

C-Peptide as a Remedy for Diabetic Microangiopathy?

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Insulin, connecting peptide (C-peptide) is part of the proinsulin molecule from which it is cleaved by a serine protease within the pancreatic β -cells and subsequently released in equimolar amounts with insulin (1–3). Primarily, C-peptide, which is predominantly cleared by the kidney, was regarded a biologically inert byproduct of insulin secretion and an unneeded contaminant of commercial insulin preparations (1,4), neither affecting glucose metabolism nor lipolysis (5). In contrast, radioimmunological determination of C-peptide turned out to be a useful tool for diagnostic purposes in diabetes research at large, including the estimation of insulin production rates in healthy humans (6) and of residual insulin release in type 1 diabetic patients (7) as well as in vitro (8).

From 1995 onwards the question of C-peptide's biological activity was raised again, and it was assigned a multitude of physiological actions affecting renal, neural, and circulatory functions as well as a wide spectrum of signaling phenomena in vitro (9,10). These reviews raised the hope that C-peptide might find a role in treatment of diabetes-associated late complications, particularly diabetic microangiopathy. Any such proof would be of great clinical importance as the global prevalence of diabetes is continuously on the rise, resulting in a high load of diabetic retinopathy and nephropathy in a large proportion of patients suffering from type 1 and type 2 diabetes (11,12). This development has been hindered through improved metabolic control (13,14), causing the annual incidence to fall for proliferative diabetic retinopathy by 57% from 1980 to 2007 in specialized centers (15) but not necessarily in routine diabetes care (16), with similar observations made in patients with diabetic nephropathy (12).

Against that background, of note are the findings of Bhatt et al. (17) reported in this issue of *Diabetes*, which show that physiological concentrations of C-peptide protect against glucose-induced endothelial apoptosis in human umbilical vein endothelial cells in vitro. Comparable effects were seen in response to exogenous C-peptide replacement approximately 20-fold above its normal secretion rate in aortic tissue of streptozotocin diabetic mice in vivo. The described effects relate to inhibition of intracellular reactive oxygen species generation and of activated transglutaminase 2. Similar observations were made in in vivo experiments in heart and renal cortex tissue.

These findings are in line with those of others reporting biological activity of C-peptide in vitro for a variety of physiological systems including membrane interactions, intracellular signaling, and effects on cell growth and apoptosis as reviewed recently (10). From this it was concluded that there could well be a slot for C-peptide as a remedy for diabetic microangiopathies because after 6 months of replacement it seems to slightly improve sensory nerve function in patients with 30 years' duration of type 1 diabetes (10). Similarly, as glycated Hb, blood pressure, and total cholesterol contribute only 9–10% of the risk of retinopathy in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, other factors including sleep apnea and serum prolactin have been discussed as potential detrimental actors in the development of diabetic retinopathy (15). Any such considerations have, however, to be put into perspective with a 60% reduction of diabetic neuropathy in the Diabetes Control and Complications Trial after long-term intensive insulin therapy demonstrating the superiority of good metabolic control for avoiding late diabetes complications in type 1 diabetes (14).

Reasons to resist the notion that C-peptide replacement could serve as a specific remedy for the treatment of diabetic endotheliopathies (10,17) lie, however, also 1) in its failure to affect ocular blood flow (18); 2) in the inability to identify a clinical C-peptide deficiency syndrome that could be reversed by C-peptide replacement; 3) in the absence of any metabolic action of C-peptide on carbohydrate, lipid, and protein metabolism comparable with that of insulin, which affects these major metabolic systems simultaneously; and 4) in the failure of C-peptide to counteract intracellular cell damage-specific dysregulations such as elevation of nitric oxide synthase and of intracellular calcium²⁺ (Table 1). From these in particular the latter argues against the contention that C-peptide could specifically overcome glucose-dependent cell damage as the influx of calcium across the cell membrane is cytotoxic, impairs signaling as well as mitochondrial function, and activates proteases triggering cell necrosis (19). In addition, the clinical potential of anaphylactic reactions against C-peptide has to be considered (18).

Thus, although the study of Bhatt et al. (17) seems to be supportive of the C-peptide hypothesis, it does not yet resolve the conundrum of why C-peptide should have a role in the maintenance of a healthy endothelium. The observed functional changes in nerve conduction velocity and of some surrogate markers of cell damage including apoptosis do not as yet warrant translation into clinical action. To this end, additional experiments are required to show that C-peptide has a specific receptor and can interfere with key players of diabetic microangiopathy, such as vascular endothelial growth factor or aldose reductase, e.g., in diabetic retinopathy. And if so, it remains to be demonstrated that such interaction has the capacity to change to the better the morphological appearance of microangiopathic capillaries in experimental diabetes of long duration (20). Only once such data are available from

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TABLE 1
Comparison of molecular and functional dysregulation in diabetic retinopathy (11,15), cell death (19), and C-peptide action (10)

Dysregulations in diabetic retinopathy and cell death	C-peptide actions
↑ (11) Reactive oxygen species	↓ (17)
↑ (11,15) Protein kinase C	↓ (10,17)
↑ (11) Nitric oxide synthase	↑ (10)
↑ (11) NEG	no change
↑ (11) Apoptosis	↓ (17)
↑ (19) -intracellular calcium ²⁺	↑ (10,17)
↑ (11,15) VEGF	(?)
↑ (11) Aldose reductase	(?)

Note the failure of C-peptide to normalize intracellular calcium²⁺ and nitric oxide synthase concentrations. NEG, nonenzymatic glycation; VEGF, vascular endothelial growth factor.

preclinical studies could the focus of research shift to costly long-term clinical trials similar to the Wisconsin Epidemiologic Study testing the hypothesis that C-peptide is really a remedy in the treatment of diabetic endotheliopathy in humans.

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