MAHEC | MOUNTAIN AREA HEALTH EDUCATION CENTER

GLP-1 Agonists & Lifestyle Medicine: A Powerful Duo for Sustainable Health

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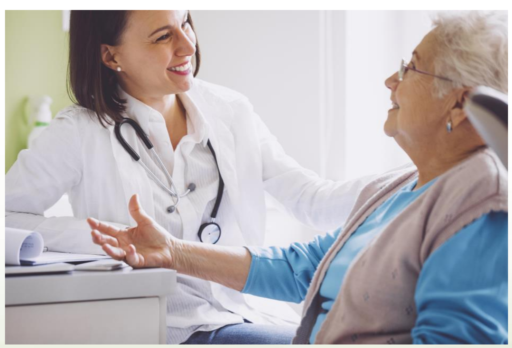
Disclosures:

There are no relevant financial or nonfinancial relationships to disclose.

A Note on Language

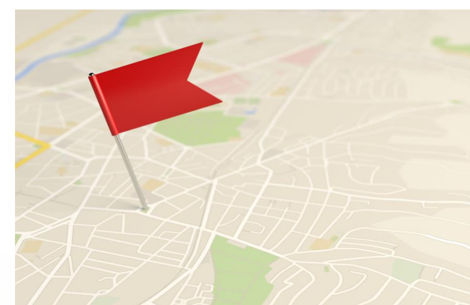
- Person with diabetes instead of "Diabetic"
- Elevated BMI or higher weight instead of "Morbidly Obese"
- Unhealthy weight instead of "Severe Obesity with Comorbidity"
- Okay to reflect the language the patient is using
- *Obesity was recognized as a disease in 2013, which was likely delayed due to social stigma



Objectives

Lifestyle is Medicine!

- How we got here
- Benefits of GLP-1 RAs
- Benefits of Lifestyle Medicine
- The GLP-1 Mechanism
- Stimulating GLP-1 naturally with food
- The hidden side effects of GLP-1 RAs
- Why we need lifestyle changes with medication changes



Why This Topic?

Completed LMRC and LM board certification

Many pts unaware of side effects & lacking support for lifestyle change

Rise of GLP-1 Agonists

Interest in Lifestyle Med

Knowledge Gap

Increasing number of patients on weight loss medications

"... when doctors tell patients you need to stop smoking, you need to sleep, you need to exercise, you need to eat better, **here's your verbal prescription, there's nowhere to fill it. And for most many Americans, it's not paid for."**

"So we have a ... system where the **most important things** that we should be prescribing **are not covered by healthcare**." - Dr. Dariush Mozaffarian

Being Overweight is Now Normal

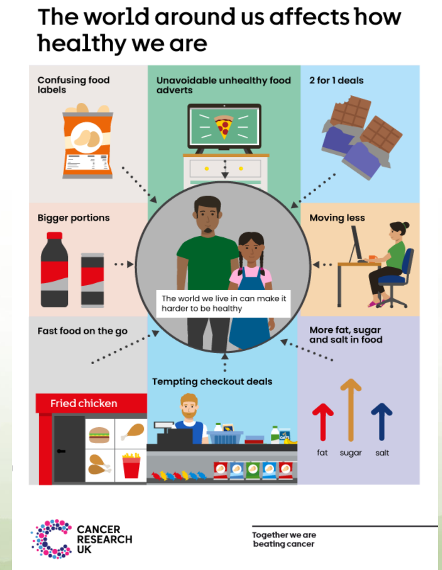
According to 2017–2018 data from the National Health and Nutrition Examination Survey (NHANES)

- Nearly 1 in 3 adults (30.7%) are overweight (BMI>25).
- More than 2 in 5 adults (42.4%) have obesity (BMI>30).
- About 1 in 11 adults (9.2%) have severe obesity (BMI>40).

Taking notes from tobacco

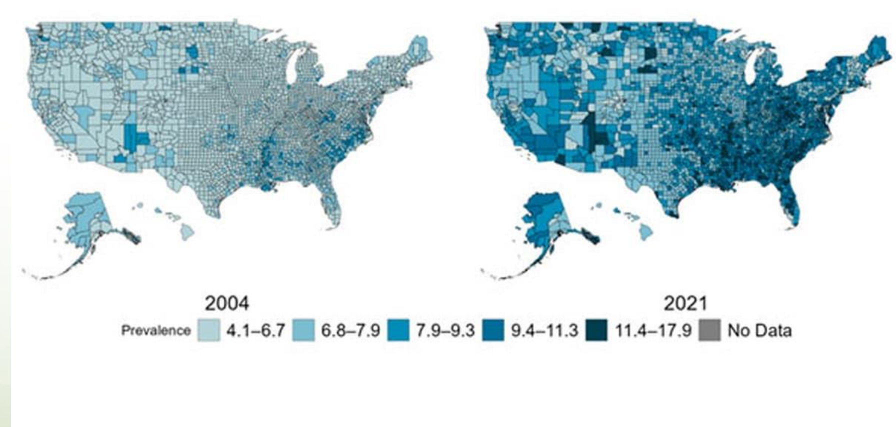
- Cigarettes consumed when rolled by hand to machine rolled went from 50/yr to 4000/yr (1/2 ppd)

Every industry benefits from people eating more junk food!



The Result of Environmental Change?

