ECHO Diabetes

Review of Hypertriglyceridemia – Focus on Reducing the Risk of Pancreatitis

November 18, 2021

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Pre-quiz

Triglyceride levels are:

A. Increased by treatment with insulin
B. Best lowered with a statin as first-line medication therapy
C. Associated with increasing risk of pancreatitis at 500 mg/dl or higher
D. Minimally impacted by diet, co-existing conditions and/or medications

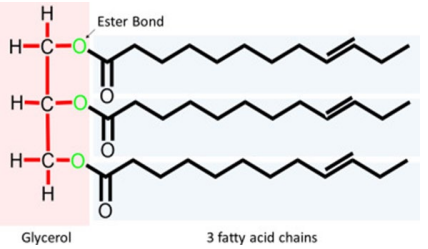
Triglycerides and Pancreatitis

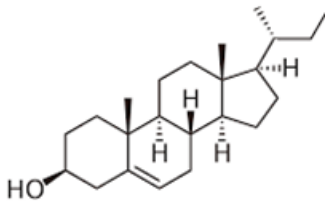
- Background
  - The most common causes of pancreatitis are gallstones and alcohol
  - Hypertriglyceridemia is the third most common cause but significantly less common
    - acute pancreatitis associated with triglycerides > 1,000 mg/dL
    - begin to focus on prevention when triglycerides ≥ 500 mg/dL

  - Alcohol ingestion can lead directly to pancreatitis or can exacerbate hypertriglyceridemia and lead to pancreatitis

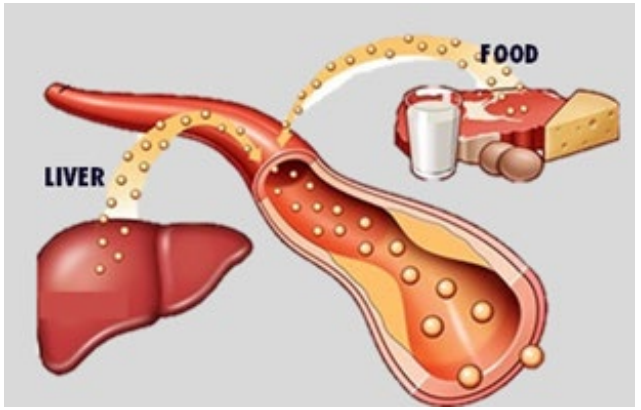
Triglycerides

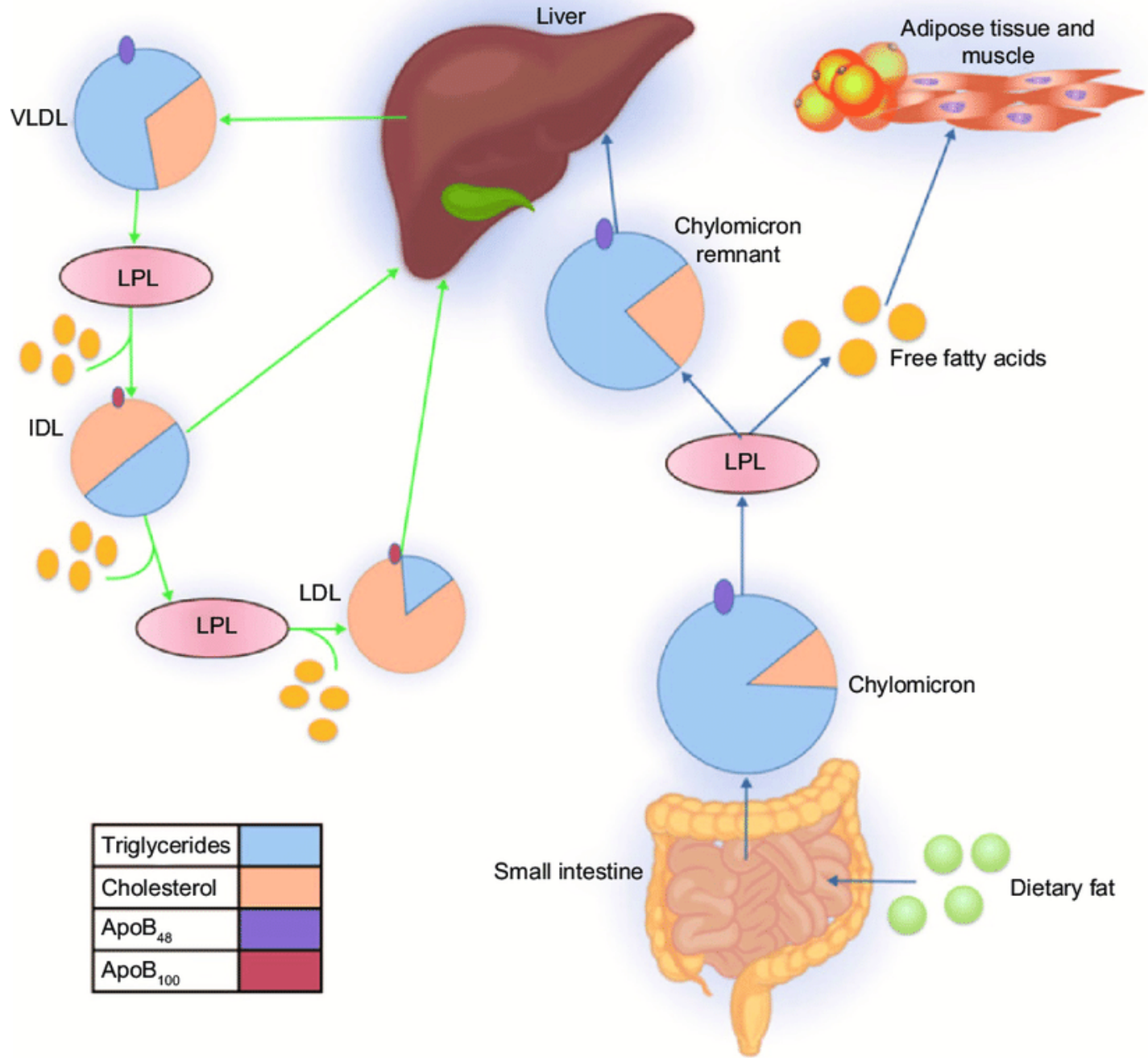
- Triglycerides are one of the two main forms of lipid in the body
  - Triglycerides are a form of stored ***energy*** (3 fatty acid chains attached to glycerol) ("fats")
  - Cholesterol which is used for ***structural purposes*** (steroid hormones, cell walls, etc.)





