

October 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Revised Manuscript).

Title: Pathological consequences of C-peptide deficiency in insulin-dependent diabetes mellitus

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Name of Journal: *World Journal of Diabetes*

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

(1) Comment: In “C-peptide synthesis and secretion” session of this paper, author described that C-peptide is primarily metabolized by kidney and has a longer half-life than insulin. If C-peptide is primarily metabolized by kidney, C-peptide levels are high in CKD and hemodialysis patients? And C-peptide levels of hemodialysis patients are differences in dialysis days or non-dialysis days? Author must report the change of C-peptide levels by renal function.

Answer: In agreement with your comments, results of study by Covic et al. showed that the mean C-peptide concentration was 2.5-fold higher in diabetic patients suffer from renal disease compared with those with normal renal function (*Kidney International* 2000, Vol. 58, pp. 1742-1750). Also, it has been proposed that decrease in the glomerular filtration rate to less than 15-20 mL/min makes the C-peptide assay unsuitable to assess residual beta-cell function (Marques et al., *Pancreas* 2004, Vol. 29, pp. 231-238). Therefore, it seems rational that C-peptide level of hemodialysis patients be different between dialysis days and non-dialysis days (if C-peptide be able to diffuse through dialysis filters).

(2) Comment: In “Effects on diabetic nephropathy” session of this paper, author described that in STZ-induced diabetic rats, C-peptide decreases urinary protein excretion, reduces glomerular hyperfiltration rate and restores the renal functional reserve. CKD patients with high C-peptide levels have renoprotective effects?

Answer: Regarding biological actions of C-peptide, it has been proposed that some of the actions appear only when it administered to animals or patients who show very low or missing C-peptide plasma levels (Kunt et al., *Diabetologia* 1999, Vol. 42, pp. 465-471; Nordquist et al., *Diabetes Metab Res Rev* 2007, Vol. 23, pp. 400-405). Therefore, nephroprotective and neuroprotective effects of C-peptide are most probably happened only in insulin-dependent diabetes. As mentioned in "conclusion" section, patients with T1D who conserve low but sustained secretion of endogenous C-peptide show better metabolic control and less retinopathy, nephropathy and neuropathy compared with patients who have become fully C-peptide deficient^[57-61]. Therefore, we may not conclude that CKD patients with high C-peptide levels have renoprotective effects.

(3) **Comment:** In "Effects of C-peptide on glucose utilization" session of this paper, author described that C-peptide stimulates muscle glucose transport by a mechanism which is inhibited by cAMP but is independent of insulin receptor or tyrosine kinase activation. Please add the details of the mechanism which is inhibited by cAMP. What is inhibited by cAMP?

Answer: In the study of Zierath et al. (*Diabetologia* 1996, Vol. 39, pp. 306-313) C-peptide stimulated muscle glucose transport by a mechanism which was inhibited by a cAMP analogue, N6, 2'-O-dibutyryl adenosine 3': 5'-cyclic monophosphate. However, the exact pathway is still unknown. The related sentence was revised in the manuscript.

(4) **Comment:** In "Effects of C-peptide on circulation" sessions of this paper, author described that the vasodilator effect of C-peptide is mediated by stimulation of nitric oxide release from endothelial cells with the activation of endothelial nitric oxide synthase (eNOS). And, in "Other biological effects of C-peptide" sessions of this paper, author described that C-peptide is able to inhibit leukocyte-endothelium interaction induced by thrombin or by NG-nitro-L-arginine methyl ester. Glucagon-like peptide-1 analogues and DPP-4 inhibitors also may have the same effects. Are there the interaction between C-peptide and incretin?

Answer: To the best of our knowledge there is no report in literature that shows interaction between C-peptide and incretin. This is a good question and can be subject of future studies.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*

Sincerely yours,

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