

Hypertriglyceridemia

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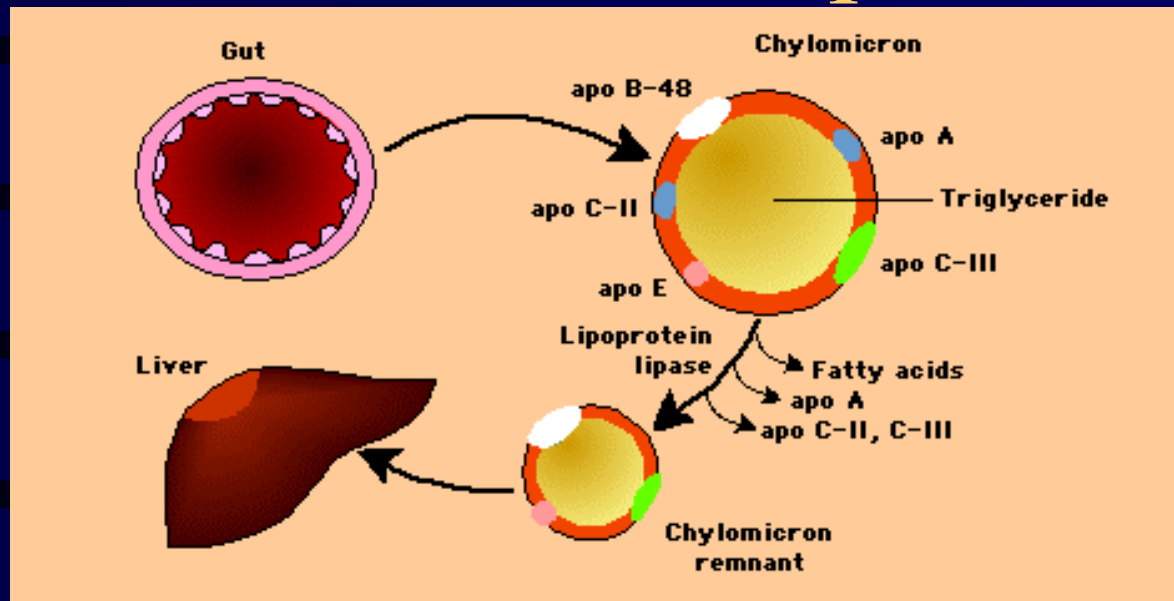
Resident's Report

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Review of Lipids

- Chylomicrons (CM):
 - Dietary lipids absorbed through the GI tract are assembled intracellularly into CM.
- Very Low Density Lipoprotein (VLDL):
 - Filled with endogenous triglycerides (TG) and some cholesterol.

Review of Lipids



Exogenous pathway of lipid metabolism In the intestinal cell, absorbed free fatty acids combine with glycerol to form triglycerides, and, to a lesser degree, absorbed cholesterol is esterified to form cholesteryl esters. These lipids are assembled as chylomicrons; the main apolipoprotein (apo) is B-48, but apo C-II and E are acquired as the chylomicrons enter the circulation. Apo C-II is a cofactor for lipoprotein lipase which makes the chylomicrons progressively smaller in part by hydrolyzing the core triglycerides and releasing free fatty acids. The chylomicron remnants that are cleared from the circulation by hepatic chylomicron remnant receptors for which apo E is a high-affinity ligand.

Review of Lipids

- Intermediate Density Lipoprotein (IDL):
 - Carries cholesterol esters and triglycerides
- Low Density Lipoprotein (LDL):
 - Mostly cholesterol esters and Apo B-100.
- High Density Lipoprotein (HDL):
 - Cholesterol esters.
 - Antiatherogenic because it removes excess cholesterol in cells and plaques.

Review of Lipids

- Apolipoproteins:
 - Have major effects on lipid handling.
 - These are the protein components of Lipoproteins.
 - They serve as cofactors for enzymes and ligands for receptors.

