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Triple Incretin Agonists in Diabetes Mellitus: Retatrutide Improves Lipid Profile and Decreases Blood Pressure

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ABSTRACT

This opinion article discusses the emerging potential of retatrutide, a triple incretin agonist, in managing lipid profiles and blood pressure in patients with diabetes mellitus. Retatrutide has shown promise in improving lipid parameters and lowering blood pressure in clinical trials, making it a valuable addition to the therapeutic arsenal for diabetes and its associated metabolic disorders. While its precise mechanisms remain to be fully elucidated, the observed benefits highlight its potential to challenge current paradigms in metabolic disease management. The evidence discussed herein, though compelling, requires further validation through larger and more diverse clinical studies.

Keywords: Retatrutide, dyslipidemia, diabetes mellitus, blood pressure

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INTRODUCTION

Diabetes mellitus has a global prevalence of 9.3% in adults, leading to 66.3 million disease-adjusted life-year loss (DALY) in 2019, with an approximate age-adjusted DALY increase of 27.6% since 1990.[1,2] Multiple therapeutic options are available in the management of diabetes mellitus. Nevertheless, incretin-based therapies gained clinical significance initially via the development of glucagon-like peptide (GLP)-1 agonists and dipeptidyl peptidase (DPP)-IV inhibitors for the treatment of hyperglycemia. Beyond single GLP1RA therapies, dual agonists such as tirzepatide, with agonistic activity on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, have been approved by the United States Food and Drug Administration in 2022 for the glycemic management of type 2 diabetes mellitus (T2D).[3] Besides their effectiveness in improving HbA1c, fasting plasma glucose level, and body weight, incretin-based therapies are also studied for their lipoprotein lipid changes and blood pressure improvements. Glucagon-like peptide-1 has a dual effect on adipocyte lipid metabolism by being lipogenic at low doses and lipolytic at higher doses. At the same time, GLP-1 receptor agonists have been shown to improve serum lipid profile by attenuating hepatic very low density lipoprotein (VLDL) production and impairing lipid metabolism.[4,5] Tirzepatide with dual agonistic activity on GLP-1 and GIP receptors was shown to induce superior outcomes in terms of weight loss, serum lipid profile, and blood pressure; in a meta-analysis, it was demonstrated to decrease systolic blood pressure, decrease total cholesterol, and increase HDL levels.[6-8] In addition to the enhancement of GLP-1 receptor effects, activation of the GIP receptor leads to increased blood flow and fat accumulation in white adipose tissue and a decline in the release of pro-inflammatory cytokines and chemokines.[9]

Glucagon-like peptide-1 agonists were also demonstrated to lower blood pressure.[10] Experiments on different mice models showed GLP-1 analogues increase

ANP-mediated natriuresis through the stimulation of atrial GLP-1R.[10] Moreover, another study on SHRs (spontaneously hypertensive rats) and Wistar rats found that blockage of GLP-1R signalling increased NHE3 (Na+/ H+ exchanger isoform 3) mediated sodium uptake in the proximal tubules and angiotensin II secretion from the kidney cortex.[11] Collectively, these results support the blood pressure-lowering effect of GLP-1R agonists. However, it is unclear whether the same mechanistic pathways are operational in humans.

More recently, a single-molecule triple agonist, retatrutide, has been investigated as a once-weekly glucose-lowering medication with agonistic activity for GLP-1, GIP, and, different from previously approved medications, glucagon receptor (GcgR) agonist.[12] Glucagon receptor is a 7-transmembrane G-protein coupled receptor that predominantly transmits glucagon into intracellular signal.[13] It is mainly expressed in the liver, although it is also found in the brain, heart, kidney, adipose tissue, and gastrointestinal tract. Glucagon receptor agonism is postulated to decrease food intake via GcgR-expressing hepatic vagal nerve afferents and direct action on the hypothalamic arcuate nucleus.[13] Besides, increased hepatic gluconeogenesis with GcgR agonism increases energy expenditure.[14] The GcgR has also been shown to be involved in PCSK9 stabilization, which plays a role in LDL receptor regulation.[15] The additional physiologic mechanisms of GcgR regulating energy homeostasis incorporate GcgR agonism to GLP-1 and GIP agonism.

We conducted a search using PubMed, Ovid, Web of Science, Scopus, and Cochrane Library using the keyword “retatrutide” without a publication date restriction. Randomized controlled trials studying retatrutide vs. a control group, reporting both lipid profile and blood pressure measurements, were included.

