Answer to the comments

Thank you very much for your magazine's email of 2024.3.10. We appreciate the detailed corrections you gave us and are willing to accept your suggestions and submit a revised manuscript. If there are any areas that you feel need further improvement, we would be happy to work with you.

The authors have carefully read "Checklist for Authors to Revise a Manuscript Clinical Research" and revised the article formatting as required, meanwhile, we have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Below is our response to the reviewers' comments. Thank you for giving us this opportunity, and we wish all of you at your journal a happy, healthy and prosperous day!

Reviewer :

1. LINE 40-42 : BETTER TO REWRITE THIS SENTENCE “Insulin antibodies (IAs), which were found commonly developed in patients treated with exogenous insulin, might affect glycemic control due to their tendency to bind and/or release insulin in an unpredictable fashion” - You can remove “commonly” from this sentence.

Line 57 : “that act similarly” can be removed. Remove this sentence “which may be considered in patients with T2DM who need insulin therapy, especially those who had positive IAs” from conclusion as it implies causal association between OADs and lower IA levles which is not proven in this study.

Response: Thank you for your comments. As you have pointed out, we have deleted the inappropriate parts as requested in lines 40, 57 and conclusion.

2. Line 58-59 : Rewrite this sentence.

Response: Thank you for your comments. We replaced “The different effects of all the types of insulin currently being used, as well as oral glucose-lowering drugs on IA have not been reported yet as we are aware of.” with "Previous studies have tended to compare IA levels after the action of two similarly acting insulins, and comprehensive comparisons of different types of insulin are lacking, while the effect of the combination of oral hypoglycemic agents on IA after insulin
administration has been even more rarely reported.” to emphasize the innovative nature of this study.

*Relevant content has been replaced in the second paragraph of the “introduction”. Located on page 5, line 101-105.

3. Line 68-69: “The methods were conducted in accordance with the Declaration of Helsinki guidelines, including any relevant details” better to write as “this study was conducted in accordance with the Declaration of Helsinki guidelines”.

Line 72: Replace “was” with “were”.

Line 80-81: Replace “autoimmune” with “antibody”

Line 137-145: Replace “highe age” with “older people”

Line 146-147: “Moreover, HOMA2-IR was higher in patients with IA>10% than in patients with IA≤1%” - Better to write as “Patients having higher IA levels > 10% were having higher HOMA-IR as compared to those having IA < 1%”

Response: Thank you for your comments. We have replaced the contents of lines 114, 125, 128, 192 and 202 as requested.

4. Line 83: Specify what do you mean by systemic diseases.

Response: Thank you for your comments. Patients with serious systemic diseases in the opinion of the investigator, may interfere with the results of the trial or are considered unsuitable for participation will not be enrolled in the trial. Severe systemic diseases including cardiovascular, gastrointestinal, respiratory, urinary, neurological or hematological systems, such as stroke, myocardial infarction, coronary artery bypass grafting, heart failure, inflammatory bowel disease, acute pancreatitis, Roemheld's syndrome, a history of malignant neoplasm, thyroid dysfunction, liver function with ALT, AST > 2 times the normal laboratory value; ACR > 33.9 mg/mmol, etc.

*Relevant content has been added in the second paragraph of the "Materials and methods". Located on page 6, lines 131-132.

5. Rewrite entire process of insulin antibody measurement. It is better to discuss why this method was chosen for insulin antibody measurement and what are the limitations of this
method.

Response: We have rewritten this paragraph according to your kind advice. Please see in page 7, lines 147-149.

6. Line 151-159: Entire paragraph related to logistic regression analysis requires rewriting and proper editing. It is better to write about baseline characteristics of total sample size with proportion of patients on different insulin regimens and different combination of oral antidiabetic drugs with insulin initially in results section.

Response: Thank you for your comments. We have rewritten the results of logistic regression. Please see page 9, lines 209-218. The baseline characteristics of the total sample size have been added in page 8, lines 191-207. The proportion of patients using different insulin regimens and different combinations of oral antidiabetic drugs and insulin were described in detail in the paragraph "Distribution and IA levels of patients treated with different insulin regimens "and can also be found in Figure 2B; Located on page 9, lines 221-232.

7. Line 170-172: This study only shows lower levels of antibodies in patients on galrgine therapy as compared to human insulin - it does not imply that glargine therapy induces lowest antibody levels. Authors have to correct this throughout the entire manuscript.

Response: Thank you for your comments. We have corrected the description as you suggested throughout the entire manuscript.

8. Line 194-198 Same has been written about oral antidiabetic agents in discussion section - which is to be removed and requires rewriting.

Response: We have corrected the discussion about about oral antidiabetic agents. Thank you.

9. Line 207-208: more insulin is linked with increased costs but is it linked with higher weight gain - please mention reference for this sentence.

Response: Thank you for your comments. We have added reference 19 to support this point, please see page 11, line 271. This prospective study found that after 12 months of insulin treatment, subjects gained an average of 3.0 ± 2.5 kg (P < 0.001).
10. Line 212-213: “the choose of therapeutic regimen in patients with positive IAs is important.” Please write it in a more meaningful way. Do you mean higher IA levels require modification of therapy?
Response: Thank you for your comments. We have revised this sentence. Please see page 10, line 253.

11. Need to rewrite conclusion of this study - mention only about findings of this study.
Response: We have revised the conclusion. Thank you.

