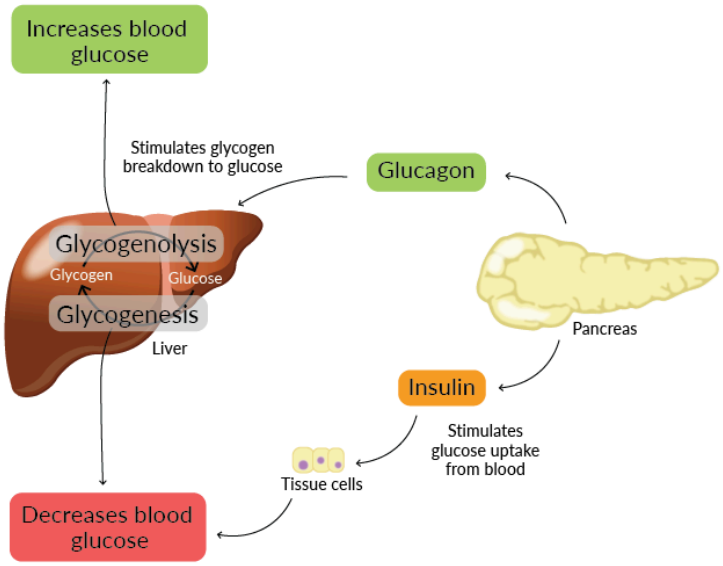
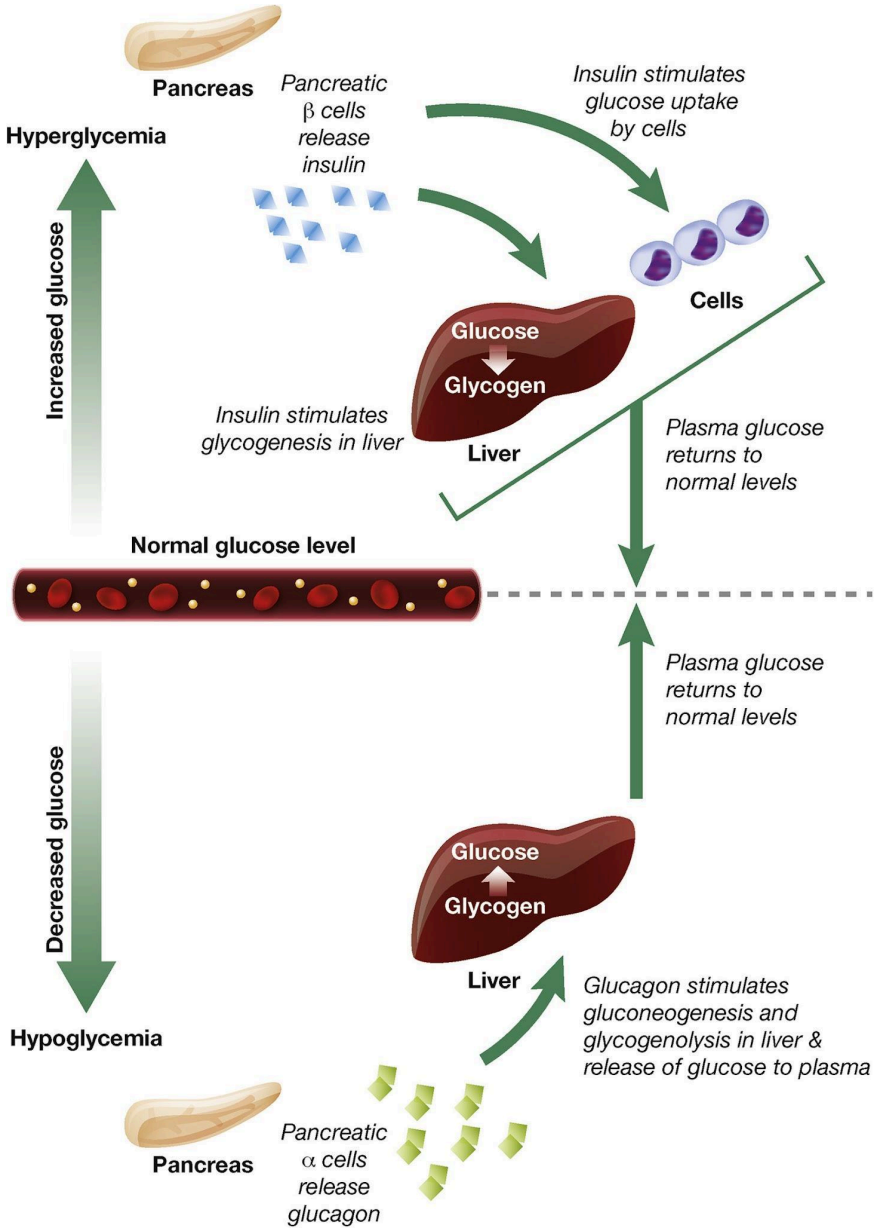
Glucagon antagonist? Glucagon agonist? Which is better? Why are all the multi-agonist peptides choosing to add glucagon as an agonist? Well let's review the risks, & major benefits of each. (Hint, the agonists won for a reason!) This is gonna be counter-intuitive! Let's go (thread)



Glucagon was discovered a year after insulin in 1922, it's a portmanteau of two words GLUcose AGONist, which is perfect as it stimulates glucose release from the liver! Because it raised glucose, it wasn't purified chemically until the 1950s(!!) and hasn't been studied nearly as much as insulin

Oversimplified, glucagon acts primarily in the liver, stimulates glycogenolysis & gluconeogenesis, freeing glucose into the bloodstream, pausing glycogenesis, raising blood glucose. It also increases hepatic fatty acid oxidation for energy for gluconeogenesis(spoiler alert this is important!)

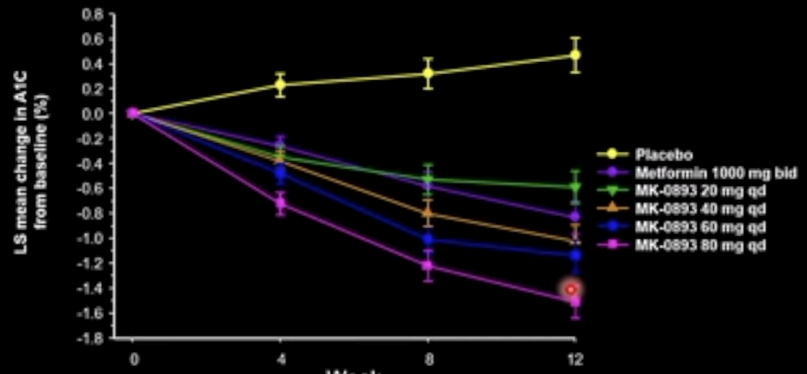


So we know it raises glucose, so it would seem simple enough to create a glucagon antagonist drug. Block the action, and glucose should drop. Right….right??? Well yes and no. Lets review some data from failed clinical trials and see where we got it wrong, and why agonist will win the day.

