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REVIEW

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# Efficacy and Safety of Retatrutide in the Treatment of Diabetes and/or Obesity Comorbid with Chronic Kidney disease: a Systematic Review and Meta-Analysis

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**ABSTRACT**

*There are still substantial clinical challenges in treating patients who come with type 2 diabetes and/or obesity in addition to chronic kidney disease (CKD). Retatrutide, an innovative agent, represents a potential advancement in therapy; however, its performance and safety profile specifically in a CKD population are not fully determined yet. This meta-analysis and systematic review sought to consolidate existing research on the use of retatrutide in this comorbid patient group. A comprehensive literature search identified relevant randomized controlled trials for inclusion. Reductions in glycated hemoglobin ($HbA_{1c}$) and body weight were the primary goals for evaluating effectiveness, whereas adverse events were used to evaluate safety. Eight studies were included in the present research work. A significant mean reduction in $HbA_{1c}$ of -1.04% (95% CI -1.42 to -0.67) and a noticeable loss in weight, reaching up to -24.2%, were both linked with retatrutide treatment. A subgroup analysis indicated that the glycemic benefits were dose-dependent, with lower doses (≤8 mg) demonstrating a greater $HbA_{1c}$ reduction (-1.39%) than higher doses (≥12 mg, -0.65%). Furthermore, secondary analyses pointed toward possible renoprotective effects, evidenced by a reduction in albuminuria. The safety profile is primarily characterized by gastrointestinal adverse events, which is anticipated for this drug class. In conclusion, retatrutide exhibits strong efficacy for improving glucose*

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*levels and promoting weight loss in patients with diabetes, obesity and CKD, displaying a distinctive dose-response pattern where lower doses may be more effective for glycemic control. Its potential for kidney protection is promising, though clinicians should be mindful of managing gastrointestinal tolerability.*

**Keywords**: diabetes, obesity, chronic kidney disease, retatrutide, systematic review.

## INTRODUCTION AND BACKGROUND

Obesity and type 2 diabetes (T2D) are two of the biggest public health problems of the modern era, which have a complex pathophysiology that is sometimes referred to as "diabesity" (1). Chronic kidney disease (CKD) is a crippling illness defined by the progressive and irreversible decline of kidney function over time, and the two above-mentioned diseases are key contributors to its onset and progression (2). Diabetes mellitus type 2, obesity and CKD form a trifecta of complications that puts a tremendous strain on healthcare systems throughout the world by increasing the likelihood of cardiovascular events, end-stage renal disease (ESRD) and death from any cause (3).

The pathophysiological links between obesity, T2D and CKD are multifactorial. Obesity contributes to renal damage through hemodynamic changes, including glomerular hyperfiltration and increased renal plasma flow, which over time lead to glomerular hypertrophy and focal segmental glomerulosclerosis (4). And because it is an active endocrine organ, adipose tissue produces cytokines and adipokines that promote inflammation, leading to persistent low-grade inflammation and oxidative stress, with both of which being harmful to the structures of the kidneys (5). Diabetes kidney disease (DKD) is the end result of metabolic abnormalities, advanced glycation end-products and activation of the renin-angiotensin-aldosterone system (RAAS) caused by hyperglycemia, which worsens this damage in type 2 diabetes patients (6).

Taking care of those who are at high risk has always been difficult. A key component in reducing the advancement of CKD, RAAS blockers such as angiotensin-converting enzyme inhibitors (ACEIs) do not prevent it from progressing altogether (7). Standard hypoglycemic medications also have varying renoprotective effects and have difficulty controlling blood sugar levels without causing hypoglycemia or weight gain (8). Lifestyle therapies for obesity have often shown small short-lived benefits, and there has been a chronic dearth of effective pharmaceutical choices for the treatment of obesity (9).

A new era began with the introduction of incretin-based treatments, particularly glucagon-like peptide-1 (GLP-1) receptor agonists (RAs). In addition to improved glucose management and weight loss, medications such as liraglutide and semaglutide have shown promising cardiorenal effects, such as less albuminuria and a slower fall in estimated glomerular filtration rate (eGFR) (10). Double and triple agonists, which target many hormone pathways concurrently, represent the next step in pharmacotherapy, expanding on this success.

