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Biochemistry, Chylomicron

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Introduction

Triglycerides (TG) and cholesterol esters are insoluble in plasma, and, to be transported to tissues where they are needed, such as muscle and adipose tissue, they must get packaged as lipoprotein particles. Lipoprotein particles comprise a core of TG and cholesteryl ester and a coat comprising phospholipid, free cholesterol, and apolipoproteins.[1][2] There are four major lipoprotein particles: chylomicrons (CMs), very low-density lipoprotein (VLDL), LDL (low-density lipoprotein), and high-density lipoprotein (HDL).

This short review will focus on the primary TG carrying particles, chylomicrons, and discuss relevant biochemistry, metabolism, and clinical syndromes pertaining specifically to chylomicrons.

Chylomicrons are large triglyceride-rich lipoproteins produced in enterocytes from dietary lipids—namely, fatty acids, and cholesterol. Chylomicrons are composed of a main central lipid core that consists primarily of triglycerides, however like other lipoproteins, they carry esterified cholesterol and phospholipids.

The backbone structural protein is the truncated apolipoprotein B-48, which is the main non-exchangeable protein. However, it does contain other apolipoproteins, including ApoA1, A2, A3, A5 C2, C3, and ApoE.[2] Chylomicrons have a density below 0.94 g/ml and remain at the origin of lipoprotein electrophoresis.[1] Their major lipid is triglycerides, which comprise more than 75% of the particle, and they have the lowest protein content of all lipoproteins of around 2 percent, explaining why they have such low density on ultracentrifugation.

Issues of Concern

Chylomicronemia can be due to genetic causes (Type 1) or both genetic and secondary factors (Type 5) such as in adults. The most significant risk is for pancreatitis. Novel therapies such inhibition of apoCIII could greatly improve the treatment of familial chylomicronemia syndrome in the future.

Cellular Level

Apolipoproteins:

Apolipoproteins are instrumental in the synthesis and metabolism of chylomicrons.

Apolipoprotein B-48 is vital for chylomicron synthesis, assembly, and secretion into the lymphatics via lacteals into the systemic circulation.[2] It is only attached to particles originating from the small intestine, in response to the dietary fat that transports through chylomicrons. There is one apoB-48 protein per chylomicron particle. The lipidation of apoB-48 in enterocytes undergoes mediation via microsomal triglyceride transfer protein (MTP).[2]

Apolipoprotein C-II is another component that both VLDL and chylomicrons acquire from HDLs. ApoC-II plays a significant role in the metabolism of triglycerides since it is a cofactor for the pivotal enzyme in TG metabolism,

lipoprotein lipase (LPL).[3]

LPL which, is attached to endothelium following synthesis by various cells, cleaves of fatty acids form TG for energy utilization or storage. Lipase maturation factor1 (LMF1) plays a key role in the stabilization of LPL and the movement of LPL to the endothelial surface. Glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (GPIHBP1) serves to anchor the LPL to the endothelium. This protein plays a crucial role in transporting LPL from the subendothelial spaces to the capillary lumen to execute its vital function. A mutation in this protein like with LMF1, can lead to hyperchylomicronemia. ApoA5 plays a role in the activation of LPL and promoting TG lipolysis and mutations in this protein can also result in familial hyperchylomicronemia. ApoC-III inhibits LPL activity. Hence LPL and its modulators are pivotal in the metabolism of chylomicrons.

Apolipoprotein E is another component derived from HDL that facilitates the clearance of chylomicron remnants by the liver.

While ApoAs are present in chylomicrons, their roles are not well defined in chylomicron metabolism, except for apo -A5, which activates LPL.

Metabolism

Chylomicrons exit the enterocyte via the lacteals into the systemic circulation. Here they are acted on by LPL with its cofactor Apo-CII, which cleaves off FA moieties, which in muscle and adipose tissue are immediately mobilized for energy or stored for future use. In addition to Apo-CII, other important modulators of LPL include apoA5, LMF1, GPIHBP1 as reviewed above.

