Author’s response to reviews

Title: Effect of imatinib on plasma glucose concentration in subjects with chronic myeloid leukemia and gastrointestinal stromal tumor. A retrospective cohort study

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Author’s response to reviews:

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Dear

Editorial Team

BMC Endocrine Disorders
Thank you for giving us the opportunity of resubmission after this minor revision. We have tried to amend and improve the paper according to the reviewer’s comments. The point-by-point response to each comment suggested by the reviewers is given on the next page. We hope that the revised version will fulfill the requirements for publication in BMC Endocrine Disorders.

We are looking forward to your response.

Sincerely,

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RESPONSE TO Technical Comments:

- Authors contributions: please move this from the title page so that it appears in the Declarations section

Thank you we have moved authors contributions onto declarations section.

- Consent: even though this is a retrospective study, a statement is required in the 'Ethical approval and consent to participate' section of the Declarations regarding consent. Did the ethics committee waive the need for consent or did they indicate that the study was exempt. This needs to be clarified.

The study was submitted and approved by the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran Comite de Etica en Investigacion/Comite de investigacion on 11th of July 2016. REF 1974. The ethics committee waived the need for consent from each patient since we do not include personal information.
- Funding: rather than simply stating 'self-funding' perhaps the following sentence should be used:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

- References: for published papers, please do not include a link to the paper on PubMed. Just the bibliographic details of the paper should be provided.

Thank you we have corrected references.

Section Editor Comments:

The authors have provided a reasonable response to most of the reviewers' comments, except for their response to comment 2 of reviewer 1 regarding the lack of response in patients with normal A1c and FPG. I suggest that they simply highlight that the magnitude of improvement in HbA1c in most diabetes clinical trials is related to baseline A1c, the higher the A1c the greater the drop, so when A1c is normal you cannot expect a lot of improvement.

Thank you we have changed the discussion.

Also in terms of discussing mechanisms, I think the authors need to consider this paper https://www.cell.com/trends/endocrinology-metabolism/pdf/S1043-2760(15)00177-0.pdf . Otherwise paper is fine

We have added this reference in discussion.

In addition, inhibition of vascular endothelial growth factor receptor 2 (VEGFR2) reduces the degree of islet cell inflammation (insulitis) [19]
RESPONSE TO THE REVIEWERS

Reviewer #1.

Comment #1

“It is recommended that the ethnicity of the study group is discussed. It may be that the divergent reported effects of imatinib are due to differences in ethnicity.”

Response:

Thank you for your suggestion. We specify that our subjects were Hispanic and added in the discussion a section where we talk about ethnicity and imatinib response.

“Ethnicity could affect imatinib's treatment response. Several studies compared the difference of imatinib therapy response between different ethnic groups, but few studies have enough Hispanic subjects to compare against other ethnic groups. Lee et al performed a study with more Hispanic subjects with CML compared to non-Hispanics [60.9% vs 39.1%, respectively], and concluded that Hispanic subjects achieved better treatment responses to imatinib when compared to non-Hispanic subjects.”

Discussion section, page 13, line 5-11.

Comment #2

2. Some of the T2D patients had normal fasting blood glucose and normal HbA1c before start of imatinib treatment. These patients did not respond to imatinib, which is not very surprising. This should be discussed.

Response:

Thank you for this suggestion. We included a short paragraph explaining the lack of response of T2DM subjects with normal fasting glucose and HbA1c.

“HbA1c reduction indicates that FG was reduced, especially in subjects with high-starting HbA1c values; as in most diabetes clinical trials the magnitude of improvement in HbA1c is
related to baseline A1c, the higher the A1c the greater the drop, so when A1c is normal you cannot expect a lot of improvement.”

Discussion section, page 12, line 15-19.

Comment #3

3. HbA1c should be described statistically and discussed better. It looks like imatinib reduces HbA1c in patients with high starting HbA1c values.

Response:

We included in the results section the statistical analysis of HbA1c between groups, thank you for your recommendation.

“HbA1c decreased from 7.48 (±1.82) to 6.2 (±0.57), with a significant reduction at 1 and 6 months after imatinib treatment (p = 0.040).” Results section, page 11, line 7-9.

“HbA1c reduction indicates that FG was reduced, especially in subjects with high-starting HbA1c values. Imatinib inhibits the phosphorylation of proteins which may result in better signaling, better function of effectors, or both, with improvement in insulin sensitivity; thus, decreasing HbA1c levels in patients with high-starting values. Therefore, we can assume there is a therapeutic benefit in patients with T2DM.”

Discussion section, page 12, line 7-12.

Comment #4

4. Can other metabolic markers (cholesterol, CRP…) be added to the results?

We thank you for this suggestion, but sadly, this study was retrospective and not all patients had all data available.
Comment #5

5. The text needs linguistic revision.

Thank you for your suggestion, linguistic revision was performed.

Reviewer #2.

“This is a small, minor-impact retrospective study of the effects of the tyrosine kinase inhibitor imatinib mesylate on fasting plasma glucose (FPG) levels (and other diabetes associated metrics). The statistical methods employed seem to be appropriate and are well described. The results are discussed appropriately and placed within the context of previous work in this area. The figure is clear and informative. In summary, this is a reasonably well written study on a small patient population that may be of some interest to specialists in the field.”

Comment #1:

“The main issue is the small number of patients included, especially in the subgroup analysis. Otherwise, it is fairly well written, with some minor grammatical errors. Clear meaning is sometimes hampered by assuming that the reader has specific knowledge in this area, and the appeal could be broadened by including more exposition of the nature of the disease under investigation. The tables are a little unwieldy but otherwise informative.”

Response:

Thank you for your suggestion, we included a brief summary of imatinib effects in fasting plasma glucose concentration.

“We reviewed the pathophysiology of T2DM and several animal and human studies that aimed to establish the mechanism by which imatinib lowers FPG concentration. T2DM derives from the abnormal metabolism of carbohydrates, fats and proteins which leads to hyperglycemia and hyperlipidemia. Within time, high levels of glucose and lipids induce changes in the metabolic pathways of insulin causing impaired insulin secretion from the β-cells of pancreatic islets,
insulin resistance and decreased glucose use in peripheral tissues, and abnormal hepatic glucose production. Imatinib has shown to interfere in these pathways”.

Discussion section, page 13, line 12-19.

Dear Reviewers; we want to thank you for your comments on our manuscript. We hope that this new submission fulfills BMC Endocrine Disorders requirements to be published.