- Triglycerides
  - come into the body from fats stored in foods (as ***chylomicrons***) or
  - are synthesized in the liver (as ***VLDL*** particles)
  - both require **Lipoprotein Lipase** for their clearance




Liver
Adipose tissue and muscle
VLDL
LPL
IDL
LPL
LDL
LPL
Chylomicron remnant
Free fatty acids
LPL
Chylomicron
Small intestine
Dietary fat
Triglycerides
Cholesterol
ApoB48
ApoB100

Hypertriglyceridemia

- Hypertriglyceridemia may occur from either decreased catabolism and/or increased production of triglyceride-rich lipoproteins (TRL) (from exogenous or endogenous sources)
- **Saturation of triglyceride clearance** might occur owing to defective triglyceride hydrolysis by LpL and/or reduced clearance of VLDL and chylomicron remnants by the liver.
- In patients with severe or very high triglyceride levels (≥1000 mg/dl), the LpL removal system is saturated.
  - This saturation occurs whether hypertriglyceridemia is primarily due to *defective lipolysis* or *excessive production of endogenous triglyceride (VLDL),* and it leads to **reduced catabolism** of dietary triglyceride incorporated into **chylomicrons**
  - For this reason*, triglyceride levels can rapidly increase after a fat-rich meal*.

Table 2 Proposed Criteria for Diagnosing Elevated Triglyceride Levels Under Fasting Conditions

NCEP-ATP III		Endocrine Society*	
Normal	<150 mg/dl	Normal	<150 mg/dl
Borderline-high triglycerides	150-199 mg/dl	Mild hypertriglyceridemia	150-199 mg/dl
High triglycerides	200-499 mg/dl	Moderate hypertriglyceridemia	200-999 mg/dl
Very high triglycerides	≥500 mg/dl	Severe hypertriglyceridemia	1,000-1,999 mg/dl
		Very severe hypertriglyceridemia	≥2,000 mg/dl

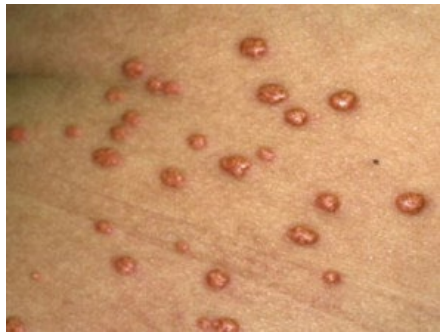
*These criteria focus on the ability to assess risk for premature cardiovascular disease (CVD) versus risk for pancreatitis. The designations of mild and moderate hypertriglyceridemia correspond to the range of levels predominant in risk assessment for premature CVD. This range includes the vast majority of subjects with hypertriglyceridemia. Severe hypertriglyceridemia carries a susceptibility for intermittent increases in levels >2,000 mg/dl and subsequent risk of pancreatitis; very severe hypertriglyceridemia is indicative of risk for pancreatitis. In addition, these levels suggest different etiologies. Presence of mild or moderate hypertriglyceridemia is commonly due to a dominant underlying cause in each patient, whereas severe or very severe hypertriglyceridemia is more likely due to several contributing factors.

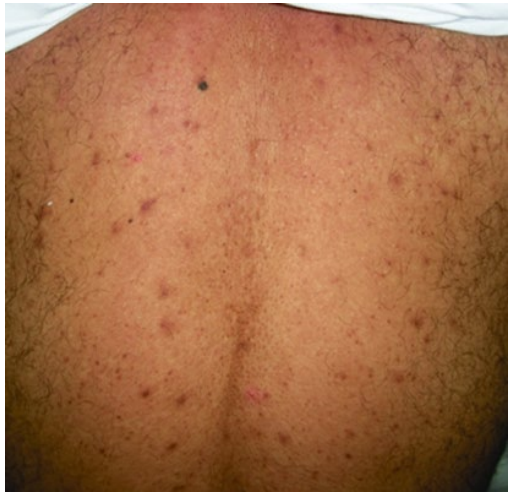
Abbreviation: NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III.

Source: Adapted from: Berglund L, et al. *J Clin Endocrinol Metab.* 2012;97:2969-2989.

Chylomicronemia syndrome

- occurs when triglyceride levels > 2,000 mg/dL
  - should be treated with urgency
- complications of chylomicronemia syndrome include
  - high risk for acute pancreatitis
  - abdominal pain
  - hepatosplenomegaly
  - eruptive skin xanthomas
  - lipemia retinalis
  - transient memory loss
  - artifactual alterations in laboratory analysis

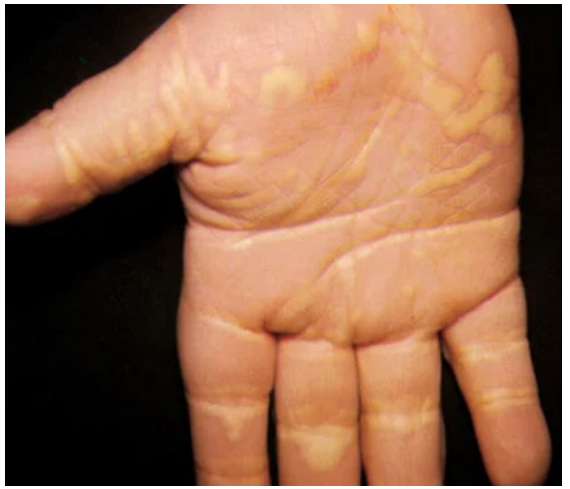




- Most commonly, chylomicronemia is caused by the **coexistence** of a **common genetic** form of hypertriglyceridemia **combined with an acquired disorder** of plasma triglyceride metabolism, the most common being *untreated diabetes* or the use of *drugs* that raise triglyceride levels.
  - The chylomicronemia syndrome occasionally occurs with a genetic defect in the LpL-related triglyceride clearance system (familial lipoprotein lipase deficiency or familial apoprotein C-II deficiency)

Primary causes of hypertriglyceridemia	Etiology
Familial combined hyperlipidemia	Decreased LPL activity; overproduction of VLDL; mutation in APOA1/C3/A4/A5 gene cluster
Familial hypertriglyceridemia	LPL, apo C-II, apo A-V, or glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 deficiency
Familial dysbetalipoproteinemia/remnant removal disease	Impaired hepatic clearance; mutation in apo E (generally E2/E2 genotype)

