Injecting hope: GLP-1 drugs and the impact on health and disease.

Are these drugs really the “Swiss Army Knife” of Medicine ?

Sommer Lecture 2025
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Multisystem beneficial effects of GLP-1 agonist medications: From diabetes wonder drug to panacea !!

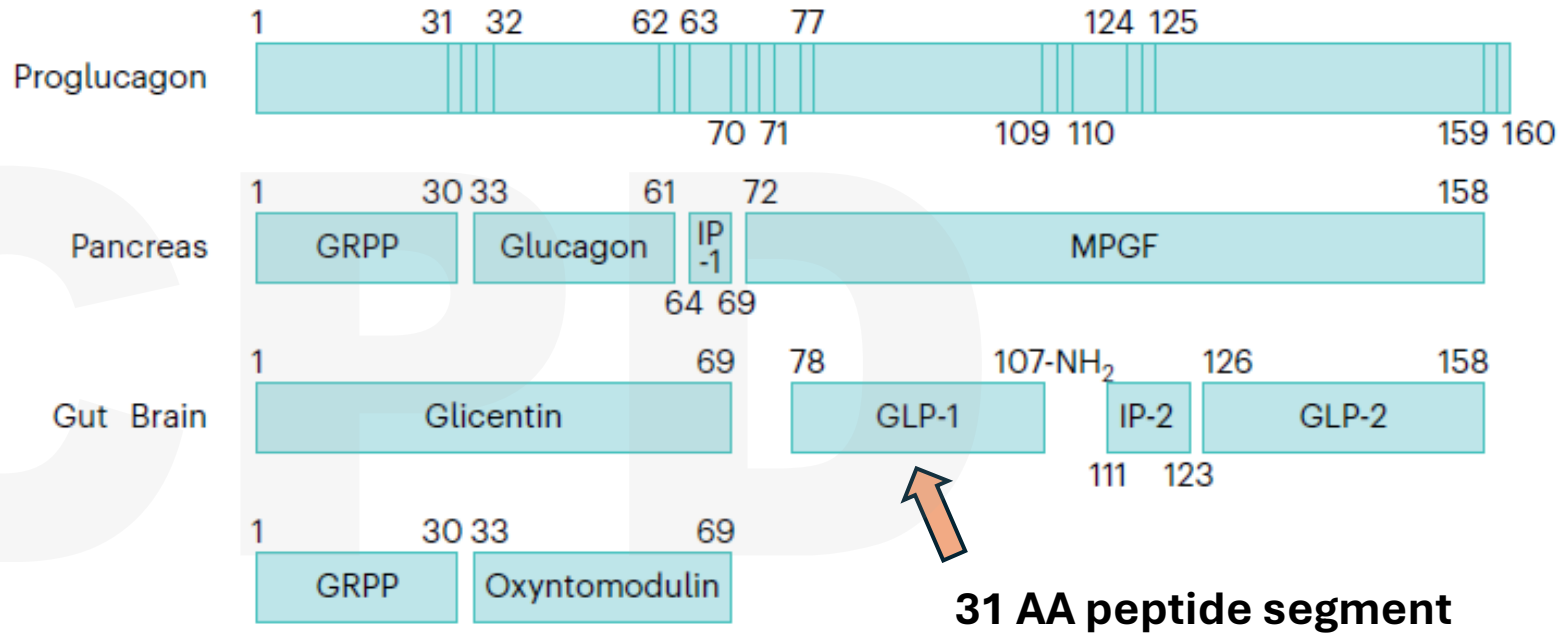
- Diabetes (type 2)
- Obesity
- Cardiometabolic context
  - Reducing risk of cardiovascular events
    - Leader, Select, Surpass trials all show +CV major event reduction
  - decrease atherosclerosis, increase EF, decrease cardiac events
- Nephroprotective
  - Slows decrease in GFR
  - Decrease albuminuria
- Neurodegenerative diseases:
  - Parkinson's – improved motor scores
  - Alzheimer's – enhanced glucose metabolism in brain
- Depression
  - improved mood, emotional well-being, and QOL
- Dementia
  - Slows progression of disease
  - May decrease incidence

- Sepsis / ICU
  - Reduced sepsis mortality in DM2
  - Animal models- multiple mxs
- Hepatic
  - Effect on hepatic steatosis (NAFLD)
- Use in addiction medicine
  - Chemical dependence, others
- Chronic inflammatory diseases
  - RA
- IBD
- Sleep Apnea
- Polycystic ovary disease

Loomba R et al NEJM 2024
Am Diab Assoc Practice Committee 2024
Laurindo LF et al Int J Molecular Sci 2022
Guo J et al Shock 2024

What is GLP-1 ?

- **Peptide produced in L cells of the intestine from jejunum to anus** (high concentration rectum)
  - If nutrient is delivered into distal intestine significant increase in serum is noted
    - This may be one of the mechanisms for weight loss for RYGB
- **Stimulated by all macronutrients**
  - Bile secretion and composition is altered by GLP-1
  - Fermentation products (SCFA) alter microbiome to increase GLP-1 release
  - **GLP-1 receptors are present on most cells and in CNS**



Holst JJ Nature Metabolism 2024
Zhang Z et al Metabolism: Clin and Experimental 2021

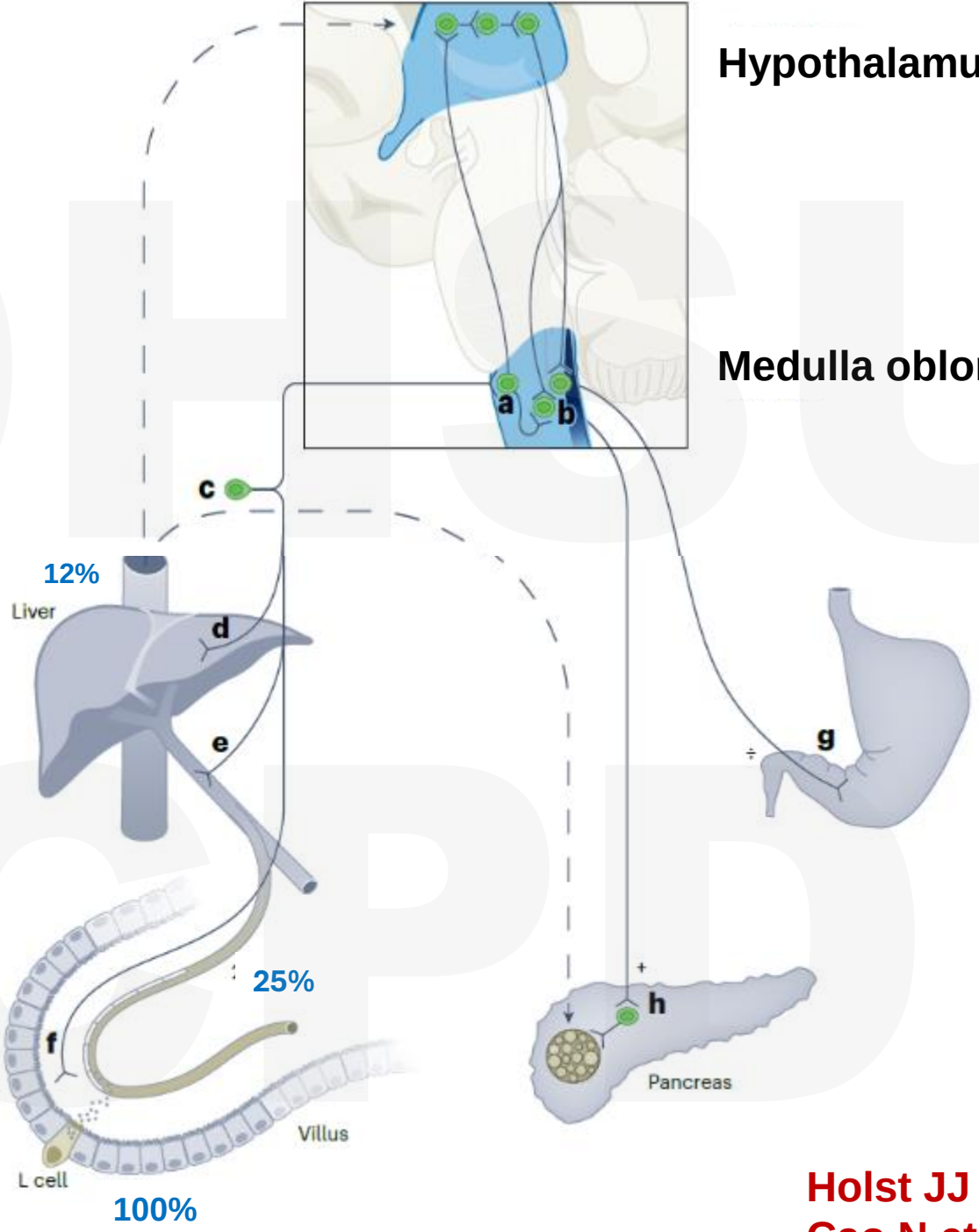
Physiologic mechanisms of action for glucose and weight control:

- **Insulinotrophic –**
  - **increases insulin secretion with luminal nutrient** (both 1st and 2nd phase)
- **Inhibits glucagon secretion**
  - **dual** action
    - 1) Increases glucose update in muscle
    - 2) inhibits hepatic glucose production
    - 3) stimulates adipose breakdown in liver
- **Slows GI proximal gut motility via vagus nerve (central effect)**
    - The decrease in gastric motility yields additional mechanism to level glucose absorption, slows nutrient load to small intestine
  - Ileal brake – nutrient in distal small bowel sends signal of nutrient abundance which leads to terminate ingestion
  -
- **GLP-1 and reduction in food intake**
  - **Animal models: CNS and peripheral delivery GLP-1 deceased food intake**
  - **Infusions into humans**
    - **Increased sensation of fullness and satiety and reduced food intake**

- **Multiple other effects on tissues and organs**

Holst JJ Nature Metabolism 2024

Native GLP-1 has short $t^{1/2}$ (about 1 to 2 minutes) and is partially degraded in post mucosal capillary bed



Note: most of effect of GLP-1 via CNS via vagus nerve

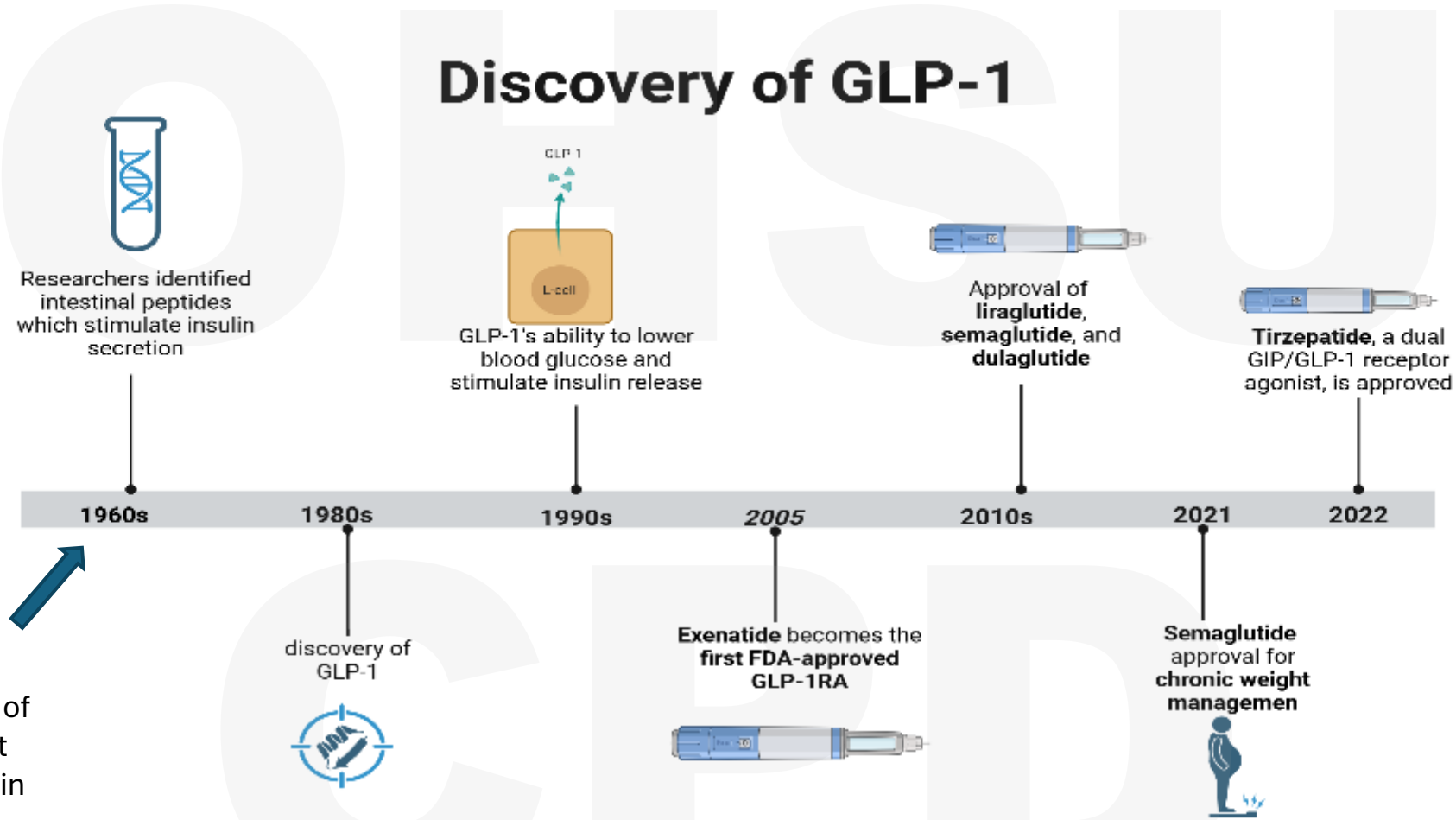
Locally in the GI GLP-1 acts via **paracrine mechanism**, binding GLP-1 receptors on vagal afferent neurons yielding the effects on appetite, glycemia, and GI motility

