Author’s response to reviews

Title: An in-depth analysis of glycosylated haemoglobin level, body mass index and left ventricular diastolic dysfunction in patients with type 2 diabetes

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Author’s response to reviews:

Dear Dr Muscogiuri,

Thank you very much for your email to invite us to submit a revised manuscript. We were pleased to learn that the reviewers found that our manuscript presents an interesting study with in-depth analysis of HbA1c, BMI and left ventricular diastolic dysfunction in patients with type 2 diabetes. We appreciate the reviewers’ helpful suggestions and comments. We have revised the manuscript and answered all of their concerns. We hope that it is now acceptable for publication. Below are our point-by-point responses. The reviewer’s comment is given in bold, with our response following after. We have also submitted the revised paper with all changes marked in red, along with an unmarked draft (please see our pdf file with the attach file)s.

Reviewer 1:

This is an interesting study with in-depth analysis. It included an adequate number of participants.

Thanks for the reviewer’s comments. It is a large study to analyse the relationships between HbA1c levels, BMI levels and left ventricular diastolic dysfunction of 925 patients with type 2 diabetes in South China.
The rationale of the analysis is questionable and needs to be convincingly explained.

We appreciate the reviewer suggestion and added a whole paragraph text to explain the rationale of the analysis in the discussion (Discussion Section, Line 273, page 13):

Understanding the relationships between BMI levels, HbA1c levels and LV diastolic dysfunction in the patients with type 2 diabetes will help clinicians to have appropriate management plans for the patients and reduce heart failure rates in patients.

Please do not use the term "systematic analysis".

We agreed with the reviewer and edited the term to “in-depth analysis” accordingly. (Title)

Please consider shortening the Introduction.

We agreed with the reviewer and made the introduction shorter and more concise. (Section introduction)

Please correct grammar (verbs, repetitions of identical phrases).

We went through the manuscripts and corrected the mistakes and typos.

Perhaps the Abstract can be improved in clarity and simplicity.

We improved the texts of the Abstract and made it in clarity and simplicity (Abstract section).

Please discuss the limitations.

We discussed the limitations in the discussion. We added a paragraph as (Discussion section, page 15, line 333):

There are some limitations in this study. The current investigation applied the evaluation index using the E/A ratio in the echocardiogram, it did not investigate the state of the heart load; the HbA1c levels which represented glycemic control in this study, only corresponded to changes in blood glucose levels for nearly three months, while diabetes cardiomyopathy and obesity are metabolic diseases and the pathological processes that change gradually over a long period of time. Single HbA1c may not reflect the historical impact of hyperglycemia on diastolic dysfunction. The effects of some medications and other confounders such as blood pressure and blood lipids were not fully considered, these confounders are needed to further research in detail.

The clinical implications are again dubious and need to be explained.

We added a paragraph to the manuscript as (Discussion section Page 16, Line 341):

The current investigation provides clinical implication about the importance of weight control in patients with type 2 diabetes as higher BMI was clearly a risk of LV diastolic dysfunction. It
also indicates monitoring both HbA1c levels and BMI levels could assist us for correctly predicting early heart function changes for the patients. The results can help clinicians for appropriate management of patients with type 2 diabetes.

Referee #2

This is a large study attempting to establish the association between HbA1c and diastolic dysfunction. As such the data are robust.

We appreciate the reviewer’s comments.

The use of a single HbA1c measure, which does not reflect the historical impact of hyperglycemia on diastolic dysfunction. I would therefore recommend reanalysis using a cumulative HbA1c.

We agreed with the reviewer that the HbA1c does not reflect the historical impact of hyperglycemia on diastolic dysfunction. The relationships between HbA1c and LV diastolic dysfunction have already been reported in many literatures. Our manuscript does not simply analyse the specific relationship between HbA1c and left ventricular diastolic dysfunction, we focus on exploring the influence of relationship between HbA1c and left ventricular diastolic dysfunction in different body weight states from the perspective of stratification. The HbA1c levels in overweight/obesity group and in normal weight group were no difference, suggesting the two groups were comparable. Thus, though we did not apply the cumulative HbA1c, the current conclusions from the investigation are still reliable.

