Response to Reviewer 03489437

We are grateful for the reviewer's constructive comments and criticisms.
For clarity, we have prepared our responses in black while your comments are in blue.

In the article authors describe the statistical analysis of the most frequent complications of the gastrointestinal tract in patients with different duration of diabetes of type II. Complications from the digestive system are one of the most common systemic disorders occurring during long lasting diabetes. The pathogenesis of this type of disorders is still poorly understood. Unfortunately, the article is lacking some important information.

Introduction

The authors do not present any current information on the cellular mechanisms for the development of gastrointestinal disturbances. There is no information on the aim of this work.

In order to clearly present the most current information on the cellular mechanisms, we have modified the Introduction section, from line 1 of the third paragraph on page 6 to line 2 of first paragraph on page 7.

As originally indicated in the last paragraph of the Introduction section, we aimed to unravel the relation between gastrointestinal (GI) symptoms and the clinical profiles of patients with diabetes mellitus (DM), including factors such as medical history, diabetic complications, and the use of medications. Symptom severity is now presented based on the questionnaire response to how a symptom impairs quality of life (QOL). We have appropriately corrected the expressions used in the AIM of the Abstract, in lines 1 to 3, the first paragraph on page 4.

Material and methods

The information about drugs used in the course of the experiment for example dose of oral antidiabetic drugs, dose of insulin supplementation (e. g insulin glargine/ levemir or others) as well as dietary information presented in table 1 is incomplete. Moreover, in the main text there is a lack of reference to table 1.
What is more, there is a lack of other blood parameters like lipids or blood clotting factors. If results mentioned above are present then they should be

placed in the section of results.

We have added detailed information about the treatment of diabetes as well as the baseline laboratory data of our patients in Table 1, with the relevant explanations in the Results section from line 7 on page 10 to line 1 on page 11. Unfortunately, we are unable to present data on blood clotting factors because levels were not measured except in users of warfarin. It is virtually impossible to investigate these factors in routine diabetes care in Japan.

In the discussion part, authors should also focus on the pathophysiological causes of the development of complications as well as possible disturbances in the functioning of the enteric nervous system as the cause of autonomic neuropathy.

Possible disturbances caused by diabetes in the functioning of the enteric nervous system are discussed in response to a previous query and we have now mentioned this issue in the Introduction section, in lines 1 to 7, the second paragraph on page 7.

What does, according to the authors, significant diarrhea mean ?

Thank you for this comment. We have deleted the sentence including the word "significant diarrhea" as it was ambiguous, from line 7 of the first paragraph on page 16.

In the last paragraph authors mentioned several limitations, which could not be carried out in the present study. Has there been any information about such research being done in other centers ?. If yes it should be presented in the current manuscript.

As suggested, we have added the reason for our belief that we should needed to mention the limitations, in lines 2 to 8, the third paragraph on page 16.

What is the cause of a more rapid development of complications in the lower GI as compared to the upper GI?

In the Discussion, we have added the possible causes of a more rapid development of complications in the lower GI as compared to the upper GI tract, from line 1 of the second paragraph on page 15 to line 1 on page 16.

Generally, there are differences between the title of the work and its purpose. In the title there is no information on quality of life. Therefore the question arise - what it is the quality of life in people with T2DM.

Thank you for this comment. We did not focus on QOL in those with T2DM, but rather the relationship between clinical features and GI symptoms potentially reducing QOL ("uncomfortable" was the term used in the questionnaire). Therefore, to address the issue you have raised, we modified the sentences in the AIM of the Abstract, in lines 1 to 3, the first paragraph on page 4.

Response to Reviewer 00498408

We are grateful for the reviewer's constructive comments and criticisms.
For clarity, we have prepared our responses in black while your comments are in blue.

The paper by Fujishuro and Colleagues analyzes the occurrence of gastrointestinal symptoms in a cohort of individuals with type 2 diabetes. In particular, it emphasizes the fact that rates of symptoms differed with regard to disease duration, with the lower abdominal symptoms being present both early and later on, thus representing a distinctive tract of the intestinal disease in diabetes. It is important to note that even without concomitant complications individuals with T2D develop GI symptoms, thus highlighting that the intestine may be targeted directly by the disease.