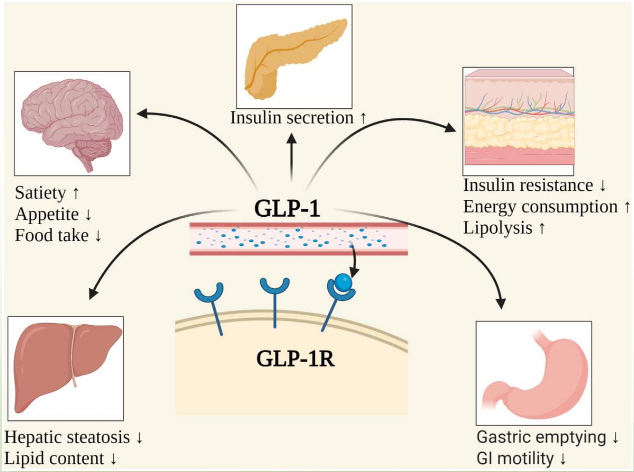
The Prevalence of T2DM Increases



Age-adjusted, county-level prevalence of diagnosed diabetes among adults aged 20 years or older, United States, 2004 and 2021.
Source CDC

More Disease = More Drugs
What is a GLP-1 RA?

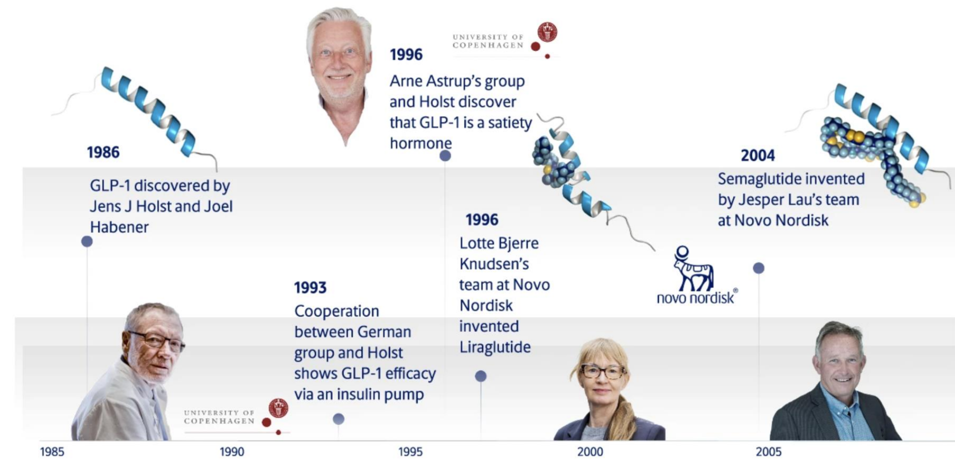
GLP-1RAs mimic the hormone GLP-1, which is naturally produced in the intestines after eating.
Examples: liraglutide, dulaglutide, semaglutide, tirzepatide



Rashid, F., Sethi, J., Sharma, P., & Puri, N. (2023). GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach. *Frontiers in Endocrinology*, *14*.

The Discovery of GLP-1

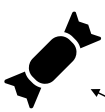
From native GLP-1 to liraglutide and semaglutide



Time line showing the discovery of GLP-1 i 1986, the satiety hormone effect i 1996, and the synthesis of the long-acting analogues liraglutide and semaglutide, and the key persons involved.

Astrup, A. Reflections on the discovery GLP-1 as a satiety hormone: Implications for obesity therapy and future directions. *Eur J Clin Nutr* **78**, 551–556 (2024).

Health Benefits of GLP-1s



T2DM
Sustain Trials

Weight Loss
STEP/SURMOUNT
Trials

MASLD
Addiction?

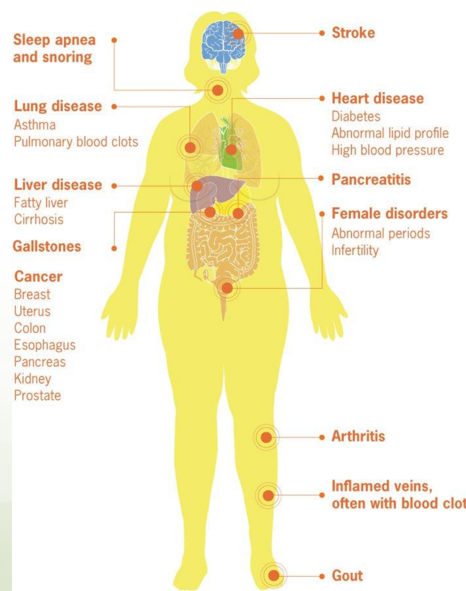
<u>And More</u>
STEP-HFPEF
FLOW Trial (CKD)
SURMOUNT-OSA

Heart Disease
SELECT Trial

Lancet Diabetes Endocrinol. 2022;10:393–406. & N Engl J Med. 2021;384:1113–24.

N Engl J Med 2023;389:2221-2232

The Health Impacts of Excess Weight



"The average life expectancy of a person with BMI>40 is reduced 5-20 years depending on comorbidities."

Ann Transl Med. 2017 Apr;5(7):161.