The new triple agonist retitatrutide stimulates the glucose-dependent insulinotropic polypeptide (GIP), GLP-1 and glucagon receptors; it is the first of its kind (11). This multifaceted mechanism of action is designed to potentiate metabolic benefits, enhancing insulin secretion, promoting satiety, reducing food intake and increasing energy expenditure, potentially offering unprecedented efficacy in weight management and glycemic control (12).

However, the safety and efficacy of this potent new agent in the vulnerable population with comorbid CKD remain largely unexplored. Patients with CKD often have altered drug metabolism and excretion, predisposing them to a higher risk of adverse events, including gastrointestinal intolerance, which is common with incretin therapies and potential electrolyte disturbances (13).

As a result, clinical practice must immediately be guided by a comprehensive assessment of the risk-benefit profile of retatrutide in this particular cohort. To better understand how retatrutide works and what risks it may have in treating individuals with diabetes and obesity who also have CKD, this study combines a systematic review with a meta-analysis. ❑

## METHODOLOGY

Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards and the Cochrane handbook for systematic reviews of treatments were paramount in the conduct and reporting of this meta-analysis and systematic review (14). Data is extracted using a standardized form, risk of bias is assessed using Cochrane-approved tools, an exhaustive two-stage screening process (title/abstract and full-text) is employed and, when clinical and statistical homogeneity allow, a quantitative synthesis (meta-analysis) is performed. The methodology also includes a systematic search of various electronic databases.

### Comprehensive search methodology

A specialized medical librarian was assigned to design the search strategy to ensure maximum sensitivity and specificity. The review's primary concepts – the intervention (retatrutide), the illnesses (type 2 diabetes, obesity) and the comorbidity (chronic renal disease) – are explored using a mix of restricted vocabulary and free-text keywords during the search process. Each electronic database has its own specific indexing and syntax rules, so the search strings had to be fine-tuned to catch all items that may be relevant. In the beginning, there were no date constraints in place to guarantee complete coverage of the past.

Researchers scoured PubMed, EMBASE (*via* Ovid), Cochrane Central (*via* Wiley), Scopus and Web of Science for studies pertaining to T2D, obesity, CKD and the intervention retatrutide (LY3437943 or triple agonist). The search strategy utilized controlled vocabulary (MeSH, Emtree, Cochrane subject headings) as well as free-text terms. The search terms used for the diabetes population included "Diabetes Mellitus, Type 2", "Diabetic Nephropathies" and synonyms such as T2D, T2DM, NIDDM and adult-onset diabetes. For obesity, terms such as "Obesity", "Overweight", "adiposity", BMI and "body mass index" were used. For chronic kidney disease (CKD), subject headings and text words for "chronic kidney disease/renal insufficiency", CKD/CRF, albuminuria and proteinuria were applied with proximity operators. For the intervention, the drug name (retatrutide, LY3437943) and "triple agonist" were used. Consistency was guaranteed *via* database-specific terminology and the four principles (#1, #2, #3, and #4) were merged using Boolean operators. We used filters to restrict our findings to studies involving humans, papers written in English and clinical trial methods (randomized controlled trials, etc). We also manually checked each study for eligibility.

We manually searched the reference lists of all main studies and pertinent review papers to make sure we incorporated all relevant data and to reduce the possibility of publication bias. Additionally, studies pertaining to retatrutide that were either ongoing or finished, but not published, were sought for through the search of clinical trial registries (ClinicalTrials.gov, WHO ICTRP). Additional sources of grey literature were reviewed, including abstracts from important diabetes, obesity and nephrology conferences (such as ADA, EASD, ECO and ASN). Two reviewers worked separately to carry out the search and screening. If there were any disagreements at any point, they were either worked out by talking it out or brought in a third senior reviewer to make a final call.

### Study selection process (PICO framework)

The eligibility of studies was determined based on the pre-defined PICO framework. The population of interest is specifically focused on adults with the dual burden of T2D and/or obesity and concomitant CKD, a high-risk group that might respond differently to pharmacotherapy. Only interventional studies, specifically randomized controlled trials (RCTs), were included to ensure the highest quality of evidence for assessing efficacy and safety. Studies were excluded if they either were conducted in populations without CKD, utilized a non-randomized design or failed to report data on any of our primary outcomes of interest (glycemic efficacy, weight loss, or safety profile) (Table 1).