Baseline participant characteristics of age, sex, body mass index (BMI), HbA1c, blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were extracted. The blood pressure and lipid profile changes from baseline to follow-up, and confidence intervals with *P*-values compared to placebo, if available, were extracted.

MAIN POINTS

- A single-molecule triple agonist, retatrutide, has been investigated as a once-weekly glucose-lowering medication with agonistic activity for glucagon-like peptide (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and, different from previously approved medications, glucagon receptor agonists.
- Our findings reveal a favorable safety profile of retatrutide compared to current treatments, with fewer adverse effects, underlining its potential as a safer therapeutic option for CKD.
- The study elucidates retatrutide’s novel mechanism of action, offering insights into how it uniquely addresses underlying CKD pathophysiology.

Selection and Description of the Studies

Two double-blind, phase 2 randomized clinical trials on the effectiveness of retatrutide in obesity and T2DM were published in 2023. Rosenstock et al[16] investigated the efficacy and safety of retatrutide therapy over a 36-week treatment period in 281 adult T2D patients with HbA1c levels of 7.0-10.5% who had been treated with lifestyle changes and/or metformin therapy for at least 3 months. Jastreboff et al[17] investigated the efficacy of retatrutide in obesity over 48 weeks in patients with obesity (BMI = 37-40 kg/m^2) and excluded diabetic patients.

Effect of Retatrutide on Lipid Profile

Rosenstock et al[16] found that retatrutide has led to declines in serum LDL cholesterol levels by 6.24% to 12.54%, serum triglyceride levels by 9.76% to 35.02%, and serum total cholesterol levels by 7.0% to 14.83% at 36 weeks of follow-up (Figure 1A, 1C and 1D). They found nonsignificant changes in HDL cholesterol levels (Figure 1D). The decline in serum triglycerides only reached significance compared to placebo for the 8 mg slow escalation group (95% CI [−40.10, −13.18], *P* = .0006), for the 8 mg fast escalation group (95% CI [−38.02, −7.92], *P* = .0055), and for the 12 mg escalation group (95% CI [−39.13, −12.79], *P* = .0006) (Figure 1D). The decline in serum total cholesterol only reached significance compared to placebo for the 8 mg slow escalation group (95% CI [−22.24, −6.56], *P* = .0007) and for the 12 mg escalation group (95% CI [−20.98, −3.95], *P* = .0056) (Figure 1C). In contrast, changes in LDL cholesterol levels did not reach significance at any dose (Figure 1A). Jastreboff et al[17] found a remarkable decrease in fasting triglyceride levels (17.90-39.90%), LDL cholesterol (4.70-21.70%), and total cholesterol (4.50-17.80%) at the end of the 48 weeks of follow-up (Figure 1A, 1C, and 1D). They also observed a significant increase in HDL cholesterol levels (1.20-3.50%)[17] (Figure 1B).

Effect of Retatrutide on BP

Rosenstock et al[16] found that retatrutide led to a considerable decline in systolic blood pressure (−2.79 to −8.79 mm Hg) (Figure 2A). At the same time, such improvements only reached statistical significance compared to placebo for the 8 mg slow escalation group (95% CI [−14.50, −0.20], *P* = .0438), for the 8 mg fast escalation group (95% CI [−16.15, −3.35], p=0.0028), and for the 12 mg escalation group (95% CI [−15·29, −5·26], *P* < .0001) (Figure 2A).[16] Similarly, decrease in diastolic blood pressure (−1.64 to −3.89 mm Hg) only reached statistical significance compared to placebo for the 12 mg escalation group (95% CI [−5.35, −0.10], *P* = .0418) (Figure 2B).[16] Jastreboff et al[17] found that at the end of the 36-week follow-up period, a significant decrease in systolic blood pressure (4.80-8.80 mm Hg) and diastolic blood pressure (2.20-2.80 mm Hg) compared to placebo was observed (Figure 2A and B). Moreover, the effect

