for patients prior to withdrawal of insulin especially for those who were misdiagnosed to have type 1 diabetes or those

who have been receiving insulin for type 2 diabetes for a long period of time.

In patients with type 1 diabetes, monitoring C-peptide level in the early phase of disease helps to measure insulin secretion and this allows explanation for a decline in glycemic control which may be either related to a rapid decline in insulin secretion or due to patient related factors (poor compliance with treatment etc).[21] In patients with type 2 diabetes, C-peptide levels have shown promise to have a potential role in predicting the response to treatment with basal insulin and risk of hypoglycemia. In a post hoc analysis of 9 randomized studies 2165 insulin naïve patients were stratified according to fasting C-peptide-FCP (<0.40 nmol/L, >0.40-1.20, >1.20-2.00, >2.00 nmol/L). Persons with low FCP(<0.40 nmol/L) had lower BMI, longer duration of diabetes and higher fasting plasma glucose (FPG). Basal insulin treatment with insulin glargine resulted in similar Hba1c reductions across the groups, with a smaller number of people reaching Hba1c of <7% in lowest FCP group. However the greatest reduction in FPG levels, and the highest proportion of individuals reaching an FPG of ⩽5.6 mmol/L, occurred in the group with the lowest FCP levels. As the FCP levels increased, both the reduction in FPG and the proportion achieving this target decreased. This implies a relationship between FCP levels and the effectiveness of interventions aimed at reducing FPG. However, the risk for overall, nocturnal and severe hypoglycemia was increased in lowest baseline FCP, likely due to robust insulin sensitivity. Low dose insulin initiation, close monitoring and gradual titration should be considered in this group.[69]

In patients with type 2 diabetes, time to insulin treatment may be also associated with C-peptide response. In a retrospective study it was found that the time to insulin prescription was much earlier (2.5 years [1.5-3.0 years]) in patients who had low C-peptide level of <0.2 nmol/L after a mixed meal stimulation in comparison to those who had levels > 0.2 nmol/L and needed insulin 6 years after diagnosis (3-10.7 years).[70]

C-Peptide and Other Non-Insulin Based Pharmacotherapy

There is variable and limited evidence to support the use of C-peptide for predicting response to non-insulin treatments for patients with type 2 diabetes. A combination of metformin and glibenclamide has shown good response for controlling hyperglycemia and the efficacy of this regime could be predicted using baseline glycemic status and stimulated C-peptide level.[60] Although higher mixed meal stimulated C-peptide has been shown to be present in patients who respond to this combination treatment, but glucagon stimulated C-peptide did not predict response to glibenclamide alone.[71,72]

Pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist, enhances peripheral insulin sensitivity, lower blood glucose levels, and reduces circulating free fatty acids. High fasting C-peptide is associated with response to thiazolidinedione's, which is in keeping with the mechanism of action to reduce insulin resistance.[73] In a 24-week study in individuals with established type 2 diabetes, use of pioglitazone demonstrated an average 50% reduction in C-peptide levels from baseline. This reduction correlated with significant decreases in HbA1c levels and HOMA-IR scores.[74] The paradoxical decrease in C-peptide was associated with enhanced insulin sensitivity and signified the effectiveness of pioglitazone. There is also evidence to suggest that patients with high insulin resistance and higher C-peptide values have greater response to thiazolidinedione's.[73,75]

GLP-1 RAs (Glucagon like peptide receptor agonist) have become pivotal in the early management of type 2 diabetes and obesity. Their mechanism of action is multifaceted, involving delayed gastric emptying, increased satiety, and stimulation of beta cells. Stimulated C-peptide response has been suggested as a marker to predict response to Liraglutide in a Japanese study.[76] In a large prospective study, measurement of C-peptide helped to predict the response to therapy with a GLP-1 RA's. It has been also observed that patients with higher fasting C-peptide levels (>0.25 nmol/L) and negative auto-antibodies show greater reductions of HbA1c with the use of GLP1 RA in comparison to patients with low C-peptide reserve and positive auto-antibody status.[77] The clinical relevance of these findings confirms that fasting C-peptide and post meal UCPCR can both predict reduction of HbA1c after GLP1 RA's are initiated.[78] Evidence of the clinical utility of C-peptide in predicting response to other classes of oral hypoglycemic agents (SGLT2 inhibitors and DPPIV inhibitors) is limited and weak. There may be a role of C-peptide in aiding the decision-making process between oral or insulin therapy. Patient's with type 2 diabetes who have fasting C-peptide levels < 0.2 nmol/L invariably do better with insulin rather than treatment with oral hypoglycemic agents.

