IS THIS (GLP) ONE TOO GOOD TO BE TRUE?

Navigating New Incretin Therapies

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Learning Objectives

1. Review non-incretin-based methods for obesity management
2. Discuss the pathophysiology and mechanism of action of GLP-1/GIP analogues
3. Demonstrate potential benefits of incretin therapies such as weight loss, glycemic control, cardiovascular and renal protection
4. Identify common and rare adverse effects and contraindications to incretin therapies
5. Discuss initial dosing, titration, and approach to interruptions in therapy of GLP/GIP analogues
6. Compare weight loss between incretin therapy and bariatric surgery

Obesity Management

Lifestyle changes	At least 150 minutes of exercise per week Less processed foods, fresh fruit/vegetables Most have tried changes and failed
Stimulants (Phentermine)	CI if HTN or ASCVD
Naltrexone/Bupropion	Targeting appetite and reward center of brain
Topiramate	Can be combined with Phentermine for appetite suppression
Orlistat	Limited due to GI side effects
Bariatric Surgery	Vitamin deficiencies, hypoglycemia, and Dumping syndrome

PATHOPHYSIOLOGY AND HISTORY OF INCRETIN ANALOGUES

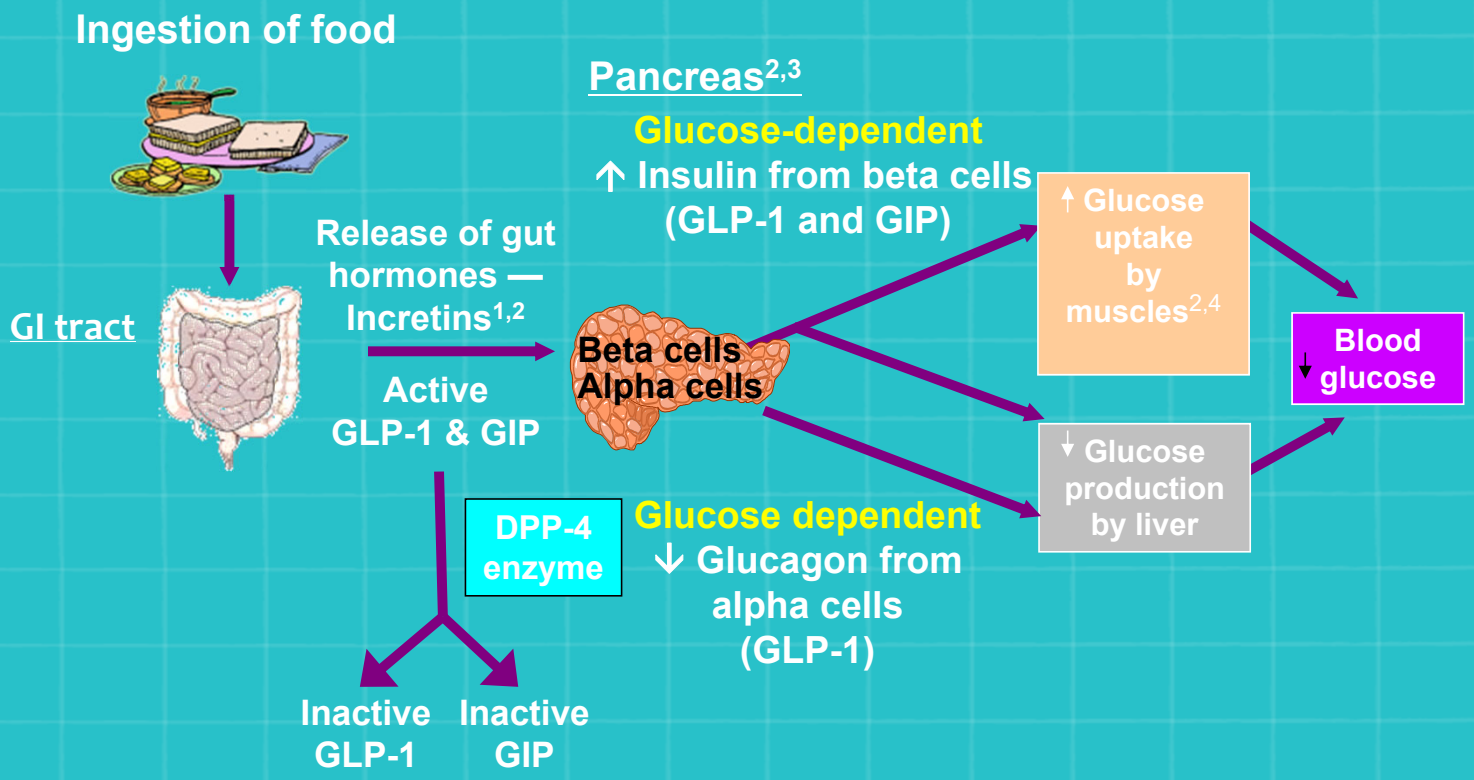
Pathophysiology of Incretins

- Incretins refer to gut hormones which include GLP-1 (glucagon-like peptide 1) and GIP (glucose dependent insulinotropic peptide)
- These hormones have also been isolated in mammalian salivary glands, eyes, and even brain
- They help stimulate insulin secretion while also increasing insulin synthesis through increasing beta cell proliferation and reducing beta cell apoptosis
- They have also been shown to increase lipolysis and decreases lipogenesis

Pathophysiology of Incretins

- When glucose is high, incretins help amplify stimulation of insulin secretion through cAMP while also suppressing glucagon secretion
