

## REVIEW ARTICLE

### ROLE OF C- PEPTIDE AS A BIOMARKER FOR DIABETES – A MINI REVIEW

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#### ABSTRACT

Diabetes is accumulation of higher glucose content in the blood. When the glucose level is increased it indicates the low insulin secretion or no response to the insulin production in the body. C-peptide is cleaved from the proinsulin chains A and B during insulin synthesis. C- peptide produced in the same amount to insulin because; C-peptide is removed when insulin is formed. As per the amount is same for both the C-peptide and insulin, the C-peptide works as a biomarker for finding the insulin secretion and to finding of diabetes type accurately. In this review it has been focused on C-peptide and its role as a biomarker in diabetes and predictor of complications and other risks caused by the diabetes.

**Keywords:** Diabetes, Insulin, Biomarker, C-peptide.

#### 1. INTRODUCTION

Diabetes is caused by the way our body makes or uses insulin. Insulin is made to move blood glucose into the cells, where it is stored and then used for the energy. Diabetes mellitus is one of the most burdensome chronic diseases and is associated with shorter lifetime, diminished quality of the life and economic burdens on the patient and the society as a result of healthcare, medication (1). Type1 diabetes mellitus originated from an immune-mediated destruction of insulin-producing-cells found in the pancreatic islets of Langerhans. Type 1 is the most common form of diabetes. 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 play a major role in the etiology of type1 diabetes.

There are clear differences in the immunogenetic predisposition to type1 diabetes between countries and the disease incidence seems to vary along with the differences in the predisposition (2). In type 2 diabetes mellitus, endogenous insulin secretion may be insufficient to maintain glucose homeostasis during additional, stress-induced insulin resistance as occurs during critical illness (3). Diabetes mellitus imposes a considerable burden on the health systems and the societies, leading to a variety of disabling, life-threatening and expensive complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy (1). The most common biomarkers used for the diagnosis of diabetes are oral glucose, Glycated Albumin (HbA1c), C-peptide, insulin, fructosamine. One of the early detection of diabetes

is done by the oral glucose in which false positive results are seen in normal subjects. Similarly, the common test used is HbA1c which shows the effective of drug in the diabetes subjects rather than the insulin levels. As mention with the fluctuations in the biomarkers in the diabetic subjects C- Peptide shows the exact insulin secretion levels which are a potential biomarker for early diagnosis of diabetes.

C-peptide is cleaved from the proinsulin chains A and B during insulin synthesis. C-peptide is produced in same quantity to the insulin and is the best measure of insulin secretion in the patients with diabetes. Measurement of insulin secretion using C-peptide will be helpful in clinical practice: differences in insulin secretion are fundamental requirements in the treatment of diabetes. C-peptide level may be used as a good predictor of the diabetes. Range of C-peptide is 0.8-3.1 ng/mL or 0.26-1.03 nmol/L (SI). C-peptide can be used to assist in patient selection for islet cell transplantation and post-transplant monitoring. High uncorrected fasting C-peptide in the presence of hyperglycemia may suggest insulin resistance (4). The C-peptide, product of proinsulin proteolysis, is a chaperone for insulin during its storage in the transport vesicles of pancreatic beta-cells and further after its secretion into the bloodstream. Along with this, C-peptide functions as regulator of the intracellular effector proteins, including phospholipase C $\beta$ , phosphatidylinositol 3-kinase, mitogen-activated protein kinases, non-receptor tyrosine kinases, and controls cAMP- and cGMP-dependent cascades (5). C-peptide also works as an important regulator of physiology and biochemical processes (6).

This review reveal about the functions of C-peptide in diabetes and other complications or risk caused by the diabetes. The C-peptide is used a

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biomarker for the diabetes and also it predict the risk or onset of other disease. It works as a good marker for the detection of insulin level, insulin resistance and corrects diagnosis of the diabetes and type and differentiates those from the Latent autoimmune diabetes in adult (LADA).