Holst JJ Nature Metabolism 2024
Cao N et al Scientific Reports 2024

Historical -The birth of gastrointestinal endocrinology

- **Bayliss and Starling "The mechanism of pancreatic secretion" 1904, Secretin**
    - introduced the word "hormone"
  - 1920's and 30's search for mucosal based compound that acted on pancreas to lower blood sugar.
    - 1869 Dr Langerhans described tissue noted in pancreas
    - 1889 pancreas removal lead to hyperglycemic death in dogs
    - 1910 Sir Edward Sharply named groups of cells in pancreas "insula" Latin for island. Suggested insulin for name of compound
  - First modern "incretin" concept in 1960's, after RIA for insulin developed (Berson and Yalow) a new search for "incretin" was on. Prior numerous failures because not tested with higher glucose background
  - McIntyre in London and Elrick in Denver. simultaneously showed with "incretin" effect with extracts of mucosa
    - Greater increase insulin release to oral glucose load vs parenteral
    - Levin UCLA (Levin SR, Martindale R et al "Nutrient dependent incretin" 1976)
- **GIP – originally Gastric Inhibitory Polypeptide**
  - Isolated from porcine gastric extracts by JC Brown in Victor Mutts lab in Stockholm - GIP
  - Characterized in late 1970's, name changed to "Glucose-dependent insulinotropic polypeptide"
- **Soon after GLP-1 identified**

Drucker DJ JCI 2024
Creutzfeldt W. Regulatory Peptides 2004

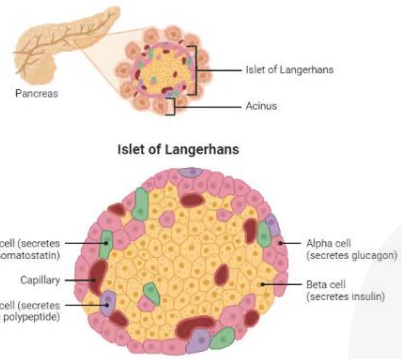


Origins if modern of incretin concept after RIA for Insulin

Jogani VG, Hurt R, Martindale R, Mundi M Current Nutrition Reports 20

Physiologic actions of GLP-1

New area of interest



Brain
Food intake ↓
Water intake ↓
Learning & memory ↑
Neuroprotection ↑
Inflammation ↓
Reward behavior ↓
Palatability ↓
Apoptosis ↓

Pancreas
Insulin secretion ↑
Insulin synthesis ↑
Glucagon secretion ↓
β-cell proliferation ↑
Apoptosis ↓
β-cell survival ↑

Liver
Gluconeogenesis ↓
Steatosis ↓

GLP-1

Kidney
Diuresis ↑
Natriuresis ↑

GI Tract
Gastric emptying ↓
GI motility ↓

Muscle
Insulin sensitivity ↑
Glucose uptake ↑

Heart
Contractility ↑
Cardiac output ↑
Myocyte survival ↑
Cardioprotection ↑
Glucose utilization ↑
Vasodilation ↑
Glucose uptake ↑
Left ventricular function ↑
Blood pressure ↑↓→
Heart rate ↑↓→
ANP production ↑
Natriuresis ↑

Bone
Bone formation ↑
Bone mass ↑

Muller TD et al Mol Metabolism 2019;30:72-130

Evidence that GLP-1 medications can regulate β Cell proliferation

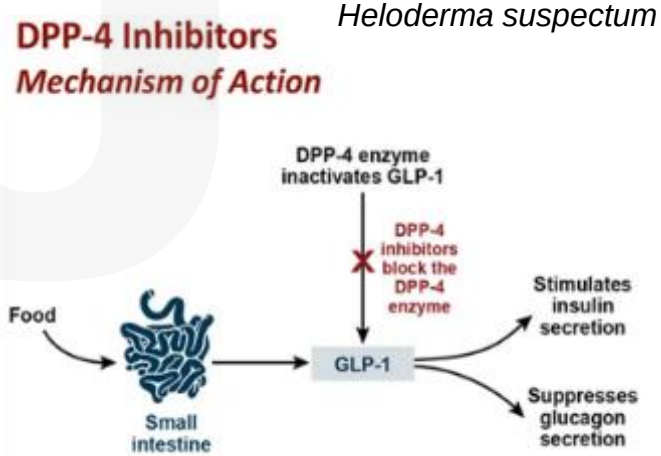
- 1. **Alpha- to Beta-Cell Transdifferentiation**: Increase beta-cell regeneration by promoting the transdifferentiation of alpha-cells into beta-cells. This process involves the induction of fibroblast growth factor 21 (FGF21)[1]
- 2. **Central Nervous System Pathways**: The GLP-1 receptor agonist liraglutide has been found to induce beta-cell proliferation through central actions involving the medulla and vagal pathways.[2]
- 3. **Insulin-Like Growth Factor-1 Receptor (IGF-1R) Pathway**: Upregulating IGF-1R expression through a cAMP/protein kinase A-dependent mechanism. This upregulation enhances the activity of an IGF-2/IGF-1R autocrine loop, which is crucial for beta-cell proliferation.[3]
- 4. **WNT Signaling Pathway**: GLP-1 activation of TCF7L2-dependent WNT signaling enhances beta-cell proliferation. This pathway involves the upregulation of cyclin D1 and c-Myc, which are key determinants of cell proliferation.[4]
- 5. **Epidermal Growth Factor Receptor (EGFR) Pathway**: Exendin-4, a GLP-1 analogue, induces beta-cell proliferation via the EGFR.[5]

1. Lee YS, Lee C, Choung JS, Jung HS, Jun HS.
Glucagon-Like Peptide 1 Increases B-Cell Regeneration by Promoting A- To B-Cell Transdifferentiation.
Diabetes. 2018;67(12):2601-2614.
2. Kumari P, Nakata M, Zhang BY, Otgon-Uul Z, Yada T.
GLP-1 Receptor Agonist Liraglutide Exerts Central Action to Induce B-Cell Proliferation Through Medulla to Vagal Pathway in Mice.
Biochemical and Biophysical Research Communications. 2018;499(3):618-625.
3. Cornu M, Modi H, Kawamori D, et al.
Glucagon-Like Peptide-1 Increases Beta-Cell Glucose Competence and Proliferation by Translational Induction of Insulin-Like Growth Factor-1 Receptor Expression.
The Journal of Biological Chemistry. 2010;285(14):10538-45
4. Liu Z, Habener JF.
Glucagon-Like Peptide-1 Activation of TCF7L2-dependent WNT Signaling Enhances Pancreatic Beta Cell Proliferation.
The Journal of Biological Chemistry. 2008;283(13):8723-35.
5. Fusco J, Xiao X, Prasadan K, et al.
GLP-1/Exendin-4 Induces B-Cell Proliferation via the Epidermal Growth Factor Receptor.
Scientific Reports. 2017

DM / Weight loss medications based on GLP-1

Heloderma suspectum

- **GLP-1 based medications**
  - Exenatide (5-10% wt loss) (Byetta) FDA approval in 2005
    - Endogenously produced GLP-1 is degraded by dipeptidyl peptidase (DPP)
      - Saliva of Gila Monster contains an analog of GLP-1 which is resistant to DPP
      - Exendin-4 shares 50% amino acid sequence identity with human GLP-1
  - Liraglutide (10-16% wt loss) (Victoza)
    - Analog with palmitic acid attached which protects from DPP
    - Requires **daily** injections – decreasingly used in 2024
  - Semaglutide (10-20% wt loss) (Wegovy for weight management, Ozempic for DM2) (Rybelsus is po form)
    - Changes in peptide yielded better insulin binding extending $t^{1/2}$ significantly
    - Once per week injection



- **Combination meds**
  - Tirzepatide (15-25% wt loss) (GLP-1 and gastric inhibitory peptide) (GIP) (Mounjaro –DM2 while Zepbound – weight management)
    - Less muscle loss by ratios
    - GIP synthesized in enteroendocrine K cells in duodenum and jejunum.
  - Semaglutide-amylin (CagliSema) (Novo Nordisk expects regulatory approval first quarter 2026)
    - Amylin 37 AA peptide from islets (beta-cells) and co-released with insulin
    - Acts at postrema in brain to inhibit appetite and gastric emptying. It may also decrease glucagon
    - Amylin can alter beta cell function via fibril formation, Cagrilintide is potentially less injurious to beta cell derivative

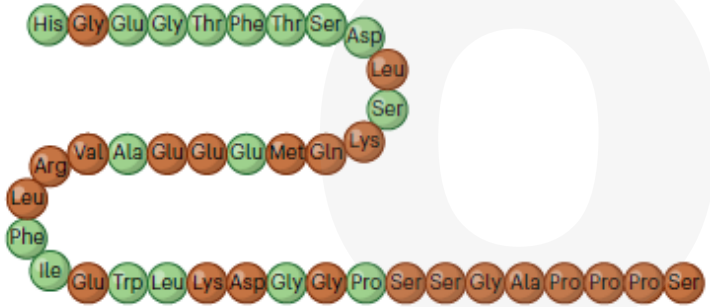
- **Oral meds**
  - Tirzepatide **–**
    - **Tirzepatide RDT,**
  - Semaglutide – salcaprozate (Rybelsus)
    - Salcaprozate is an GI absorption enhancer

Holst JJ Nature Metabolism 2024
Drucker DJ Diabetes Care 2007

Structure of GLP-1RA

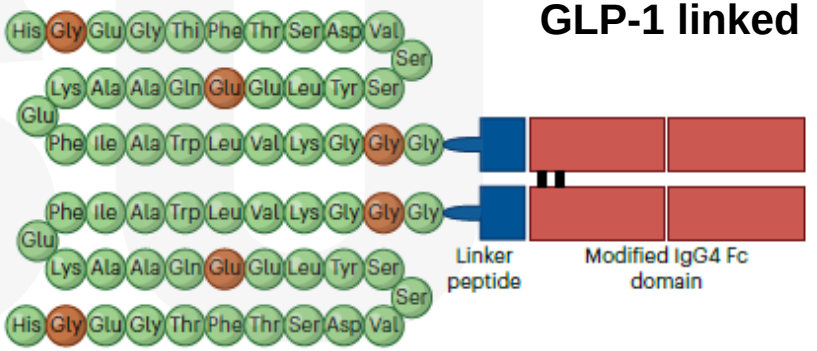
Dulaglutide essentially 2 GLP-1 linked

Exenatide

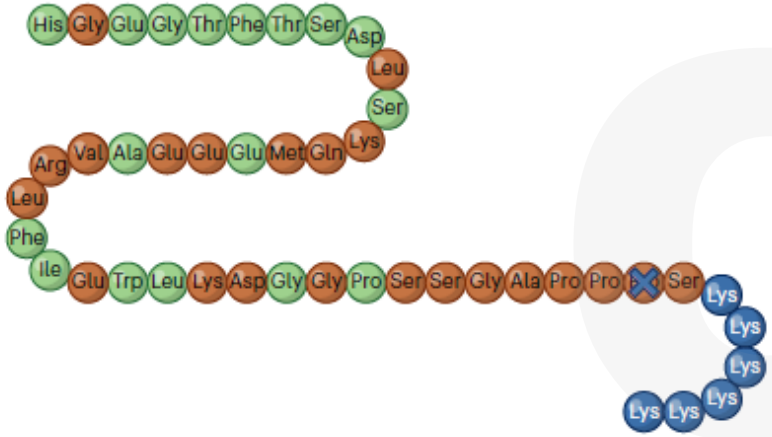


Liraglutide

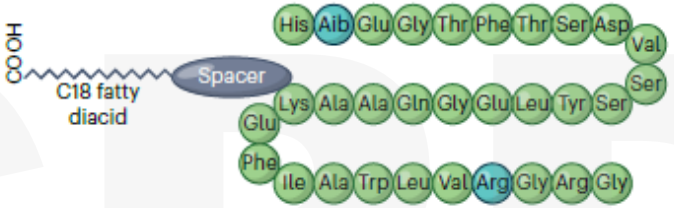
Dulaglutide



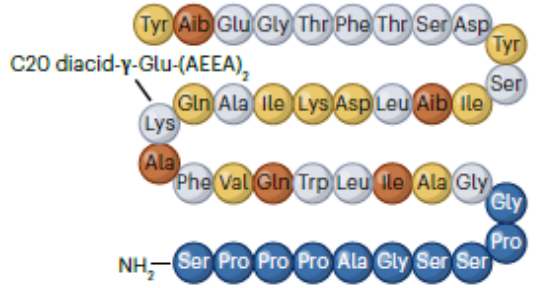
Lixisenatide



Semaglutide



Tirzepatide



Gray GLP-1
Yellow GIP
Blue Exenatide

Holst JJ Nature Metabolism 2024
Syed YY. Drugs 2022

A lot of work going on across the globe !

	On the market	Clinical trial status	Route of administration	Receptor target
Exenatide	Yes	Finished	Injection	GLP-1
Liraglutide	Yes	Finished	Injection	GLP-1
Semaglutide	Yes	Finished	Injection or oral	GLP-1
Tirzepatide	Yes	Finished	Injection	GLP-1, GIP
Dulaglutide	Yes	Finished	Injection	GLP-1
Albiglutide	Yes	Finished	Injection	GLP-1
Lixisenatide	Yes	Finished	Injection	GLP-1
Cagrisema	No	Phase 3	Injection	GLP1, amylin
Survodutide	No	Phase 3	Injection	GLP-1, glucagon
Retatrutide	No	Phase 2	Injection	GLP-1, GIP, and glucagon
NNC0165-1875 + semaglutide	No	Phase 2	Injection	GLP-1, PPY
Efinopegdutide	No	Phase 2	Injection	GLP-1, glucagon
Danuglipron	No	Phase 2b	Oral	GLP-1
Orforglipron	No	Phase 1b	Oral	GLP-1
Amycretin	No	Phase 1	Oral	GLP-1, amylin

GIP=glucose-dependent insulinotropic polypeptide. PPY=pancreatic polypeptide.

Table: **List of selected currently available and future GLP-1 receptor agonists and their targets**

Zushin PJH Lancet 2025

Summary: Benefits of GLP-1 RA in Diabetes Management

- 1. **Glycemic Control**: Augmenting ***glucose-dependent insulin secretion*** and suppressing glucagon release
- 2. **Weight Loss**: promotes weight loss by reducing appetite and food intake, and by slowing gastric emptying
- 3. **Cardiovascular Benefits**: demonstrated cardiovascular benefits, including a reduction in major adverse cardiovascular events (MACE)
- 4. **Renal Protection**: reducing the progression of diabetic kidney disease, primarily by preventing the onset of macroalbuminuria
- 5. **Low Risk of Hypoglycemia**: low intrinsic risk of hypoglycemia
- 6. **Additional Metabolic Benefits**: Improve lipid profiles by decreasing triglyceride levels and increasing high-density lipoprotein (HDL) levels
- 7. **β Cell Proliferation:** Induces beta-cell proliferation through multiple pathways

Global Crisis
Could GLP-1 RA be of assistance?