  - Their effect on insulin secretion is less pronounced if glucose is normal thus less risk for hypoglycemia which has been seen through hyperglycemic clamp trials
- Incretins slow down gastric emptying which leads to feeling less hungry and eating smaller portions
- Possible CNS appetite suppression
  - Thought that GLP-1 receptors are within arcuate nucleus of hypothalamus
- Development of GLP-1 RA are made to prolong endogenous activity of incretins

Role of Incretins in Glucose Homeostasis



DPP-4 = dipeptidyl-peptidase 4

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GLP-1 Agonist Drugs Comparison

	DOSAGE	DOSAGE FORM	APPROVED FOR	WHO CAN TAKE IT?	OTHER BENEFITS
Ozempic (SEMAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Rybelsus (SEMAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS
Wegovy (SEMAGLUTIDE)	1 WEEKLY		WEIGHT LOSS	12+ KIDS + ADULTS	N/A
Trulicity (DULAGLUTIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Victoza (LIRAGLUTIDE)	1 DAILY		TYPE 2 DIABETES	10+ KIDS + ADULTS	HEART, KIDNEYS, WEIGHT LOSS
Saxenda (LIRAGLUTIDE)	1 DAILY		WEIGHT LOSS	12+ KIDS + ADULTS	N/A
Byetta (EXENATIDE)	2 DAILY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS
Bydureon BCise (EXENATIDE)	1 WEEKLY		TYPE 2 DIABETES	10+ KIDS + ADULTS	WEIGHT LOSS
Mounjaro (TIRZEPATIDE) ★	1 WEEKLY		TYPE 2 DIABETES	ADULTS	WEIGHT LOSS

GoodRx Health

History of Incretin Therapies

★ = GLP/GIP analogue

BENEFITS OF INCRETIN THERAPIES

Weight Loss

- Amount of weight loss has varied between different incretin therapies but has been shown to be effective compared to placebo
- During the **STEP 2 trial**, which was a randomized trial using Semaglutide 2.4 mg weekly plus lifestyle changes achieved 9.6% weight loss from baseline versus 3.4% with only lifestyle changes at 68 weeks
- **SCALE Diabetes trial**, which used Liraglutide 3.0 mg daily achieved 6.0% weight loss compared to 2.0% in behavioral weight loss program plus placebo