The removal of triglycerides from chylomicrons in the peripheral tissues results in the formation of chylomicron remnants. The remnants are smaller particles that are mainly composed of cholesterol and are taken up by the liver via the Remnant and LDL receptors by recognition of ApoE.[2]

Monogenic familial chylomicronemia syndrome is sporadic and arises from homozygous or compound heterozygote mutations in LPL and/or other modulators including, but not limited to: ApoA5, LMFI, GPIHBP1and ApoC2 These rare disorders are discussed briefly later in the review. Familial chylomicronemia syndrome refers to chylomicronemia plus one of the following clinical features: eruptive xanthoma, pancreatitis, and hepatosplenomegaly or lipemia retinalis.[4]

Testing

Familial chylomicronemia syndrome presents with fasting triglycerides above 1000 mg/dL generally over 2000 mg/dl in the blood. Notably, the “refrigerator test” is performed to diagnose the elevated chylomicron levels in the blood; this method involves evaluating serum samples one day following overnight storage in the refrigerator: if the serum has a creamy supernatant only, then the patient has chylomicronemia (Type 1 hyperlipidemia).[5] If the infranatant is turbid (lactescent) also then there is an increase in VLDL also like in Type 5 hyperlipidemia which has both increased VLDL and chylomicrons.

The elevated circulating triglycerides in the blood can pose a risk to the pancreas and cause acute pancreatitis, along with their deposition in both the liver and spleen, causing hepatosplenomegaly. It is also recommended to evaluate the total cholesterol at the time of the highest triglyceride level along with the ratio of the triglyceride to total cholesterol. TG/TC ratio elevation is with circulating chylomicrons and VLDL. The TG/TC ratio exceeds 5.0 with type1 and types 5 hyperlipidemia.

For patients suffering from symptoms of acute pancreatitis, a computerized tomography (CT) scan of the abdomen should be done to confirm the diagnosis and severity of the condition, along with the serum lipase and amylase levels which present as elevated.

Rarely, patients with autoimmune diseases, such as SLE, can make autoantibodies to LPL, resulting in severe chylomicronemia, which should be kept in mind when dealing with adult patients, especially.[6]

Clinical Significance

Chylomicronemia syndrome defined as a plasma TG greater than 1000 mg/dl,[6] and can be genetic or acquired. Familial chylomicronemia syndrome is a rarely seen autosomal recessive disorder known to result from mutations in lipoprotein lipase and its modulators including apoA5, LMPI, GPIHBP1and Apo-CII. The acquired variety usually present in adults as Type 5 hyperlipidemia.[7] Type 5 hyperlipidemia is polygenic and in addition to familial hypertriglyceridemia, familial combined hyperlipidemia, and other rarer disorders such as dysbetalipoproteinemia (Type 3), there are secondary factors, such as obesity, diabetes mellitus, excess alcohol intake, steroids, retinoids, oral estrogen, thiazides, bile acid sequestrants and protease inhibitors that result in chylomicronemia. These adult patients carry an increased risk for ASCVD. In addition to chylomicrons, they have elevated VLDL levels in Type 5 hyperlipidemia.

Although familial chylomicronemia syndrome is a rare inherited hyperlipoproteinemia, it poses a burden on those that it affects. The commonest cause is LPL deficiency, which can present in infancy and childhood. It may result in the presence of recurrent abdominal pain, acute pancreatitis, and hepatosplenomegaly. While the prevalence of the disease is unknown, there is an estimate of 1 to 2 individuals in every million who are diagnosed, with potentially more who are undiagnosed. [8] Proper screening via lipid panels, which can identify individuals with triglyceride levels of over 1000mg/dL, along with evaluating the electronic medical record for the possible history of pancreatitis, are both crucial for diagnosing and treating familial chylomicronemia syndrome.

Signs and Symptoms

The high circulating levels of chylomicrons can accumulate in tissues and organs such as the liver and spleen (resulting in organomegaly), skin (eruptive xanthomas), retinal blood vessels (lipemia retinalis). The most sinister complication is acute pancreatitis. Patients with Type 5 can also have sensory neuropathy and memory loss.[7]

Treatment

Unfortunately, the traditional triglyceride-lowering agents, including fibrates, niacin, statins, and fish oil, are not effective in the treatment of Type1-familial chylomicronemia syndrome. However, management for familial chylomicronemia syndrome patients is with severely restricted low-fat diets of less than 15% of the calories (20g/day) coming from fat, medium-chain triglycerides, and alcohol avoidance.[9] Some therapies currently in development include LPL Gene therapy, lomitapide (an inhibitor of MTP), and RNA interference of apoCIII, the latter of which is considered the most promising of these new potential treatments.[10]

For patients with adult chylomicronemia, weight loss, fibrates, fish oil (2 to 4g/d), niacin and avoidance of secondary factors are used to control the HTG.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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