Semaglutide (Wegovy)

- **Mechanism:**
  - Glucagon-like peptide 1 (GLP1) receptor agonist. For weight loss, works by slowing gastric emptying and increasing satiety.
- **Dose:**
  - Month 1: 0.25 mg subcutaneously (subQ) once weekly
  - Month 2: 0.5 mg weekly
  - Month 3: 1 mg weekly
  - Month 4: 1.7 mg weekly
  - Month 5 on onward: 2.4 mg subcutaneously once weekly
  - Maintenances doses include 1.7 mg and 2.4 mg subQ once weekly (not adjusted in renal or liver disease)
- **Side effects:** nausea/vomiting, abdominal pain, constipation or diarrhea, headache, hypoglycemia, dyspepsia (all generally decrease over time)
- **Precautions:** acute gallbladder disease, pancreatitis, thyroid C-cell tumors, gastroparesis, suicide ideation/behavior

Wegovy. Package Insert.

Semaglutide (Wegovy)

- **Efficacy:**
  - In a review of 8 RCTs (2658 participants) assessing semaglutide 2.4 mg subQ with a follow-up period ranging from 52 to 72 weeks mean difference in percent total body weight lost was **10.76%** in favor of semaglutide.
    - 82.3% of participants lost >5% of total body weight vs. 30.6% placebo.
    - 64.9% lost >10% vs 12.3% placebo
    - 46.1% lost >15% vs 5.4% placebo

-11%
average difference from placebo

Grunvald et al. *AGA*. 2022

Tirzepatide (Zepbound)

- **Mechanism:**
  - Glucagon-like peptide 1 (GLP1) receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. For weight loss, works by slowing gastric emptying and increasing satiety.
- **Dose:**
  - Month 1: 2.5 mg subcutaneously (subQ) once weekly
  - Month 2 and onward: 5 mg weekly
  - Can increase monthly in 2.5 mg increments up to 15 mg subQ once weekly
  - Maintenance doses include: 5 mg, 10 mg, 15 mg
  - Dose not adjusted in renal or liver disease.
- **Side effects:** nausea/vomiting, abdominal pain, constipation or diarrhea, headache, hypoglycemia, dyspepsia (all generally decrease over time)
- **Precautions:** acute gallbladder disease, pancreatitis, thyroid C-cell tumors, gastroparesis, suicide ideation/behavior, decreased efficacy of oral contraception

Zepbound. Package Insert.

Tirzepatide (Zepbound)

- **SURMOUNT-1 (July 2022)**
  - Randomized, placebo-controlled, phase 3 trial in adults with BMI ≥30 kg/m² or at least 27 kg/m² with at least one weight-related complication **(excluding diabetes).**
  - 2,539 participants were randomized to receive tirzepatide 5mg, tirzepatide 10mg, tirzepatide 15mg or placebo subcutaneously once weekly for 72 weeks.
  - **Mean percent weight loss:**

Placebo -3.1%

5 mg -15%

10 mg -19.5%

15 mg -20.9%

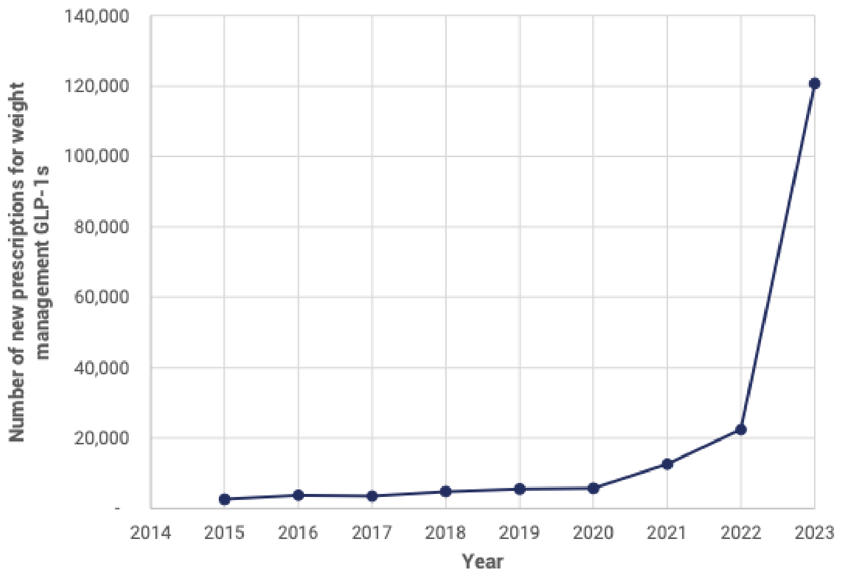
-17%
average difference from placebo

- 50% and 57% of participants in the 10mg and 15mg groups, respectfully, lost at least 20% of body weight.

Jastreboff AM, et al. *NEJM.*

1 in 8 adults have tried a GLP-1

Figure 2: Trends in use of GLP-1 products for weight management 2014-2023

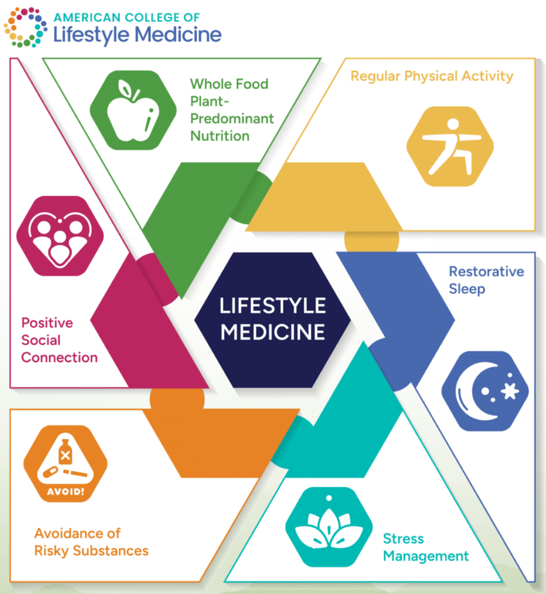


How Much Does Lifestyle Change Matter?