Main comments

1) In the Introduction section: Citation of recent literature in the field will improve the paper in this section. The recent discovery of Colonic stem cells alteration in diabetic enteropathy should be mentioned as this may represent an independent mechanism whereby GI symptoms occur despite the duration of the disease (Cell Stem Cell 2015) and may also represent a target for hyperglycemia and inflammation during T2D. A review has been also published on GI disorders in diabetes in 2016 in Trend Endocrinology and Metabolism, which should be also included in the References. Given the scarce data available on this topic every paper that address its importance especially in the field of diabetes may reinforce the Authors findings.

We are very grateful for these helpful suggestions. Changes in colonic stem cells in diabetic enteropathy are extremely important, but the application of such data to our present report would be rather speculative, because this was a cross-sectional survey. We have, however, revised the Introduction citing the suggested references, from line 1 of the third paragraph on page 6 to line 2 of the first paragraph on page 7.

2) In the Results section: It has been reported in other studies that glycemic control correlates with the severity of symptoms. The authors showed that higher levels of HbA1C are associated with a score of 5 or higher for the

Izumo test. Did the Authors perform a correlation analysis between HbA1C levels and occurrence of specific symptoms such as diarrhea or constipation? Can they comment on that?

Diarrhea and constipation showed no relationships, with only fullness among the five GI symptoms being related to an HbA1c increase by the trend test. The correlation analysis using the score and HbA1c as a continuous variable, possibly due to small relevance, revealed no correlations. We have accordingly modified the sentence explaining Figure 2, in line 13 of the second paragraph on page 11.

3) In the Results section: Is insulin therapy associated with a lower or a higher score? Which symptom is more represented in individuals treated with insulin therapy?

As shown in the top row of Figure 3B, scores are not related to insulin therapy. We now explain these results, in lines 1 to 3, the first paragraph on page 12.

4) In the Results section: It would be interesting for the Izumo score having a comparison with non T2D patients. How big is the impact of GI disorders in T2D as compared to nonT2D in their cohort? Can the Author comment on that?

We agree with the Reviewer's opinion. T1DM was included in this database, but had to be excluded from the statistical analysis due to the small number of subjects. Unfortunately, we have not as yet obtained sufficient nonT2DM data. Since, in our dataset, the disease duration of T2DM was found to be extremely important and to be related nonlinearly to the scores, necessitating careful comparison of T2DM with nonT2DM, there is a possibility that different results might be obtained depending on features of the particular T2DM population studied. We believe that comparison would be desirable and this is one of our future goals, but we are also confident that the involvement of T2DM pathology in determining the GI score is a novel result that merits publication on its own.

5) In the Discussion section: A small paragraph on what's known and what has been published on mechanisms underlying GI disorders in diabetes (very few data) before assessing the limitation of the study may counteract the lack of data in support (endoscopy exc.) as claimed by the Authors.

We have added the suggested sentences to both the Introduction and the Discussion section, as the other reviewer requested; in lines 1 to 7, the second paragraph on page 7 and from line 1 of the second paragraph on page 15 to line 1 on page 16. As a result, the paragraphs describing the mechanisms are now somewhat long.

Minor points

Results page 7: "diabetic triopathy", please edit the grammar or spell out appropriately Legend of Figure 3 reports "maicroangioapthy". Please correct with the appropriate term

We have unified the term 'diabetic triopathy' to 'diabetic microangioapthy,' in line 1 of the second paragraph on page 8.

Figure 4 has panel (a) and (b) but the description in the legend is missing. Please edit accordingly or remove the (a) and (b) in the figure.

We have corrected (a) or (b) to (A) or (B), in Figure 4 with the corresponding figure legend.

Considering the scanty data available in the literature on this topic, this study may certainly reinforce the clinical relevance of intestinal disorders in diabetes and increase the interest of the scientific community around it. Overall the paper describes some relevant novel aspects that may be further addressed and confirmed with some experimental detailed studies. Following an appropriate revision, the paper might be considered for publication.

We deeply appreciate the reviewer's constructive and positive comments.