Let's start with the good, trial data shows a large drop in A1c, about 1.5% in 12 weeks, lowered fasting insulin, blocking hepatic glucose release and lowered fasting glucose. So that's the good part. Like, that's the *ONLY* good thing about these glucagon antagonists(cringe emoji)

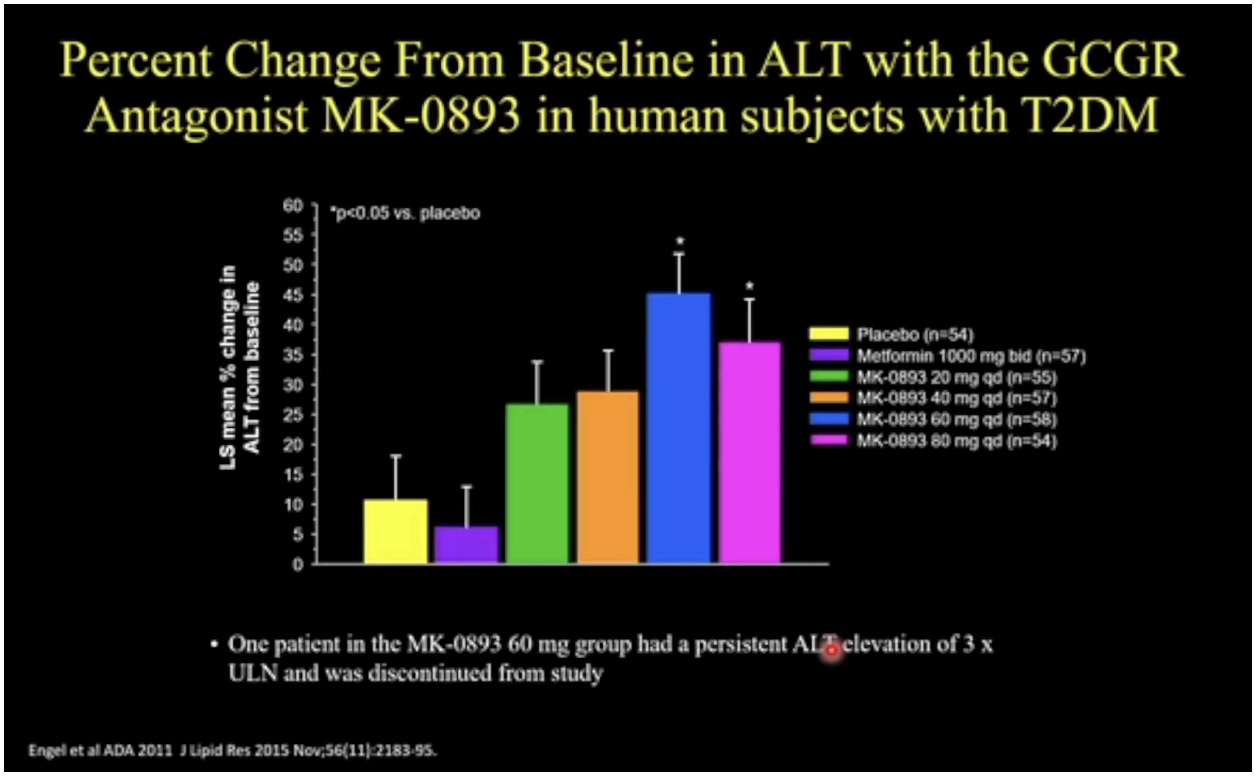
The GCGR antagonist MK-0893: robust reductions in A1C after 12 weeks in human subjects with T2DM

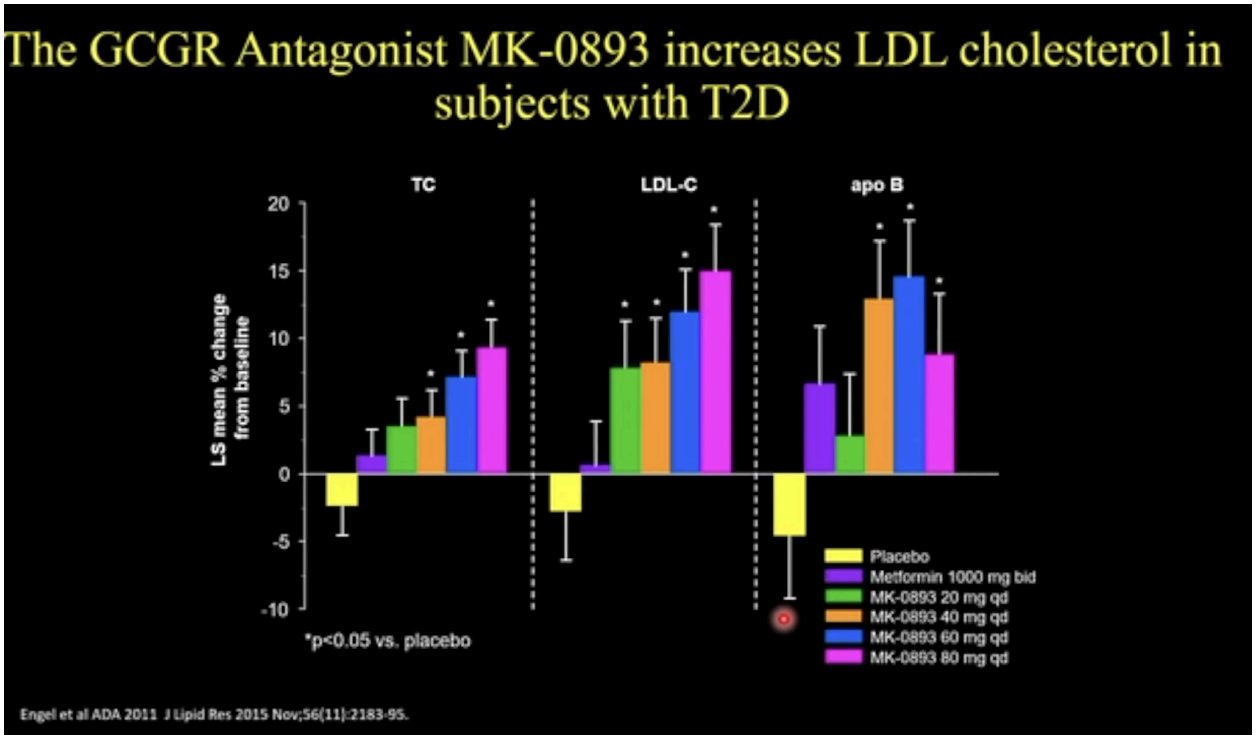
	Placebo N=54	Metformin 1000 mg bid N=57	MK-0893 20 mg qd N=55	MK-0893 40 mg qd N=57	MK-0893 60 mg qd N=57	MK-0893 80 mg qd N=54
Mean baseline A1C, %	8.3	8.5	8.3	8.5	8.4	8.5
LS mean change in A1C from baseline (95% CI), %	0.54 (0.27, 0.82)	-0.78 (-1.04, -0.52)	-0.60 (-0.87, -0.33)	-0.99 (-1.25, -0.73)	-1.14 (-1.40, -0.89)	-1.52 (-1.79, -1.25)
p<0.001 for all active treatments vs. placebo						



