Diabetes ECHO
Case Discussion

12/12/24

The Clinical Question

- *“Should GLP-1 medications be discontinued in patients with elevated triglycerides and no signs/symptoms of pancreatitis?*
- *Or can we add fenofibrate and continue the GLP-1?”*

What does your clinic or care team do?

Causes of Pancreatitis

- For pancreatitis to occur, an initial event must overwhelm defense mechanisms - **gallstone obstruction** and **ethanol abuse** are the two most prevalent causes.
  - **Gallstone obstruction** of the ampulla of Vater, which is responsible for **35%-40%** of acute pancreatitis cases in the United States,
  - **Ethanol abuse** is the second most common cause of pancreatitis in the United States, responsible for approximately **30%** of cases.

- Other etiologies involve
  - smoking
  - scorpion venom
  - **hypertriglyceridemia**
  - endoscopic retrograde cholangiopancreatography (ERCP)
  - hypercalcemia
  - steroids
  - malignancy
  - infection
  - trauma
  - **drugs** - 0.1%-2% of acute pancreatitis incidents

Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study.

Diabetes Care. **2010** Dec;33(12):2580-5. Gonzalez-Perez A, Schlienger RG, Rodríguez LA.

- Incidence rates were
  - 30.1 per 100,000 in the general population
  - 54.0 per 100,000 person-years in the diabetes cohort
- The adjusted **incidence rate ratio of acute pancreatitis in diabetic patients** versus that in the general population was **1.77** (95% CI 1.46–2.15).
  - The risk of acute pancreatitis was
    - Higher in untreated patients vs treated patients
      - decreased among Insulin-treated diabetic patients (0.35 [0.20–0.61])
      - increased with Sulfonylureas (1.66 [1.01-2.74])
  - In addition, the risk of acute pancreatitis was significantly increased among
    - ***current smokers***,
    - those ***taking ≥30 units of alcohol per week***,
    - individuals with a previous ***history of gastrointestinal disease***, and
    - ***current users of paracetamol and ACE inhibitors***.

Always a challenge to determine if AP due to diabetes or to medication

Up-to Date
Hypertriglyceridemia- induce Acute Pancreatitis

https://www.uptodate.com/contents/hypertriglyceridemia-induced-acute-pancreatitis

- The risk of developing acute pancreatitis is approximately
  - 5 percent with serum triglycerides >1000 mg/dL
  - 10 to 20 percent with triglycerides >2000 mg/dL
  - In a prospective study of 116,500 individuals with triglyceride levels between *443 mg/dL and 885 mg/dL*, the incidence rate of acute pancreatitis was *0.12 percent*.

- The degree of triglyceride elevation is associated with the severity of acute pancreatitis

Magnified Risk of Pancreatitis by GLP-1: A Case of Necrotizing Pancreatitis in a Patient on Dulaglutide with Baseline Elevated Triglycerides

J Endocr Soc. 2022 Nov 1;6(Suppl 2):A399–A400. doi: 10.1210/jendso/bvac150.831

- While ***several META analyses have not shown significant association between GLP-1 RA and pancreatitis***, there still is a proportion of patients who have developed pancreatitis on GLP-1 RA.
- Our patient had baseline elevated triglycerides[in 300s], but they were below the typical threshold for treatment. With minimal alcohol consumption [*one bottle of sparkling wine – 9 to 10 units of alcohol*], he still developed pancreatitis.
- *We **suspect** that his **risk for pancreatitis was magnified by his GLP-1 RA**.*
  - *We believe that in patients such as ours who have baseline **independent risk factors** for pancreatitis, GLP-1 RA should be **carefully considered** before initiation.*

