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The Clinical Significance Of C-Peptide As A Biomarker In Patients With Diabetes Mellitus: A Comprehensive Review

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Abstract: C-peptide, a byproduct of insulin production, is an essential biomarker for evaluating pancreatic β-cell function in diabetes mellitus. This comprehensive review highlights the clinical significance of C-peptide in distinguishing between various forms of diabetes, including type 1, type 2, and latent autoimmune diabetes in adults (LADA). In type 1 diabetes, low or undetectable C-peptide levels reflect the loss of insulin-producing β-cells, while in type 2 diabetes, elevated levels indicate residual β-cell activity and insulin resistance. Beyond diagnosis, C-peptide plays a critical role in monitoring disease progression and guiding personalized treatment strategies. Its measurement helps assess endogenous insulin production, making it a key tool in determining the need for exogenous insulin therapy or alternative treatments. Additionally, emerging research suggests that C-peptide may have protective effects on microvascular and cardiovascular complications in diabetic patients, potentially reducing the risk of nephropathy, neuropathy, and retinopathy. This review gives the importance of C-peptide in clinical practice, enhancing its utility as a comprehensive biomarker in diabetes management.

Index Terms - C-peptide, Biomarker, Pancreatic β-cell function, Diabetes mellitus, Type 1 diabetes, Type 2 diabetes, Latent autoimmune diabetes in adults (LADA), Nephropathy, Neuropathy, Retinopathy, Clinical significance.

I. INTRODUCTION:

Diabetes Mellitus is one of the most prevalent chronic metabolic endocrine disorders is characterized by increased blood glucose levels (Hyperglycemia) resulting from defect in insulin function, secretion or both [1,2,3&4]. Diabetes is the worrying global health predicament in the modern age and a biggest cause of disease related mortality that affects 537 million people worldwide and associated with economic burdens on the patient and the society [1,2,5&6].

The pancreas is a complex organ in the body responsible for both digestive and metabolic functions. It is an exocrine gland, an organ that secretes elementary products like α-amylase, trypsin, chymotrypsin, and carboxypeptidase. These secretions are necessary for the breaking down of carbohydrates, proteins, and fats within the small intestine [2]. It also serves as an endocrine gland and secretes hormones such as insulin, glucagon, and pancreatic polypeptide that are really important in the modulation of various metabolic activities [2]. Bile, required for fat digestion, is secreted by the liver into the small intestine via the bile duct, often simultaneously with pancreatic secretions [2].

Proinsulin, the first precursor protein discovered by Steiner, is cleaved into insulin and a connecting peptide (C-peptide), a 31-amino-acid polypeptide stored in the secretory granules of pancreatic cells [2,7,8,9,10&11]. Both insulin and C-peptide are eventually released together in equimolar amounts [9,10&12].

C-peptide plays an important role in facilitating the correct folding of insulin and the formation of the correct secondary and tertiary structure of its disulfide bridges [13]. Unlike insulin, C-peptide exhibits a prolonged biological half-life, resulting in higher plasma concentrations compared to insulin and it is not a product of therapeutically administered exogenous insulin in which a considerable portion is cleared by the liver at first pass transit, all synthesized C-peptide reaches the systemic circulation, making it a more accurate marker and widely used measure of endogenous insulin secretion [9,10&13]. It has negligible hepatic clearance and cleared in the peripheral circulation at a constant rate [9].

