Course # 148

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The Intersection of GLP-1 Therapy and Ocular Health: What Clinicians Need to Know

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Disclosure statements:

No financial relationships with ineligible companies to disclose.

All relevant relationships have been mitigated.

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Overview

GLP-1 Receptor Agonists: Expanding Therapeutic Horizons

Initially introduced to enhance insulin secretion and regulate blood sugar in type 2 diabetes, GLP-1 receptor agonists have rapidly expanded their therapeutic scope. These medications not only support significant and sustained weight loss but also reduce the risk of major cardiovascular events. Recent research suggests a promising role in protecting ocular health, particularly in slowing the progression of diabetic retinopathy and providing neuroprotection in retinal and optic nerve tissues. Ongoing studies are investigating their impact on conditions like nonarteritic ischemic optic neuropathy and glaucoma, indicating a broadening future for GLP-1 therapy across multiple organ systems.

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Glucagon-like Peptide-1 (GLP-1) Receptor Agonists (GLP-1RA)

Approved by FDA
- Type 2 DM
- Cardiovascular risk reduction
- Weight loss / management
- Obstructive sleep apnea

Adverse gastrointestinal effects
- Nausea
- Delayed gastric emptying
  - Reduced with long-term use
  - Tachyphylaxis at vagal nerve activation
  - Increases risk of regurgitation and pulmonary aspiration during general anesthesia and deep sedation

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Introduction

Introduction to GLP-1 Therapy

GLP-1 Agonists Overview

GLP-1 agonists are a class of medications that mimic glucagon-like peptide-1, used primarily to treat type 2 diabetes mellitus (T2DM) and obesity by enhancing insulin secretion and reducing appetite.

Clinical Uses

These medications improve blood glucose control and promote weight loss, making them key options for T2DM patients with cardiovascular risks and individuals managing obesity.

Link to Ocular Health

Emerging evidence suggests GLP-1 agonists may impact ocular conditions such as diabetic retinopathy, nonarteritic ischemic optic neuropathy, and glaucoma, offering potential protective effects on the retina and optic nerve.

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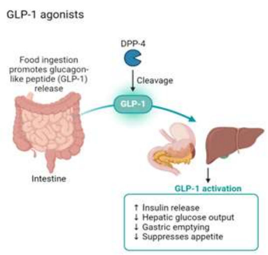

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Historical Perspective

- **1920s**: Insulin discovered, no explanation between oral and IV glucose tolerance
- **1930s**: Hormone in GI tract responsible for stimulation insulin release
  - "Incretin" : ingestion + secretion
- **1960s**: Incretin effect responsible for 2/3 of insulin response; GIP discovered
  - Glucose-dependent insulinotropic polypeptide
- **1980s**: Additional hormone discovered – GLP -1
  - Cloning GLP-1 gene demonstrated insulin secretion
  - 1/100th of concentration of GIP

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Exendin-4

- Gila monster studies
  - Poisonous lizard venom
- Exendin-4 peptide
  - Stimulates insulin secretion at same receptors as GLP-1
  - Not as quickly metabolized as GLP-1
  - Synthetic peptide normalized bG in T2DM murine studies
    - 2005 FDA approval of exenatide (Byetta)

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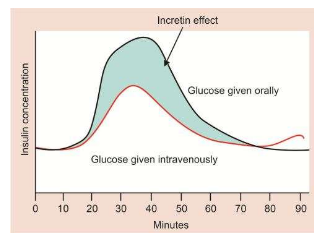
Incretin Effect

- Phenomenon where oral glucose elicits higher insulin secretion compared to IV glucose
- Humoral substance released from intestinal wall during glucose absorption
  - Stimulates insulin release from pancreatic islet cells



https://www.jaypeedigital.com/book/9789351526476/chapter/ch13

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Incretin Effect T2DM

- Possibly reduced or absent in T2DM
  - Started developing incretin-based therapies in the 1990s
  - Structural modifications to endogenous GLP-1
    - Attempt to replicate pharmacological functions
    - Impede hydrolysis by DPP-4
      - Increases half-life

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Incretin Hormones

GIP	GLP-1
• Glucose-dependent insulinotropic polypeptide • Release in response to carbohydrate and fat absorption • Released from K cells in the upper GI tract • Similar effects to GLP-1agonists but not as strong	• Glucagon-like peptide-1 • Released from L cells in the lower GI tract

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Incretin Hormones – GLP-1

Impede glucagon release from pancreatic alpha cells	• Decreases glucose production in the liver
Beta cell proliferation and longevity	• Compromised in T2DM

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Glucagon – Friend or Foe?