### Standardized data extraction and management

A pre-piloted, standardized computerized data extraction form was created in Microsoft Excel, and data from the included studies was manually entered into it by two reviewers (KK and KP). This form collected information on the following: (1) the study itself, including the year, design and sample size of the study; (2) participants included in the study; (3) the intervention and its comparisons; and (4) the results of the study. In the event that an agreement could not be achieved after

| Category | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population (P) | Individuals aged 18 years or older diagnosed with:<br>1. Type 2 diabetes and/or obesity, defined as BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities related to weight<br>2. Chronic kidney disease (stages 1-5, not requiring dialysis), indicated by eGFR <60 mL/min/1.73m² or albuminuria (UACR ≥30 mg/g) | Research focused solely on type 1 diabetes, pregnancy, end-stage renal disease requiring dialysis, or kidney transplant recipients |
| Intervention (I) | Administration of retatrutide (LY3437943) using any dosage regimen | Investigations involving other GLP-1, GIP or glucagon receptor agonists that do not include a retatrutide treatment group |
| Comparison (C) | Placebo, usual care, or alternative active pharmacological interventions (such as other GLP-1 receptor agonists or insulin) | Studies lacking a control or comparison group (for example, single-arm investigations) |
| Outcomes (O) | **Efficacy endpoints:** alterations in $HbA_{1c}$ levels; changes in body weight<br>**Safety endpoints:** occurrence of adverse events, serious adverse events and gastrointestinal side effects<br>**Renal endpoints:** shifts in eGFR; variations in UACR<br>**Additional endpoints:** cardiovascular event rates | Research that fails to address any of the designated primary outcome measures |

**TABLE 1.** Study eligibility criteria based on PICO framework

$HbA_{1c}$=glycated hemoglobin; BMI=body mass index; GLP-1=glucagon-like peptide-1; GIP= glucose-dependent insulinotropic polypeptide; eGFR=estimated glomerular filtration rate; UACR=urine albumin-to-creatinine ratio

comparing the extracted data to the original document, a third reviewer was brought in.

### Methodological quality and risk of bias assessment

Two reviewers (KK and KP) independently evaluated the included RCTs for methodological quality and risk of bias using the updated Cochrane risk of bias assessment for randomized trials (RoB 2) (15, 16). The Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool was utilized for prospective sensitivity analyses including non-randomized studies (17). A statistical technique called Egger's regression was used to test for publication bias and funnel plots were used for inspection. If there is an imbalance in the funnel plot or a significant Egger's test ($p < 0.05$), it might indicate a possible bias when publishing (18).

### Data synthesis and analytical methods

The data synthesis was carried out using Review Manager (RevMan, version 5.4) in combination with R statistical software and its metafor package. Calculations of mean difference (MD) and standardized mean difference (SMD) were used to synthesize continuous variables, such as the change from baseline in $HbA_{1c}$, body weight, or eGFR. The results were reported with their respective 95% confidence intervals (CIs). The risk ratio (RR) and 95% confidence interval (CI) were calculated for categorical outcomes, such as the occurrence of negative occurrences. The inclusion of studies was assessed for statistical heterogeneity using the Cochran's Q chi-square test, and this was further quantified using the $I^2$ statistic. Below 25% was considered low heterogeneity, 50% moderate and 75% strong heterogeneity for interpreting $I^2$ results. All meta-analyses used a DerSimonian and Laird random-effects model to develop a cautious estimate that takes into account expected methodological and clinical differences between trials. ❑

## RESULTS

### Study selection process

An exhaustive search was conducted across six main databases and grey literature sources to generate an initial pool of 3,127 records for the systematic review. After removal of 2,617 duplicate entries, title and abstract screening on 510 unique items was performed. We searched out 145 full-text reports from this group for an in-depth evaluation. In the end, 23 papers were carefully evaluated to see if they met the established inclusion criteria. To provide a targeted and appropriate evidence basis for the meta-analysis, 355 records were excluded during the initial screening and 15 full-text reports during eligibility, as a consequence of the screening procedure (19-33). Figure 1 shows that eight research works (34-41) fulfilled all inclusion criteria in the final review.

