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NEW ERA IN DIABETES AND OBESITY TREATMENT - THE EFFECTS OF GLP-1R, GIPR AND GCGR TRIAGONISTS

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ABSTRACT

Background: In recent years, the number of people affected by obesity or diabetes has increased dramatically. This growing prevalence resulted in an intensified interest in new methods to fight this problem. More and more drugs have emerged on the pharmaceutical market such as next-generation triagonists targeting glucagon-like peptide-1 (GLP-1R), glucose-dependent insulinotropic polypeptide (GIPR), and glucagon (GCGR) receptors.
Aim of the study: This article reviews the information about the effects of GLP-1R, GIPR, GCCR with particular emphasis on it being an obesity treatment, as well as the mechanisms, safety and potential therapeutic effect.
Scope of review: The goal of this review was to gather knowledge about the effect of GLP-1R, GIPR and GCGR triagonists in preexperimental and clinical studies.
Results: In experimental models triagonists successfully restricted weight gain and prevented hyperglycemia through promoting energy use and thermogenesis via the GCGR component. Triagonist NN1706 has shown to induce dose-dependent weight loss in early stages of clinical trials, however they also triggered specific adverse effects such as second degree atrioventricular blocks. In contrast, Retratrutide has shown an unprecedented clinical efficacy in phase 2 trials. After 48 weekends of a 12 mg dosage there was a 24.2% mean body weight reduction, a result comparable to bariatric surgery. Moreover 72% of prediabetic patients reverted to normoglycemia. Across all cohorts the most common adverse effects were gastrointestinal symptoms and temporary heart rate elevations.
Conclusion: GLP-1R/GIPR/GCGR triagonists represent a significant shift in obesity and type 2 diabetes mellitus (T2DM) management. Their effect extend beyond simple appetite suppression to accelerate
Their synergism extends beyond simple appetite inhibition for example to increase lipid metabolism, reduce fatty liver disease and accelerate energy expenditure. Clinical implementation will depend on confirming long-term safety in patients ongoing the stage 3 trials.
Further research is crucial to ensure the safety of this therapeutic option and confirm these findings.

KEYWORDS

Triple Receptor Agonists, GLP-1, GIP, Obesity Management, Weight Loss

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1. Introduction

The evolution of pharmacotherapy in type 2 diabetes mellitus (T2DM) over the last decade has been exponential, from the therapies based on drugs with potential hypoglycemic side effects to pharmacological agents that are not only safe but more effective (Davies et al., 2022; Nauck et al., 2021). Currently, it is crucial to underline the holistic effect of the therapy on metabolic and cardiovascular health. Metformin, as well as other classic hypoglycemic drugs still are an important element of therapy (Aroda & Ratner, 2018), however with more and more drugs (based on the incretin effect) we are leading towards the era in diabetology (Nauck, 2016). Currently, we are standing at the verge of another turn, from the single- and dual-receptor drugs to advanced and precise polipharmacotherapy with triagonists of glucagon-like peptide 1 receptor (GLP-1R), glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon (GCG) (Jakubowska et al., 2024).

Triagonism conception is based on the unique synergy of three diverse hormonal tracks. The first one, GLP-1R, is the base of incretin therapy, being responsible for the glucose-dependent insulin secretion, glucagon suppression and satiety induction (Ramracheya et al., 2018). The following one, GIPR, which was first marginalised is now a key component in optimisation of visceral and subcutaneous fat metabolism (Rudovich et al., 2007). It also helps with gastrointestinal tract tolerance on GLP-1 agonists (Hayes et al., 2021). The last component, GCGR, is the innovative chain of this triad. While it was traditionally associated with hiperglycemic effects, within this triad it catalyzes the energy expenditure by promoting thermogenesis and reduces hepatic steatosis (Nason et al., 2020).

