Obesity: New Injectables Implications and Use

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Learning Objectives

- Describe the benefits GLP-1 RA provide for diabetes treatment
- Explain the physiologic effects of incretins on appetite and weight
- Discuss the results of key incretin obesity treatment studies
- Identify the risk, benefits, and future opportunities of incretins for obesity treatment

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GILA MONSTER

Venomous lizard
-Non-fatal but painful toxic venom
-Venom contains bioactive peptides
-Exendin-4
-Exenatide – synthetic blueprint of exendin-4.

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Incretin Receptor Agonists

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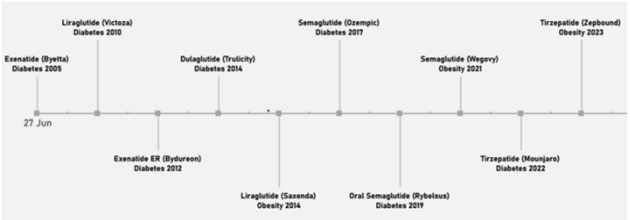
Timeline of GLP-1 & GLP-1/GIP RA's



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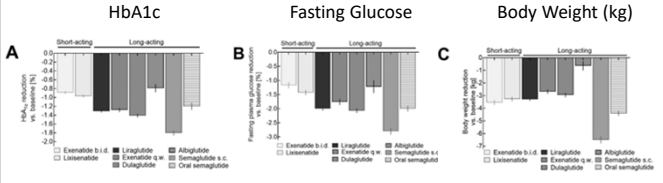
From Diabetes to Obesity



Nauck, *Molec Metab,* 2021

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From Diabetes to Obesity

Semaglutide v. Insulin Glargine

THE LANCET
Diabetes & Endocrinology

Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial

Vanita R Aroda, Stephen C Bain, Bertrand Cariou, Milivoj Piletič, Ludger Rose, Mads Axelsen, Everton Rowe, J Hans DeVries

Semaglutide
Greater ↓ HbA_{1c}
Greater ↓ weight
Less hypoglycemia

Aroda, *Diab & Endo,* 2017

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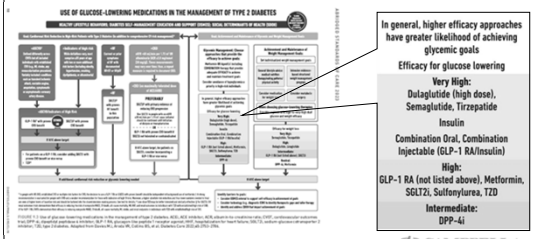
From Diabetes to Obesity

2024 ADA Standard of Care in Diabetes



ADA, *Diabetes Care,* 2024

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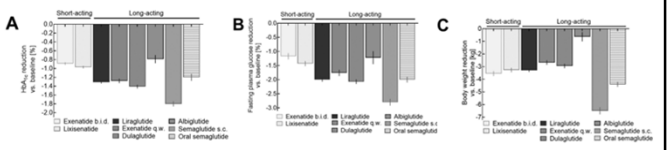
From Diabetes to Obesity

HbA1c | Fasting Glucose | Body Weight (kg)



Nauck, *Molec Metab,* 2021

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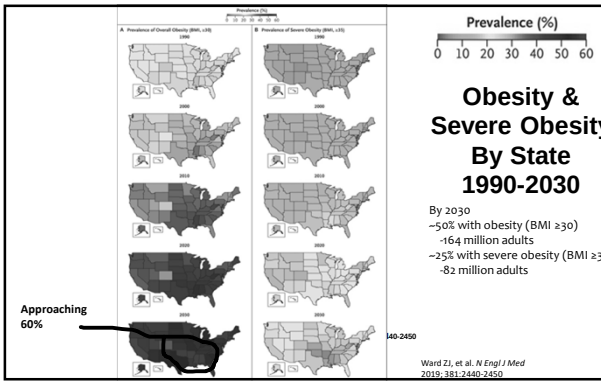

Ward ZJ, et al. *N Engl J Med* 2019; 381:2440-2450

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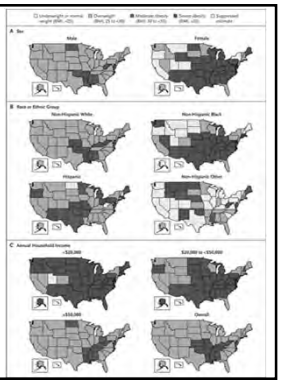
Gender, Racial & Income Disparities

- Women
- Non-Hispanic Black
- Hispanic
- Low income



The NEW ENGLAND JOURNAL of MEDICINE

Ward, 2019

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Why Do People Develop Obesity?