NASA Photo

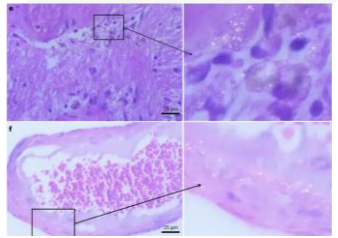
In 131 countries, 31K outlets
54 million served per day

- **Global obesity has tripled since 1975 (WHO)**
  - In 2030 estimated 78% of USA > 25 BMI (overweight)
  - In 2030 estimated 50% of USA > 30 BMI (obese)
- **USA populations currently at highest risk**
  - Young adults 18-24 - weight transition to higher BMI
  - Ethnic and racial minorities:
    - Black individuals, female > male
    - Mexican American youths
  - Low socioeconomic status
  - Geographical variations: western Appalachians and south
  - Children with disabilities
- **Some clues show obesity trajectory my have reached plateau**
  - In high income populations (adults, adolescents, children)
  - Low income populations still un-interrupted growth of obesity

Katsoulis M et al The Lancet, Diabetes and Endocrinology 2021
Avery CL et al PloS One 2016
Koliaki C et al Curr Obesity Reports 2023

Obesity: What are the primary origins of the pandemic for USA ?

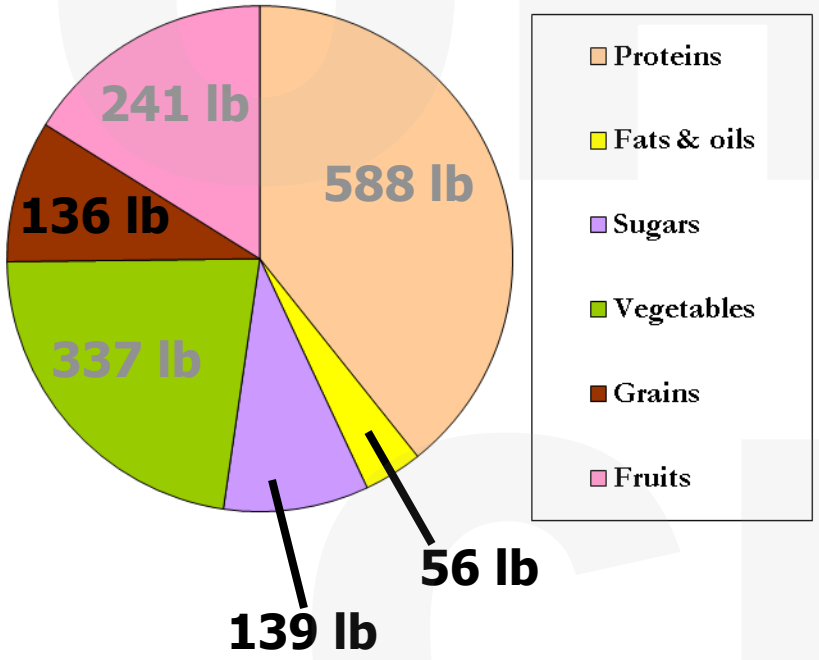
- **Major current theories of obesity**
  - 1) Carbohydrate-Insulin Model 2) Neuroendocrine regulation of appetite/satiety
  - 3) Inflammation (hypothalamus) 4) Set point theory (energy balance model)
- **Multifactorial Disease** ("Globesity")
  - Genetics and epigenetics
  - Socioeconomic / cultural issues
  - Obesogenic environment
    - Portion size / energy balance*
      - calorically dense, inexpensive, highly palatable, low fiber
        - 74% of grocery packaged foods have added sugar
    - UPF, fast foods, high fructose corn syrup
      - Increased adipogenesis-visceral fat
      - Primary metabolism in liver –stimulates de nova lipogenesis – increasing TG fat storage
      - Alters satiety –decreases leptin, does not suppress ghrelin
      - Fructose metabolism generates uric acid – mitochondrial stress
    - Changes in the microbiome
    - Decreased physical activity
    - Obesogens – most sensitive periods are in utero and early childhood- epigenetic changes
      - Chemical toxins (bisphenol A, phthalates, heavy metals, pesticides, etc)
      - Endocrine disrupting chemicals (via peroxisome proliferator-activated receptor PPRγ)
        - Increase adipose size and adipocyte differentiation
      - Metabolic disrupting chemical
    - Microplastics



Heindel J et al Am J Clin Nutrition 2022
Magkos F et al Nature Metabolism 2024
Koliaki C et al Current Obesity Reports 2023
Sonnefeld L et al Euro J of Endocrinology 2023
Yilmaz B et al Neuroendocrinology 2025
Nihart et al Nature Medicine 2025

Bottom Line:
Eating More of Everything

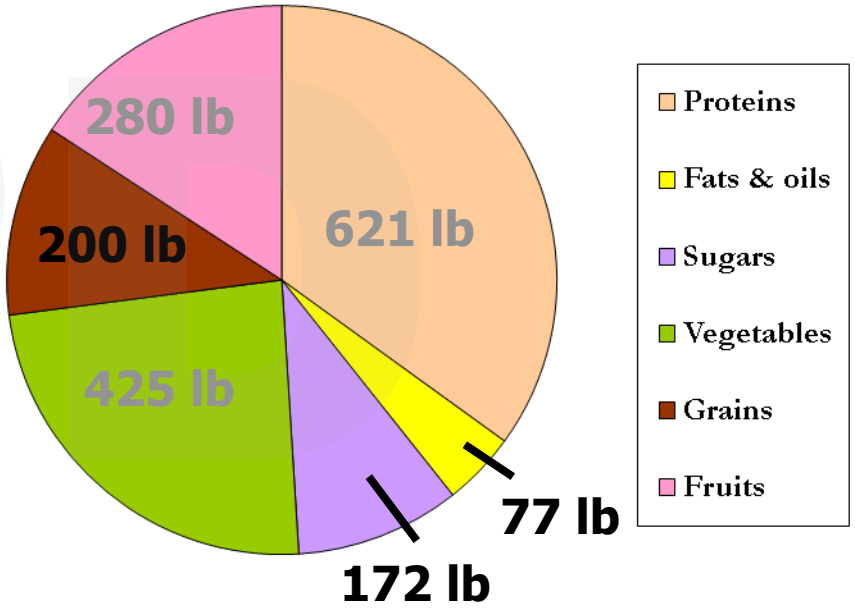
1970



Pounds consumed per person: 1,497

Pounds consumed per person: 1,775

2000



Paulin GD et al Monthly Labor Review 1998 and 2004
US Government Scientific Report of the 2020 Dietary Council Advisory Committee
Chapter 8: Dietary Patterns

Co-Morbidities and Complications of Obesity

60

Metabolic	Diabetes, NAFLD, dyslipidemia, gallstones, metabolic syndrome
Structural	GERD, pseudotumor cerebri, obstructive sleep apnea
Inflammatory	CV disease, osteoarthritis, autoimmune, stroke
Degenerative	Degenerative joint disease
Neoplastic	Prostate, breast, ovarian, endometrial, cervical, lymphoma, renal cell
Psychological	Depression, anxiety panic attacks, eating disorders

Bray GA The Journal of Clinical Endo and Metab 2004

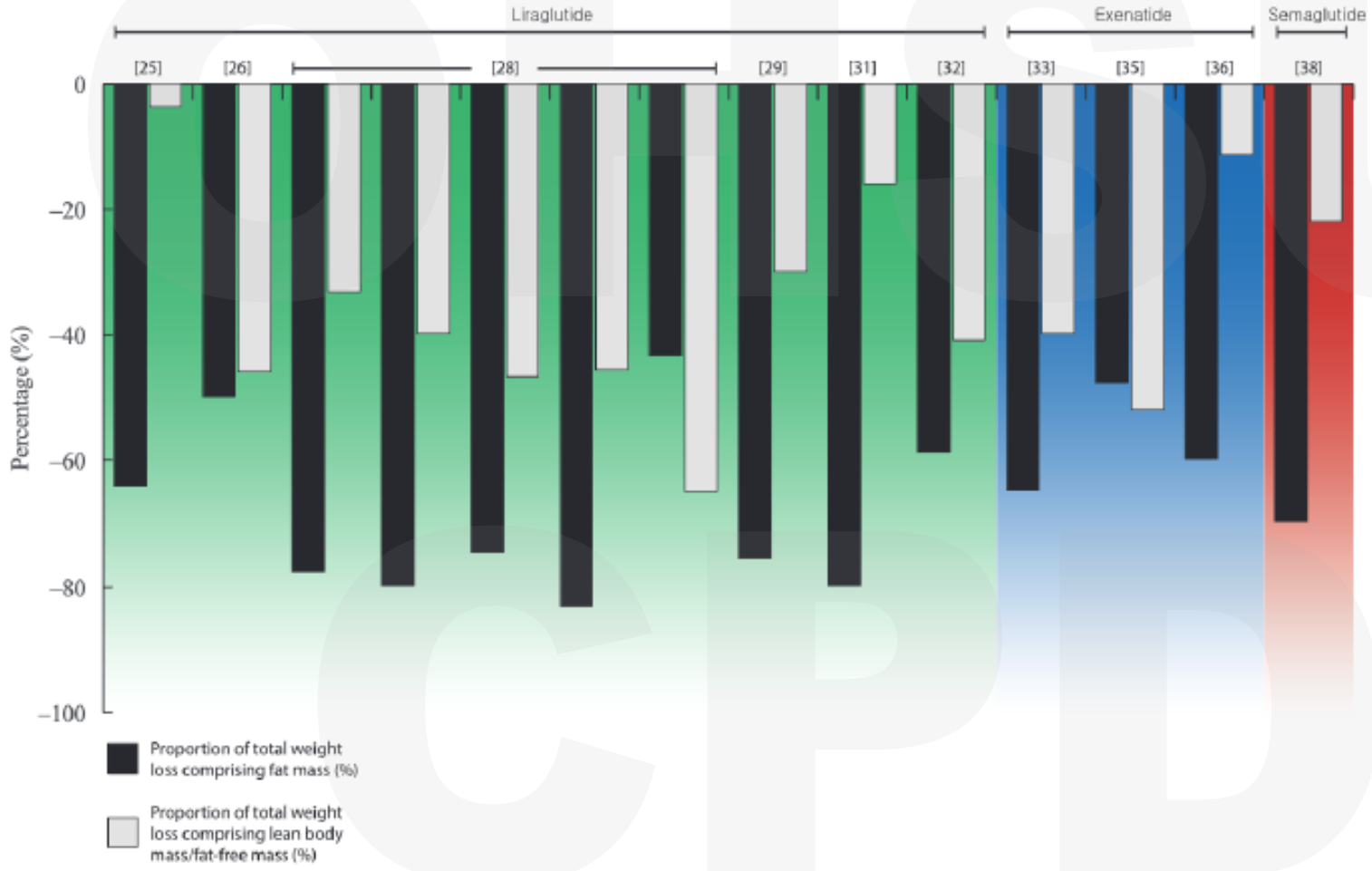
Options for weight loss strategy for patients

- Dietary restrictions diets – healthy eating
  - 95% recidivism within 2-yrs
- Increase metabolic expenditure – consistent exercise
  - >90% return to normal activity within 6 months
- Medications – pre GLP-1 meds
  - Orlistat
  - Naltrexone-bupropion
  - Phentermine-topiramate
  - Etc.
- Endoscopic methods
  - Endoscopic plications
  - Aspiration therapy
  - Balloons
- Surgery
  - Gastric Bands – now mainly of historic interest only
  - Sleeve gastrectomy
  - Roux en y gastric bypass
  - Biliopancreatic bypass / SADI