## 2. C-PEPTIDE AS A BIOMARKER IN PREDICTION OF TYPE IN DIABETES

Becht *et al.* (7) worked on correct diagnosis of diabetes type and the insulin requirement using the fasting C-peptide level. C-peptide allows estimation of insulin secretion even in the presence of insulin treatment. Relating ambient glucose levels to C-peptide concentrations can improve the diagnostic potential. The study included 303 patients with type1 diabetes and 841 patients with type2 diabetes. As a result they have got low C-peptide concentrations were associated with a high odds ratio for type1 diabetes and vice versa. C-peptide/glucose ratios or HOMA- $\beta$ C-Peptide did not perform better. By the result it have been concluded that fasting C-peptide and derived parameters help to differentiate type1 from type2 diabetes. Relating C-peptide to glucose did not improve diagnostic accuracy and also C-peptide does not help predicting a need for insulin treatment in patients with type2 diabetes.

### 2.1. C-Peptide and type1 diabetes

Shpakov and Granstrem, (6) studied the C-peptide and its physiological effect. C-peptide is one of the key regulators of physiological processes. Type1 diabetes complication can be prevented by C-peptide replacement therapy. It can also prevent from some other complications such as atherosclerosis, diabetic peripheral neuropathy, and nephropathy. By the replacement therapy the 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. From this study, it has been concluded that C-peptide is an important regulator of physiological and biochemical processes.

Kuhreiber *et al.*, (8) determined whether the low C-peptide levels produced by the pancreas for decades after onset of type1 diabetes and also to study the relationship between C-peptide and HbA1c control as well as diabetic complications and presence of hypoglycaemia. It has been concluded that C-peptide levels and the full range of C-peptide levels was compared with 1,5-anhydroglucitol, a glucose responsive marker low C-peptide levels may be used as a biomarker for characterizing at-risk

patients with type 1 diabetes as there was low insulin secretion.

Buckingham *et al.* (9) estimated that the association between HbA1c, insulin-dose-adjusted HbA1c and C-peptide responses to the diagnosis of type1 diabetes. It included 67 participants. As a result it has been concluded that in the first 2 years after diagnosis of type1 diabetes, higher C-peptide levels are associated with increased glucose levels in the target range and with lower glucose variability.

Wahren *et al.* (10) worked on type1 diabetes with including the long acting C-peptide and neuropathy. A total of 250 patients with type1 diabetes and peripheral neuropathy included in the study and it received long-acting C-peptide in weekly dosages of 0.8 mg for 52 weeks. As a result, plasma C-peptide rose during the study to 1.8-2.2 nmol/L (low dose) and to 5.6-6.8 nmol/L (high dose). It is concluded that, once-weekly subcutaneous administration of long-acting C-peptide for 52 weeks did not improve bilateral sural nerve conduction velocity (SNCV)

### 2.2. C-Peptide and type2 diabetes

Shklovskii *et al.* worked on C-peptide and its role as a predictor of the cardiovascular complications in type 2 diabetes patients. It is found that C-peptide leads to different capillary actions and macrovascular complications in patients with type 2 diabetes mellitus. As a result C-peptide as a possible predictor of cardiovascular complications in patients with type2 diabetes mellitus and without diabetes.

Beliakin *et al.* (11) the aim of the study was to investigate the relationship of C-peptide levels with insulin, resistance; components of metabolic syndrome and cardiovascular disease in patients with type 2 diabetes mellitus. The study included 98 patients with type 2 diabetes mellitus. The patients with elevated C-peptide level found to have all components of metabolic syndrome and also the high incidence of arterial hypertension and ischemic heart disease. This study concluded that the detection of C-peptide level with the comparison with insulin for the assessment of insulin resistance, metabolic syndrome, risk of cardiovascular disease in type 2 diabetes patients.

Pikkemaat *et al.* (12) examined about the C-peptide concentration and cardiovascular risk in type 2 diabetes patients. The study included 399 patients. As a result it has been concluded that measurement of C-peptide concentration at diagnosis could help identify patients with high risk of cardiovascular disease.

Mallipedhi *et al.* (13) investigated on resolution of type 2 diabetes 6 months following bariatric surgery with the association between the preoperative fasting and postprandial C-peptide. The study included 24 participants with type 2 diabetes undergoing bariatric surgery. C-peptide levels for both fasting C-peptide and 2-hour C-peptide had a sensitivity and negative predictive value of 100% to predict type 2 diabetes mellitus remission. This work provides insight into C-peptide dynamics as a predictor of response to bariatric surgery.

