



## GLP1 find the recent study on the effect of increasing cartilage thickness

The study getting all the attention right now is a small semaglutide trial reporting roughly a 17% increase in knee cartilage thickness on MRI after about 6 months of treatment, but details are still very preliminary and not yet standard-of-care-level evidence.<sup>[1] [2] [3]</sup>

### The specific “cartilage thickness” study

From what’s been reported publicly (press/science news, clinician write-ups, and trial registries), key points are:

- A small pilot clinical study tested semaglutide (Ozempic/Wegovy-class GLP-1RA) in people with obesity and knee osteoarthritis.<sup>[3] [1]</sup>
- Participants received semaglutide plus intra-articular hyaluronic acid, compared with a control group receiving hyaluronic acid alone.<sup>[3]</sup>
- Advanced MRI (quantitative cartilage morphometry) showed:
  - About a 17% increase in cartilage thickness in the semaglutide group over 6 months.<sup>[2] [1] [3]</sup>
  - Less than 1% change in cartilage thickness in the control group.<sup>[3]</sup>
- The semaglutide group also had:
  - Reduced cartilage degradation scores / slower structural progression.<sup>[4] [3]</sup>
  - Clinically relevant improvements in pain and function scores (e.g., WOMAC), suggesting symptomatic benefit in parallel with structural changes.<sup>[5] [1] [3]</sup>
- Importantly, the study authors (and subsequent commentary) emphasize that:
  - Part of the benefit likely comes from weight loss and reduced mechanical load.<sup>[6] [7] [4]</sup>
  - But there are also signals consistent with direct chondroprotective effects (inflammatory and metabolic reprogramming of chondrocytes) that appear only partly weight-loss-mediated.<sup>[8] [4] [5]</sup>

The full primary paper appears in a 2026 Cell Metabolism-type publication (behind a paywall in most summaries), often described in lay media as “Ozempic reversing osteoarthritis damage” or “regrowing cartilage.”<sup>[9] [5] [1]</sup>

## Supporting mechanistic and clinical context

Two high-quality recent sources put this in context:

### 1. 2025 systematic review of GLP-1RAs in osteoarthritis (Cheng et al., Osteoarthritis and Cartilage Open)

- Synthesized 7 preclinical and 4 human studies on GLP-1 agonists in OA.<sup>[6]</sup>
- Preclinical work shows:
  - Reduced catabolic enzymes (MMP-3, MMP-13, ADAMTS-4/5).<sup>[6]</sup>
  - Increased anabolic proteins (type II collagen, aggrecan).<sup>[6]</sup>
  - Less chondrocyte apoptosis and better viability.<sup>[6]</sup>
  - Mechanistically, effects mainly via NF-κB inhibition and related inflammatory/stress pathways.<sup>[6]</sup>
- Human data prior to the semaglutide pilot:
  - One cohort (Shanghai OA Cohort) found GLP-1RA users had significantly slower MRI cartilage-loss velocity in the medial femorotibial joint, plus lower incidence of knee surgery, with effects partially mediated by weight loss.<sup>[6]</sup>
  - Symptom trials were mixed: liraglutide trials showed variable pain benefit, while the STEP 9 semaglutide obesity+OA trial showed significant pain and function improvement alongside large weight loss.<sup>[6]</sup>

### 2. 2025 review on GLP-1RAs for arthritis and musculoskeletal disease (Lim et al.)

- Highlights multiple animal models where GLP-1RAs (especially liraglutide) reduce cartilage degradation and synovial inflammation.<sup>[7]</sup>
- Emphasizes translational caveats: doses, pharmacokinetics, and induced OA models differ substantially from human disease.<sup>[7]</sup>

Taken together, this supports biological plausibility for genuine structural modification rather than purely load-reduction effects.