- In the STEP Trial for Semaglutide, at week 68, 31% of participants who received placebo had lost at least 5% of baseline body weight, with 12% and 5% having achieved reductions of at least 10% and at least 15%, respectively.

- Participants received individual **counseling sessions every 4 weeks** to help them adhere to a reduced-calorie diet (**500-kcal deficit per day** relative to the energy expenditure estimated at the time they underwent randomization) and increased physical activity (**with 150 minutes per week of physical activity**, such as walking, encouraged).

What is Lifestyle Medicine?



Lifestyle medicine is a medical specialty that uses evidence-based interventions in patient's behavioral choices to prevent, treat, and even reverse diseases driven by chronic systemic inflammation.

https://lifestylemedicine.org/about-us/

Lifestyle Medicine: Addressing the Root Cause

"You don't need a $1000 drug or surgery to de-crap your diet." -Dr. Michael Greger

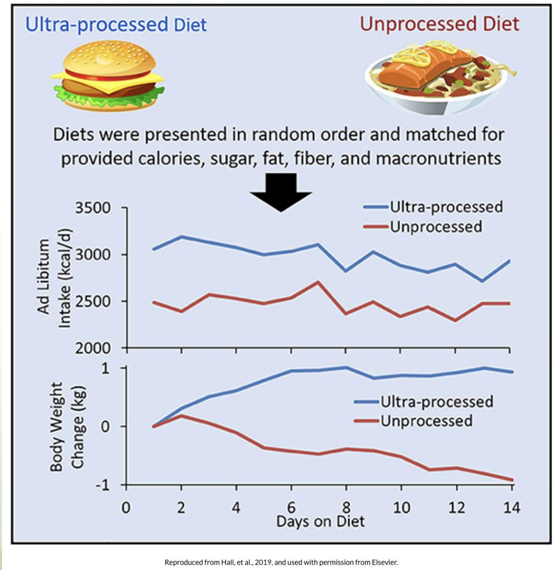
"You miss 100% of the shots you don't take." - Wayne Gretzky -Michael Scott

Whole-Food, Plant Predominant Eating Pattern

60-90 min mod physical activity daily + 2-3 x weekly strength training

Nutrition for Weight Loss

A study from the large AHS-2 cohort showed that increased ultra-processed food consumption resulted in a **hazard ratio (HR) of 1.14 (95% CI: 1.07–1.21) for all-cause mortality.** The increase in mortality was rivaled only by red meat consumption (HR: 1.14; 95% CI: 1.08–1.22).

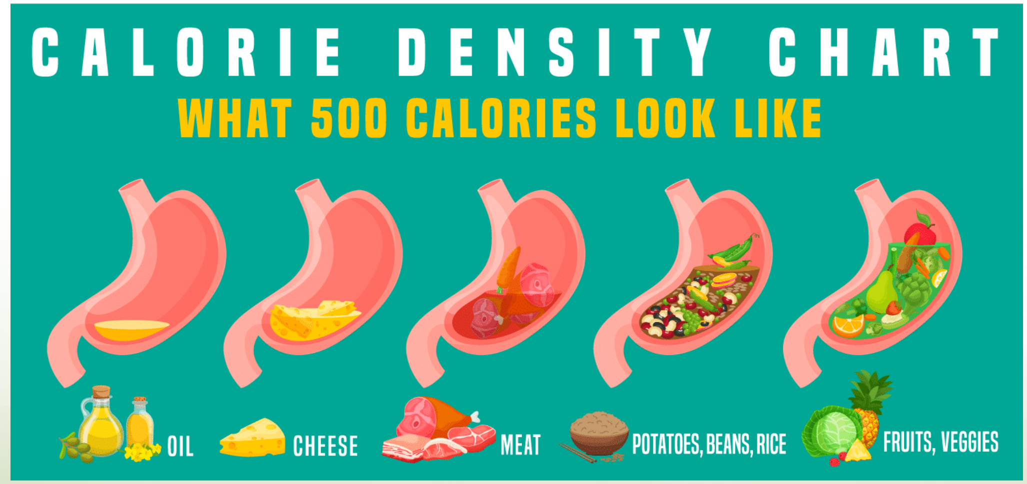


Reproduced from Hall, et al., 2019, and used with permission from Elsevier.

Hall KD, Ayuketah A, Brychta R, Cai H, Cassimatis T, Chen KY, Chung ST, Costa E, Courville A, Darcey V, Fletcher LA, Forde CG, Gharib AM, Guo J Howard R, Joseph PV, McGehee S, Ouwerkerk R, Raisinger K, Rozga I, Stagliano M, Walter M, Walter PJ, Yang S, Zhou M. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. Cell Metab. 2019 Jul 2;30(1):67-77.e3.

Nutrition for Weight Loss

Research shows that you can lose weight on any restrictive eating pattern. However, the more important question is if the selected eating pattern contributes to overall health long-term.