- Dysbetalipoproteinemia (type III hyperlipoproteinemia or remnant removal disease)
  - In the absence of ***additional genetic, hormonal, or environmental factors***, remnants *do not accumulate* to a degree sufficient to cause hyperlipidemia in fasting blood.
  - Dysbetalipoproteinemia results when an apoE defect (almost always the E2/E2 genotype) occurs in **conjunction with a second genetic or acquired defect** (*Hypothyroidism* can lead to the expression of dysbetalipoproteinemia)
- Patients with dysbetalipoproteinemia have elevations in both cholesterol and triglyceride levels with *total cholesterol and triglyceride levels that range from 300 to 1000 mg/dl and are roughly equal*
  - They are likely to develop premature CVD and are at increased risk for peripheral vascular disease.
  - **Palmar xanthomas**, orange lipid deposits in the palmar creases, are pathognomonic, but are not always present



"We recommend that individuals found to have any elevation of fasting triglycerides should be *evaluated for secondary causes of hyperlipidemia* including endocrine conditions and medications. *Treatment should be focused on such secondary causes." (Endocrine Society)*

Secondary causes of hypertriglyceridemia	Etiology
Excess alcohol consumption	Increased hepatic fatty acid synthesis; decreased fatty acid oxidation; increased hepatic VLDL secretion
Drug-induced (corticosteroids, estrogens, antiretroviral protease inhibitors, immunosuppressants, etc.)	Varies
Diabetes type 2	Increased production of TGs from carbohydrates; decreased LPL activity
Lipodystrophy	Increased hepatic VLDL synthesis and reduced clearance of TG particles
Hypothyroidism	Reduction in LDL receptor activity
Renal disease	Nephrotic syndrome causes increased hepatic production of VLDL; renal disease may cause reduced LPL and hepatic lipase activity
Liver disease	Increased VLDL production
Pregnancy	Hyperphagia causing increased chylomicron production; increased hepatic VLDL synthesis; suppression of hepatic lipase activity
Multiple myeloma, systemic lupus erythematosus	Autoantibodies against LPL or apoC-II

Abbreviations: LPL = lipoprotein lipase; TG = triglyceride; VLDL = very-low-density lipoprotein.
[a]Table adapted from references (1,3,4).

The Effect of Alcohol on Postprandial and Fasting Triglycerides

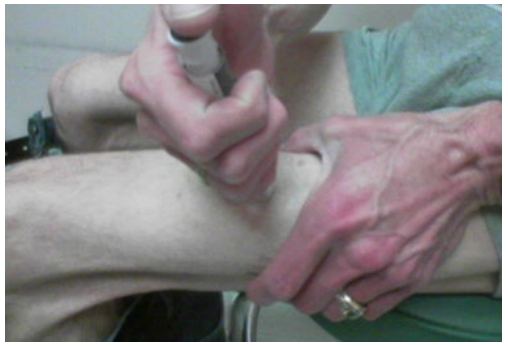
International Journal of Vascular Medicine / 2012 /

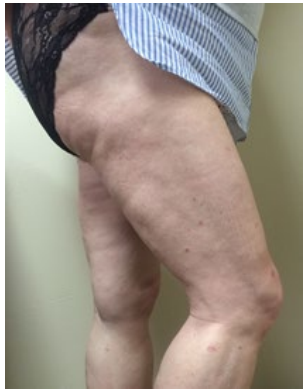
- Alcohol intake ***stimulates the hepatic synthesis and secretion of large VLDL particles*** (the main form hypertriglyceridemia associated with chronic excessive alcohol intake)
- Alcohol has an acute ***inhibitory effect on lipoprotein lipase*** activity –
  - this can result in a significant additive effect on the *postprandial triglyceride peak* when it accompanies a meal containing fat, especially saturated fat, due to a ***decrease in the breakdown of chylomicrons and VLDL remnants***
- Sometimes, a ***severe hypertriglyceridemia*** induced by alcohol (SHIBA) can be observed, *especially in patients with type 2 diabetes mellitus and/or obesity* increasing the risk of *pancreatitis*
- The effects of alcohol vary interindividually:
  - ***amplified in subjects with underlying lipid disorders***
  - ***obesity*** exaggerates alcohol-associated hypertriglyceridemia (and the the risk of pancreatitis)
  - dose-dependent

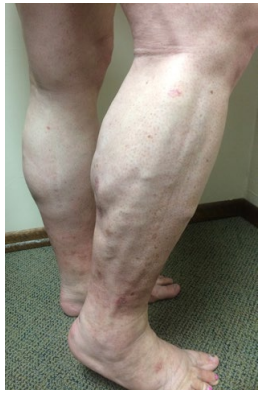
Diabetes

- Patients with *untreated diabetes mellitus* and *insulin deficiency* commonly have severe hypertriglyceridemia; this condition occurs more frequently in type 2 than in type 1 diabetes mellitus.
  - *Appropriate diabetes management* reduces triglyceride levels
    - Poorly controlled diabetes can represent a medical emergency **requiring urgent insulin therapy** when it leads to extreme hypertriglyceridemia and risk of pancreatitis
    - "Even with triglycerides in the thousands, *dietary and glycemic control, alone, will strikingly ameliorate the hypertriglyceridemia"*
  - Mild hypertriglyceridemia, typically seen in *treated type 2 diabetes*, is probably related to the presence of central obesity and insulin resistance (may increase CVD risk)

- *Lipodystrophies* (inherited or acquired) are characterized by *loss of adipose tissue* and are associated with moderate-to-severe hypertriglyceridemia (and often severe IR and Diabetes) (reduced storage for fat/triglycerides with loss of adipose tissue)







Glucose-lowering medications - varying effects on tri-glycerides.

