Addressing Elevated Triglycerides: Causes and Interventions for Pharmacists

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Objectives

At the end of the lecture and with the use of supplemental reading the participant should be able to

- State the importance of hypertriglyceridemia on an individual's health
- List 5 common cause of elevated triglycerides
- Discuss some non-pharmacological approaches to managing elevated triglycerides with a patient

Objectives (con't)

At the end of the lecture and with the use of supplemental reading the participant should be able to

- Recognize when pharmacotherapy is needed to address elevated triglycerides and which medications might be most appropriate
- Discuss the pharmacology of medications for elevated triglyceride and recognize important drug interactions

Case 1

- 61 year old female patient being evaluated for coronary disease was referred for evaluation of elevated triglycerides.

- Was relatively well until 30 years ago when a thyroid nodule was discovered. Partial thyroidectomy was performed, thyroid replacement commenced 15 years later when she was noted to be hypothyroid

Case 1

- Was first discovered to have elevated triglycerides in 1988, initially treated with Gemfibrozil but was later switched to Simvastatin
- Not known to have coronary disease but she was diagnosed with peripheral vascular disease and had bilateral stent placement
- A chronic smoker she stopped smoking when diagnosed with peripheral vascular disease

Case 1

Past Medical History

- Hysterectomy 30 years ago, on premarin since that time
- Had a history of fibrocystic breast disease, no malignancy

Medications

- Premarin 1.25mg QD, ASA 81mg, Simvastatin 40mg, Norvasc 10mg QD, HCTZ 12.5mg QD, L-thyroxine 100mcg alternating with 150mcg tablets daily

Family History

- Father had his first heart attack in his 40's.

Case 1

On examination

- BP= 116/55, Pulse=72/min, Height – 179cm, Weight = 98.1kg, BMI = 30.1 kg/m^2

- A scar from previous thyroidectomy. No stigmata of hyperlipidemia, Heart sounds normal, abdomen obese, no organomegaly. Peripheral pulses reduced

Case 1

Labs

1988 – Cholesterol - 331 mg/dl (8.56mmol/L), LDL - 201mg/dl(5.20mmol/L) HDL – 39.9mg/dl (1.03mmol/L), Triglycerides – 449 mg/dl (5.0mmol/L)

2005 – Creatinine 97umol/L, Fasting glucose – 6.1mmol/L, Cholesterol – 9.47mmol/L, Triglycerides – 16.12 mmol/L, HDL - not available, TSH – 13.0 (0.3-7.0)IU/mL, Free T4 12.1 (10.3-26.0)pmol/L

Case 1

- Dobutamine Stress Test – Normal systolic function, no significant ischemia, scar on imaging study
- Bilateral Lower Extremity Doppler – aorta showed atherosclerotic change but no focal anneurysms. Some stenosis present at the site of the stents in both legs more on the right than the left
- Carotid Doppler Ultrasound –Left Common Carotid 25% stenosis, Right Common Carotid 30% stenosis.

Questions

- What do you think were some factors in her history that contributed to the elevated triglycerides?

Case 1

- With Triglycerides that high treatment is indicated due to increased risk of complications.
- Has established cardiovascular disease and therefore a very high risk of additional cardiovascular events.

- Where to begin?

Manifestations of Elevated Triglycerides

- Mostly asymptomatic or symptomatic if triglycerides are elevated.