Traditional Thinking	Additional Understanding
Purposeful behavior regulates weight - **Calories in & Calories out** regulates weight	**Biology** Regulates weight - **Hormonal Response** regulates weight

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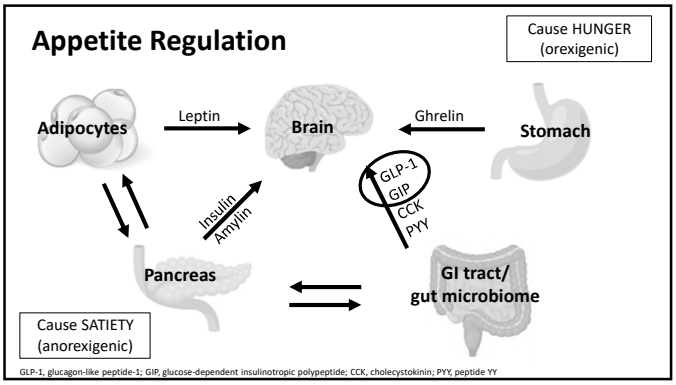
Appetite Regulation



GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; CCK, cholecystokinin; PYY, peptide YY

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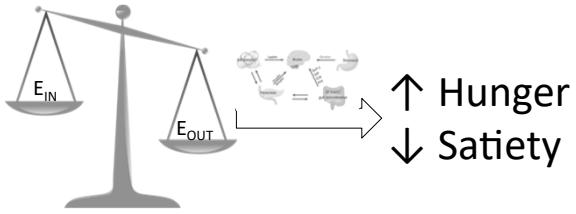
Physiologic Response to a Calorie Deficit

- Negative energy balance triggers a physiologic increase in hunger and decrease in satiety



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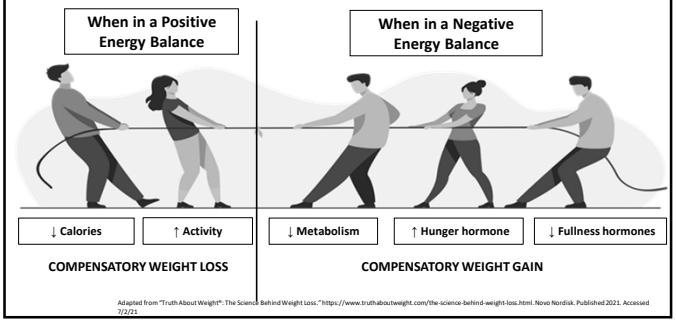
The Tug-of-War of Weight Management



Adapted from "Truth About Weight®: The Science Behind Weight Loss." https://www.truthaboutweight.com/the-science-behind-weight-loss.html. Novo Nordisk. Published 2021. Accessed 7/2/21

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Long-Term Impact of Weight Loss on Appetite Regulators

62-week study measuring appetite regulators after weight loss
- Levels after 10-week weight loss phase (mean weight loss 14%)
- Levels after 52-week maintenance phase

	Ghrelin	Leptin	PYY	GLP-1	CCK
Effect	Hunger	Satiety	Satiety	Satiety	Satiety
10 weeks	↑47%	↓64%	↓12%	↓7%	↓15%
62 weeks	↑21%	↓35%	↓20%	↓4%	↓5%

	Perceived Hunger	Desire to Eat
10 weeks	↑20%	↑11%
62 weeks	↑37%	↑26%

Sumithran P et al. *New Engl J Med.* 2011;365(17):1597-1604. (supplementary data)

