

Peer Review File

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Reviewer A

The review described and summarized the studies that related to the relationship between metformin and tuberculosis. However, several issues should be seriously considered:

Comment 1: The review listed several retrospective observational studies to support the arguments. Seriously, how could observational studies confirm the therapeutic and preventive effects of metformin on tuberculosis? Observational studies could only indicate the potential association between factors. The review recorded that metformin can prevent the establishment of TB, metformin can prevent the development of TB, and metformin can change the disease course in active TB. That's not rigorous, and please correct the expression.

Reply 1: We understand that strictly observational studies may not provide concrete answers to clinical problems. The studies used for this editorial included retrospective studies with propensity matched cohorts, prospective studies including 2 randomized control trials, and one cross-sectional study. In most of the studies the statistical analysis is reasonably sophisticated in an effort to identify adjusted outcomes. We have changed the language in the text to indicate that some results are not definitive.

Comment 2: The paper just listed many positive results to support the arguments. However, in every single clinical study, there are positive and negative results. For example, in studies conducted by Magee et al., reduced prevalence of LTBI was observed in patients used metformin and statins together, but not in patients used metformin alone. Please list the negative results. Some negative results were listed in the systematic review: Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review.

Reply 2: We reviewed the studies again and included negative results in the text.

Comment 3: I suggest a table to list the results from clinical observational studies.

Reply 3: We have added a table which summarizes these studies.

Reviewer B

Comment 1: Authors state that “These similarities have led to the consideration of metformin as a possible adjunctive 46 therapeutic agents in tuberculous infections in patients with and without type 2 DM (7).” I do not think the “similarities” between this two diseases are what led to the use of Metformin.

Reply 1: This sentence has been rewritten.

Comment 2: The subsequent entries are just a repetition of the subtitles followed by a tedious listing of studies.

Reply 2: We are trying to provide brief summaries of somewhat complicated studies that try to determine whether or not metformin has any beneficial effect in patients with tuberculosis. We are assuming that many readers have not looked into this topic in any detail.

Comment 3: An immunology section, could have had its own entry and probably a nice diagram or model.

Reply 3: We will add a figure for this section.

Comment 4: Too generic statements such as “Several in vitro studies with human cells provide evidence of improved immune responses associated with metformin treatment that could provide the basis for improved clinical outcomes.” Are simply not useful.

Reply 4: We will review the text carefully and try to avoid broad generalizations. When possible we will add in specific details to the sentences.