Submission Window Closes: August 31, 2025

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Participating in the Webinar

Moderator:
Catherine T. Hudson, MD, MPH

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them.
Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.

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ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 26 – Thursday June 26, 2025
GI Nutrition Care Series: Weight Inclusive Care & Bias
Faculty: Carolyn Newberry, MD
Moderator: Beth Rosen, MS, RD, CDN
At Noon and 8pm Eastern

Week 27 – Thursday, July 3, 2025 - NO VGR

Week 28 – Thursday July 10, 2025
Evaluation and Management of Chronic Abdominal Pain and Suspected IBS
Faculty: Jill K. Deutsch, MD
Moderator: Amy L. Ogurick, MD
At Noon and 8pm Eastern

Visit **gi.org/ACGVGR** to Register

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Disclosures

Michael Camilleri, MD, MACG: Alfasigma: Consultant; Amylyx Pharmaceuticals: Consultant (Funds go to Mayo Clinic); BioKier: Consultant; Biocodex: Research Grant; Brightseed Bio: Research Grant (Funds go to Mayo Clinic); Coloplast: Consultant (Funds go to Mayo Clinic); Dignify Therapeutics: Stock options; Invea Therapeutics: Consultant (Funds go to Mayo Clinic); Intercept Pharmaceuticals: Consultant; Kallyope: Consultant (Funds go to Mayo Clinic); Kellyope Monteresearech S.r.L.: Consultant (Funds go to Mayo Clinic); McDermott Willl: Consultant (Funds go to Mayo Clinic); Medpace: Consultant; Neurogastrx: Consultant (Funds go to Mayo Clinic); NGM Biopharmaceuticals: Research Grant; Phenomix: Stock options; Pfizer: Research Grant; Renexxion: Consultant (Funds go to Mayo Clinic); ; SKYE Bioscience: Consultant, Other (Funds go to Mayo Clinic); Sumitomo Pharmaceuticals: Consultant (Funds go to Mayo Clinic); Synlogic: Consultant (Funds go to Mayo Clinic); Vanda: Research Grant.

Catherine T. Hudson, MD, MPH: No relevant financial relationships with ineligible companies.

**All of the relevant financial relationships listed for these individuals have been mitigated*

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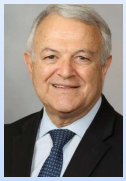
GLP-1s and GI Complications What Every Clinician Needs to Know



Michael Camilleri, MD, MACG
C.E.N.T.E.R Program, Mayo Clinic, Rochester, MN

MAYO CLINIC

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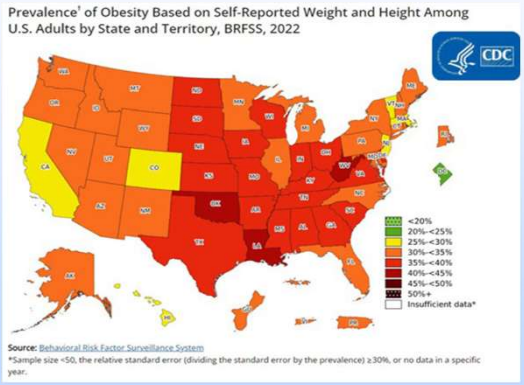
Overall Objective

To explain mechanisms and management of GLP-1-induced effects in gastroenterology and endoscopic practice



Specific Objectives

- Case Study
- Neurohormonal responses to nutrient intake
- Actions of GLP-1
- Currently approved incretin agonists
- Beneficial effects on obesity, co-morbidities, GI and liver
- Effects on gastric emptying: positives and negatives
- EGD: Retained gastric content, Risk of aspiration, gastroparesis
- Recommendations

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MOC Statement #1

- I will learn about the beneficial effects of GLP-1 agents on weight loss, diabetes control and other health benefits

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MOC Statement #2

- I will learn about the potential effects of GLP-1 agents on gastrointestinal adverse effects I may encounter in my GI practice including nausea and vomiting, intestinal obstruction, pancreatitis
- I will learn risks of complications I may encounter in the endoscopy room including:
  - Risk of retained gastric content
  - Risk of needing to re-schedule the procedure
  - Risk of aspiration of gastric contents

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MOC Statement #3

- I will learn how to pre-procedurally manage patients in accordance with guidance from national organizations, with particular focus, in patients on GLP-1 agents on
  - Screening patients for symptoms of gastroparesis
  - Using 24 h liquid diet instead of just overnight fast
  - Deciding who should have GLP-1 agent stopped on the day before (liraglutide) or the week before (semaglutide, dulaglutide, extended exenatide, tirzepatide) the procedure
  - Point of care ultrasound?

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Case Study

1 year ago: 44 y/o female, gravida 2, depressed since no amount of exercise or dieting has worked despite 5 years of effort and "yo-yo" weight

BMI 42.1kg/m^2; weight 85kg (187 lb)
Fasting Blood Glucose 185mg/dL; HbA1c 9.8%
AST 90 iu/L; ALT 75 iu/L; fatty infiltration of liver on Ultrasound

1yr ago: Hypertension on amlodipine, bendrofluazide; DM2 on metformin
Started on Semaglutide, dose-titrated from 0.25mg/week to 1.7mg/week

Last month: BMI 34kg/m^2; weight 75kg (165 lb); FBG 102mg/dL; HbA1c 6%; off metformin

Delighted with outcome: dress size ↓ 2 sizes; off antihypertensives

"Background symptoms" nausea, postprandial fullness, constipation
vomiting twice per month, mostly after eating large green salad

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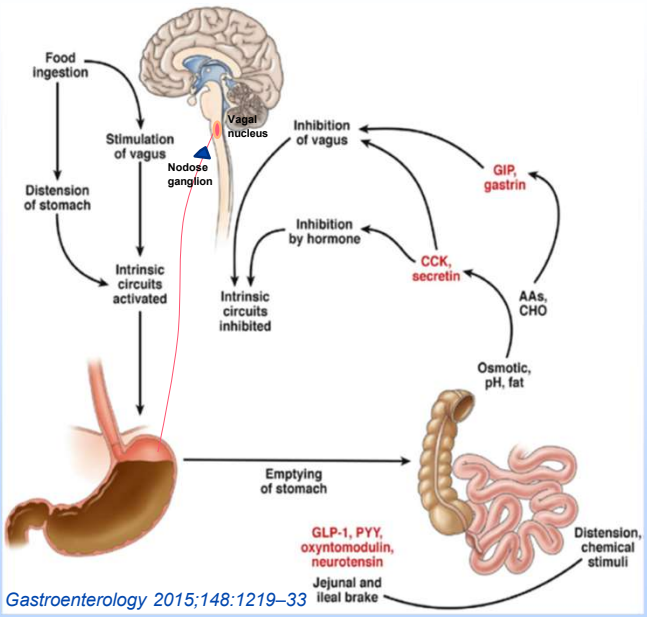
Interaction of nutrient intake & neurohormonal responses



Gastroenterology 2015;148:1219–33

Arrival of monosaccharides and disaccharides in the upper gastrointestinal tract stimulate leads to release of glucagon like peptide-1 (GLP-1) from the intestinal mucosa and insulin from the pancreatic beta cells. Arrival of nutrients in the more distal small intestine and colon is associated with release of several hormones such as GLP-1, peptide tyrosine tyrosine (PYY), oxyntomodulin, and neurotensin

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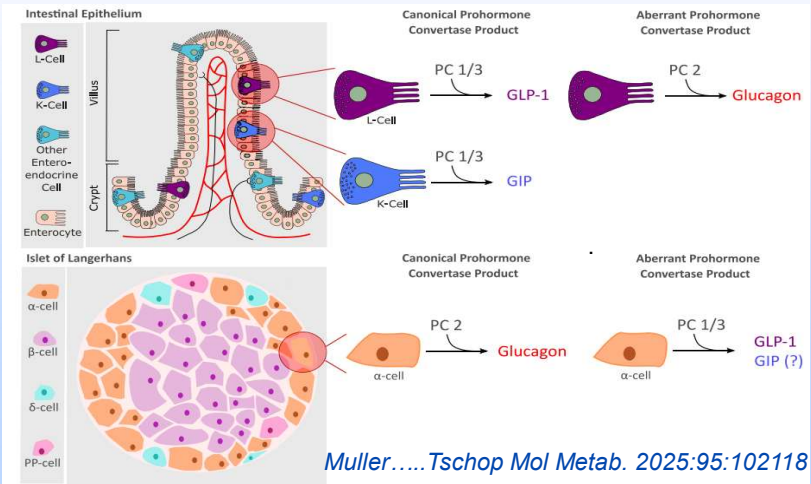
Processing of incretins by prohormone convertase

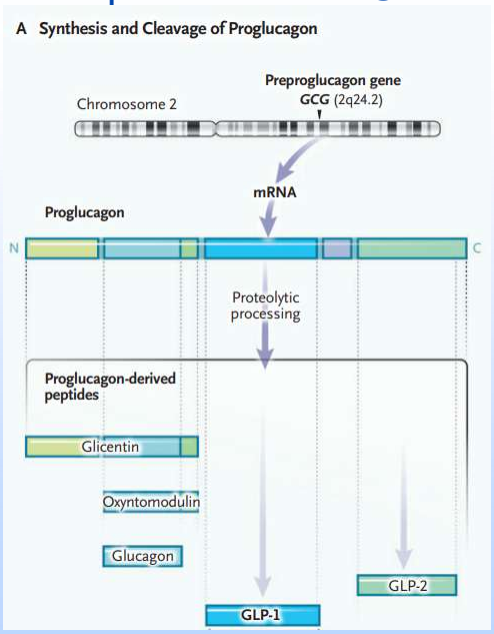
- In normal physiology: proglucagon is processed into glucagon by prohormone convertase 2 (PC2) in the islet alpha cells, and into GLP-1 by prohormone convertase 1/3 (PC1/3) in intestine L-cells. ProGIP is processed into GIP by PC1/3 in intestine K-cells
- Under certain conditions intra-islet production of GLP-1 and GIP potentially occurs through increased PC1/3 activity. Glucagon may be aberrantly produced in intestinal L-cells via PC2



Muller…..Tschop Mol Metab. 2025:95:102118

16

Endogenous production of GLP-1



Drucker DJ. N Engl J Med. 2025;392:612-615

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Glucagon-like Peptide 1

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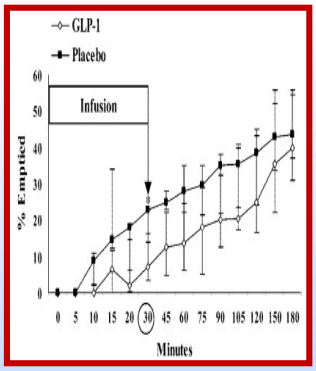
- Inhibits gastric emptying and motility
- Reduces appetite
- Increases insulin secretion, pancreatic β cell proliferation
- Reduces glucagon secretion
- Hypothalamus GLP-1 receptors regulate food intake through
  - Processes in nucleus tract solitarius
  - Direct stimulation of proopiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART)-expressing arcuate nucleus neurons and
  - Indirect inhibition of neuropeptide Y (NPY) and agouti-related peptide (AgRP) to increase satiety and decrease hunger