- Glucagon secreted from liver and kidney
- Energy
- Increases bG during periods of fasting
- Long-term dosing causes weight loss in obese mice
  - Retatrutide

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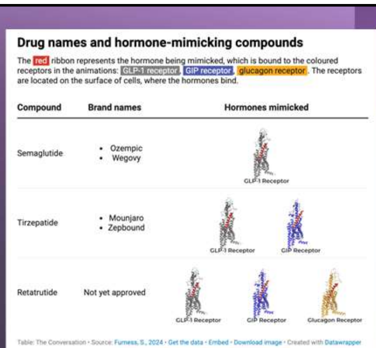

Drug names and hormone-mimicking compounds

The red ribbon represents the hormone being mimicked, which is bound to the coloured receptors in the animations: GLP-1 receptor, GIP receptor, glucagon receptor. The receptors are located on the surface of cells, where the hormones bind.

Compound	Brand names	Hormones mimicked
Semaglutide	• Ozempic • Wegovy	GLP-1 Receptor
Tirzepatide	• Mounjaro • Zepbound	GLP-1 Receptor, GIP Receptor
Retatrutide	Not yet approved	GLP-1 Receptor, GIP Receptor, Glucagon Receptor

Table: The Conversation • Source: Furness, S., 2024 • Get the data • Embed • Download image • Created with Datawrapper

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Physiology

Overview of Endogenous GLP-1

Source of GLP-1

GLP-1 is an incretin hormone produced by L-cells in the small intestine in response to food intake, playing a key role in glucose metabolism.

Insulin Secretion Stimulation

GLP-1 stimulates glucose-dependent insulin release from pancreatic β-cells, enhancing blood sugar regulation after meals.

Glucagon Inhibition

GLP-1 inhibits glucagon secretion from pancreatic α-cells, reducing glucose production and helping maintain balanced blood sugar levels.

Effects on Digestion and Appetite

It slows gastric emptying to minimize post-meal glucose spikes and promotes satiety, contributing to reduced food intake and weight control.

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Mechanism

GLP-1 enhances glucose-dependent insulin secretion from pancreatic β-cells, helping to lower blood glucose levels after meals.

Stimulates Insulin Secretion

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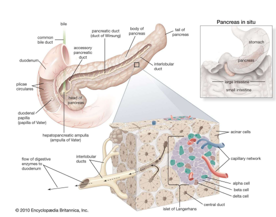
Mechanism

- It suppresses glucagon secretion from pancreatic α-cells, reducing inappropriate glucose release by the liver during high blood sugar states.



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Glucagon Synthesis

- Glucagon stimulates glucose release into the bloodstream during fasting periods
- By reducing glucagon levels, blood glucose levels are also lowered

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Physiology

GLP-1 delays gastric emptying, which slows the rate at which glucose enters the bloodstream, preventing rapid postprandial glucose spikes.

By slowing gastric emptying, GLP-1 helps maintain steady blood glucose levels after meals, reducing the risk of sudden spikes. This physiological action is an important mechanism for glycemic control in diabetes management.

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Physiology

By acting on the central nervous system, GLP-1 increases feelings of fullness, reducing food intake and supporting weight management.

GLP-1 promotes satiety by signaling the brain to reduce hunger, helping individuals eat less and maintain a healthier weight.

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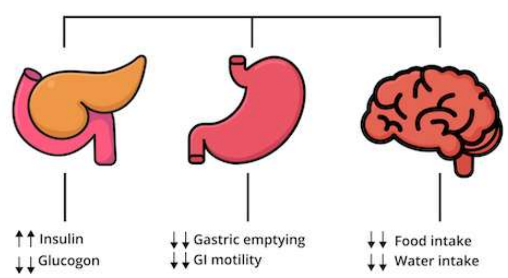

https://www.healthpopuli.com/2023/03/10/growing-dtc-for-health-beyond-the-rx/glp-1-mechanism-of-action-glucagon-like-peptide-target-organs/

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Glucose-dependent Release

- GLP-1 and GIP stimulate insulin secretion in a glucose-dependent manner
- Insulin release intensifies in response to elevated plasma glucose levels
- Maintains glucose homeostasis post-prandial

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Glucose Regulation

GLP-1 in Glucose Homeostasis

Enhancement of Insulin Secretion

GLP-1 stimulates pancreatic β-cells to release insulin in a glucose-dependent manner, increasing glucose uptake by tissues and lowering blood sugar levels.

Balancing Glucose Utilization

GLP-1 helps balance glucose production and usage by inhibiting glucagon release and promoting storage of glucose, contributing to stable blood glucose homeostasis.

Rapid Degradation Limits Use

Endogenous GLP-1 is quickly broken down by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a short half-life that restricts its natural therapeutic potential.

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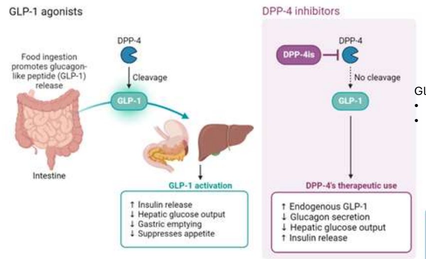

Gliptins

- Januvia
- Tradjenta

https://myendoconsult.com/learn/mechanism-of-action-of-glp-1-agonists/

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Degradation

Degradation by DPP-4 Enzyme

Dipeptidyl peptidase-4 (DPP-4) is a key enzyme that rapidly degrades endogenous GLP-1 shortly after its release, reducing its half-life to just a few minutes. This swift inactivation limits the natural hormone's ability to sustain glucose regulation and therapeutic effects. Consequently, native GLP-1 is not practical for long-term treatment of conditions like type 2 diabetes. This pharmacological challenge led to the creation of synthetic GLP-1 receptor agonists that resist DPP-4 degradation, extending their activity and effectiveness in managing blood glucose and related metabolic disorders.

