Author’s response to reviews

Title: Enhancement of postprandial endogenous insulin secretion rather than exogenous insulin injection ameliorated insulin antibody-induced unstable diabetes: a case report

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Author’s response to reviews:

November 5th, 2018

Dear Prof. Muscogiuri,

Thank you very much for your and the reviewers’ positive comments on our manuscript entitled “Enhancement of postprandial endogenous insulin secretion rather than exogenous insulin injection ameliorated insulin antibody-induced unstable diabetes: a case report” (Ms#: BEND-D-18-00251).

We have addressed the comments made by the reviewers. In particular, the diagnosis of the diabetes type is now discussed more fully, with the addition of new information including that all
autoantibodies examined were negative and that his endogenous insulin secretory capacity had essentially been maintained for at least 15 years after the onset of diabetes. Point-by point responses have also been uploaded herewith.

We very much appreciate these comments, which were helpful for improving the manuscript. We hope that the revised version is acceptable for publication in BMC Endocrine Disorders. We thank you again for your help in this matter.

We look forward to hearing from you at your earliest convenience.

Sincerely yours,

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We are very grateful to the Reviewers for carefully reading our manuscript and providing important suggestions, which have helped us to significantly improve the paper.
Our responses to the Reviewers’ comments are as follows:

Responses to Prof. D’Onofrio (Reviewer 2)

Case presentation

1) page 4 line 6 - specify the symptoms and signs at the moment of diagnosis (es polyuria, polydipsia, loss of weight etc)

We added the symptoms of polyuria to the indicated sentence. (page 4, line 4 in the revised manuscript)

2) please, add the value of HbA1c expressed also in mmol/mol, and the value of glycaemia in mmol/L?

We added the HbA1c (mmol/mol) and glycemia (mmol/L) values to the revised manuscript.

3) Page 5 - line 34 "liraglutide and/or voglibose" it is not clear, please revised the sentence.

As the reviewer mentioned, we revised the sentence from “liraglutide and/or voglibose” to “liraglutide, and then voglibose” to provide a precise description of the treatment time course (page 6, line 9 in the revised manuscript).

4) More detailed description of clinical condition of patient is needed, as presence of diabetic complications, comorbidity, other concomitant therapies and presence of other autoimmune diseases.

We now describe the clinical conditions, such as diabetic ketoacidosis (page 4, lines 13-14), retinopathy (page 4, lines 10-11), nephropathy (page 4 lines 22-24) and peripheral artery disease (page 4, lines 24-25), in more detail. He had hypothyroidism, though all thyroid autoantibodies examined were negative (page 5, lines 2-3).

Discussion and conclusion

1) Considering the age of onset of diabetes, it would be useful a small paragraph of possible differential diagnosis with Type 1 diabetes and LADA. I suggest to refer to this review: Nat Rev Endocrinol. 2017 Nov;13(11):674-686. doi: 10.1038/nrendo.2017.99 in order to focus on the differential diagnosis.
We agree that the differential diagnosis from Type 1 diabetes and LADA should be considered, according to the clinical time course of this patient. Although we could not completely rule out the possibility that his diabetes had been caused by autoimmune disorders, such as type 1 diabetes and LADA, we diagnosed this patient as having type 2 diabetes with low insulin secretory capacity based on the following observations and parameters. 1) The patient did not require insulin therapy 15 years after the onset. 2) His insulin secretory capacity had decreased substantially, though gradually. 3) The islet-related “auto”-antibodies, such as those against GAD and IA-2, were negative, although IAS-like insulin antibody was detectable later in his clinical course.

As the reviewer suggested, we now discuss the possible differential diagnoses in this patient and have included a paragraph with citation of the suggested review as reference #17 (page 7, lines 16-22 in the revised manuscript). We also added further information about his C-peptide level (1.41 ng/mL), measured 15 years after the onset (page 4, lines 8-9 in the revised manuscript).

Table

1) Can you add the value of HbA1c expressed also in mmol/mol, and the value of glycaemia in mmol/L?

We added the HbA1c (mmol/mol) and glycemia (mmol/L) values to Tables 1 and 2.

SUGGESTION

1) page 4 line 8 - consider to change "necessitating" with "requiring"

We changed “necessitating” to “requiring” (page 4, line 5 in the revised manuscript).

2) page 4 line 8 - consider English revision of the following sentence: "His clinic visits were often skipped leading to poor glycemic control."