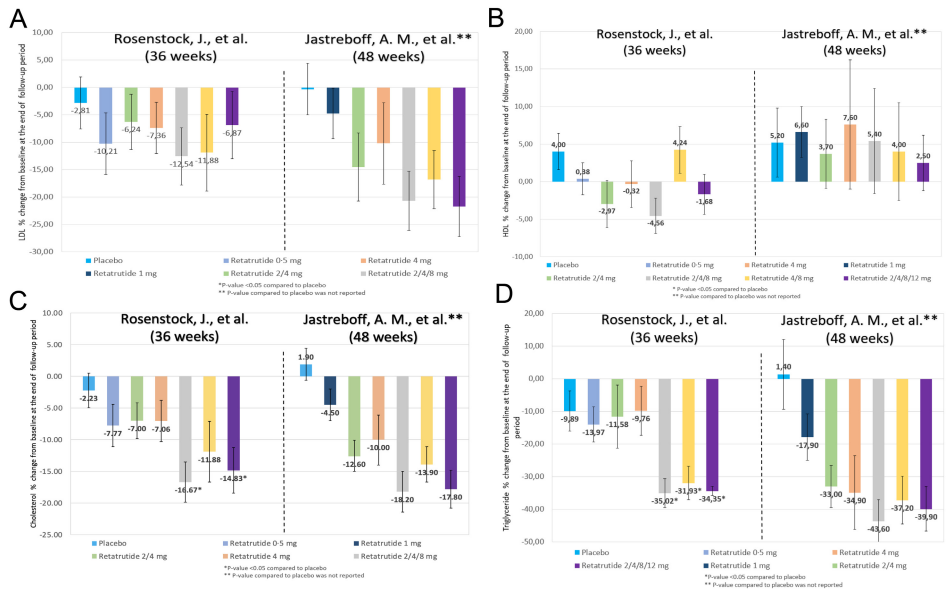

Figure 1. Figure 1A. The changes in LDL cholesterol at baseline and at the end of the follow-up period reported in seven trials with retatrutide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs. Figure 1B. The changes in HDL cholesterol at baseline and at the end of the follow-up period reported in seven trials with retatrutide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs. Figure 1C. The changes in total cholesterol at baseline and at the end of the follow-up period reported in 2 trials with retatrutide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs. Figure 1D. The changes in triglyceride at baseline and at the end of the follow-up period reported in 2 trials with retatrutide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs.

of retatrutide is dose-dependent, and improvements in blood pressure and lipid profile can be seen as early as the end of the 24 weeks.[17]

DISCUSSION

The phase 2 studies of retatrutide reveal that, apart from DM management and weight loss, it has significant potential to improve blood pressure and lipid profile. Even though the weight loss effect of the triple incretin receptor agonist retatrutide appears related to lower blood pressure and a better lipid profile, the exact underlying pathophysiological mechanisms of these new medications on blood pressure and lipid profile are unclear. Numerous mechanisms have been postulated based on their multiple agonist effects.[18]

Increases in glucagon can increase insulin resistance and gluconeogenesis. Therefore, glucagon antagonists were previously studied as treatments for T2D. However, clinical trials conducted with a glucagon antagonist (Bay 27-9955) demonstrated an increased risk of hepatosteatosis and hyperlipidemia.[19,20] These findings resulted in an appreciation of the role of glucagon in metabolism beyond the control of glycemia.[21] Conversely, glucagon receptor agonism may have beneficial effects on several metabolic processes. For instance, glucagon agonists promote lipolysis in the liver and adipose tissue via protein kinase A/phospholipase C signaling, the decline in appetite via an increase in c-Fos expression in the hypothalamus, increased thermogenesis, and downregulation of glycogen synthesis via protein kinase A signaling.[22-24] In a double-blind, cross-over, placebo-controlled study conducted over 10 weeks in overweight or obese patients without T2D, resting energy expenditure measured via indirect calorimetry increased with either glucagon alone or GLP-1 plus glucagon infusion.[25] Furthermore, phase 2 clinical trials investigating the effects of cotadutide therapy, a GLP-1/glucagon co-agonist, have demonstrated beneficial outcomes in terms of hepatosteatosis via upregulation of hepatic lipolysis and beta-oxidation.[26,27] The lipolytic properties of retatrutide therapy were also evident in the trial conducted by Rosenstock et al[16], demonstrating a significant decline in serum-free fatty acid levels and an increase in ketone bodies, namely beta-hydroxybutyrate. Moreover, induction of gluconeogenesis via glucagon agonists is correlated with the decline in serum levels of amino acids, especially in branched-chain amino acids such as leucine, isoleucine, and valine, and to a lesser degree in ketogenic amino acids.[16] Spolitu et al[15] demonstrated that GcgR signaling through the GcgR–Epac2–Rap1 pathway regulates PCSK9 degradation and, consequently, circulating LDL levels, which, different from other incretin-based therapies, could advance the role of retatrutide in metabolic profile.