The study of a group of patients with T2DM who are on different therapies not just for their glucose, but also for lipids and BP, which will undoubtedly impact on the echocardiographic findings

We appreciate the reviewer’s comments. We have revised the manuscript to add a new table as table 2. We compared the baseline characteristics in normal LV diastolic function group and LV diastolic dysfunction group. We found no statistical difference in blood glucose, lipid, and diastolic pressure between two groups. Though the systolic pressure was a little higher in LV diastolic dysfunction group, the level was still in normal. We believe that these confounders were balanced between the two groups and did not affect the results of the analysis.

Exclusion of patients without CAD and EF >50%, leaves a cohort of patients who are atypical of typical T2DM.

We know many T2DM patients have heart conditions. The main purpose for this investigation was to focus on the LV diastolic dysfunction. LV diastolic dysfunction is one of the early manifestations of diabetic cardiomyopathy. We excluded patients with CAD and with systolic dysfunction as these patients had advanced heart conditions. In clinical practice the diagnosis of diabetic cardiomyopathy relies on an exclusive diagnosis, and the primary goal for diagnosis is
to exclude coronary heart disease. Systolic dysfunction is also a manifestation of advanced diabetic cardiomyopathy.

Was the echocardiographic assessment of diastolic dysfunction standardized?

The criteria of left ventricular diastolic dysfunction were determined by the ratio of E and A. In order to exclude the false results caused by increased preload and other reasons in clinical practice, the data were judged by two experienced professional ultrasound physicians.

Was there any relationship to the severity of diastolic dysfunction (I=\(<0.8, II=0.8-1.5, III=\geq 2).\)

This is a very useful suggestion. As the main purpose of this analysis was not to analyse the specific relationship between HbA1c and left ventricular systolic dysfunction, we did not classify the left ventricular diastolic dysfunction in current investigation. It is a valuable advice and will be applied in the our future similar studies.

What was the impact of lipids or BP?

Lipid and blood pressure can impact LV diastolic function. But in our table 2, there was no statistical difference of lipid in the two groups, and blood pressure in two groups was in the normal range too. We had added these factors in the subsequent hierarchical interaction analysis.

The English and grammar need significant improvement: What does compressively denote in 'In this investigation, we had compressively analyzed the relationships among BMI….

Thanks for your comment; this issue has been revised(Discussion section, page 13, line 276)

These data challenge recent detailed CMR studies showing a link between diastolic dysfunction and glycemia (Clarke et al Endocrinol Diabetes Metab. 2018 Apr 6;1(2):e00014).

Thanks for recommending the paper. We cited it in our discussion (Discussion section page 14, line 294). It is a very useful article, the article evaluated LV diastolic function in more than one way. As we knew HbA1c was closely related to the LV diastolic dysfunction from many literatures, we further analysed the hierarchical interaction to understand whether obesity might impact on the relationship between the two. We did not find the relationship between HbA1c and LV diastolic dysfunction in our patients; the results may be affected by the blood glucose control and other confounding factors. We extended our explanations in the discussion section.

What treatments were these patients on? Given the potential benefits of the newer agents like GLP-1 agonists and SGLT2i on diastolic dysfunction (Tanaka et al Heart Fail Rev. 2018 May;23(3):439-444).

The purpose of this study was to investigate whether the effect of HbA1c on LV diastolic dysfunction was consistent between the normal weight group and the overweight/obese group. After ensuring the blood glucose, lipid, blood pressure were no statistical difference between the two groups, we did not collect data of the patients using some of the new medications.
The eGFR is remarkably high for a group of T2DM patients aged 57.

The reviewer correctly spotted the eGFR values in T2DM patients. Patients with diabetes may come up with diabetic nephropathy; they may have glomerular hypertransfusion and hyperfiltration. Thus eGFR of diabetic patients might have higher eGFR than normal people in our investigation.

At last, we are grateful reviewer’s for these positive remarks. The main purpose of this study was to investigate whether the impact of HbA1c on LV diastolic dysfunction was consistent between the normal weight group and the overweight/obese group. Our results indicated the difference was shown in two groups and we believe our results will help clinicians to manage patients with type 2 diabetes efficiently.

Yours sincerely,

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