Review of Lipids

- A-I Structural protein for HDL, activates Lecithin-Cholesterol Acyltransferase (LCAT).
- A-II Also in HDL, it activates hepatic Lipase.
- A-IV Activates Lipoprotein Lipase (LPL) and LCAT.

Review of Lipids

- B-100 In VLDL, IDL, LDL, and Lp(a)
 - It is the ligand for the LDL receptor and is required for the assembly and secretion of VLDL.
- B-48 48% of B-100

Review of Lipids

- C-I Activates LCAT
- C-II Essential cofactor for LPL
- C-III Inhibits Apo-E, LPL, and hepatic Lipase.

Review of Lipids

- E Ligand for hepatic CM , VLDL, and LDL receptors, leading to plasma clearance of those lipoproteins.
 - Apo E2 is associated with Familial Dysbetalipoproteinemia (due to less efficient clearance of VLDL and CM).
 - Apo E4 carries increased risk of hypercholesterolemia and CHD.

Review of Lipids

- Apo(a) Found on Lp(a), it inhibits plasminogen activation on Lp(a).
- Lp(a) A specialized form of LDL, it is a combination of Apo(a) and LDL that is formed extracellularly.
 - Contains 5 “kringle” domains.

Review of Lipids

- Lp(a) (cont'd):
 - The 4th kringle domain is homologous with the fibrin-binding domain of plasminogen.
 - This impairs plasminogen activation, leading to decreased thrombolysis.

Diagnosis

- Usually made after an overnight fast.
- The label, “hypertriglyceridemia” is made when levels are greater than the 90-95th percentile.
- Normal Levels: <150 mg/dL
- Borderline: 150 - 199 mg/dL
- High: 200 - 499 mg/dL

Diagnosis

- Very High: ≥ 500 mg/dl
 - At this level, the plasma is cloudy/creamy, reflecting the Chylomicronemia.
- Can be due to elevations in VLDL, VLDL + (CM), or *rarely* CM.
- The high levels of TG in the blood cause an increase in hepatic synthesis of VLDL.

What Is It?

- Serum TG concentrations reflect the amount of triglycerides in Chylomicrons, VLDL, β -VLDL, and IDL.
- Since CM and VLDL have little cholesterol within them, they do not raise the overall level of serum cholesterol
- On the other hand, small VLDL, β -VLDL, and IDL are enriched with...

What Is It?

- ...cholesterol, thereby increasing the total serum cholesterol.
- CM's/VLDL's are not as atherogenic, yet can cause pancreatitis.
 - If associated with severe DKA, it has a worse prognosis.

Classifications

- Acquired:
 - Obesity
 - Hypothyroidism
 - Diabetes Mellitus II
 - Nephrotic Syndrome
 - Estrogen/Tamoxifen, Steroids
 - EtOH, β -Blockers, Cyclosporine

Classifications

FREDERICKSON PHENOTYPE	LP ABNORMALITY	LIPID LEVELS
I	CM	TG >99%
IIa	LDL	TC >90; +/- TG and/or ApoB >90
IIb	LDL and VLDL	TC and/or TG >90% and Apo B >90%
III	VLDL and CM Remnants	TC and TG > 90%
IV	VLDL	TC >90%; +/- TG >90% or low HDL
V	CM and VLDL	TG >99%