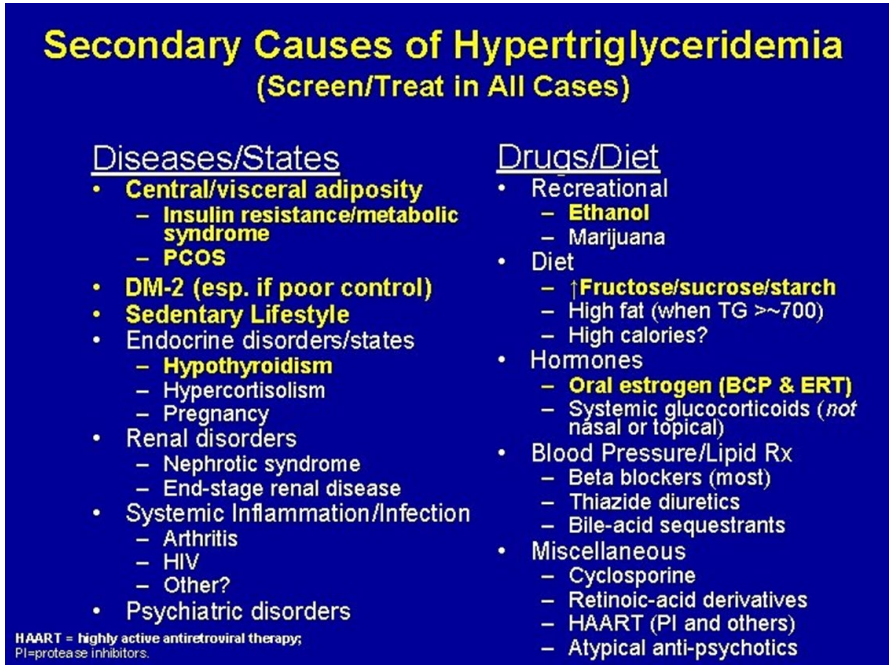
- **Insulin:** lowers circulating triglycerides by several mechanisms, including ***induction of LPL***
- **Metformin** is a modest insulin sensitizer that can lower triglycerides, an effect that appears independent of its effects on weight and glycemic control
  - A systematic review of 37 studies revealed a **decrease in serum triglycerides averaging 11.5 mg/dL** with metformin use, although higher doses (> 1700 mg per day) are required to achieve this.
- **Pioglitazone** is a peroxisome proliferator-activated receptor-ϒ (PPAR-ϒ) agonist; a strong insulin sensitizer with potent effect on triglycerides.
  - Pioglitazone can **reduce triglycerides by up to 50 mg/dL** and raise HDL cholesterol (HDL-C) by 5 mg/dL, although LDL cholesterol (LDL-C) also rises (this rise in LDL-C does not necessarily impart higher cardiovascular risk since Pioglitazone reduces dense atherogenic LDL particles.)
- **Sulfonylureas**, which act by augmenting beta cell insulin release, have not demonstrated a consistent effect on lipids.
- **Glucagon-like peptide-1 (GLP-1) receptor agonists** improve both fasting and postprandial hypertriglyceridemia
  - mean **reduction up to 27 mg/dL**, but with no consistent effect on HDL levels
- **Dipeptidyl peptidase 4 (DPP4) inhibitors** generally exert a *more modest effect* on triglycerides,
  - although mean triglyceride reductions as high as 26 mg/dL have been reported
  - saxagliptin is an exception to the typical DPP-4 inhibitor effect, as it consistently appears lipid-neutral
- **Sodium glucose cotransporter-2 (SGLT2) inhibitors** increase HDL and lead to a **10% reduction** in triglycerides, but also raise LDL-C.
  - Despite the concern of increasing LDL-C, SGLT2 inhibitors have cardioprotective effects in type 2 diabetes, and like pioglitazone, they reduce small, dense LDL particles with a consequent shift towards large, buoyant, less atherogenic LDL

Medications associated with Hypertriglyceridemia

- atypical antipsychotics (such as, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone)
- beta blockers (non-selective)
- corticosteroids
- thiazide diuretics
- Bile-acid-binding resins
- oral estrogens
- selective estrogen receptor modulators (tamoxifen, raloxifene, clomiphene)
- cyclosporine, sirolimus
- retinoids (isotretinoin, acetretin, bexarotene)
- asparaginase, capecitabine
- propofol
- protease inhibitors
- Interferon
- Among selective serotonin reuptake inhibitors, **sertraline** may raise triglycerides

Other Secondary Causes

- Insulin resistance - obesity, metabolic syndrome
- Hypothyroidism (mostly increase LDL cholesterol)
- Cushing disease
- Excessive carbohydrate intake (> 60% of total energy) (especially refined)
- Nephrotic syndrome
- Uremia
- Hepatitis
- Pregnancy



Management of Hypertriglyceridemia

- Address secondary causes, including
  - Discontinue alcohol and medications that may increase triglycerides
  - Discontinue tobacco use
- Lifestyle modification remains the mainstay of therapy for hypertriglyceridemia.
  - Much of the increase in serum triglycerides that occurs in adult life is caused by weight gain, lack of exercise, and a diet rich in simple carbohydrates and sugar-sweetened beverages
  - Combining dietary regulation, exercise, and moderation of alcohol intake can reduce triglycerides by up to 60%.
  - Weight loss of 5–10% of initial body weight reduces triglycerides by 25% and increases HDL-C by 8%
    - Regain of weight loss might exacerbate pancreatitis risk

Management of Hypertriglyceridemia
Diet and Lifestyle

Dietary approaches

- *Minimize dietary intake* of **carbohydrates**, especially **avoidance of high glycemic index foods** (such as potatoes, white bread, and rice vs other carbohydrate-rich foods such as apples, legumes, nuts, pasta, and densely-baked whole grain breads)
  - **elimination of sugar-sweetened or naturally sweet beverages** (whether composed mainly of high-fructose corn syrup or sucrose)
  - triglyceride-lowering effects of low-carbohydrate diets may be partly caused by **protein**
    - Compared with a diet that emphasized carbohydrate, a similar diet that emphasized protein decreased triglyceride levels further, and this decrease was about twice the effect of a diet that emphasized unsaturated fat.
  - n-3 Polyunsaturated fat lowers serum triglycerides uniquely among the fatty acids
- Limit Saturated fats (due to LDL component of most TRLs/ sat fat can increase IR & inflammation)
  - C - cheese (and other sources of dairy fats - whole milk, ice cream, whole fat yogurt)
  - A - animal fats (ground meat, deli meats, fried foods)
  - G - got it away from home (high-fat meals either prepackaged or from restaurant)
  - E - extra amounts of high-fat commercial products including candy and pastries

Management of Hypertriglyceridemia
Diet and Lifestyle

Physical Activity

- The minimum exercise required to reduce a postprandial triglyceride increase has not been determined, but a period of *30–60 min of intermittent aerobic exercise or mild resistance exercise* has been shown to be effective in lowering triglycerides
  - These findings suggest a benefit from an active lifestyle that does not require intense or prolonged exercise
  - Some studies suggest a ***combination of aerobic and resistance exercise*** was associated with lower triglyceride levels in men as compared with aerobic exercise alone.
  - Exercise the day before ingestion of a high-fat meal is associated with a marked dampening of the postprandial triglyceride increase.
    - The mechanisms for this are not clear, and the exercise benefits are relatively short-lived.