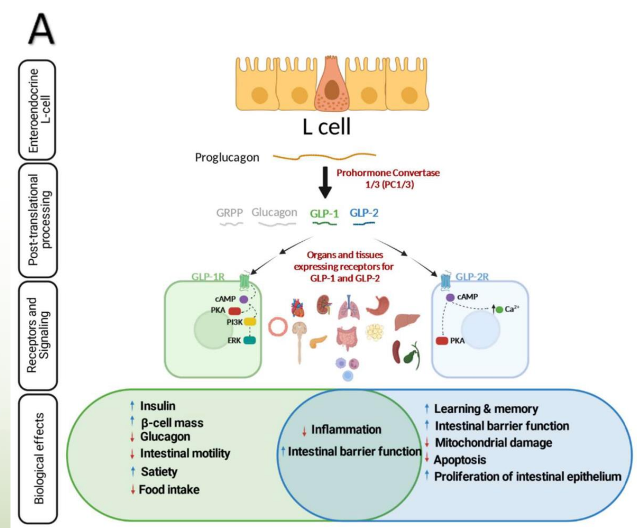


Nutrition for Weight Loss

The 2017 BROAD study showed that an ***ad libitum*** plant-based dietary pattern resulted in greater sustained weight loss than any other *ad libitum* eating pattern published to that point. Those in the BROAD study had a mean weight loss of 26 pounds at 6 months post intervention, which was also maintained at 12 months post intervention

Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: A randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. Nutr Diabetes. 2017 Mar 20;7(3):e256.

How it Works: GLP-1 is a Natural Mechanism



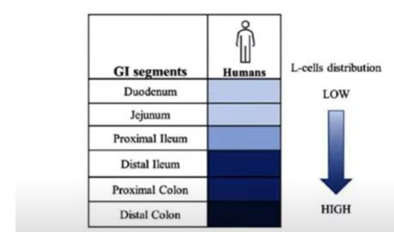
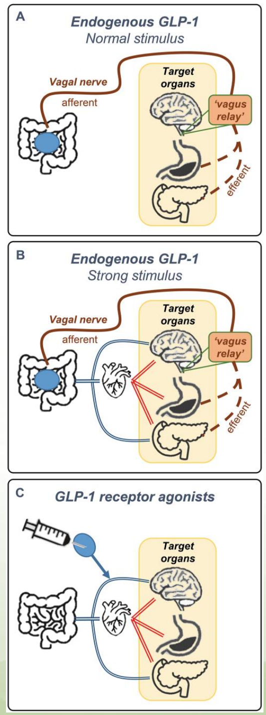


Figure 1. L-cells distribution in the intestinal tract of human.[24-26]

Microorganisms **2022**, *10*(10), 2061

GLP-1 is a Natural Mechanism

- GLP-1 released from the intestinal L-cells is very rapidly degraded, leading to low systemic levels, and its effects appear to be mediated by vagus nerve stimulation.
- GLP-1RAs stimulate the GLP-1 receptors directly in the peripheral targets, particularly in the pancreas, as well as in the CNS via the circumventricular organs and do not need vagus signalling.
- Why GLP-1 receptors are present on the peripheral tissue even though endogenous GLP-1 acts mainly through the vagus system is an unanswered question



Smits MM, Holst JJ. Endogenous glucagon-like peptide (GLP)-1 as alternative for GLP-1 receptor agonists: could this work and how? Diabetes Metab Res Rev. 2023;39(8):e3699.

Foods Impacting the GLP-1 Mechanism

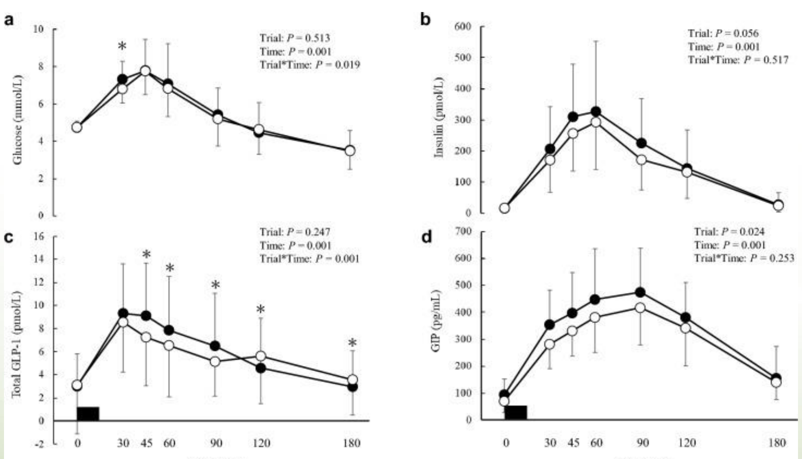
- Dark Green Leafy vegetables
  - Decrease calories & cravings
  - Kale, Spinach, Collards
- Whole Intact Grains (Groats)
  - Oat Groats, Rye Berries, Barley, etc.
- Spices
  - Decrease weight, Decrease calorie intake
  - Turmeric, Cinnamon, Cayenne