Immunotherapy in type 1 diabetes is a topic of great interest to researchers and Teplizumab is already licensed for use in stage 2 autoimmunity in type 1 diabetes for immune response modulation and preservation of beta cell function. Multiple studies have demonstrated the efficacy of C-peptide as an efficient marker of β cell function to derive clinically meaningful outcomes defining the β cell preservation or restoration in clinical trials using disease modifying therapies.[6] A systematic review[79] assessed the effects of immunotherapy of C-peptide levels in type 1 diabetes. The authors demonstrated that Teplizumab has remarkable impact on beta cell function with 75% increase in C-peptide area under curve (AUC). Otelixizumab treated group showed elevated C-peptide at 18 months whereas Rituximab demonstrated enhanced C-peptide response over 3 to 12 months while abatacept reduced C-peptide loss over 2 years. This area of research is evolving, and C-peptide would be a crucial guide for assessing the usefulness of various immunomodulatory therapies in the years to come.

C Peptide and Diabetes Related Vascular Complications

Variability of glucose level in diabetes can be often attributed to low levels of C-peptide and poor β cell function. C-peptide levels may be associated with diabetes related

complications through a glycemic mechanism, but it has been postulated C-peptide may have direct molecular effects and can serve as a predictor of future outcomes in diabetes independent of HbA1c levels. In vitro studies have shown C-peptide to inhibit endothelial reactive oxygen species (ROS) in presence of hyperglycaemia[80] and downregulates production of adhesion molecules like vascular cell adhesion molecule 1 (VCAM1) thereby preventing early stages of atherosclerosis plaque formation.[2]

The Diabetes Control and Complications Trial (DCCT) have found correlation between C-peptide levels and clinical outcomes in patients with type 1 diabetes.[65] The authors suggested that for patients with duration of type 1 diabetes between 1 and 5 years, a 50% higher value of stimulated C-peptide (0.10-0.15 nmol/L) was associated with 25% reduction of sustained retinopathy.[81] The risk reduction of retinopathy between "responders" (C-peptide level between 0.2 and 0.5 nmol/L) and "non-responders" (C-peptide $<$ 0.2 nmol/L) was 58% (26%-76%; $P = .0025$). The C-peptide levels in this group were also related to a reduced risk of nephropathy and the number of renal events were low. For severe hypoglycemia, the risk reductions between the 2 groups (responders vs non-responders), the risk reduction was 45% (38%-52%, $P < .0001$).[81] Data from the Scottish Diabetes Research Group have shown that in people with type 1 diabetes, a random (non-fasting) C-peptide level of $\geqslant$0.2 nmol/L have 50% less probability of developing diabetic retinopathy in comparison to people with random C-peptide level of $<$.005 nmol/L after adjustments were made for age and duration of diabetes.[82] This observation has been also replicated in patients with type 2 diabetes who demonstrated low incidence of retinopathy with higher C-peptide levels after all confounders were adjusted.[83] Other authors have also confirmed that there is a 73% lower risk of nephropathy and 61% lower risk of neuropathy in patients with type 2 diabetes if their C-peptide levels were in the highest tertile.[84] Similarly, it has been also reported that the risk of development of nephropathy or neuropathy is 1.5 times higher if C-peptide levels are low in patients with type 2 diabetes.[83]

The association between C-peptide and macrovascular complications in diabetes is debatable and the evidence is weak although some authors have suggested that C-peptide may have direct effects on inflammatory and vascular cells.[85,86] In patients with type 1 diabetes, detectable C-peptide levels indicate preserved β cell function which in turn is associated with less glycemic variability, better metabolic control and fewer cardiovascular events. On the contrary, in patients with type 2 diabetes, higher C-peptide levels indicate insulin resistance and phenotype of metabolic syndrome, and this has been associated with higher rates of cardiovascular events and mortality.[87,88] Higher levels have been also found to be associated with high cardiovascular and all-cause mortality even in people without diabetes.[89,90] More research is needed in this area to unfold the actual relationship between C-peptide levels and macrovascular complications.