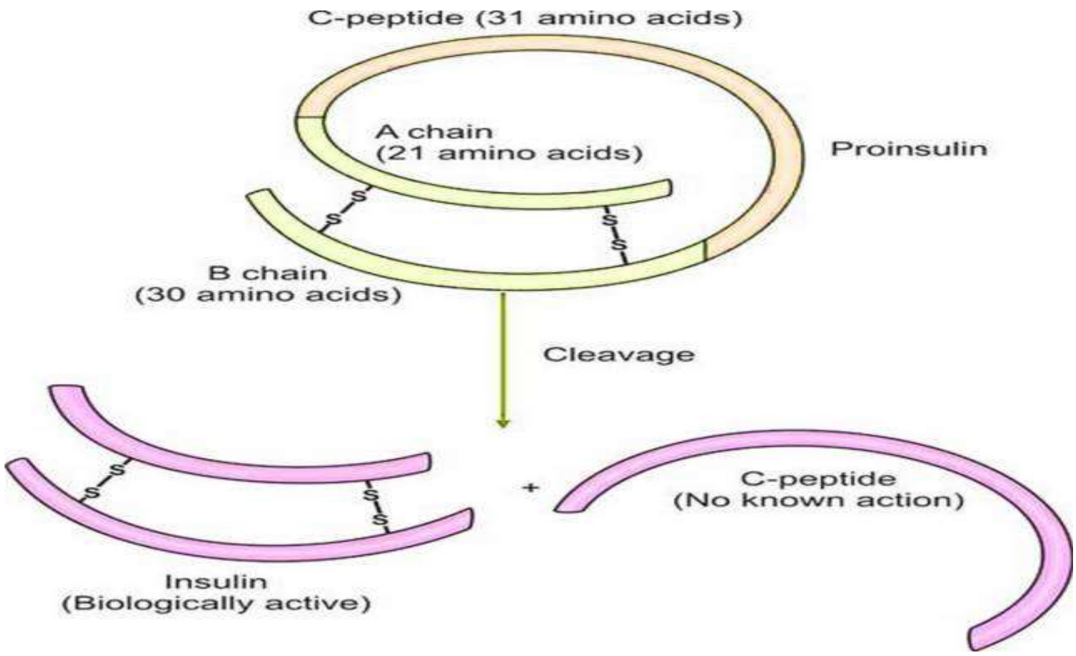

Figure 1.1: Shows the Synthesis of C-Peptide

The degradation rate of c-peptide in the body is slower than that of insulin (half-life of 20–30 min, compared with the half-life of insulin of just 3–5 min), affords a more stable test window of fluctuating beta cell response [9,11]. In healthy individuals the plasma concentration of c-peptide in the fasting state is 0.3–0.6 nmol/l, with a postprandial increase to 1–3 nmol/L and modern ultrasensitive c-peptide assays are able to detect c-peptide values as low as 0.0015–0.0025 nmol/l [9]. The most common biomarkers used for the diagnosis of diabetes are oral glucose, Glycated Albumin (HbA1c), C-peptide, insulin, fructosamine [1].

For many years, the measurement of C-peptide in blood and urine has been used as a biomarker of pancreatic beta-cell function. It is useful for assessing endogenous insulin secretion, distinguishing between type 1, type 2, and other specific types of diabetes, differentiates those from the Latent autoimmune diabetes in adult (LADA), and for the differential diagnosis of fasting hypoglycemia. C-peptide measurement is a good marker for the detection of insulin level, also employed in the calculation of HOMA (homeostatic model assessment) indices (e.g., HOMA-2B or HOMA-IR) to estimate insulin secretion and insulin resistance, especially in patients undergoing insulin therapy [10]

Table 1.1: Shows the Factors that effect the value of C-Peptide [7]

S. NO	FACTOR	EFFECT ON C-PEPTIDE
1	Blood glucose concentrations	• Low blood glucose may result in low C peptide concentrations • When blood glucose >7.8 mmol/L (140 mg/dl), C-peptide concentrations should be interpreted as stimulated values
2	Incretins	• Impairments in incretin physiology may result in impaired ß-cell response to meals • Time from last meal and meal composition may influence C-peptide values because of an incretin effect on ß-cells
3	Insulin resistance	• Higher C-peptide values
4	Renal function	• C-peptide clearance is lower in people with reduced GFR
5	Lack of standardization	• C-peptide values from different laboratories may not similarly reflect ß-cell reservoir

Type 1 is the most common form of diabetes originated from an immune mediated destruction of insulin-producing-cells found in the pancreatic islets of Langerhans. It is characterized by the destruction of pancreatic beta cells resulting in the absence of insulin secretion, thus requiring exogenous insulin for the survival. The activation of auto reactive lymphocytes and the cytokine induced apoptosis of pancreatic-cells plays a major role in the etiology of type1 diabetes [1]. Insulin resistance is defined as a reduced response of insulin target tissues to the biological action of insulin and it is the earliest metabolic defect detected in people likely to develop type 2 diabetes (T2D) [14].

Table 1.2: Explains the Indications of C-Peptide [9]

INDICATIONS OF C-PEPTIDE MEASUREMENT	
Diagnostic	• To define T1DM • Criteria for acceptance for CSII • To determine whether T1DM or T2DM • Diagnostic test for MODY • Diagnostic test for LADA, in addition to antibody testing
Prognostic	• Marker of duration of diabetes • Lower levels are associated with microvascular complication risk in T1DM • Lower levels are associated with greater hypoglycemia risk
Therapeutic response	• Lower baseline levels associated with increased need for insulin • Lower baseline levels associated with shorter time to insulin treatment • Higher levels present in patients who respond to metformin and glibenclamide in combination • Higher levels associated with response to thiazolidinediones • Correlates with reduction in HbA1C following initiation of GLP-1 agonist therapy

CSII = Continuous Subcutaneous Insulin Infusion, MODY = Maturity-Onset Diabetes of the Young, LADA = Latent Autoimmune Diabetes of Adults.

