# The Hidden Costs of Anti-Obesity Medications: Navigating Side Effects in the Quest for Weight Loss

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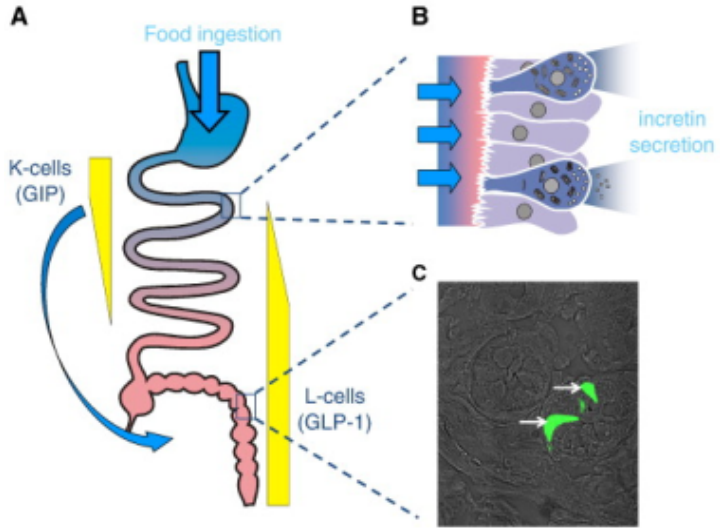
# Incretin Hormones

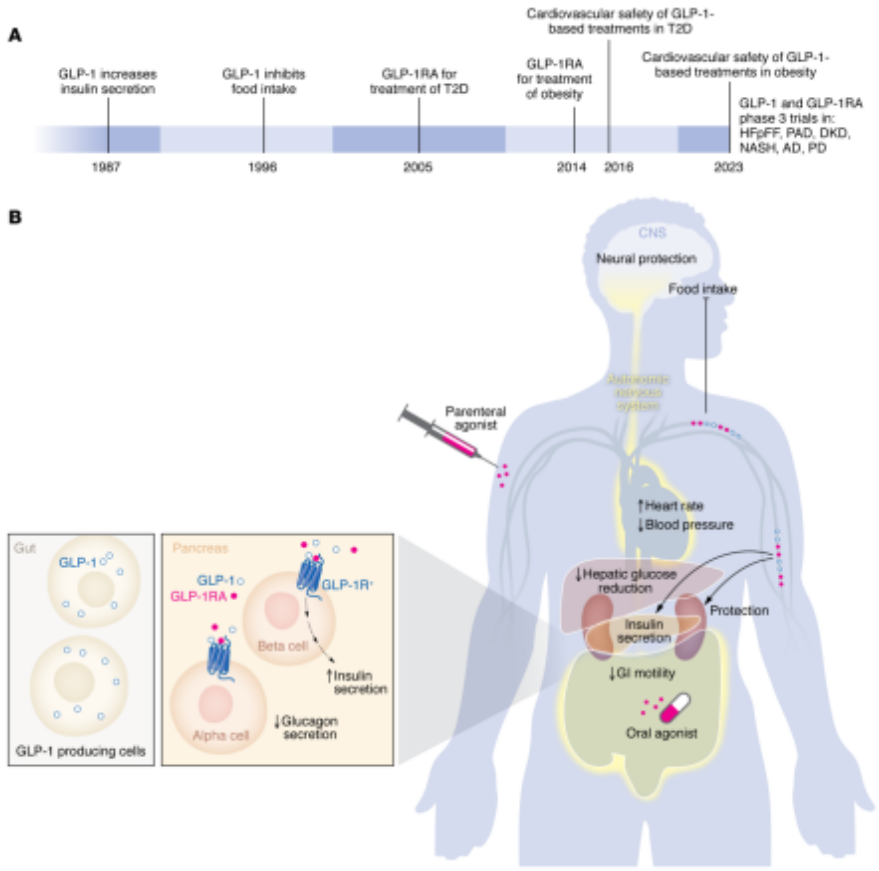
- Stimulated by meal ingestion
  - Glucagon-like peptide-1 (GLP-1)
    - Secreted by epithelial intestinal L cells (ileum and colon)
  - Glucose-dependent insulinotropic peptide (GIP)
    - Secreted by L cells and K cells (proximal small bowel)
- Receptors expressed in the gut, pancreas, brainstem, hypothalamus, vagal afferent nerves






Diakogiannaki E et al. Physiol Behav 2012

# GLP-1 and Glycemic Control




- Role of GLP-1 in glycemic control
  - Pancreatic islet cell functions
    - β cells: increases insulin secretion
    - α cells: reduces glucagon secretion
  - Increases insulin sensitivity
    - Reduces hepatic gluconeogenesis
    - Enhances muscular glucose uptake and storage