The use of such molecular chimera is not only reserved for normoglycemic effects, but also for body mass reduction on the level, which was previously reserved for surgical interventions. In the era of global diabetes combined with obesity pandemic (Ruze et al., 2023), triagonists like retatrutide provide a fighting chance for life modifications, and in some the clinical remission.

This review provides the analysis on current knowledge of triagonists on metabolic parameters in animals and patients with diabetes. This work analyzes clinical data on their effectiveness and safety profile.

2. Materials and methods

2.1. Literature Search

Our search focused on the impact of GLP-1R, GIPR and GCGR triagonists on the metabolic outcomes of both animals and humans, including those and with accompanying conditions like obesity, prediabetes, or diabetes. Our systematic search was conducted of PubMed, SCOPUS and Embase databases on 22.04.2026. We searched the databases with the triagonists, GLP-1R, GIPR and GCGR agonists, retatrutide. These keywords were then associated with diabetes, diabetic, obesity, and overweight. Furthermore, we manually searched the reference list to check for any publications of interest. Our search focused on publications written in English.

2.2. Study Selection

We read the abstracts of all articles to assess their eligibility. We have rejected all studies showing the impact of any other treatment than triagonist therapy on the treatment outcome. Moreover, we rejected all studies that did not state which type of drug was used. In the following step, we excluded studies containing duplicate data or those from the basic sciences. The eligibility and relevance of retrieved articles were considered by two authors independently. All discrepancies were resolved by the authors consensus.

2.3. Data Collection Process

The data collection was carried out by using Microsoft Excel. This process was carried out by two authors, while another checked it for reliability. The file included data containing study treatment, characteristics and participant information. Any discrepancies were resolved by consensus between the authors.

3. Results

3.1 Evidence from Preclinical and Clinical Studies

Experimental studies can provide crucial insight to the way the glucagon and GLP-1 influence the patients. Different studies used a variety of mice including: male BKS-db/ db, winstar, diet- induced obesity (DIO), and western diet-fed C57Bl/6 mice.

Intraperitoneal injections of acyl-glucagon on db/ db mice resulted in such an increase in blood glucose levels, that it surpassed the detection threshold and didn't allow for a precise confirmation of change. The heterozygous Db/ + mice that were used as a control group had a significant elevation of blood glucose 30-minutes post- injection (Wu et al., 2024).

Acyl-glucagon treatment resulted in a significant decrease in liver glycogen levels in both db/db and db/+ mice. Db/db mice showed higher glycogen levels compared to control groups. Some liver metabolites (such as N- Acetylglucosamine 6-phosphate and 5-hydroxyindoleacetylglycine) have undergone more significant changes in db/db mice in comparison to db/+ mice. Db/ + mice had increased liver carnitine, hypotaurine and 50 -phosphoribosyl-N-formylglycinamide levels after the treatment, whereas db/db mice were not affected in these areas. Moreover db/+ mice had decreased liver amino acid levels (histidine and glutamine), in db/db mice such changes were not observed. Glutamic acid was lowered both in db/db and db/+ mice. The "purine metabolism" was increased in both groups. Several metabolites from purine metabolism (uric acid, inosine, deoxyinosine, xanthosine, and hypoxanthine) were decreased in db/+ mice. There weren't any significant changes in db/db mice in this area and the baseline was already lower Additionally some pathways such as "Taurine and Hypotaurine Metabolism" as well as in the "Amino Sugar Metabolism" were enriched in db/+ mice. Both db/db and db/+ groups had significantly increased "Glutamate Metabolism" (Wu et al., 2024).

The acyl- glucagon treatment increased phospho-PKA motif immunoreactivity in db/+ mice and even more significantly in db/db mice (Wu et al., 2024).

The acyl- glucagon injection did not impact serum triglycerides in db/db mice, whereas it reduced serum triglycerides in db/+ mice. The serum cholesterol levels were not affected in either group (Wu et al., 2024).