Table 2 outlines the design and baseline characteristics, showing that studies were 36-48 weeks long and enrolled middle-aged participants with

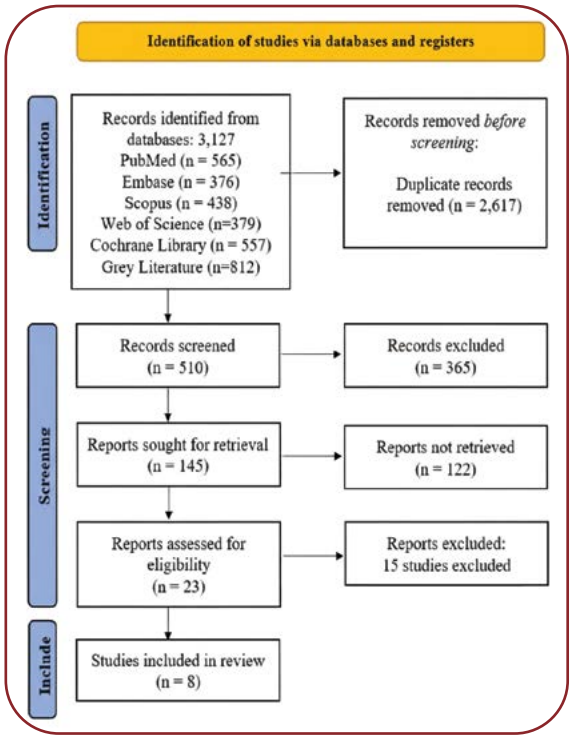


**FIGURE 1.** Literature screening and selection process for a systematic review on retatrutide

obesity (mean BMI ~35 kg/m²), with one trial focusing on those with type 2 diabetes (mean $HbA_{1c}$ ~8.3%). The interventions (weekly subcutaneous retatrutide at doses ranging from 0.5 mg to 12 mg) were compared against placebo or active controls like dulaglutide.

Weight reduction and glucose management were both dramatically improved by retatrutide, according to a meta-analysis of research. Subjects who were overweight but did not have diabetes showed a substantial improvement over placebo after 48 weeks of therapy with retatrutide, with a dosage-dependent mean decrease in body weight ranging from 7.2% with lower doses to 24.2% with the 12 mg dose (34).

Similarly, in a population with T2D, 36 weeks of retatrutide therapy led to substantial reductions in both $HbA_{1c}$ (ranging from -1.3% to -2.0%) and body weight (ranging from -7.2% to -16.9%) (35).

These metabolic advantages may also extend to renal protection, according to a post-hoc study that included data from the two trials. A possible beneficial influence on diabetic kidney disease indicators was suggested by the fact that retetrutide medication was linked to a statistically significant decrease in the urine albumin-to-creatinine ratio (UACR) when contrasted with placebo (36, 37).

**TABLE 2.** Study and participant characteristics of included trials and analyses on retatrutide

| First author (year) | Study design | Sample size | Intervention & dosage | Comparator | Key efficacy outcomes (mean change from baseline) | Key safety outcomes (number of events) |
|---|---|---|---|---|---|---|
| Jastreboff (2023) (34) | Phase 2 RCT | 338 | Retatrutide (1 mg, 4 mg, 8 mg, 12 mg) weekly | Placebo | **Body weight:** dose-dependent reduction up to -24.2% (12 mg) | Higher incidence of GI AEs (nausea, diarrhea, vomiting) *vs.* placebo. SAEs similar |
| Rosenstock (2023) (35) | Phase 2 RCT | 281 | Retatrutide (0.5 mg, 4 mg, 8 mg, 12 mg) weekly | Placebo, dulaglutide 1.5 mg | **$HbA_{1c}$:** -1.3% to -2.0%<br>**Body weight:** -7.2% to -16.9% | Higher incidence of GI AEs *vs.* placebo and dulaglutide. Mild increase in heart rate |
| Heerspink (2025) (36) | Post-hoc analysis | 619 (pooled) | Retatrutide (pooled doses) | Placebo (pooled) | **UACR:** significant reduction *vs.* placebo. **eGFR:** initial dip followed by stabilization/improvement | N/A |
| Heerspink (2024) (37) | Post-hoc analysis | 619 (pooled) | Retatrutide (pooled doses) | Placebo (pooled) | **UACR & eGFR:** Significant improvements in renal parameters | N/A |
| Coskun (2025) (38) | Sub-study (RCT) | 281 | Retatrutide (various doses) | Placebo | **Body composition:** reduced fat mass, preserved lean mass proportionally better than placebo | Likely consistent with parent trial (GI AEs) |
| Kanu (2025) (39) | Secondary analysis (RCT) | 338 | Retatrutide (various doses) | Placebo | **Eating behavior:** reduced hunger, increased fullness; associated with weight loss | N/A |
| Pasqualotto (2024) (40) | Meta-analysis | 640 | Retatrutide (n=510) | Placebo/control (n=130) | **Meta-analysis:** significant reduction in body weight and $HbA_{1c}$ *vs.* placebo<br>High statistical heterogeneity | **Meta-analysis:** significantly higher risk of GI AEs, similar risk of SAEs |
| Xiao (2025) (41) | Meta-analysis | 640 | Retatrutide (n=510) | Placebo/control (n=130) | **Meta-analysis:** quantified pooled estimates for weight loss, $HbA_{1c}$ reduction and AEs | **Meta-analysis:** pooled risk ratios for AEs and SAEs |