Drucker DJ. J Clin Invest 2024

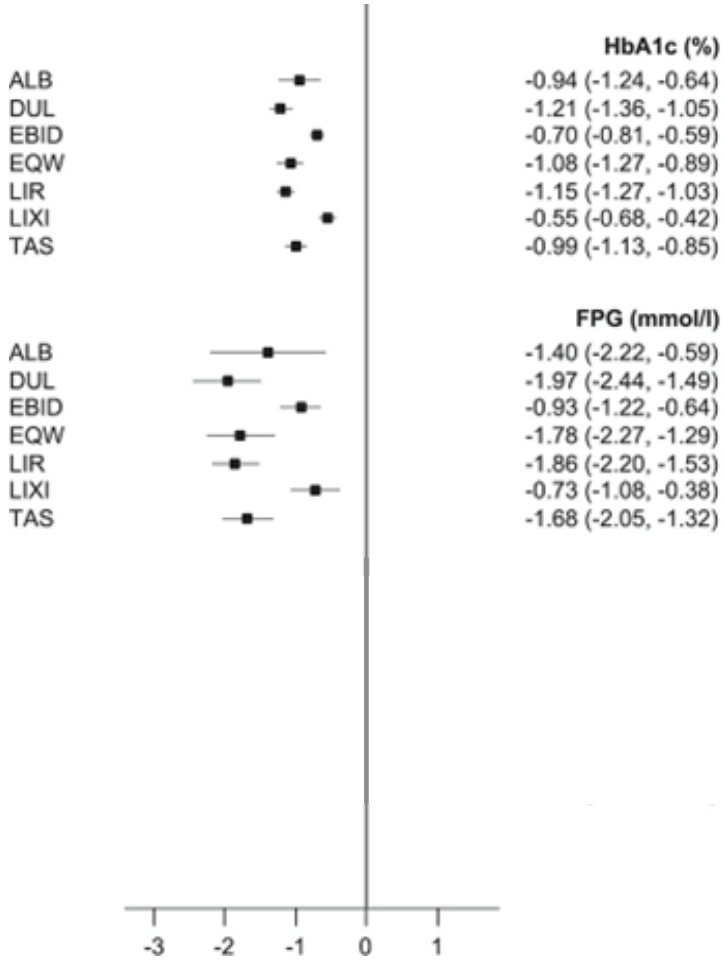
# Incretin Agonists

| | Dosing Frequency/ Route of Administration | Indications | Elimination Half-Life | Approved Dosages |
|---|---|---|---|---|
| **Short-Acting GLP-1 RA** | | | | |
| Exenatide | Twice daily SQ | Type II Diabetes | 2.4 hours | 5-10 mg BID |
| **Long-Acting GLP-1 RA (SQ)** | | | | |
| Liraglutide | Once daily SQ | Type II Diabetes Weight Management | 13 hours | 0.6-3 mg QD |
| Semaglutide SQ | Once weekly SQ | | 5 days | 0.25-1.5 mg weekly |
| Exenatide ER | Once weekly SQ | Type II Diabetes | 8-16 hours | 2 mg weekly |
| **Long-Acting GLP-1 RA (oral)** | | | | |
| Semaglutide PO | Once daily PO | Type II Diabetes | 7 days | 3-14 mg QD |
| **Long-Acting Dual Incretin GIP/GLP-1 RA** | | | | |
| Tirzepatide | Once weekly SQ | Type II Diabetes | 5 days | 2.5-15 mg weekly |



Camilleri M et al. Am J Gastroenterol 2024.

# GLP-1 Agonists: Effect in Type II Diabetes



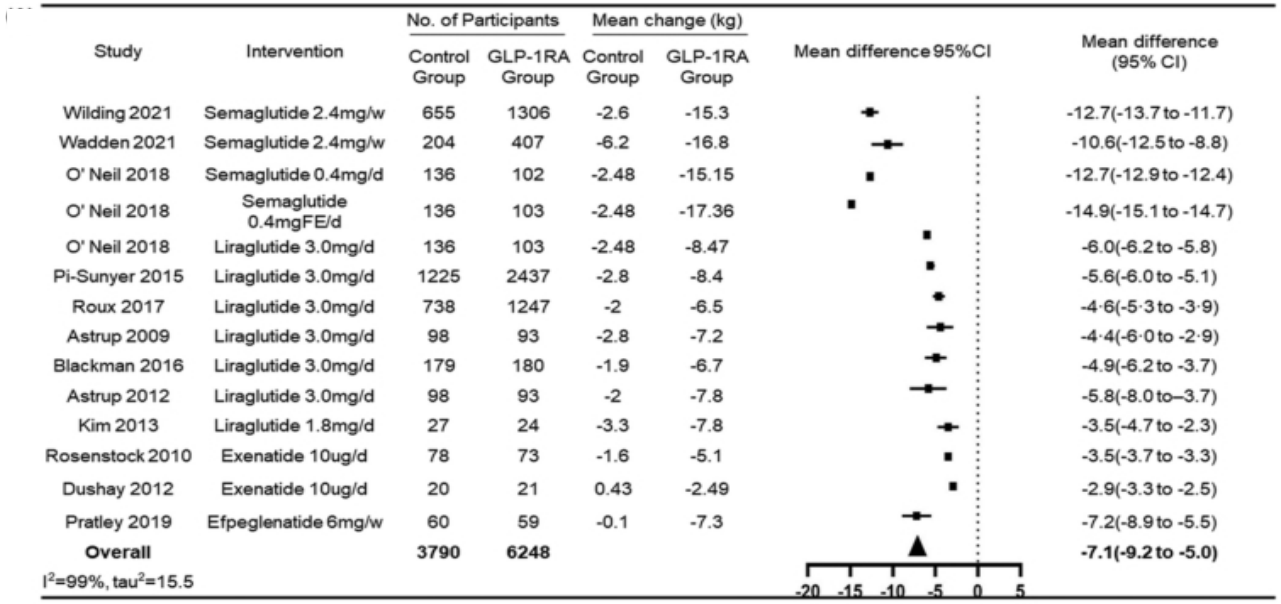

- Significant improvement in glycemic control compared to placebo in all formulations (n=14,464)
  - HbA1c
  - Fasting plasma glucose
- Significant reduction in body weight compared to placebo (n=14,054)



Htike ZZ et al. Diabetes Obes Metab 2017

# GLP-1 Agonists: Effect in Non-Diabetic Patients with Obesity

- Significant reduction in body weight compared to placebo (n=10,038)
  - Weight loss effect in both daily and weekly formulations
  - Reduction in fasting blood glucose (-3.6 mg/dl), SBP (-3.4 mmHg), DBP (-0.7 mmHg)