Body Composition

GLP-1 Receptor Agonists

- 20-50% of total weight loss is due to reduction in lean body mass

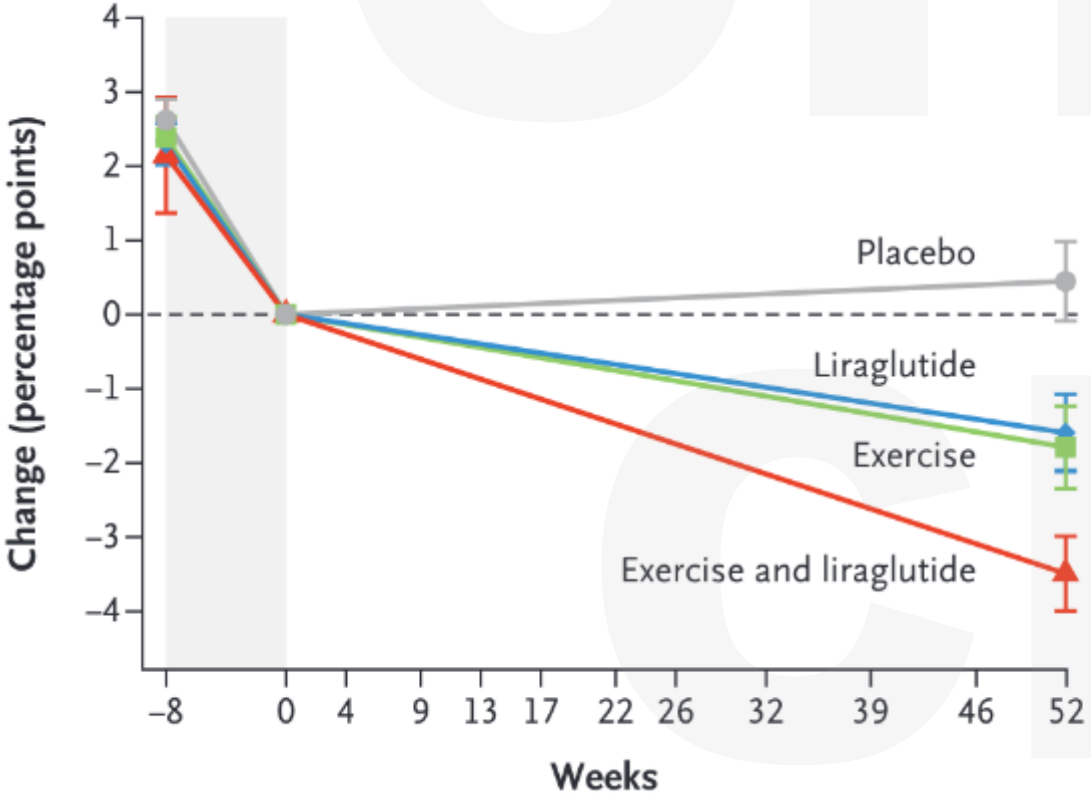


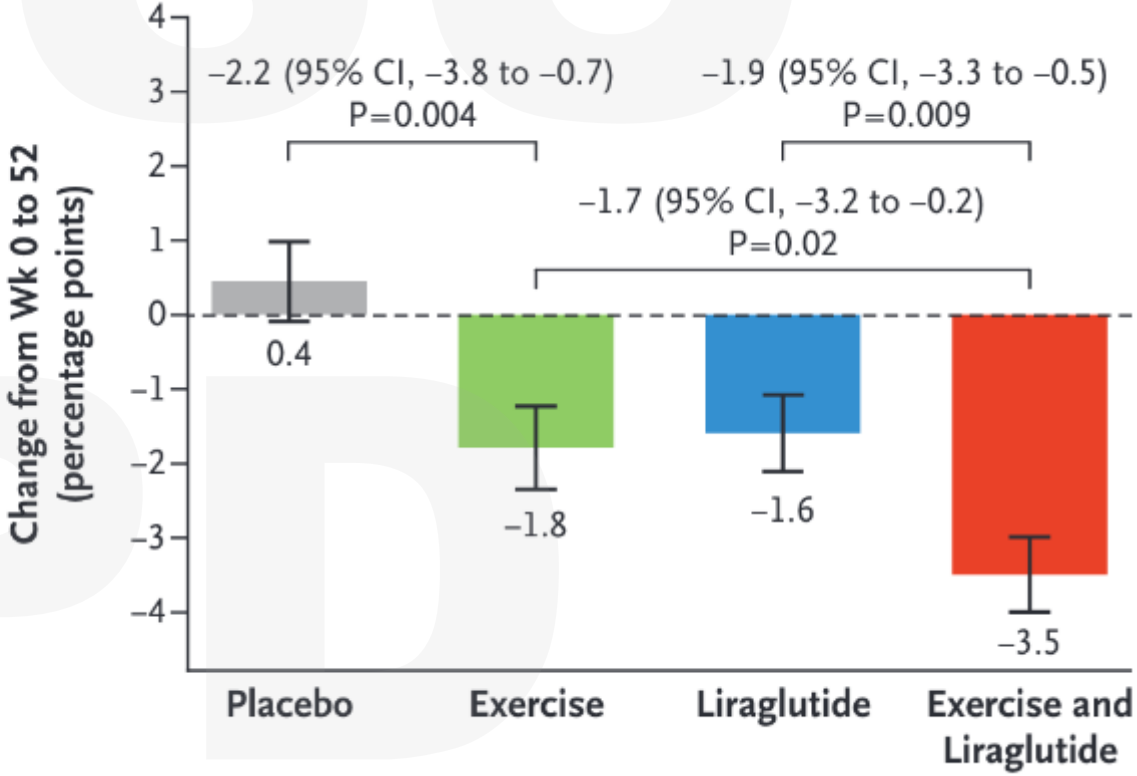
Sargeant JA et al Endocrinology Metabolism 2019

Lean Mass Preservation

Liraglutide+ Exercise

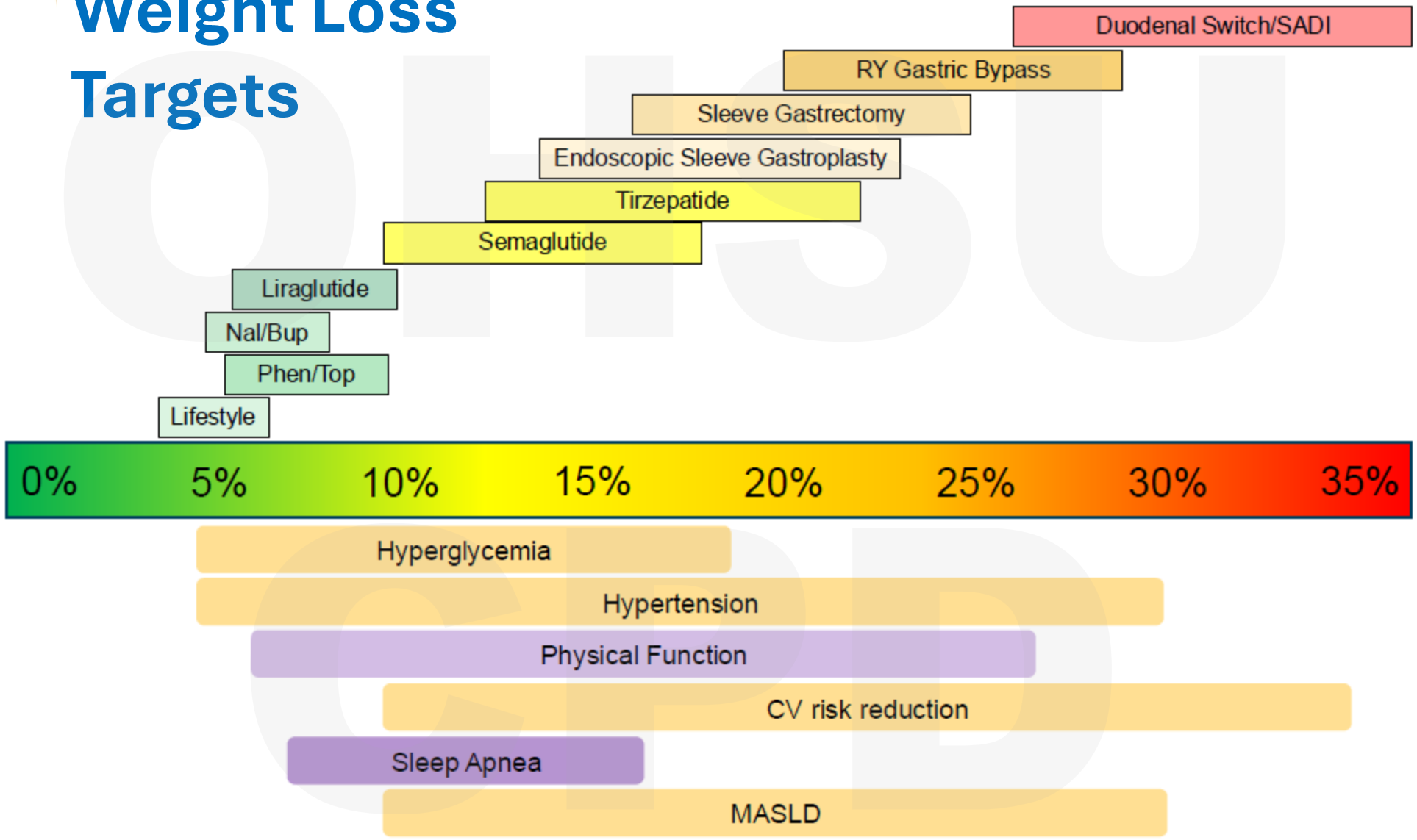
- Change in body fat percentage





Lundgren et al. *N Engl J Med*. 2021;384(18):1719-1730.

Weight Loss Targets



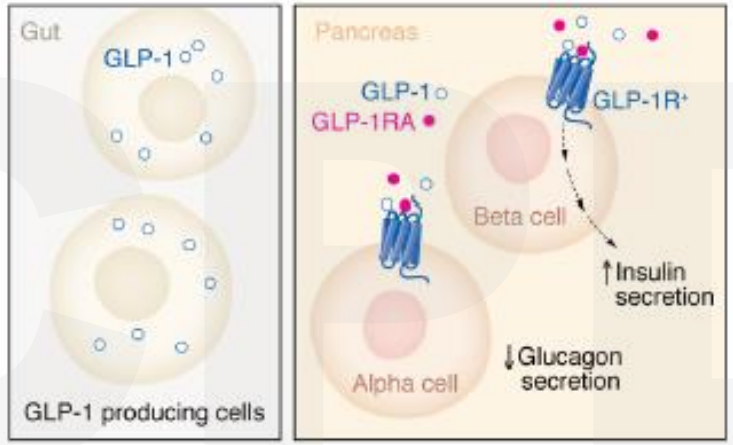
Mundi M et al 2024

Reducing risk of major cardiovascular events

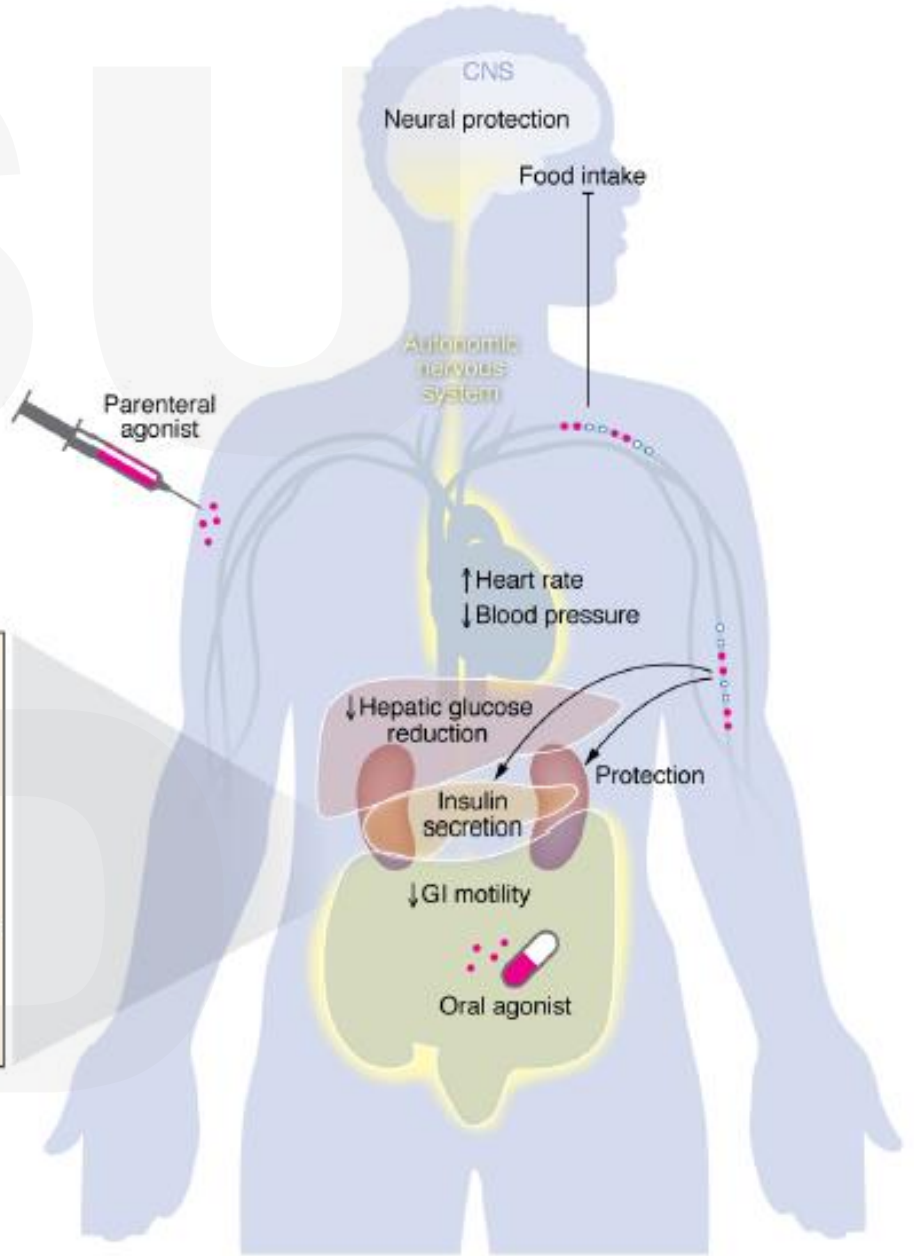
Completed Trials:

- **Leader**
- **Select**
- **Surpass**

ALL trials reported major cardiac event reduction



Drucker DJ JCI 2024



Cardiometabolic Effects of GLP-1 receptor agonists

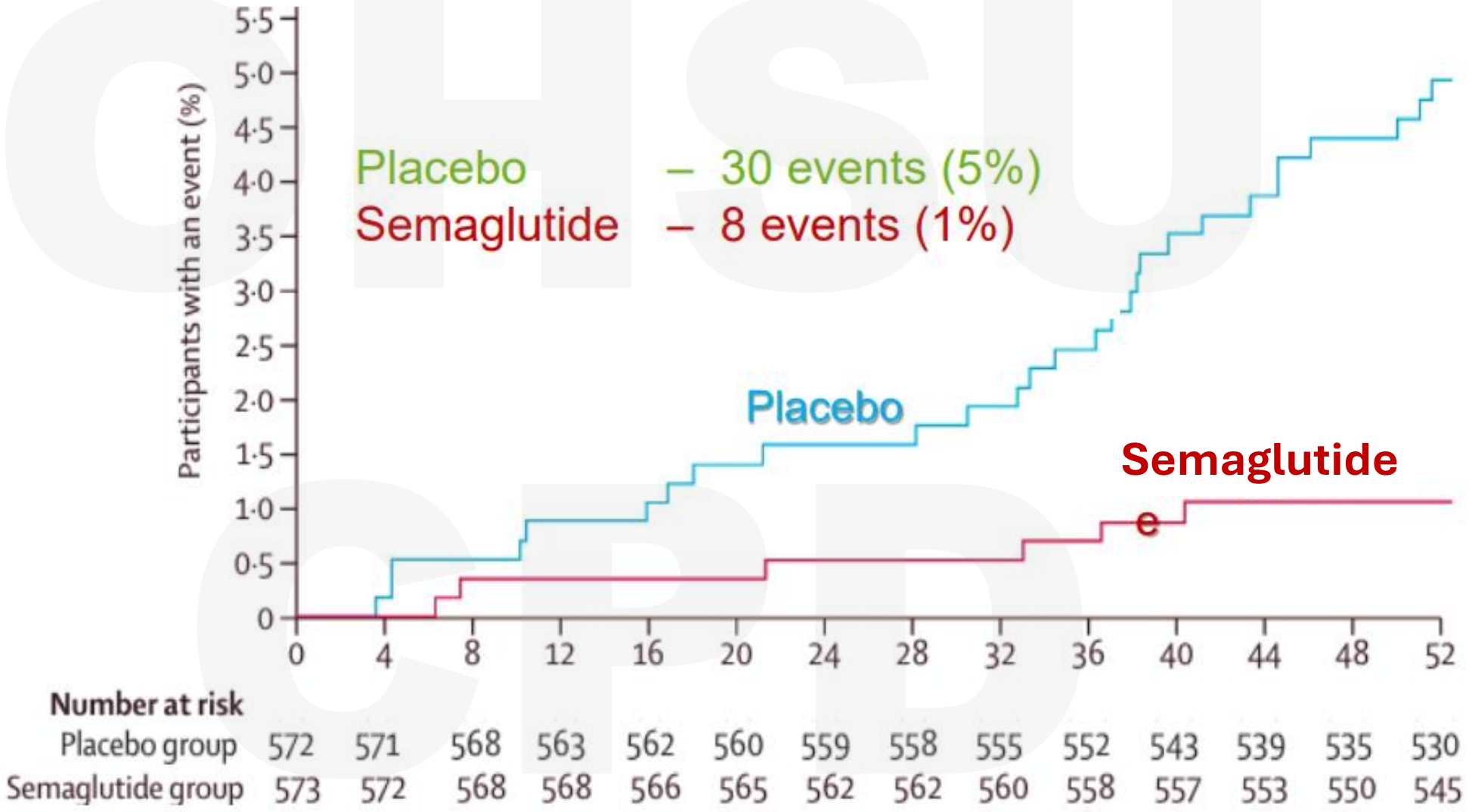
Reducing risk of major cardiovascular events