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GLP-1 Receptor Agonists

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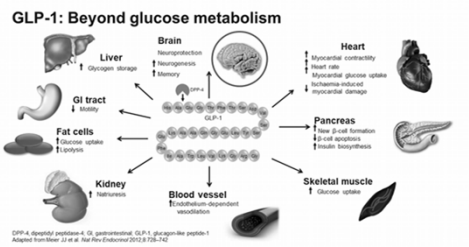
Glucagon-Like Peptide – 1 Receptor Agonist

GLP-1



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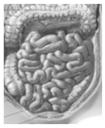
GLP-1



- Glucagon-like Peptide-1
  - Produced in distal small intestine and colon
  - Stimulated primarily by dietary carbohydrates
  - Increases satiety – central effect
  - Accentuates glucose-dependent insulin release
  - Reduces hepatic gluconeogenesis by decreasing glucagon
  - Delays gastric emptying
  - Inactivated by Dipeptidyl peptidase-4 (DPP-4)

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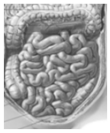
GLP-1



- Glucagon-like Peptide-1
  - GLP-1 levels reduced in
    - Obesity
    - Pre-diabetes
    - T2D
  - Increases significantly after gastric bypass
  - Liraglutide and semaglutide are GLP-1 receptor agonists and are approved for obesity treatment

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GLP-1 Receptor Agonists - Obesity Treatment

Liraglutide (Saxenda)	Semaglutide (Wegovy)
Daily subcutaneous injection	Weekly subcutaneous injection
Dosing Titration	Dosing Titration
• 0.6mg x 7 days	• 0.25mg x 4 weeks
• 1.2mg x 7 days	• 0.5mg x 4 weeks
• 1.8mg x 7 days	• 1.0mg x 4 weeks
• 2.4mg x 7 days	• 1.7mg x 4 weeks
• 3.0mg x 7 days	• 2.4mg x 4 weeks

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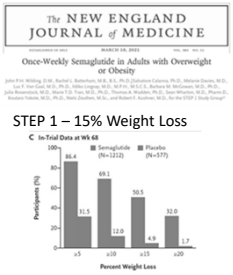
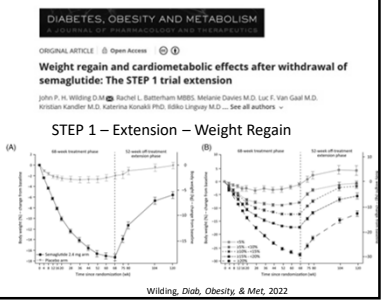
Key Studies - Semaglutide



Wilding, *NEJM*, 2021



Wilding, *Diab, Obesity, & Met*, 2022

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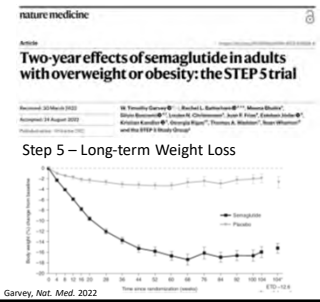
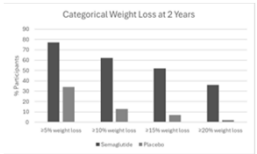
Key Studies - Semaglutide



Garvey, *Nat. Med.* 2022



CV RF	Semaglutide	Placebo
WC (cm)	–14.4	–5.2
SBP mmHg	–5.7	–1.6
DBP mmHg	–4.4	–0.8
% WL	–15.6%	–3.0%
HbA_{1c} %	–0.4%	–0.1%
HDLc	9.6	8.10
LDLc	–6.1	–2.7
Trig	–19.0	3.7
CRP %Δ	–56.7	–7.8

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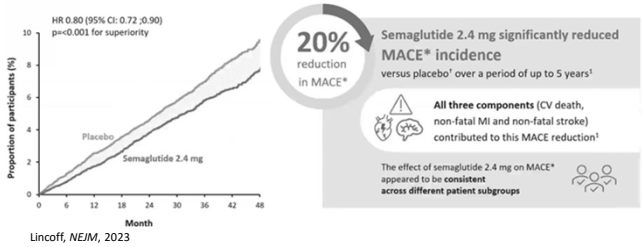
Key Studies - Semaglutide