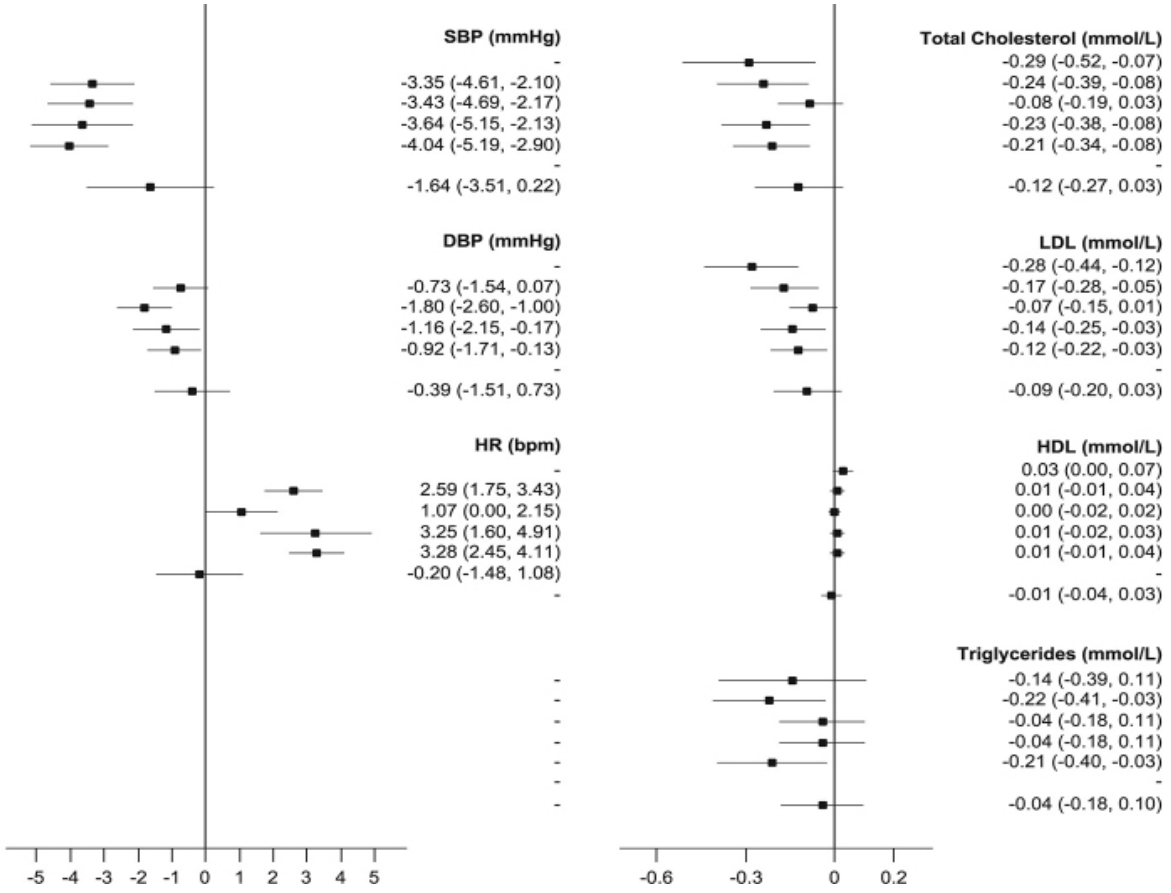
| Study | Intervention | No. of Participants | | Mean change (kg) | | Mean difference (95% CI) |
|---|---|---|---|---|---|---|
| | | Control Group | GLP-1RA Group | Control Group | GLP-1RA Group | |
| Wilding 2021 | Semaglutide 2.4mg/w | 655 | 1306 | -2.6 | -15.3 | -12.7(-13.7 to -11.7) |
| Wadden 2021 | Semaglutide 2.4mg/w | 204 | 407 | -6.2 | -16.8 | -10.6(-12.5 to -8.8) |
| O' Neil 2018 | Semaglutide 0.4mg/d | 136 | 102 | -2.48 | -15.15 | -12.7(-12.9 to -12.4) |
| O' Neil 2018 | Semaglutide 0.4mgFE/d | 136 | 103 | -2.48 | -17.36 | -14.9(-15.1 to -14.7) |
| O' Neil 2018 | Liraglutide 3.0mg/d | 136 | 103 | -2.48 | -8.47 | -6.0(-6.2 to -5.8) |
| Pi-Sunyer 2015 | Liraglutide 3.0mg/d | 1225 | 2437 | -2.8 | -8.4 | -5.6(-6.0 to -5.1) |
| Roux 2017 | Liraglutide 3.0mg/d | 738 | 1247 | -2 | -6.5 | -4·6(-5·3 to -3·9) |
| Astrup 2009 | Liraglutide 3.0mg/d | 98 | 93 | -2.8 | -7.2 | -4·4(-6·0 to -2·9) |
| Blackman 2016 | Liraglutide 3.0mg/d | 179 | 180 | -1.9 | -6.7 | -4.9(-6.2 to -3.7) |
| Astrup 2012 | Liraglutide 3.0mg/d | 98 | 93 | -2 | -7.8 | -5.8(-8.0 to–3.7) |
| Kim 2013 | Liraglutide 1.8mg/d | 27 | 24 | -3.3 | -7.8 | -3.5(-4.7 to -2.3) |
| Rosenstock 2010 | Exenatide 10ug/d | 78 | 73 | -1.6 | -5.1 | -3.5(-3.7 to -3.3) |
| Dushay 2012 | Exenatide 10ug/d | 20 | 21 | 0.43 | -2.49 | -2.9(-3.3 to -2.5) |
| Pratley 2019 | Efpeglenatide 6mg/w | 60 | 59 | -0.1 | -7.3 | -7.2(-8.9 to -5.5) |
| **Overall** | | **3790** | **6248** | | | **-7.1(-9.2 to -5.0)** |
| $I^2$=99%, $tau^2$=15.5 | | | | | | |





Iqbal J et al. Obes Rev 2023

# GLP-1 Agonists: Other Effects in Patients with Type II Diabetes

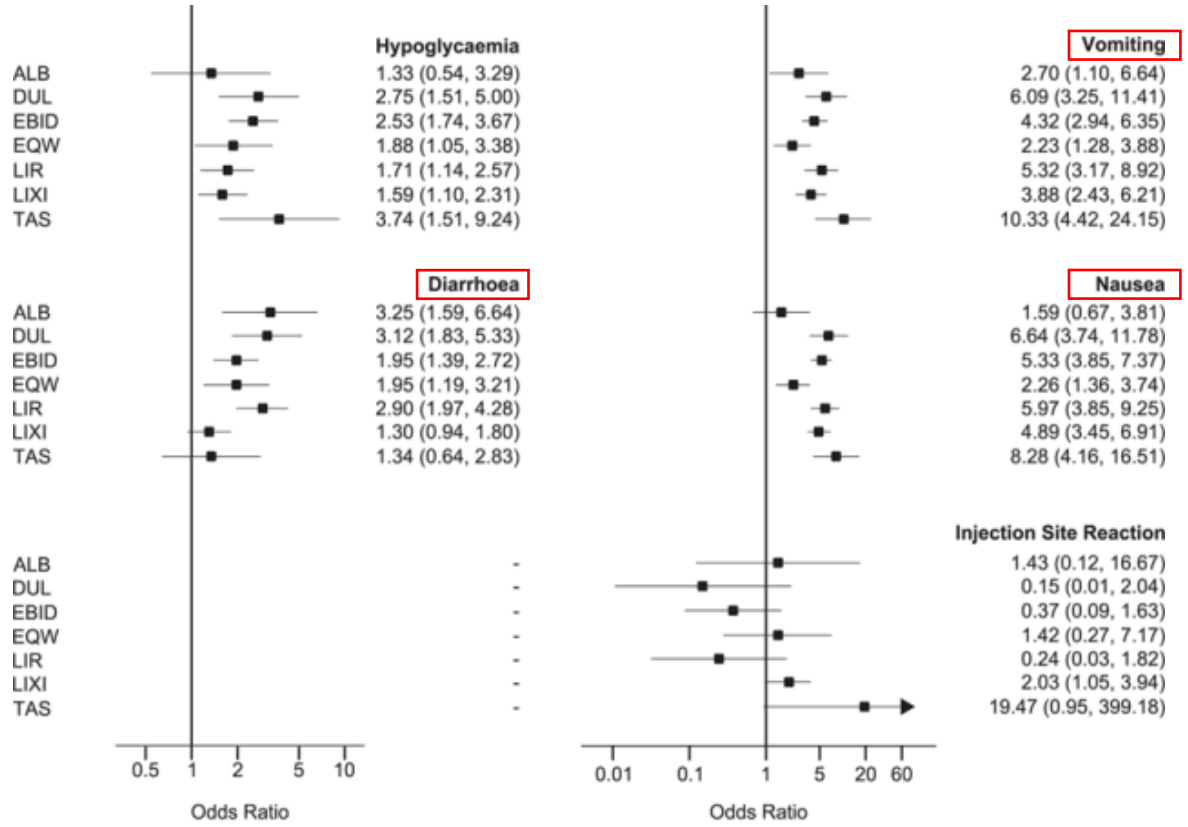



- Improvement in other cardiometabolic outcomes compared to placebo among type II diabetics
  - Hypertension
  - Hypercholesterolemia
  - Hypertriglyceridemia