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GLP-1 Therapy

Discovery and Development of GLP-1 Agonists

1990s

Identification of Native GLP-1

Native GLP-1 discovered as an incretin hormone with beneficial effects on insulin secretion but limited by rapid degradation by DPP-4 enzyme.

Early 2000s

Challenge of Rapid Degradation

The short half-life of native GLP-1 due to enzymatic breakdown limited its therapeutic use, prompting research into more stable analogs.

2005

Development of Exenatide

Exenatide, a synthetic GLP-1 receptor agonist resistant to DPP-4 degradation, was introduced as the first GLP-1 agonist for clinical use.

2010s

Introduction of Semaglutide

Semaglutide, a longer-acting GLP-1 analog with improved efficacy and dosing convenience, became a leading therapy for T2DM and obesity.

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Mechanism

Mechanism of GLP-1 Agonists

Activation of GLP-1 Receptors

GLP-1 agonists bind to receptors on pancreatic β-cells, triggering signaling that boosts insulin secretion in a glucose-dependent way, reducing hypoglycemia risk.

Increased insulin release
Improved glucose uptake
Reduced hypoglycemia risk

Glucagon Suppression

They inhibit glucagon release from pancreatic α-cells during high blood sugar, lowering hepatic glucose production and stabilizing blood glucose levels.

Decreased glucagon levels
Reduced hepatic glucose output
Stabilized blood glucose

Slowed Gastric Emptying

GLP-1 agonists delay stomach emptying, slowing glucose absorption into the bloodstream and preventing rapid post-meal glucose spikes.

Slower nutrient absorption
Reduced post-meal glucose peaks
Improved glycemic control

Increased Satiety

By acting on the brain, GLP-1 agonists promote fullness, reduce appetite, and help decrease food intake, supporting weight loss in T2DM and obesity.

Increased satiety signals
Decreased caloric intake
Support for weight management

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Mechanism

GLP-1 Receptor Activation

GLP-1 agonists bind to and activate GLP-1 receptors located on pancreatic β-cells. This activation enhances insulin secretion in a glucose-dependent manner, meaning insulin release is increased primarily when blood glucose levels are elevated. This selective mechanism reduces the risk of hypoglycemia, making GLP-1 agonists effective and safer options for managing blood sugar in patients with type 2 diabetes.

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Pharmacology

Effects on Gastric Emptying and Appetite

GLP-1 agonists slow the rate at which food leaves the stomach, leading to delayed gastric emptying. This mechanism reduces postprandial blood glucose spikes by controlling the absorption rate of nutrients. Additionally, these agonists act on the central nervous system to promote feelings of fullness or satiety, thereby reducing overall food intake. Together, these effects support significant weight loss in patients, making GLP-1 agonists effective not only for glucose control but also for obesity management.

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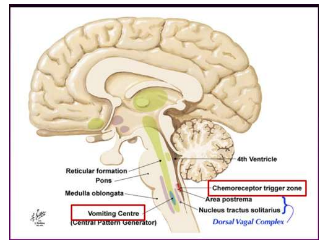
GLP-1RA GI Adverse Effects

- GLP-1 Receptors found in the CNS
  - Circumventricular organ
  - Area Postrema
    - Nausea and vomiting
  - Nucleus of Solitary Tract
    - Appetite suppression



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Urgent or Emergent Procedures

- Proceed and treat the patient as a "full stomach" and manage accordingly

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Elective Procedures: Prior to the Procedure

- Daily dosing – consider holding on the day of surgery
- Weekly dosing – consider holding a week prior to surgery
- Suggestion irrespective of
  - Indication
  - Dose
  - Type of surgery
- Endocrinology / PCP consult for bridging antidiabetic therapy

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Elective Procedures: Day of Procedure

If GI symptoms noted by patient,

Severe nausea / vomiting
Abdominal bloating
Abdominal pain

Consider delaying surgery

Review and discuss concerns potential risks with surgeon and patient

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Clinical Applications

Clinical Applications Overview

Type 2 Diabetes Management

GLP-1 agonists effectively lower blood glucose by enhancing insulin secretion and reducing glucagon, significantly improving HbA1c levels in patients with type 2 diabetes.

Obesity Treatment

Medications like Semaglutide promote satiety and weight loss, making GLP-1 agonists an approved and effective therapy for chronic weight management in obesity.