- Most worrisome complication of elevated triglycerides is pancreatitis – especially if serum triglycerides are > 11mmol/L. Most commonly this may occur in a patient with diabetes (may require intensive insulin to lower triglycerides), alcoholic patients and may be drug induced in patients who are predisposed

Approach to the patient with Elevated Triglycerides

- Evaluate the patient to determine whether dsylpidemia is primary or secondary
- If secondary treat underlying secondary cause as this may result in significant improvement in the lipid profile
- Usually when triglycerides extremely elevated it may indicate an underlying lipid disorder that is exacerbated by precipitant

Elevated Triglycerides Secondary Causes

- Obesity – associated with high LDL-cholesterol, VLDL-cholesterol, and low HDL cholesterol
- Type 2 diabetes / Impaired Glucose Tolerance – usually a result of insulin resistance and associated with low HDL cholesterol. Increased triglycerides from increased substrate (glucose and free fatty acids) and decreased lipolysis
- Cholestatic Liver Disease – primary biliary cirrhosis and similar disorders resulting in high levels of lipoprotein-X

Elevated Triglycerides Secondary Causes

- Nephrotic Syndrome & Chronic Renal Failure - associated with high total and LDL cholesterol due to increased hepatic production of lipoproteins and diminished lipid catabolism.
- Hypothyroidism – hypercholesterolemia common and hyperlipidemia is very common
- Alcohol abuse – may exacerbate genetic predisposition

Elevated Triglycerides Secondary Causes

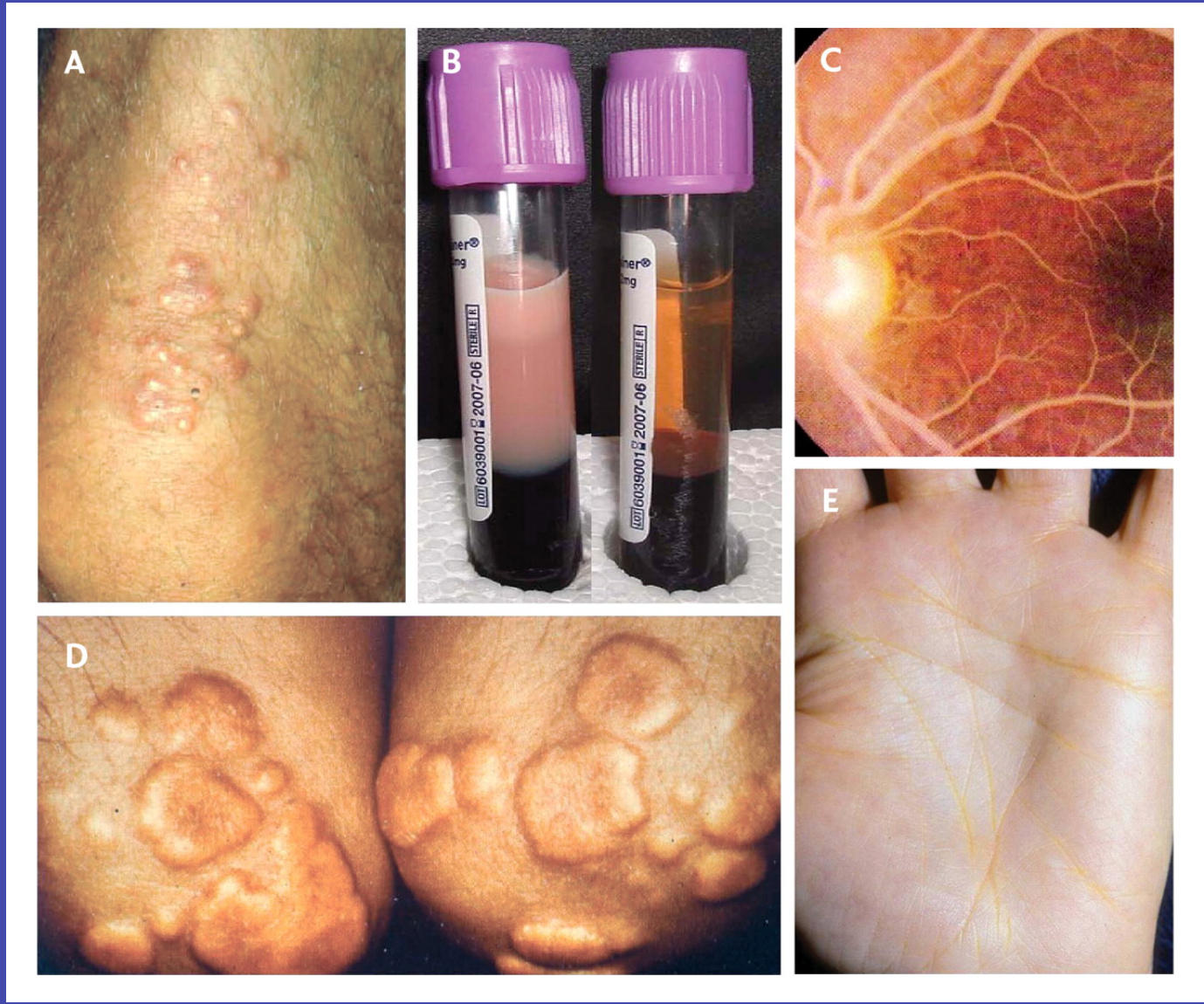
- Medications – Thiazides, beta-blockers – mild to moderate changes, negligible at lower doses, alpha blockers and carvedilol may lower triglycerides, oral estrogens (HRT or OCP) but not transdermal estrogen– modest changes particularly in triglycerides, tamoxifen, protease inhibitors for HIV tend to increase lipids and glucose, immunosuppressive agents – cyclosporine, steroids

