Global journal of
Pharmacy & pharmaceutical Science
ISSN:2573-2250

Juniper Publishers
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Mini Review
Volume 2 Issue 1 - May 2017
DOI: 10.19080/GJPPS.2017.02.555578

Glob J Pharmaceu Sci

C-Peptide-Boon or Bane in Diabetes

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Submission: March 10, 2017; **Published:** May 03, 2017

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Abstract

Chronic hyperglycemia in diabetes will produce microvascualr & macrovascular complications. Strict glycemic control can reduce but not completely prevent the microvascular complications. C-peptide, a connecting peptide is one of the drugs under clinical trials for treatment of diabetic complications. Previously C-peptide was considered as a byproduct of insulin synthesis, but now it has been proven, as an active hormone with various actions. Replacement with C-peptide has been proven to reduce the type-1 diabetic complications but not in type 2 diabetic complications. This review is focusing on mechanism of action and actions of C-peptide, its role in type1 & type 2 diabetic complications, clinical trials related to C-peptide has been discussed.

Keywords: Hyperglycemia; Microvascular complications; C-peptide; Diabetes; Clinical trial

Abbreviations: DM: Diabetes Mellitus; WHO: World Health Organization; cGMP: cyclic Guanosine Monophosphate; eNOS: Endothelial Nitric Oxide Synthase; GLUT: Glucose Transporter; NO: Nitric Oxide: TNF: Tumor Necrosis Factor; NGF: Nerve Growth Factor; IGF-1: Insulin like Growth Factor-1

Introduction

Diabetes mellitus (DM) is the one of common metabolic disorder characterized by hyperglycemia. Prevalence of diabetes is steadily increasing. It has been estimated that 422million adults were suffering with diabetes in 2014 (8.5% of adult population). WHO projected that diabetes will be the 7th leading cause of death in 2030 [1]. Diabetic complications are classified into acute and chronic or long term complications. Acute complications include diabetic ketoacidosis & hyperglycaemic hyperosmolar state. Chronic complications are classified into vascular & non vascular. Depending on size of the blood vessel involved, vascular complications are divided into microvascular & macrovacular. Microvascualr complications include diabetic retinopathy, nephropathy & neuropathy. The exact etiology by which chronic hyperglycemia will produce these complications is not known.

Studies showed that hyperglycemia is directly linked with development of diabetic complications [2]. Strict glycemic control can reduce, but not completely prevent the morbidity & mortality due to chronic complications [3]. For the past 2 decades a lot of research is going on new drugs for diabetes and its complications. New drugs under trial are Ranirestat, is an aldose reductase inhibitor for diabetic neuropathy and protein kinase beta inhibitor, Ruboxistaurin & Fenofibrate [4] for diabetic retinopathy. Recently Fenofibrate, a hypolipidemic drug was approved in Australia for diabetic retinopathy. C-peptide, a peptide is also under trial for treatment of diabetic complications. The role of C-peptide in diabetic complications with mechanism and clinical trials related to c-peptide has been discussed.

Discussion

C-peptide, discovered in 1967 by Steiner [5], is a connecting peptide which connects insulin's A-chain to its B-chain in the proinsulin molecule. C-peptide and insulin are co-secreted in equal amounts into circulation. It consists of 31 amino acids with molecular weight of 3600kDa. The half-life of C-peptide is about 2-5times longer than that of insulin. Hence, serum C-peptide is used as a substitute marker for monitoring of endogenous insulin production. C-peptide test has been used as a substitute marker for monitoring the course of type 1 and type 2 diabetes and determining the effects of interventions designed to preserve and improve residual pancreatic beta cell function. C-peptide is removed from the peripheral circulation at a constant rate. Metabolised in the proximal renal tubules, and about 5-10% is excreted unchanged in the urine. This is in contrast to insulin

where most of the insulin will undergo metabolism in portal circulation.

In patients with type 1 & some patients with type 2 diabetes, destruction of the beta cells results in deficiency of both insulin and C-peptide. These patients routinely receive insulin injections to compensate for the lack of endogenous insulin production, but no replacement of C-peptide is given. Till 1980 C-peptide was considered as inert and by product during insulin synthesis. Now it is considered a bioactive peptide with diverse tissue and cell-specific actions in various physiologic states and diseases [6].

J Wahren [7] first started looking at C-peptide effects in diabetes in the 1980s. In1990, he had published part of research on the beneficial effects of C-peptide in animal studies. The Diabetes Control and Complications Trial also showed that this C-peptide had relation with diabetic complications. Results of a cross sectional study conducted from 1994 to 2004 on 471 type 1 diabetic patients was showed that subjects with the lowest fasting C-peptide levels were found to have the highest rate of microvascular complications [7]. All these studies are showing that C-peptide has definitive role in diabetes especially chronic complications.