Cardiovascular Benefits

Long-term studies show GLP-1 therapies reduce major adverse cardiovascular events, offering protective benefits for patients with established cardiovascular disease.

Emerging Neuroprotection Research

Ongoing investigations are exploring GLP-1 agonists' potential in neurodegenerative diseases such as Alzheimer's, highlighting promising neuroprotective effects.

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T2DM

GLP-1 Agonists in T2DM

GLP-1 receptor agonists are proven to significantly lower HbA1c levels in patients with type 2 diabetes mellitus (T2DM). They enhance glucose-dependent insulin secretion and suppress glucagon release, resulting in better glycemic control. Importantly, these agents also provide cardiovascular benefits, reducing major adverse cardiovascular events in patients with elevated cardiovascular risk. Their dual action on blood sugar and heart health makes GLP-1 agonists a valuable treatment option for managing T2DM, especially in those with high cardiovascular risk profiles.

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T2DM

- Possible link to GLP-1 impairment and slowed GLP-1 activation after eating
- Augmenting endogenous GLP-1 with synthetic GLP-1 agonists, increase overall concentration of the peptide
- Remember, without proper GLP-1 activation
  - Insulin is NOT released promptly
  - Glucagon production releases glucose into circulation
    - Resultant increase in blood glucose levels

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Obesity

GLP-1 Agonists in Obesity Management

GLP-1 agonists like semaglutide have gained approval for chronic weight management in adults with obesity or overweight with related health conditions. These medications work by promoting satiety and reducing appetite, leading to substantial and sustained weight loss as demonstrated in clinical trials. Semaglutide's efficacy in obesity treatment has made it a cornerstone therapy, offering significant improvements in metabolic parameters and overall health outcomes for patients struggling with obesity.

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Obesity Management

1. Underlying weight loss mechanism poorly understood
2. GLP-1s curb hunger leading to a reduction in food intake
3. Slow gastric emptying from stomach to small intestine
   - Promoting satiety more quickly and lasting for a longer period of time

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Drug Absorption and Slowed Gastric Emptying

Calvarysky B, Dotan I, Shepshelovich D, et al. Drug-drug interactions between glucagon-like peptide 1 receptor agonists and oral medications: a systematic review. *Drug Saf.* 2024;47(5):439-451.

Should we be concerned with co-administered drug absorption?

Not clinically significant and no dosing adjustments necessary for most oral drugs**

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Semaglutide

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Medications

Semaglutide Medications

Brand Names

Semaglutide is marketed as :

Ozempic (injectable for T2DM & cardiovascular risk)

Rybelsus (oral for T2DM)

Wegovy (injectable for weight management).

Formulations & Concentrations

Ozempic pens: 0.25, 0.5, 1, 2 mg

Rybelsus tablets: 3, 7, 14 mg

Wegovy pens: 0.25 to 2.4 mg weekly

Indications

Ozempic treats T2DM & cardiovascular risk; Rybelsus for adults with T2DM; Wegovy for chronic weight management in obesity or overweight with related conditions.

Delivery Systems

Ozempic & Wegovy use once-weekly subcutaneous injections

Rybelsus is oral, taken daily on an empty stomach.

Dosing Schedules

Ozempic starts at 0.25 mg weekly, increasing to 0.5 mg and up to 2 mg

Rybelsus starts at 3 mg daily, rising to 7 mg or 14 mg

Wegovy starts at 0.25 mg weekly, increasing to 2.4 mg.

Combination Therapies

Ozempic & Rybelsus can be combined with metformin, insulin, and other antidiabetic agents for better glycemic control.

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Pill Options

- GLP-1s are large molecules (peptides)
  - They are usually injected with Rybelsus being the exception
  - 2019, Novo Nordisk reformulated semaglutide
    - ~1% absorbed and it is enough to be clinically effrective
      - Assists with T2DM
      - 100x the dose needed for weight loss

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Liraglutide

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Medications

Liraglutide Medications

Brand Names

Liraglutide is marketed as:

Victoza for type 2 diabetes mellitus

Saxenda for chronic weight management at higher doses.

Concentrations and Formulations

Victoza is available as 6 mg/mL prefilled pens with doses of 0.6 mg, 1.2 mg, or 1.8 mg per injection

Saxenda uses the same concentration but delivers 3 mg doses for weight management.

Indications

Victoza is approved for T2DM in adults and children 10 years and older, with cardiovascular risk reduction

Saxenda is indicated for chronic weight management in adults and adolescents with obesity.

Delivery Systems

Both Victoza and Saxenda are administered via prefilled pens for subcutaneous injection once daily.

Dosing Schedule

Victoza starts at 0.6 mg daily for one week, increasing to 1.2 mg daily; can be further increased to 1.8 mg if needed

Saxenda starts at 0.6 mg daily, increasing weekly by 0.6 mg increments to 3 mg daily.

Combination Therapies

Victoza can be combined with other antidiabetic agents such as metformin, sulfonylureas, or insulin to optimize glycemic control.