Radiolabeled Ensure at 30kcal/min to Maximum Tolerated Volume



Delgado-Aros, Camilleri, Vella, Rizza et al AJP 282: G424–G431, 2002

18

Effect of GLP-1 infusion on caloric intake: 9 RCTs

TABLE 1. Characteristics of nine randomized cross-over trails investigating the effect of iv GLP-1 infusion on *ad libitum* energy intake

Author, yr (Ref.)	No.	BMI (kg/m^2)	Infusion rate $pmol/kg^{-1}\cdot min^{-1}$	Duration of infusion prior to *ad libitum* meal (min)	Difference in *ad libitum* energy intake (kJ)
Flint *et al.*, 1998 (1)	19	22.9 (0.3)	0.83	240	−528 (150)
Näslund *et al.*, 1998 (5)	6	35.7 (1.8)	0.75	0	−15 (176)
Näslund *et al.*, 1999 (6)	8	45.5 (2.3)	0.75	240	−520 (164)
Long *et al.*, 1999 (7)	10	23.2 (0.6)	1.2	40	−417 (243)
Gutzwiller *et al.*, 1999 (8)	16	23.3 (0.2)	0.375	60	−452 (225)
			0.75	60	−739 (281)
			1.5	60	−2179 (299)
Gutzwiller *et al.*, 1999 (9)	12	29.0 (1.2)	1.5	60	−1046 (401)
Flint *et al.*, 2001 (10)	17	33.6 (0.6)	0.50[a]	240	−87 (176)
Beglinger *et al.*, unpublished data	12	22.8 (0.2)	0.9	60	−559 (313)
Beglinger *et al.*, unpublished data	15	22.5 (0.5)	0.9	60	−925 (313)

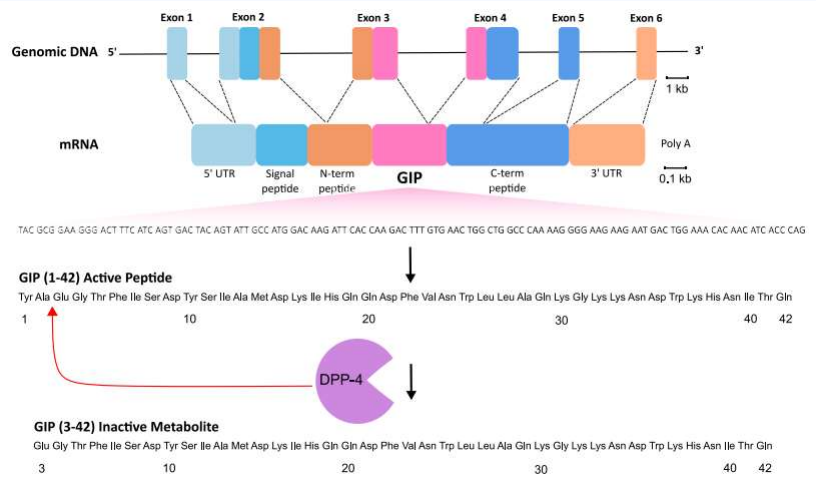
Data are expressed as mean (SEM).
[a] Range 0.45–0.52 $pmol/kg^{-1}\cdot min^{-1}$ (SEM, 0.005).

Verdich C, et al. J Clin Endo Metatab. 2001;86:4382-9.

19

Genetic encoding and peptide processing of GIP

- GIP in encoded by the GIP gene on chromosome 17, consisting of six exons. The majority of the sequence encoding GIP peptide is localized to exon 3 (highlighted in pink). A 153-amino acid long proGIP precursor is processed by prohormone convertase 1/3 to produce bioactive GIP1-42. GIP1-42 is rapidly degraded by dipeptidyl peptidase-4 (DPP4) into the inactive GIP3-42



Muller…..Tschop Mol Metab. 2025:95:102118

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GIP: glucose-dependent insulinotropic peptide

- Inhibits acid secretion
- Increases insulin secretion and β cell proliferation in healthy humans, with markedly reduced insulinotropic effect in T2DM (*Nauck, Heimesaat, et al. 1993; Meier, Nauck, 2004*)
- Acute administration of GIP does not influence appetite and food intake in human participants e.g. in patients with T2DM receiving metformin and a long-acting GLP-1 receptor agonist (*Bergmann, Gasbjerg, et al. 2020*)

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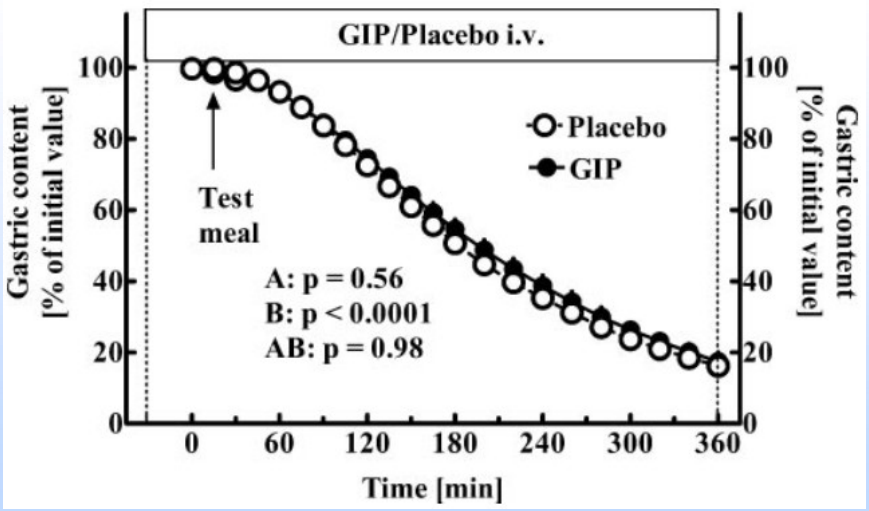
GIP: NO significant effect on gastric emptying of solids (250kcal)

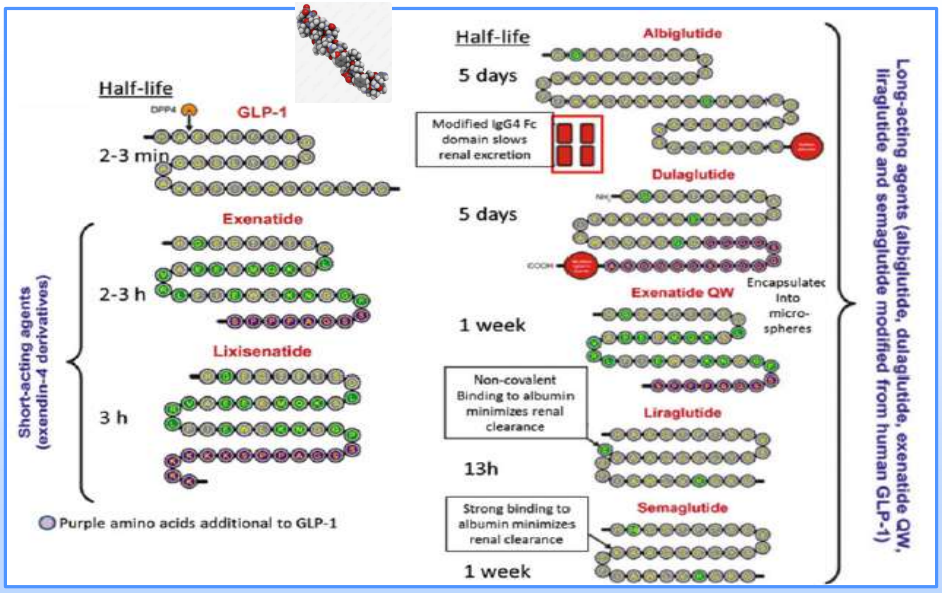
i.v. GIP (2 pmol/kg/1min) or placebo (human serum albumin) from -30 to 360 min in 15 healthy male subjects.



Meier JJ…Nauck MA Am J Physiol Endocrinol Metab. 2004;286(4):E621-5.

22

Structure and properties of GLP-1 receptor agonists: From $T_{1/2}$ of 2-3 min to daily, to weekly, to oral therapy



Gentilella et al. Diabetes Metab Res Rev. 2019;35(1):e3070)

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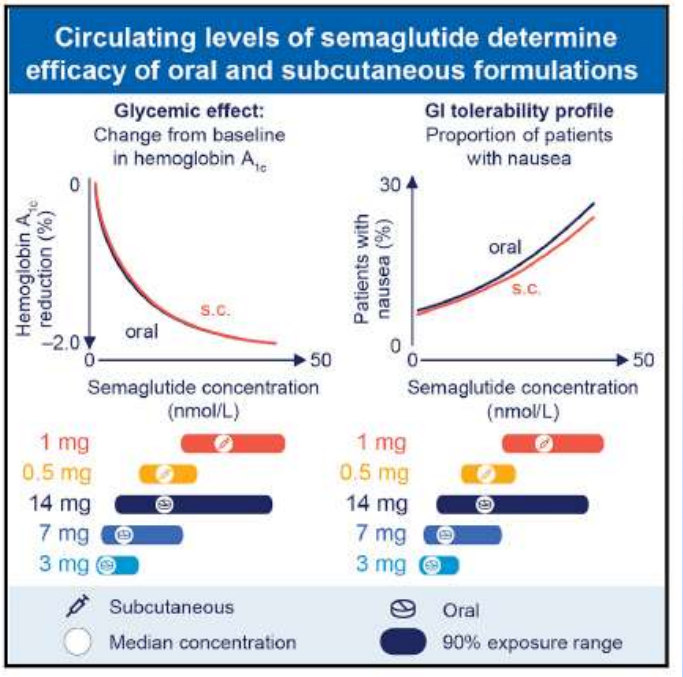
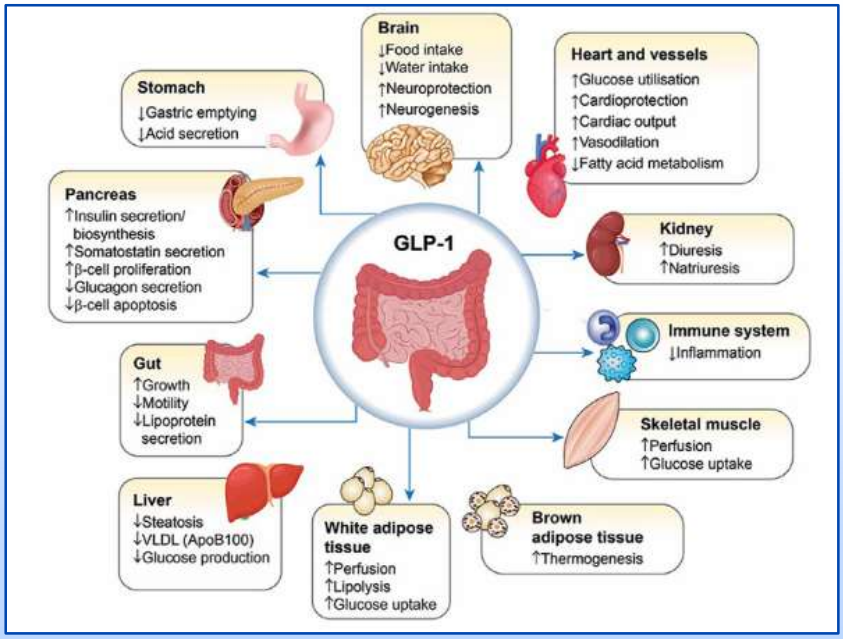
Oral formulation of semaglutide is based on co-formulation with SNAC (sodium N-[8-(2 hydroxybenzoyl) amino] caprylate



Overgaard…Drucker Cell Reports Medicine (2021),

24

GLP-1 receptor activation mechanism of action by organ



Myerson M, Paparodis RD. J Clin Pharmacol. 2024; 64: 1204-1221.