- **Mechanisms:**
  - **Increases EF**
    - **Improved glucose uptake**
    - **Decrease inflammation**
    - **Inhibits apoptosis – promotes autophagy and mitophagy**
  - **Enhances bioenergetics –increase ATP production (in cardiomyocytes)**
    - **Improves recovery from I/R**
  - **Decrease atherosclerosis, stabilize atherosclerotic plaques (via reduction in inflammation)**
  - **Improve microvascular and coronary artery blood flow**
  - **Weight reduction (decreases systemic inflammation)**

- **Major Trials:**
  - **Semaglutide**
    - **STEP – improve BP, HBa1c, CRP, fasting lipid levels**
    - **CVOT SELECT – obesity w/o DM with existing CV disease.**
      - **Reduced non-fatal MI, non-fatal stroke, and death from CVD**
    - **STEP-HFpEF trial – significant improvements HF symptoms, symptoms linear with weight loss**
  - **Tirzepatide**
    - **SUMMIT Trial — decreases risk of death from heart failure, and worsening HFpEF**
      - **Also reported decreased hospitalization from CVD,**
      - **Improved health status, functional capacity, general well being, QOL, exercise tolerance**
    - **SURMOUNT-1 and 3**
      - **Improvements in all CV and metabolic risk factors**
      - **Improvements – BP, CV risk factors, HbA1c, fasting glucose and insulin, lipid profiles**

Zuchin Lancet 2025

STEP-HFpEF and STEP-HFpEF DM:
Pooled Analysis on Cardiac Outcomes- First Heart Failure Event



Hazard ratio =0.27 (95% CI 0.12 to 0.56) p=0.0004

Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials

	Number of events/analysed participants		Incidence rate per 100 person-years (semaglutide:placebo)	Hazard ratio (95% CI)	p value
	Semaglutide	Placebo			
Composite of cardiovascular death or worsening heart failure event					0·0045
SELECT	53/1174	66/1099	1·4/1·8	0·75 (0·52–1·07)	
FLOW	40/167	40/158	8·1/9·2	0·87 (0·56–1·36)	
STEP-HFpEF	1/263	12/266	0·3/4·2	0·08 (0·00–0·42)	
STEP-HFpEF DM	9/310	20/306	2·7/6·2	0·46 (0·20–0·98)	
Overall	**103/1914**	**138/1829**	**2·1/3·0**	**0·69 (0·53–0·89)**	
Worsening heart failure event					0·0019
SELECT	17/1174	27/1099	0·4/0·7	0·58 (0·31–1·06)	
FLOW	29/167	29/158	5·9/6·7	0·88 (0·53–1·48)	
STEP-HFpEF	1/263	12/266	0·3/4·2	0·08 (0·00–0·42)	
STEP-HFpEF DM	7/310	18/306	2·1/5·5	0·40 (0·15–0·92)	
Overall	**54/1914**	**86/1829**	**1·1/1·8**	**0·59 (0·41–0·82)**	
Cardiovascular death*					0·25
SELECT	40/1174	43/1099	1·0/1·2	0·87 (0·56–1·34)	
FLOW	17/167	19/158	3·2/4·0	0·78 (0·40–1·51)	
STEP-HFpEF DM	2/310	4/306	0·6/1·2	0·49 (0·07–2·53)	
Overall	**59/1914**	**67/1829**	**1·2/1·4**	**0·82 (0·57–1·16)**	

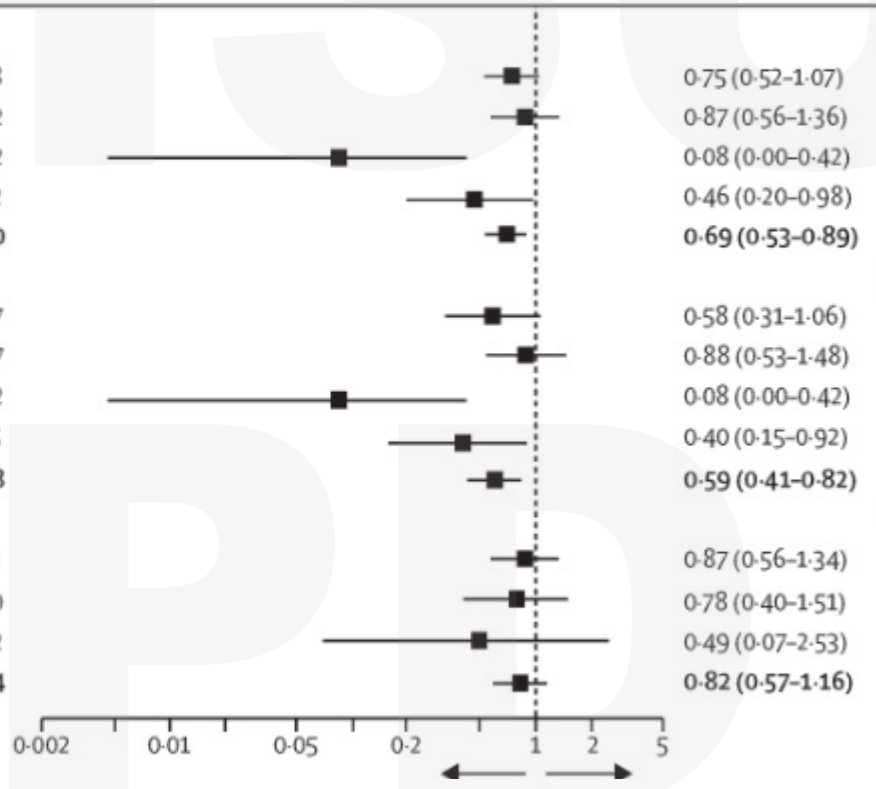
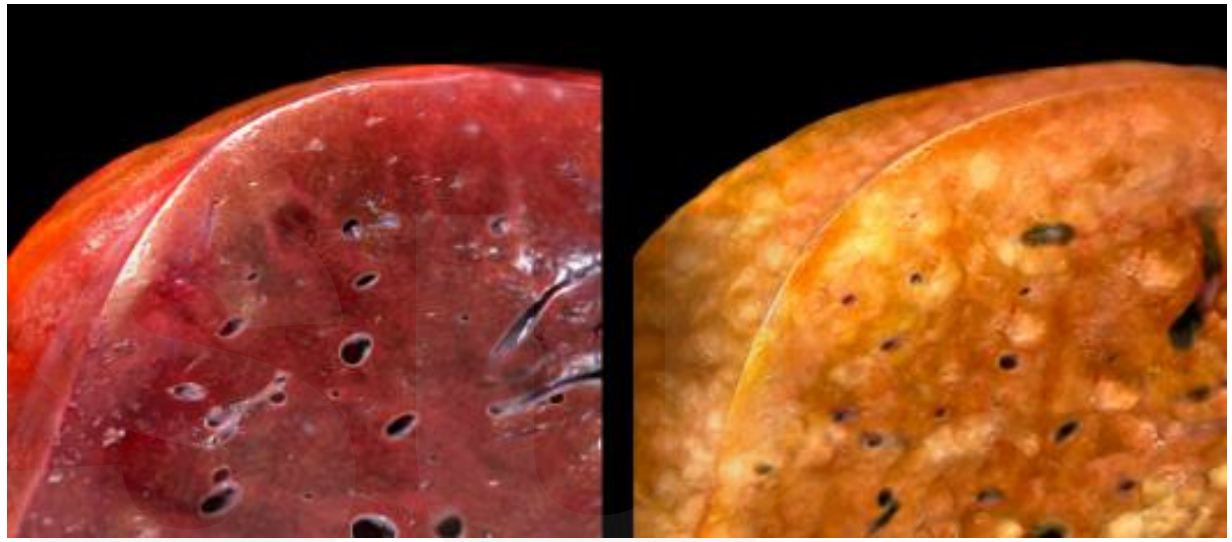


Figure 2 Time from randomisation to first endpoint of interest (composite of cardiovascular death or worsening heart failure event, worsening heart failure event, and cardiovascular death), overall and by trial

Hepatic effects



5% total weight loss decreases liver volume by 10% and visceral adipose by 10% while decreasing hepatic triglyceride content by 40%

- Improve hepatic lipid metabolism
  - Reduction in hepatic steatosis
  - Reduction in circulating lipids
  - Decrease risk of developing NAFLD
  - Enhanced insulin sensitivity
    - Inhibits glucagon-mediated gluconeogenesis
    - Enhancing mitochondrial efficiency and autophagy in hepatocytes

- NAFLD – MASLD (redefined as metabolic dysfunction-associated steatotic liver disease)
- MASLD can progress to MASH (metabolic dysfunction associated steatohepatitis)
  - Liver fibrosis
    - Phase 2 LEAN trial – Liraglutide 39% NASH resolution vs 9 % for placebo
    - Semaglutide – 59% NASH resolution vs 17% with placebo
  - GLP-1 reduces food intake, body weight, hepatic steatosis, and fibrosis
    - Reduces progression of fibrosis
    - Reversing fibrosis still questionable
    - Tirzepatide > semaglutide > liraglutide

Targher G et al The Lancet – Gastroenterology and Hepatology 2023
Jogani VG, Martindale R, Hurt R, Mundi M , Curr Nutr Reports 2025

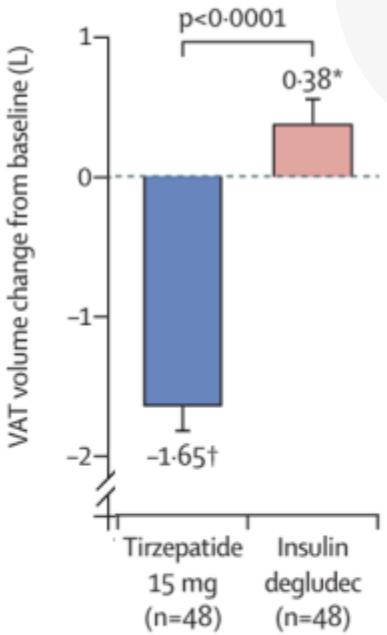
SURPASS-3 MRI:
Treatment-related Changes in Abdominal and Liver Fat Content

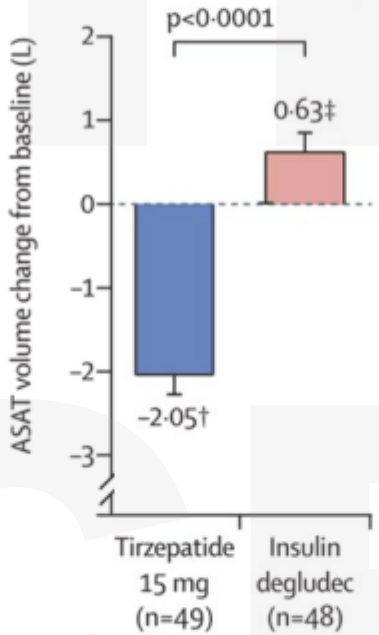
Adult patients with T2DM

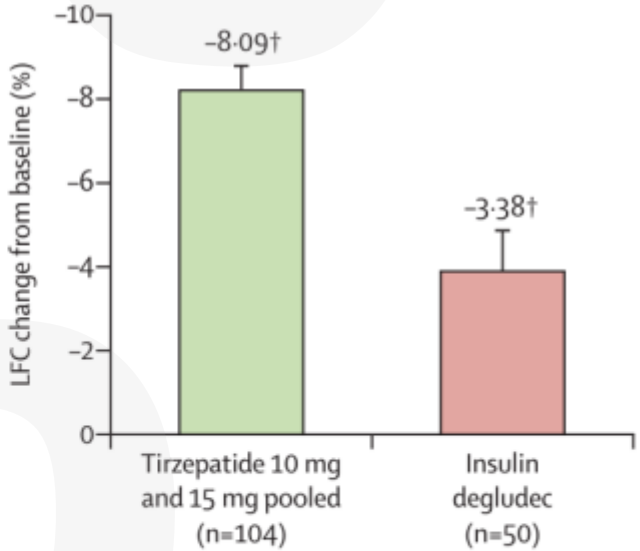
VAT: Visceral Adipose Tissue

ASAT: Abdominal Subcutaneous Adipose Tissue

LFC: Liver Fat Content







Gastaldelli A et al Lancet Diabetes Endocrinology 2022;10:393-406

Example of GIP-GLP-1 Receptor Agonist in Reversing Hepatic Fat Deposition in a Patient with T2DM