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Semaglutide v. Liraglutide

Semaglutide

- Weight loss of 15% of body weight
- More effective at reducing bG levels by 0.5% or 5.5 mmol/mol
- Fewer adverse events and side effects

Liraglutide

- Weight loss of ~6%
- Generic available
  - $$$

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	Month 1	Month 2	Month 3	Month 4	Month 5+
Semaglutide (Wegovy®)	0.25mg/week	0.5mg/week	1mg/week	1.7mg/week	2.4mg/week
Semaglutide (Ozempic®)	0.25mg/week	0.5mg/week (up to 1mg)	0.5mg/week (up to 1mg)	0.5mg/week (up to 1mg)	0.5mg/week (up to 1mg)
	Week 1	Week 2	Week 3	Week 4	Week 5+
Liraglutide (Saxenda®)	0.6mg/day	1.2mg/day	1.8mg/day	2.4mg/day	3mg/day

Dosing Schedule

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Medications

Dulaglutide Medication Profile

Brand Name

Dulaglutide is marketed under the brand name Trulicity, widely prescribed for type 2 diabetes mellitus (T2DM).

Formulations and Concentrations

Available in prefilled autoinjectors with doses of 0.75 mg/0.5 mL, 1.5 mg/0.5 mL, 3 mg/0.5 mL, and 4.5 mg/0.5 mL for tailored glycemic control.

Indications

Indicated for treatment of T2DM in adults and to reduce cardiovascular risk in patients with T2DM and established cardiovascular disease.

Delivery System and Dosing

Administered via a once-weekly subcutaneous injection using a prefilled autoinjector pen. Initial dose is 0.75 mg once weekly, which can be increased to 1.5 mg or higher doses (3 mg, 4.5 mg) based on glycemic response and tolerance.

Combination Therapies

Can be used alongside other antidiabetic medications such as metformin, sulfonylureas, or insulin to optimize glucose control.

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Medications

Tirzepatide Medications – “Twincretin”

Brand Names

Tirzepatide is marketed as:

Mounjaro for type 2 diabetes

Zepbound for chronic weight management in adults with obesity or overweight conditions.

Formulations

Available in prefilled pens containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg doses to allow precise titration.

Indications

Mounjaro is approved for adults with type 2 diabetes

Zepbound targets chronic weight management in adults with obesity or related conditions.

Delivery System

Administered via prefilled pen for subcutaneous injection once weekly, providing convenience and adherence support.

Dosing Schedule

Starting dose is 2.5 mg once weekly, increased to 5 mg after 4 weeks; further increases up to 15 mg weekly depend on glycemic control.

Combination Therapies

Can be combined with other glucose-lowering agents such as metformin or basal insulin for enhanced glycemic control.

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Tirzepatide

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Efficacy

Comparative Efficacy With Other Agents

GLP-1 Agonists

Offer robust HbA1c reduction with low hypoglycemia risk. Provide weight loss benefits and cardiovascular risk reduction, making them favorable in patients with comorbid obesity and heart disease.

Insulin Therapy

Highly effective in lowering blood glucose but associated with weight gain and higher hypoglycemia risk.

Requires careful dose titration and monitoring.

SGLT-2 and DPP-4 Inhibitors

SGLT-2 inhibitors aid glucose excretion with cardiovascular and renal benefits; may cause genitourinary infections.

DPP-4 inhibitors have modest HbA1c effects and favorable safety but lack significant weight or cardiovascular benefits.

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Safety

Safety Profile and Side Effects

Common Side Effects

- Nausea is the most frequently reported side effect, often transient and dose-dependent.
- Other gastrointestinal symptoms include vomiting and diarrhea, typically mild to moderate.
- Low risk of hypoglycemia when used as monotherapy due to glucose-dependent insulin secretion.
- Weight loss benefits may improve overall metabolic profile and reduce cardiovascular risk.
- Generally well tolerated with a favorable safety profile compared to some other antidiabetic agents.

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Safety

Safety Profile and Side Effects

Risks and Considerations

- Potential risk of pancreatitis has been reported; patients should be monitored for symptoms like severe abdominal pain.
- Animal studies have indicated a risk of thyroid C-cell tumors, though this has not been confirmed in humans; caution advised in patients with personal or family history of medullary thyroid carcinoma.
- Gastrointestinal adverse effects may lead to treatment discontinuation in some cases.
- Rare cases of hypersensitivity reactions or injection site reactions have been documented.
- Regular clinical monitoring is essential to manage side effects and detect any emerging safety concerns early.

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Therapy

Combination Therapies in Diabetes Management

- GLP-1 agonists are frequently used alongside metformin to improve glycemic control by complementary mechanisms.
- Combination therapy with insulin and GLP-1 agonists can reduce insulin dose requirements and lower the risk of hypoglycemia.
- Using GLP-1 agonists with other oral antidiabetics, such as sulfonylureas or SGLT-2 inhibitors, can provide additive benefits in blood glucose regulation.
- Combination therapies aim to address multiple pathophysiologic defects in type 2 diabetes for more effective management.
- Personalized therapy plans consider patient-specific factors including efficacy, side effect profile, and cardiovascular benefits.