GLP-1 Agonist Use in a Patient With an Explainable Cause of Pancreatitis

The Case: 51-yo male presented to ED with abdominal pain

- His presenting laboratory values included serum lipase 7,901 U/L, serum amylase 39 U/L, and ***triglycerides 7,686 mg/dL***.
  - Abdominal computed tomography scan results were consistent with diffuse pancreatitis; ultrasound ruled out the presence of gallstones and the patient denied any history of alcohol abuse.
- The patient was diagnosed with ***acute pancreatitis due to hypertriglyceridemia.***
- After discharge, the patient's serum **triglyceride concentration was aggressively managed** with combination anti-lipidemia therapy **(TGS 252)**and his ***diabetes*** was subsequently ***treated with a GLP-1 receptor agonist.***
- After **15 months of GLP-1** therapy, the patient remains symptom-free and off insulin – and **TGS 102**

GLP-1 Agonist Use in a Patient With an Explainable Cause of Pancreatitis

Sean M. Brady , Michael P. Kane PharmD, FCCP, BCPS, BCACP, Robert S. Busch MD, FACE

- CONCLUSION: This case report illustrates the point that the **use of a GLP-1 receptor agonist is not absolutely contraindicated in patients with diabetes and a history of pancreatitis.**
- The *rare incidence and uncertain causality* of pancreatitis associated with GLP-1 receptor agonist use should *not automatically preclude* the consideration of these agents in a patient with a *history of pancreatitis* [*? or risk of pancreatitis*?].
- As seen in this case, healthcare providers may consider GLP-1 receptor agonist therapy for patients with a *history of pancreatitis originating from a **known cause has been adequately managed***.
  - We recommend that
    - the risks and benefits of therapy be considered and discussed with such patients
    - as a precaution, vigilant monitoring for pancreatitis recurrence be conducted in patients subsequently receiving GLP-1 receptor agonist therapy.

- https://www.aaceclinicalcasereports.com/article/S2376-0605(20)30288-1/pdf

Question posed to GLP1 Expert at Grand Rounds

- *Is it necessary to withhold or withdraw GLP1 RA meds if patient has hypertriglyceridemia?*

- Response *"It is NOT necessary"*
  - It deprives those patients of beneficial effects.
  - Pancreatitis not increased with GLP1 RA meds in CVOT Trials
    - "Pancreatitis is *associated* with GLP1 use *not caused* by."
    - Pancreatitis from hypertriglyceridemia is not common unless TGs >2000 – (should be on treatment to prevent pancreatitis)
  - GLP1 RA & Dual agonists reduce triglyceride levels

Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials.

Diabetes Obes Metab. 2020 Apr;22(4):699-704. Abd El Aziz M, Cahyadi O, Meier JJ, Schmidt WE, Nauck MA

- According to multiple large cardiovascular outcome trials (CVOTs), there is **no significant increase in the risk of pancreatitis associated with GLP-1 receptor agonists (GLP-1 RAs)** in patients with type 2 diabetes - ***meta-analyses of these trials*** consistently support this finding.

- All individual DPP-4 inhibitors displayed a non-significant trend towards an increased risk of acute pancreatitis, which was significant in the meta-analysis [1.75 (1.14-2.70); P = 0.01].
  - However, a **75% risk increase for the development of an acute pancreatitis was seen in the meta-analysis of DPP-4 inhibitor CVOTs**.

- Neither GLP-1 receptor agonists nor DPP-4 inhibitors were associated with a significantly elevated or reduced risk of pancreatic cancer or for the totality of all malignant neoplasms.

Curr Diabetes Rev. 2014;10(4):238-50. doi: 10.2174/1573399810666140707092506.

Effect of GLP-1 based therapies on diabetic dyslipidemia

Vishal J Patel, Amit A Joharapurkar, Gaurang B Shah, Mukul R Jain

- *Apart from its actions on body weight and glucose*, GLP-1 can also regulate cholesterol and triglycerides by numerous ways.
- Acute and long-term treatment with either GLP-1 or its stable analogs **reduced fasting as well as postprandial lipids** in healthy as well as T2DM patients.

“Semaglutide Reduces Mace Consistently Across Baseline Triglyceride Levels in Patients With Type 2 Diabetes: A Post Hoc Analysis of the Sustain 6 and Pioneer 6 Trials,” was presented at AHA 2020.