For triglycerides ≥ 1,000 mg/dL (or > 500 mg/dL based on National Cholesterol Education Program guidelines)

- Primary goal is triglyceride lowering to prevent pancreatitis
- Determination and treatment of ***underlying causes*** of very severe hypertriglyceridemia should be considered first
- *"For severe and very severe hypertriglyceridemia (>1000 mg/dl), we recommend combining **reduction of dietary fat and simple carbohydrate** intake with **drug treatment** to reduce the risk of pancreatitis"* (Endocrine Society)
  - For triglycerides ≥ 1,000 mg/dL (> 11.2 mmol/L) also ***consider very low-fat diet (< 15% calorie intake)*** with restriction of ***both saturated and unsaturated dietary fat***,
    - Design of the dietary intervention may benefit from input from nutrition specialists

For triglycerides ≥ 1,000 mg/dL (or > 500 mg/dL based on National Cholesterol Education Program guidelines) - Medications

- Use **fibrates** as *first-line agents* to lower risk of developing pancreatitis
  - Fibrates ***decrease triglyceride levels by 30–50%*** and sometimes increase HDL cholesterol
    - Fibrates increase fatty acid oxidation, increase LpL synthesis, and reduce expression of apoC-III, all of which ***decrease VLDL triglyceride production*** and ***increase LpL-mediated catabolism*** of triglyceride-rich lipoproteins
  - In patients with high triglyceride levels, LDL cholesterol levels may increase with fibrate
- Consider adding niacin or ***omega-3 fatty acids*** for persistent hypertriglyceridemia
  - The long-chain marine omega-3 fatty acids [eicosapentaenoic acid, C20:5n-3 (**EPA**) and docosahexaenoic acid, C22:6n-3 (**DHA**)] lower fasting and postprandial triglyceride levels in a dose-dependent fashion.
  - Approximately 3 to 4 g/d of EPA plus DHA are necessary to **reduce hypertriglyceridemia by 20–50%**

For triglycerides ≥ 1,000 mg/dL (or > 500 mg/dL based on National Cholesterol Education Program guidelines) - Medications

- Consider adding statins for patients with mixed dyslipidemias
  - Statins are *not recommended as first-line therapy or as monotherapy*
  - Statin therapy (if LDL-C is elevated) in combination with a fibrate, or long-chain omega-3 fatty acid may be required.
    - The Food and Drug Administration **withdrew approval for niacin** in combination with statins in April 2016 citing unfavorable benefit-risk profiles.
    - One should avoid gemfibrozil in statin-treated patients for this reason (unfavorable risk), but fenofibrate can be used safely with some caution

Summary

- Genetics, lifestyle, co-existing disorders and medications/drugs can all contribute to hypertriglyceridemia
- Severe hypertriglyceridemia (SH), except for rare genetic defects in triglyceride clearance, is most often due to a *combination* of factors.
- Severe hypertriglyceridemia is most effectively managed and prevented by addressing lifestyle factors and co-existing disorders and medications
- A lower carbohydrate diet (<60% of calories) with restriction of refined carbs is first line dietary therapy (along with calorie restriction for weight loss in most)
  - Restriction of Sat fats is preferable
  - When triglycerides are markedly elevated, total fat restriction needed
- Fibrates, preferably fenofibrate, should be first line drug therapy for SH

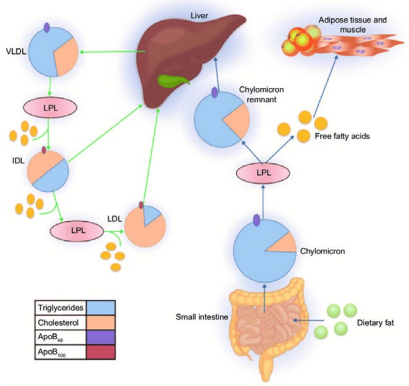
Post-quiz

Triglyceride levels are:

A. Increased by treatment with insulin
B. Best lowered with a statin as first-line medication therapy
C. Associated with increasing risk of pancreatitis at 500 mg/dl or higher
D. Minimally impacted by diet, co-existing conditions and/or medications

Extra slides

Metabolism of Triglycerides*



- dietary triglycerides are absorbed by small intestine and incorporated into core of chylomicrons
- triglycerides transported in bloodstream primarily by
  - intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), and remnants (VLDL3) under fasting conditions
  - chylomicrons and their remnants under postprandial conditions
- lipid composition of newly formed chylomicrons 80%-95% triglyceride
- chylomicrons secreted into lymphatic system and enter systemic circulation at junction of internal jugular and subclavian veins
- chylomicrons acquire apoproteins CII, CIII, and E in the lymph and blood
- in capillary beds of muscle and adipose tissue
  - chylomicrons bind to glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) where triglyceride core is hydrolyzed by lipoprotein lipase after activation by apoprotein CII
  - resulting free fatty acids used for energy by muscle cells or reincorporated into triglyceride
- after hydrolysis, chylomicron remnant removed by liver and metabolized into cholesterol-rich lipoprotein
- VLDL produced in endoplasmic reticulum of hepatocytes
  - VLDL triglyceride derived from combination of glycerol with fatty acids (from plasma or synthesized by liver)
- VLDL triglyceride hydrolyzed by lipoprotein lipase in plasma, creating denser and smaller VLDL, and subsequently intermediate-density lipoprotein (IDL)
- IDL particles may be further catabolized to become low-density lipoprotein (LDL)

Handout/Information for Patients

- https://www.hormone.org/diseases-and-conditions/triglycerides

- Renal and hepatic disease can be associated with hypertriglyceridemia.
  - Nephrotic syndrome causes increased production of apoB-containing lipoproteins, including VLDL, by the liver.
  - Hypertriglyceridemia is common in patients with renal failure and may be related to decreased clearance of triglyceride-rich lipoproteins via reduced LpL and hepatic lipase activities.
  - Acute hepatitis may be associated with increased VLDL production and hypertriglyceridemia.
-