Acyl -glucagon treatment had more impact on db/ + mice, where it altered more metabolites. There were 90 changed metabolites in db/+ mice, compared to 42 in db/db mice. Responses to some typical glucagon-

regulated metabolites, such as cyclic adenosine monophosphate (cAMP), were attenuated in db/db mice compared to db/+ mice. This injection 29-fold increase in ureidosuccinic acid, which is a part of pyrimidine biosynthesis compared to db/+ vehicle treatment. The increase in db/db mice was only 4- fold. Likewise there was a 10-fold increase in sorbitol-6-phosphate (a monosaccharide phosphate) in db/+ mice and only 3- fold increase in db/db mice. This may dictate that ureidosuccinic acid and sorbitol-6-phosphate could be biomarkers for glucagon action.

Triagonist consisting of GLP-1R, GIPR and GcgR, have prevented excessive weight gain in db/db that happened in the vehicle- treated mice. None of the treatments altered the food intake. Moreover, the triagonist prevented from fasting hyperglycemia at both doses that were tested. The treatment was successful in lowering the glucose intolerance and maintaining the correct islet architecture (Finan et al., 2015).

In a dose dependent matter, the triagonist had promising results in in Zucker diabetic

fatty (ZDF) rats. It improved body weight, fasting blood glucose, increased glucose tolerance and HbA1c levels. These effects have lasted up to 3 weeks in the high- dose group (Finan et al., 2015).

In DIO mice the triagonist treatment resulted in a decreased body weight by 22.8%. However the sequence-matched coagonist reduced body weight by 14.9% (Finan et al., 2015).

NN1706 is a second-generation triagonist created differently in order to preserve strong GLP-1R and GIPR agonism while intentionally reducing glucagon receptor (GcgR) potency. Injection with this treatment resulted in dose-dependent body weight loss in DOI mice. There was an improvement in glucose tolerance compared to the vehicle, reduction in acute food intake and in postprandial glucose insulin levels relative to vehicle and liraglutide. NN1706 administration on winstar rats has resulted in an increased heart rate and in mean blood pressure after the injection (Finan et al., 2025).

3.2 Clinical evidence

Clinical studies have been conducted to further verify the effects of acyl- glucagon, triagonist and NN1706 on the human body.

A single ascending dose, randomized, double blind, single-center, placebo-controlled study about the influence NN1706 has on the human body has been made with different doses: 5, 15, 50, 150, and 300 μg.

The biggest change in mean body weight was observed at 150 μg of NN1706 (2.2%). A decrease in fasting blood plasma was seen in all the doses. There was an increase in fasting insulin and fasting C-peptide levels at all doses except for the 5μg. A dose-dependent elevation in heart rate was noticed in the 50μg and 150 μg group 48 hours after dosing.

Emergent adverse effects were noticed in 38.2% of participants most of them were gastrointestinal origin. There were no deaths or serious adverse effects. There was a correlation between the increased dose and increased number of adverse effects.

Another study was conducted with the use of multiple ascending dose (MAD), randomized, double-blind within cohorts, single-center, placebo-controlled. Patients were either overweight or obese but without type 2 diabetes. The planned doses were: 25 (C1), 60 (C2), 150 (C3), 300 (C4), and 600 mg (C5). Three cases of second degree atrioventricular (AV) block were reported in three participants under the 150 ug dose, thus the dose was changed. The committee decided to to stop treatment in the 150-mg cohort (C3) and adjust dosing for the 300-mg cohort (C4) to 100 mg and repeat 150 mg dosing in the 600-mg cohort (C5). The greater the dose, the bigger weight loss was observed. The change in weight in the 100 and 150 ug group was significant and did not plateau after the 10- week period. There was not a deterioration in OGTT in the NN1706 vs placebo. Adverse effects were reported in 93% of patients, 311 events occurred, 84% of these reports could be related to the treatment. No deaths or serious events were reported. Most of the effects were gastrointestinal. Fasting levels of beta-hydroxybutyrate progressively increased during the treatment, but went down to baseline after 2 weeks. Fasting total cholesterol and triglycerides were decreased after the start of the treatment, but went up later (Finan et al., 2025).