- Investigators determined semaglutide reduced triglycerides versus placebo by
  - **5%** in the SUSTAIN 6 trial and
  - **6%** in the PIONEER 6 trial (P <.01).

J Lipid Atheroscler. 2023 Sep;12(3):213-222.

The Cardiovascular Effect of Tirzepatide: A Glucagon-Like Peptide-1 and Glucose-Dependent Insulinotropic Polypeptide Dual Agonist

Yun Kyung Cho,1,2 Yoo La Lee,3 and Chang Hee Jung1,2

- Tirzepatide has been shown to improve lipid profiles in clinical studies.
  - For instance, in the SURPASS-4 trial, where *tirzepatide was compared with insulin glargine in patients* with T2DM and a high cardiovascular risk, *15 mg* of tirzepatide ***reduced*** the levels of TC by 5.6%, LDL-C by 7.9%, and **TGs by 22.5%,** and increased the levels of HDL-C by 10.8%.
  - In the SURPASS-5 trial, where *tirzepatide was added to basal insulin treatment*, tirzepatide ***reduced*** the levels of TC by 12.9%, LDL-C by 15.5%, and **TGs by 24.9%,** and increased the levels of HDL-C by 0.9%.
- In both trials, the effects of tirzepatide on lipid profile were *dose-dependent*, with greater improvements observed at higher doses and these improvements were sustained over the duration of the trials.

SGLT2-inhibition increases total, LDL, and HDL cholesterol and lowers triglycerides: Meta-analyses of 60 randomized trials, overall and by dose, ethnicity, and drug type

Atherosclerosis Volume 394, July 2024, 117236

- Highlights
  - SGLT2-inhibitor treatment *increases* total, LDL, and HDL cholesterol slightly.
  - **SGLT2-inhibitor treatment lowers triglycerides slightly.**
  - Higher vs. lower treatment dose had minimal influence on the results.
  - Results were generally robust across different types of SGLT2-inhibitors.
  - ***Overall, changes were modest and not likely to be of clinical relevance***.

Study presented at ENDO 2024

Mahmoud Nassar MD PhD
University of Buffalo

- 638,501 individuals with a history of acute pancreatitis and taking either a GLP-1 RA, an SGLT2i or a DPP4i medication (across 15 countries) – compared their risk of acute pancreatitis recurrence.
- **The GLP-1 group showed a lower risk of recurrence of acute pancreatitis**
  - **GLP-1 group – 15.2%**
  - SGLT2i group – 24.0%
  - DPP4i group – 23.3%

?? Instead of magnifying risk do GLP1 RA meds mitigate risk??

On the other hand,... .

Why it is not straightforward for us...

October 5, 2023

Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Mohit Sodhi, MSc1; Ramin Rezaeianzadeh, BSc1; Abbas Kezouh, PhD2; et al

- Use of GLP-1 agonists compared with bupropion-naltrexone [for weight loss] was associated with increased risk of
  - **pancreatitis (adjusted HR, 9.09** [95% CI, 1.25-66.00])
  - bowel obstruction (HR, 4.22 [95% CI, 1.02-17.40])
  - gastroparesis (HR, 3.67 [95% CI, 1.15-11.90)
  - but not biliary disease (HR, 1.50 [95% CI, 0.89-2.53])
    - From another source: *"Cholelithiasis-induced AP (driven by a quick and/or robust weight loss) appears to be one of the key mechanisms driving the development of AP in patients with T2D exposed to GLP-1RA"*
- *Exclusion of hyperlipidemia* from the analysis did not change the results.
- https://jamanetwork.com/journals/jama/fullarticle/2810542

Factors That Increase Pancreatitis Risk With GLP-1 Initiation

October 24, 2022, at the American College of Gastroenterology's Annual Scientific Meeting in Charlotte, North Carolina.