Chung *et al.* (14) studied that whether the C-peptide level would relate to the risk of diabetic retinopathy in type 2 diabetic patients independently of estimated glomerular filtration rate (eGFR). 2,062 patients with type 2 diabetes were studied with the measures of fasting C-peptide, 2-hour postprandial C-peptide, and  $\Delta$ C-peptide (postprandial C-peptide minus fasting C-peptide) levels. As a result the patients with and without renal impairment and with diabetic retinopathy showed lower levels of fasting C-peptide, postprandial C-peptide and  $\Delta$ C-peptide and so it has been concluded that serum C-peptide levels are inversely associated with the prevalence of diabetic retinopathy in type 2 diabetic patients independently of eGFR.

Sonoda *et al.* (15) had done study on type 2 diabetes patients along with the C-peptide, HbA1c, and pooled urine. Monitored 202 diabetes patients. In univariate analysis, fasting plasma C-peptide immunoreactivity (F-CPR) and pooled urine CPR (U-CPR) were significantly associated with HbA1c, in contrast to  $\Delta$ CPR and C-peptide index (CPI). This study indicated that patients with type 2 diabetes mellitus, F-CPR and U-CPR may predict improved glycemic control after six months.

### 2.3. C-Peptide as a potential biomarker for other risks

Dickson *et al.* (16) worked on, C-peptide concentrations used to develop insulin-secretion for the purposes of glycemic control. The study included 41 hyperglycemic infants. C-peptide kinetics was used to estimate insulin secretion. Insulin secretion was examined with respect to nutritional intake. As a result, insulin secretion was found to be highly variable and could not be predicted with respect to age, weight, or protein or dextrose intake. Insulin secretion was increase with blood glucose, with a stronger association it is found in female infants. This means nutritional intake was not a correct predictor for the insulin secretion.

Shpakov (5) studied the structural-functional organization of C-peptide and the molecular mechanisms of its action on the cell and identified the specific receptor GPR146 for C-

peptide, which belongs to the superfamily of G protein-coupled receptors. The decrease in the level of C-peptide and the activity of signalling cascades in diabetes mellitus leads to a wide range of complications of this disease including diabetic nephropathy, cardiomyopathy, angiopathy, and neuropathy. The change in C-peptide level is also found in non-diabetic patients with cardiovascular system disorder and renal failure.

Gonzalez-Mejia *et al.* (17) worked on the C-peptide and the insulin as a marker for metabolic syndrome. They studied it with 156 females and 144 males, they were determined with anthropometrics, glucose, insulin, C-peptide, triglycerides, and high-density lipoproteins. Insulin resistance was determined by the HOMA2 calculator using insulin or C-peptide. As a result the C-peptide and insulin correlated with all components of MetS, for waist circumference, waist-to-hip ratio, and fasting plasma glucose, C-peptide correlated better than the insulin. HOMA2-IR calculated with C-peptide was more accurate than HOMA2-IR calculated with insulin at determining MetS. Therefore, C-peptide is a strong indicator of MetS than the insulin.

Taylor *et al.* (18) worked on the intact of C-peptide and insulin. The insulin and C-peptide were collected from the serum using the monoclonal antibodies immobilized on magnetic beads. As a result, an analytical measurement range of 3 to 320  $\mu$ IU/ml (18 to 1920 pmol/l) for insulin and 0.11 to 27.2 ng/ml (36 to 9006 pmol/l) for C-peptide, only the recommended drug insulin lispro caused significance for the determination of endogenous insulin.

G protein-coupled receptors (GPCRs) are the most common receptor family encoded by the human genome. Kolar *et al.* (19) worked on the therapeutic potential of orphan GPCRs with a special focus on C-peptide and GPR146. It is the target of drugs for the treatment of diseases such as diabetes and its associated complications and found to have regulating function of the retinal pigment epithelium, a monolayer of cells in the retina that serves as part of the blood-retinal barrier and is disrupted in diabetic macular oedema.

### 3. CONCLUSION

From this review it has been highlighted about the role of C-peptide as a biomarker for diabetes. C-peptide can be also used as a predictor of risk of heart disease and also some other complications caused by diabetes. C-peptide may be used as a diagnostic tool mainly for diabetes.

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