Weight Loss

- Usually, less weight loss is appreciated when medication is used alone rather than in conjunction with lifestyle modifications
  - **SUSTAIN-1**, which used Semaglutide 1 mg weekly achieved 4.5 kg weight loss (4.7%) while placebo achieved 1.0 kg (1.1%) at 30 weeks
  - **LEAD-2**, which used Liraglutide 1.8 mg daily had a loss of 2.8 kg (3.3%) versus 1.5 kg (2.0%) in control group (Metformin only) at 26 weeks
  - Retrospective study out of Western Pennsylvania (2400 patients) with average BMI 37 using dosing for only glycemic control saw an average of 6 lbs weight loss at 72 weeks

Glycemic Control

- **LEADER** showed Liraglutide group had reduction of –0.4% in A1C compared to placebo
- **SUSTAIN-6** showed patients receiving Semaglutide 0.5 mg showed –1.1% reduction in A1C and Semaglutide 1.0 mg showed –1.4% reduction
- **SURPASS-1** trial assessed Tirzepatide compared to placebo
  - After 40 weeks, patients' A1C reduced by 2.07% from baseline of 7.9%
  - 87.9% of participants receiving 15 mg of Tirzepatide achieved A1C <7% while placebo group was 19.6%
  - 51.7% of participants receiving 15 mg of Tirzepatide achieved A1C <5.7% while 0.9% of placebo group achieved this

Cardiovascular Risk Reduction

- Incretin therapies have shown reduction in cardiovascular events compared to placebo in various studies
- **SUSTAIN-6 (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes**) showed reduction in cardiovascular events compared to placebo in 2016
  - Inclusion criteria was A1C 7% or higher without prior treatment or had not been treated with more than 2 diabetic medications with insulin, age 50 or more with established cardiovascular disease, or age 60 or more with risk factors for CVD
- **LEADER (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes)** in 2016 showed reduction in MACE compared to placebo
  - Inclusion criteria was A1C 7% or higher, age 50 or more with one cardiovascular condition which included coronary artery disease, cerebrovascular disease, PVD, CKD, or HF, and age 60 or more with one risk factor for CVD (microalbuminuria, HTN, LVH, etc)
- **ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome)** in 2015 was non-inferior to placebo
  - Should be noted study did include patients with acute coronary syndrome while other studies did not and used patients with stable CVD
  - Primary outcome of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina occurred in 13.4% of the lixisenatide group versus 13.2% of the placebo group

Improvement in Renal Disease

- According to ADA, diagnosis of diabetic nephropathy is made due to the presence of albuminuria and/or reduction in eGFR
- Most of information regarding GLP-1/GIP therapy and effects on CKD have been extrapolated from studies looking at cardiovascular disease
- Beneficial from glucose lowering, BP reductions, and weight loss but also GLP-1 has been localized in proximal tubular cells

Improvement in Renal Disease

- Can sometimes be difficult to assess incretin therapy effects alone on CKD as patients in these other studies have been on SGLT-2 inhibitors as well
  - **AMPLITUDE-O** trial had 15.2% of patients receiving SGLT-2 inhibitors at baseline
- **PRECIDENTD (Prevention of Cardiovascular and Kindey Disease in Type 2 DM)** trial is currently ongoing which is assessing SGLT-2 inhibitor and GLP-1 RA combination therapy versus either therapy alone on CKD and CVD
- **FLOW (Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes)** included 3533 patients with Type 2 DM and CKD was randomized to receive either 1 mg Semagltuide or placebo and primary outcome was major kidney events such as onset of kidney failure, eGFR <15, 50% reduction eGFR from baseline, or death related to kidney disease or CVD
  - Trial was ended early as primary outcome was met during interim analysis