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Currently approved incretin agonists for treatment of type 2 DM and weight loss

Drug name (brand name)	Dose/ routes of Administration	Mechanisms of action	Indications	Elimination $T_{1/2}$	Common GI-related AEs	Recommendation on drug titration
Short-acting GLP-1 RA						
Exenatide (Byetta®)	Twice-daily SQ injection	↑ glucose-dependent insulin secretion from pancreatic β cells Suppress glucagon secretion Delays gastric emptying	Glycemic control in T2DM	2.4hr	nausea, diarrhea, vomiting	Start: 5mg BID Week 4: 10mg BID
Long-acting SQ GLP-1 RA						
Liraglutide (Victoza®)	Once-daily SQ injection	↑ glucose-dependent insulin secretion from pancreatic β cells Suppression of glucagon secretion Delay gastric emptying	Glycemic control in T2DM Weight management in adults with BMI >30 or BMI >27 + 1 weight related comorbidity (HTN, T2DM, HLD)	13hr	nausea, vomiting, diarrhea, decreased appetite, constipation, dyspepsia and abdominal pain, eructation	Start: 0.6mg daily; increase dose by 0.6mg/week until full maintenance dose of 3mg)
Semaglutide SQ (Ozempic® or Wegovy®)	Once-weekly SQ injection			7 days	nausea, vomiting, diarrhea, abdominal pain, and constipation	Start: 0.25mg/week; Week 4: 0.50mg/week; Week 8: 1 mg/ week
Dulaglutide (Trulicity®)			Glycemic control in T2DM	5 days	nausea, diarrhea, vomiting, dyspepsia	1.5mg q. week
Exenatide ER (Bydureon®)				8-16hrs	nausea, diarrhea, vomiting	2mg weekly (no dose adjustment)
Long-acting Oral GLP-1 RA						
Semaglutide PO (Rybelsus®)	Once-daily per oral	↑ glucose-dependent insulin secretion from pancreatic β cells; suppresses glucagon secretion; delays gastric emptying	Glycemic control in T2DM	7 days	nausea, abdominal pain, diarrhea, decreased appetite, vomiting, constipation	Start: 3mg daily; Week 4: 7mg daily; Week 8: 14mg daily
Long-acting Dual Incretin GIP/GLP-1 RA						
Tirzepatide (Mounjaro®)	Once-weekly SQ injection	↑ insulin response; suppresses glucagon secretion; promotes satiety; improves insulin sensitivity	Glycemic control in T2DM and obesity	5 days	nausea, vomiting, diarrhea, decreased appetite, constipation, dyspepsia, and abdominal pain	Start 2.5mg weekly; increase dose by 2.5mg/4 weeks until full maintenance dose of 15mg at week 20

Camilleri, Lupianez-Merly AJG 2024;119:1028–1037.

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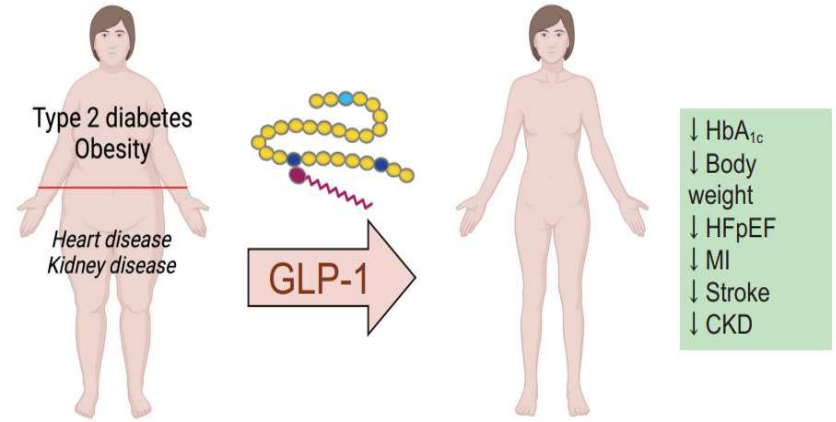
Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity



Adverse Events
Nausea, vomiting, constipation, diarrhea, abdominal discomfort, fatigue, gallbladder disease, acute kidney injury

CKD, chronic kidney disease; GLP-1, glucagon-like peptide 1; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction.

Daniel J. Drucker Diabetes Care 2024;47: 1873-1888

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Benefits of GLP-1 RAs on Obesity co-morbidities

- Cardiovascular outcomes in obesity with or without diabetes *Lincoff et al NEJM 2023;389:2221-32; Kosiborod et al NEJM 2024;390:1394-1407*
- Slowing the motor progression of early Parkinson's disease with lixisenatide *Meissner et al N Engl J Med 2024;390(13):1176-1185*
- Beneficial effects for primary stroke, major adverse cardiovascular events, and cardiovascular mortality prevention based on a SRMA of patients with diabetes treated with GLP-1 RAs in 8 randomized controlled trials *Malhotra et al N Engl J Med 2024;390: 1176-1185*.

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Benefits of glycemic control and GLP-1RAs in diverse GI diseases

- Reduction of 10-year risk of major adverse liver outcomes (MALO): decompensated cirrhosis, HCC, liver transplantation or MALO-related death, based on Swedish healthcare registers (2010–2020). *Wester et al Gut 2024;73(5):835-843*
- NAFLD increases risk of T2D, malignancy, and other cardiometabolic disorders including incident major adverse cardiovascular events (MACE): THEREFORE, treat MASLD in obese young people *Byrne and Targher Gut 2023;72(7):1238-1239*
- Detrimental effects of lifestyle and diet on metabolic disorders and developing IBD and a poor disease course *Adolph et al Gut. 2024 May 22:gutjnl-2024-331914.*
- Optimal glycemic control (HbA1c <7%) in diabetes reduced risk of colorectal adenoma and cancer in left-sided colon and rectum *Mao et al Gut. 2024 Apr 3:gutjnl-2023-331701*.

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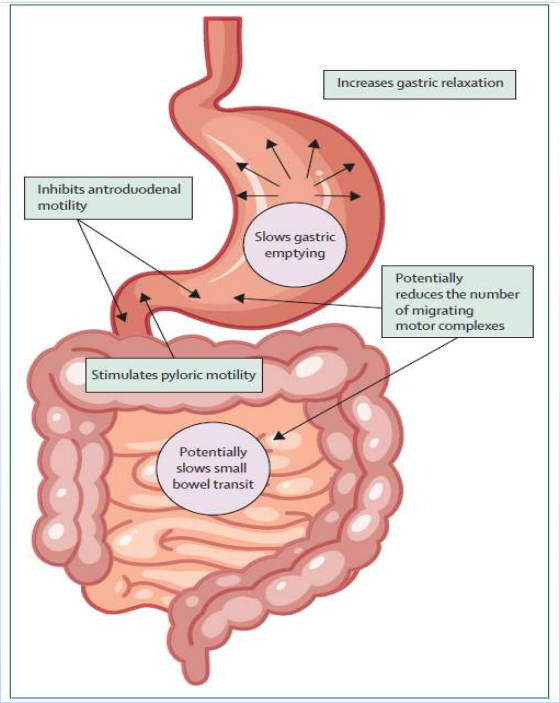
Effects of GLP-1 on gastric and small intestinal motility



Jalleh….. Horowitz et al Lancet Gastro Hepatol 2024;9: 957-964

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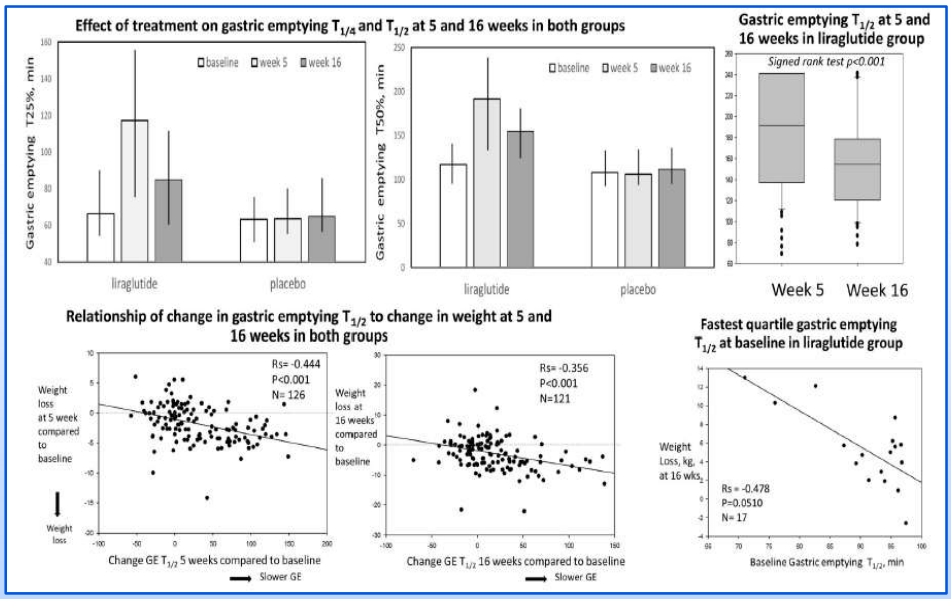
Slowing gastric emptying is associated with weight loss



Maselli, Atieh et al Obesity (Silver Spring). 2022;30:1608–1620.

