

Will C-Peptide Substitution Make a Difference in Combating Complications in Insulin-Deficient Diabetes?

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C-peptide is part of proinsulin and necessary for the spacing and secondary and tertiary configuration of insulin [1]. It is secreted in equimolar concentrations with insulin. It was long believed to have no physiological functions. However, in recent years it has become clear that C-peptide has a myriad of functions (see reviews [2, 3]) and that it synergizes the non-hypoglycemic effects of insulin, particularly at low insulin concentrations [4-6].

The chronic complications of diabetes constitute a major component of the costs of the increasing global epidemic of diabetes. The microvascular complications strike type 1 patients disproportionately with a higher prevalence, more rapid developments and more severe clinical pictures as compared to type 2 diabetes. Until recently, it was generally believed that the microvascular complications in type 1 and type 2 diabetes were the same and that the overriding culprit was hyperglycemia and its downstream consequences such as activation of the polyol-pathway and oxidative stress [7, 8]. Only recently has it become clear that underlying pathogenetic mechanisms, as well as structural substrates for the complications, differ between those associated with type 1 and type 2 diabetes [9]. These differences have been extensively explored in diabetic neuropathy and have been accounted for by perturbed insulin and C-peptide actions [10] in addition to hyperglycemia common for both types of diabetes.

Although commonly overlooked in the past, it is now increasingly evident that the combined effects of insulin and C-peptide have important regulatory effects on key metabolic factors, on various transcription factors, trophic factors and their receptors, cell adhesive molecules and their posttranslational modifications, as well as protection against apoptotic phenomena [10-14]. The trophic support has implications as to the expression of a multitude of proteins such as neurotubulins, neurofilaments, neuropeptides and cell adhesive molecules specific for the nervous system. Moreover, downstream signaling by these factors impacts on posttranslational phosphorylation and modifications of a variety of molecules, with consequences as to their activations and protein-protein interactions. Perturbations in this networking of functional and structural proteins translate into a variety of structural abnormalities such as axonal degeneration, degradation of physiologic compartmentalizing barrier systems, impaired regeneration and aberrations in C-fiber integrity. These abnormalities will eventually translate into both positive symptoms such as pain, a common and debilitating symptom in diabetic subjects, and negative symptoms such as loss of sensation, erectile dysfunction and impaired cardiac function.

Clinical investigations have demonstrated that C-peptide has beneficial effects on blood flow in several capillary beds in skin, muscle and forearm [3, 11-13,

15, 16]. It has beneficial effects on glomerular filtration rates and micro-albuminuria in patients with incipient nephropathy [7]. In the retina it protects against vascular permeability. In diabetic neuropathy it improves sensory nerve conduction velocity, thermal and vibratory perceptions as well as heart rate variability [18]. These effects were achieved in addition to the effects provided by tight hyperglycemic control. They suggest that optimal hyperglycemic control with insulin alone is not sufficient to optimize the protection against microvascular complications. This is also born out by the DCCT study demonstrating significant residual incidences of microvascular complications, despite intensive hyperglycemic control [19].

The additional beneficial effects provided by C-peptide can be explained by its synergistic effects on insulin-signaling intermediaries. The half-life of circulating insulin secreted postprandially is measured in a few minutes, whereas the simultaneously secreted C-peptide remains in the circulation for hours. It has been demonstrated experimentally [4, 5] that, at high hormone concentration, C-peptide suppresses the non-hypoglycemic effects of insulin, whereas at low concentrations of insulin, it enhances and synergizes the effects of insulin. This is, of course, important in sustaining gene-regulatory and anti-apoptotic effects and posttranslational modifications of functional and structural proteins.

The molecular underpinnings of the beneficial effects of C-peptide are now being explored experimentally by several laboratories. Among early metabolic

abnormalities pertaining to the development of several complications, the effect on Na⁺/K⁺-ATPase and eNOS activities has been clarified [20-22]. The gene-regulatory effects on several neurotrophic factors and their receptors have been shown to be mediated by transcription factors like c-jun, c-fos and NFκB [12, 13]. These effects in turn influence downstream effects on neuroskeletal proteins in peripheral nerve and anti-apoptotic effects in primary diabetic encephalopathy [23]. A specific abnormality occurring in type 1 human and animal diabetic neuropathy is nodal/paranodal degeneration, which contributes to the more severe functional consequences of neuropathy in type 1 diabetes. It was recently demonstrated that C-peptide prevents the molecular aberrations underlying this degenerative change [14]. Furthermore the molecular and functional abnormalities responsible for aspects of painful diabetic neuropathy are ameliorated by C-peptide [24], as are some of the molecular aberrations responsible for erectile dysfunction [25]. Interestingly, despite C-peptide's effects on endothelial NO and capillary blood flow, it has no effects on various aspects of oxidative stress [26].

In summary, therefore, C-peptide has evolved as an important physiological hormone, whose deficiency appears to play important pathogenetic roles in several aspects of microvascular complications in insulin (C-peptide)-deficient diabetic conditions. In order to bring this promising compound into the clinical arena, approved clinical trials are urgently needed.

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