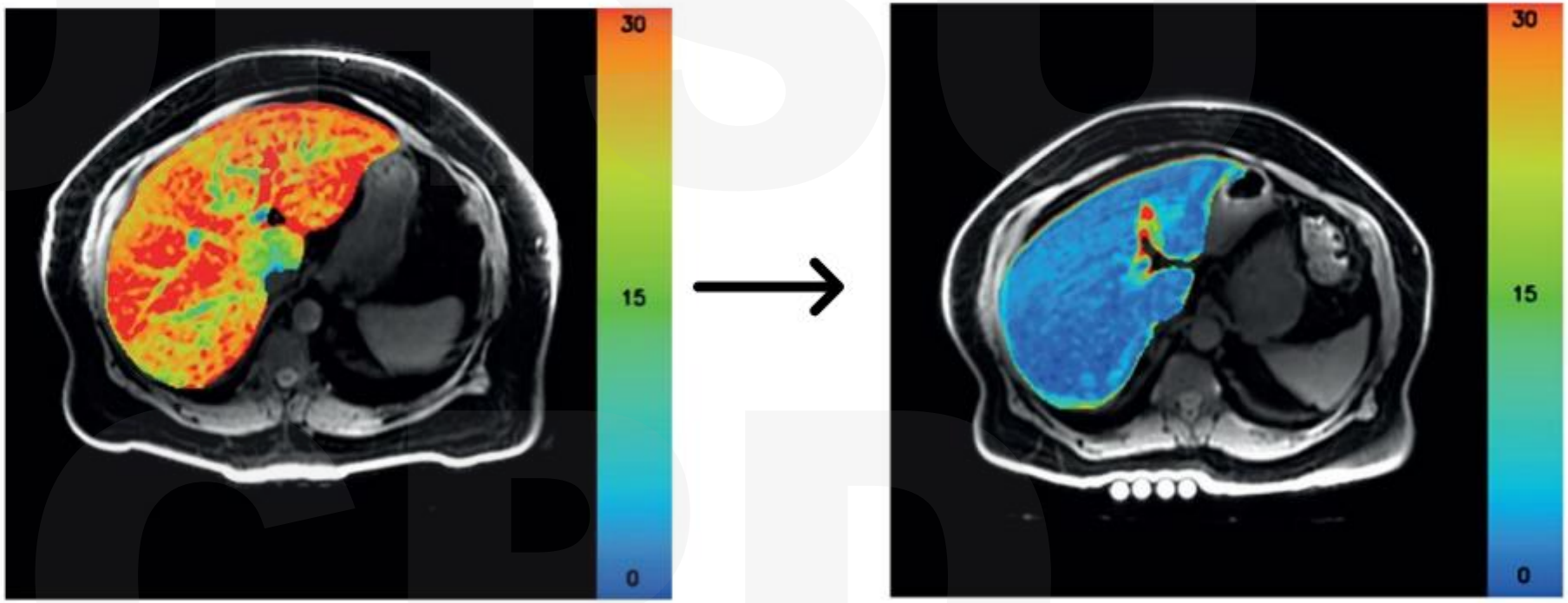
SURPASS-3 MRI --- Mean intrahepatic fat loss = - 8.09%

A 59 year-old man with T2DM

Receiving metformin with a SGLT2 inhibitor at baseline

Not reaching treatment goal prior to study entrance

Tirzepatide 5 mg after 52 weeks

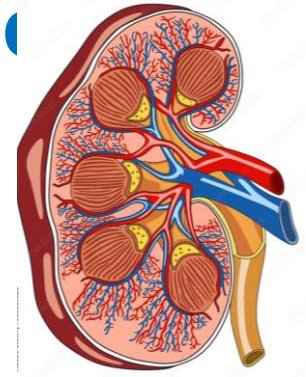


LFC at baseline: 27·3%

LFC at week 52: 2·6%

Gastaldelli A et al Lancet Diabetes Endocrinology 2022;10:393-406

Protect renal function / Chronic kidney disease



- **Benefits shown:**
  - Diabetic kidney disease
  - Chronic kidney disease
  - Acute kidney dysfunction
  - Decrease # of hospitalization for worsening renal failure
  - SELECT Trial– decreased death from renal disease, need for CRRT, macroalbuminuria
  - Slowing decline in GFR

- **Mechanisms**
  - Reducing renal inflammation
    - Inhibits the RAGE pathway and NLRP3 inflammasome
    - Induce CD+ T cell exhaustion (in transplant)
  - Promote natriuresis by inhibiting Na-Hydrogen exchanger 3 in proximal tubule
  - Inhibit renin-angiotensin-aldosterone system
    - Helps manage glomerular hyperfiltration and volume overload

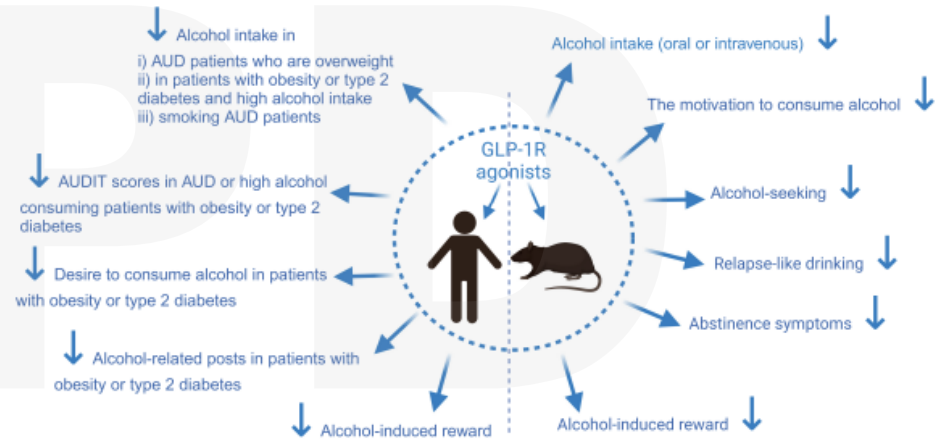
Westermeier F et al Cardiovas Diabetology 2025

GLP-1 in the Critical Illness

- **Multi-organ protective effects**
  - CV, hepatic, renal, gut, lung
  - GLP-1 felt to be immunomodulatory
  - GLP-1Ra exhibit anti-fibrotic effects in multiple solid organs –liver, lung, heart, kidney
- **Mechanisms**
  - Anti-inflammatory
    - GLP-1 suppresses pro-inflammatory cytokines (TNF-a, IL-1, Il-6 and NFkB)
  - Metabolic
    - Preserves mitochondrial integrity
  - Cytoprotective
    - Maintains mitochondrial function
- **ARDS, Sepsis, MOF**
  - Improve glucose homeostasis
  - Attenuate systemic inflammation
  - Preserve mitochondrial function (FA oxidation and ATP production)
  - Mitigate muscle wasting
  - Neuroprotective
  - Gut microbiome influences
    - SCFA directly stimulate GLP-1 secretion
    - Prevents development pathobiome

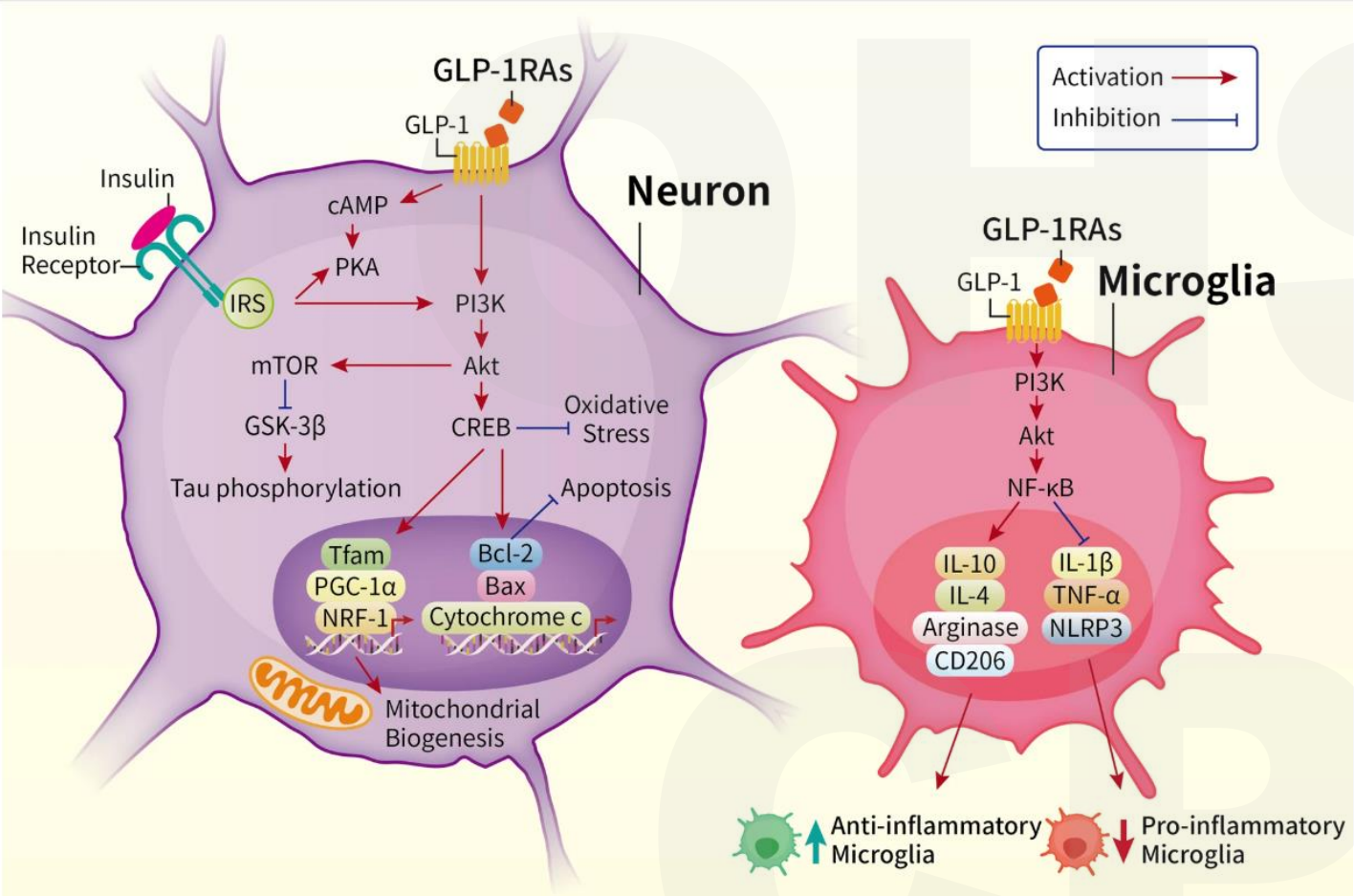
GLP-1ra for addiction

- Long reported “anti-hedonic” effects
  - Mechanism felt to be via modulation of reward processing i
    - Dopamine release in mesolimbic system at nucleus accumbens
- Animal studies
  - Dampens compulsive pleasure-seeking behaviors
    - Alcohol, nicotine, cocaine, opioids
- Human studies
  - reduces alcohol consumption in patients with alcohol use disorder (AUD), especially in those with comorbid obesity or type 2 diabetes
    - RCT semaglutide vs placebo
      - 48 adults with alcohol use disorder
      - 9 weeks trial
    - Significant reduction in consumption
    - Significantly reduced craving



Jerlhag E. Endocrinology 2025
Petrie GN, Mayo LM. JCI 2025
Klausen MK et al Brit J Pharm 2022

GLP-1 in neurodegenerative diseases: Parkinson’s and Alzheimer's diseases



Clinical Evidence for GLP-1 Receptor Agonists in Alzheimer’s Disease: A Systematic Review

J of Alzheimer’s Disease Reports 2024

Conclusions: GLP-1 RA therapy did not alter amyloid- and tau biomarkers nor show improvements in cognition but showed potential metabolic and neuroprotective benefits.

Incretin-based therapeutics for the treatment of neurodegenerative diseases

Vear A et al Nature Metabolism 2025

GLP-1R and GIPR agonists are emerging as promising treatments for NDDs. Their pleiotropic ability to reduce neuroinflammation, enhance neuronal energy metabolism and promote synaptic plasticity positions them as potential disease-modifying NDD interventions

Controversy:

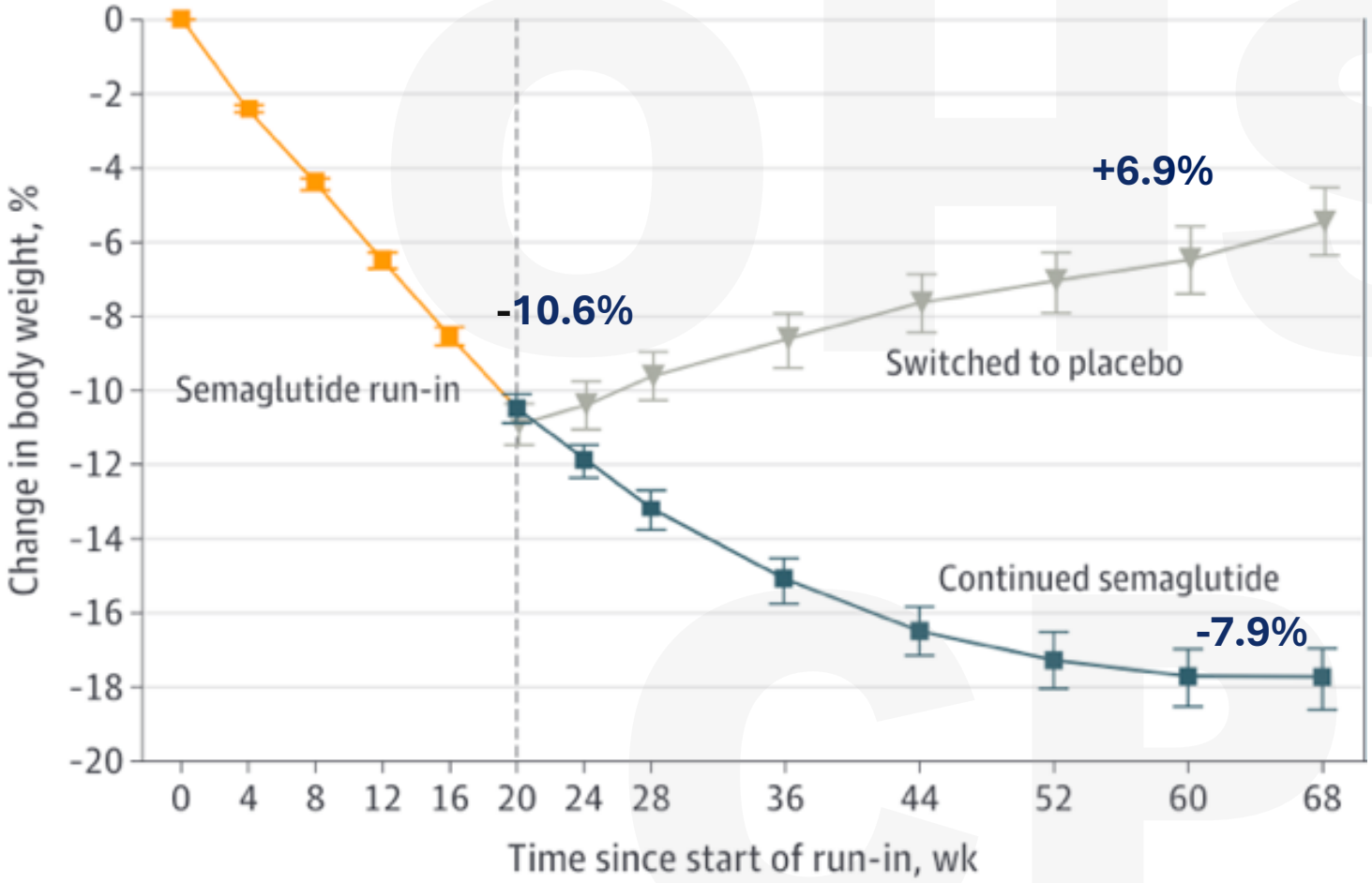
- Direct effect via GLP-1 RA or indirectly driven by systemic health effects like DM and weight
  - GLP-1R is expressed at low levels in heart and blood vessels
  - GLP-1R in kidney localized in subset of vascular smooth muscles
    - Absent in glomerular epithelial or tubular cells
  - Liver – Receptors absent in hepatocytes, Kupffer cells and stellate cells