Engel et al ADA 2011 J Lipid Res 2015 Nov;56(11):2183-95.

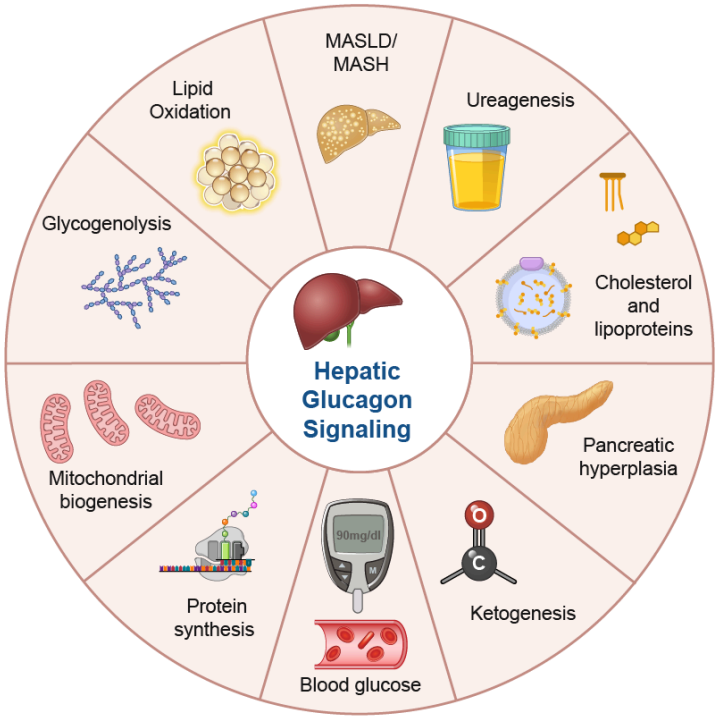
So the bad, is real bad. Increased body weight, liver enzymes, liver fat amount, LDL cholesterol(!!), increased pancreatic alpha cells and large intestine cell size, increased glucagon levels, decreased renal function and even caused a DELAYED recovery from hypoglycemic events. Holy Yikes.





In plain english, increased risk of liver failure, liver, bowel and pancreatic cancer, increased risk of cardiovascular disease, increased risk of kidney disease. So yeah…all development of these drugs stopped, for a really good reason. So, enter glucagon agonists

Yesterday we saw that blocking glucagon was really bad!!! Today we'll discuss what happens when you agonize it instead. Yes it'll raise glucose, but only briefly! Grab a Coke, and let's (thread)



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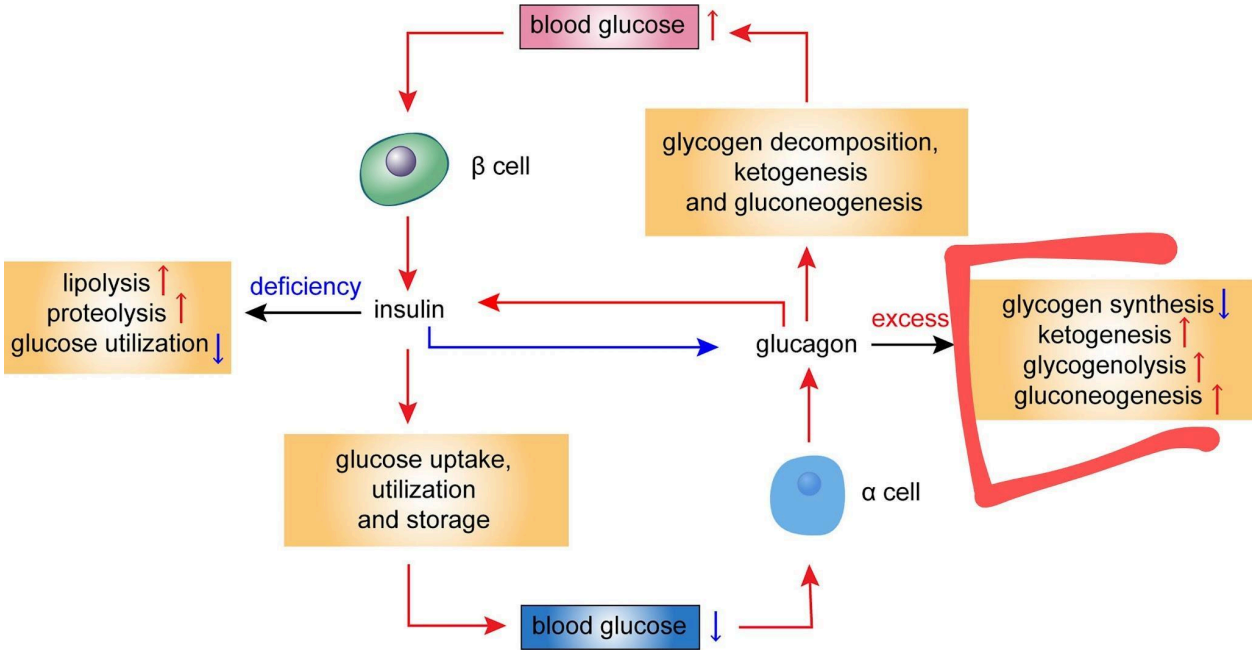
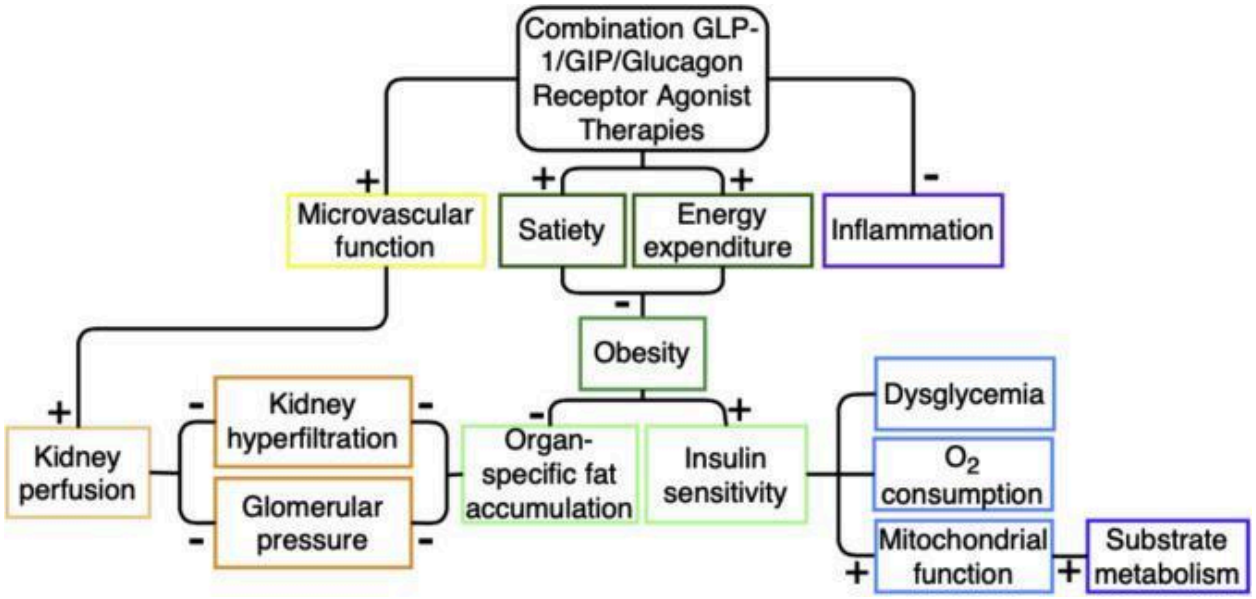
So why is the glucose rise brief? Well you don't have unlimited glucose in your liver. A glucagon agonist(GCGR) makes your liver dump all it's glycogen BUT it also inhibits glycogenesis!