Htike ZZ et al. Diabetes Obes Metab 2017

# GLP-1 Agonists: GI Adverse Effects

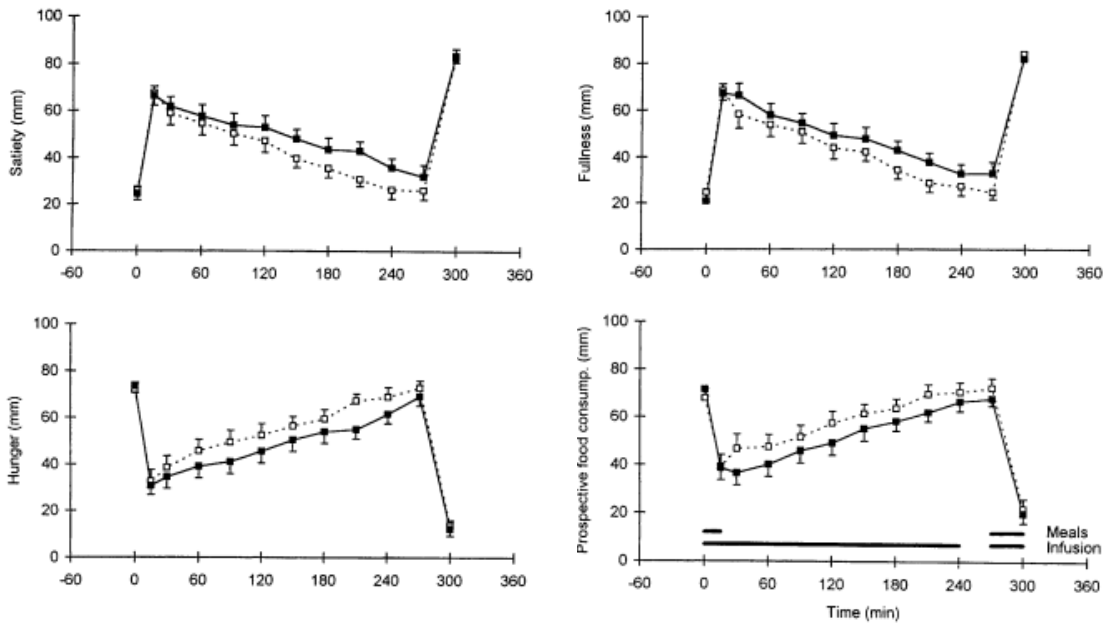



- GI symptoms = major adverse effects of GLP-1 agonists
  - Most common: **nausea** (25-44%), **diarrhea** (19-30%)
  - **Vomiting** (8-24%), **constipation** (11-24%), **abdominal pain** (9-20%), **dyspepsia** (9-10%)
  - Decreased appetite
  - Mostly <u>mild/moderate</u> in severity
  - Usually during initial dose escalation and most are <u>transient</u>



Htike ZZ et al. Diabetes Obes Metab 2017

# GLP-1: Satiation and Energy Intake




- Flint et al infused GLP-1 vs placebo in 20 healthy individuals with ingestion of test meal. Compared to placebo, GLP-1:
  - Increases satiation, fullness and plasma insulin after test meal
  - Decreases hunger, food/energy consumption, plasma glucagon, blood glucose

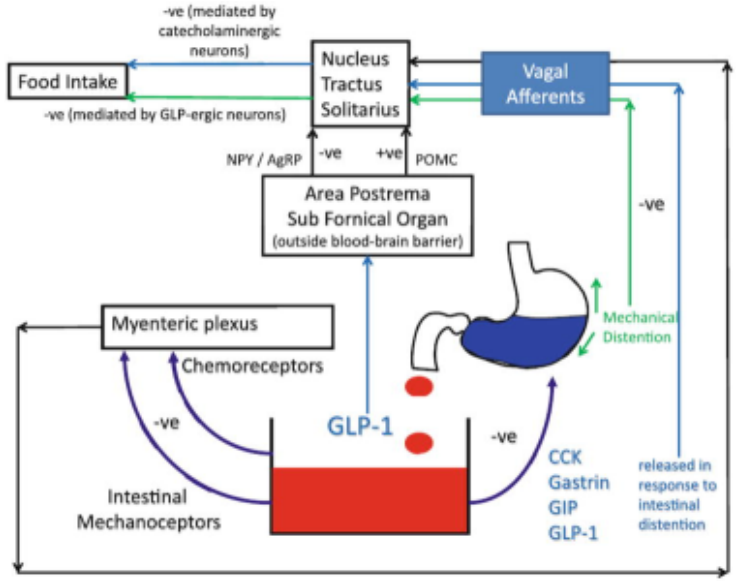


Flint A et al. J Clin Invest 1998

# GLP-1 and Satiation

- Meal-Induced Satiation


- GLP-1 may affect satiation through actions in both the brain and the gut
  - Effects on gastric function and vagal nerve signaling
  - Direct impact on central neuronal processes involved in regulation of feeding

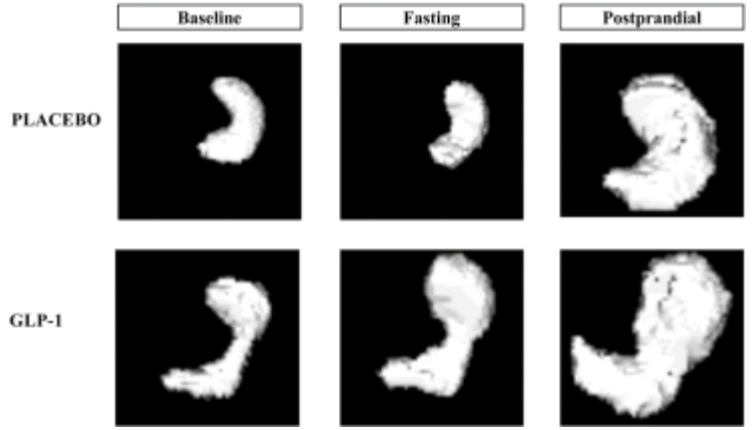





Shah M et al. Rev Endocr Metab Disord 2015

# GLP-1 and Gastric Function

- 24 healthy volunteers received GLP-1 (n=13) and placebo (n=11)
  - Scintigraphy at baseline, fasting, and post-prandially
  - Higher total and proximal gastric volume post-prandially in GLP-1 group
- Increase in gastric volume by GLP-1 is absent in diabetic patients with vagal neuropathy
  - GLP-1 effect on gastric volume is vagally-mediated