ADVERSE EFFECTS OF INCRETIN THERAPIES

Gastrointestinal Side Effects

- The most common side effect reported from incretin therapies is gastrointestinal disturbances which is related to its MOA
- Nausea and vomiting is the most common with reported incidence of 6-50% among different formulations of GLP-1/GIP analogues
- Diarrhea and constipation rates can vary between 9-30%
- Patients can experience GERD due to delayed gastric emptying and usually worse if they have pre-existing GERD prior to starting incretin therapy
- Try to avoid providing chronic anti-emetic medications to help make these analogues more tolerable
- Typically, symptoms improve with time and slower titration but should also discuss with patients that avoiding larger portions and meals that are heavy in carbohydrates as these will worsen symptoms

Pancreatitis

- Concern for increased incidence of pancreatitis due to thought that chronic over expression of GLP-1 receptors in exocrine pancreas cells could lead to pancreatitis
- Meta-analysis looked at 33,192 patients and 17,623 of those were receiving GLP-1 therapy and had reported 60 events of pancreatitis while 15,569 comparators had 55 events of pancreatitis
- **STEP-1 (Semaglutide Treatment Effect on People with Obesity)** had 1306 within treatment group and 3 people developed pancreatitis (0.2%)
- **SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes)** had 8803 patients within treatment group and had 17 cases of acute pancreatitis (0.2%) and 8801 in placebo group which had 24 reported cases of acute pancreatitis (0.3%)
- Should assess for additional risk factors for pancreatitis such as gallbladder disease, excess alcohol use, and hypertriglyceridemia
  - Hypertriglyceridemia is not a contraindication to incretin therapy
  - Uncontrolled DM can worsen hypertriglyceridemia so can see improvement in TG levels with treatment of DM using incretin therapy

Retinopathy

- In the **SUSTAIN-6 trial**, there was a reported increased in retinopathy with Semaglutide whereas in the LEADER trial using Liraglutide there was a statistically nonsignificant higher incidence of retinopathy
- The **AngioSafe study**, designed to determine the safety of GLP-1 RAs in the retina, in both clinical models with liraglutide and experimental models with exenatide, negative effects on retinal angiogenesis and severe DR were not confirmed
- These effects seem to be transient and more likely are related to drastic change in glycemic levels rather than drug mechanism effect
- If severe DR, should discuss with Ophthalmology prior to initiation
  - May require slower titration of GLP/GIP and close monitoring with Ophthalmology

Thyroid Cancer

- Concern that chronic expression of GLP-1 Receptors could lead to proliferation of thyroid C cells and increase risk of medullary thyroid cancer
- Initial animal studies using rats and mice had shown were associated with C cell hyperproliferation of thyroid and then were extrapolated to humans
- When examining prior studies such as LEADER, the incidence of thyroid cancer among patients receiving Liraglutide and placebo were similar and there was only one reported case of medullary thyroid cancer
- **No recommendations to monitor calcitonin levels while on therapy**
- **No recommendations for obtaining a thyroid US prior to initiation of incretin therapy**

Contraindications to Incretin Therapies

- Personal history of medullary thyroid cancer or MEN 2A/B
- First degree relative with medullary thyroid cancer or MEN 2A/B
  - Consider genetic testing for RET mutation
- History of idiopathic pancreatitis or severe pancreatitis (such as necrotizing)
  - Could consider use if cause was reversible such as gallstone pancreatitis and underwent CCY
- History of gastroparesis
  - If gastroparesis is related to uncontrolled DM, then there are some that will trial low dose if gastroparesis is mild in nature
- Women who are pregnant and breastfeeding
  - Women of childbearing age can use but should be counseled to use two forms of contraception
- **Severe diabetic retinopathy
  - No necessarily contraindicated but recommend discussion with Ophthalmology and close monitoring

MANAGEMENT OF INCRETIN THERAPIES

Incretin Therapy Management: Initial Dosing and Titration

- Start with lowest dose of each GLP-1 or GLP-1/GIP mimetic
- Continue this dose for at least **4 weeks and if tolerating well, can increase to next dose**
  - If having side effects such as nausea or constipation, can maintain at lower dose for longer time (i.e., 3 months instead of 1 month) and can also try dosing Q2weeks instead
- **May need to lower dose of other glycemic medications while titrating dose of incretins**
  - Typically instruct patients to **reduce their insulin doses by 10-20% at initiation and with each titration of dose to avoid hypoglycemia**
- Can trial a different incretin if patient has side effects from one or does not see benefits such as A1C lowering or weight loss