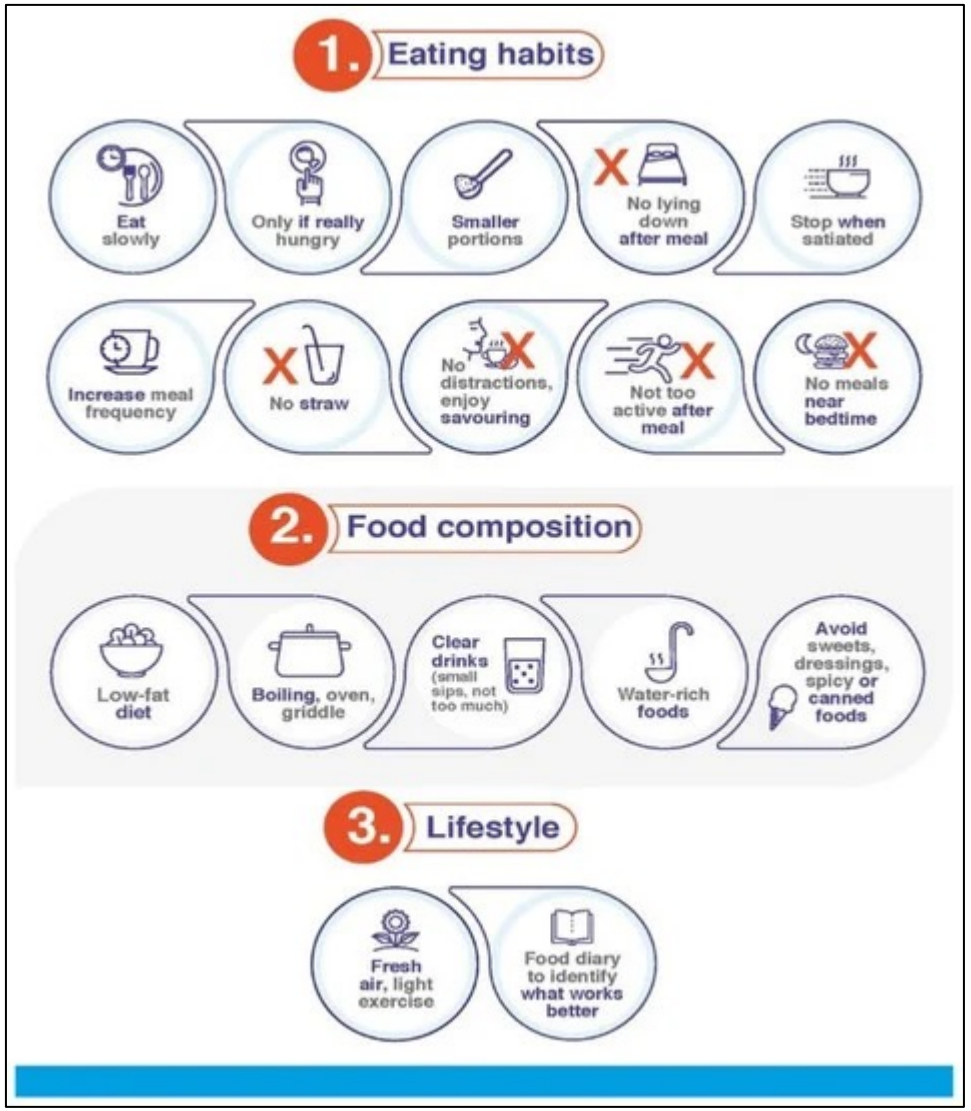
- The study team performed a retrospective, single-center study in patients seen at an academic institution's ***Weight Wellness*** program
  - 2,245 participants with an average age of 49.5 years. Most (80.5%) were female, and participants had an average BMI of 39.7 kg/m2.
- Of the 2,245 patients, 49 **(2.2%) developed AP after starting a GLP-1RA**.
  - Patients may be at an increased risk of developing acute pancreatitis after being started on a GLP-1 receptor agonist for the goal of weight loss if patients have a history of
    - **type 2 diabetes mellitus**
    - **tobacco use**
    - **advanced chronic kidney disease**