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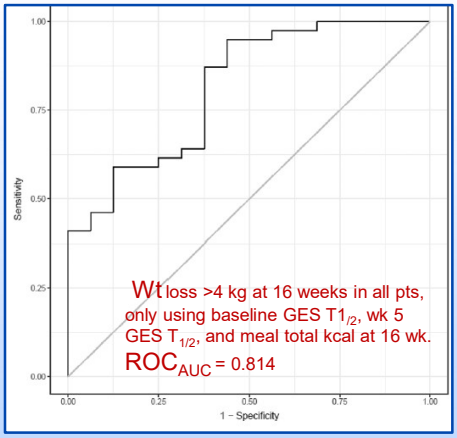
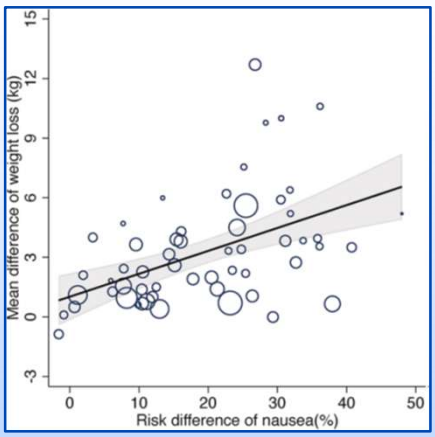
Factors associated with successful weight loss after liraglutide Rx for obesity



Sannaa, Dilmaghani, Camilleri et al Diab Obes Metab. 2023;25:377-386.

Univariate meta-regression: **Association of risk difference of nausea with absolute excess weight loss** vs. placebo; analysis of >24,000 randomized participants



Vosoughi, Roghani, Camilleri Obesity Medicine 35 (2022), 100456

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Lower risk of IBD-related surgery in UC or CD in T2DM in pts on GLP-1RA

- Retrospective cohort study utilizing the TriNetX database comparing IBD-specific outcomes in patients with ulcerative colitis or Crohn's disease and type 2 diabetes mellitus (T2DM) on GLP-1RA compared to oral hypoglycemics
- 1:1 propensity score matching (PSM) for demographics, co-morbid conditions, BMI, laboratory values, HbA1c, and IBD medications including steroids.
- 1130 UC and 1140 CD on GLP-1 RAs
- RESULTS: no difference in the risk of intravenous steroid use, oral steroid use or advanced therapy initiation for UC or CD
- Lower risk of colectomy (aHR: 0.37, 95% CI:0.14–0.97) in UC GLP-1RA vs control
- Lower risk of surgery (aHR: 0.55, 95% CI: 0.36–0.84) in CD GLP-1RA vs control
- NO increased GI adverse effects (biliary disease, pancreatitis, gastroparesis, ileus)

Desai….Hashash…. Farraye Aliment Pharmacol Ther. 2024;60:620–632

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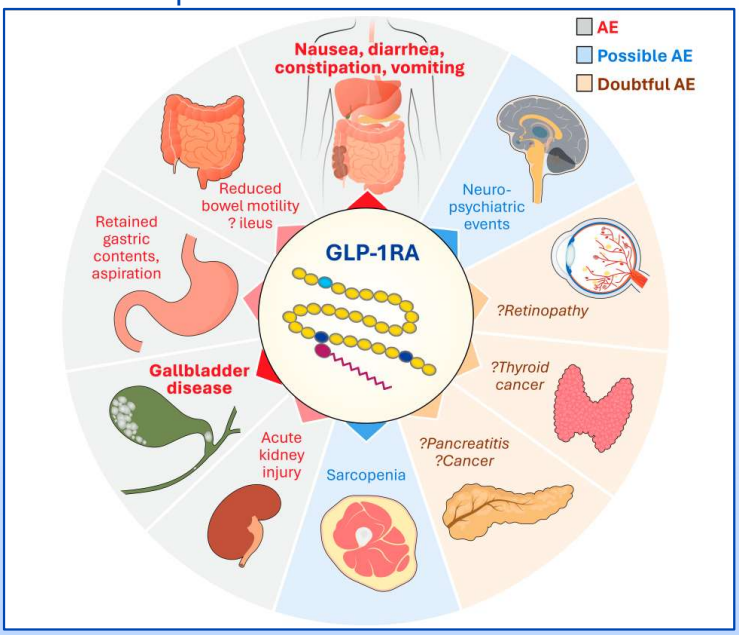
Established and putative AEs associated with GLP-1 medicines



Daniel J. Drucker Diabetes Care 2024;47: 1873-1888

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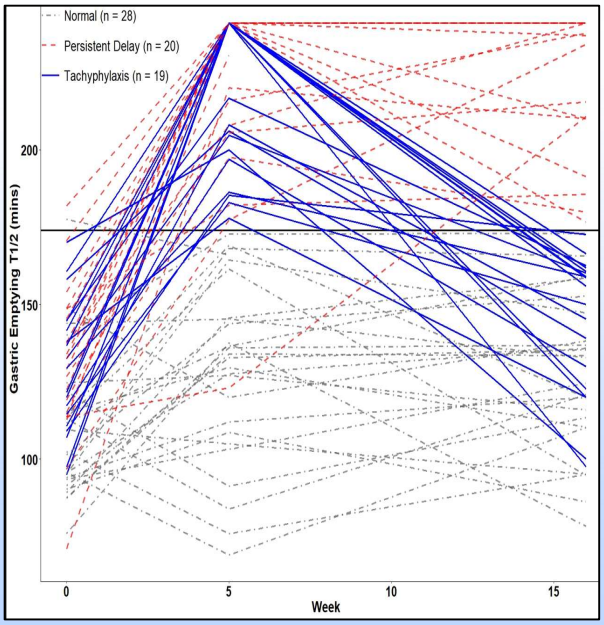
Gastric emptying delay in response to GLP-1 RA liraglutide

Effect of liraglutide escalated up to 3.0 mg/day on gastric emptying of solid 320kcal 30% fat meal in 67 patients with obesity without DM2: 42% had no slowing of GE $T_{1/2}$ at any time, whereas **57% had very significant delay in GE $T_{1/2}$ at 5 weeks** and 1 participant developed delay by 16 weeks.
In those who developed delay, 20/39 (51%) had persistent slowing of GE $T_{1/2}$, whereas 19/39 had marked improvement or normalization of GE $T_{1/2}$ at 16 weeks.
Data censored at maximum 240min
In summary, **20/67 (30%) pts have persisted GE delay for at least 16 wks**



Camilleri M et al Obesity (Silver Spring). 2024;32: 232-233

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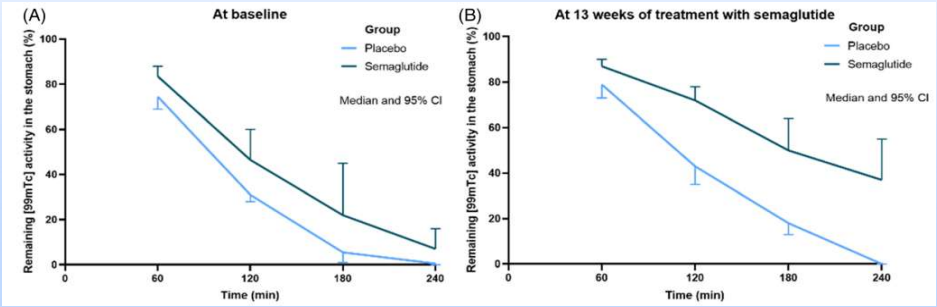
Semaglutide delays 4-h GE of ^{99m}Tc pancake in women with PCOS and obesity

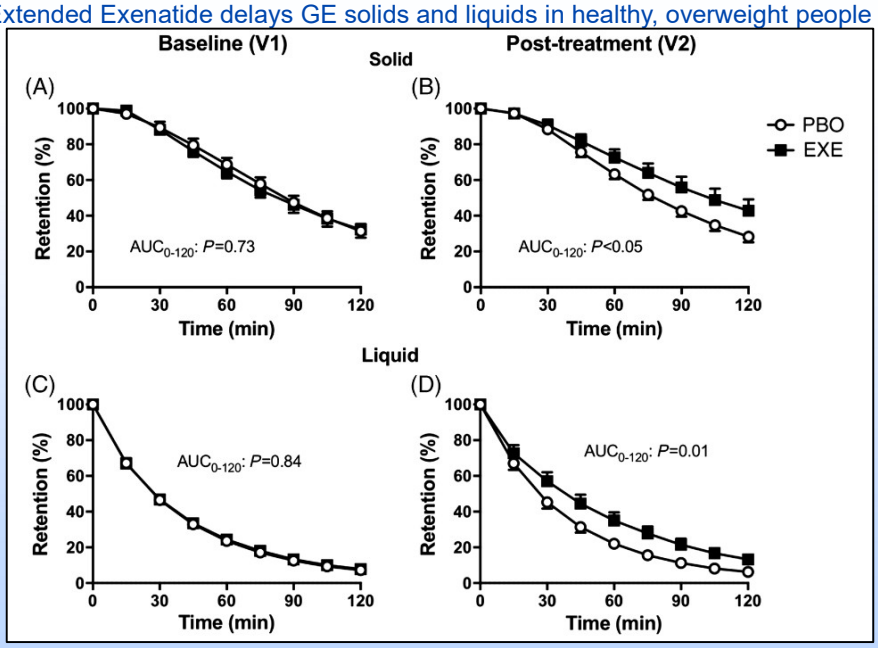
Characteristic, % of estimated retention of gastric contents	Placebo group, N = 9			Semaglutide group, N = 10			Between-group comparison posttreatment
	Pretreatment Median value (25%-75%)	Posttreatment Median value (25%-75%)	P[a]	Pretreatment Median value (25%-75%)	Posttreatment Median value (25%-75%)	P[a]	P[b]
Dynamic imaging							
Td 15 min	94 (92.5-96.5)	94 (91.5-95.5)	0.726	95 (92.8-97)	96.5 (93.8-99)	0.311	0.113
Td 30 min	89 (87-91.5)	89 (84.5-90)	0.310	91 (89-93.3)	92.5 (87.8-95)	0.283	0.050
Td 45 min	83 (77.5-85)	82 (78.5-86)	0.953	87.5 (85.5-88.5)	90 (83.8-93.3)	0.256	0.013
Td 60 min	79 (69.5-81.5)	78 (73-82.5)	0.678	83 (80.8-87.3)	85.5 (82.3-90.5)	0.332	0.017
Static imaging							
Ts 1 h	73 (69.5-78)	79 (74.5-81)	0.327	83.5 (79.8-87.3)	87 (84.8-89.3)	0.092	<0.001
Ts 2 h	31 (29-36.5)	43 (36.5-53)	0.109	46.5 (25-55.5)	72 (60-78)	0.009	0.001
Ts 3 h	5 (2-9)	18 (13-32.5)	0.061	22 (6.5-34.5)	50 (35.5-58.8)	0.046	0.008
Ts 4 h	0 (0-1.5)	0 (0-10.5)	0.262	7 (0.8-14.5)	37 (17-47.5)	0.028	0.002
$T_{1/2}$, min	105 (90.5-117)	118 (108-132)	0.139	128 (108.5-141.8)	171 (154-187.5)	0.036	<0.001



