

The Relevance of C-Peptide in Diabetes and its Complications: An Introduction to the Special Issue

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It is well accepted that the connecting peptide (C-peptide) of proinsulin is a critical element in the biosynthesis of insulin. It facilitates the proinsulin molecule's proper folding. Following cleavage of proinsulin, the two resultant peptides are stored in secretory granules in the beta-cells and eventually co-released into the circulation in equal concentrations. The possibility that C-peptide may possess biological activity on its own was a consideration at the time of its discovery in 1968. However, no detectable influence on glucose metabolism in humans, or on lipolysis of isolated fat cells, could be observed. Consequently, the focus on C-peptide as a bioactive peptide diminished, and instead, interest centered on its usefulness as a marker of insulin secretion.

In the early 1990s, direct C-peptide effects were re-evaluated in a new setting. Several studies were undertaken involving administration of the peptide to type 1 diabetes patients, who otherwise lacked C-peptide. This approach gave positive results. It emerged that replacement of physiological concentrations of C-peptide in this patient group resulted in significant improvements of diabetes-induced abnormalities in peripheral nerves and kidney functions. In addition, C-peptide was found to significantly augment the blood flow in skeletal muscle, myocardium, skin, and the kidney.

These surprising findings prompted renewed interest in C-peptide physiology. During the past 15 years, a steadily increasing number of reports on new aspects of C-peptide physiology have been presented. Currently available information includes *in vitro* studies of the peptide's membrane interaction, interaction with insulin signaling activities, and extensive cellular effects. *In vivo* studies in animal models of type 1 diabetes has defined C-peptide's influence on functional and structural abnormalities of the kidney, peripheral nerves, and central nervous system. Also, several clinical studies have appeared, describing the effects of C-peptide replacement on nerve and kidney function in patients with type 1 diabetes. The wealth of information now available attests to a wide spectrum of physiological effects being mediated by C-peptide. The findings also support the notion that C-peptide administration, in combination with regular insulin therapy, is likely to be beneficial in the prevention and treatment of microvascular complications of type 1 diabetes.

In the present Special Issue of *The Review of Diabetic Studies*, the most significant recent developments in C-peptide research are reviewed. The multifaceted and seemingly contradictory intracellular effects of C-peptide in different cell systems are systematically described and updated. New findings regarding the peptide's beneficial ef-

fects on diabetes-induced dysfunctions and degeneration of peripheral nerves are presented. The preventive effects of C-peptide on the recently recognized complication affecting the central nervous system, diabetic encephalopathy, are dealt with in detail. The Issue provides discussion on the possibility that C-peptide may require metal ion activation for its effect, e.g. by zinc ions. Renal physiology and C-peptide's regulatory influence on glomerular vessels are presented to provide a background to the peptide's ability to diminish glomerular hyperfiltration, and to reduce urinary albumin excretion. In addition, C-peptide is discussed in the context of the vessel wall. There is evidence to assume that elevated levels of the peptide may contribute to smooth muscle cell proliferation and atherogenesis in the vascular system. Other findings point to an anti-inflammatory effect of C-peptide in the microvasculature and the central nervous system.

This Special Issue provides a state-of-art of the current knowledge of C-peptide physiology and the role of C-peptide deficiency in the development of microvascular complications in type 1 diabetes. We have sought to compile detailed reviews on the most influential aspects of C-peptide in diabetes, its complications, and therapy. We are pleased to offer it a comprehensive reference work on the topic. We trust that the evidence summarized and reviewed here will convey the urgency with which both basic science studies and clinical trials are needed to further explore the full potential of C-peptide physiology. It is more than 90 years since the discovery of insulin, and yet we still have no causal therapy for the microvascular complications of diabetes. The emerging evidence indicates that type 1 diabetes is a dual hormone deficiency disorder. Consequently, diabetes therapy requires a dual approach, namely C-peptide replacement in combination with regular insulin therapy.