Elevated Triglycerides
Genetic Causes

Type IV hyperlipdemia – TGs mainly affected

- Familial Lipoprotein Lipase deficiency
- Familial apo CII deficiency
- Familial hypertriglyceridemia
- Familial Combined Hyperlipidemia
- Dysbetalipoproteinemia

Elevated Triglycerides



Lipid Deposition

Case 1

- Already on modfied Pritikin Diet, obese but active – has peripheral vascular disease. Avoid alcohol
- Discontinue Premarin, preferred switch to transdermal oestrogen despite risks, no change in antihypertensive agents, adjust thyroid medications
- Evaluation – Rule out Diabetes, renal disease,
- Review Triglycerides ?start pharmacotherapy, Ezetamide added due to CVD risk

Case 1

Repeat Labs

- Serum creatinine – 77umol/L Fasting glucose – 5.8mmol/L, 2 hour glucose – 6.1mmol/L, TSH – 2.0 (10.3-26.0), Free T4 – 13.6 (0.3-7.0) IU/mL
- Urinalysis – no proteinuria
- Total cholesterol – 4.05mmo/L, Triglycerides – 6.32mmol/L, HDL- not available, LDL could not be calculated

Case 1

- After completing second lipid profile the patient developed leg and muscle pain, simvastin discontinued and ezetamide continued.
- Gemfibrozil prescribed and patient was to return to have a repeat lipid profile with a view to resuming another statin if LDL remained elevated
- Went overseas on holiday for the summer and has not returned for a follow up appointment…

Case 2

- 63 year old gentleman referred for evaluation of elevated triglycerides
- Type 2 diabetes for over 30 years. Diagnosis made on the basis of a routine insurance medical. No known coronary disease, Hypertensive. Referred for cardiac evaluation
- Reportedly had normal triglycerides previously

Past Medical History

- As above, No known renal disease or eye disease from diabetes

Case 2

Habits

- Denied alcohol use, stopped smoking
- Drinks a lot of natural juices, fruits, Herbal Supplements, exercises more regularly than before

Family History

- Diabetes

Case 2

On examination

- Physical examination was unremarkable except for obesity. No stigmata of a genetic dyslipidemic syndromes

Case 2

Labs –

- HbA1c – 9.9%, Fasting glucose – 8.3mmol/L, creatinine – 68umol/L, Total cholesterol – 7.4mmol/L, triglycerides – 8.66 mmol/L, HDL – 0.8mmol/L, LDL-could not be calculated, TSH – 1.83 IU/L

- Urinalysis – no proteinuria

Case 2

Repeat Labs

- Fasting glucose – 6.3mmol/L,
- Total cholesterol – 9.3mmol/L, Triglycerides – 8.6mmol/L
- Thyroid function normal, no proteinuria

Case 2

- Focus on achieving better glucose targets
- HbA1c requested, finger stick glucose measurements to be reviewed and medications adjusted to achieve better glycemic control.
- Gemfibrozil commenced given level of triglycerides, advised on possible drug interractions

Elevated Triglycerides
To treat or not to treat?