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Diabetic Retinopathy

Impact on Diabetic Retinopathy

Clinical Evidence Overview

Studies reveal that GLP-1 agonists can influence diabetic retinopathy progression, with early transient worsening followed by stabilization or improvement over time.

Initial Worsening Effects

Some patients experience a short-term worsening of diabetic retinopathy after starting GLP-1 therapy, likely related to rapid glucose control changes.

Long-Term Benefits

Over extended treatment, GLP-1 agonists are associated with reduced rates of diabetic retinopathy progression and improvements in retinal vascular health.

Recommendations for Care

Regular eye exams are essential for patients on GLP-1 therapy, with closer monitoring during therapy initiation to detect and manage potential ocular changes early.

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Monitoring

Monitoring Recommendations for Eye Health

- Recommend baseline comprehensive eye exam before initiating GLP-1 therapy to assess existing ocular conditions.
- Schedule follow-up eye exams every 3 to 6 months during the first year of GLP-1 treatment to monitor diabetic retinopathy progression.
- Increase frequency of monitoring if early signs of diabetic retinopathy or other ocular changes are detected.
- Advise patients to report any sudden changes in vision promptly for immediate assessment.
- Coordinate with endocrinologists and primary care providers to integrate ocular health monitoring into overall diabetes management.

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GLP-1 Receptors

- Pancreatic beta cells
- GI tract
- Cardiovascular system
- CNS

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Ocular Health

GLP-1 Receptors in Ocular Tissues

Retinal Ganglion Cells

GLP-1 receptors are expressed on retinal ganglion cells, which are critical for transmitting visual information from the retina to the brain. Activation may support neuroprotection and cell survival.

Endothelial Cells

GLP-1 receptors are found on endothelial cells in ocular blood vessels, where they may help regulate vascular health and reduce inflammation, contributing to retinal protection.

Müller Cells

Müller glial cells in the retina express GLP-1 receptors, potentially mediating anti-inflammatory and antioxidant effects that protect retinal neurons from damage.

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Ocular Health

Mechanisms of Ocular Protection

Anti-Apoptotic Effects

GLP-1 agonists inhibit cell death pathways in retinal ganglion cells and optic nerve neurons, preserving cellular integrity and function in ocular tissues.

Anti-Oxidative Mechanisms

These agonists reduce oxidative stress by neutralizing reactive oxygen species (ROS), decreasing cellular damage and promoting retinal cell survival.

Anti-Inflammatory Actions

GLP-1 receptor activation modulates inflammatory responses in ocular tissues, lowering pro-inflammatory cytokines to protect against neurodegeneration.

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Preclinical Evidence

Preclinical Evidence from Animal Studies

Reduction of Oxidative Stress

Animal models show that GLP-1 agonists significantly decrease reactive oxygen species in retinal cells, protecting against oxidative damage linked to diabetic retinopathy and other retinal diseases.

Anti-inflammatory Effects

Studies reveal GLP-1 receptor activation reduces inflammatory cytokines in retinal tissue, helping to mitigate inflammation-driven retinal damage and support tissue health.

Neuroprotective Mechanisms

GLP-1 agonists promote survival of retinal ganglion cells by activating anti-apoptotic pathways and reducing cell death, suggesting benefits for neurodegenerative ocular conditions.

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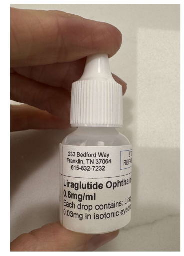
Glp1s are known to be anti-inflammatory and to work on neuro-inflammation.

Stay tuned..

#dryeye #glp1 #inflammation #medical



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Ocular Health

GLP-1 Therapy and NAION

Recent studies indicate that GLP-1 receptor agonists may provide neuroprotection in ocular tissues vulnerable to ischemic injury, such as in NAION. These agents could reduce oxidative stress and inflammation in the optic nerve, potentially mitigating damage and improving outcomes. For eye care providers, understanding this emerging evidence is crucial for monitoring patients with diabetes or metabolic syndrome who are on GLP-1 therapy, as it may influence risk assessment and treatment strategies for NAION.