***Note:** Protein makes you feel more full initially, but doesn't reduce calorie intake later

Foods Impacting the GLP-1 Mechanism

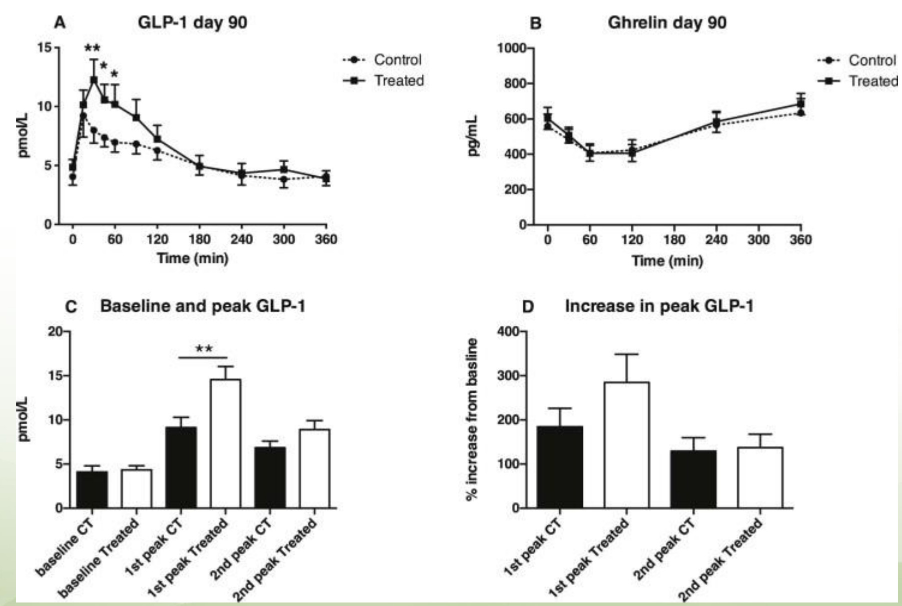
Chewing your food!

● = chew



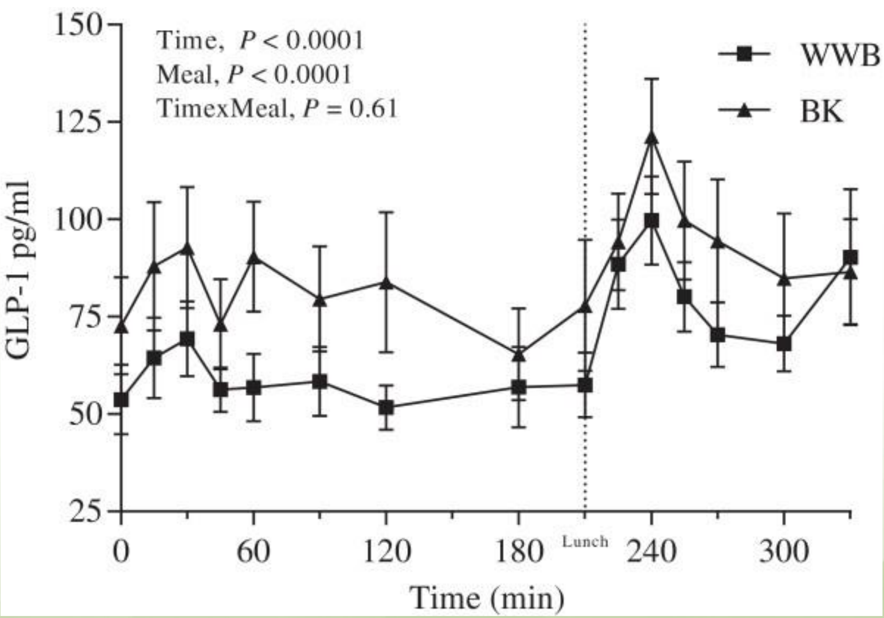
Kamemoto K, Tataka Y, Hiratsu A, Nagayama C, Hamada Y, Kurata K, Chiyoda M, Ito M, Miyashita M. Effect of vegetable consumption with chewing on postprandial glucose metabolism in healthy young men: a randomised controlled study. Sci Rep. 2024 Mar 30;14(1):7557.

Foods Impacting the GLP-1 Mechanism



1.Roberts JL, Moreau R. Functional properties of spinach (Spinacia oleracea L.) phytochemicals andbioactives. Food Funct. 2016;7(8):3337–53.
2. Stenblom EL, Montelius C, Östbring K, et al. Supplementation by thylakoids to a high carbohydrate meal decreases feelings of hunger, elevates CCK levels and prevents postprandial hypoglycaemia in overweight women. Appetite. 2013;68:118–23.
3. Pourteymour Fard Tabrizi F, Abbasalizad Farhangi M. A systematic review of the potential effects of thylakoids in the management of obesity and its related issues. Food Rev Int. 2021;37(5):469–90.

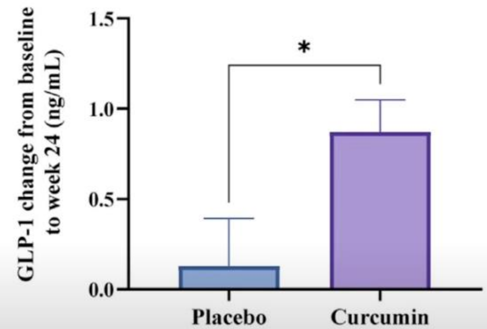
Foods Impacting the GLP-1 Mechanism



Johansson EV, Nilsson AC, Östman EM, Björck IM. Effects of indigestible carbohydrates in barley on glucose metabolism, appetite and voluntary food intake over 16 h in healthy adults. Nutr J. 2013 Apr 11;12:46

Foods Impacting the GLP-1 Mechanism

- Curcumin (500 g/day)



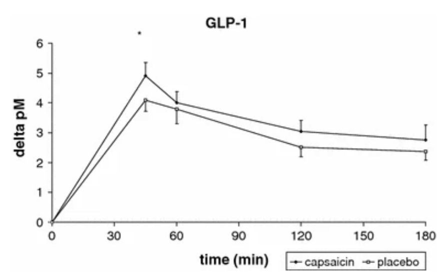
Changes in TGR5 mRNA expression of serum GLP-1 levels observed at baseline and at week 24 in the placebo (n = 40) and curcumin (n = 40) groups. ANCOVA was used to calculate intervention effect using intervention as a fixed factor, week 24 values as the dependent variable, and baseline values as the covariate. *P < 0.05. Abbreviations: ANCOVA, analysis of covariance.