The hemodynamic effect of glucagon signaling is not well studied, and current studies report inconsistent results.[28] Therefore, retatrutide's additional effect on blood pressure via GcgR agonism, apart from GLP-1 and GIP agonism, is not well understood yet. However, GcgR polymorphisms that cause loss of function

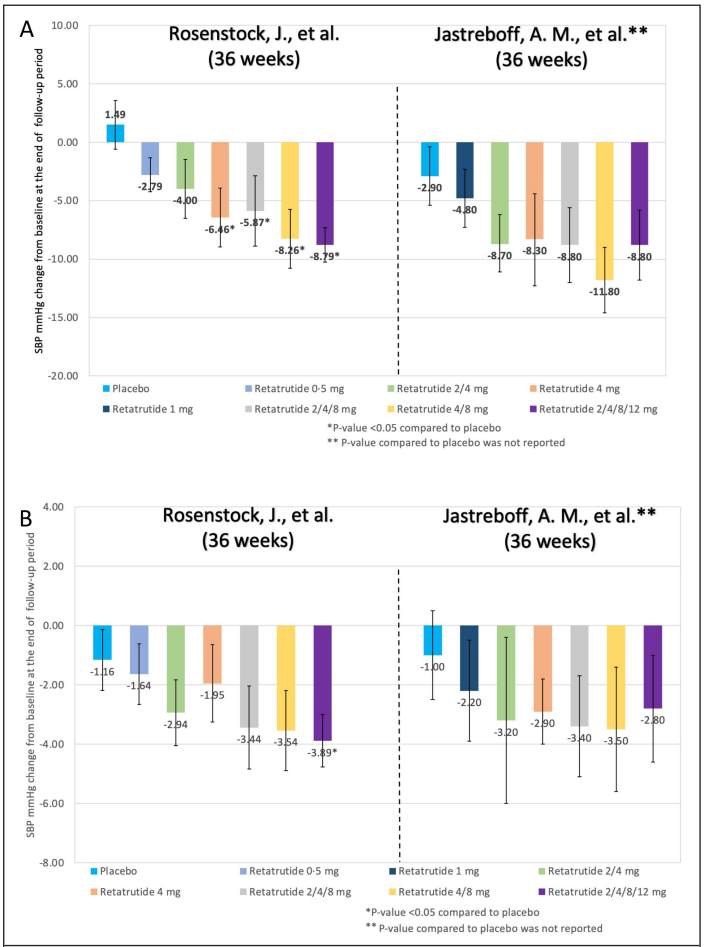

Figure 2. The changes in systolic blood pressure at baseline and at the end of the follow-up period reported in 2 trials with retatrutide are shown in the bar graph. The names of the trials and (the duration of their follow-up periods) are mentioned at the top of the graphs.

mutations are demonstrated to increase susceptibility to hypertension, possibly due to deprivation of glucagon's natriuretic effect.[29] Conversely, agonism of GcgR by retatrutide can further augment the natriuresis effect of glucagon, in addition to the beneficial effects of GLP-1 and GIP agonism.

CONCLUSION

Triple agonists such as retatrutide are promising therapeutic approaches in the management of T2D, obesity, metabolic syndrome, non-alcoholic fatty liver disease, and dyslipidemia. Multiple clinical trials (NCT05929066, NCT05929079, NCT05882045, NCT05936151, NCT05611957, NCT05916560) are being conducted to evaluate the efficacy of retatrutide therapy on body weight, glycemic control, kidney function, and cardiovascular health. The management of obesity, T2D, and its complications has been revolutionized by novel incretin therapies with steady progress in this field by shifting toward dual and triple agonists.

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REFERENCES

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 2019;157:107843. [CrossRef]
2. Safiri S, Karamzad N, Kaufman JS, et al. Prevalence, deaths and disability-adjusted-life-years (DALYs) due to type 2 diabetes and its attributable risk factors in 204 countries and territories, 1990-2019: results from the global burden of disease Study 2019. *Front Endocrinol (Lausanne)*. 2022;13:838027. [CrossRef]
3. Farzam K, Patel P. Tirzepatide. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2024; 1-3.
4. Villanueva-Peñacarrillo ML, Márquez L, González N, Díaz-Miguel M, Valverde I. Effect of GLP-1 on lipid metabolism in human adipocytes. *Horm Metab Res*. 2001;33(2):73-77. [CrossRef]
5. Patel VJ, Joharapurkar AA, Shah GB, Jain MR. Effect of GLP-1 based therapies on diabetic dyslipidemia. *Curr Diabetes Rev*. 2014;10(4):238-250. [CrossRef]
6. Copur S, Tanriover C, Yavuz F, Tuttle KR, Kanbay M. Tirzepatide and potential use for metabolically healthy obesity. *Eur J Intern Med*. 2023;113:1-5. [CrossRef]
7. Kanbay M, Copur S, Siriopol D, et al. Effect of tirzepatide on blood pressure and lipids: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2023;25(12):3766-3778. [CrossRef]
8. Copur S, Demiray A, Cherney D, Tuttle K, Kanbay M. Tirzepatide decreases systolic and diastolic blood pressure. *Eur J Intern Med*. 2023;114:135-137. [CrossRef]
9. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):410-421. [CrossRef]
10. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: a review of the evidence. *Curr Hypertens Rep*. 2016;18(2):16. [CrossRef]
11. Martins FL, Bailey MA, Girardi ACC. Endogenous activation of glucagon-like Peptide-1 receptor contributes to blood pressure control: role of proximal tubule Na(+)/H(+) exchanger Isoform 3, renal angiotensin II, and insulin sensitivity. *Hypertension*. 2020;76(3):839-848. [CrossRef]
12. Urva S, Coskun T, Loh MT, et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet*. 2022;400(10366):1869-1881. [CrossRef]
13. Novikoff A, Müller TD. The molecular pharmacology of glucagon agonists in diabetes and obesity. *Peptides*. 2023;165:171003. [CrossRef]