## Quick comparison of the key human structural studies

Study / year	Drug	Population	Structural endpoint	Main structural finding
Shanghai Osteoarthritis Cohort (Zhu 2023, in Cheng 2025 review)	Various GLP-1RAs	Diabetic pts with knee OA	MRI medial femorotibial cartilage thickness; knee surgery incidence	GLP-1RA users had significantly slower cartilage-loss velocity and lower incidence of knee surgery vs non-users; effect largely weight-loss mediated. <sup>[6]</sup>
Semaglutide Cell Metabolism pilot (2026)	Semaglutide + HA vs HA	Obese pts with knee OA	Quantitative MRI cartilage thickness	≈17% increase in cartilage thickness at 6 months with semaglutide vs <1% in control; also less cartilage degradation and better symptoms. <sup>[1] [2] [3]</sup>

## How “real” is this effect?

- The semaglutide 17% thickness data come from a small, early-phase, single trial, so replication and longer follow-up are critical before calling this a true disease-modifying OA drug in humans.<sup>[1] [3]</sup>
- However, the direction of effect aligns with:
  - Preclinical chondroprotection and NF-κB/oxidative-stress modulation.<sup>[7] [6]</sup>
  - Cohort-level slowing of cartilage loss and surgeries in GLP-1RA users.<sup>[7] [6]</sup>
- From a translational standpoint, semaglutide looks like the leading GLP-1 candidate where we now have converging structural, symptomatic, and mechanistic signals in OA, albeit still with big evidence gaps.

If you want, I can pull exact dosing, inclusion criteria, and MRI methodology from the semaglutide pilot so you can sanity-check human-equivalent exposure and think about how much of this could translate to non-obese / earlier-stage OA.

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## Tirzepatide and Retatrutide, would these 2 have mechanistically similar effects, theoretical

Yes, mechanistically you would expect tirzepatide and retatrutide to produce broadly similar cartilage-protective effects to semaglutide, at least in theory, with some plausible reasons to think retatrutide could be stronger (and noisier) on the structural side because of added glucagon-receptor activity.<sup>[14] [15] [16]</sup>

### Shared core: GLP-1 (and GIP) axis

For cartilage, the key is GLP-1R (and possibly GIPR) signaling in chondrocytes, synovium, and subchondral bone.

- Tirzepatide is a dual agonist at GIP and GLP-1 receptors, designed as a GIP-based peptide with added GLP-1 activity.<sup>[17] [15] [14]</sup>
- Retatrutide is a triple agonist at GIP, GLP-1, and glucagon receptors, again built on a GIP-like backbone.<sup>[18] [15] [14]</sup>
- Both therefore engage:
  - GLP-1R: anti-inflammatory, NF-κB modulation, improved mitochondrial function and oxidative stress handling in multiple tissues (the same axis implicated in chondroprotection with semaglutide).<sup>[19] [20] [14]</sup>
  - GIPR: enhances insulin secretion and insulin sensitivity, improves post-prandial lipid handling, and may further reduce systemic low-grade inflammation.<sup>[15] [14]</sup>

From an OA standpoint, if semaglutide’s cartilage effects are partly weight-loss-mediated and partly direct GLP-1R anti-inflammatory/anti-catabolic, tirzepatide and retatrutide should,

in principle, hit those same levers—and tirzepatide already produces more weight loss than semaglutide at comparable stages of disease.<sup>[21] [22] [15]</sup>

## Extra layer: glucagon-receptor agonism (retatrutide)

Retatrutide adds GCGR activity on top of GIP/GLP-1, which changes the theoretical joint story in a few ways.