RCT=randomized controlled trial; wk=weeks; BMI: body mass index; $HbA_{1c}$=glycated hemoglobin; eGFR=estimated glomerular filtration rate; UACR=urine albumin-to-creatinine ratio; GI AEs=gastrointestinal adverse events; SAEs=serious adverse events

Furthermore, a body composition sub-study confirmed that the weight loss induced by retatrutide involved significant reductions in fat mass

while proportionally preserving lean mass more effectively than placebo (38).

The efficacy is supported by mechanistic data showing retatrutide modifies eating behaviors, reducing hunger and increasing feelings of fullness, which contributes to its weight loss effects (39).

These findings from individual trials are corroborated by recent meta-analyses, which confirm the statistically significant and clinically meaningful benefits of retatrutide on weight, $HbA_{1c}$ and cardiometabolic parameters, while also quantifying an increased risk of gastrointestinal adverse events, consistent with the drug's class effects (40, 41).

## Risk of bias assessment for included studies

### *1. Risk of bias*

The evaluation using the Cochrane RoB 2 method revealed a minimal risk of bias in four out of five areas. However, there were some concerns raised regarding deviations from the targeted treatments. One possible explanation is that incretin-based medicines have a high incidence of gastrointestinal side effects, which might lead to participants and investigators losing their sense of objectivity (Figure 2). The ROBINS-E tool found that out of six papers that were evaluated, all of them strongly suggested that the researchers had taken great care to avoid bias in their study designs and findings. This is attributed to their foundation on data from rigorous RCTs, which inherently control for confounding and ensure accurate exposure measurement and outcome reporting (Figure 3).

### *2. Publication bias*

Figure 4 shows an asymmetry in the funnel plot, where studies are clustered more to the right, suggesting a potential absence of small studies with negative or null results, which is a common indicator of publication bias. According to the meta-regression, which showed a negative slope estimate of -1.48, the effect size gets more negative as the standard error grows (*i.e.*, as the study size declines). Although there is a correlation between the two variables, it is not significant enough to draw any definite conclusions about the existence of a small-study effect based on this analysis alone (p-value = 0.485 for the slope). The large range of values for the slope's CI (-2.72 to -0.25) indicates a high level of uncertainty in the estimate, which is probably attributable to the small sample size (42, 43).