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NAION

Pathogenesis of NAION not well understood

Incidence is 2-10 cases / 100,000 people in people older than 50

- 0.54 / 100,000 for all ages
- 6000 new cases annually

No causal relationship explored

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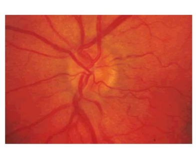
NAION

- Atherosclerosis, diabetes, hypertension, hyperlipidemia, smoking, sleep apnea, nocturnal hypotension, medications
  - Associated risk factors but causation unknown
  - Ischemic Optic Neuropathy Decompression Trial (IONDT), at least one risk factor present in >60% of cases
    - Subsequent trial, one risk factor in almost 90% of cases



- Small / absent physiologic cupping - "Disc at risk"
  - Noted in 82% of patient in a study
  - Some suggest structural crowding leads to mechanical obstruction of axoplasmic flow

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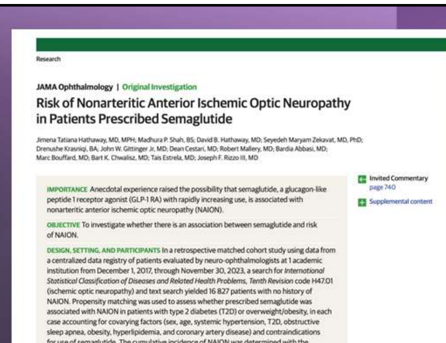

Research

JAMA Ophthalmology | Original Investigation

Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

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Supplemental content

IMPORTANCE Anecdotal experience raised the possibility that semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1 RA) with rapidly increasing use, is associated with nonarteritic anterior ischemic optic neuropathy (NAION).

OBJECTIVE To investigate whether there is an association between semaglutide and risk of NAION.

DESIGN, SETTING, AND PARTICIPANTS In a retrospective matched cohort study using data from a centralized data registry of patients evaluated by neuro-ophthalmologists at 1 academic institution from December 1, 2017, through November 30, 2023, a search for *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code H47.01 (ischemic optic neuropathy) and text search yielded 16 827 patients with no history of NAION. Propensity matching was used to assess whether prescribed semaglutide was associated with NAION in patients with type 2 diabetes (T2D) or overweight/obesity, in each case accounting for covarying factors (sex, age, systemic hypertension, T2D, obstructive sleep apnea, obesity, hyperlipidemia, and coronary artery disease) and contraindications for use of semaglutide. The cumulative incidence of NAION was determined with the

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GLP-1s and NAION

- JAMA study
  - Retrospective study with at Mass Eye and Ear from December 2017 – November 2023
    - 16, 827 patients
    - 710 with T2DM
      - 194 prescribed semaglutide → 17 NAION events (8.9% over 36 months)
      - 516 prescribed non-GLP-1 antidiabetic medication → 6 NAION events (1.8% over 36 months)
    - 979 overweight or obese
      - 361 prescribed semaglutide → 20 NAION events (6.7% over 36 months)
      - 618 prescribed non-GLP-1 weight loss medication → 3 NAION events (0.8% over 36 months)

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The Effect of Semaglutide and GLP-1 RAs on Risk of Nonarteritic Anterior Ischemic Optic Neuropathy

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• PURPOSE: The association between GLP-1 receptor agonists (GLP-1RA) and nonarteritic anterior ischemic optic neuropathy (NAION) remains unclear. Given the debilitating sequelae of NAION and rapid increase of GLP-1RA use, further research is essential to investigate this potential relationship. This study seeks to determine the risk of NAION and ischemic optic neuropathy (ION) in patients prescribed GLP-1RAs.
• DESIGN: Retrospective matched cohort study.
• SETTING: TriNetX United States collaborative network.
• PARTICIPANTS: Patients ≥12 years old with type 2 diabetes (T2DM) and considered overweight or obese (high ... on various demographic and risk factors to balance baseline cohorts.
• MAIN OUTCOMES AND MEASURES: Cumulative incidence and risk of NAION and ION. Risk ratios (RR) with 95% confidence intervals (CI) were reported, with significance defined as CI <0.9 or > 1.1.
• RESULTS: In T2DM patients prescribed semaglutide, the risk of NAION (RR = 0.7, 95% CI: 0.523-0.937) and ION (RR = 0.788, 95% CI: 0.609-1.102) after 5 years was not significantly increased compared to matched T2DM controls. Similarly, T2DM patients on any GLP-1RA demonstrated no significant difference in the risk of NAION (RR = 0.887, 95% CI: 0.735-1.071)

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TABLE 1. Study Design, Inclusion, and Exclusion Criteria

	All Patients (+) Ophthalmology or Neurology Services [> 12 YO]			
	T2DM (+) T2DM [On/After Dec 5, 2017]		High BMI (+) BMI > 25 [On/After June 4, 2021]	
	Study Group	Control Group	Study Group	Control Group
Semaglutide vs Non-GLP-1 RAs GLP-1 RAs vs Non-GLP-1RAs	(+) Semaglutide (+) All GLP-1 RA medications approved for T2DM[a]	(+) Insulin and analogues, Metformin, Sulfonylureas, α-glucosidase inhibitors, Thiazolidinediones, Dipeptidyl peptidase-4 inhibitors, Sodium-glucose transport protein 2 inhibitors (-) All GLP-1 RA Medications	(+) Semaglutide (+) All GLP-1 RA medications approved for weight loss[b]	(+) Bupropion, Naltrexone, Orlistat, Topiramate, Phentermine, Setmelanotide (-)All GLP-1 RA

(+) = inclusion criteria, (–) = exclusion criteria, [] = filter.
[a]Tirzepatide, Liraglutide, Semaglutide, Lixisetanide, Dulaglutide, Exenatide.
[b]Tirzepatide, Liraglutide, Semaglutide.