So once that liver glycogen store is depleted, you can hammer the glucagon receptor all day, but your sugar won't rise AND then the other benefits happen. Namely gluconeogenesis from other sources.

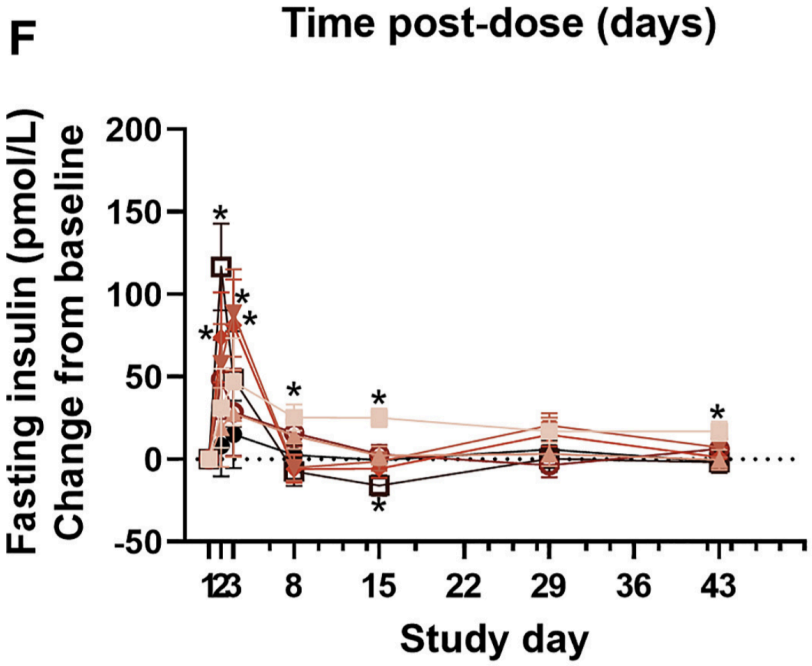


But we still need to blunt the blood sugar rise, enter GLP-1(and GIP w/retatrutide) both of these peptides potently stimulate insulin, and if you get the ratio of receptor binding correct, they'll cancel the glucose rise.

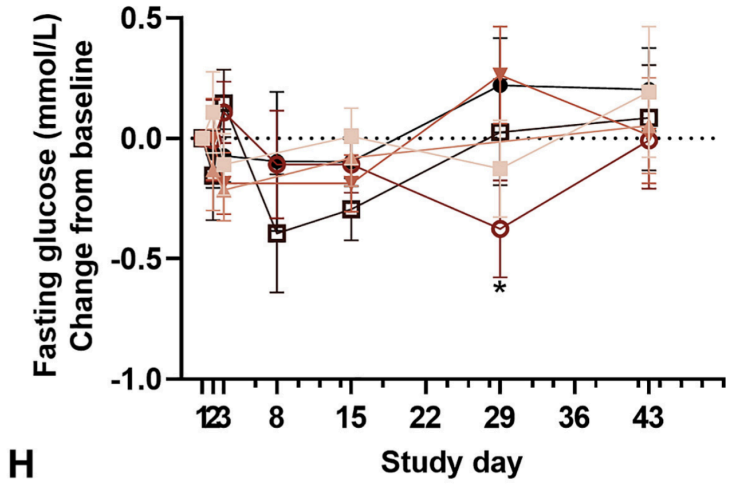
What this means is biased agonists win out. Retatrutide for example has a receptor binding ratio of 8x GIP, 0.7x GCGR and 0.6x GLP-1. In English, the GCGR can't overpower the other two receptors.



What's this glycogen dumping effect look like clinically? Well it should cause a massive spike in fasting insulin but only for a day or two. Enter retatrutide phase 1 data. Massive insulin spike for ~2 days then it drops and no glucose rise! This is from a single dose of retatrutide that lasted about 14 days. Furthermore in phase 2 data, retatrutide decreased plasma glucagon levels between 60 to 89 PERCENT over 6 months. Fasting insulin levels dropped 25-40% in 6 months.



Moreover using that same data we see relatively stable glucose levels! Our biased receptor signalling is working! We're past the blood glucose rise, now let's reap the metabolic rewards. Enter gluconeogenesis and hepatic fatty acid oxidation.