- Antihypertensive drugs with a potential to increase triglyceride levels are thiazide (and furosemide) diuretics and β-adrenergic blocking agents. The hypertriglyceridemic effect of β-adrenergic blocking agents is greater for atenolol, metoprolol, and propranolol than for carvedilol. These effects are most relevant in patients with underlying genetic hypertriglyceridemia (94).
- Oral estrogens increase the hepatic secretion of VLDL, leading in turn to an increase in serum triglyceride levels (108). In patients with familial hypertriglyceridemia or LpL deficiency, the use of oral estrogens can provoke severe pancreatitis (
- An increase in hepatic VLDL and apoC-III production and perhaps a decrease in LpL leading to increased triglyceride levels are also seen during use of retinoids such as isotretinoin and the anticancer drug bexarotene (110–112).
- Bile acid sequestrants (cholestyramine, colestipol, colesevelam) can worsen hypertriglyceridemia and are contraindicated in patients with severe hypertriglyceridemia (>1000 mg/dl) and in patients with dysbetalipoproteinemia. Patients with normal baseline triglyceride levels experience minimal triglyceride increases with bile acid sequestrant therapy, but those with moderate hypertriglyceridemia (triglycerides > 200 mg/dl) may experience substantial further elevation (113).
- Dyslipidemia is a frequent complication of antiretroviral therapy for HIV infection. In particular, the protease inhibitors ritonavir and lopinavir can increase plasma triglyceride levels (114).
- Immunosuppressants such as sirolimus also increase triglyceride levels
- Certain second-generation antipsychotic medications such as clozapine, olanzepine, risperidone, and quetiapine can be associated with hypertriglyceridemia, but this effect has not been seen for aripiprazol or ziprasidone. Those that are associated with weight gain, insulin resistance, and worsening of the metabolic syndrome are particularly important contributors to secondary hyperlipidemia. Among selective serotonin reuptake inhibitors, sertraline may raise triglycerides

“What medications might prevent pancreatic flares and how is this tying into the patient’s diabetes?”

“Real patients cannot be easily reduced to five-sentence clinical vignettes….we need to see right answers as layered and complex, not a single choice”

- Chronic Lipase elevation with GLP1 RA medication
- Treatment to prevent severe hypertriglyceridemia (HT) in context of diabetes and other co-existing conditions
  - Lifestyle/Diet recommendations for HT in context of gastroparesis & CKD
  - Medication management of HT in context of gastroparesis & CKD
    - Fenofibrate – renal impact (renal dosing, CKD progression)
    - Review of other medications for aggravating or beneficial impact
      - Hypertriglyceridemia
      - Gastroparesis
      - CKD
- Polypharmacy concerns

Chronic Lipase elevation with GLP1 RA medication

- **GLP-1 analogue in T2DM leads to amylase and lipase elevations but not acute pancreatitis: Amylase, Lipase, and Acute Pancreatitis in People With Type 2 Diabetes Treated With Liraglutide**: Results From the LEADER Randomized Trial- STEINBERG WM, BUSE JB, GHORBANI MLM, ET AL; LEADER STEERING COMMITTEE; LEADER TRIAL INVESTIGATORS - DIABETES CARE. 2017

- Background: *Liraglutide*, a GLP-1 analogue, is an established therapy for type 2 diabetes mellitus (T2DM), however, it has been associated with increased levels of serum lipase and amylase, as well as a potential for an increased risk of acute pancreatitis.
  - In the LEADER trial**, 9,340 T2DM patients** at cardiovascular risk were randomized to liraglutide or placebo, on top of standard of care, and **followed for 3.5–5.0 years.**
- Conclusion: In the LEADER study, numerically *fewer events of acute pancreatitis were observed in the liraglutide group* compared with the placebo group.
  - **Liraglutide increased serum amylase and lipase levels, but these elevations were not predictive of the development of acute pancreatitis in asymptomatic T2DM patients.**

Chronic Lipase elevation with GLP1 RA medication

DIABETES CARE. 2017;

- Main results: In the *liraglutide* arm, *elevated levels of lipase and amylase were seen 6 months after initiation of treatment and persisted for the duration of the study.*
  - Compared with placebo, liraglutide was associated with an estimated relative *28.0% increase* in **lipase** at 36 months (Mean lipase changed from 40.0 units/L to 55.2 units/L for liraglutide).
    - 51.3% of patients had at least one time an elevated lipase level compared with 31.8% in placebo group.
    - **8.3%** vs in placebo group 5.3% had ***lipase increases of threefold or more***.
  - In addition, in the **liraglutide** group:
    - an estimated 7.0% increase in **amylase** was seen with an observed amylase change from 59.4 units/L to 70.9 units/L

Chronic Lipase elevation with GLP1 RA medication

DIABETES CARE. 2017;

- **0.4%** of patients in the liraglutide group and **0.5%** of patients in the placebo group had **an acute pancreatitis event** that was confirmed by adjudication.
    - The corresponding event rates were ***1.1/1,000 PYO (patient years of observation) for the liraglutide group and 1.7/1,000 PYO for the placebo*** group.

- In both the liraglutide and placebo groups, there was **no association between onefold or threefold elevated lipase and the subsequent risk of acute pancreatitis** in patients without acute pancreatitis at the time of measurement.

Chronic Lipase elevation with GLP1 RA medication

- "A biological explanation for an asymptomatic increase of pancreatic enzymes has been suggested: **GLP-1 acts on receptors** that are also located on the ***exocrine*** pancreas, thus **stimulating trophism and secretive function and causing growth-dependent release of pancreatic enzymes from the acinar cells**"

- "In conclusion, the results of our study confirm that serum pancreatic enzymes increase during incretin-mimetics therapy is not associated with acute pancreatitis and pancreatic cancer suggesting that this elevation might represent a **physiologic response of exocrine pancreas** to incretin-mimetics drugs rather than a potential adverse effect of these molecules, unlike previously suggested."