CVOT – Secondary MACE Prevention



Lincoff, *NEJM*, 2023

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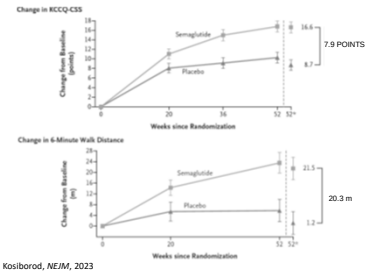
Key Studies - Semaglutide

STEP - HFpEF



Patients with heart failure w/ preserved ejection fraction

- -↓symptoms
- -↓ physical limitations
- -↑ exercise function
- -↓ weight

Kosiborod, *NEJM*, 2023

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GIP Receptor Agonists

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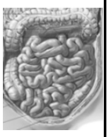
GIP

- **Glucose-dependent insulinotropic polypeptide**
  - **Produced in proximal & distal small intestine**
  - **Stimulated primarily by dietary carbohydrates**
  - **Decrease food intake – central effect**
  - **Accentuates glucose-dependent insulin release**
  - **Increases glucagon release – glucose dependent**
  - **Increases gastric emptying**
  - **Inactivated by Dipeptidyl peptidase-4 (DPP-4)**
  - **Tirzepatide is a GLP-1/GIP receptor agonist used for obesity treatment**



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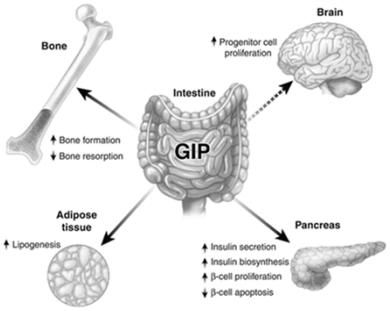
Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist

GIP



Chandarana, 2012

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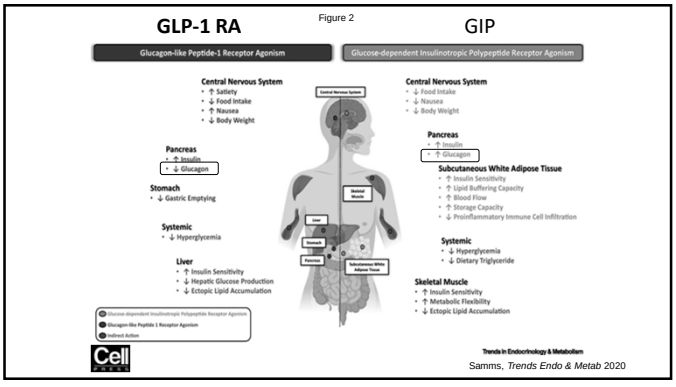
Figure 2



Samms, *Trends Endo & Metab* 2020

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GLP-1/GIP Receptor Agonist Obesity Treatment

Tirzepatide (Zepbound)	
Weekly subcutaneous injection Dosing Titration	
• 2.5mg x 4 weeks • 5.0mg x 4 weeks • 7.5mg x 4 weeks	• 10mg x 4 weeks • 12.5mg x 4 weeks • 15mg x 4 weeks

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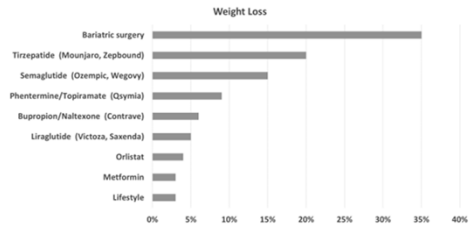
Key Studies - Tirzepatide



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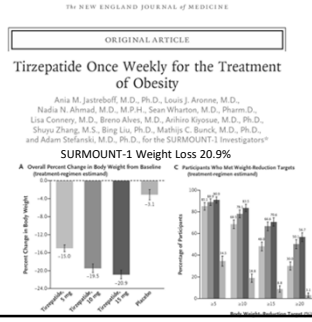
Key Studies - Tirzepatide



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Downside Risks – GLP-1 & GLP-1/GIP RA's

- Contraindications
  - Personal or family history of medullary thyroid carcinoma
  - Personal history of MEN2
- Warnings
  - Acute Pancreatitis
  - Gallbladder disease
  - Hypoglycemia
  - Acute kidney injury
  - Diabetic retinopathy (T2D)
  - Increased heart rate
  - Suicidal ideation