- GLP-1RA need to be tailored to sex, BMI and ethnic diversity
- Lifelong drugs ?
- Variable species differences in GLP-1 receptor in various tissues

Risks and complications with GLP-1 medications

- **Regain in weight when stopping drug**
  - **Most of weight regain is adipose – leading to worsening sarcopenia**
- **GLP-1 induced frailty**
  - **This is real, especially in those with preexisting sarcopenia**
- **Gaunt appearance of face (Ozempic face)**
- **Gallstones +/- data is widely variable**
- **Pancreatitis – data variable – trending toward, no significant differences, reported mostly in acceleration of dosing**
- **Alters relationships**
- **Headaches**
- **Kidney stones**
- **Aspiration during induction of anesthesia**

Weight Regain with Cessation of GLP-1 Rx: Data from Novo Nordisk



Implication:

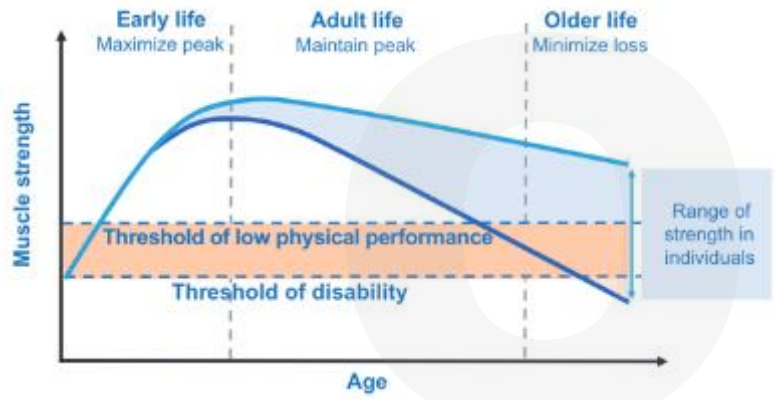
Results indicate need for life-long treatment

Set point of obesity mechanisms remain operative despite lifestyle intervention, weight loss, medications

D Rubino [JAMA 2021;325(14):1414)

TM Garvey (Endocrine Practice 2022;28:214)

Sarcopenia

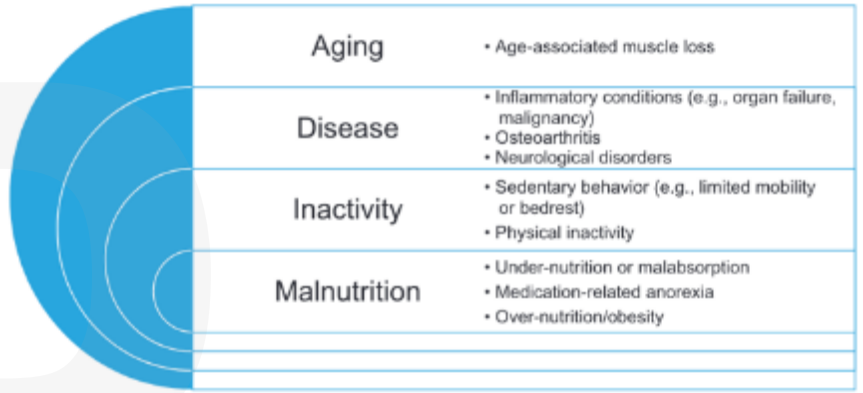


Myocyte Derangement	Etiology
Accumulation of damaged mitochondria	Chronic disuse resulting in excess oxidative radical production
Increased muscle apoptosis	Mitochondrial damage
Decreased $V0_{2max}$	Mitochondrial damage, decreased mitochondrial protein content
Increased muscle proteolysis	Muscle unloading, malnutrition
Decreased muscle protein synthesis	Malnutrition, chronic inflammation via mammalian target of rapamycin
Myocyte autophagy and type II fiber loss	Malnutrition, starvation

Sarcopenia is a progressive and generalized skeletal muscle disorder associated with increased likelihood of adverse outcomes.

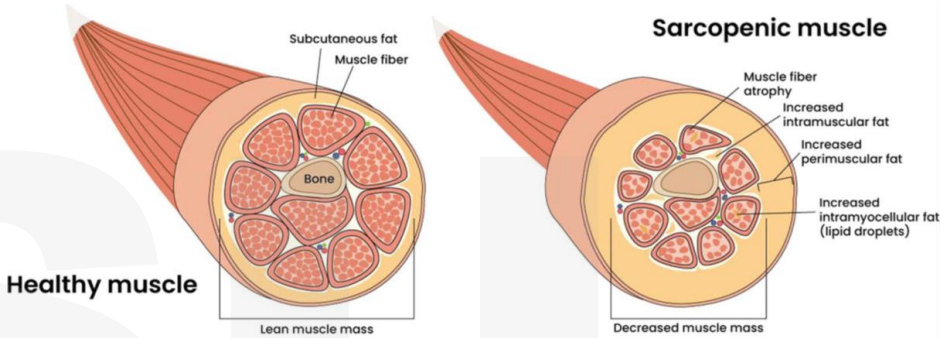
Powered by DALL·E 3

- **Muscle loss naturally begins around the age of 30 at a rate of 1-2% per year.**
- **After age 60, up to 3-5% loss annually**
- **By 80 years of age, most have lost up to 50% of muscle compared to age 30.**



Hanna JS. *JPEN*. 2015
Cruz-Jentoft AJ, et al. *Age Ageing*. 2019;48(1):16-31.

Sarcopenia –



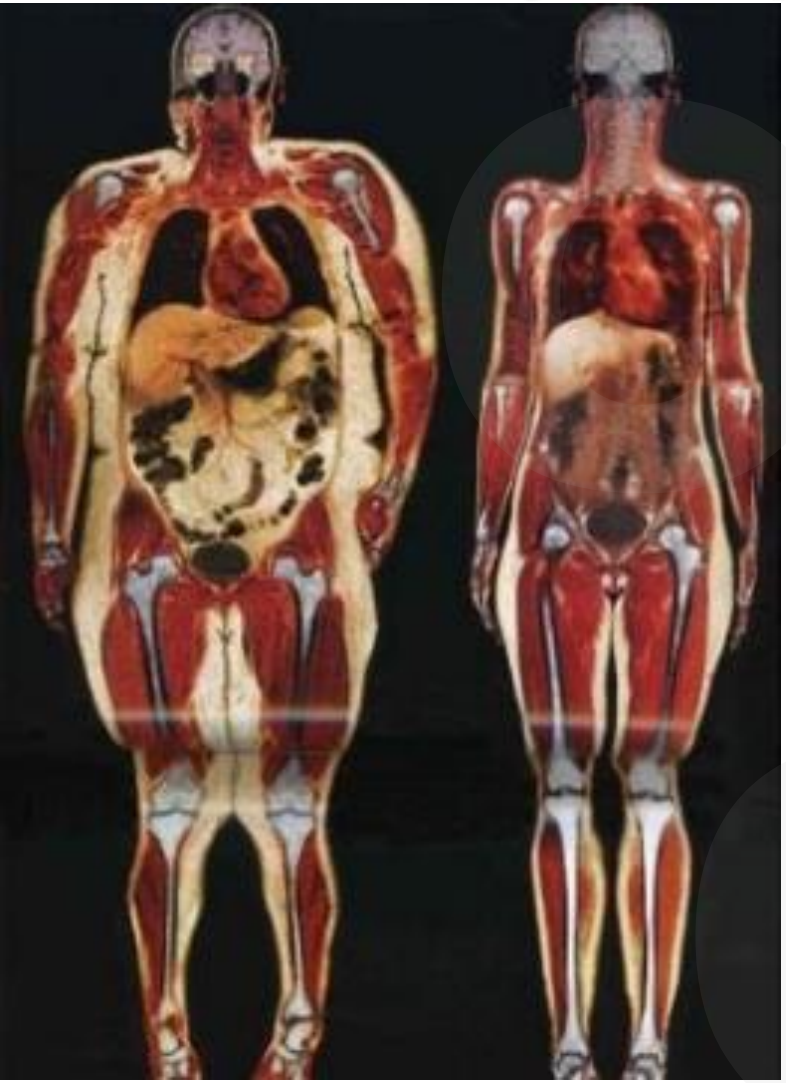
- **Definition**
  - **No consensus**
    - **loss of muscle mass, loss of function, and weakne**
  - **Newer concepts include: sarcopenia-- frailty– mobility**
  - **Sarcopenia not recognized as disease until 2016**

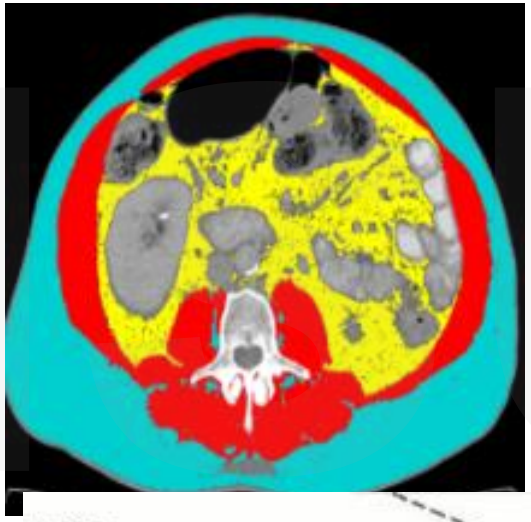
- **1/3 of Medicare beneficiaries will undergo surgery in last year of life**

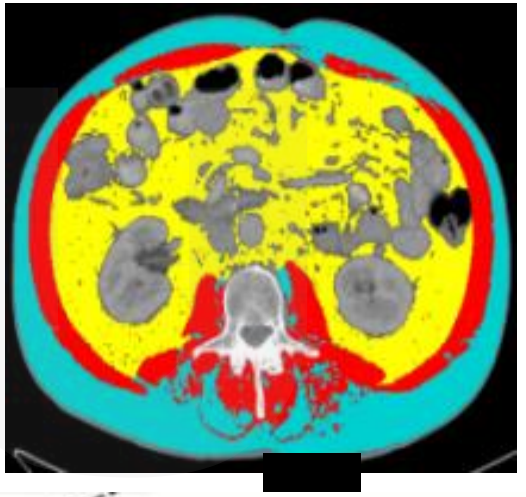
- **Manifestations of sarcopenia are often concealed by body compositional changes associated with age or lack of resistance exercise**

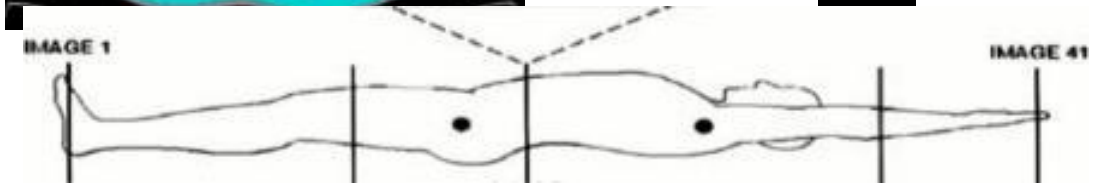
- **GLP-1 medications are showing significant levels of sarcopenia**

Body composition useful or just “sarcomania”









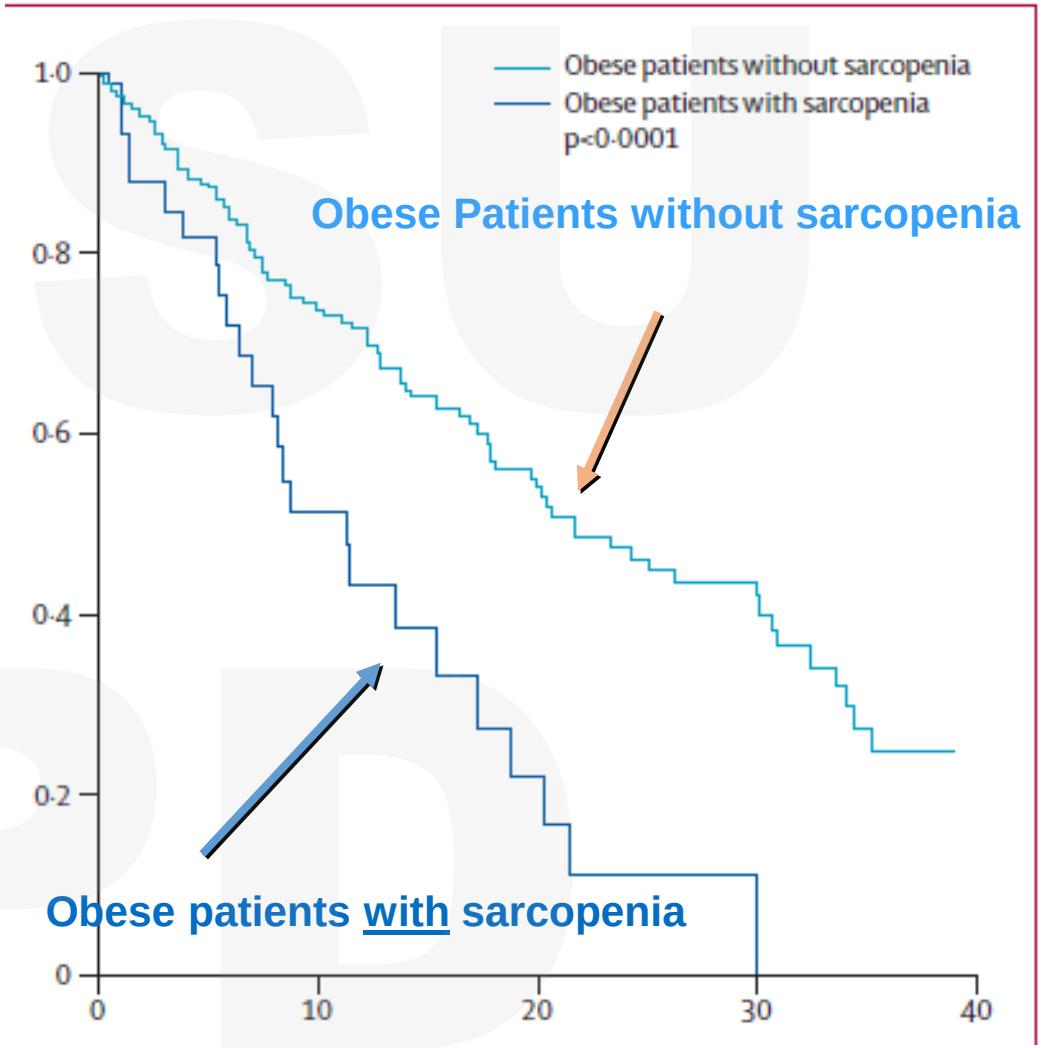
Diseases now proven to have correlated body composition to outcome

Ca, pancreatic Ca, esophageal Ca, lymphoma, elderly trauma in ICU, hepatoma, lung Ca, AWR and ventral hernia, liver transplant, 30 d mortality in sepsis, ECMO, etc ?