- From: www.omicsonline.org/open-access-pdfs/increase-in-pancreatic-amylase-and-lipase-during-incretin-therapy-is-not-associated-with-acute-pancreatitis-or-pancreati.pdf

Treatment of Hypertriglyceridemia in the context of Gastroparesis & CKD (& Fatty Liver)

- Gastroparesis - delayed gastric emptying with associated symptoms in the absence of mechanical obstruction
- Symptoms of gastroparesis include:
  - Nausea (especially after eating)
  - Vomiting, especially Vomiting undigested food a few hours after eating
  - Feeling of fullness even after eating very little --- “sulfa burps”
  - Acid reflux or heartburn
  - Abdominal pain and/or bloating
    - Mild to severe pain in the “epigastric” or upper section stomach after eating
  - Changes in blood sugar levels
  - Lack of appetite and malnutrition
  - Weight loss

Treatment of Gastroparesis - Options

- **Restoration of hydration, electrolytes and nutrition**
  - Liquid soft diet, low fat – low fiber
  - Caloric liquid supplements
- Treat nausea – **antiemetics**
- Restore coordinated gastric and small bowel motility with **prokinetic agents** (Erythromycin, Reglan® (Metoclopramide), Motilum® (Domperidone))
- **Glycemic control**
- **Pain control** (Recognition that abdominal pain can be present as an important symptom in GP patients)
  - NSAID's, Tylenol
  - TCA, SSRI, SNRI (Cymbalta), gabapentin, pregabalin, etc. could be considered
  - **Avoid narcotics !!!!!!!**
- Psychological measures
- Botulinum toxin pyloric injections
- Feeding tubes – endoscopic or oral
- Surgery
  - A) Jejunal feeding tube, full thickness gastric biopsy
  - B) Placement of gastric electrical stimulation (GES) system
  - C) Pyloroplasty
  - D) Gastric resection – total gastrectomy

Lifestyle/Diet recommendations for HT in context of gastroparesis & CKD

- Alcohol elimination/restriction
- Dietary suggestions for gastroparesis
  - chewing food well
  - drinking noncarbonated liquids with a meal (avoiding carbonated liquids)
  - walking or sitting for 2 hours after a meal—instead of lying down—may assist with gastric emptying.
  - avoiding high-fat and fibrous foods.
    - Fat naturally slows digestion
    - Some raw vegetables and fruits, such as oranges and broccoli, contain fibrous parts that do not digest well. People with gastroparesis should minimize their intake of large portions of these foods because the undigested parts may remain in the stomach too long. The undigested parts can form bezoars.
  - when symptoms are severe, a liquid or puréed diet may be prescribed
    - Liquids tend to empty more quickly from the stomach, some people may find a puréed diet helps improve symptoms.
    - Puréed fresh or cooked fruits and vegetables can be incorporated into shakes and soups.
- A health care provider may recommend a dietitian to help a person plan meals that minimize symptoms and ensure all nutritional needs are met - & other conditions considered
  - **Candy Jackson RD**

Medication management of Hypertriglyceridemia in context of gastroparesis & CKD

- Fenofibrate
  - FDA
    - Severe Hypertriglyceridemia: The initial dose is 54 to 160 mg per day. Dosage should be individualized according to patient response and should be adjusted if necessary following repeat lipid determinations at 4-to-8-week intervals. The maximum dose is 160 mg once daily.

    - **Impaired Renal Function**: Treatment with Fenofibrate Tablets should be initiated at a dose of 54 mg per day in patients having mild to moderately impaired renal function and increased only after evaluation of the effects on renal function and lipid levels at this dose. The use of Fenofibrate Tablets should be avoided in patients with severe renal impairment
  - Fenofibrate is *renally cleared* and it causes a *rise in serum Cr*, giving rise to concern for renal toxicity and worsening renal function ….
  - But newer data….

Increased Serum Creatinine with Fenofibrate … not due to nephrotoxicity

- The most consistent and reassuring finding is that when renal function is measured by *inulin clearance*, **fenofibrate *does not reduce GFR*,** despite the rise in serum creatinine (SCr) values.
  - *One possibility for the rise in SCr seen with fenofibrate is interference with the proximal tubular active secretion pathway*.
    - The kidneys excrete creatinine by a process that involves a combination of both filtration at the glomerular level and secretion at the tubular level (accounting for ~10% of total urinary creatinine).
  - Another is an *increase in creatinine production* – perhaps due to fenofibrate-associated *increased muscle turnover* that may contribute in part to the increase in creatinine.

Fenofibrate Therapy Slows CKD Progression in Diabetics

April 13, 2018, National Kidney Foundation Annual Meeting

- In a post-hoc analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial found that **fenofibrate therapy** was associated with ***less rapid decline in estimated glomerular filtration rate*** (eGFR) and incident ***micro- and macroalbuminuria*** compared with placebo among patients with CKD and type 2 diabetes.
  - In a fully adjusted model, *eGFR declined annually* by a mean
    - 0.28 mL/min/1.73 m2 among **fenofibrate**-treated patients
    - 1.25 mL/min/1.73 m2 among **placebo** recipients.
  - In addition, compared with the placebo arm, the fenofibrate-treated patients had a significant
    - 46% risk of developing microalbuminuria
    - 28% decreased risk of developing macroalbuminuria

Fenofibrate and Renal Protection (slowing progression of CKD)

- Apart from its lipid-lowering properties, there is now evidence that fenofibrate exerts pleiotropic effects on the microvascular complications of diabetes.
  - It has been found to reduce the need for laser photocoagulation therapy in patients with *diabetic retinopathy* and to reduce the risk of *microvascular amputations*.
  - In terms of renal pathology, fenofibrate has recently been shown to beneficially attenuate diabetic albuminuria and to reduce the loss of estimated glomerular filtration rate (eGFR) over 5 years.
- Fenofibrate upregulates PPAR-α activity
  - Helps in the management of dyslipidemia; in particular, of elevated concentrations of TG-rich lipoproteins (VLDL and VLDL remnants) and low levels of HDL cholesterol, by tending to reverse these abnormalities.
    - **Hyperlipidemi**a is considered an ***independent and major determinant*** of the induction and progression of **diabetic nephropathy** - accumulation of VLDL particles in the kidney may be involved in the development of diabetic renal injury.
    - Therefore, pharmacological interventions that can address lipid-related renal damage could be of therapeutic value in the management of diabetic nephropathy
  - Evidence clearly supports a central role for PPAR-α in *suppressing inflammation* and *improving vascular endothelial function*.

Renal Dosing of Fenofibrate?

