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## Preface

It is well known that C-peptide, the connecting peptide of the proinsulin molecule, is an important part in the biosynthesis of insulin in that it facilitates its correct folding. Following the cleavage of proinsulin into insulin and C-peptide, both peptides are stored in the secretory granules of pancreatic b-cells and are released into the circulation in equimolar concentrations. After its discovery in 1967 by Steiner et al, C-peptide was anticipated to have physiological effects similar to those of insulin. Disappointingly, no effects could be documented with respect to glucose or lipid metabolism, and C-peptide was written off as a non-bioactive peptide. It was not until the 1990s that C-peptide was revisited in a clinical setting. A series of studies were performed on type 1 diabetic patients to whom C-peptide was administered. These studies demonstrated that replacement of physiological levels of C-peptide led to improvements in kidney function and nerve conduction velocities in type 1 diabetic patients. C-peptide also augmented capillary blood flow in skeletal muscle, skin, and the kidney. These findings led to a renewed interest in the physiological function of C-peptide and possible pathophysiological roles of its deficiency in type 1 diabetes. During the last decade and a half there has been a steadily increasing number of reports on C-peptide, its physiology, as well as the effects of its replacement on type 1 diabetic complications. The information to date includes, *in vitro* studies pertaining to its interaction with cell membranes, internalization into endosomes and nucleoli, its function in red blood cells, its interaction with insulin signaling mechanisms as well as direct interaction between insulin and C-peptide. However, a remaining obstacle in the characterization of the physiological role of C-peptide is the existence of a specific C-peptide receptor, which remains elusive. Instead it has been suggested that the effects are mediated via G-protein coupled receptor mechanisms and/or by enhancing insulin signaling via its direct interaction with insulin signaling and with oligomeric insulin.

The revealed actions of C-peptide result in a myriad of cellular effects, including anti-inflammatory effects on the vasculature and the central nervous system, anti-apoptotic and anti-oxidative effects, gene regulatory effects pertaining to trophic factors, and cell-adhesive molecules perturbed in type 1 diabetes. *In vivo* animal studies of type 1 diabetes have described functional and structural benefits on complications affecting the vasculature, kidney, and peripheral and central nervous systems. Several clinical studies have appeared recently, confirming the benefits of C-peptide replacement on peripheral

nerve and kidney function. Therefore, there exists today a wealth of information attesting to a multitude of sometimes contradictory physiological effects in different tissue systems mediated by C-peptide. The data to date strongly support the notion that together with regular insulin therapy in type 1 diabetes, replacement of C-peptide will have additional beneficial effects on the prevention and treatment of complications accompanying type 1 diabetes.

This volume of *Contemporary Diabetes* provides an update of the current knowledge of C-peptide's physiological function and the role of its deficiency in the development of type 1 diabetic complications. This rapidly moving field is dealt with in detail by the most prominent investigators in the field. The evidence summarized in this volume will hopefully convey the urgency with which both continuing mechanistic studies and clinical trials are needed. In reflection, it is nearly 100 years since the discovery of insulin and yet we have no causal and effective therapy for the complications accompanying type 1 diabetes.

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