

Jan. 3, 2024

Lu Cai, Michael Horowitz, and Md. Shahidul Islam
Editors-in-Chief

Yun-XiaoJian Wu
Assistant Editor
World Journal of Diabetes
Dear Editors,

We wish to re-submit the manuscript titled “**Metabolic disorders in prediabetes: From mechanisms to therapeutic management.**” The manuscript ID is 90324, Review.

We express our gratitude to you and the reviewers for your valuable suggestions and insightful perspectives. The manuscript has greatly benefited from these astute recommendations.

Attached is the revised version of our manuscript. In the following pages, we provide point-by-point responses to the reviewers' comments and have highlighted the revised and newly added content in yellow in the revised manuscript. We hope that the revisions in the manuscript and our accompanying responses would be sufficient to make our manuscript suitable for publication in *World Journal of Diabetes*.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Responses to the comments of Reviewer #1

1. The manuscript contains some typing errors and grammatical mistakes that need to be corrected.

Response:

We greatly appreciate the reviewer's invaluable suggestion and have made the following corrections:

1. Page 6: Changed 'impede' to 'impedes' and 'lifestyle' to 'lifestyles';
2. Page 8: Replaced 'GLP-1R' with 'Glucagon-like peptide receptor' and 'hormone stimulated' with 'hormone-stimulated';
3. Page 9: Updated 'level' to 'levels' and 'SGLT2' to 'Sodium-glucose cotransporter 2';
4. Page 10: Altered 'GLP-1' to 'Glucagon-like peptide -1';
5. Page 13: Modified 'AGEs/RAGE/Nox4/NF- κ B' to 'advanced glycation end-products (AGEs)/receptor of advanced glycation end-products (RAGE)/ NADPH oxidase 4 (Nox4)/nuclear factor kappa-B (NF- κ B) '.

2. The authors are encouraged to add subtitles for example healthy diet, and lifestyle.

Response:

Thank you for your comment. We apologize for the omissions and have incorporated the suggested behavioral and dietary interventions on pages 13-14, highlighted in yellow for ease of reference.

BEHAVIORAL INTERVENTION

In addressing prediabetes, obesity is a key factor. To delay diabetes onset, increasing exercise intensity and duration is crucial. For prediabetic patients, a weekly increase of 150 minutes in exercise or 30 minutes daily can significantly lower the fasting glycemic index^[135]. Six months of high-intensity exercise effectively improves oral glucose tolerance^[136], and 20 weeks of sustained exercise normalizes blood glucose levels^[137]. A Meta-analysis confirms that both aerobic and resistance training, individually or combined, benefit insulin resistance and glycemic control in prediabetic patients^[138].

Enhancing behavioral interventions requires a comprehensive, adaptable strategy that accounts for patient preferences, risks, and comorbidities, ensuring long-term adherence. This strategy should include building supportive relationships that encourage healthy behaviors, timely plan adjustments based on patient progress, and incorporating incentives for sustained motivation and adherence^[139].

DIETARY INTERVENTION

A high-calorie diet contributes to prediabetes development. Epidemiologic evidence supports increasing intake of non-starchy vegetables, fruits, and whole grains ^[140], while limiting added sugars to effectively reduce glycated hemoglobin, fasting glycemic index, serum insulin,

insulin resistance, cholesterol levels, body weight, and BMI^[141]. This approach also lowers type 2 diabetes risk^[142]. Early time-restricted feeding (eTRF), involving a 6-hour eating window ending by 3 p.m., improves insulin sensitivity, β -cell responsiveness, blood pressure, oxidative stress, and appetite within 5 weeks, aiding diabetes prevention^[143]. This study aims to concisely highlight the importance of dietary protein and fiber in mitigating prediabetes.

3. Specify the intended lifestyle and the relation to pre-diabetic status.

Response:

Thank you for your feedback. We have addressed the omission by detailing the intended lifestyle and its relation to pre-diabetic status on page 15. The additions are specified below: A combination of a nutritious diet and increased physical activity plays a crucial role in preventing or delaying the onset of diabetes and its complications

4. Some abbreviations need to be fully named AGEs/RAGE/Nox4/NF- κ B.

Response:

We would like to extend our heartfelt appreciation for the invaluable suggestion put forth by the reviewer. The following changes have been made in Page 13:

Expanded the abbreviations AGEs/RAGE/Nox4/NF- κ B to advanced glycation end-products (AGEs)/receptor of advanced glycation end-products (RAGE)/ NADPH oxidase 4 (Nox4)/nuclear factor kappa-B (NF- κ B).

Responses to the comments of EDITORIAL OFFICE'S

1. Table(s) and figure(s): There are 8 tables and 4 figures, and all should be improved.

Response:

Thank you for your feedback. To address your comments, we have revised the headers and annotations in our tables and figures, highlighting these changes in yellow. The specific modifications are as follows:

1. Figure 1: Renamed 'AMP-activated protein kinase (AMPK)' to 'Adenosine 5'-monophosphate (AMP)-activated protein kinase'; Added annotations for AMP, GLUT4, GS, and BECN1.
2. Figure 2 & 4: Included annotations for K⁺, Ca⁺, and β cell;
3. Figure 3: Added annotations for SGLT2 and Na⁺;
4. Figure 3 & Tables 5, 6, 7: Replaced 'SGLT2' with 'Sodium-glucose cotransporter 2';
5. Table 5: Updated 'GLP-1' to 'Glucagon-like peptide-1';
6. Tables 1-8: Reformatted for clarity;
7. Table 8: Introduced annotations for IU, D2, and D3.