We changed "His clinic visits were often skipped leading to poor glycemic control.” to “He often missed clinic visits, which contributed to very poor glycemic control.” (page 4, lines 6-7 in the revised manuscript)
Response to Prof. Andreeva-Gateva (Reviewer 3)

Comments:

1. The type of diabetes has to be indicated.

We diagnosed this patient as having type 2 diabetes with low insulin secretory capacity based on the following observations and parameters. 1) The patient did not require insulin therapy 15 years after the onset. 2) His insulin secretory capacity had decreased substantially, though gradually. 3) The islet-related “auto”-antibodies, such as those against GAD and IA-2, were negative, although IAS-like insulin antibody was detectable.

As the reviewer suggested, we now discuss the type of diabetes diagnosed in this patient (page 7, lines 16-22 in the revised manuscript) and provide further information about his C-peptide level (1.41 ng/mL), measured 15 years after the onset (page 4, lines 8-9 in the revised manuscript).

2. In the Background the second sentence about scatchard plot - please add the reference. It is not clear when exactly this evaluation was performed.

We added Reference 1 pertaining to the Scatchard plot (page 3, line 6 in the revised manuscript). The analyses in the present report were performed on the 2nd and 61st days after hospitalization (page 5, line 11 and page 6, line 25 and page 7 line 1 in the revised manuscript).

3. Fig. 3 - it is not clear how the p-value was obtained. Please describe how many times and when the C-peptide was measured. The n is missing.

I would suggest to add the information about C-peptide measurement in the table 2.

We added descriptions of how many times and when the C-peptide levels were measured to the figure 3 legend. We also added information on C-peptide measurement to table 2.

Response to Prof. Arrieta-Cruz (Reviewer 4)

1. There is no information about action mechanisms of liraglutide, mitiglinide and voglibos drugs. The authors must discuss how these drugs help to prevent hypoglycemia in the hyperinsulinemic environment in the present patient.
In the original manuscript, we described the action mechanism of mitiglinide and discussed how this drug ameliorated glycemic control (page 8, lines 20-25 and page 9 line 1 in the revised manuscript). In addition to that pertaining to mitiglinide, we now provide the relevant information about the mechanisms of action of liraglutide and voglibose, based on our expectation that they would prevent hypoglycemia in our present patient (page 8, lines 16-18 in the revised manuscript).

2. The authors did not mention the management of the kidney failure in the patient and how their treatment with oral hypoglycemic agents will not affect the kidney function or will induce more hypoglycemic episodes in the future versus insulin analogs. This is very important because the authors stated in the conclusion section that patients with chronic renal failure are reportedly more susceptible to hypoglycemia events.

To treat hypertension and prevent proteinuria progression, this patient had been treated with an angiotensin II receptor blocker. Nevertheless, his plasma creatinine level rose to around 2.0mg/dL. We now describe this information in the revised manuscript (page 4, line 25 and page 5 line 1-2). Renal failure reportedly impairs insulin clearance, leading to greater susceptibility to hypoglycemia. We added this description to the Discussion section (page 8, lines 13-14 in the revised manuscript).

3. The authors must include the recommended management to the patient outside the hospital.

As the reviewer suggested, we added the recommended management as follows: When we encounter insulin-treated patients who exhibit glycemic instability and are positive for insulin antibodies, we should be careful to not simply rely on adjustment of insulin dosages. We should also consider enhancing endogenous insulin secretion to prevent hypoglycemic episodes (page 9, lines 5-8 in the revised manuscript).

Response to Prof. Defeudis (Reviewer 5)

- Did you checked any other autoantibodies? Please, explain better the role, and their mechanisms, of autoantibodies during exogenous therapy.

The islet-related “auto”-antibodies, such as those against GAD and IA-2, were negative, although IAS-like insulin antibody was detectable. He had hypothyroidism, though all thyroid autoantibodies examined were negative. We added the information regarding autoantibodies to the revised manuscript (page 7, lines 19-21). The mechanism producing IAS-like insulin antibody remains unclear but, as already described in the original manuscript, his HLA type,
which is associated with the highest risk of susceptibility to IAS, might be involved (page 7, lines 11-12 in the revised manuscript).

- Which was the time of duration in use of CGM? Please, explain your decision.

We performed CGM for three days from 51st to 53rd days and from the 61st to 63rd days after hospitalization. We then compared the mean amplitudes of glycemic excursion values to evaluate the glucose fluctuations before and after the replacement of insulin lispro with mitiglinide. We have now added this information to the revised manuscript (page 6, lines 16-17).

- In this CR, how do you explain more episodes of fasting hypo than postprandial?

Compared to IAS patients, our patient with diabetes showed low insulin secretory capacity and insulin resistance. The post-prandial hyperglycemic conditions of this patient might be one of the reasons for hypoglycemic events shifting from the postprandial state to the fasting state. We added this discussion to the revised manuscript (page 7, lines 14-15).