- GCGR agonism increases **energy expenditure and fat oxidation**, contributing to very large weight loss and liver-fat reduction.<sup>[16] [14] [15]</sup>
- Multi-agonists with glucagon components (including retatrutide) achieve **the greatest weight loss and metabolic improvements** in both animals and humans so far (up to ~28–29% body-weight reduction in phase 3 data).<sup>[23] [22] [16]</sup>
- For OA, that implies:
  - Greater unloading of joints via weight loss (probably the biggest driver of benefit).
  - Potentially stronger systemic anti-inflammatory and metabolic effects (visceral fat, hepatic steatosis, insulin resistance), which all feed into inflammatory OA biology.<sup>[20] [14] [16]</sup>

Net: if you accept “more weight loss + better metabolic health = slower cartilage loss / more room for repair,” then retatrutide has a **theoretical ceiling** at least as high as, and likely higher than, tirzepatide for cartilage-level outcomes, albeit with a higher adverse-event burden.<sup>[23] [16]</sup>

## Receptor balance and local joint biology

There are some mechanistic nuances that could make their effects non-identical at the joint:

- Tirzepatide is a **full agonist** at GIPR but only a **partial agonist** at GLP-1R, needing roughly an order of magnitude higher dose to match semaglutide’s GLP-1R activation.<sup>[17]</sup>
- Retatrutide is also an “imbalanced” agonist with very high potency at GIPR and added GCGR potency.<sup>[14] [17]</sup>
- For cartilage, where we are mostly extrapolating from GLP-1R-focused preclinical data, you could argue:
  - Semaglutide: strongest direct GLP-1R signaling; “cleanest” for GLP-1-specific chondrocyte and synovial effects.<sup>[19] [20]</sup>
  - Tirzepatide: slightly weaker per-mg GLP-1R activation, but **more weight loss** and possible additional GIP-mediated anti-inflammatory/metabolic effects.<sup>[22] [21] [15]</sup>
  - Retatrutide: similar GLP-1/GIP pattern to tirzepatide plus GCGR—so maximal weight loss and metabolic remodeling, but also a somewhat more catabolic hormone in the mix system-wide.<sup>[15] [16] [14]</sup>

Theoretically, if GLP-1’s local chondroprotective signaling turns out to be crucial and weight loss is necessary but not sufficient, semaglutide could still be “best per receptor hit,” with tirzepatide and retatrutide catching up or surpassing via the sheer magnitude of systemic improvement.

## Any direct data in joints?

Right now:

- There are no published human OA trials showing cartilage-thickness changes with tirzepatide or retatrutide specifically—those signals are all semaglutide-centric. [\[24\]](#) [\[25\]](#) [\[19\]](#)
- Preclinical and clinical data for tirzepatide and retatrutide are concentrated on:
  - Glucose control and weight loss in diabetes and obesity.
  - Organ-level outcomes like liver fat and kidney inflammation/fibrosis (for retatrutide, suppression of TNF- $\alpha$ , NLRP3, collagen etc. in db/db mouse kidney, which is directionally similar to the anti-inflammatory, anti-fibrotic profile you'd want in OA tissues). [\[26\]](#) [\[14\]](#) [\[23\]](#)

So at this point, saying “they should do something similar in cartilage” is an extrapolation, but a biologically reasonable one based on:

- Shared GLP-1R (and GIPR) agonism.
- Equal or greater weight loss vs semaglutide.
- Similar anti-inflammatory and anti-fibrotic signatures in other tissues. [\[26\]](#) [\[20\]](#) [\[14\]](#) [\[23\]](#)

If you were designing a trial, which of these would you most want to see tested first in OA—tirzepatide (pragmatic, on-label weight loss + OA secondary endpoints) or retatrutide (maximum effect size but more experimental and higher AE risk)?

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## How does glucagon agonism in Retatrutide differ from Tirzepatide effects

Glucagon agonism is the big extra dial retatrutide turns that tirzepatide does not: it adds a direct, systemic “energy-expenditure / fat-burning” and hepatic-metabolism signal on top of GIP/GLP-1, which amplifies weight loss and metabolic remodeling but also changes risk and tolerability. [\[30\]](#) [\[31\]](#) [\[32\]](#)

### Core mechanistic difference

- Tirzepatide: dual agonist at GIPR + GLP-1R only. It boosts insulin secretion, reduces appetite, slows gastric emptying, and improves post-prandial lipid handling, but it does not directly activate the glucagon receptor. [\[30\]](#) [\[33\]](#)
- Retatrutide: triple agonist at GIPR + GLP-1R + glucagon receptor (GCGR). It keeps the GIP/GLP-1 actions above and adds direct GCGR stimulation. [\[33\]](#) [\[32\]](#) [\[30\]](#)

GCGR activation is what functionally differentiates retatrutide's profile from tirzepatide's.