- Retrospective study
- 116 million patients from 65 health care institutions searched
- Multiple cohorts designed
- Control groups created
  - T2DM: non-GLP-1 medications
  - High GMI: non-GLP-1 medications

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Semaglutide v. Matched Controls

- T2DM: 130,000 patients in each cohort
  - Semaglutide group
    - No increased risk in developing NAION at.1 year and 5 years
    - Cumulative incidence 0.039%, 0.057%, 0.065% (1, 3, 5 years)
      - JAMA study showed 8.9% incidence at 3 years
- High BMI: 85,000 in each cohort
  - Semaglutide group
    - No increased risk in developing NAION at 1 or 2 years
    - Cumulative incidence 0.036% and 0.038% (1 year and 2 years)

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Ocular Therapeutics

Potential Role in Glaucoma Treatment

GLP-1 Agonists and Glaucoma Research

- Studies suggest GLP-1 receptor activation may protect retinal ganglion cells from degeneration.
- Animal models of open-angle glaucoma show reduced retinal damage with GLP-1 agonist treatment.
- GLP-1 agonists may reduce oxidative stress and inflammation in ocular tissues.
- Neuroprotective effects could slow progression of glaucomatous optic neuropathy.

Mechanisms and Clinical Implications

- GLP-1 agonists exert anti-apoptotic and anti-inflammatory effects on optic nerve cells.
- Potential to improve mitochondrial function and reduce cellular stress in the retina.
- Could complement intraocular pressure lowering treatments by targeting neurodegeneration.
- Future clinical trials are needed to confirm safety and efficacy in glaucoma patients.

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GLP-1s and Glaucoma

Study in Ophthalmology (Sept 2024)

1737 glaucoma cases from 264,708 individuals
Treated with GLP-1 medication

Matched to 8685 glaucoma-free controls
Metformin and a second-line non-GLP-1 medication

Individuals on GLP-1 treatment exhibited lower risk of glaucoma
Prolonged treatment beyond 3 years lowered risk even more

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Ocular Therapeutics

Future Directions in Ocular Therapeutics

- Exploration of GLP-1 agonists as neuroprotective agents in glaucoma to prevent retinal ganglion cell death and preserve vision.
- Potential development of topical or intraocular GLP-1 formulations to directly target ocular tissues for enhanced efficacy.
- Investigation into anti-inflammatory and anti-oxidative effects of GLP-1 agonists for treating diabetic retinopathy and other retinal diseases.
- Research on combining GLP-1 therapy with existing ocular treatments to improve outcomes in optic neuropathies and retinal degeneration.
- Emerging studies on GLP-1's role in modulating ocular blood flow and vascular health for broader ocular disease management.

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Clinical Insights

Key Clinical Takeaways for Eye Care Providers

- GLP-1 receptor agonists may influence diabetic retinopathy progression; initial worsening can occur but long-term benefits include slowed progression and retinal protection.
- Regular and accelerated eye exams are recommended when initiating GLP-1 therapy, especially in patients with pre-existing diabetic retinopathy.
- GLP-1 receptors are present in retinal ganglion cells and other ocular tissues, suggesting potential neuroprotective and anti-inflammatory effects.
- Be aware of possible ocular side effects and educate patients to report vision changes promptly.
- GLP-1 therapy shows promise in managing other ocular conditions such as nonarteritic ischemic optic neuropathy (NAION) and glaucoma, though clinical applications are still emerging.

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Patient Education

Patient Education Points

Benefits of GLP-1 Therapy

Explain how GLP-1 agonists help improve blood sugar control, promote weight loss, and reduce cardiovascular risks in type 2 diabetes.

Common Side Effects

Inform patients about nausea, vomiting, and diarrhea as frequent side effects, and advise on when to seek medical attention for severe symptoms.

Ocular Health Monitoring

Stress the need for regular eye exams to detect any changes in diabetic retinopathy or other ocular conditions early during therapy.

Medication Adherence

Encourage patients to follow dosing schedules strictly and communicate any side effects or concerns with their healthcare provider.

Lifestyle and Support

Advise on maintaining a healthy diet, regular exercise, and support resources to enhance the overall effectiveness of GLP-1 therapy.

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Summary

Summary of GLP-1's Intersection with Ocular Health

GLP-1 receptor agonists, widely used for managing type 2 diabetes and obesity, also impact ocular health by targeting GLP-1 receptors expressed in retinal and optic nerve tissues. Emerging evidence indicates these therapies may slow diabetic retinopathy progression and provide neuroprotection to retinal ganglion cells, reducing oxidative stress and inflammation. Clinical monitoring of ocular status during GLP-1 therapy is essential, especially in early treatment phases. Future research may establish GLP-1 agonists as novel treatments for ocular neurodegenerative diseases such as glaucoma, expanding their therapeutic role beyond metabolic control.

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