Jensterle et al Diabetes Obes Metab. 2023;25: 975-984

36

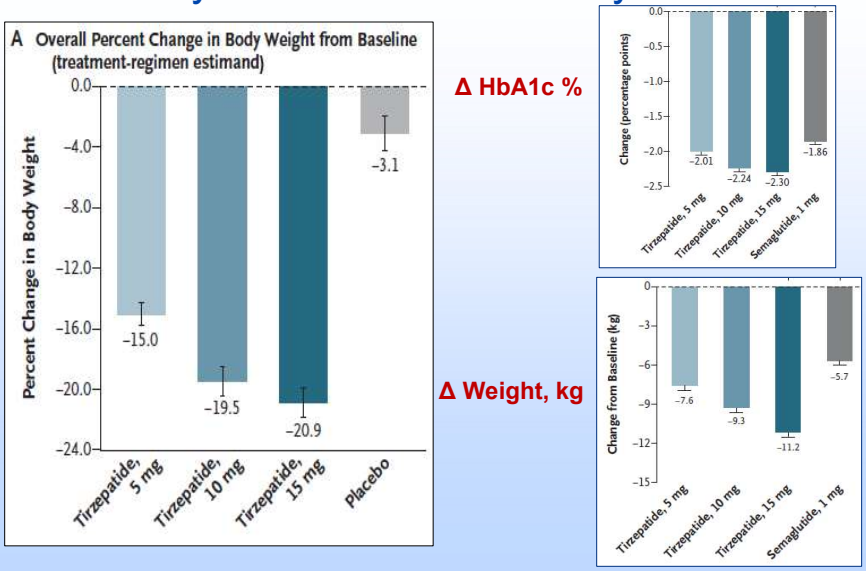
Extended Exenatide delays GE solids and liquids in healthy, overweight people



Jones KL et al Diabetes Obes Metab 2020;22:788-797

37

Dual incretin agonist tirzepatide (GLP-1 and GIP) SQ weekly efficacious for obesity and T2DM



Jastreboff et al NEJM 2022;387:205-16; Frias et al N Engl J Med 2021;385:503-15

38

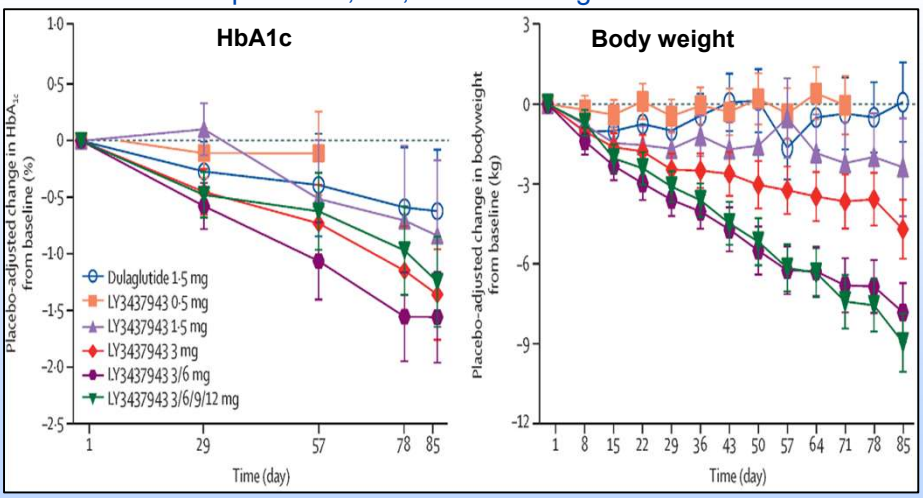
Glucagon

- Glucagon is produced by islet α-cells and is an important insulin secretagogue at least at the concentrations found within the islet.
- α-cell dysfunction as occurs in T2DM, prediabetes results in increased glucagon concentrations.
- Abnormal α-cell function represents an effort to stimulate (failing) β-cell function in these situations.
- Glucagon can signal through GLP1R on β-cells
- Intra-islet concentrations of glucagon are sufficiently high to stimulate GLP1R
- Glucagon receptor (Gcgr) is unnecessary for glucagon-induced insulin secretion

39

Triple agonist Retatrutide SQ weekly efficacious for obesity and T2DM

Novel triple GIP, GLP-1, and glucagon receptor agonist, retatrutide, in DM2: a phase 1b, DB, PC ascending dose RCT

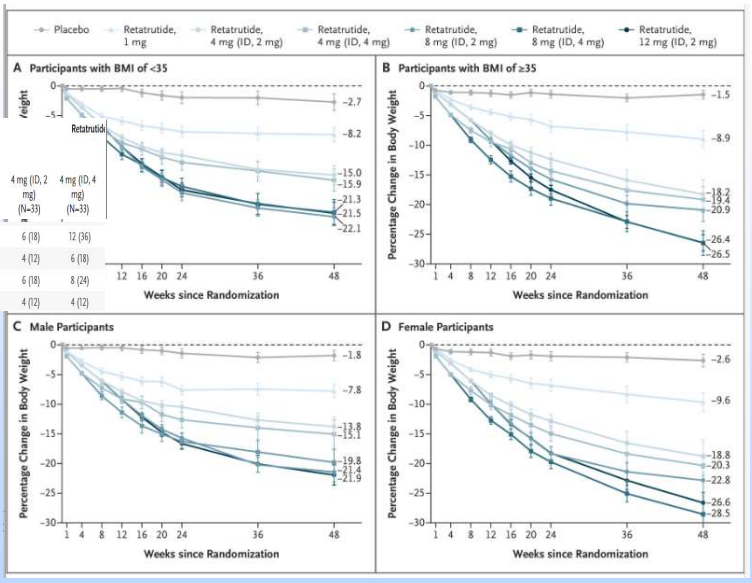


Urva et al Lancet 2022; 400:1869-1881.

40

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — Phase 2 RCT

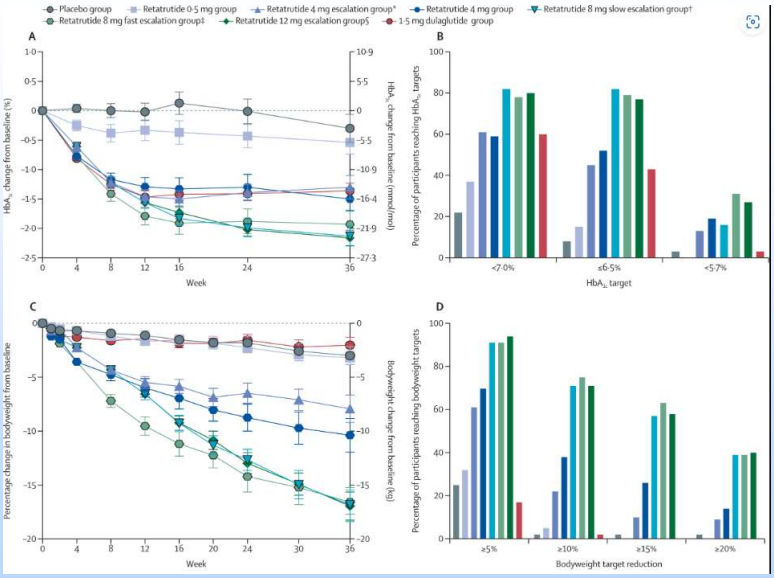
Adverse Event	Placebo Group (N=70)	Retatrutide 1 mg (N=69)	Retatrutide 4 mg (ID, 2 mg) (N=33)	Retatrutide 4 mg (ID, 4 mg) (N=33)
Nausea	8 (11)	10 (14)	6 (18)	12 (36)
Covid-19	14 (20)	13 (19)	4 (12)	6 (18)
Decreased appetite	6 (9)	9 (13)	6 (18)	8 (24)
Diarrhea	8 (11)	6 (9)	4 (12)	4 (12)



Jastreboff, Kaplan, Frias et al NEJM June 26,2023

41

Retatrutide, GIP-GLP-1-glucagon receptor agonist, for type 2 diabetes: phase 2 DB, PG, pla/active-control RCT in USA



Rosenstock, Frias, Jastreboff et al The LANCET June 26,2023

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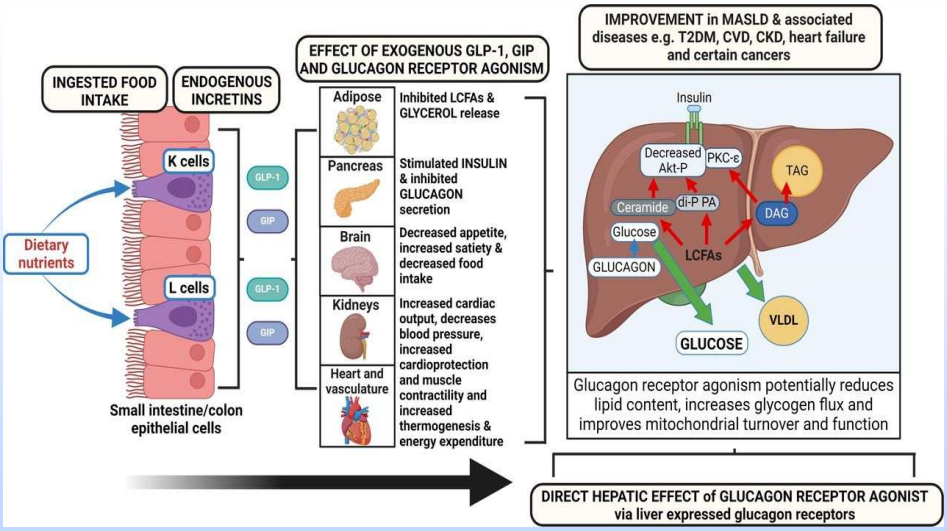
What about the liver and MASLD?