Glucagon is lipolytic. Meaning it'll burn fat. This makes sense in a prolonged fast or starvation you need to mobilize energy. That's one of glucagon's primary evolutionary benefits. Keeping you alive to find food. Looking at this very old graph, we can see as fasting progresses, insulin

drops while glucagon stays high and blood sugar is stable. Except as noted above it's decreasing your insulin and glucagon levels at the same time while your body “thinks” it's fasting, except you're not. You're still eating carbs. But you're burning fat too. A metabolic 2 for 1!

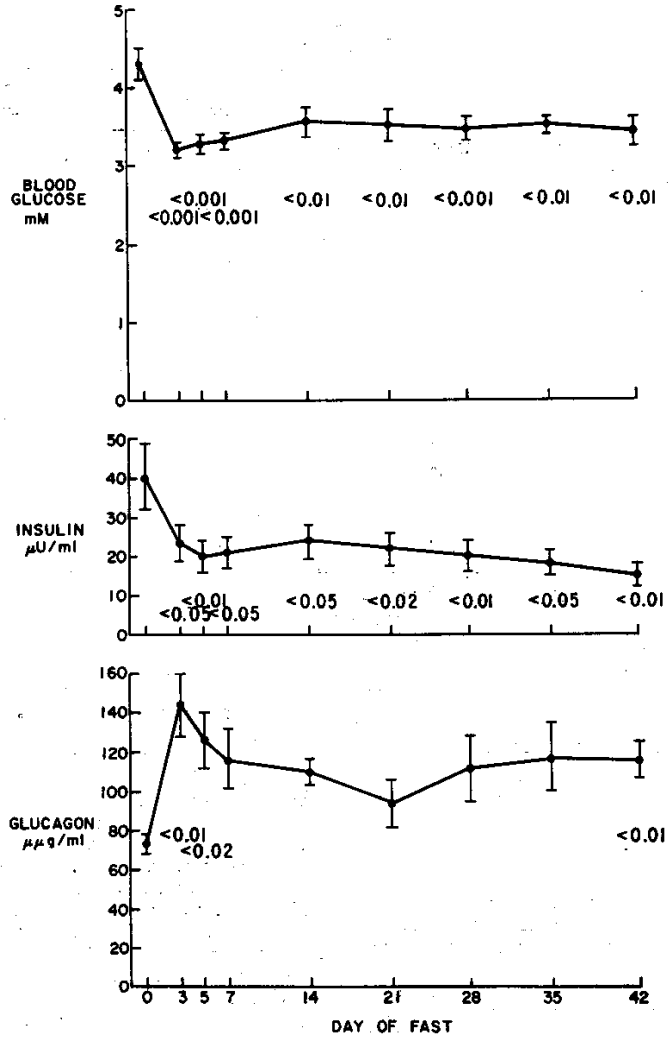
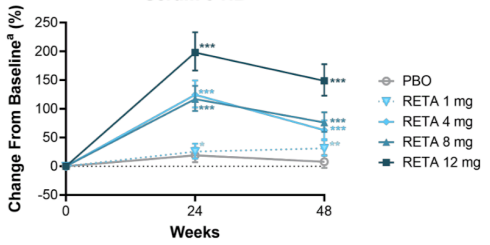


FIGURE 1 Concentration of blood glucose, serum insulin, and plasma glucagon in seven obese subjects at various intervals throughout a prolonged fast. Values are mean ±SEM and show the probability that non

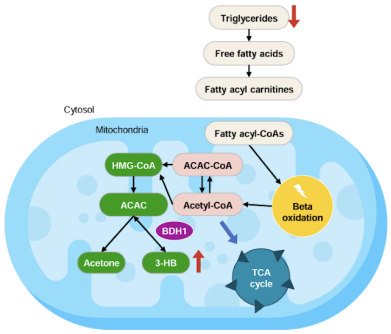
GCGR agonism harnesses this fact. With your hepatic glucose stores depleted you start burning fat stores. We can see a rise in ketones to reflect this. And now the metabolic benefits start piling on, ketones are a preferred fuel for the heart, kidney & brain, this chart shows ketones rising over 48 weeks of continuous retatrutide dosing. So you get the fatty acid oxidation and carb burning simultaneously! This may explain some of the profound weight loss benefits seen with retatrutide

Ketone Body 3-Hydroxybutyrate (3-HB)

Serum 3-HB



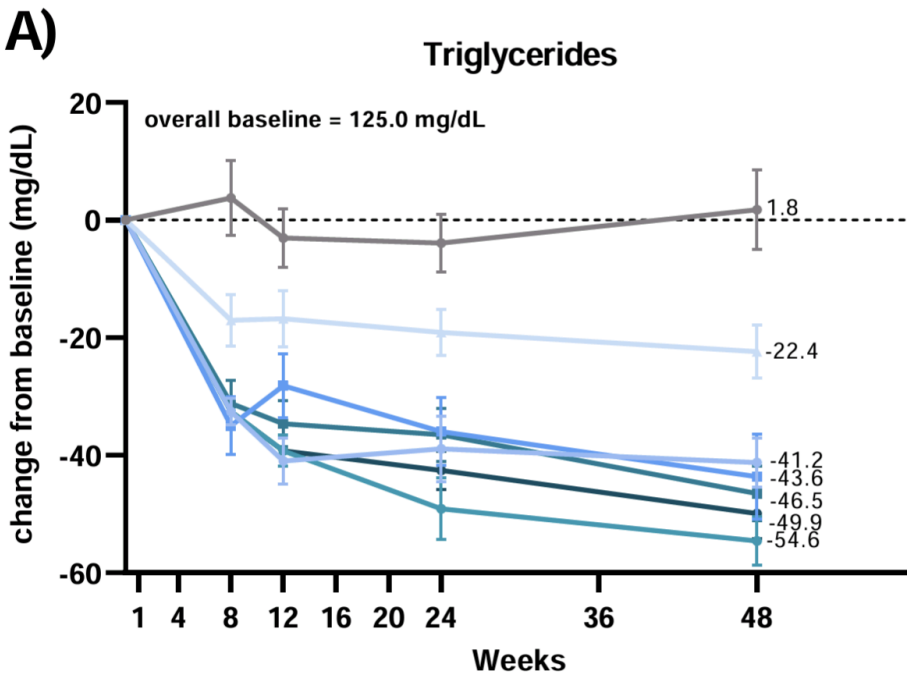
Ketone Body Synthesis[3]