- Fenofibrate and its active metabolite, fenofibric acid, are primarily excreted by the kidneys.
  - It is nondialyzable, and studies in patients with moderate chronic kidney disease (GFR <50 ml/min/1.73 m2) demonstrated a reduced rate of fenofibrate excretion and *accumulation* of the drug with persistent usage.
- The National Kidney Foundation recommends fenofibrate dosing should be
  - reduced by 50% in patients with a GFR between 60 and 90 ml/min/1.73 m2
  - Reduced by 75% in those with a GFR between 15 and 59 ml/min/1.73 m2.
- However, recent findings would suggest that these thresholds may be too restrictive and that fenofibrate dose reductions *may not be required until eGFR falls below 30 ml/min/1.73 m2.*

Proposed use of metformin in renal disease

eGFR* level	
>60	Maximum daily dose of 2,550 mg Monitor renal function annually
45-60	Maximum daily dose of 2,000 mg Monitor renal function every 3-6 months Avoid in patients with rapidly decreasing renal function
30-44	Maximum daily dose of 1,000 mg Check renal function every 3 months Do not initiate therapy (can continue patients who are on it)
<30	Do not use

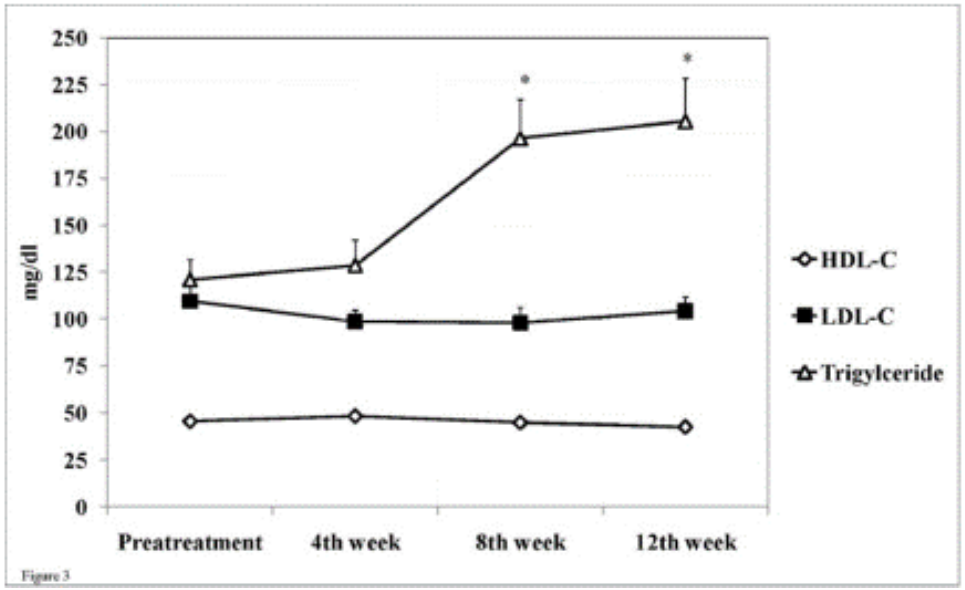
*estimated glomerular filtration rate

Note: Adapted from JAMA 2014;312:2668-75 and Diabetes Care 2011;34:1431-7.

Other Medications with Aggravating or Beneficial Impact

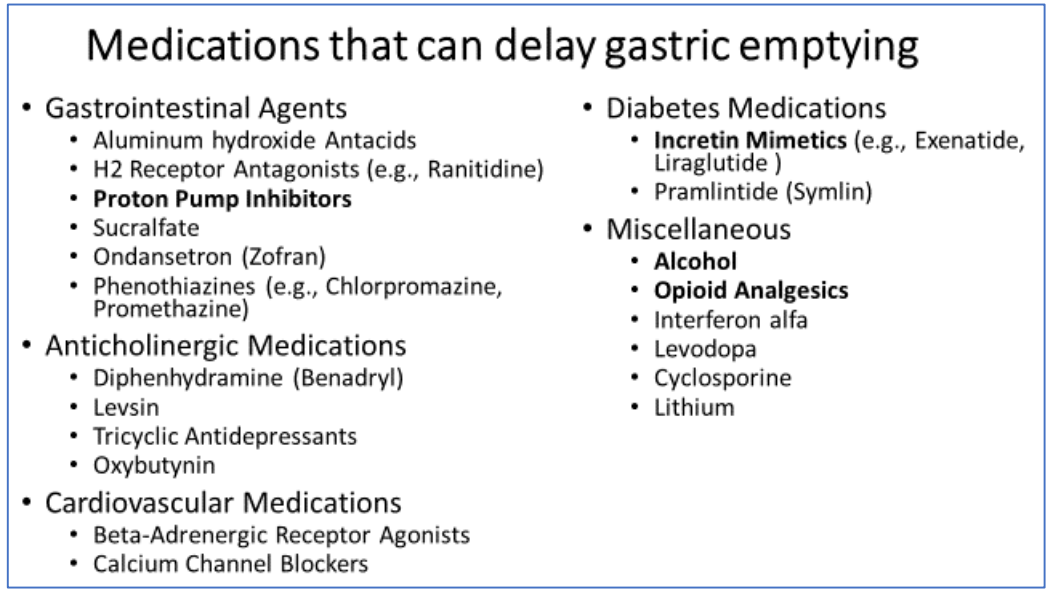
- Hypertriglyceridemia
  - Potentially Aggravating
    - Sertraline
    - Alcohol
  - Potentially Beneficial
    - Semaglutide (GLP-1 RA)
    - Metformin

Pretreatment and post-treatment blood HDL-C, LDL-C and triglyceride levels at the 4th, 8th and 12th weeks of sertraline treatment *: Compared with pretreatment value ($p < 0.05$).



Other medications with aggravating or beneficial impact

- Gastroparesis
  - Potentially Aggravating
    - Alcohol
    - Norco
    - Pantoprazole
    - *Semaglutide (GLP1 RA)*
  - Potentially beneficial
    - Gabapentin



- ***Exenatide Delays Gastric Emptying in Patients with Type 2 Diabetes Mellitus but not in Those with Gastroparetic Conditions*** Horm Metab Res. 2019 Apr;51(4):267-273.
  - Treatment with GLP-1 receptor agonists may be applied in patients with **pre-existing gastroparesis**; ***no effect in terms of worsening*** of symptoms compared to those without gastroparesis was detected. Patients reported outcome was independent from underlying gastroparesis.
  - **Negative effects on gastric emptying were only detected in patients without or with mild gastroparesis.**

Other medications with aggravating or beneficial impact

- CKD 3 – progression of renal impairment & CVD risk
  - Potentially Aggravating
    - Celecoxib
  - Potentially Beneficial
    - Lisinopril
    - Semaglutide (GLP1 RA)
    - Fenofibrate

  - Consider SGLT2i for renal preservation, fatty liver, hypertriglyceridemia and perhaps reduce risk of heart failure?