43

Biology of endogenous GLP-1 and GIP, and effects of Incretin and glucagon receptor agonists in MASLD or MASH

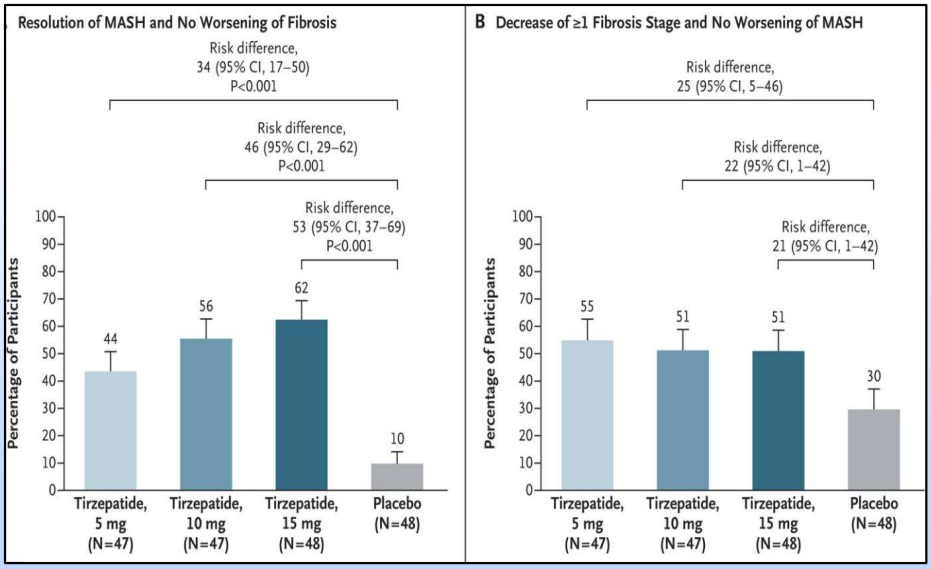


Phase 2 RCTs show that GLP-1RAs and other incretin receptor co-agonists have beneficial effects on histological liver endpoints in MASLD)MASH.

Targher, Mantovani, Byrne, Tilg Gut 2024

44

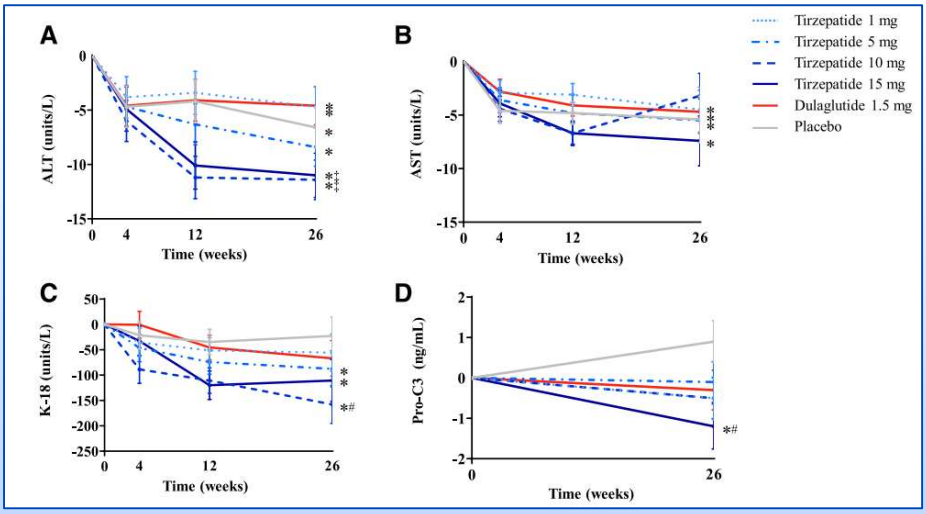
Tirzepatide (GLP-1/GIP agonist) for Metabolic Dys-function–Associated Steatohepatitis with Liver Fibrosis



Loomba et al N Engl J Med 2024;391:299-310.

45

Obesity is associated with liver diseases that respond to tirzepatide: AST, ALT, fibrosis



hepatocyte apoptosis biomarker fibrosis biomarker

Hartman et al Diabetes Care. 2020;43:1352-1355.

46

Drug	Doses SQ tested	Receptor agonism	Effects	Reference
Semaglutide	Daily SQ 0.4 mg	GLP-1	Reduced liver fat by MRI proton density fat fraction (MRI-PDFF); no difference in fibrosis stage	*Flint et al Aliment Pharmacol Ther. 2021;54: 1150-1161.*
Semaglutide	Daily SQ 0.1, 0.2, or 0.4 mg		NASH resolution with no worsening of fibrosis in 59% with 0.4-mg vs. 17% placebo (P<0.001); no difference in fibrosis stage	*Newsome PN, et al. N Engl J Med 2021;384: 1113–24*
SRMA GLP-1RAs: liraglu-tide (n=6), exenatide (n=3), dulaglutide, semaglutide (n=1 each)	11 RCTs		Significant reductions in liver fat content (MR-based), serum liver enzymes levels, liraglutide 1.8mg/day or semaglutide (0.1mg, 0.2mg or 0.4mg daily) greater resolution of MASH without worsening of fibrosis; but no effect on fibrosis	*Mantovani et al Metabolites 2021;11:73.*
Tirzepatide	5, 10, 15mg weekly	GLP-1/ GIP	Reduced ALT, AST; resolution of MASH with no worsening of fibrosis; decrease of >1 fibrosis stage with no worsening of MASH	*Hartman et al Diabetes Care. 2020;43:1352-1355*
Tirzepatide	5, 10, 15mg weekly		resolution of MASH with no worsening of fibrosis; decrease of >1 fibrosis stage with no worsening of MASH	*Loomba et al N Engl J Med 2024;391:299-310*
Survodutide	2.4, 4.8, 6.0 mg weekly	GLP-1/ Glu	histologic improvement (reduction) MASH with no worsening of fibrosis at week 48	*Sanyal et al N Engl J Med 2024;391:311-319*
Efinopegdutide	10mg weekly		greater reduction in liver fat content compared to semaglutide (1 mg weekly)	*Romero-Gomez et al J Hepatol 2023;79:888-897.*
Pemvidutide	1.2, 1.8, 2.4 mg weekly		reduced liver fat content and reduced non-invasive biomarkers of liver inflammation	*Harrison et al J Hepatol. 2024 Jul 11:*
Retatrutide	1, 4, 8,12 mg weekly	GLP-1/ GIP/Glu	Dose-related liver fat reduction which was significantly related to changes in body weight, abdo. fat and metabolic measures	*Sanyal et al Nature Medicine 2024: 30; 2037–2048*

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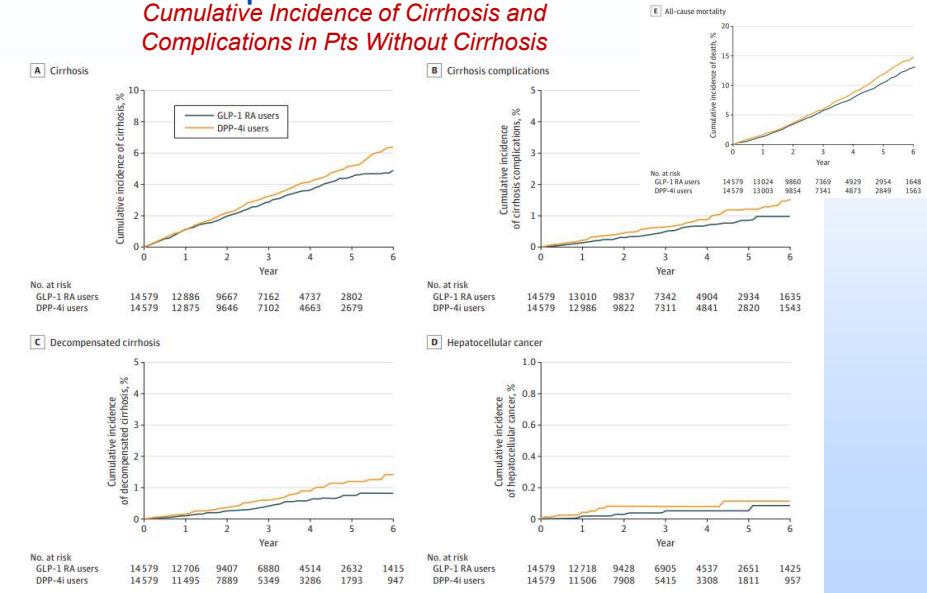
GLP-1 RAs and Risk for Cirrhosis and Related Complications in Pts With MASLD

Cumulative Incidence of Cirrhosis and Complications in Pts Without Cirrhosis



Kanwal F et al JAMA Intern Med. 2024 Sep 16:e244661

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GLP-1/Incretin agonists and GI:

- Food retention
- Pulmonary aspiration
- Intestinal Obstruction
- National Organization guidance

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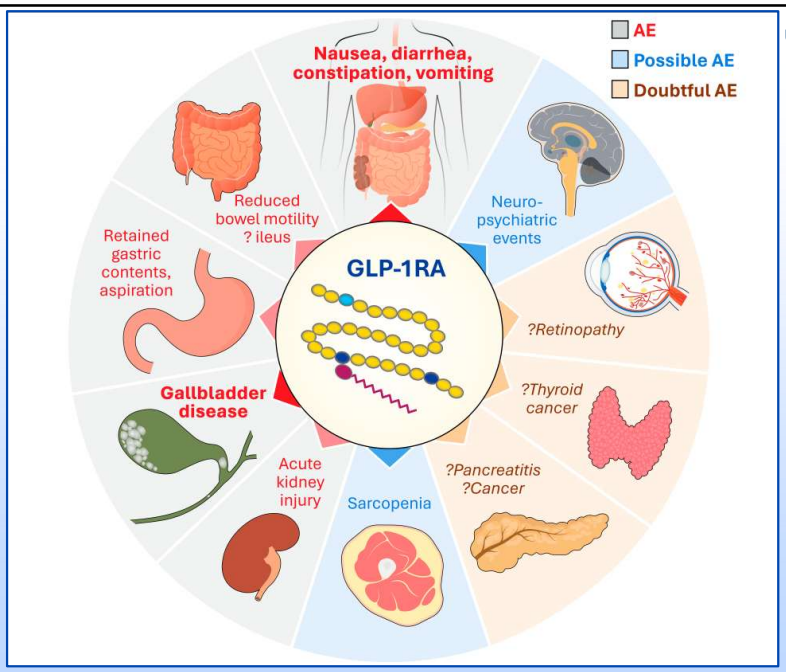
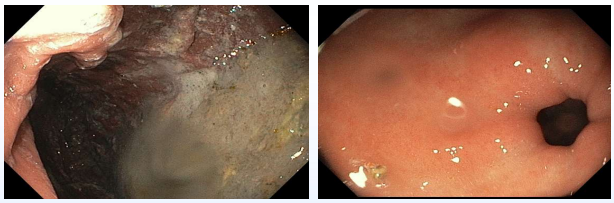
Established and putative **Adverse Effects** associated with GLP-1 medicines



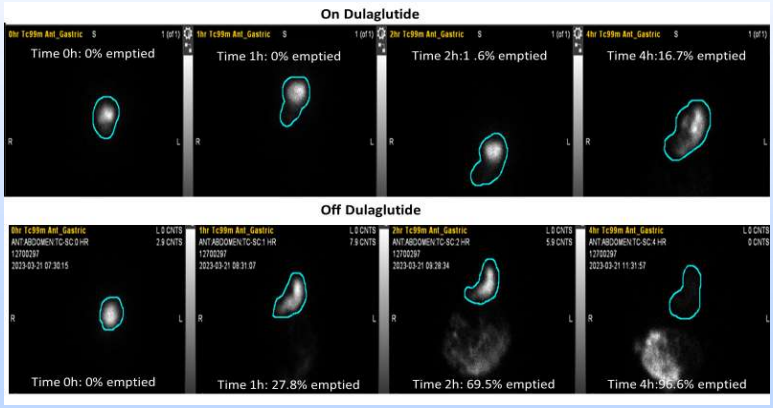
Daniel J. Drucker Diabetes Care 2024;47: 1873-1888