Building upon earlier experimental triagonists such as NN1706, Retatrutide represents a clinically optimized next-generation GLP-1/GIP/glucagon receptor triagonist with a more refined balance of receptor agonism. Unlike NN1706, retatrutide retains a more pronounced glucagon receptor component aimed at enhancing energy expenditure and body weight reduction.

A phase 2, double-blind, randomized, placebo-controlled study that was dose dependent showed promising results. The biggest mean change in weight (−17.9%)was in the 8-mg group with an initial dose of 4 mg at week 24. At 48 weeks the biggest change (−24.2%) was in the 12-mg group with an initial dose of 2 mg, as compared with −2.1% in the placebo group. After 48 weeks 64 to 100% participants have lost weight

of at least 5%, while in the placebo group the percentage was 27%. Participants who were treated with Retatrutide had a higher chance of losing 10% or more and 15% or more of their body-weight. Mean changes in waist circumference ranged from −6.5 cm to −19.6 cm compared to -2,6cm in placebo. The 12-mg retatrutide dosage resulted in 26% of the participants having a body-weight reduction of 30% or more. The treatment improved cardiovascular parameters including systolic and diastolic blood pressure and levels of glycated hemoglobin, fasting glucose, insulin, and lipids (with the exception of high-density lipoprotein) at 24 and 48 weeks. At 48 weeks, 72% of the participants who were baseline prediabetic had reverted to normoglycemia (glycated hemoglobin level, <5.7%) compared with the 22% in the placebo group. Adverse effects were reported in 70% of the placebo group and 73 to 94% in the treated group. Highest incidents were in the 8mg and 12mg groups. Discontinuance of treatment happened in 6 to 16% of patients with adverse effects after retatrutide. Gastrointestinal problems such as nausea, diarrhea, vomiting, and constipation were the main culprit. Cardiac arrhythmias that were reported were mild to moderate in severity (Jastreboff et al., 2023).

4. Discussion

This review uptakes the attempt to systematize current knowledge on GLP-1R, GIPR and GCGR triagonist in the treatment of diabetes and obesity. Collected material of both preclinical, as well as first clinical studies, shows a great potential in the treatment of these diseases of this drug class, however it concurrently shows a number of challenges, which need to be addressed.

Results obtained in animal models provide valuable information on the triagonist mechanisms, which need to be interpreted with caution. Administration of acyl-glucagon in db/db mice inducted a significantly weaker response than in heterozygous db/+ mice (Ahlkvist et al. 2016). This covered not only the change in cAMP concentration, but also hepatic metabolites profile. This dependence suggests that both insulin resistance and chronic hyperglycemia can significantly weaken GCGR signaling, which is an important translational issue (Ahlkvist et al. 2016). Patients with advanced T2DM can demonstrate adverse responses to the glucagon triagonist component than patients with correct glucose tolerance. It is worth underlining the fact that Ureidosuccinate and Sorbitol-6-phosphate, showed a great potential as glucagon function biomarkers, which could find a place in the future to monitor the effectiveness of this treatment.

Triagonist use in db/db mice and ZDF rats showed clear antihyperglycaemic effect and it prevented increase in body mass irrespective of food intake (Conceição-Furber et al., 2022). This fact distinguishes this mechanism from simple appetite braking and suggests participation of thermogenesis and increased energy expenditure induced by the GCGR component of triagonists. Body mass reduction of 22,8% in DIO mice compared to 14,9% with the use of co-agonists clearly indicates an additive role of GCGR activation in the slimming effect. This observation provides a strong argument for the triple receptor therapeutic approach.

NN1706 is an interesting piece of engineering trying to tune up triagonism. It deliberately tries to lessen the activity of GCGR with preserved strong GLP-1R and GIPR activity. SAD study results show an acceptable safety profile with predominance of mild adverse effects, mainly gastrointestinal. This is a phenomenon which is normally described for GLP-1R agonist usage and is nothing surprising. Important safety signals are three cases of second-degree atrioventricular block in MAD study in 150 μg use group. These cases forced the modification of the protocol and gives questions on triagonists impact on the cardiac conduction system. An increase in heart rate was observed not only in Wistar rats, but also in clinical study, which is a phenomenon requesting immediate attention (Lorenz et al., 2017). This effect is known for GLP-1R agonists, however an additional GCGR activation, given the chronotropic effects of glucagon, can potentially enhance the given effect. MAD study results show durable therapeutic effect on body mass reduction given no plateau phase after 10 weeks of both 100 and 150 μg dosage groups.

Out of all analyzed drugs retatrutide is possibly the closest to reach the actual clinical appliance. Body mass reduction of 24,2% after 48 weeks of therapy in a 12 mg group is a result comparable to bariatric surgery effects (Hanipah et al., 2023). This could be a potential turn in obesity pharmacotherapy. For comparison, semaglutide, which was one of the most effective drugs in this class, reached 15-17% body mass reduction in STEP 1 study (Wilding et al., 2021). Tirzepatide, dual GLP-1R/GIPR agonist, reache] the result of 22,5% body mass reduction in SURMOUNT-1 study (Jastreboff et al., 2022). Retatrutide results overcome those shown by comparable drugs and extend accessible standards of care.

Equally important is the observation that 72% of patients with initial prediabetes reached normoglycaemia state after 48 weeks of therapy. This opens a discussion about diabetes remission in pharmacological context. This intervention was previously reserved only for bariatric surgery. Improvement

in key parameters such as, blood pressure, HbA1c, fasting glucose and lipids is a confirmation of holistic therapeutic effect described in introduction.

Retatrutide's safety profile is a key issue demanding further observation. Adverse effects were present in 73-94% of treated patients and in 6-16% of them was the reason for therapy termination. Dominant gastrointestinal adverse effects such as nausea, diarrhea, vomiting and constipation fit into characteristics of GLP-1R agonist group (Gorgojo-Martínez et al., 2022). However, their high frequency in the higher dose groups constitutes a significant practical limitation. Mild to moderate cardiac arrhythmias did not require therapy discontinuation. They do, though, confirm the need for cardiac monitoring in ongoing phase 3 studies.

One of the key conclusions coming from this review is a confirmation that the clinical effect of triagonists is not from addiction, but from synergic interaction between three separate hormonal tracks.

GLP-1R component assures basic glycemic control and satiety. GIPR component, which was for long underrated due to its weakened insulinotropic effect in type 2 diabetes (T2D), contributes by a beneficial effect on the metabolism of fat tissue. Moreover, it may alleviate gastro-intestinal symptoms induced by GLP-1R agonism, which could potentially improve treatment tolerance (Hayes et al., 2021). GCGR component, traditionally associated with hyperglycemic effect of glucagone, in triagonists plays a different role - it speeds energy expenditure, stimulates thermogenesis and reduces hepatic steatosis through increased fatty acid oxidation and inhibition of de novo lipogenesis (Nason et al., 2020).

The complexity of this mechanism is at the same time a challenge. An optimal balance of activity of different hormonal pathways can differ among patients depending on metabolic profile. This problem implicates the necessity of personalized therapy.

5. Limitations and further directions

Future perspectives look fairly promising to glucagon and triagonist therapies. Preclinical and clinical studies discussed in this work prove that these therapies can significantly improve glycemic control, reduce body weight, and positively influence lipid metabolism. Moreover there could be various metabolic benefits for patients with obesity or type 2 diabetes.

It is necessary to point out several significant limitations of the analyzed research material. Firstly, there is only data from phase 1 and 2 studies, which means there is still limited data regarding long-term effects of body mass reduction durability and overall safety.

Further studies about glucagon and triagonists need to be conducted in order to develop the best approach to diabetic patients. Research should focus on how to minimize the adverse effects and to find a balance between the benefits and disadvantages. Studies involving NN1706 and retatrutide had shown elevated heart rate or arrhythmias, thus it is crucial to ensure the safety of the treatment before a global implementation. Further studies need to investigate the reduced response in diabetic models, particularly db/db mice.

Finally, bigger and longer studies need to be conducted to analyse durability of the weight loss, possibility of type 2 diabetes remission and long- term effects on the cardiovascular system. There is a need for studies analogous to LEADER, SUSTAIN-6 or EMPA-REG, which were specially designed studies aiming to analyze the effect of other drugs on the cardiovascular system.

Further studies should also focus on other potential illnesses apart from diabetes and obesity such as MASLD/MASH in which triagonists, thanks to the GCGR component could play a groundbreaking role. The results from Retatrutide are promising and may become a major breakthrough in the management of obesity and type 2 diabetes in the coming years.

6. Summary

GLP-1R/GIPR/GCGR triagonists represented mostly through retatrutide are the next logical step in the evolution of the pharmacotherapy in both diabetes and obesity. Their profile combining glycemic control, body mass reduction (at the level of bariatric surgery) and multidimensional metabolic effect can significantly change the approach for the treatment of these illnesses. However before their broad clinical implementation there is a need for broad phase 3 study trials verifying their long-term safety, with particular emphasis on the cardiovascular effects. There is also a need for the identification of the group of patients benefiting the most from this form of therapy.