CLINICAL SIGNIFICANCE:

- C-peptide is one of the key regulators of physiological processes and biochemical processes. It functions as regulator of the intracellular effector proteins, including phospholipase Cβ, phosphatidylinositol 3-kinase, mitogen-activated protein kinases, non-receptor tyrosine kinases, and controls cAMP- and cGMP-dependent cascades and allows estimation of insulin secretion even in the presence of insulin treatment [1].
- C-peptide may help identify insulin-treated patients with sufficient b-cell function to safely replace insulin with other hypoglycaemia therapies, changes in treatment requirement with time in Type 2 diabetes also primarily relate to progressive loss of insulin secretion capacity [11].
- Samples for the measurement of C-peptide in the blood may be collected in the fasting or non-fasting (so-called 'random C-peptide') state, or after a stimulation test. Differences in cut-off values, interpretation and clinical or research convenience between the tests primarily derive from the physiological differences between fasting, random or stimulated C-peptide. Fasting C-peptide is the expression of steady state, a static response of beta cell to ambient (arterial) plasma glucose concentration and hence fasting C-peptide and derived parameters help to differentiate type1 from type2 diabetes. In contrast random (non-fasting) C-peptide is chiefly under the control of the incretin effect and increase in plasma glucose following ingestion of the preceding [7].
- It also notable that cross-reaction with proinsulin should be < 10%, a situation commonly encountered with commercial assays. The presence of large numbers of anti-insulin antibodies that may bind both proinsulin and c-peptide can lead to a falsely high c-peptide reading [9].
- C-peptide as a possible predicator of cardiovascular complications in patients with type2 diabetes mellitus and without diabetes. Type1 diabetes complication can be prevented by C peptide replacement where c peptide interacts with the insulin hexamer complexes and indicates its

dissociation, as a result it regulates the functional activity of the insulin signalling system. It can also prevent from some other complications such as atherosclerosis, diabetic peripheral neuropathy, and nephropathy [1].

Table 1.3: Explains the clinical uses of C-Peptide

S.NO	PRODUCT	CLINICAL USES
1	Insulin	▪ Evaluation of fasting hypoglycemia ▪ Evaluation of PCOS ▪ Classification of DM ▪ Predict DM ▪ Assessment of ß-cell activity ▪ Select optimal therapy for diabetes ▪ Investigation of insulin resistance ▪ Predict the development of coronary artery disease
2	Pro insulin	▪ Diagnosis of ß-cell tumour ▪ Familial hyperproinsulinemia ▪ Cross-reactivity of insulin types
3	C-Peptide	▪ Evaluation of fasting hypoglycemia ▪ Evaluation of ß-cell tumours ▪ Classification of DM ▪ Assessment of ß-cell activity ▪ Obtain insurance coverage for insulin pump ▪ Monitoring therapy for pancreatectomy ▪ Monitoring therapy for pancreatic islet cell transplant
4	Glucagon	▪ Diagnosis of α-cell tumours

I. DISCUSSION:

C-peptide, a marker used to assess pancreatic beta-cell function and differentiate between types of diabetes and it is produced during insulin synthesis and is secreted in equimolar amounts with insulin. It has a longer half-life level than insulin and hence measurement of C-peptide is found to be more stable for endogenous insulin secretion which is essential in distinguishing between Type-1 and Type-2 DM. This differential is crucial for diagnosis, prognosis and for the management of DM. In Type 1 diabetes, low C-peptide levels indicate the necessity of administering insulin externally, but lower levels in type 2 diabetes indicates the effectiveness of medications such as metformin or glibenclamide. C-peptide can also help patients who have retained beta-cell function, which provides the alternative treatments in the form of insulin. It also helps in the diagnosis of hypoglycemia and beta-cell tumors. Factors that regulate C-peptide levels like blood glucose concentrations, insulin resistance, renal function, and Incretin. C-peptide assays to have certainty in the accuracy of correct interpretation after having the results and the interference of proinsulin and insulin antibodies, that do cross reactivity that may change the original values.

II. CONCLUSION:

Diabetes Mellitus is a prevalent chronic condition with significant health and economic impacts, requiring careful management. C-peptide, a key marker of insulin production, is crucial for diagnosing and managing diabetes by distinguishing between type 1 and type 2 diabetes. Its measurement provides insights into beta-cell function, guiding treatment decisions and predicting complications like cardiovascular issues. With its longer half-life than insulin, C-peptide offers reliable monitoring of disease progression and treatment efficacy. Understanding factors that influence C-peptide levels is essential, making it a valuable tool for optimizing diabetes care and improving patient outcomes.

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