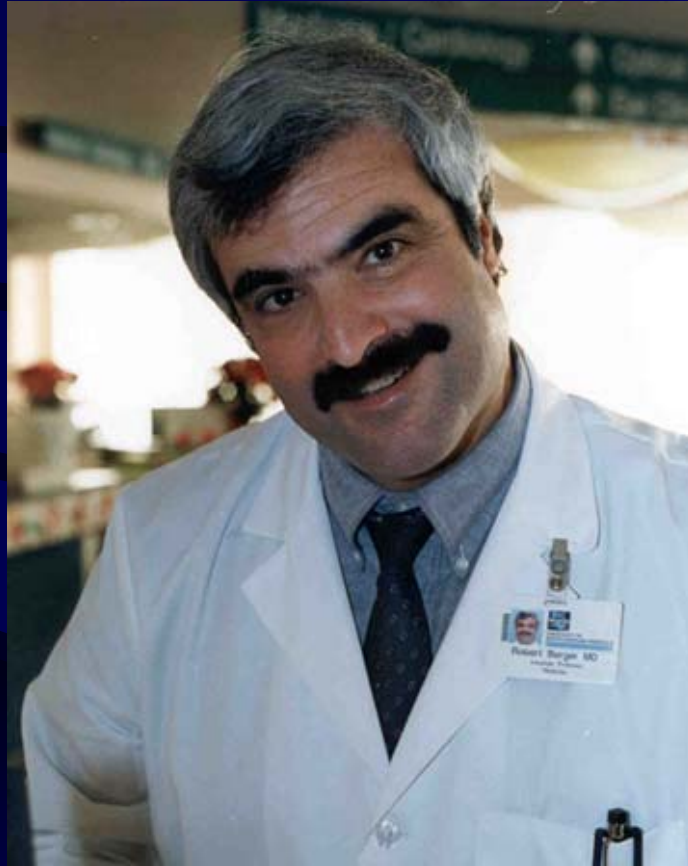
Classifications

- Mixed Hypertriglyceridemia:
 - a.k.a. type V of the Frederickson classification, triglyceride levels are above the 99th percentile.
 - Patients have hepatosplenomegaly and eruptive xanthomas.
 - It is usually secondary to some other dyslipidemia that is exacerbated by the aforementioned acquired forms.

Classification

- Mixed Hypertriglyceridemia (cont'd)
 - An excess formation of Chylomicrons can lead to the “Chylomicronemia Syndrome”
 - S/Sx's include recent memory loss, abdominal pain and/or pancreatitis, dyspnea, eruptive xanthoma, flushing with alcohol, and lipemia retinalis.
 - The supernatant is extra creamy. Yummy!

Xanthomas



Xanthomas



Xanthomas



Classifications

- Familial Lipoprotein Lipase Deficiency:
 - Can have Type I, IV phenotype.
 - Chylomicrons are elevated with a milky supernatant.
 - Very similar to...
- Familial apo CII Deficiency

Classifications

- Familial Hypertriglyceridemia:
 - a.k.a. Type IV, it is autosomal dominant with modest TG elevations.
 - An inactivating LPL gene mutation is found in patients, raising TG levels 20% - 80%.
 - Accompanied by insulin resistance, hyperuricemia, HTN, and obesity.

Treatment

- Fibrates: Preferred treatment.
 - Increases LPL, TG, and LDL hydrolysis
 - Tends to cause hepatic dysfunction.
- Statins: Can be used to control both the LDL as well as the triglycerides.
 - Decreases TC synthesis and upregulates LDL receptors

Treatment

- Niacin: Used as an adjunct with statins.
 - Decreases VLDL and LDL synthesis by unknown mechanism(s).
 - Flushing, hepatic dysfunction, tachycardia, pruritus, nausea, diarrhea, glucose intolerance.
- Bile Sequestrants: Should be AVOIDED...

Treatment

- Bile Sequestrants (cont'd):
 - ...until the triglycerides have normalized since they can increase VLDL synthesis and make the triglyceridemia worse.
 - Increases synthesis of bile from cholesterol and upregulates LDL receptors.
 - Causes constipation and gastric discomfort.

Treatment

- Fish Oil: Sure, why not. Used in refractory cases.
- Orlistat: Ditto above. When you are running out of options.

Treatment

- Of course, modification of lifestyle is VERY important:
 - Losing weight, Smoking cessation
 - Glucose Control, EtOH
 - Stopping medications which may be exacerbating hyperlipidemia:
 - Thiazides, β -Blockers, Estrogens.

Sources That Were Plagiarized

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