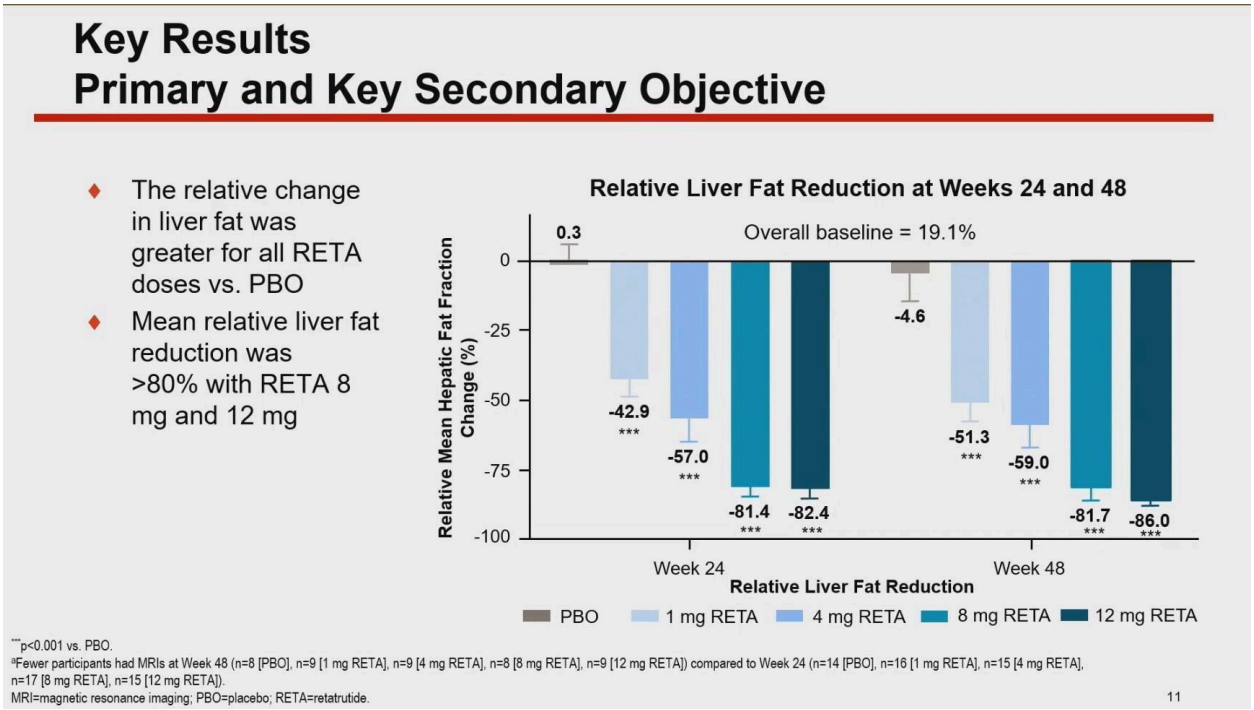
- Hepatic ketogenesis reflects a metabolic compensation for the stimulation of fatty acid oxidation[1]
- Over 80% reduction in liver fat in participants with metabolic dysfunction–associated steatotic liver disease (MASLD) with retatrutide 12 mg[2]

*p<0.05, p**<0.01, ***p<0.001 vs. baseline.
[a]Data are LSM (SE); statistical significance is shown using nominal p-values.
1. Mooli RGR, et al. *Front Physiol.* 2022;13:946474. 2. Sanyal AJ, et al. *Nat Med.* 2024;(ahead of print). 3. Dilliraj LN, et al. *Nutrients.* 2022;14:3613.
ACAC=acetoacetate; BDH1=3-hydroxybutyrate dehydrogenase; CoA=coenzyme A; HMG=3-hydroxy-3-methyl glutaryl; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SE=standard error; TCA=tricarboxylic acid cycle.

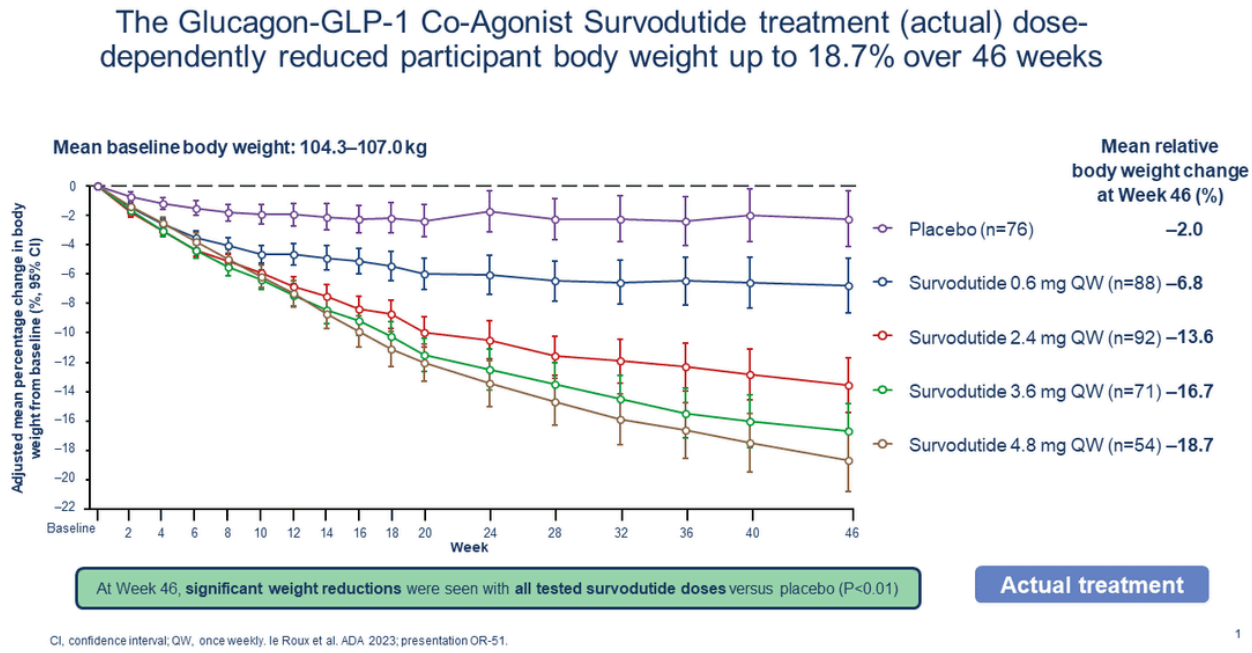
Triglycerides also drop rapidly in the blood. Cholesterol follows. Across 3 drugs with GCGR, retatrutide, survodutide & pemvidutide we see ⬇️ 40-50% in triglycerides, & ⬇️ 20% in total cholesterol & LDL, this cholesterol effects deserves its own thread but suffice to say it's a significant effect.