He Y, Chen X, Li Y, Liang Y, Hong T, Yang J, Cao Z, Mai H, Yao J, Zhang T, Wu K, Zou J, Feng D. Curcumin supplementation alleviates hepatic fat content associated with modulation of gut microbiota-dependent bile acid metabolism in patients with nonalcoholic simple fatty liver disease: a randomized controlled trial. Am J Clin Nutr. 2024 Jul;120(1):66-79.

Foods Impacting the GLP-1 Mechanism

- Cayenne (1/2 tsp)

Fig. 1

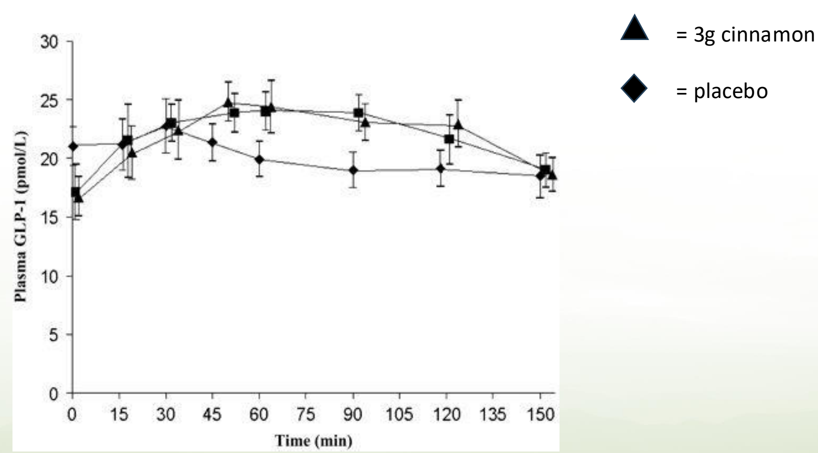


Mean (±SEM) changes in GLP-1 plasma concentrations from baseline for the capsaicin (n = 30) and control (n = 30) lunch. * $p < 0.05$

Smeets, A.J., Westerterp-Plantenga, M.S. The acute effects of a lunch containing capsaicin on energy and substrate utilisation, hormones, and satiety. *Eur J Nutr* **48**, 229–234 (2009).

Foods Impacting the GLP-1 Mechanism

- 3g (½-1 tsp) cinnamon increase GLP-1 and decreases insulin response



Hlebowicz J, Hlebowicz A, Lindstedt S, Björgell O, Höglund P, Holst JJ, Darwiche G, Almér LO. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr. 2009 Mar;89(3):815-21.

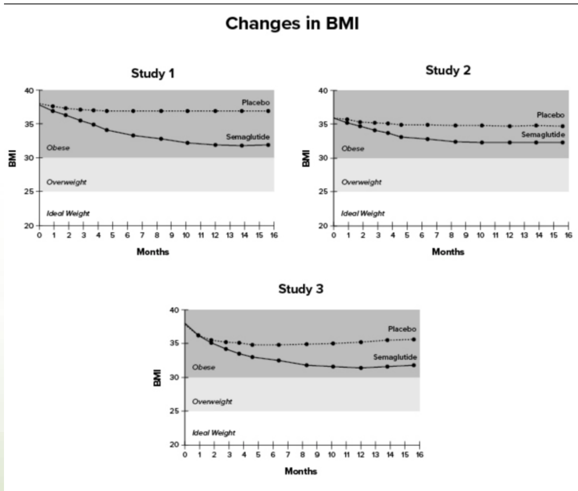
Side Effects - Common

- **Side effects you know:**
  - Nausea/vomiting
  - Abdominal pain
  - constipation or diarrhea
  - Headache
  - Hypoglycemia
  - Dyspepsia
  - Risk of pancreatitis

Wegovy. Package Insert.

Side Effects – It might not work

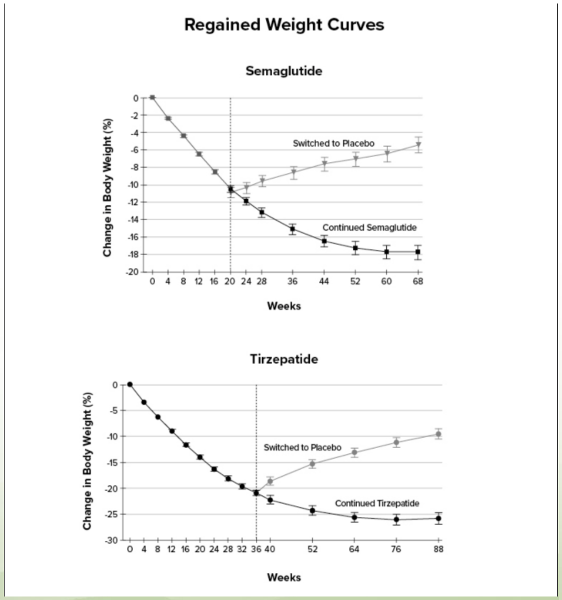
- Patients are not counseled that these medications do not cure excess weight gain
- Majority have plateau of weight loss at 12-18 months
- Patients often start w/ BMI>30 and end up with BMI > 30
- 1/5 do not experience meaningful weight loss at all (i.e. >5% weight loss)



Wegovy. Package Insert.
Singh A, Nissen SE. Contemporary management of obesity: a comparison of bariatric metabolic surgery and novel incretin mimetic drugs. Diabetes Technol Ther. Published online May 16, 2024.