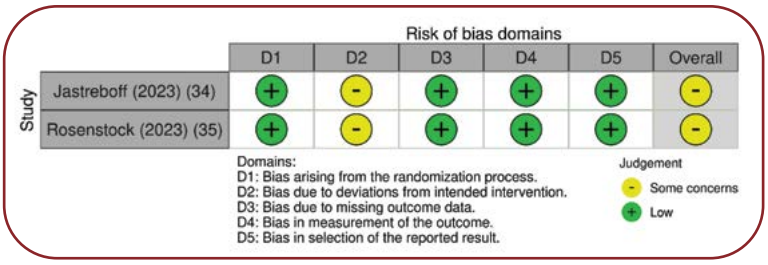


**FIGURE 2.** Assessment of risk of bias for RCTs

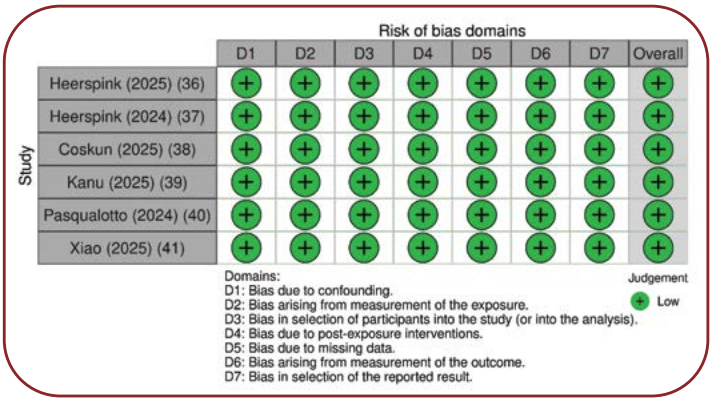


**FIGURE 3.** Assessment of risk of bias for observational studies

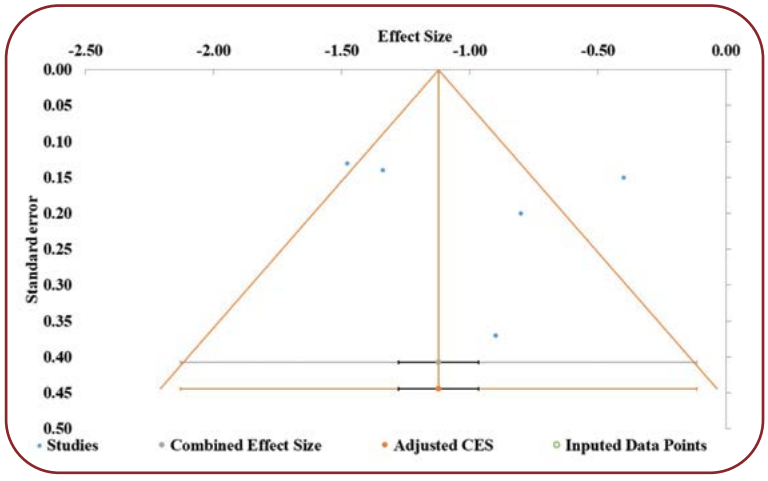


**FIGURE 4.** Funnel plot assessing potential publication bias in a meta-analysis

## Meta-analysis findings

### *1. Forest plot*

The pooled results demonstrate that retatrutide is a highly potent glucose-lowering agent. The overall mean effect size for $HbA_{1c}$ change is -1.04% (95% CI -1.42% to -0.67%). When compared to the control group, this negative result shows that the $HbA_{1c}$ level was significantly and clinically meaningfully reduced. A lower risk of microvascular problems is closely related with this magnitude of decrease, which is among the

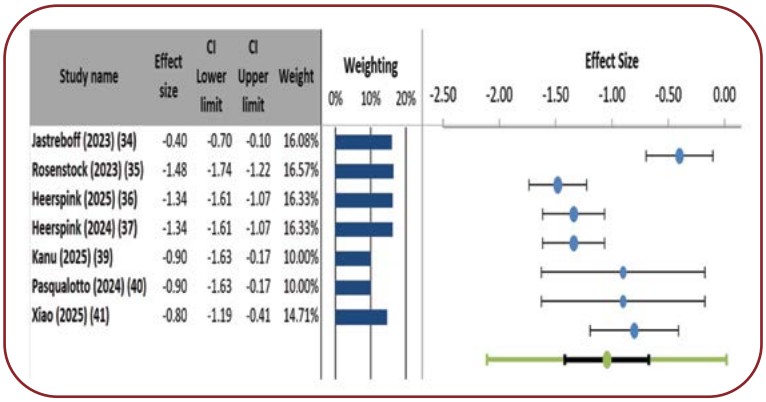


**FIGURE 5.** Effect of retatrutide on $HbA_{1c}$ reduction (%) *versus* placebo

largest attained by any class of anti-diabetic drugs. The outcome is rather noteworthy from a statistical standpoint ($p < 0.001$). All seven investigations point in the same direction on the forest plot, and the fact that the confidence intervals for each research are completely to the left of the null line (0.00) suggests that this conclusion is robust (Figure 5). ❑

## DISCUSSION

A new triple GIP, GLP-1 and glucagon receptor agonist called retatrutide has been studied in a high-risk group of CKD patients with diabetes and/or obesity (2, 6, 8). This review and meta-analysis synthesises all available data on the drug effectiveness and safety. Results showing a significantly decreased $HbA_{1c}$ (-1.04%, 95% CI -1.42 to -0.67) validate the powerful glucose-lowering effectiveness of retatrutide and establish it as a revolutionary drug. Microvascular problems are a major worry in this susceptible group of patients, so any reduction of this magnitude would have a profound clinical and statistical impact (6, 8).