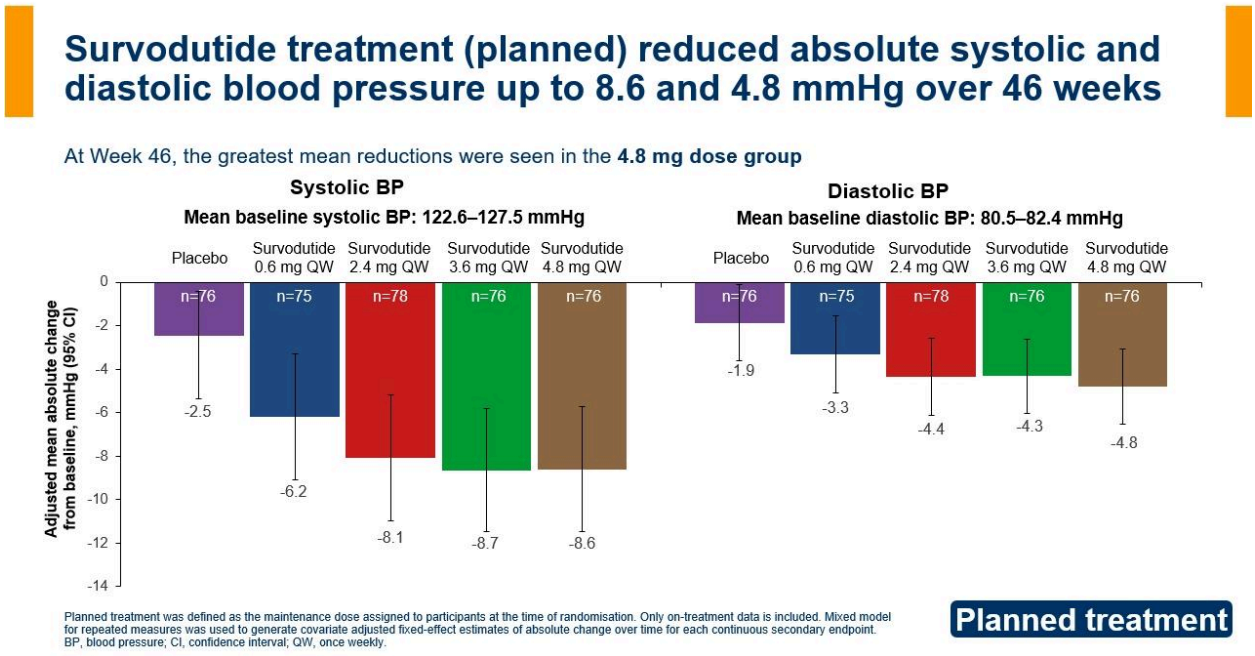
This mobilization of fat also occurs in the liver, where glucagon potently stimulates hepatic fat oxidation, in english, if you have a fatty liver, then activating glucagon will rapidly clear liver fat. Both pemvidutide and retatrutide led to resolution of fatty liver in >75% of patients!



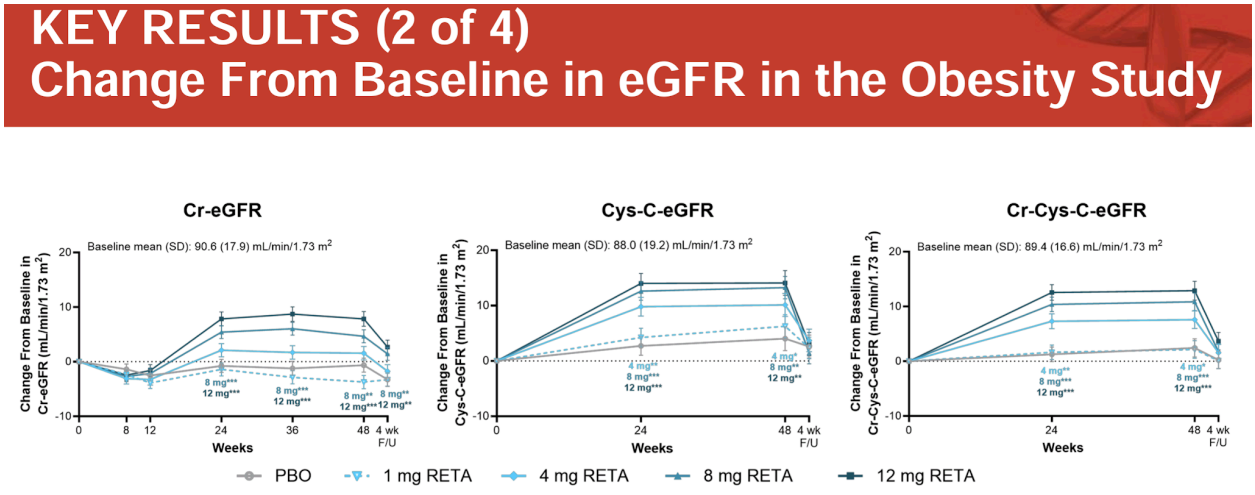
The loss of weight is also apparent, and synergistic with GLP-1, given it is causing your body to burn excess fat, we may see more prolonged and potentially sustained weight loss with GCGR drugs, but we need more data to confirm this.