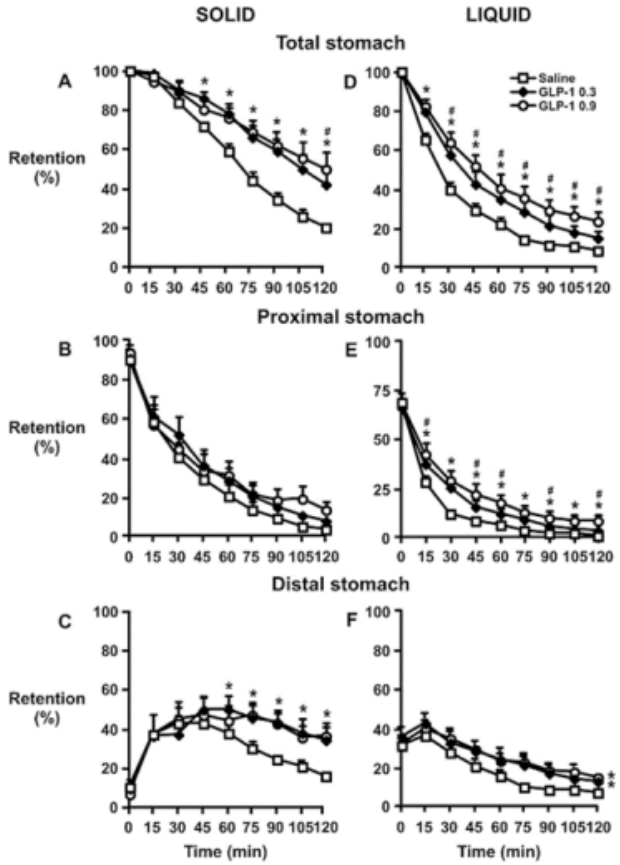





Delgado-Aros S et al. Am J Physiol Gastrointest Liver Physiol 2002
Delgado-Aros S et al. Neurogastroenterol Motil 2003

# GLP-1 and Gastric Function

- Increased accommodation is associated with slower gastric emptying
  - Higher total/proximal post-prandial volume correlates with rate of emptying
- Exogenous GLP-1 leads to delayed emptying of solids and liquids in healthy subjects
  - Increased meal retention in distal stomach
  - Rise in blood glucose attenuated by GLP-1
    - Blood glucose inversely correlates with gastric emptying time

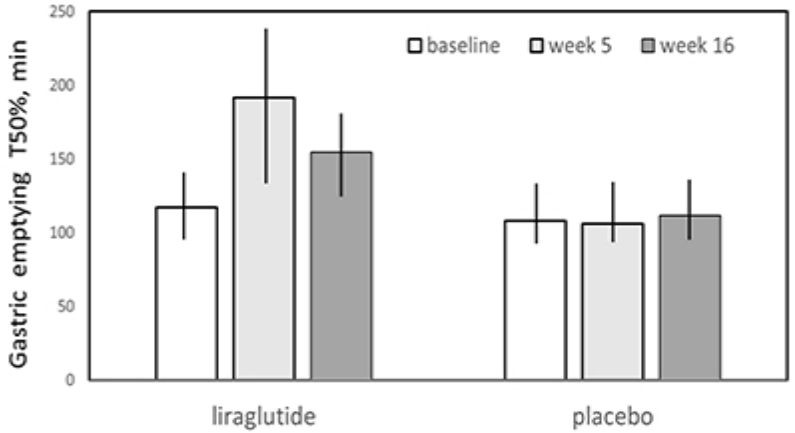


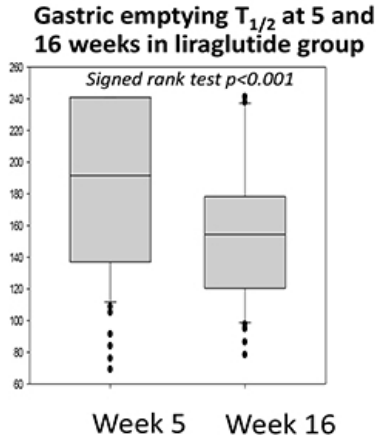



Wang XJ et al. Am J Physiol Gastrointest Liver Physiol 2021
Little TJ et al. J Clin Endocrinol Metab 2006

# GLP-1 Agonists and Gastric Function

- Randomized, placebo-controlled trial of liraglutide (n=59) vs placebo (n=65) in patients with obesity
  - Liraglutide associated with increased weight loss and satiation
  - $T_{1/2}$ on gastric emptying scintigraphy was prolonged in liraglutide group compared to placebo
    - Gastric emptying shorter at 16 weeks compared to 5 weeks after initiation of therapy -> tachyphylaxis






Maselli D et al. Obesity 2022

# GLP-1 Agonists and Gastric Function

- How much do GLP-1 agonists delay gastric emptying?
  - Meta-analysis of randomized placebo-controlled trials of GLP-1 agonists
  - Pooled delay in $T_{1/2}$ on scintigraphy (solid emptying) = **~36 minutes**
  - Pooled delay in $T_{max}$ on acetaminophen absorption test (liquid emptying) = **no significant delay**

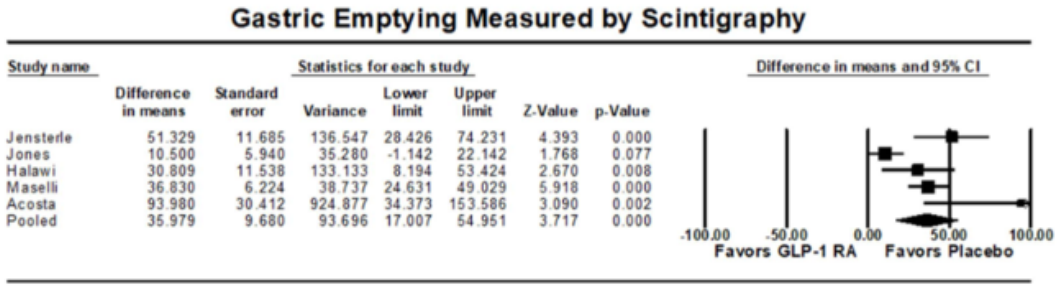



Figure 2. Gastric emptying study (scintigraphy) primary outcome ($T_{1/2}$, minutes), pooled mean difference. CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