Editorial office’s comments

1. The “Author Contributions” section is missing. Please provide the author contributions.
Response: Thank you for your comments. We have added the section at the end of the article.
* Located on page 1, lines 17-23.

2. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).
Response: We have uploaded the relevant material as requested. Thank you.

3. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. If the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2024.
Response: We have mapped as requested. Thank you.
4. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: Thank you for your comments. We have made the requested changes to the form.

5. Please provide the PubMed numbers (https://pubmed.ncbi.nlm.nih.gov/) and DOI citation numbers (https://doi.crossref.org/simpleTextQuery) to the reference list and list all authors of the references. If a reference has no PMID and DOI, please provide the source website address of this reference.

Response: We have made the requested changes to the formatting of the references. Thank you.

6. Medical ethics: Please provide the primary version (PDF) of the Institutional Review Board’s official approval, prepared in the official language of the authors’ country. Please provide the filled conflict-of-interest disclosure form. Please provide the Biostatistics Review Certificate.

Response: We have uploaded the relevant material as requested. Thank you.

Finally, we sincerely hope that this study will be published in your journal, and we are more than willing to cooperate if any further improvements are needed!

Interesting study. But there are a huge lot of technical errors in the whole paper, some of which I have pointed out in the attached tracked version of the paper. Needs a thorough language revision and ideally revision with the help of a medical writer to improve the manuscript quality. Prof Joseph M Pappachan MD, FRCP, Associate Editor - World J Diabetes

We appreciate the detailed corrections you gave us and are willing to accept your suggestions and submit a revised manuscript. If there are any areas that you feel need further improvement, we would be happy to work with you. Below are our responses to the reviewers' comments. Thank you for giving us this opportunity, and we wish all of you at
your journal a happy, healthy and prosperous day!

1. Gross modification is needed to improve the whole section Response: We have finished the language revision, and the changes were highlighted. Thank you.

2. Which human insulin? Response: There is only one type of human insulin, which has the same structure as the insulin secreted by the human islets.

3. “Therefore, endocrinologists should assess IA levels in patients receiving insulin therapy.” This is a very vague statement without reference to an appropriate context. It is impossible and impractical to test every patient on insulin therapy. Response: The IA levels were tested in all patients who were using insulin therapy in Nanjing First Hospital. The tests of IA levels help to find the reason for poor blood glucose control and lipodystrophy at the sites of insulin injection. It is not difficult or expensive and can be easily carried out in the clinic. Given the adverse effects of positive IA antibodies found in the previous study that were mentioned above, we believe that IA testing should be recommended. However, we deleted this sentence as you suggested. Thank you.

4. From the description below, the study appears cross section (that even without patient consent) but authors claim this is retrospective - needs clarification Does it mean serum samples were collected for the study purpose without patient consent? Response: As we mentioned in the Study design section, we retrospectively extracted and analyzed the data from the medical records of patients admitted to Nanjing First Hospital. All of the tests that patients undergo have already been done in the real world. We had no additional serum sample collection, tests, or treatment for the study purpose. We just used the medical records of these patients, and we have explained this in the next sentence.

5. The data appears to be from more than 5 years ago which is not usually unacceptable for biomedical research reporting. Explain Response: We took a long time to collect and digest data from such a large sample size and our findings are novel. Moreover, the IA test assay was changed after January 2019, so we did not include patients after that. Such a condition is quite common, e.g A J Hayes et al, UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013 Sep;56(9):1925-33. doi: 10.1007/s00125-013-2940-y. Lei X, et al, Association of oxidative...

6. Explain the dependent and other variables in this analysis. Response: The dependent and other variables in this analysis were described in the “Results” section.

7. There is no mention about the mean duration of insulin use (in total and subpopulations of different insulin types). This is crucial in the text and analyses. Response: We have added the results about the duration of insulin use. Please see page 7 of the article, section "Study populations". Thank you.

8. Which were the dependent variables? And why not a multivariate analysis? Response: We have added the dependent variables, and the Logistics regression analysis can be used when the dependent variable is binary. Please see page 8 of the article, section "Logistics regression analysis for risk factors of IA". Thank you.

9. Why supplementary table are not in the main text? Response: We think there are too many tables and figures in the main text. We can move the supplementary table into the main text if necessary. Thank you.

10. "The present study found that the positive IAs were significantly lower in patients using insulin glargine than in those using other insulin therapy regimens, while DPP-4 inhibitors, metformin, and insulin secretagogues may also have potential effects on reducing IA levels". This sentence doesn’t make much sense as these patients may have better endogenous insulin reserve and lower levels of extrinsic insulin use. Response: We have corrected this sentence into “while the use of DPP-4 inhibitors, metformin, and insulin secretagogues may also have associated with reducing IA levels.” Please see page 10 of the article.

11. These two lines and the statistical analysis do not make much sense as those with anti-GAD was an exclusion criteria and already the parameters tested are insulin levels at various percentages. Response: We have deleted these two lines. Thank you.

12. Interesting - needs explanation though. Response: We think the higher proportion of cancer in patients with positive IA may be attributed to the elderly of these patients. We have added the explanation in the page 12 of the article, “Discussion” section. Thank you very much.

13. This was an exclusion criteria. Response: Although the patients had negative GAD-Ab, the
levels of GAD-Ab were different between the groups. However, we deleted the GAD-Abs in the results according to your advice.