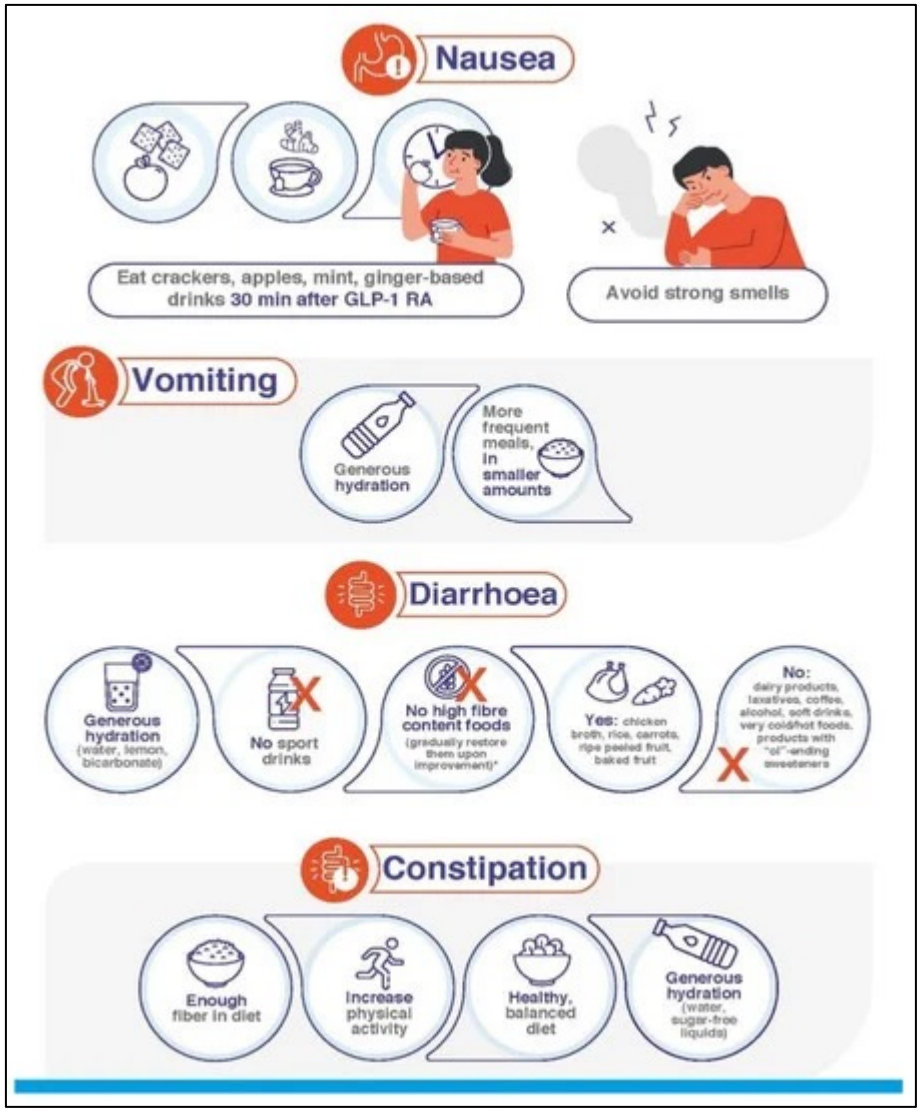
Hypertriglyceridemia not on the risk list

  - Also, a **BMI >36** at the initiation of a GLP-1RA ***may protect*** patients against developing acute pancreatitis.
  - Last, if patients have had ***acute pancreatitis in the past***, there is no evidence that patients are at a higher risk of developing a subsequent episode of acute pancreatitis after starting a GLP-1RA.
    - Therefore, this class of medications should not be withheld for this reason, especially given the significant glycemic, cardiovascular, and weight loss effects.

Summary: What do you think/What will you do?

