

Ref: **Manuscript No 41868 – revision- Answer to Reviewers**
„Update on Biomarkers of Glycaemic Control“

The authors are very grateful for the time and effort reviewers engaged in reviewing this manuscript. Their suggestions have been carefully considered and amendments carried out throughout the manuscript.

Detailed answers to the points raised by reviewers are listed below (highlighted in yellow).

Reviewer 1

Anonymous

Review Date: 2018-09-20 10:50

Specific Comments To Authors:

In this review, the authors discussed the merits and demerits of four biomarkers including HbA1c, fructosamine, 1,5-anhydroglucitol and direct glucose analysis for measuring the glycemic control. The review appears to be quite comprehensive and includes pertinent literature.

The text flow is optimal except a few minor modifications need to be performed.

- Page 6: Please rephrase the last sentence “The comparison between.....as previously evidenced” for correctness.

Rephrased as requested (highlighted in yellow in the revised version of the manuscript).

- Page 7: Please use decimal (.) instead of comma (,) in numerical values. Please follow the same rule elsewhere in the text.

Amended as requested (highlighted in yellow in the revised version of the manuscript)..

- HbA1c is still the most commonly used biomarker for testing the glycemic control. This marker has also been suggested for the screening of diabetes. Most of the text under HbA1c heading is somehow pertaining to its demerits. I would suggest modifying the text by including relevant literature on the advantages of HbA1c as well. Some core literature on fructosamine and continuous glucose monitoring is also missing. The authors may include the following literature for more updated information.

Amended, wherever possible/relevant. Please see the updated list of references (highlighted in yellow in the revised version of the manuscript).

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2. Chiu CJ, Rabbani N, Rowan S, Chang ML, Sawyer S, Hu FB, Willett W, Thornalley PJ, Anwar A, Bar L, Kang JH, Taylor A. Studies of advanced glycation end products and oxidation biomarkers for type 2 diabetes. *Biofactors*. 2018 May;44(3):281-288.
3. Chan CL, Hope E, Thurston J, Vigers T, Pyle L, Zeitler PS, Nadeau KJ. Hemoglobin A(1c) Accurately Predicts Continuous Glucose Monitoring-Derived Average Glucose in Youth and Young Adults With Cystic Fibrosis. *Diabetes Care*. 2018 Jul;41(7):1406-1413.
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6. Shohat N, Tarabichi M, Tischler EH, Jabbour S, Parvizi J. Serum Fructosamine: A Simple and Inexpensive Test for Assessing Preoperative Glycemic Control. *J Bone Joint Surg Am*. 2017 Nov 15;99(22):1900-1907.
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10. Chan CL, Pyle L, Kelsey MM, Newnes L, Baumgartner A, Zeitler PS, Nadeau KJ. Alternate glycemic markers reflect glycemic variability in continuous glucose monitoring in youth with prediabetes and type 2 diabetes. *Pediatr Diabetes*. 2017 Nov;18(7):629-636.
11. Blecker S, Park H, Katz SD. Association of HbA1c with hospitalization and mortality among patients with heart failure and diabetes. *BMC Cardiovasc Disord*. 2016 May 20;16:99.
12. Sonoda R, Tanaka K, Kikuchi T, et al. C-Peptide Level in Fasting Plasma and Pooled Urine Predicts HbA1c after Hospitalization in Patients with Type 2 Diabetes Mellitus. *PLoS One*. 2016 Feb 5;11(2):e0147303.
13. Cahill AG, Tuuli MG, Colvin R, Cade WT, Macones GA. Markers of Glycemic Control and Neonatal Morbidity in High-Risk Insulin-Resistant Pregnancies. *Am J Perinatol*. 2016;33:151-6.
14. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomark Insights*. 2016;11:95-104.

15. Lee JE. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol. *Ann Pediatr Endocrinol Metab*. 2015 Jun;20(2):74-8.
16. Fukami K, Shibata R, Nakayama H, Yamada K, Okuda S, Koga M. Serum albumin-adjusted glycated albumin reflects glycemic excursion in diabetic patients with severe chronic kidney disease not treated with dialysis. *J Diabetes Complications*. 2015 Sep-Oct;29(7):913-7.
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Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments To Authors (File):

Reviewer 2

Anonymous

Review Date: 2018-10-01 15:53

Specific Comments To Authors: The manuscript presents a narrative review focused on the state of the art on the use of non-traditional glycaemic markers in comparison to the well-established markers such as HbA1c or glucose-based measures. Overall, the manuscript described the use of non-traditional biomarkers of glucose homeostasis in details.

A main comment on the paragraph Fructosamine and glycated albumin:

Authors comment the use of these two biomarkers but they didn't underlie the differences between them. Fructosamine and glycated albumin reflect distinct glucose measures and they are measured with different analytical methods. These differences, together with the clinical implications, should be described in details. Probably, different paragraphs for each biomarker can be useful to highlight these differences. Moreover, a significant body of evidence is not considered in the text. For example, GA has been tested in relation to diabetes diagnosis and preliminary studies suggest that it can reliably document the efficacy of anti-diabetic therapy preceding the decrease of HbA1c (Bellia C et al. Clin Biochem. 2018;54:68-72. Lu JM et al. J Diabetes Complications. 2016;30(8):1609-1613). Moreover, the distribution of GA in healthy subjects has been described in several population [Bellia C et al, Clin Chem Lab Med. 2017 Nov 27;56(1):120-125. Araki T et al. J Diabetes Investig. 2012 Dec 20;3(6):492-7]. These aspect should be considered in the text.

Amended as requested within the text and the list of references. Amendments are highlighted in yellow.

Minor comment: careful English language editing as well as scientific language editing would be necessary to ensure that all points come across as intended.

The manuscript was edited by American Journal Experts. Please see the attached certificate.

Scientific Quality: Grade B (Very good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision