# compare GLP1's semaglutide vs tirzepatide vs retatrutide in VAT reduction

Semaglutide, tirzepatide, and retatrutide all substantially reduce visceral adipose tissue (VAT), but the strongest VAT effects track with overall potency for weight loss: semaglutide < tirzepatide < retatrutide, based on currently available imaging and body-composition data.[1] [2] [3]

## Mechanisms and implications for VAT

- Semaglutide: selective GLP-1 receptor agonist; reduces appetite and slows gastric emptying, driving weight and VAT loss.[4] [5]
- Tirzepatide: dual GIP/GLP-1 agonist; produces greater weight and fat loss than semaglutide, with exploratory data suggesting a **targeted** effect on visceral and liver fat beyond what weight loss alone would predict.[3] [1]
- Retatrutide: triple GIP/GLP-1/glucagon agonist; yields the largest average weight loss in trials so far, with marked reductions in abdominal VAT and liver fat, consistent with a strong effect on ectopic fat depots.[2] [6] [4]

## Quantitative VAT and fat-mass data

Direct head-to-head VAT imaging data are limited, so comparison relies on within-trial body-composition substudies and imaging:

- Semaglutide
  - CT-based series in real-world patients show meaningful declines in VAT area alongside weight loss; for example, one cohort showed a reduction in visceral adipose tissue area from about 341 $cm^2$ to 309 $cm^2$ in the weight-loss subgroup.[7]
  - Narrative reviews and trial analyses indicate VAT tends to shrink proportionally more than subcutaneous fat, with double-digit percentage VAT reductions over months vs minimal change on placebo.[8] [5]
- Tirzepatide
  - SURMOUNT-1 DXA substudy: visceral fat mass decreased by about 40% with tirzepatide vs about 7% with placebo (estimated treatment difference roughly –33 percentage points).[1]
  - SURPASS-3 MRI: exploratory analyses show significant reductions in visceral fat and liver fat “z-scores,” suggesting a possible preferential effect on central/ectopic fat compared with the magnitude of weight loss.[3]

- Retatrutide
  - Phase 2 obesity study: at 48 weeks, retatrutide 8–12 mg produced weight loss around 22.8–24.2%, with significant reductions in abdominal VAT and abdominal subcutaneous adipose tissue vs placebo.[2]
  - MASLD/MASH substudy: very large reductions in liver fat and high rates (>85%) of steatosis resolution, consistent with robust mobilization of ectopic fat; abdominal VAT was significantly reduced at all studied doses.[6] [2]

### Weight-loss–anchored comparison

Because VAT scales with weight loss, a practical way to compare is by maximum weight-loss efficacy (high dose, obesity trials without diabetes):

| Drug | Receptors targeted | Max reported mean weight loss (obesity trials) | Reported visceral/ectopic fat findings (qualitative) |
|---|---|---|---|
| Semaglutide | GLP-1 | ~15–17% at ~68 weeks. [4] [9] | Clear VAT reduction; CT and reviews show meaningful VAT area drop and relatively greater visceral vs subcutaneous fat loss. [7] [8] [5] |
| Tirzepatide | GLP-1 + GIP | ~20–22.5% at ~72 weeks. [4] [9] [1] | ~40% reduction in visceral fat mass on DXA; MRI data suggest targeted visceral and liver fat reduction beyond weight loss expectation. [1] [3] |
| Retatrutide | GLP-1 + GIP + glucagon | ~22–24% at 48 weeks; up to ~28–29% at 68 weeks in later trials. [4] [9] [2] | Significant reductions in abdominal VAT and ASAT with very large liver fat reductions and high steatosis resolution rates. [2] [6] |

Overall, for VAT reduction per patient, tirzepatide already shows larger proportional visceral fat loss than placebo and greater total fat loss than semaglutide, while early retatrutide data indicate at least comparable, and likely greater, VAT and ectopic fat reductions in line with its higher total weight loss. Direct, head-to-head imaging studies comparing all three on VAT specifically have not yet been published, so current inferences are based on separate trials and should be interpreted accordingly.[10] [11] [9] [12] [13] [4] [6] [1] [2] [3]

⁂

# Does retatrutide's glucagon receptor activation uniquely target ectopic fat

Current data do not show that retatrutide's glucagon receptor activation *uniquely* targets ectopic fat, but glucagon activity likely contributes disproportionately to its strong liver and visceral fat reductions when combined with GLP-1 and GIP agonism.[16] [17] [18]

### What glucagon activation does

- Glucagon receptor activation increases hepatic fatty-acid oxidation, raises energy expenditure, and promotes lipolysis of stored fat, especially in the liver.[19] [18] [16]
- In retatrutide, this glucagon signal is intentionally "moderate" so that energy mobilization and fat burning rise without excessive hyperglycemia.[18] [19]

### Evidence in retatrutide trials

- In the phase 2 MASLD/MASH trial, retatrutide produced up to ~82–86% relative liver fat reduction at higher doses, with most of the drop occurring in the first 24 weeks.[17] [20] [18]
- Reductions in liver fat were significantly related to decreases in body weight, abdominal subcutaneous fat, and visceral adipose tissue, suggesting a strong but *not exclusive* effect on ectopic depots.[17] [18]
- β-hydroxybutyrate levels increased 2–3-fold in a dose-related fashion, consistent with enhanced whole-body and hepatic fat oxidation driven in part by glucagon receptor activation.[18]

### Is the effect "unique" to glucagon?

- GLP-1 receptor agonists alone already reduce VAT and liver fat, and meta-analyses do not show strict selectivity for VAT over subcutaneous fat; changes largely track with weight loss.[21] [22]
- Triple agonists (GLP-1/GIP/glucagon) and GLP-1/glucagon dual agonists as a class show some of the largest liver fat reductions reported, implying that glucagon signaling amplifies ectopic fat clearance when layered onto GLP-1/GIP.[23] [17] [18]
- However, current human data cannot cleanly separate "glucagon-specific" targeting from overall higher weight loss and energy expenditure; the liver and visceral benefits appear **enhanced**, but not proven to be uniquely targeted, by glucagon receptor activation.[19] [23] [17] [18]

⁂

# How does the GIP/GLP-1 receptor ratio affect VAT loss in tirzepatide

Evidence suggests tirzepatide's **GIP-dominant** profile enhances adipose-tissue effects and VAT reduction versus pure GLP-1 agonism, but there are no human data that quantify "optimal" GIP:GLP-1 ratio for VAT specifically; the link is mechanistic and inferential rather than directly measured.[31] [32] [33] [34]

## What the GIP>GLP-1 bias looks like

- Tirzepatide is an "imbalanced" dual agonist: it has near-native affinity and potency at the GIP receptor, but about 5-fold lower affinity and ~20-fold lower potency at the GLP-1 receptor compared with native GLP-1.[32] [33]
- In receptor-occupancy models, pharmacodynamic readouts show higher and more sustained engagement of GIPR than GLP-1R at clinical doses, by design.[35] [32]

## GIP signaling in adipose tissue

- GIP receptors are expressed in white adipose tissue, including visceral depots, where GIPR agonism modulates nutrient handling.[36] [34] [35]
- Long-acting GIPR agonists (and tirzepatide-like molecules) in human adipocytes and mouse models enhance insulin signaling and glucose uptake in the fed state, increase conversion of glucose to glycerol, and reduce circulating triglycerides during lipid challenge, while promoting lipolysis when insulin is low.[37]
- In obese mouse models, tirzepatide improves insulin sensitivity partly through adipose-specific effects, with enhanced insulin-stimulated glucose uptake in white adipose tissue even when GLP-1R is absent, implicating GIPR-driven adipose actions.[36]

## Links to VAT and ectopic fat loss

- Clinical body-composition data show tirzepatide produces larger reductions in total fat mass and VAT than placebo and greater fat-mass loss than GLP-1-only drugs given over similar durations.[31]
- Mechanistic reviews interpret this as GLP-1 providing strong appetite suppression and central effects, while GIPR activation improves adipose-tissue function (nutrient trapping in fed state, more efficient lipid mobilization when fasting), which may favor loss of metabolically active, insulin-resistant depots such as VAT and ectopic fat.[34] [38] [35] [31]

## What is not yet known

- No published human data systematically vary the GIP:GLP-1 receptor potency ratio in tirzepatide-like molecules to map VAT changes against that ratio, so we cannot say "more GIP" or "more GLP-1" linearly increases VAT loss.[39] [40] [31]
- Current interpretation is that a GIP-dominant ratio allows higher dosing (less GLP-1–driven GI intolerance) and leverages GIP's adipose-tissue actions, yielding greater overall fat and VAT loss than GLP-1 alone, but the specific contribution of the ratio vs total receptor engagement and weight loss magnitude remains unresolved.[41] [42] [32] [31]

⁂


1. https://pmc.ncbi.nlm.nih.gov/articles/PMC11965027/
2. https://www.nature.com/articles/s41591-024-03018-2
3. https://www.bariatricnews.net/post/tirzepatide-associated-with-a-potential-targeted-effect-on-visceral-fat-and-liver-fat

4. https://lolahealth.com/blogs/longevity/retatrutide-vs-semaglutide-comparison
5. https://www.philadelphialiposuction.com/surgery/semaglutide-induced-redistribution-of-adipose-tissue-and-its-impact-on-body-composition-and-clinical-outcomes/
6. https://www.aasld.org/the-liver-meeting/triple-hormone-receptor-agonist-retatrutide-resolves-steatosis-85-subjects-masld
7. https://www.auntminnie.com/clinical-news/ct/article/15683619/ct-shows-body-composition-changes-in-patients-treated-with-ozempic
8. https://pubmed.ncbi.nlm.nih.gov/39230989/
9. https://www.joinvoy.com/blog/retatrutide-vs-tirzepatide-vs-semaglutide
10. https://pubmed.ncbi.nlm.nih.gov/41723268/
11. https://thennt.com/nnt/efficacy-of-tirzepatide-retatrutide-and-semaglutide-for-weight-loss-in-obese-individuals-without-diabetes/
12. https://iapam.com/medical-weight-management-library/retatrutide-vs-tirzepatide
13. https://tideslabaustralia.com.au/blogs/tides-lab-australia-education/peptides-for-weight-loss
14. https://www.joinmidi.com/post/tirzepatide-vs-retatrutide
15. https://www.sciencedirect.com/science/article/pii/S2213858725000270
16. https://www.droracle.ai/articles/879779/what-are-the-mechanisms-of-action-of-retatrutide-a
17. https://pmc.ncbi.nlm.nih.gov/articles/PMC11271400/
18. https://www.nature.com/articles/s41591-024-03018-2
19. https://synapse.patsnap.com/article/what-is-the-mechanism-of-action-of-retatrutide
20. https://gertitashkomd.com/retatrutide-a-triple-agonist-shaping-the-future-of-metabolic-care/
21. https://pmc.ncbi.nlm.nih.gov/articles/PMC9262225/
22. https://www.sciencedirect.com/science/article/abs/pii/S1056872724000692
23. https://www.nature.com/articles/s41366-024-01473-y
24. https://pmc.ncbi.nlm.nih.gov/articles/PMC12026077/
25. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01053-X/abstract
26. https://www.infiniskin.com/blog/retatrutide-mechanism-clinical-evidence-dosage/
27. https://lolahealth.com/blogs/longevity/what-is-retatrutide
28. https://www.sciencedirect.com/science/article/abs/pii/S2468125322003387
29. https://blogs.oregonstate.edu/footprint/start/?id=how-retatrutide-changes-metabolism-realistic-results-after-6-months
30. https://www.joinvoy.com/blog/how-retatrutide-works
31. https://www.explorationpub.com/Journals/eemd/Article/101452
32. https://insight.jci.org/articles/view/140532
33. https://pmc.ncbi.nlm.nih.gov/articles/PMC7526454/
34. https://pmc.ncbi.nlm.nih.gov/articles/PMC9438179/
35. https://www.pnas.org/doi/10.1073/pnas.2116506119

36. https://www.jci.org/articles/view/146353
37. https://pubmed.ncbi.nlm.nih.gov/38878772/
38. https://synapse.patsnap.com/article/what-is-the-mechanism-of-action-of-tirzepatide
39. https://www.sciencedirect.com/science/article/pii/S0003426624000763
40. https://onlinelibrary.wiley.com/doi/10.1155/2023/5891532
41. https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2022.1004044/full
42. https://pmc.ncbi.nlm.nih.gov/articles/PMC10697893/
43. https://pmc.ncbi.nlm.nih.gov/articles/PMC12361993/
44. https://www.ncbi.nlm.nih.gov/books/NBK585056/
45. https://www.nature.com/articles/s41366-026-02025-2