Reply to the reviewers' comments:

Reviewer Number	Original comments of the reviewer	Reply by the author(s)
Reviewer #1	The subject is of general and current interest, not just for endocrinologists and nephrologists. In recent years, we have had drugs with kidney benefits and not just neutrality. Evaluating these benefits, besides renal security, is essential, especially in populations at risk of chronic kidney disease, such as patients with diabetes and obesity. I congratulate the authors for the interest in doing a job addressing the topic. I congratulate the authors for the interest in doing a job by addressing the topic and with a drug still so new, but has already shown so much benefit in weight loss and glycemic control. 1) The study is interesting and highlights a topic of actuality. 2) The study is well written. 3) The article follows the PRISMA. 4) The analyzes were adequate. 5) The methods are well described. 6) The tables are good. 7) The graphics are suitable. 8) he limitations of the study are acknowledged and discussed. 9) The results of the study support the conclusion. 10) The study compiles the most up to date evidence about renal safety of tirzepatide. 11) The study was recorded in Prospero. 12) The overall quality of the manuscript, a well done systematic review with meta-analysis. **Here are some considerations to be reviewed:**	Thank you, sir, for your observation.
	1) The title does not report the population studied.	All included studies are published RCTS on tirzepatide. We have changed the title to "Renal effects and safety of tirzepatide in subjects with and without diabetes: A systematic review and meta-analysis." This title indicates the study population.
	2) The introduction addresses the use of tirzepatide in patients with type	The introduction has been revised addressing

	2 diabetes, but the inclusion was from patients using tirzepatide for any indication.	this issue.
	3) It would be interesting a subanalysis separating studies with people with type 2 diabetes and people with obesity, to check the difference. Obesity and diabetic nephropathy are not the same disease.	Thank you for this valuable input. We have done subgroup analysis of placebo-controlled trials involving subjects with diabetes and without diabetes. Please refer to Supplementary Figure S2 and description in the result section (page 10,11).
	4) The authors could address the hyperfiltration present in the early stages of the kidney disease of diabetes and the kidney disease of obesity.	The introduction has been revised addressing this issue.
	5) In the introduction, it is lacking the definition of the mechanism of action of the Tirzepatide.	The introduction has been revised addressing this issue.
	6) In the introduction, It is not clear which was an inclusive population.	The introduction has been revised addressing this issue.
Reviewer #2	I am very grateful to the editor-in-chief for inviting me to review the manuscript titled "Renal Effects and Safety of Tirzepatide: A Systematic Review and Meta-Analysis." This manuscript explores the renal effects and safety of Tirzepatide, a novel dual agonist targeting GIP and GLP-1 receptors, particularly focusing on its role in reducing albuminuria and maintaining estimated glomerular filtration rate (eGFR) levels based on data from randomized controlled trials (RCTs) in type 2 diabetes (T2D) patients. The study aims to assess the renal benefits and safety of Tirzepatide compared to placebo, insulin, and GLP-1 receptor agonists. It includes 15 RCTs involving 14,471 participants, primarily T2D patients. The findings indicate that Tirzepatide at 10 mg and 15 mg doses significantly reduced UACR compared to placebo and insulin, suggesting potential benefits in preventing diabetic nephropathy	Thank you, sir, for your observation.

	progression. However, in short-term trials, Tirzepatide had no significant effect on eGFR. Its safety profile was comparable to other treatments, with no significant increase in renal adverse events. The clinical significance of reduced UACR, particularly in patients with higher baseline UACR, was highlighted as an improvement in kidney health.	
	Although this study provides a comprehensive analysis of short-term data, a notable limitation is the lack of long-term RCTs. Given the chronic nature of diabetes and its slow progression to kidney disease, the short follow-up periods (26 to 72 weeks) limit the assessment of Tirzepatide's ability to prevent long-term declines in eGFR. The authors should more critically emphasize this point in the discussion and add a dedicated section addressing the impact of short follow-up on long-term renal outcomes, thereby enhancing the manuscript's impact.	We have already discussed the short duration of the included trials as a limitation of the study.
	Additionally, the heterogeneity of the study population, which includes trials with varying baseline UACR, eGFR, and diabetes duration, introduces variability. While the authors addressed this using a random-effects model, further discussion on how this heterogeneity affects the generalizability of the results is warranted.	We have added this limitation as a limitation of this study.
	Subgroup analyses by baseline renal function or albuminuria might provide more targeted clinical insights.	-We have conducted subgroup analysis for the tirzepatide dose, nature of the control groups, presence of T2D. - Subject-level data for baseline UACR >30 was available for four studies which was separately analyzed (Supplementary Figure S2). All included RCTs had mean baseline UACR <30.

		So, subgroup analysis could not be done on this basis. - RCTs including subjects without T2D had baseline mean eGFR >90. We have done subgroup analysis of RCTs involving subjects with T2D with mean baseline eGFR <90 and ≥90.
	In conclusion, this manuscript is well-structured and provides valuable insights into the renal effects of Tirzepatide, particularly its potential role in reducing albuminuria. However, due to the lack of long-term data, study heterogeneity, and insufficient safety data, the authors should be cautious in drawing conclusions. Emphasizing the need for long-term studies and exploring advanced statistical methods to address heterogeneity will significantly enhance the manuscript's rigor. If revised accordingly, this paper could make a meaningful contribution to the field of diabetic nephropathy and drug safety.	The need for long-term larger RCTs is already mentioned in the conclusion. We have suggested appropriate involvement of diverse ethnic groups in the future RCTs in the revised article. We have performed sensitivity analyses for the primary outcomes (Supplementary Table S5).
Reviewer #3	This manuscript addresses an important and timely topic in the management of type 2 diabetes (T2D), particularly focusing on the renal effects and safety profile of tirzepatide. The systematic review and meta-analysis involving data from 15 randomized controlled trials (RCTs) provide valuable insights into the potential benefits of tirzepatide on key renal parameters, including the urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Given the rising global prevalence of T2D and its major role in chronic kidney disease (CKD), this study offers essential information for clinicians seeking to optimize therapeutic choices for patients at risk of diabetic kidney disease (DKD). The manuscript is innovative in that it expands	Thank you, sir, for your observation.

	on prior reviews of tirzepatide's renal effects by including all relevant trials to date and by providing a thorough assessment of its safety profile across a range of doses. The study shows that tirzepatide significantly reduces UACR at multiple dosages when compared to both placebo and insulin, which is clinically meaningful given the strong association between albuminuria and CKD progression in T2D. While the impact on eGFR was not significantly different from comparators, the consistency of these findings with short-term follow-up suggests a neutral renal safety profile, supporting the use of tirzepatide in patients with T2D, including those at risk for CKD. These results contribute valuable evidence to a growing body of literature supporting the potential reno-protective effects of glucose-lowering therapies beyond glycemic control alone. The manuscript is well-structured and concise, following the PRISMA guidelines and presenting its findings with clear statistical rigor. Figures and tables are effective in conveying the results, and the discussion critically assesses the strengths and limitations of the data. The authors also provide a clear rationale for further research, particularly the need for longer-term studies to confirm the renal benefits of tirzepatide. In summary, this manuscript is important because it provides new therapeutic insights for managing renal risks in T2D and consolidates existing data on tirzepatide's safety profile. I recommend its acceptance, as it is well-written, logically organized, and contributes meaningfully to both clinical practice and future research directions.	