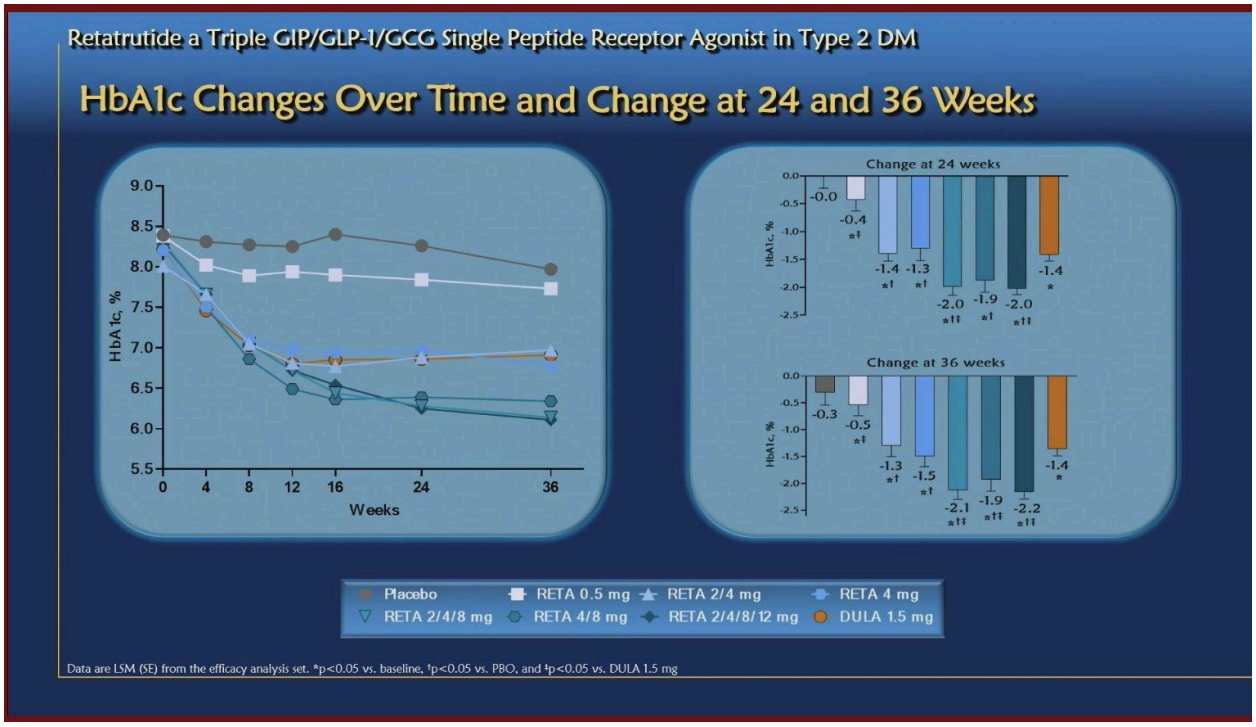
It seems to improve, or at least protect kidney function and reduce blood pressure, again looking at survodutide and retatrutide we see an 8-14mmHg drop in systolic BP depending on dose and drug studied.

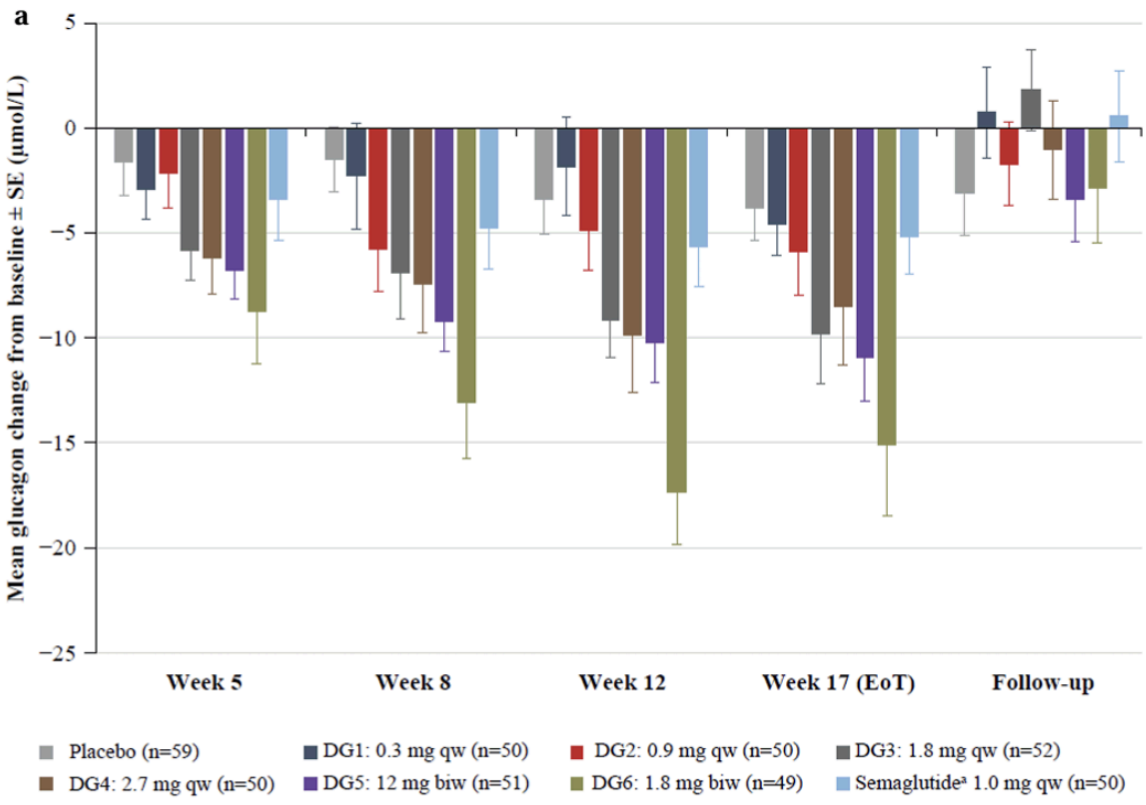


Retatrutide at least seems to preserve and enhance GFR by almost 10ml/min based on phase 2 obesity data, ongoing trials are looking into this effect to see if it's real, as this would be ground breaking if it was real.



Finally we'll end with glucose, after that initial dump of glycogen, blood sugar levels in diabetics tend to drop rapidly, up to 1.7% with survodutide and nearly 2.2% with retatrutide. It also lowers fasting insulin & glucose levels and glucagon levels!


Retatrutide a Triple GIP/GLP-1/GCG Single Peptide Receptor Agonist in Type 2 DM
HbA1c Changes Over Time and Change at 24 and 36 Weeks
HbA1c, %
Weeks
Change at 24 weeks
Change at 36 weeks
Placebo
RETA 0.5 mg
RETA 2/4 mg
RETA 4 mg
RETA 2/4/8 mg
RETA 4/8 mg
RETA 2/4/8/12 mg
DULA 1.5 mg
Data are LSM (SE) from the efficacy analysis set. *p<0.05 vs. baseline, †p<0.05 vs. PBO, and ‡p<0.05 vs. DULA 1.5 mg


a
Mean glucagon change from baseline ± SE (µmol/L)
Week 5
Week 8
Week 12
Week 17 (EoT)
Follow-up
Placebo (n=59)
DG1: 0.3 mg qw (n=50)
DG2: 0.9 mg qw (n=50)
DG3: 1.8 mg qw (n=52)
DG4: 2.7 mg qw (n=50)
DG5: 12 mg biw (n=51)
DG6: 1.8 mg biw (n=49)
Semaglutide[a] 1.0 mg qw (n=50)

So in sum the agonists are literally opposite the antagonist. Lower cholesterol, glucose, weight, reduce liver fat, lower BP, protect the kidney and potentially more! Maybe reduce ASCVD with its lipid lowering effect?? We'll find out in the coming years.