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Li Ma
Science Editor
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Dear Reviewers,

The following is our responses to the reviewer comments for our manuscript.

Reviewer #1:

1. Comment: For section about current or being evaluated interventions for NAFLD, it is better to distinguish simple steatosis and NASH.

> Response: In the "NAFLD definitions section," simple steatosis/NAFL versus NASH were more clearly defined. In the NAFLD interventions sections, steatosis and NASH were more clearly delineated, such as liraglutide for patients with NASH. However, some studies did not describe patients more specifically than under the categorization of NAFLD, such as the studies regarding SGLT2 inhibitors.

2. Comment: Could FXR agonists be classified as Therapies Targeting Insulin Resistance?

> Response: FXR agonists moved to "lipid metabolism" section.

3. Comment: After summary of interventions for NAFLD, authors should provide some prospective opinion for future therapies.

> Response: Added a section titled "Future Directions for NAFLD Therapy" to discuss future therapies.

Reviewer #2:

1. Comment: Regarding NAFLD pathology, the author should specify the most important and common reasons.

Response: In the NAFLD pathogenesis section, sentence was edited: "The complex pathophysiology of NAFLD is driven by multiple hits. The major drivers include increased insulin resistance and impaired lipid metabolism. Other factors such as hormonal influences, gut-liver interactions, and genetics also play a significant role."

2. Comment: On GLP-1 Receptor agonist and SGL T2 inhibitors, the author should clarify the previously done studies and indicate references.

> Response: Regarding GLP1R agonists, references on exenatide and liraglutide with associated studies were included. For SGLT2 inhibitors, the same was done with canagliflozin, dapagliflozin, and empagliflozin.

3. Comment: In targeted lipid metabolism treatments, the author should indicate which drugs were the most promising for clinical application.

> Response: Added a section under “Lipid Metabolism” listing the drugs that are currently in phase 3 trials, making them most promising for clinical application.

Reviewer #3 response:

1. Comment: Although gut microbiota and epigenetics are not drug important targets, they are critical mechanisms of NAFLD development and progression, which should be thoroughly discussed.

> Response: Added sections 3 and 4 about gut microbiota and epigenetics respectively in pathogenesis section.

Editor in Chief:

1. Comment: The author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to **find the latest highlight articles,** which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

> Response: Utilized provided database to search through high impact journal articles regarding NAFLD and its therapies. We highlighted semaglutide and dapagliflozin, which are being evaluated in phase 3 studies. We also included MSDC-0602K and efruxifermin as therapies under evaluation. Therapies such as cenicriviroc were not included as this phase 3 study was terminated early due to lack of efficacy (AURORA trial).

Thank you for your time and consideration,

Katie Shen, MD

Achintya Singh, MD

Jamak Modaresi-Esfeh, MD

Jamile Wakim-Fleming, MD