50

Gastric retention at endoscopy in DM2 on Dulaglutide; No pyloric stenosis



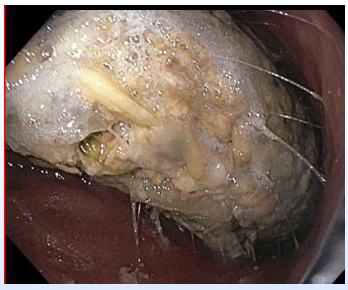
Gastric retention of radiolabeled egg meal in DM2 on, and after stopping dulaglutide



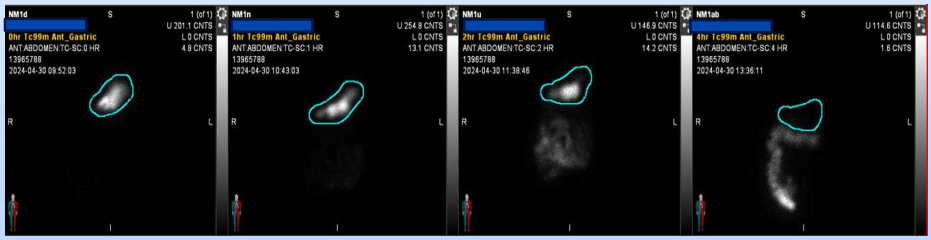
Camilleri, Lupianez-Merly AJG 2024; 119:1028-1037.

51

A Large Bezoar in the stomach in a 70y female patient receiving Dulaglutide, experiencing upper abdominal and non-cardiac chest pain



Off GLP-1 RA for 2 months



Jalleh….. Horowitz et al Lancet Gastro Hepatol 2024

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Influence of semaglutide on presence of residual gastric solids on gastric ultrasound: a prospective study in volunteers

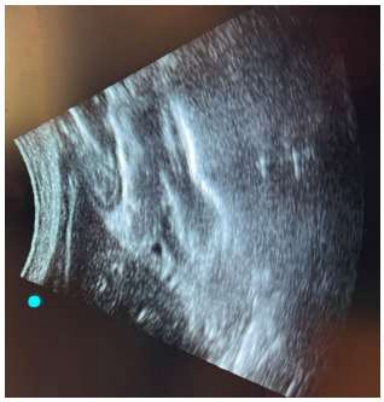

Figure Image showing layered appearance of solid contents in a patient in the semaglutide group

Variable	Semaglutide N = 10	Control N = 10	RR (95% CI)	P value
Stomach contents in supine position after overnight fast, *n*/total *N* (%) solids	7/10 (70%)	1/10 (10%)	3.50 (1.26 to 9.65)	0.02
Stomach contents in lateral position after overnight fast, *n*/total *N* (%) solids	9/10 (90%)	1/10 (10%)	7.36 (1.13 to 47.7)	0.005
Stomach contents in supine position clear ingestion and 2-hour fast				0.02
Liquids, *n*/total *N* (%)	2/10 (20%)	1/10 (10%)		
Solids, *n*/total *N* (%)	5/10 (50%)	0/10 (0%)		
Stomach contents in lateral position clear ingestion and 2-hour fast				0.06
Liquids, *n*/total *N* (%)	2/10 (20%)	3/10 (30%)		
Solids, *n*/total *N* (%)	6/10 (60%)	1/10 (10%)		

CI = confidence interval; RR = risk ratio

GLP-1RAs may affect gastric emptying and residual gastric contents following an overnight fast and two hours after clear liquids, which may have implications for aspiration risk during anesthetic care.

Sherwin et al Can J Anesthesiol 2023

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Are there other risks of GI Diseases with GLP-1 RAs?

Population/Database	GLP-1 RA and Control	Reported Significant Risk	Ref.
Specific Diagnoses Documented as Adverse Events			
Random sample of 16 million patients (2006-2020) from the PharMetrics Plus for Academics database	New users of semaglutide (n=613) or liraglutide (n=4144), and active comparator bupropion/ naltrexone (n=654)	Pancreatitis (adjusted HR, 9.09 [95% CI, 1.25-66.0]), Bowel obstruction (HR, 4.22 [95% CI, 1.02-17.4]), Gastroparesis (HR, 3.67 [95% CI, 1.15-11.0)	Sodhi et al 2023

	Semaglutide	Liraglutide	Bupropion-naltrexone
No.	613	4144	654
Age, mean (SD), y	53.5 (11.9)	51.3 (12.2)	45.2 (11.1)
Sex, %			
Male	55.8	61.0	82.4
Female	44.2	39.0	17.6
Follow-up, median (IQR), y	0.6 (0.2-1.1)	1.7 (0.8-3.1)	1.7 (0.7-2.9)
Incidence (No.)[d]			
Biliary disease	11.7 (5)	18.6 (162)	12.6 (16)
Pancreatitis	4.6 (2)	7.9 (71)	1.0 (1)
Bowel obstruction	0	8.1 (73)	1.7 (2)
Gastroparesis	9.1 (4)	7.3 (66)	3.1 (3)

Sodhi M, et al. JAMA. 2023;330:1795-7

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Are there risks with GLP-1 RAs related to anesthesia, aspiration and retained gastric contents?

Population/Database	GLP-1 RA and Control	Reported Significant Risk	Ref.
Residual Gastric Content (RGC), Aborted Endoscopic Exams (EGDs), Need for Repeat EGD			
Retrospective cohort, single-center study	59 patients prescribed a GLP-1 RA and 118 matched controls	RGC in 6.8% of GLP-1 RA cohort and 1.7% of controls (OR 4.22 [0.87, 20.34]); no need for repeat EGD	Stark et al 2022
Single-center, retrospective, 9-month study	**404** EGDs, with 33 in semaglutide group and 371 controls	RGC in 24.2% of semaglutide group, and 5.1% controls (OR 5.15 [1.92, 12.92]); Pre-procedure upper digestive symptoms increased likelihood of RGC; no difference in preoperative interruption of semaglutide with or without increased RGC	Silveira et al 2023
Matched-pair, case control study over 2 years	**1128 patients** with diabetes, with propensity score matching for groups with and without GLP-1 RA treatment	Among 205 pairs: RGC 5.4% with, compared to 0.49% without GLP-1 RA treatment (liraglutide 1.8 mg daily [n=2]; dulaglutide 0.75 mg per week [n=5]; semaglutide 0.5 mg per week [n=2]; semaglutide 1.0 mg per week [n=2])	Kobori et al 2023
Cross-sectional study prospectively enrolled patients prior to anesthesia, single-center over 5 weeks	62 patients with GLP-1 RA use (exposure group) compared with 62 not taking a GLP-1 RA drug (control group)	GLP-1 RA use: 30.5 (95% CI, 9.9%-51.2)% higher prevalence of increased RGC (adjusted prevalence ratio of 2.48 (1.23-4.97) No association between duration of GLP-1 RA interruption and risk of RGC	Sen et al 2024
Retrospective, single-center study: 35,183 patients with EGD during 2019-2023	**922** were using GLP-1-RA; analysis adjusted for age, sex, race, ethnicity, BMI and diabetes	Significant risks for GLP-1 RA users: RGC (OR=4.08, 95% CI 3.25, 5.12); aborted EGDs (OR=3.87, 95% CI 2.03, 7.37); required repeat EGD (OR=2.09, 95% CI=1.31, 3.34)	Nadeem et al 2024
Retrospective, single- center study in pts on GLP-1 RA undergoing sleeve gastroplasty	57 consecutive adults: semaglutide (45.6%), liraglutide (19.3%), dulaglutide (22.8%), tirzepatide (12.3%)	No instances of retained gastric solids or pulmonary aspiration	Maselli et al 2024

Summarized in Camilleri M: Definite Benefits of GLP-1 Receptor Agonists: What is the risk of gastroparesis and lung aspiration? GUT 2024

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Are there risks with GLP-1 RAs related to anesthesia, aspiration and retained gastric contents?

Population/Database	GLP-1 RA and Control	Reported Significant Risk	Ref.
Pulmonary Aspiration, Aspiration Pneumonia			
Single-center, retrospective, 9-month study	404 EGDs, with 33 in semaglutide group and 371 controls	1 case of pulmonary aspiration in semaglutide group	Silveira et al 2023
Retrospective study of population-based, 21-70 years old (TriNetX), 114 million de-identified records from 80 health care organizations	GLP-1 RA users for >6 months and 2 refills within 6 months before procedure; Controls: GLP-1 RA nonusers; Propensity score matching (PSM) based on 59 factors	Higher incidence rate of aspiration pneumonia (0.83% vs 0.63%) Significant risk factors for aspiration: GLP-1 RA 1.33 (1.02–1.74); Upper endoscopy 1.48 (1.07–2.05); Use of propofol 1.49 (1.08–2.06); No significant risk with use of DPP4i and SGLT2i	Yeo et al 2024
Retrospective study of single center EGD database	4134 episodes of EGDs after prescription of a GLP-1 RA; comparison with historical cohort rate	2 definite cases of pulmonary aspiration (4.8 aspirations/10,000 EGDs); previously reported historical cohort rate: 4.6 aspiration/10,000 EGDs; NO increased risk	Anazco et al 2024
4-year, retrospective study of historical cohort	Patients taking GLP-1 RAs at time of EGD (90 procedures) compared to controls (102 procedures)	5 emergent endotracheal intubations in the GLP-1 RA group vs. 1 in control group; 1 pulmonary aspiration in GLP-1 RA group vs. 0 in control	Wu et al 2024

Summarized in Camilleri M: Definite Benefits of GLP-1 Receptor Agonists: What is the risk of gastroparesis and lung aspiration? GUT 2024

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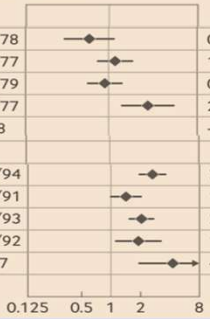
GLP-1 receptor agonists and aspiration risk

- 2 de-identified US commercial healthcare databases: 43,365 adults T2DM used GLP-1 RA (24,817) or SGLT-2*i* (18,537) within 30 days before EGD; propensity score matching
- Compared with SGLT-2*i*, GLP-1 RA use:
  - pulmonary aspiration (pooled RR 0.98, 95% CI 0.73 - 1.31),
  - discontinuation of endoscopy (RR1.99 [1.56 - 2.53])

Analysis	No of participants/ No of events: GLP-1 receptor agonists	SGLT-2 inhibitors	Risk ratio (95% CI)	Risk ratio (95% CI)
Pulmonary aspiration				
Subcutaneous semaglutide	5489/14	18 451/78		0.63 (0.35 to 1.12)
Liraglutide	6604/33	18 514/77		1.16 (0.77 to 1.74)
Dulaglutide	9184/36	18 531/79		0.91 (0.62 to 1.35)
Exenatide-lixisenatide	1519/13	18 192/77		2.49 (1.36 to 4.59)
Tirzepatide	375/0	9418/28		-
Discontinuation of procedure				
Subcutaneous semaglutide	5489/76	18 451/94		2.64 (1.94 to 3.58)
Liraglutide	6604/45	18 514/91		1.42 (0.99 to 2.02)
Dulaglutide	9184/93	18 531/93		2.04 (1.53 to 2.71)
Exenatide-lixisenatide	1519/16	18 192/92		1.90 (1.11 to 3.25)
Tirzepatide	375/suppressed*	9418/47		4.26 (1.91 to 9.49)



Alkabbani W,….. Thompson CC. Wexler DJ, Patorno E BMJ 2024;387:e080340.