Mechanism of action

It has been reported that C-peptide interacts with G-protein coupled receptor present in endothelial, fibroblast, neuronal, and renal tubular at very low concentration [8] and produce its actions through 3 post receptor mechanisms.

Interaction with Na^+ K^+ ATPase: It has been reported that Na^+ K^+ ATPase activity is reduced due to hyperglycemia in diabetes [9]. C-peptide has regulatory influence on this enzyme.

Activation of endothelial nitric oxide synthase (eNOS): In physiological range, C-peptide has been found to activate eNOS and increase in the synthesis of nitric oxide (NO) in endothelial cells. It is well known that NO causes vascular smooth muscle relaxation by increasing cGMP levels and improves blood flow through NO induced vasodilatation.

Insulin receptor mediated signalling pathway: C-peptide causes Insulin receptor substrate 1 tyrosine phosphorylation, and with downstream effects leading to glucose transporter (GLUT) mobilization, promotion of amino acid uptake & glycogen synthesis.

Pharmacological actions Anti inflammatory, Cytoprotective & antiapoptotic: Patients with type 1 diabetes and microvascular complications show increased levels of several inflammatory markers as compared with patients without complications [10]. C-peptide produce the anti-inflammatory & cytoprotective action by antagonizing adhesion molecule expression, decreases inflammatory cytokine secretion, decreases reactive oxygen species (ROS) formation in endothelial cells and leukocytes and also decreases apoptosis by decreasing caspase3 & increased Bcl_2.

Circulatory effects: In type I diabetes microvascular complications are due to endothelial dysfunction and decrease in microvascular blood flow. C- Peptide increases eNos expression in vascular endothelial cells thereby increases microvascular blood flow by relaxing vascular smooth muscles. It also increases blood flow by improving the erythrocyte deformability through enhancing Na^+ K^+ ATPase activity.

Role of C-Peptide in Type I diabetic complications

Diabetic neuropathy: Neuropathy in type 1 diabetes progresses more rapidly & shows a more marked decline of nerve conduction velocity than neuropathy in type 2 diabetes. Supplementation of C-peptide in these patients restores the activity of Na^+K^+ ATPase and also improves nitric oxide (NO) availability in dose dependent manner. It also increases endoneurial blood flow and conduction velocity even in the presence of highly elevated glucose levels. In addition, it improves nerve structural abnormalities by increasing neurotropic factors such as nerve growth factor (NGF), neurotrophin3 & insulin like growth factor (IGF-1).

Diabetic Nephropathy: C-peptide supplementation in diabetic nephropathic patient causes reduction in intraglomerular pressure by constriction of the afferent and relaxation of efferent glomerular arteriole. It also reduces diabetes-induced structural changes of the glomeruli by decreasing apoptosis & mesangial expansion through decrease in transcription factors TNF-alpha & beta and increase in IGF-1.

Diabetic retinopathy: C-peptide replacement reduces the expression of protein fibronectin, prevents vascular permeability & regulates extracellular matrix expression.

Role in Type 2 DM complication

Effect of C-peptide in type 2 DM is controversial: Type 2 DM is associated with hyper insulinemia state, so when there is an increased secretion of insulin, simultaneously C-peptide levels also will be increased. In many studies it has been found that micro vascular complications are at higher level with stimulated C-peptide levels than with basal levels. The C-peptide in type 2 diabetes showed pro inflammatory and pro atherogenic effects [11] in spite of its anti inflammatory and cytoprotective action. Kim ST et al reported that in type 2 diabetes, basal C-peptide levels can be correlated to intima media thickness and it can be used as a substitute marker of subclinical atherosclerosis [12].

It has been hypothesized that these negative effects of C-peptide in type 2 diabetes are due to

a. In type 1 and type 2 diabetes there may be difference in the levels of C-peptide and insulin in the circulation

b. Difference in the level of inflammation

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c. C-peptide may have tissue and cell specific actions.

Clinical trials

C-peptide has been tested in 300 type 1 diabetic patients in nineteen clinical trials to study its effects in diabetic complications [13]. The results were positive with early phases of clinical trials. In 2012 to 2015, phase II b clinical trials were conducted with long acting c-peptide in 250 type1 diabetic neuropathy patients. Long acting C-peptide was given as subcutaneous injection once a week dose in these trials but the results were not satisfactory. Long acting C-peptide showed marked improvement in vibration perception threshold with no effect on nerve conduction velocity compared to placebo [14]. Further research is required to find the reason for negative effects of C-peptide in these trials.

Conclusion

To conclude C-peptide has been reported to have beneficial role in type 1 diabetic microvascular complications but not in type 2 diabetic complications. It showed positive results in early phases of clinical trials but not in phase II b clinical trials in diabetic neuropathy. Further studies are required to find the reasons for the negative results of C-peptide in these trials and hoping modified form of C-peptide with positive results will come in future.

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