Author's response to reviews

Title: Insulin treatment corrects hepcidin but not YKL-40 levels in persons with type 2 diabetes mellitus matched by Body Mass Index, Waist-to-Height Ratio, C-Reactive Protein and Creatinine

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Author’s response to reviews:

Dear Editor,

Thank you for giving us the opportunity to resolve minor issues relating to reviewer comments about our work. Point-by-point corrections according to reviewer comments are as follows:

Carla Carvalho (Reviewer 1): The potential usage of hepcidin as a blood marker for diabetes and the detected enhanced in blood hepdicin concentration in metabolic controlled T2DM is an interesting data. However, it is not clear if this effect was due to insulin treatment or to the metabolic normalization of the diabetes. I think this should be discussed.

Response to reviewer comment: Our diabetic patients do not have improved glycemic parameters which is seen from the results of HbA1C and glucose in Table 1, therefore hepcidin increase in diabetes cannot be due to metabolic changes. Additionally, we have added this explanation in the “Discussion” section; page 11 (line 19-22) and page 12 (line 4-8).

Furthermore, there are some questions I would like to address to the authors:

1- There are some evidence in literature indicating that YKL-40 plasma levels are correlated with age, so it is important to include the age of the studied people;
Response to reviewer comment 1: Age has been included in the “Results” section, page 8, line 7-8.

2- Is there any information regarding the regulation of the hepcidin association to FPN?

Response to revier comment 2: Hepcidin action through FPN has been well established by the seminal work from Nemeth et al., which is included in the reference list (reference number 2). Nevertheless we have added another reference that confirms Nemeth et al. work (reference number 3). This action of hepcidin is discussed in page 3 (Background section), lines 6-12.

3- The % of HbAC should be corrected in the table 1; as well as some paragraphs that have repeated words.

Response to reviewer comment 3: Data concerning HbA1C in the Table 1 have been corrected, as well as paragraphs with repeated words.

4- The autonomic dysfunction discussed in the manuscript should be better identified and presented, since the initial component of the dysautonomia is the sudomotor dysfunction in newly diagnostic diabetes (Isak et al., 2008)

Response to reviewer comment 4: The primary purpose of this study was to evaluate YKL-40 and hepcidin levels in prediabetes and diabetic patients on insulin therapy. Detailed examination of autonomic dysfunction in our patients was not part of this study, though our data analysis showed that changes in basic parameters of autonomic dysfunction were present, which we thought should be included in the paper considering the frequency of autonomic dysfunction in diabetes mellitus. A component of autonomic dysfunction in diabetes mellitus such as sudomotor dysfunction is best evaluated with skin conductance testing or skin biopsy (which were not part of our study methodology), not with the evaluation of basic parameters such as systolic blood pressure, diastolic blood pressure or heart rate. (“The New Age of Sudomotor Function Testing: A Sensitive and Specific Biomarker for Diagnosis, Estimation of Severity, Monitoring Progression, and Regression in Response to Intervention”, Vinik et al, 2015)

Gustavo Santos (Reviewer 2):

In this presented paper, entitled "Insulin treatment corrects hepcidin but not YKL-40 levels in persons with type 2 diabetes mellitus matched by body mass index, waist-to-height ratio, C-reactive protein and creatinine", the authors showed that hepcidin is a strong marker of early
changes in glucose homeostasis in prediabetes patients. Moreover, they showed that hepcidin is a better maker than YKL-40. The paper presents huge English deficiency, which could lead to a miscommunication. It have to be solved before publication.

Response to reviewer comment: The revised version has been corrected in terms of engligh grammar deficiencies.

The Introduction of the paper is missing a lot of important information. For example, "What is the YKL-40 role and why this protein levels could be altered in a state of a glucose metabolism dysregulation?" The authors should make clearer the relationship between the proposed Markers (hepcidin and YKL-40) and the glucose metabolism. Moreover, why hepcidin and YKL-40 would be a good maker for diabetes if we already have a lot of others markers, that is used in clinics.

Response to reviewer comment: Additional clarifications relating to the role of YKL-40 and hepcidin in glucose metabolism dysregulation have been added in the “Background” section; page 3 (lines 11-12 and line 22), page 4 (lines 1-3, lines 6-10 and 19-22), page 5 (lines 1-10 and lines 17-19) but also in the last paragraph of “Discussion” section; page 11 (lines 19-22) and page 12 (lines 1-8)

Kind regards,

Ramadan B. Sopi