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Are there risks of *de novo* of gastroparesis with GLP-1 RAs?

Population/Database	GLP-1 RA and Control	Reported Significant Risk	Reference
Gastroparesis or objectively delayed gastric emptying of solids			
Retrospective study of national database (TriNetX), 113 million deidentified records with 1:1 greedy nearest neighbor propensity score matching	143,214 with obesity (diagnosis code and/or BMI ≥ 30) GLP-1 for wt loss	A new diagnosis of gastroparesis in 81 patients (0.1%) in the GLP-1 group and 1696 patients (0.04%) in the non-GLP-1 group (OR 1.52; 95% CI 1.22-1.90; P < 0.001).	Mesgun et al Cleveland Hospitals, DDW 2024
Retrospective analysis from Mayo Clinic Platform in 86,987 adults >18 years with >1 GLP-RA order from Jan 2006-Jan 2024; assessed pts who developed at least 1 GI symptom and underwent a scintigraphic GE study.	14,658 developed at least 1 GI symptom 696 had GE study (320kcal,30% fat egg meal)	• 16.9% of pts receiving GLP-RA report 1 GI symptom • 1/3 of pts who underwent GES had delayed GE. • Of the 241 with delayed GE at 4hrs, 127 had preexisting GI symptoms and 38 had documentation of a prior delayed GES; 76/296 (25.6%) POSSIBLE NEW Gp among patients with NEW GI symptoms developed on GLP-1 RA (~ 0.087%)	Lupianez-Merly, et al DDW 2024

Characteristics (Mean)	Normal GE (4hr) N=455	Delayed GE (4hr) N=241	p-value
Female	301 (66.2%)	181 (75.4%)	**0.012**
Time between GLP-RA Rx and GES study (days)	366	299	0.159
Incident Symptoms			
Nausea	70%	66%	0.3
Vomiting	55%	56%	0.7
Constipation	40%	50%	**0.01**
Diarrhea	46%	47%	0.8
Bloating	28%	28%	0.99
Abdominal pain	48%	54%	0.13

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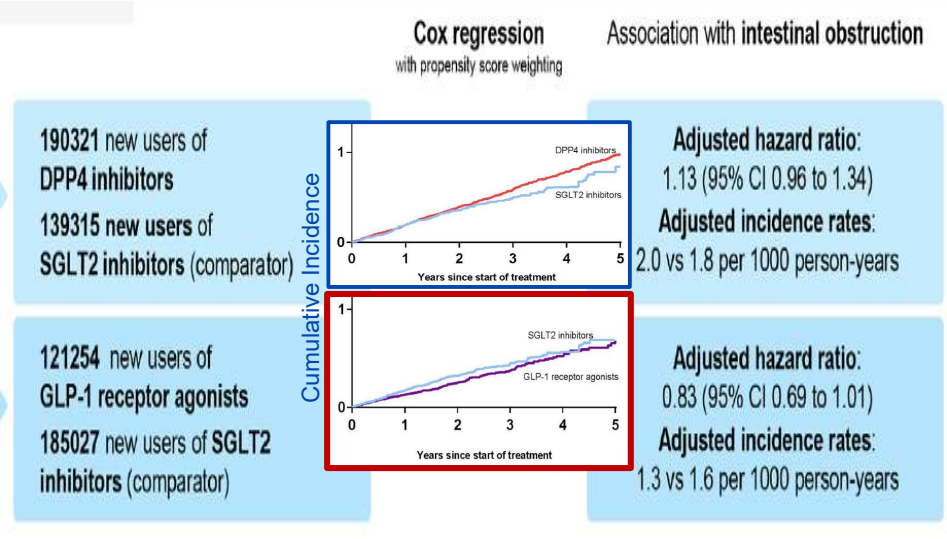
Do GLP-1 RAs cause intestinal obstruction? No

Nationwide Registers in Sweden, Denmark and Norway



Ueda et al Clinical Gastroenterology and Hepatology 2024;22:1226–1237

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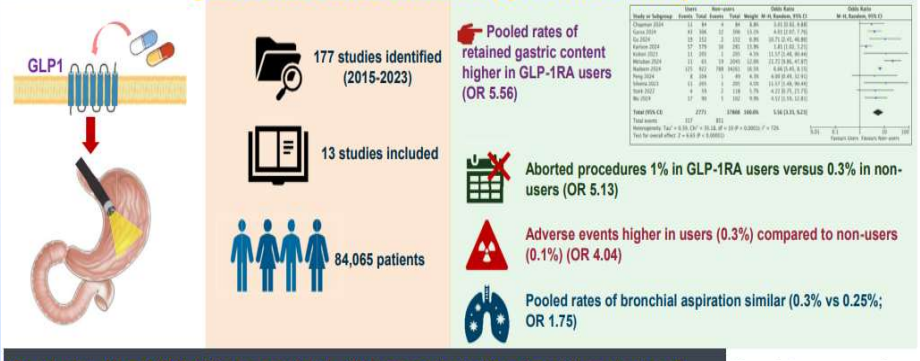
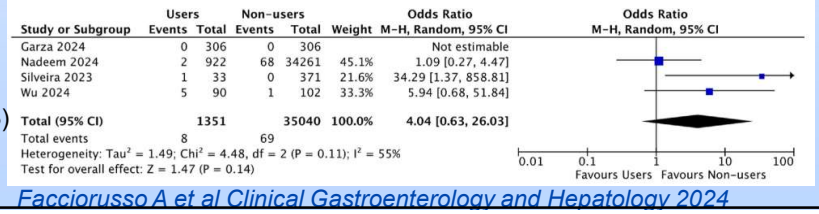
Effects of Glucagon-Like Peptide-1 receptor agonists on upper gastrointestinal endoscopy: A meta-analysis



AE Rate:
OR 4.04
(0.63, 26.03)



Facciorusso A et al Clinical Gastroenterology and Hepatology 2024

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What do national organizations recommend?

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American Society of Anesthesiologists recommendations for pts scheduled for elective procedures during week prior to procedure OR on the day of the procedure

Day or week prior to the procedure:	•Hold on the day of the procedure/surgery for patients who take the medication daily. •Hold a week prior to the procedure/surgery for patients who take the medication weekly. •Consider Endocrinology consultation for patients taking GLP-1 RA for diabetes management for better glycemic control.
Day of the procedure:	•If GI symptoms present: Consider delaying the procedure. •If no GI symptoms presents and GLP-1 held as advised: Continue with the procedure. •If the patient has no GI symptoms, but the GLP-1 RA was not held, assume the patient has a "full stomach" or consider using ultrasound to evaluate the stomach contents. If full, consider delaying procedure.

https://www.asahq.org/about-asa/newsroom/news-releases/2023/06/patients-taking-popular-medications-for-diabetes-and-weight-loss-should-stop-before-elective-surgery

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Multisociety Clinical Practice Guidance for the Safe Use of GLP-1 RAs in Perioperative Period

- **Recommendation 1** Use of GLP-1RAs in perioperative period should be based on shared decision-making of the patient with procedural, anesthesia, and prescribing care teams balancing the metabolic need for the GLP-1RA with individual pt risk:
- A. **CONSIDER**
  - Escalation phase vs maintenance phase
  - Higher dose
  - Weekly dosing: GI side AEs more common vs daily
  - Presence of GI symptoms suggestive of delayed GE
  - Medical conditions beyond GLP-1RA usage e.g. Diabetic, Parkinson
- B. Continue GLP-1RA in pts **without ↑risk** of delayed GE
- C. **If ↑ risk:** holding the day of surgery for daily formulations, and a week prior to surgery for weekly formulations.

All patients should still be assessed on the day of procedure for symptoms suggestive of delayed gastric emptying.

Kindel, Yang et al Clinical Gastroenterology and Hepatology 2024;Oct 29

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- **Recommendation 2:** Efforts to minimize the aspiration risk of delayed gastric emptying by *pre-operative diet modification and/or altering anesthesia plan*:
- A. Preoperative diet modification (preoperative liquid diet for at least 24 hours) If ↑ risk
- B. When clinical concern for RGC exists on the day of procedure:
  - point-of-care gastric ultrasound
  - shared decision-making and consider the benefits and risks of rapid sequence induction of GA for tracheal intubation to minimize aspiration risk versus procedure cancellation

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Take Home Points for Gastroenterology Practice

- There are significant benefits of GLP-1 RAs on obesity and co-morbidities including heart, GI and liver
- Currently approved incretin agonists commonly used: Dulaglutide, Liraglutide, Semaglutide, Tirzepatide
- Effects on gastric emptying: positives (weight loss) and negatives (nausea and vomiting: TITRATE the escalating dose)
- Other GI adverse effects: biliary and pancreatic, rarely gastroparesis
- EGD: Retained gastric content is rare, and repeat EGD rarely needed
- Risk of aspiration extremely rare and probably similar to control
- Recommendations: For elective EGDs, stop GLP-1 according to drug $T_{1/2}$
- For urgent EGD, request Ultrasound test or I.V. erythromycin 3mg/kg

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Case Study

Last month: BMI 34kg/m^2; weight 75kg (165 lb); FBG 102mg/dL; HbA1c 6%; off metformin

Delighted with outcome: dress size ↓ 2 sizes; off antihypertensives

"Background symptoms" nausea, postprandial fullness, constipation
vomiting twice per month, mostly after eating large green salad

Recommendations: Continue GLP-1 RA; blenderized diet when symptomatic; tell your GI if you are going to undergo endoscopy; liquid diet for 24h before procedure; work on lifestyle interventions to maximize and secure longterm weight loss and metabolic bonanza

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Questions

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