ANSWERING REVIEWERS

September 26, 2014/November 11, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name kohnert_WJD-msR1.doc)

**Title:** The utility of different glycemic control metrics for optimizing management of diabetes

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**Name of Journal:** *World Journal of Diabetes*

**ESPS Manuscript NO:** 13546

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) no suggestions
(2) Two cross-sectional studies, a Japanese and an American one, involving diabetic patients on hemodialysis[35,36], suggested that GA is a better marker of glycemic control than HbA1c. The consistent finding of significantly lower % GA/HbA1c ratios in diabetic patients without nephropathy compared to those on dialysis indicates that HbA1c underestimates glycemic control under these circumstances. It is likely that factors such as reduced survival of red blood cells and transfusions contribute to lowering of HbA1c levels in diabetic patients on hemodialysis. **(Chapter: *Fructosamin and glycated serum proteins*, p. 6, lines 1-4, from bottom, p. 7, lines 1-3, from top).**
Accordingly, we included the two corresponding references.
(3) On the basis of recent clinical trials, the relationship between HbA1c and cardiovascular outcomes in long-standing diabetes has been called into question. It becomes obvious that other surrogate and biomarkers are needed to better predict cardiovascular diabetes complications and assess efficiency of therapy. **(Abstract: p. 2, lines 6-10, from top)**

We further referred to this suggestion by including:
Prior to the Emerging Risk Factors Collaboration study[12] large trials, such as ACCORD[6] and ADVANCE[7], also failed to demonstrate the ability to alter cardiovascular outcomes upon lowering HbA1c values in patients with long-standing diabetes. This is in contrast to the effects of tight glycemic control in reducing microvascular complications. As a corollary, the uncertainty around HbA1c results in relation to clinical outcomes was augmented. **(Chapter *Hemoglobin A1c*, p. 4, lines 1-4, from bottom, p.5, lines1-2, from top)**

The discovery of new markers as reliable surrogates for clinical outcomes rather than simply glycemic control will advance the ability to assess the risk of complications and target treatment of diabetes. **(CONCLUSIONS: p. 14, lines 6-7, from top)**

We introduced the new chapter "*Biomarkers and surrogate biomarkers for diabetes complications*" along with the appropriate references.

It is agreed upon that chronic sustained hyperglycemia represents one of the today´s most important surrogate biomarker for development of microvascular diabetes complications. In addition to markers of glycemia, several novel biomarkers have been identified, capable of predicting onset or progression of nephropathy in type 2 diabetes. In a recent systematic review, Hellemons et al[102] assessed the validity of such biomarkers and found, for example, that serum interleukin 18, urinary ceruloplasmin, immunoglobulin G, and transferrin were valid markers to predict onset of diabetic nephropathy. Vascular cell adhesion molecule 1, interleukin 6, von Willebrand factor, and intercellular adhesion molecule 1 were identified as markers for progression of nephropathy. Although a number of circulating (e.g., high sensitive C-reactive protein, brain natriuretic peptide), genetic, and imaging biomarkers (carotid intima-media thickness) are significantly related with cardiovascular risk, their predictive power for individuals is restricted. The relationship of hyperglycemia with macrovascular disease is not as clear as with microvascular complications. Since large clinical trials[6,7] failed to provide convincing evidence that HbA1c is a reliable surrogate, adequate markers for cardiovascular outcomes in diabetic individuals with longer disease duration are not yet available[103]. The uncertainty related to cardiovascular disease led to the release of the New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes[104] by the U.S. Food and Drug Administration (FDA).

Given the complexity of diabetes, it is conceivable that no single biomarker can indicate the risk of complications or disease progression. New technologies, including metabolomics, proteomics, and genomics have the potential to unravel the pathogenesis of diabetes and put forward new concepts for the development of biomarkers beyond impaired glucose regulation.

**(Chapter: *Biomarkers and surrogate biomarkers for diabetes complications* pp. 11-12)**

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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