C-Peptide and Evaluation of Hypoglycemia

Spontaneous symptomatic hypoglycemia is uncommon clinical event due to the presence of robust defense mechanisms against a falling plasma glucose level. But symptoms of hypoglycemia can develop when sum of glucose utilization from circulation (largely by brain, muscles, renal medulla and erythrocytes) is greater than the sum of glucose delivery into the circulation (ingested carbohydrates and hepatic and renal glucose production).[91,92]

If the cause of hypoglycemia is not evident in a fit and well individual, it is important to measure plasma glucose, pro-insulin, insulin, C-peptide, β-hydroxybutyrate, insulin antibodies, and screen for oral hypoglycemic agents during an episode of spontaneous hypoglycemia. If spontaneous hypoglycemia is not observed, the circumstances should be created by keeping the patient fasted for 72 hours which is likely to precipitate symptomatic hypoglycemia. If patient develops symptoms of hypoglycemia at plasma glucose concentrations of $<$3 mmol/L ($<$55 mg/dL) with insulin level of at least 18 pmol/L (3 μU/mL), C-peptide of at least 0.2 nmol/L (0.6 ng/mL) and pro-insulin of at least 5 pmol/L, hypoglycemia due to endogenous hyperinsulinism can be suitably diagnosed.[93]

Patients with insulinoma or other forms of endogenous hyperinsulinemic hypoglycemia (HH) typically exhibit elevated C-peptide levels, reflecting increased insulin production by the pancreatic β cells. Conversely, in case of exogenous insulin administration, C-peptide is appropriately suppressed, generally to the lower limit of normal. In other forms of HH where C-peptide estimation may be useful are patients with nesidioblastosis, presence of insulin antibodies, post bariatric surgery syndrome and in patients using sulfonylurea or exogenous insulin.[93] These hyperinsulinemic conditions and their discriminatory features are mentioned in Table 6.[94] C-peptide levels can also aid in diagnosis when hypoglycemia occurs due to accidental, surreptitious or malicious conditions but these situations can often be tricky.[95]

Insulinoma is a rare cause of endogenous HH. Patients have features of neuroglycopenia predominantly in the fasting state, but this can also happen in the post-prandial period.[96] The non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is characterized by episodes of neuroglycopenia due to endogenous hyperinsulinemic hypoglycemia, which often, but not always, occurs post prandially (after a meal).[97] The pancreatic abnormality observed in these cases involves diffuse islet changes, specifically nesidioblastosis, which is characterized by islet hypertrophy, occasionally accompanied by hyperplasia, along with enlarged and hyperchromatic β-cell nuclei.[98] The key pathophysiological feature of endogenous hyperinsulinism is the failure of insulin secretion to decrease to very low levels as plasma glucose concentrations drop to hypoglycemic ranges. In such cases, fasting hypoglycemia arises primarily due to reduced compensatory glucose production rather than increased glucose utilization.[99] Plasma

Table 6. Differential Diagnoses of Hyperinsulinemic Hypoglycemia and Insulin and C-Peptide Levels (Adapted from Wong et al[94]).

Diagnosis	Serum insulin	Serum C-peptide	Differentiating feature
Use of Sulfonylurea	Elevated	Elevated	- Urine sulfonylurea screen - Access to sulphonylurea at home or work
Exogenous insulin use	Elevated	Low/suppressed	- History of insulin treated diabetes - Access to insulin at home or work
Insulin antibodies	Significantly Elevated	Significantly Elevated	- Rare cause - High titers of insulin antibodies
Post-bariatric surgery syndromes	Elevated	Elevated	- History of bariatric surgery
Insulinoma	Elevated	Elevated	- Classical Whipple's triad - Weight gain - Can be part of Multiple Endocrine neoplasia-1, Neuroendocrine tumors
Nesidioblastosis	Elevated	Elevated	- History of bariatric surgery

insulin, C-peptide, and proinsulin concentrations need not be high relative to normal euglycemic values but only inappropriately high in the setting of low fasting plasma glucose concentrations.[91,92] A patient with documented Whipple's triad, inappropriately high plasma insulin, C-peptide, and proinsulin levels and no detectable oral hypoglycemic agent levels during fasting hypoglycemia and no circulating antibodies to insulin usually has an insulinoma.[91,92] Some patients do not have an insulinoma but have a diffusely expanded islet cell mass [nesidioblastosis], though rare, is recognised in association with gastric bypass surgery.[98] Patients with fasting hypoglycemia and appropriately suppressed C-peptide levels but inappropriately elevated insulin levels usually reflect exogenous insulin usage but can be due to harboring an agonist antibody to the insulin receptor.[100] In a retrospective study form France, which was a designed to propose optimal cut-off points for blood glucose and plasma insulin and C-peptide level in patients with endogenous HH, it was concluded that a C-peptide level of 0.3 nmol/L with concomitant hypoglycemia (blood glucose < 2.3 mmol/L) was the best criterion to diagnose endogenous hyperinsulinism with a sensitivity of 96% and specificity of 100%.[90] In contrast, the diagnostic performance for insulin with cut-off 21.5 pmol/L with concomitant hypoglycemia had a sensitivity of 96% and a specificity of 92%.[101]