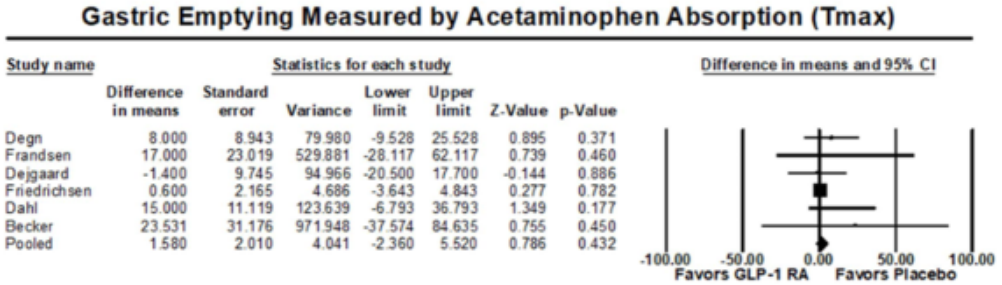


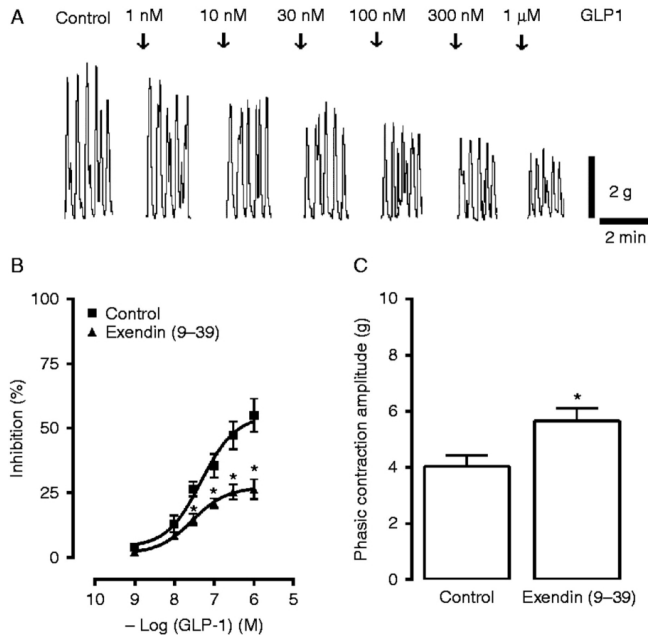

Figure 3. Acetaminophen absorption–based measurement of the gastric emptying primary outcome ($T_{max}$, minutes), pooled mean difference. CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist.



Hiramoto B / Chan WW et al. Am J Gastroenterol 2024

# GLP-1 and Intestinal Motility

- Exogenous GLP-1 inhibits colonic contraction amplitude and peristaltic function
  - Serosal GLP-1 relaxes colonic smooth muscle
  - Effect inhibited by GLP-1 receptor antagonists
- Endogenous GLP-1 secreted by luminal L cells accelerates proximal colonic motility
  - Luminally applied GLP-1 accelerated propagation of peristaltic waves in colonic segments
- GLP-1 may contribute to constipation or diarrhea

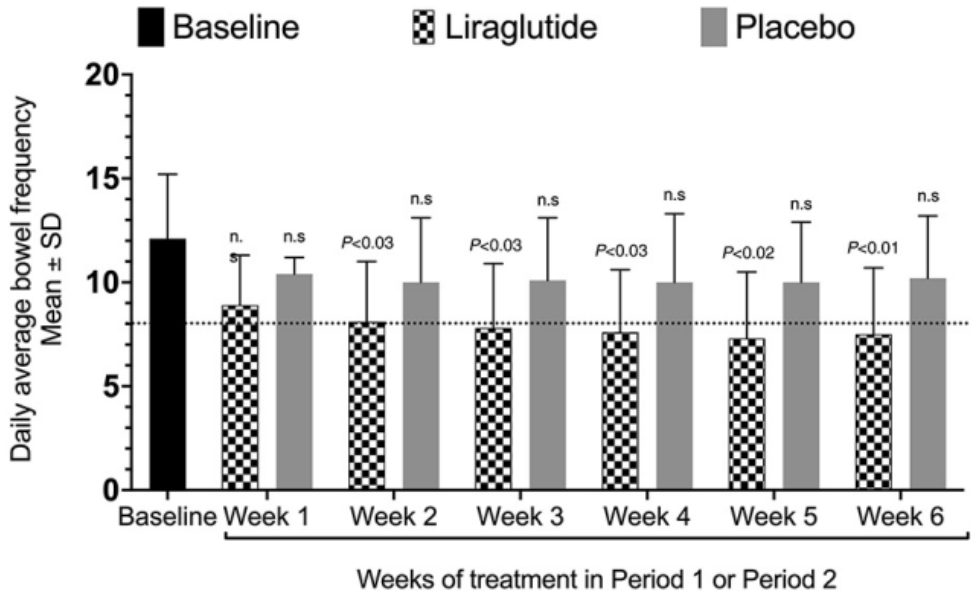





Amato A et al. J Endocrinol 2014
Nakamori H et al. Am J Physiol Gastrointest Liver Physiol 2021

# GLP-1 and Intestinal Motility

- Effect of GLP-1 on gastrointestinal motility may be leveraged for management of symptoms
  - Many post-colectomy/IPAA patients develop high bowel frequency
  - Low GLP-1 levels have been reported among colectomy patients
  - Pilot study showed decreased bowel frequency in post-colectomy/IPAA patients treated with liraglutide