Incretin Therapy Management: Initial Dosing and Titration

GLP-1 RA Therapies:

- Liraglutide (Victoza)
  - Daily dosing 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, and 3 mg
- Dulaglutide
  - Once weekly injection for DM (Trulicity)
  - 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg
- Exenatide
  - IR was twice daily dosing using 5 or 10 mcg dosing (Byetta)
  - ER was weekly dosing with 2 mg weekly (Bydureon)

Incretin Therapy Management: Initial Dosing and Titration

GLP-1 RA continued:

- Semaglutide
  - Once weekly injection for DM (Ozempic)
    - 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg
  - Oral (Rybelsus) for DM
    - 3 mg, 7 mg, and 14 mg daily
  - Approved for weight loss (Wegovy)
    - 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and. 2.4 mg

Incretin Therapy Management: Initial Dosing and Titration

GLP-1/GIP Therapy:

- Tirzepatide (Mounjaro for DM and Zepbound for Obesity)
  - Once weekly dosing
  - 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg

Interruptions in Therapy

- Most formulations of GLP-1 RA are dosed weekly, and doses are titrated every 4 weeks if tolerated and if goal weight/glycemic control has not been met
- **If patient misses one week of therapy, okay to resume prior dose**
- **If patient misses more than 2 weeks of therapy, should resume lower dose for 4 weeks and titrate back to prior dosing**
- **If patient is going to be undergoing procedure and receive anesthesia, recommended to hold dosing 1-3 weeks before procedure**
  - **Currently no studies evaluating use perioperatively, but concern related to delayed gastric emptying and increase risk for aspiration**
- If a certain formulation is not available due to shortage, can transition to another one at equivalent dose
  - Ex. Semaglutide 0.5 mg weekly would be the equivalent to Tirzepatide 5 mg weekly

"Compounded" GLP-1 Analogues

- Due to national shortages of Semaglutide and Tirzepatide, there has been a substantial increase in their demand and subsequent sells of fradulent formulations
- These "compounded" forms of Semaglutide and Tirzepatide are not approved by FDA
- They may be marketed to contain Vitamins such as B12 in addition to GLP-1
- Unsure of what GLP-1 is contained within product or even the dose of it
- Route of administration varies widely as even sublingual formulations are being marketed

INCRETIN THERAPY VS BARIATRIC SURGERY

GLP-1 Analogues versus Bariatric Surgery

- JAMA in 2024
- **Bariatric Metabolic Surgery versus GLP-1 RA and Mortality**
- Study took place in Israel in which they reviewed patients from January 1, 2008 through December 31, 2021
- Included 6070 patients which were 24 years old or older and had DM and obesity with no history of cardiovascular disease
  - 64.9% women and 35.1% men with mean BMI 41.3 and average age was 51
  - Type of BMS was gastric bypass (46.4%), sleeve gastrectomy (41.2%), and banding (12.4%)
  - Types of GLP-1: Liraglutide (61.9%), Dulaglutide (21.2%), Exenatide (13.6%), and Lixsenatide (1.4%)
- Mortality was lower for those who underwent BMS versus GLP-1 RA for those who had DM <10 years
- For those with DM >10 years, there was no mortality benefit from BMS compared to GLP-1

GLP-1 Analogues versus Bariatric Surgery

- Meta-analysis in 2022
- **Weight Loss between GLP-1 RA and BMS**
- Reviewed six studies which included 332 patients
- Across all studies, those who underwent bariatric surgery had more weight loss than GLP-1
  - Italy in 2015-2017 showed –26.2 kg with GLP-1 versus –43.3 kg with BMS
  - United States 2007-2011 showed –5.3 kg with GLP-1 versus –23.2 kg with BMS
  - Used Liraglutide and Exenatide

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