Side Effects – The weight comes back

- Switch back to placebo, you go back to your previous weight
- Weight cycling can harm mental and physical health
- One study found that 80% of people had stopped taking the medication after 6 months
- One study looked at over 3,000 individuals who started GLP-1 therapies for weight loss and after a year, they had less than 30% still on the therapy. After two years, they had one in seven.



Gleason, P., Marshall, L., Urick, B., Qiu, Y., & Leslie, R. S. (2024). Year-Two Real-World Analysis of Glucagon-Like Peptide-1 Agonist (GLP-1) Obesity Treatment Adherence and Persistency. Prime Therapeutics LLC.

Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA. 2021;325(14):1414–25.
80Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. JAMA. 2024;331(1):38–48.

Side Effects – Losing Lean Mass

•Normally, about 25% of total weight loss is fat-free mass—meaning essentially their lean mass, including their muscles

•On drugs like Ozempic, as much as 40% of the total weight lost is lean mass

•Engaging in exercise, especially resistance exercises, can cut the proportion of fat-free mass that is lost by 50 percent or more

Supportive secondary endpoints assessed in the DEXA subpopulation

	N=95	N=45	
Body composition change from baseline to week 68 (DEXA)			
Total fat mass			
Kg change	–10.40	–1.17	ETD: –9.23 [–12.72; –5.74]
Percentage-points change in total fat mass proportion§	–4.19	–0.19	ETD: –4.00 [–6.27; –1.73]
Regional visceral fat mass¶			
Kg change	–0.47	–0.03	ETD: –0.45 [–0.60; –0.30]
Percentage-points change in regional visceral fat mass proportion‖	–2.65	0.58	ETD: –3.23 [–5.35; –1.10]
Total lean body mass			
Kg change	–6.92	–1.48	ETD: –5.44 [–7.07; –3.81]
Percentage-points change in total lean body mass proportion§	3.61	0.11	ETD: 3.50 [1.35; 5.64]

Bikou A, Dermiki-Gkana F, Penteris M, Constantinides TK, Kontogiorgis C. A systematic review of the effect of semaglutide on lean mass: insights from clinical trials. Expert Opin Pharmacother. 2024;25(5):611–9.
Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., et al., for the STEP 1 Study Group. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine*, *384*(11), 989–1002

Side Effects – The Cost

- These medications are still very expensive and not always covered by insurance.
- An analysis of U.S. health insurance claims reported on by Reuters showed weight loss drugs didn't curb health costs within two years. In fact, the full-year cost of care for patients with obesity two years after starting GLP-1 drugs was $18,507, on average, a 46% jump over the average annual medical cost of $12,695 prior to taking the drugs.
- Note: Novo Nordisk could manufacture and distribute Wegovy for $40 a month and still earn a 10 percent profit margin. GLP-1 RAs are often much cheaper in other countries.

Reuters. (2024, October 24). *Weight-loss drugs didn't curb health costs within two years, data show.*
Levi J, Wang J, Venter F, Hill A. Estimated minimum prices and lowest available national prices for antiobesity medications: improving affordability and access to treatment. Obesity (Silver Spring). 2023;31(5):1270–9.

Lifestyle Medicine & Medication

- Weekly visits have historically been needed to help patients achieve clinically meaningful weight loss
- Semaglutide and tirzepatide both appear to physiologically drive a reduction in energy intake, which may make dietary behavior changes easier than conventional lifestyle counseling
- Weight loss could increase patients' ease in engaging in physical activity, thus potentially further improving their cardiometabolic health.

Wadden, T.A., Chao, A.M., Machineni, S. *et al.* Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med* **29**, 2909–2918 (2023).

Take Home Points

Lifestyle is Medicine!

GLP-1 RAs can be hugely beneficial, and participation in a structured lifestyle program should not be a barrier to accessing these medications

Lifestyle Medicine is the cornerstone of disease prevention and weight management and should not be discarded simply because medications are expedient in the short-term

Together, we can plant seeds and make a difference!

Future Areas of Study

- Lifestyle changes and programs are not well studied when stopping or tapering off GLP-1 agonists.
- There may be a psychological effect to GLP-1s, reinforcing that food does matter, not well studied.

Further Reading

- Ozempic: Risks, Benefits, and Natural Alternatives to GLP-1 Weight-Loss Drugs by Dr. Michael Greger
- How Not to Diet by Dr. Michael Greger
- Nutritionfacts.org
- ACLM "Food As Medicine" CME: https://lifestylemedicine.org/project/essentials/

Thank You! Questions, comments, or concerns?

MAHEC

MAHEC Family Medicine
123 Hendersonville Road
Asheville, NC 28803

M/R Afternoon
Wed Morning

Contact Me
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231-645-8800