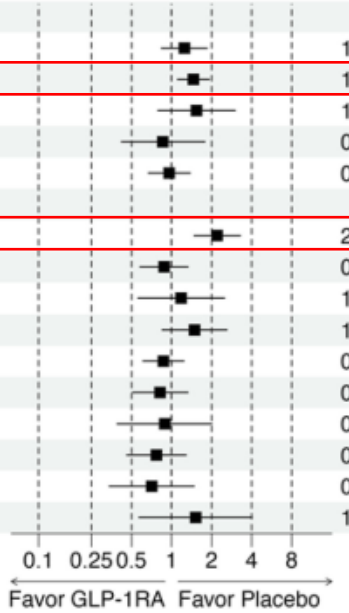





Barnes EL et al. Am J Gastroenterol 2024

# GLP-1 Agonists GI Effects

| Outcome | Number of Studies | Cases for GLP-1RA | At Risk for GLP-1RA | Cases for Control | At Risk for Control | RR (95% CI) | *P*-value | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| **Biliary adverse events** | | | | | | | | |
| Cholecystitis | 36 | 252 | 40199 | 172 | 33447 | 1.25 (0.84-1.85) | .27 | 46.59 |
| Cholelithiasis | 35 | 314 | 47580 | 186 | 40584 | 1.46 (1.11-1.92) | .01 | 21.8 |
| Cholangitis | 9 | 31 | 28489 | 17 | 27151 | 1.54 (0.79-3.01) | .20 | 15.3 |
| Cholestasis | 11 | 17 | 35370 | 19 | 33533 | 0.86 (0.42-1.78) | .69 | 11.5 |
| Pancreatitis | 24 | 148 | 44276 | 127 | 39026 | 0.96 (0.67-1.38) | .83 | 29.7 |
| **Gastrointestinal adverse events** | | | | | | | | |
| GERD | 32 | 468 | 44194 | 125 | 39404 | 2.20 (1.48-3.29) | <.01 | 61 |
| Gastritis | 20 | 91 | 39389 | 94 | 36679 | 0.88 (0.58-1.33) | .54 | 28.5 |
| Esophagitis | 11 | 19 | 35002 | 12 | 33144 | 1.18 (0.56-2.50) | .67 | 9.1 |
| Gastrointestinal ischemia | 16 | 36 | 38869 | 19 | 36572 | 1.49 (0.85-2.61) | .16 | 6.78 |
| Gastrointestinal hemorrhage | 23 | 271 | 40197 | 275 | 37289 | 0.87 (0.61-1.24) | .45 | 55.75 |
| Intestinal obstruction | 19 | 80 | 39830 | 86 | 36221 | 0.82 (0.51-1.33) | .43 | 35.3 |
| Paralytic Ileus | 8 | 18 | 34100 | 20 | 32884 | 0.89 (0.39-2.01) | .78 | 25.9 |
| Gastrointestinal ulceration | 19 | 62 | 40633 | 70 | 36808 | 0.77 (0.46-1.29) | .32 | 36 |
| Gastrointestinal perforation | 11 | 19 | 36796 | 26 | 34540 | 0.71 (0.34-1.48) | .36 | 24.2 |
| Gastroparesis | 10 | 12 | 25872 | 5 | 25531 | 1.52 (0.57-4.03) | .40 | 9.1 |




NO increased esophagitis

- Recent meta-analyses only found modestly increased risks of GERD (4 cases /1000 treated) and cholelithiasis (2/1000) with GLP-1 agonists
  - GERD risks most significant in studies with patients with overweight/obesity, MASH/MALD, or higher-dose/weight loss-inducing GLP-1 agonists



Chiang CH et al. Gastroenterology 2025

# GLP-1 Agonists GI Effects: Management

- Nausea, vomiting, constipation, diarrhea, altered appetite/satiety are common symptoms associated with GLP-1 agonists
- Potential underlying mechanisms
  - Delayed gastric emptying
  - Change in gastric accommodation
  - Altered intestinal motility
  - Impact on central control of appetite/feeding
  - Effect on gut-brain interactions / neurosensory input of GI tract

# GLP-1 Agonists GI Effects: Management

- Anti-emetics

Discontinue
GLP-1 agents

- Start at lowest dose with sl
- Dose de-escalation
- Change regimen/agent

- Reassurance: most symptoms observed during dose escalation and often improve with persistent use
- Lifestyle and dietary management of symptoms

# GLP-1 Agonists GI Effects: Management

| Symptoms | Characteristics | Conservative Measures | Pharmacotherapy | Considerations |
|---|---|---|---|---|
| **Nausea** | Often worse in morning or after long fasting<br>Usually transient | Gradual dose escalation<br>Small, frequent meals<br>Avoid high fiber and fatty foods | Prochlorperazine, dopamine D2 receptor antagonist, neuromodulators | Ondansetraon may worsen constipation<br>Promotility agents may worsen diarrhea |
| **Constipation** | May worsen baseline constipation or IBS-C symptoms<br>May be transient | Adequate hydration and increased fiber | Polyethylene glycol, fiber supplement, magnesium citrate, secretagogues, prucalopride | |
| **Diarrhea** | May worsen baseline chronicdiarrhea or IBS-D symptoms<br>May be transient | Gradual dose escalation<br>Dietary modification: avoid high fat meals, alcohol, artificial sweeteners | Fiber supplement, antidiarrheal medications | Consider overflow diarrhea |
| **Abdominal pain** | May be related to distention, bloating, dysmotility, GERD, biliary, or functional causes<br>Often transient | Gradual dose escalation<br>Dietary / conservative measures based on underlying cause | Treat underlying conditions<br>PPI, neuromodulators | IBS-related pain generally not exacerbated<br>Consider cholecystitis / choledocholithiasis |
| **GERD** | May be related to delayed gastric emptying or intestinal dysmotility | Gradual dose escalation<br>Lifestyle and dietary modifications for reflux | Acid suppression (PPI, H2RA, PCAB), promotility agents if evidence of delayed gastric emptying | |

# GLP-1 Agonists: Procedural Considerations

- Concern for possible risk of aspiration from delayed gastric emptying that may be associated with GLP-1 agonists use
- Retrospective observational studies showed increased rates of gastric residue on upper endoscopy
  - 5.4-24.2% with GLP-1 RA vs 0.5-5.1% with controls
  - Possible increased risk among those with diabetes and complications
  - Limitations:
    - Gastric residue = varying definitions of consistency and volume
    - Retrospective chart review based only on procedural reports



Kobori T et al. J Diab Invest 2023. Silveira SQ et al. J Clin Anesth 2023
Nadeem D et al. Gastrointest Endosc 2024. Garza K et al. Am J Gastroenterol 2024

# GLP-1 Agonists: Procedural Considerations

- Debates on proper peri-procedural management of patients taking GLP-1 agonist medications
- Initial conflicting guidelines/practice updates from professional societies
  - *American Society of Anesthesiologists* (Consensus-Based Guidance)
    - Withhold GLP-1 agents for a day (short-acting) or week (long-acting) before procedure
    - Delay procedure for patients with GI symptoms concerning for gastric residue or those who did not withhold medications
  - *American Gastroenterological Association* (Clinical Practice Update)
    - Continue GLP-1 agents
    - Liquid only diet on the day before procedure with standard fasting period



https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/american-society-of-anesthesiologists-consensus-based-guidance-on-preoperative

Hashash JG et al. Clin Gastroenterol Hepatol 2024

# GLP-1 Agonists: Procedural Considerations

- Concurrent colonoscopy (with clear liquid diet + bowel preparation) may decrease gastric residue risks with GLP-1 agonists
  - Case-control study of 612 patients undergoing endoscopy
    - Higher rates of gastric residue with GLP-1 agents (14% vs 4%), particularly in patients with type II diabetes, insulin-dependent, or with complications of diabetes
    - Lower rate of gastric residue if patients underwent prolonged fasting and clear liquids for concurrent colonoscopy (2%)
  - Retrospective cohort of 1512 GLP-1 agonist users undergoing endoscopy
    - Overall rate of retained gastric residue: 9.4%
    - Concurrent colonoscopy independently protects against retained residue (OR 0.34, $p<0.001$)



Garza K et al. Am J Gastroenterol 2024
Firkins SA et al. Clin Gastroenterol Hepatol 2024

# GLP-1 Agonists: Procedural Considerations

- Risk of respiratory complications with perioperative GLP-1 agonists
  - Large claim-based database (TriNetX) study of ~15,000 users vs non-users
    - 126 events in GLP-1 group vs 94 in non-users (absolute risk difference: 0.2%)
    - Limitation: inadequate control of confounding (lack of non-active comparator)
  - Large national database (Merative MarketScan) of 3502 GLP-1 agent users vs 20,177 non-users
    - Included only patients with same-day, emergent surgery (i.e. no withholding of meds)
    - Active comparator group of diabetes patients without prescription for GLP-1 agents
    - No difference in respiratory complication risks (OR 1.03, p=0.80)