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Downside Risks – GLP-1 & GLP-1/GIP RA's

- Adverse Reactions
  - GI – nausea, vomiting, diarrhea, constipation, GERD
  - Elevated heart rate
  - Elevated amylase & lipase (~30-40% increase)
- Other considerations
  - Pregnancy
  - Breastfeeding

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Downside Risks – GLP-1 & GLP-1/GIP RA's

- Nutritional Concerns
  - Paradigm shift – eating enough
  - Nutrient quality
  - Protein
  - Vegetables
  - 3 F's
    - Eating too **Fast**
    - Eating until too **Full**
    - Eating too much **Fat**
- Physical Activity
  - Maintaining Muscle mass

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Future of Anti-Obesity Medications

Mechanism	Medication	Route	Study	Weight Loss
GLP-1 RA	Semaglutide	Oral	OASIS – Phase 3	17.4%
GLP-1 RA/Amylin RA	CargriSema	SC	REDEFINE – Phase 3	
GLP-1/Glucagon RA	Survodutide Pemvidutide Cotadtide Efinopegdutide	SC	SYNCRONIZE – Phase 2 MOMENTUM – Phase 2	14.9%
GLP-1/GIP/Glucagon RA	Retudatride	SC	TRIUMPH – Phase 2	24.2%
GLP-1 sm. molecule RA	Orforglipron	SC	ATTAIN – Phase 2	14.7%
Monoclonal AB blocks activin pathway	Bimagrumab	SC	Phase 2	

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Future of Anti-Obesity Medications

- Benefits Beyond Weight Loss
  - 237 disease caused or made worse by obesity
  - Type 2 Diabetes treatment
    - Treating insulin resistance vs. glucose control
  - Cardiovascular risk reduction
  - Improved cardiovascular outcomes – MACE reduction
  - Osteoarthritis improvement – weight and inflammation
  - Metabolic dysfunction-associated steatotic liver disease (MASLD formally NAFLD)
    - Particularly agents that have glucagon receptor agonist activity
  - Addiction behaviors
  - Immobility
  - Chronic pain

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References

- Samms, R. J., Coghlan, M. P., & Sloop, K. W. (2020). How may GIP enhance the therapeutic efficacy of GLP-1?. Trends in Endocrinology & Metabolism, 31(6), 410-421.
- Chartoumpekis, D. V., Habeos, E. E., & Psilopanagioti, A. (2024). Evaluating the effectiveness and underlying mechanisms of incretin-based treatments for hypothalamic obesity: A narrative review. Obesity Pillars, 100104.
- Malikah Aldawsari, Fatima A Almadani, Nujud Almuhammadi, Sarah Algabsani, Yara Alamro & Madhawi Aldhwayan (2024) The Efficacy of GLP-1 Analogues on Appetite Parameters, Gastric Emptying, Food Preference and Taste Among Adults with Obesity: Systematic Review of Randomized Controlled Trials, Diabetes, Metabolic Syndrome and Obesity, 16:, 575-595, DOI: 10.2147/DMSO.S387116
- Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes–state-of-the-art. *Molecular metabolism*, *46*, 101102.
- Chandarana, R., D'Souza, J.S., Coutinho, E.C. (2012). Glucose-Dependent Insulinotropic Polypeptide Receptor (*GIPR*). In: Choi, S. (eds) Encyclopedia of Signaling Molecules. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-0461-4_116
- Samms, R. J., Coghlan, M. P., & Sloop, K. W. (2020). How may GIP enhance the therapeutic efficacy of GLP-1?. *Trends in Endocrinology & Metabolism*, *31*(6), 410-421.
- Jastreboff, A. M., Aronne, L. J., Ahmad, N. N., Wharton, S., Connery, L., Alves, B., ... & Stefanski, A. (2022). Tirzepatide once weekly for the treatment of obesity. *New England Journal of Medicine*, *387*(3), 205-216.
- Wadden, T. A., Chao, A. M., Machineni, S., Kushner, R., Ard, J., Srivastava, G., ... & Forrester, T. (2023). Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nature Medicine*, *29*(11), 2909-2918.

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