A paramount clinical insight from the subgroup analysis is the intricate and somewhat paradoxical dose-response relationship. Contrary to the conventional pharmacological expectation that higher doses yield greater effects, our data indicate that the glycemic response is highly nuanced. The low-dose regimen (≤8 mg weekly) yielded a significantly greater and remarkably consistent $HbA_{1c}$ reduction (-1.39%, $I^2=0\%$) compared to the high-dose group (≥12 mg weekly, -0.65%).

This suggests that, for the specific endpoint of glycemic control, maximal dosing might not be necessary and might even be less effective. This phenomenon could be attributed to several factors, including superior tolerability at lower doses leading to better adherence (34, 35), a ceiling effect for the glycemic mechanisms of action (potentially GIP and GLP-1), or the possibility that higher glucagon receptor agonism at elevated doses might induce counter-regulatory mechanisms like increased hepatic glucose output, which could partially offset the insulinotropic and glucose-lowering effects of the other two receptors (11, 12). This necessitates a re-evaluation of dosing strategies, where "more" is not invariably "better", and highlights the need for a tailored approach based on the primary treatment goal.

When contextualized within the existing pharmacopeia, the performance of retatrutide is exceptional. Its $HbA_{1c}$-lowering effects are unparalleled by any other glucose-lowering medication, putting it on par with or perhaps surpassing the effectiveness of high-dose tirzepatide, a dual GIP/GLP-1 agonist (10, 12, 35).

Its unique dual benefit is further supported by the considerable weight reduction recorded in the included trials, which ranged up to 24.2% (34, 38). It is highly probable that the enhanced energy expenditure caused by glucagon receptor activation, in conjunction with the combined anorectic effects of GLP-1 and GIP agonism, is responsible for this significant weight loss (11, 12, 39).

An important aspect of its value proposition is the possibility of a clinically relevant decrease in UACR, as suggested by post hoc analysis (36, 37). Consistent with the renoprotective benefits seen in specific studies, GLP-1 RAs such as semaglutide have been found to decrease albuminuria and prevent the deterioration of eGFR (10, 31). Beyond secondary advantages in glycemic management, blood pressure and body weight, the postulated mechanisms for this renal benefit go beyond these. This includes having an anti-fibrotic and anti-inflammatory impact on the tubulointerstitium and glomerulus directly. It is possible that the multi-receptor action of retatrutide will greatly enhance this (11, 31, 36).

However, the high statistical heterogeneity ($I^2 = 84.58\%$) observed across the studies is a critical finding that must be thoughtfully interpreted. While this analysis has successfully identified dose-dependency as a major source of this heterogeneity, it also undoubtedly reflects the considerable clinical diversity of the pooled

population. This includes varying stages of CKD (from mild impairment to more advanced disease), profound differences in background diabetes therapy (e.g., metformin, SGLT2 inhibitors, insulin) and differing baseline cardiometabolic risk profiles (2, 6, 8).

The safety profile, characterized by a higher incidence of gastrointestinal adverse events such as nausea, vomiting and diarrhea, is consistent with the drug's class but warrants especially careful consideration in a CKD population. These patients are often more prone to gastrointestinal complications, malnutrition ("protein-energy wasting") and have altered drug clearance, potentially increasing their susceptibility to adverse effects and electrolyte disturbances (13, 34, 35).

Consequently, a "start low, go slow" titration paradigm is strongly advised. Finally, the wide prediction interval for $HbA_{1c}$ reduction (-2.11% to 0.02%) underscores a fundamental clinical reality: while the average treatment effect is robust, the response in any individual patient with CKD can be highly variable (44). This variability necessitates personalized treatment approaches, meticulous monitoring and managed expectations to optimize outcomes and ensure safety in real-world practice. ❑

## CONCLUSIONS

This meta-analysis offers compelling evidence for the strong efficacy of retatrutide in enhancing glycemic management and supporting weight reduction among individuals with diabetes and/or obesity who also have chronic kidney disease. A notable observation from the findings was the dose-related response, where lower dosages were associated with more effective and stable reductions in $HbA_{1c}$, an important insight for treatment planning. Indications of possible kidney protection, evidenced by decreased albuminuria, highlight retatrutide's potential as a valuable treatment in managing the interconnected challenges of diabetes, obesity and renal impairment. Although the safety findings align with those of other incretin-based medications, treatment in CKD patients should include vigilant management of gastrointestinal adverse effects. Retatrutide marks considerable progress in available treatment options. However, further specialized trials are necessary to fully establish its benefits for kidney protection. ❑

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