Yeo YH et al. Gastroenterology 2024
Dixit AA et al. JAMA 2024

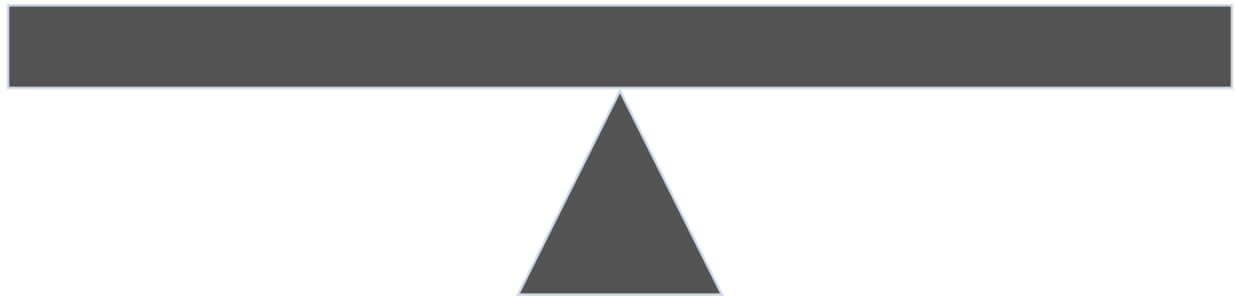
# GLP-1 Agonists, Foregut Motility, and Endoscopy Considerations

- What do we know about the endoscopy and peri-procedural considerations of GLP-1 agonists use?
  - Evidence of ↑ gastric residue
  - Some delay in solid emptying (but likely mild relative to pre-procedural fasting)
  - No/minimal delay in liquid emptying
    - Concurrent colonoscopy (with clear liquid diet + bowel prep) ↓ risk of gastric residue
  - No clear evidence of increased respiratory complication related to GLP-1 agonists use
  - Modestly increased risk for inadequate bowel preparation and incomplete/aborted examinations

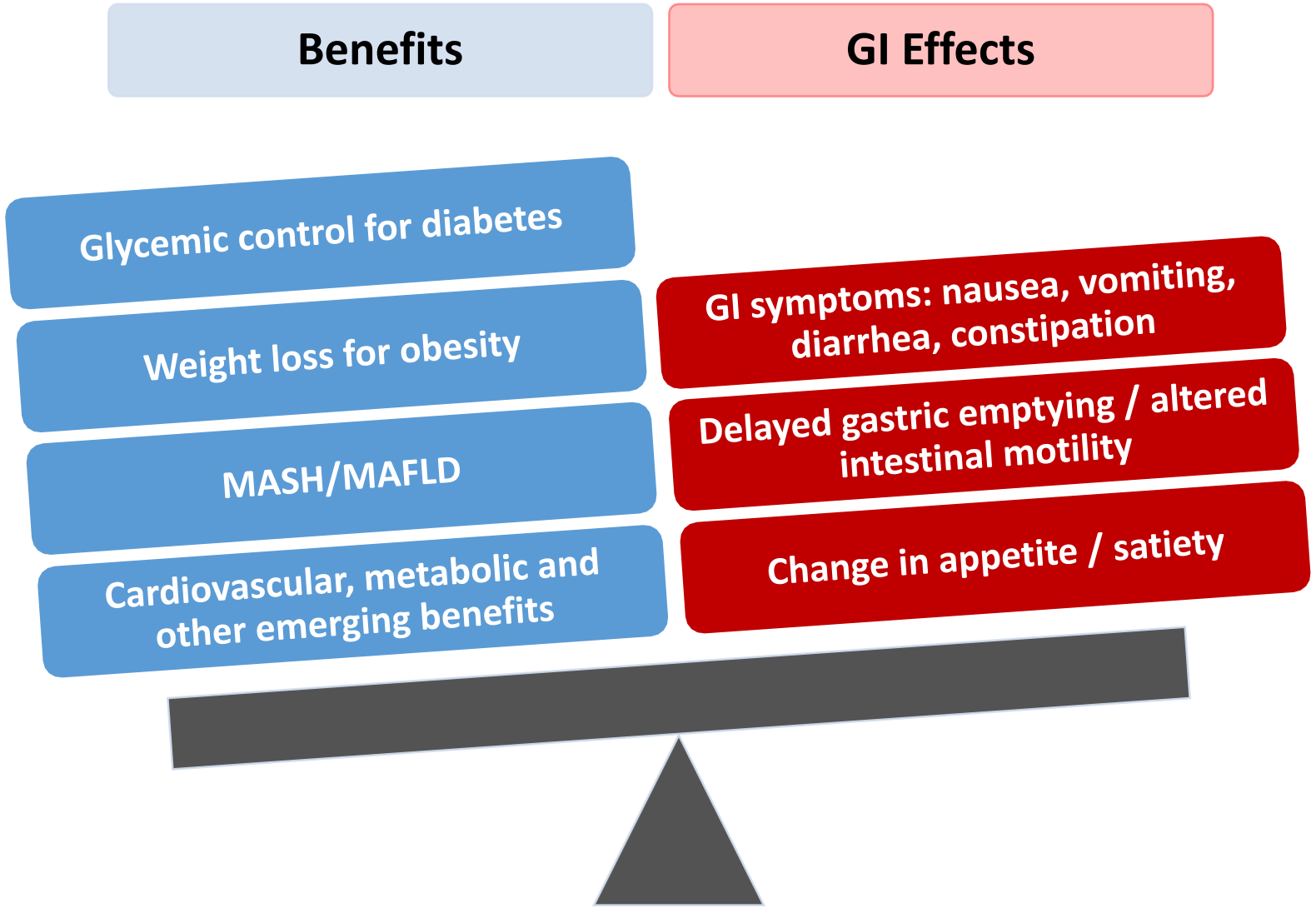
# GLP-1 Agonists: Friend or Foe?

**Benefits**

**GI Effects**



# GLP-1 Agonists: Friend or Foe?



# Take-Home Points

- Common GI effects of GLP-1 agonists: nausea, diarrhea, constipation, vomiting, abdominal pain, dyspepsia, reflux
  - GLP-1 effects on GI tract may be due to different mechanisms:
    - Dysmotility, central impact on satiety/appetite, altered gut-brain interactions
- Management of symptoms
  - Conservative – most symptoms improve over time
  - Dosage / agent adjustment – slower titration, dose de-escalation, change agents
  - Pharmacotherapy – anti-emetics, bowel regimen, promotility agents, neuromodulators
- Multidisciplinary approach to pre-procedural GLP-1 users management
  - Respiratory complication risk appears to be low, and may be further modulated with clear liquid diet prior to procedure

# Thank You

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