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REFERENCES

1. Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., . . . Buse, J. B. (2022). Management of hyperglycaemia in type 2 diabetes, 2022: A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia, 65*(12), 1925–1966.
2. Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. *Molecular Metabolism, 46*, Article 101102.
3. Aroda, V. R., & Ratner, R. E. (2018). Metformin and type 2 diabetes prevention. *Diabetes Spectrum, 31*(4), 336–342.
4. Nauck, M. (2016). Incretin therapies: Highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes, Obesity and Metabolism, 18*(3), 203–216.
5. Jakubowska, A., le Roux, C. W., & Viljoen, A. (2024). The road towards triple agonists: Glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and glucagon receptor—An update. *Endocrinology and Metabolism, 39*(1), 12–22.
6. Ramracheya, R., Chapman, C., Chibalina, M., Dou, H., Miranda, C., González, A., . . . Briant, L. J. (2018). GLP-1 suppresses glucagon secretion in human pancreatic alpha-cells by inhibition of P/Q-type Ca^{2+} channels. *Physiological Reports, 6*(17), Article e13852.
7. Rudovich, N., Kaiser, S., Engeli, S., Osterhoff, M., Gögebakan, Ö., Blüher, M., & Pfeiffer, A. F. (2007). GIP receptor mRNA expression in different fat tissue depots in postmenopausal non-diabetic women. *Regulatory Peptides, 142*(3), 138–145.
8. Hayes, M. R., Borner, T., & De Jonghe, B. C. (2021). The role of GIP in the regulation of GLP-1 satiety and nausea. *Diabetes, 70*(9), 1956–1961.
9. Nason, S. R., Kim, T., Antipenko, J. P., Finan, B., DiMarchi, R., Hunter, C. S., & Habegger, K. M. (2020). Glucagon-receptor signaling reverses hepatic steatosis independent of leptin receptor expression. *Endocrinology, 161*(1), Article bqz013.
10. Ruze, R., Liu, T., Zou, X., Song, J., Chen, Y., Xu, R., . . . Xu, Q. (2023). Obesity and type 2 diabetes mellitus: Connections in epidemiology, pathogenesis, and treatments. *Frontiers in Endocrinology, 14*, Article 1161521.
11. Wu, Y., Chan, A. Y., Hauke, J., Htin Aung, O., Foollee, A., Cleofe, M. A. S., Stölting, H., Han, M. L., Jeppe, K. J., Barlow, C. K., Okun, J. G., Rusu, P. M., & Rose, A. J. (2024). Variable glucagon metabolic actions in diverse mouse models of obesity and type 2 diabetes. *Molecular Metabolism, 90*, Article 102064. https://doi.org/10.1016/j.molmet.2024.102064
12. Finan, B., Yang, B., Ottaway, N., Smiley, D. L., Ma, T., Clemmensen, C., . . . Tschöp, M. H. (2015). A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nature Medicine, 21*(1), 27–36.
13. Finan, B., Douros, J. D., Goldwater, R., Hansen, A. M. K., Hjerpsted, J. B., Hjøllund, K. R., Kankam, M. K., Knerr, P. J., Konkar, A., Mowery, S. A., Müller, T. D., Nielsen, J. R., Nygård, S. B., Perez-Tilve, D., Raun, K., Yang, B., Tschöp, M. H., & DiMarchi, R. D. (2025). A once-daily GLP-1/GIP/glucagon receptor tri-agonist (NN1706) lowers body weight in rodents, monkeys and humans. *Molecular Metabolism, 96*, Article 102129. https://doi.org/10.1016/j.molmet.2025.102129
14. Jastreboff, A. M., Kaplan, L. M., Frías, J. P., Wu, Q., Du, Y., Gurbuz, S., Coskun, T., Haupt, A., Milicevic, Z., Hartman, M. L., & Retatrutide Phase 2 Obesity Trial Investigators. (2023). Triple-hormone-receptor agonist retatrutide for obesity—A phase 2 trial. *The New England Journal of Medicine, 389*(6), 514–526. https://doi.org/10.1056/NEJMoa2301972
15. Ahlkvist, L., Omar, B., Valeur, A., Fosgerau, K., & Ahrén, B. (2016). Defective insulin secretion by chronic glucagon receptor activation in glucose-intolerant mice. *Journal of Endocrinology, 228*, 171–178.
16. Conceição-Furber, E., Coskun, T., Sloop, K. W., & Samms, R. J. (2022). Is glucagon receptor activation the thermogenic solution for treating obesity? *Frontiers in Endocrinology, 13*, Article 868037.
17. Lorenz, M., Lawson, F., Owens, D., Raccah, D., Roy-Duval, C., Lehmann, A., . . . Blonde, L. (2017). Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovascular Diabetology, 16*(1), Article 6.
18. Hanipah, Z. N., Rubino, F., & Schauer, P. R. (2023). Remission with an intervention: Is metabolic surgery the ultimate solution? *Endocrinology and Metabolism Clinics, 52*(1), 65–88.
19. Wilding, J. P., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., . . . Kushner, R. F. (2021). Once-weekly semaglutide in adults with overweight or obesity. *The New England Journal of Medicine, 384*(11), 989–1002.
20. Jastreboff, A. M., Aronne, L. J., Ahmad, N. N., Wharton, S., Connery, L., Alves, B., . . . Stefanski, A. (2022). Tirzepatide once weekly for the treatment of obesity. *The New England Journal of Medicine, 387*(3), 205–216.
21. Gorgojo-Martínez, J. J., Mezquita-Raya, P., Carretero-Gómez, J., Castro, A., Cebrián-Cuenca, A., de Torres-Sánchez, A., . . . Rubio-Herrera, M. Á. (2022). Clinical recommendations to manage gastrointestinal adverse events in patients treated with GLP-1 receptor agonists: A multidisciplinary expert consensus. *Journal of Clinical Medicine, 12*(1), Article 145.
22. Hayes, M. R., Borner, T., & De Jonghe, B. C. (2021). The role of GIP in the regulation of GLP-1 satiety and nausea. *Diabetes, 70*(9), 1956–1961. https://doi.org/10.2337/dbi21-0004
23. Nason, S. R., Kim, T., Antipenko, J. P., et al. (2020). Glucagon-receptor signaling reverses hepatic steatosis independent of leptin receptor expression. *Endocrinology, 161*(1), Article bqz013. https://doi.org/10.1210/endocr/bqz013