Author's response to reviews

Title: Effect of Glycemic Control on Soluble RAGE and Oxidative Stress in Type 2 Diabetic Patients

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Version: 3 Date: 14 August 2013

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Dear Editor,

We have revised our revised manuscript, which addresses the comments of Associate Editor "Naila Rabbani" and those made by the referee 1. Modifications to the manuscript are shown in blue color. Below we have detailed our response to the points made. We hope this addresses all comments.

Sincerely,
Mohamed O. Mahmoud
Reviewer 1
Reviewer: Barry Hudson

Reviewer's report:
The authors have submitted a revised article on the relationship between glycemia and sRAGE levels in type 2 diabetic subjects. The authors made changes to the manuscript, however, major comments were not adequately addressed.

1. As previously mentioned in the current study, the authors find controls (n=20) compared to poorly controlled (n=42), but not well controlled (n=28) diabetic subjects, display differences in sRAGE levels (804, 600, and 634 pg/ml respectively). The authors were requested to perform power analysis as their findings in such small numbers and with the large variability seen in sRAGE levels may be a type II error (false positive). The authors mentioned power analysis was performed:

"the power analysis of sample sizes between the main studied groups (GCD, PCD and control) indicated that the number of patients in these groups was satisfactory (power = 95%)."

What did they have 95% power to detect? What is the effect size (eg. OR) in these calculations? The authors need to provide more information on this.

Response: We agree. We have rewritten the paragraph that discusses power to provide necessary information as suggested.

2. The authors pointed out that there are multiple studies of similar sample numbers for sRAGE. This may be true, but what is currently needed in this field of study, is either larger well-designed cohorts or prospective analysis of sRAGE levels with disease. The current study therefore does not add largely to this, and due to the multiple comparisons the authors performed, may be underpowered to do so. As pointed out given both the low sample number studied here, and the large variability in sRAGE levels even in healthy subjects (Brown et al (Ann Clin Biochem 2008) and Wittwer et al (Anticancer Res 2012)), the current study is most likely underpowered to detect the differences seen here. This needs to be discussed if the authors are not planning to increase their study sample size

Response: We agree with the reviewer that the current need in this field of study, is either larger well-designed cohorts or prospective analysis of sRAGE levels with disease. Unfortunately, in the current state, we cannot increase our study sample size as we have no fund even to buy chemicals for laboratory analysis but we intend to perform future studies with larger population and request large fund.

- We have added a paragraph before the conclusion to discuss the large variability in sRAGE marker as suggested.
3. The authors present univariant analysis of the relationship of sRAGE with diabetes, however, did the authors perform analysis adjusted for various risk factors (age, BMI, gender, eGFR, blood pressure, etc) to assess whether this relationship still exists after correcting for confounding factors? This needs to be shown as there are multiple factors that independently affect sRAGE levels.

Response: We agree. Multivariate linear regression analysis was performed. We added this in a paragraph at the end of results section.
**Additional points made by Associate Editor "Naila Rabbani"**

It is important that authors acknowledge in the text that AGE-RAGE interaction is still not clear. There is no evidence that in vivo glycated protein binds to the RAGE rather S100/calgranulin proteins, HMGB1 and other proteins are candidate agonists (Ref: Molecular Nutrition and food research, Wiley, Vol 1 No 9 1107-1110)

**Response:** We agree. Additional data has been added in background section (line 17) as suggested.