1) Peng P et al J GI Surgery 2012
2) Kirk PS et al J Surg Res 2015
3) Okumura S et al Surgery 2015
4) Mundi M et al Nutr Clin Practice 2019
5) Xiao J et al JAMA Surg 2020
6) Schlossse KA et al Am Surg 2019
6) Moisey LL et al CC 2013
7)Prado CM et al Ann Med 2018
8) Ji Y et al Jour Crit Care 2018
9) Bear D et al CCM 2021
10) van Rooijen MMJ WJS 2019

Sarcopenic obesity has a very poor prognosis

Sarcopenia is a predictor of survival independent of age, sex, functional status



Deutz NEP et al JAMDA 2019
Prado CMM, Baracos VE et al Lancet 2008

Systematic review and/or Meta-analysis

INTERNATIONAL JOURNAL OF SURGERY

2023

Impact of sarcopenia on outcomes in surgical patients: a systematic review and meta-analysis

- **Reviewed 294 studies including 97,643 surgical patients**
  - **33,070 patients with sarcopenia**
- **Results:**
  - Increased greater mortality (P< 0.00001)
  - Total complications (P< 0.00001)
  - Longer hospital stays (P< 0.00001)
  - Decrease discharge to home (P< 0.00001)
  - Significantly lower survival rates in years 1, 3, 5 (all P<0.00001)
- **Conclusion:**
  - **Sarcopenia is significant predictor of poorer outcomes in surgical patients**

Knoedler S et al Int J Surg 2023

Combining strategies for weight loss

Intense Lifestyle Changes:

before GLP-1 10% weight loss in 6 months -95% recidivism

Dietary modifications / resistance exercise / weight training

Current strategy

GLP-1 agonists or combination meds

Surgery

Weight loss med (GLP-1 agonists)

Surgery- with failure of meds

Significantly increases risk with this strategy

Weight loss med

Weight loss med

Continue on GLP-agonist or combination med, with and without lifestyle changes


OZEMPIC FACE
BEFORE
AFTER

Issues still needing to be sorted out with the "Incretins"

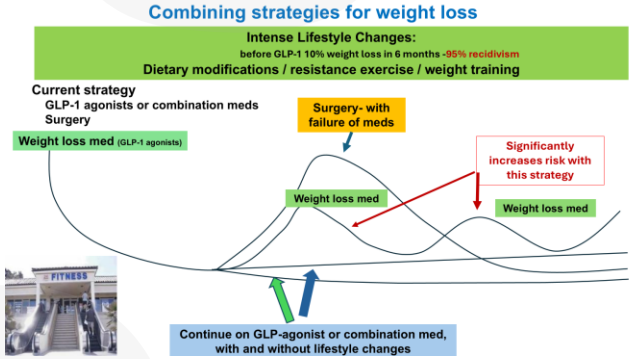
- Changes in body composition
  - Muscle mass, bone density, wound healing, fat compartments within the face
    - Gaunt appearance of face as discussed on national morning talk shows
  - Muscle quantity and quality altered
  - GLP-1 RA adipose vs lean body mass is appropriate ratios
    - The problem arises with weight gain ***after*** GLP-1 RA drugs – almost all adipose (1)
- Changes in wound healing / tissue changes post weight loss (2)
- How to manage nutrition
  - Treat as a gastroparesis patient
  - High protein, fiber, calcium, vitamin D
- For success patients need continued need for lifestyle intervention, resistance exercise (3)

(1) Conte C et al JAMA 2024
(2) Hasanbegovic E et al J Plas Recon Aesth Surg 2014
(3) Jensen SBK et al JAMA Open 2024

Economics of GLP-1

- **Estimated at > 1.5 million people in USA on GLP-1 medications in 2025**
  - **95 million Americans are potentially eligible to use GLP-1 RAs**
  - **$ GLP-1RAs for adult's w/o diabetes in 2018 $1.6 billion, in 2022 $5.8 billion**

- **Financial dilemma, long term response**
  - **Many insurers only cover limited duration of therapy**



- **Effect on multiple industries**
  - **Food industry**
  - **Travel**
    - **United airlines - if** average passenger were to lose 10lbs (4.5kg), it would save the airline $80m a year in fuel costs
  - **Plastic surgery**

- **Industry responsibilities, financial impact**
  - **GDP of Novo-Nordisc > than the GDP of Denmark in 2023 and 2024**
  - **Price reduction already seen with Tirzepatide –**
    - **Offering multidose vials - $400 / month (E Lilly)**

Shadbolt C et al Ann Int Med 2025

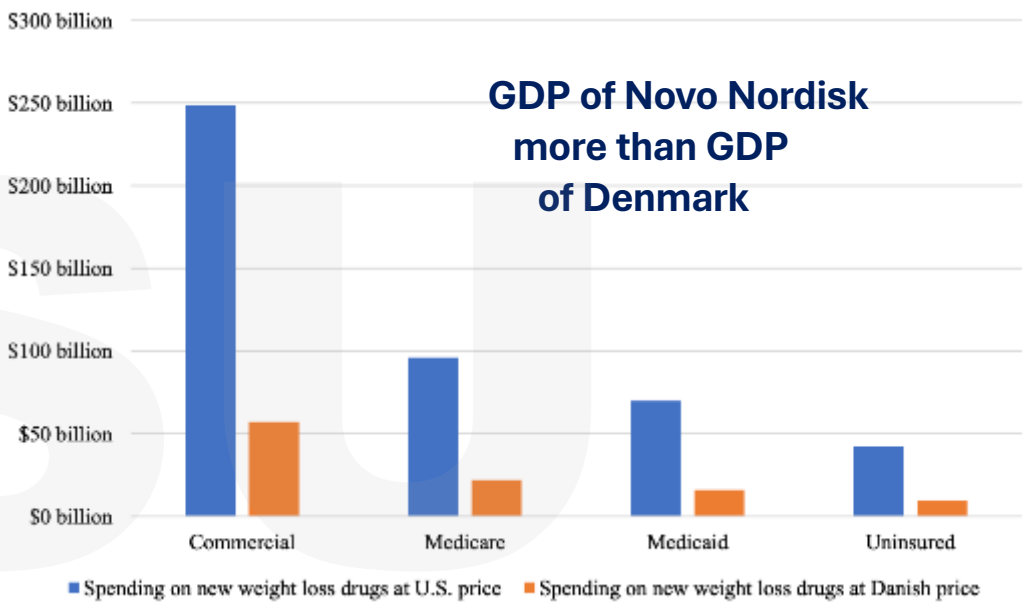
Exaggerated Cost in US

- **USA list prices $12,000-$16,000 per year**

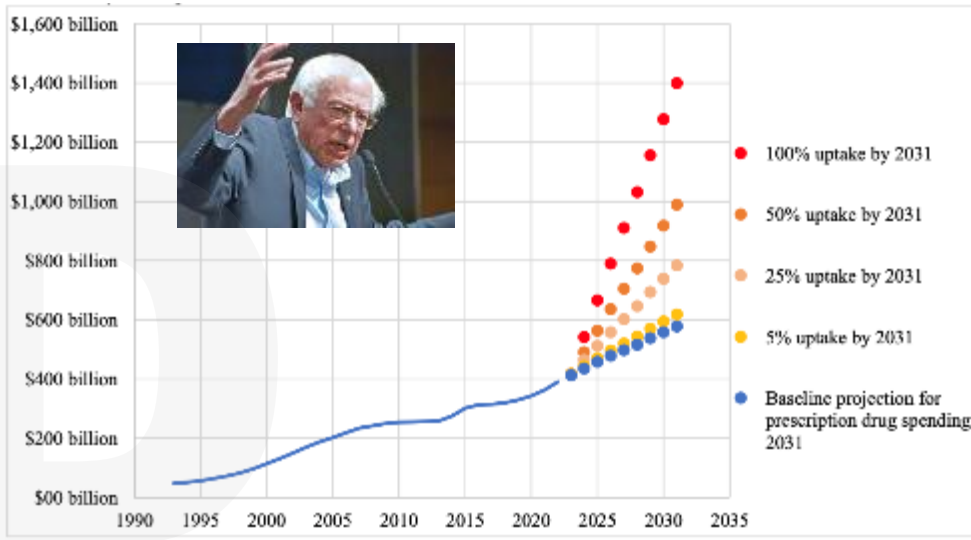
  Manufacturing price < $5.00/unit

  Cost-based pricing < $72.49/month

	Ozempic: (per month)	Wegovy: (per Month)
USA	$969	$1349
Canada	$155	
Italy	$122	
France	$71	
Germany	$59	$137



GDP of Novo Nordisk more than GDP of Denmark



- **Strategies to cover cost:**

  1) Don't pay – Medicaid only 10/47 states cover ≥1 obesity med

  Medicare Part D no coverage

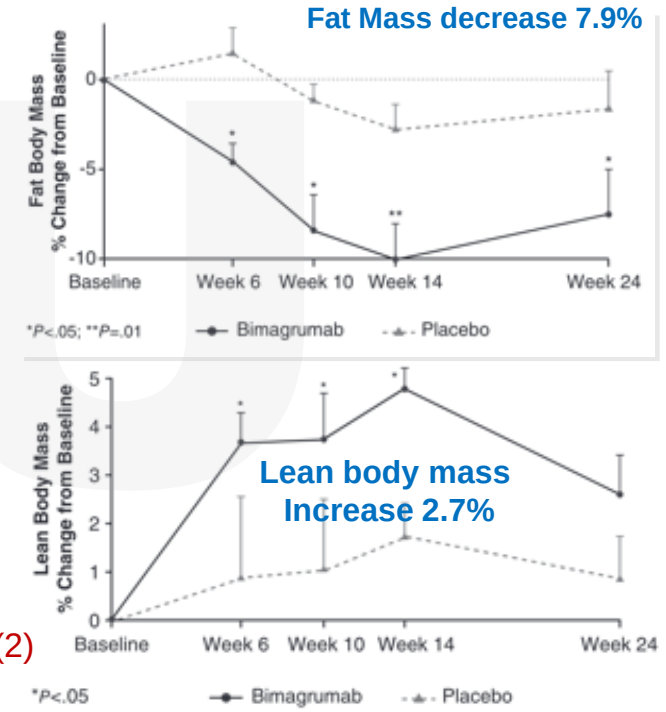
  2) Pay for only 2 years – UK NHS, Mayo have 2-year limit

  3) Stop payment if <5% weight loss over 6 months

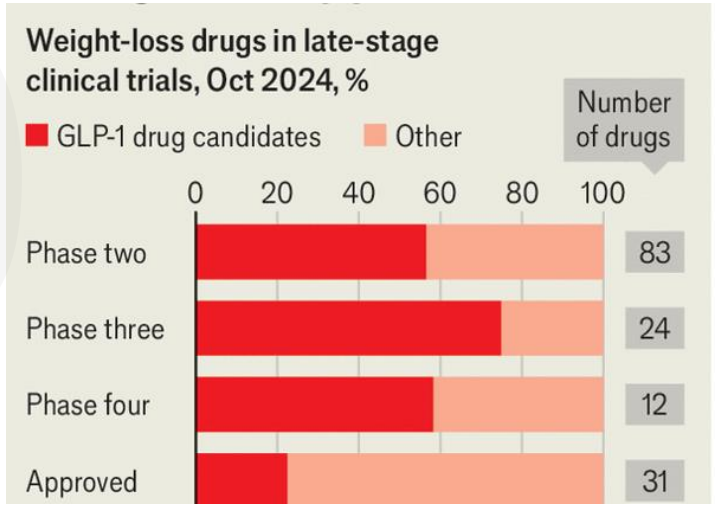
Atlas SJ (J Manag Care SpecPharm 2023;29:10.18553).
Liu BY (JAMA 2024;331:1230)
Barber MJ (JAMA Network Open 2024;7:e243474)

Possible meds not yet approved based on GLP physiology

- **Several new drugs coming**
  - **Semaglutide –bimagrumab** [(1)] **phase 2 trial**
    - Human monoclonal antibody that stimulates anabolism in muscle by blocking activin II
      - Some changes in converting white fat to brown fat
      - Fat mass 20.5 decrease vs 0.5% in control
      - Shown to **increase muscle mass** by 3.6 % vs -0.8%



  - **GLP-1 with glucagon agonists** (at least 14 undergoing study) [(2)]
    - Glucagon
      - Inhibits food intake
      - Increase energy expenditure
      - Counteract hepatic steatosis



  - **Drugs based on small molecules, receptor agonist**
    - Not peptide based—Lilly applying for approval 2026 (Orforglipron)
    - Should be much less expensive to produce

(1)Heymsfield SB et al JAMA Open 2021
(2) Holst JJ Nature Metabolism 2024

Summary

- GLP-1RA are here to stay for multiple disease states
  - 95 million Americans are potentially eligible to use GLP-1 Ras
- Compounded GLP-1 RA and microdosing ?
- Long term safety ?
  - Giving long-acting modification of hormones with short t ½ ????
- Sarcopenia
  - How to address the nutrition needs to alleviate the risk ?