- The evidence for the role of triglycerides in atherosclerosis is indirect and often conflicting.
- Triglycerides are often associated with lower HDL cholesterol and a more atherogenic lipid profile
- Limited evidence to suggest that treatment may lower the cardiovascular risk - Helskinki Heart Study and the VA-HIT trial

Elevated Triglycerides
To treat or not to treat?

- Recommendations on its management are variable and generally depend on how high the triglyceride levels are

Elevated Triglycerides
To treat or not to treat?

How high are the triglyceride levels?

- Normal < 1.7mmol/L
- Borderline high – 1.7-2.2mmol/L
- High - 2.2-5.6mmol/L
- Very high > 5.6mmol/L

Approach to the patient with Elevated Triglycerides

Non-pharmacological Therapy

- Correct underlying disorders
- Weight loss in obese patients
- Aerobic exercise
- Avoid concentrated sugars
- Avoid medications that raise triglycerides
- Control blood glucose
- Avoid alcohol
- Manage other CVD risk factors as appropriate

Approach to the patient with Elevated Triglycerides

Non-pharmacological Therapy

- Lifestyle modification is most apparent in men

Pharmacological Therapy

- At present the number of drug classes (fibrates, niacin, n-3 fatty acids, CETP –inhibitors, ezetimibe, glitazars, etc.) alone or in combination with statins have been considered as treatment options in patients with moderate to severe TG levels.

- For mild to moderate hypertriglyceridemia – statin therapy may be effective, encouraged when global CVD risk is high.

Pharmacological Therapy

- Niacin - 1500 to 2000 mg daily can reduce triglyceride levels by 15 to 25 percent, however after the negative AIM HIGH study and HPS-2 THRIVE trial results niacin has gone out of favour. May have effects on glucose control

- CETP inhibitors and glitazars are still in controversial developments and not available for clinical use.

Pharmacological Therapy

- Fish Oils - n-3 polyunsaturated fatty acids (PUFAs) - Lovaza / Omacor is available with 90% omegal-3 fatty acids and is used only in cases with TG > 5.6mmol/L - reduced triglyceride levels by 45 percent, but raised LDL-C levels by 31 percent
- GI and side effects may limit use
- Fish Oils have failed to show significant CV benefits in high risk subjects

Pharmacological Therapy

- Ezetimibe - inhibits intestinal cholesterol absorption and primarily lowers LDL cholesterol via the Niemann-Pick C1- Like 1 protein. Ezetimibe has slight positive effects in lowering plasma fasting TG (8%) & in combination with statin can reduce cardiovascular events

Approach to the patient with Elevated Triglycerides

Fibrate Therapy

- In patients with high triglycerides, fibrates - either as monotherapy or combined with statins - are consistently associated with reduced risk of cardiovascular events
- Therefore, if the primary goal is to lower TG levels, fibrates (bezafibrate and fenofibrate for monotherapy and combination with statin; gemfibrozil only for monotherapy) now are the preferable drugs

Pharmacological Therapy

- Fibrates - enhance the oxidation of fatty acids in liver and muscle and reduce the rate of hepatic lipogenesis from an increase in Liporotein Lipase activity and a decrease in the apolipoprotein CIII (apo CIII) concentration mediated transcriptionally by peroxisome proliferator activated receptor (PPAR) alpha

Fibrates – Other Effects

- Activate PPAR alpha, which binds to a PPAR alpha response element in conjunction with the retinoid X receptor. Increase in the size of LDL particles
- Increased removal of LDL
- Reduction in the levels of plasminogen activator inhibitor type I

Approach to the patient with Elevated Triglycerides

- Gemfibrozil available in Jamaica.
- Dose range 300 – 600mg BID
- Most likely to produce muscle toxicity as it interacts with medications metabolised by the CYP3A4.
- Combination with fluvastatin or pravachol less likely to produce its effect, less than 10mg of rosuvastatin.