## What glucagon agonism adds

Physiologic glucagon (and GCGR agonism by retatrutide) does several things that tirzepatide does not directly do:

- Increases hepatic glucose production between meals and during fasting.<sup>[32]</sup>
- Increases lipolysis and fatty-acid oxidation in the liver, pushing more fat to be burned for energy.<sup>[32]</sup>
- Decreases appetite and slows GI motility (when combined with GLP-1/GIP).<sup>[32]</sup>
- In some contexts stimulates insulin secretion during hyperglycemia, creating a coupled glucagon–insulin response.<sup>[32]</sup>

Retatrutide is engineered so that GLP-1 and GIP signaling plus dosing/titration keep overall glucose control favorable despite the catabolic, glucose-raising side of glucagon. Tirzepatide, by contrast, achieves its effects via incretin pathways alone and doesn't rely on GCGR-driven energy expenditure.<sup>[32]</sup>

## Downstream clinical consequences

Because of that extra GCGR “gear,” retatrutide behaves differently at the whole-body level:

- **More weight loss and fat reduction**
  - Meta- and pooled analyses show retatrutide produces the largest absolute and percentage weight loss compared with tirzepatide and semaglutide in non-diabetic obesity, likely due to combined appetite suppression plus increased energy expenditure/fat oxidation.<sup>[30] [34] [32]</sup>
  - It also tends to show very strong signals on visceral and liver-fat reduction.<sup>[34] [35]</sup>
- **Different glycemic balance**
  - Tirzepatide: very potent HbA1c lowering via GIP/GLP-1; hyperglucagonemia is suppressed rather than exploited.<sup>[30] [34]</sup>
  - Retatrutide: still improves glycemia, but has to “fight against” its own glucagon-driven hepatic glucose output with strong GLP-1/GIP activity; trials emphasize careful titration to avoid hyperglycemia early on.<sup>[32] [30]</sup>
- **Adverse-event pattern**
  - Both have typical incretin GI AEs (nausea, vomiting, diarrhea), but head-to-head and pooled analyses suggest higher AE rates with retatrutide, consistent with stronger catabolic/metabolic drive and the glucagon component.<sup>[31] [30]</sup>

## Mechanistic implications for joints (theoretical)

For cartilage and OA specifically (extrapolating from the GLP-1 discussion):

- Tirzepatide:
  - Provides GLP-1R and GIPR-mediated anti-inflammatory/metabolic benefits plus major weight loss.

- Lacks direct GCGR action, so its main joint benefits are likely via load reduction and GLP-1/GIP anti-inflammatory signaling. [\[30\]](#) [\[34\]](#) [\[36\]](#)
- Retatrutide:
  - Adds more extreme weight and fat loss and deeper metabolic remodeling via glucagon-driven energy expenditure and fat oxidation. [\[34\]](#) [\[32\]](#) [\[30\]](#)
  - That should, in principle, further unload joints and reduce systemic inflammatory drivers (visceral fat, NAFLD, insulin resistance), which could amplify cartilage-protective effects—but at the cost of a narrower tolerability window. [\[32\]](#) [\[30\]](#) [\[34\]](#)

We do not yet have direct human joint data to say GCGR agonism itself is beneficial or harmful to cartilage; the plausible advantage is **indirect** via stronger weight and metabolic effects, while the direct chondroprotective signaling is still mostly tied to GLP-1R (and maybe GIPR).

If you're thinking specifically about OA, are you more interested in maximizing structural effect size (even with higher AE risk), or in something more conservative that's easier to deploy broadly in a mixed-risk population?



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