14. Kleinert M, Sachs S, Habegger KM, Hofmann SM, Müller TD. Glucagon regulation of energy expenditure. *Int J Mol Sci*. 2019;20(21):5407. [CrossRef]
15. Spolitu S, Okamoto H, Dai W, et al. Hepatic glucagon signaling regulates PCSK9 and low-density lipoprotein cholesterol. *Circ Res*. 2019;124(1):38-51. [CrossRef]
16. Rosenstock J, Frias J, Jastreboff AM, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *The Lancet*. 2023;402(10401):529-544.
17. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–hormone-receptor agonist retatrutide for obesity—A phase 2 trial. *N Engl J Med*. 2023;389(6):514-526. [CrossRef]
18. Coskun T, Urva S, Roell WC, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: from discovery to clinical proof of concept. *Cell Metab*. 2022;34(9):1234-1247.e9. [CrossRef]
19. Magnusson I, Rothman DL, Katz LD, Shulman RG, Shulman GI. Increased rate of gluconeogenesis in type II diabetes mellitus. A 13C nuclear magnetic resonance study. *J Clin Invest*. 1992;90(4):1323-1327. [CrossRef]
20. Cheng C, Jabri S, Taoka BM, Sinz CJ. Small molecule glucagon receptor antagonists: an updated patent review (2015-2019). *Expert Opin Ther Pat*. 2020;30(7):509-526. [CrossRef]
21. Lasher AT, Srivastava H, Sun LY. Insights into the role of glucagon receptor signaling in metabolic regulation from pharmacological inhibition and tissue-specific knockout models. *Biomedicines*. 2022;10(8). [CrossRef]
22. Parker JA, McCullough KA, Field BC, et al. Glucagon and GLP-1 inhibit food intake and increase c-fos expression in similar appetite regulating centres in the brainstem and amygdala. *Int J Obes (Lond)*. 2013;37(10):1391-1398. [CrossRef]
23. Galsgaard KD, Pedersen J, Knop FK, Holst JJ, Wewer Albrechtsen NJ. Glucagon receptor signaling and lipid metabolism. *Front Physiol*. 2019;10:413. [CrossRef]
24. Geary N, Le Sauter J, Noh U. Glucagon acts in the liver to control spontaneous meal size in rats. *Am J Physiol*. 1993;264(1 Pt 2): R116-R122. [CrossRef]
25. Tan TM, Field BC, McCullough KA, et al. Coadministration of glucagon-like peptide-1 during glucagon infusion in humans results in increased energy expenditure and amelioration of hyperglycemia. *Diabetes*. 2013;62(4):1131-1138. [CrossRef]
26. Ambery P, Parker VE, Stumvoll M, et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. *Lancet*. 2018;391(10140):2607-2618. [CrossRef]
27. Nahra R, Wang T, Gadde KM, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: a 54-week randomized phase 2b study. *Diabetes Care*. 2021;44(6):1433-1442. [CrossRef]
28. Petersen KM, Bøgevig S, Holst JJ, Knop FK, Christensen MB. Hemodynamic effects of glucagon: a literature review. *J Clin Endocrinol Metab*. 2018;103(5):1804-1812. [CrossRef]
29. Strazzullo P, Iacone R, Siani A, et al. Altered renal sodium handling and hypertension in men carrying the glucagon receptor gene (Gly40Ser) variant. *J Mol Med (Berl)*. 2001;79(10):574-580. [CrossRef]