Approach to the patient with Elevated Triglycerides

- Fenofibrate –Available as nanocrystal formulation (145 mg daily taken without regard to meals), as micronized capsules (200 mg daily taken with dinner), or as fenofibric acid (also called choline fenofibrate) 135 mg daily without regard to meals

- Less likely to cause problems from drug interaction - Hopefully will be locally available soon

Approach to the patient with Elevated Triglycerides

- FIELD Study (micronized capsules (200 mg) of patients with type 2 diabetes – non significant reduction in CVD risk but reduced microvascular outcomes

- ACCORD study found that combination treatment with fenofibrate and simvastatin reduced a measure of progression of diabetic retinopathy more than simvastatin alone, but did not reduce the risk of vision loss

Fibrates Toxicity

- Can produce muscle toxicity, an effect that is more pronounced in patients also treated with a statin - mediated by competitive inhibition of CYP3A4 –

- Glucuronidation, which is an important pathway for renal excretion of lipophilic statins, appears to be significantly inhibited by gemfibrozil but not fenofibrate

Fibrate Side Effects

- Interfere with metabolism of warfarin - warfarin dose should be reduced by 30 percent when fibrate started

- May increase creatinine levels -but from FIELD Trial increased creatinine with Fenofibrate is reversable and the drug may limit renal damage and protein excretion

Approach to the patient with Elevated Triglycerides

Pharmacologic Therapy

- Plasma exchange may be used in patients with very high triglycerides

- Case reports on the use of Orlistat in patients refractory to treatment.

Approach to the patient with Elevated Triglycerides

- United States National Cholesterol Education Program (NCEP) to initiate treatment to prevent pancreatitis when triglyceride levels >500 mg/dL (5.6 mmol/L)
- The American College of Cardiology/American Heart Association (ACC/AHA) guidelines focus on statin therapy - to work on elevated triglycerides in future guidelines
- The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) - Pharmacologic therapy with high CVD risk and triglycerides > 200 mg/dL (2.3 mmol/L).

Summary

Management Approach to Hypertriglyceridemia†

Review medications

- Change to lipid neutral or favorable agents when possible (eg. alpha blockers, biguanides, thiazolidinedione)
- Lower doses of drugs that increase triglycerides such as beta blockers (particulary nonselective agents), glucocorticoids, diuretics (thiazide and loop), ticlopidine, estrogens when indicated clinically.

Laboratory studies

- Exclude secondary disorders of lipid metabolism
- Fasting blood glucose
- Serum creatine
- Thyroid function studies

Diet

- Weight loss
- Avoid concentrated sugars
- Increase omega-3 fatty acid intake through fish consumption.
- Exercise
- Aerobic exercise minimum of 3 hours weekly

†Hypertriglyceridemia is defined as a serum triglyceride concentration above 200 mg/dL (2.3 mmol/L).
Data from Rosenson, RS, Contemporary Treatments in Cardiovascular Disease. 1998.

Summary Pharmacotherapy

- Statin therapy to therapy directed at lowering triglyceride levels in patients with mild to moderate hypertriglyceridemia.

- In patients with very high triglyceride levels (>500 mg/dL [5.7 mmol/L]), fibrates and/or fish oil are preferable & after the triglyceride levels have been lowered from very high levels, a statin may be added to fenofibrate or fish oil if global risk elevated.