Patients with post-bariatric surgery syndromes can also develop HH and they mostly manifest following RYGB (Roux-En-Y gastric bypass surgery) due to the rapid delivery and absorption of glucose-rich nutrients in the intestines, leading to glucose-dependent insulin release. The L-cells of the intestine exhibit an exaggerated response with increased endogenous GLP-1 secretion, resulting in heightened beta cell stimulation and subsequent hyperinsulinemic hypoglycemia typically occurring within 1 to 2 hours of a carbohydrate-rich meal.[102] C-peptide measurement of ≥ 1.0 nmol/L, insulin ≥ 17 µU/mL and a simultaneous blood glucose of ≤ 55mg/dL was reported in a small case series (6 patients) of post RYGB HH.[103] This can be used as reference cut-off values in post RYGB HH.

Limitations of C-Peptide Estimation

C-peptide estimation should not be done routinely to diagnose type 1 diabetes but should be done predominantly in insulin treated patients (after at least 3 years from diagnosis) where there was uncertainty about initial diagnosis or if initial diagnosis was presumed and not precise. This is more relevant when clinicians are considering modification of insulin regimen or may be using medications which will require residual β cell function. As C-peptide assays show variations and levels can fluctuate depending on the stimulation method that has been used or if the patient has insulin resistance, results close to cut-off threshold should be interpreted with caution. The diagnoses should be re-visited and evaluated before a decision is made for withdrawal of insulin therapy based on C-peptide levels. A stimulated C-peptide level of < 0.2 nmol/L (or fasting < 0.08 nmol/L) is indicative of absolute insulin deficiency and hence the need for insulin treatment.

A fasting C-peptide may be used to estimate insulin resistance using HOMA modeling but this should not be used routinely for this purpose due to lack of evidence. One should be mindful that in type 2 diabetes, high uncorrected fasting C-peptide level with hyperglycemia may be suggestive of insulin resistance.

It is crucial to refrain from measuring C-peptide levels during acute hyperglycemic episodes and in the weeks following recent hyperglycemic emergencies. Prolonged hyperglycemia and resultant glucotoxicity can lead to impairment of the insulin release.[104] There are several case reports demonstrating restoration of beta cell function following resolution of glucotoxicity and accordingly, calls for clinician's diligence when dealing with such scenarios.[105] Additionally, C-peptide should not be estimated in individuals who had a hypoglycemic episode within last 12 hours. Moreover, as C-peptide is cleared by the kidneys, levels may rise in patients with end stage renal disease therefore interpretation of results in these circumstances should be done with caution.

Finally, for individuals receiving insulin therapy, it is important to consider the potential for insulin-induced hypoglycemia and the suppression of beta cells due to exogenous insulin. Therefore, obtaining a random C-peptide measurement within 5 hours of the last meal, along with a simultaneous plasma glucose is essential for accurate sampling.

Conclusion

C-peptide is a byproduct of insulin production, making it an important marker for assessing pancreatic β-cell function. It helps to determine insulin production levels, which can be useful for identifying whether a person with diabetes is insulin sufficient or deficient. This distinction is crucial in determining the type and treatment of diabetes. C-peptide testing is relatively inexpensive and easily available, making it a practical option in many clinical settings. It is especially valuable in diagnosing types of diabetes, such as distinguishing between type 1 and type 2 diabetes or determining the insulin-producing capacity of the pancreas. In type 1 diabetes, C-peptide measurement is well-established and commonly used in diagnostic and treatment algorithms but its role in type 2 diabetes is still being researched, especially in individuals with significant insulin resistance. Here, C-peptide could help assess the pancreas's ability to produce insulin in the context of insulin resistance, but its clinical utility is not yet fully defined.

There is significant variability in how C-peptide is measured (eg, random, fasting, after a mixed meal, or after stimulation with glucagon). This variation creates challenges in interpreting results and establishing standardized guidelines. It is important to consider factors like timing, food intake, and the influence of exogenous insulin (eg, insulin therapy or induced hypoglycemia) on its levels. C-peptide estimation could play an expanding role in predicting diabetes-related complications, assessing the effectiveness of newer therapies (particularly for type 1 diabetes), and even in bariatric surgery planning. In summary, while C-peptide testing holds considerable promise, particularly in refining diabetes diagnosis and treatment, standardization of testing methods are essential for its broader and more reliable application in different clinical settings.

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