- **For your patients with no prior history of pancreatitis but increased risk of pancreatitis due to hypertriglyceridemia:**
  - Risk of pancreatitis is too high – do not treat with GLP med
  - These patients could benefit from GLP meds – control high risk triglyceridemia with diet and meds & treat with GLP med -Do inform patient of
    - lifestyle precautions
      - [Include alcohol precautions (?)]
    - risk and signs/symptoms to be aware of





https://www.mdpi.com/2077-0383/12/1/145

Extra Slides

Pancreatitis Secondary to Hypertriglyceridemia

Kenneth R. Feingold, MD. Last Update: August 3, 2022.

- "One should try to ***reverse the secondary factors*** that are resulting in the marked hypertriglyceridemia.
  - For example, improving diabetic control, eliminating ethanol intake, and discontinuing drugs that raise triglyceride levels.
  - In patients with markedly elevated triglyceride levels (>1000mg/dL) initial dietary treatment should be a very low-fat diet until the triglyceride levels decrease.
  - Once the triglycerides decrease a diet that reduces carbohydrate intake particularly simple sugars and minimizes alcohol intake is appropriate.
  - Weight loss if appropriate can be helpful in lowering triglyceride levels.
- If triglycerides remain elevated after the above measures one can consider the use of drugs that lower triglyceride levels such ***as omega-3-fatty acids and fibrates***.
  - Many patients are at *high risk for atherosclerotic cardiovascular disease* and therefore once the high triglyceride levels are lowered one needs repeat a lipid panel to determine whether treatment to reduce the risk of atherosclerotic cardiovascular disease is indicated (for example statin therapy).

GLP-1 Receptor Agonist Treatment Improves Fasting and Postprandial Lipidomic Profiles Independently of Diabetes and Weight Loss

Diabetes 2024;73(10):1605–1614

- Curr Opin Lipidol. 2021 Jun 1;32(3):191-199. doi: 10.1097/MOL.0000000000000750.
- Lipid effects of glucagon-like peptide 1 receptor analogs
- Amanda J Berberich 1 2, Robert A Hegel
- Lipid data collected as secondary outcomes from large clinical trials as well as some smaller dedicated trials show that GLP-1RAs can modestly lower low-density lipoprotein (LDL) and total cholesterol (C), and most show modest fasting triglyceride (TG) lowering. Effects on high-density lipoprotein-C have been less consistent. Some have also demonstrated substantial blunting of the postprandial rise in serum TGs.

Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study.

Diabetes Care. 2010 Dec;33(12):2580-5. Gonzalez-Perez A, Schlienger RG, Rodríguez LA

- This association of an increased risk of acute pancreatitis and type 2 diabetes seems more pronounced at *younger* ages (vs increased with advancing age in gen pop).
- We were also able to assess how antidiabetic drugs might influence this association.
  - Interestingly, **use of insulin and long-term use of metformin** [>3y 0.50 (0.28–0.91)]were associated with a ***decreased risk*** of pancreatitis*
  - **Long-term use of sulfonylureas**, seems to ***increase the risk*** [1.66 (1.01–2.74)]
    - A previous case-control study, found that the sulfonylurea **glyburide** increased the risk of acute pancreatitis, but neither insulin nor metformin seemed to lower the risk.
    - There are reports of cases of acute pancreatitis in patients using metformin after an episode of acute renal failure.

*To the best of our knowledge, this is the first study suggesting a reduced risk associated with these antidiabetic drugs.

Curr Diabetes Rev. 2014;10(4):238-50. doi: 10.2174/1573399810666140707092506.

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- Apart from its actions on body weight and glucose, GLP-1 can also regulate cholesterol and triglycerides by numerous ways.
- Acute and long-term treatment with either GLP-1 or its stable analogs **reduced fasting as well as postprandial lipids** in healthy as well as T2DM patients.
  - GLP-1R signaling reduces VLDL-TG production rate from liver, reduces hepatic TG content by modulating key enzymes of lipid metabolism in liver, and impairs hepatocyte de novo lipogenesis and β-oxidation.
  - GLP-1 can also modulate reverse cholesterol transport.
  - Apart from these direct effects on lipid metabolism, GLP-1 also reduces atherosclerotic events by inhibiting expression of atherogenic inflammatory mediators, suppressing smooth muscle cell proliferation and stimulating NO production.