

Understanding atherosclerosis necessitates knowledge of various lipids, including how they are synthesized and transported in lipoproteins. Understanding lipoproteins requires a review of their synthesis, their catabolism, their ability to be influenced by other metabolites (such as glucose, reactive oxygen species, etc.), their lipid and surface composition and especially their kinetics or how they interact with each other and the arterial wall. Understanding lipoproteins also requires a realization that there is a constant, continually on-going dynamic flow of particles and lipid interchange between particles: ie. lipids and lipoproteins are in constant flux. The more we understand this, the more we can begin to understand the etiology of atherogenesis and the far better we can understand how to influence lipoprotein pathobiology using lifestyle and pharmacological methods. Of prime importance is totally understanding what laboratory tests best help us understand lipoprotein structure, composition and kinetics.

This week I thought I would discuss the chylomicron. The enterocytes of the small intestine is where absorption of lipids (cholesterol and noncholesterol sterols, fatty acids) occurs. Once in the hepatocyte the lipids are either re-excreted back to the intestinal lumen (especially noncholesterol sterols) via the ABCG5 and G8 transporters to be prepared for systemic use. Without these "efflux sterol pumps" the body would accumulate noncholesterol sterols (dozens exist, from plant, yeast and shellfish sources). Such massive accumulation sterols cause premature atherosclerosis (phytosterolemia previously termed sitosterolemia).

The enterocyte takes the absorbed free cholesterol and esterifies it using ACAT (acyl-CoA cholesterol acyl transferase) creating cholesteryl ester. This joins with intestinally synthesized triglycerides (from fatty acids & glycerol). The enterocyte synthesizes apolipoprotein B48. Facilitated by microsomal triglyceride transfer protein, the TG and cholesteryl ester join to apoB48 creating a chylomicron particle. Note that the apoB created in the liver is termed apoB100. The intestinal apoB is a truncated version having 48% of the molecular weight of apoB100. ApoB48 cannot bind to LDL receptors as can apoB100. The apoB48 provides structural stability and solubility to the chylomicron. Chylomicrons are in the family of betalipoproteins. ApoA molecules are also synthesized in the enterocyte and attached to the particle. ApoA of course is destined to become part of an HDL particle.

Chylomicrons are extremely large and buoyant (98% fat) lipoproteins whose purpose is to transfer fatty acids, into the form of TG to the body. Of course as they leave the intestine chylomicrons also carry phospholipids, apoA (I and IV), cholesteryl ester and at times noncholesterol esters. The TG/Cholesterol ratio is 10 or greater. Chylomicrons are secreted into the lymphatic circulation via intestinal lacteals. There is a short journey to the thoracic duct and entry into the venous circulation before entering the arterial system on their journey to the liver. Once in the lymph and plasma chylomicrons receive other apolipoproteins mostly from HDL particles notably apoE, CI, CII and CIII. These apoproteins are critical to effective catabolism (lipolysis) of the particle.

Once the chylomicron enters the arterial system the surface apoCII binds to lipoprotein lipase (LPL). Hydrolysis of TG (lipolysis) occurs. The TG become free fatty acids (FFA) used for energy or stored in adipocytes (as resynthesized TG). As TG leave the chylomicron, the very large lipoprotein particle shrinks and is termed a chylomicron remnant.

Hepatocytes have various ligands (hepatic lipase, heparan sulfate proteoglycans) and apoE receptors which fixate the remnants and facilitate its endocytosis and lipolysis). The half-life of a chylomicron is typically several minutes.

Patients who lack apoCII cannot catabolize chylomicrons and have massive hypertriglyceridemia with levels of several thousand. This is the very rare Fredrickson Type I Familial Hyperlipidemia. Other than fat restriction there is no treatment. The massive chylomicronemia is not associated with CHD as the particles are much too large to penetrate the arterial intima.

Insulin resistant states (metabolic syndrome and Type 2 diabetes) can be associated with chylomicronemia. Such patients lack the proper amounts of hepatic receptors and ligands that fixate and internalize chylomicrons. The half life of the chylomicron remnant becomes several hours. Chylomicron remnants are often small enough to enter the arterial intima via Scavenger A and CD 36 receptors. Such

chylomicrons are in effect atherogenic betalipoproteins (carrying cholesterol) and contribute to atherosclerosis so prevalent in such patients.

Patients with elevations of chylomicrons have elevated apoB levels, elevated TG levels, elevated postprandial TG levels and elevated non HDL-C levels. Chylomicron remnants show up as VLDL particles on NMR. You see such patients everyday in your practice. If one discards postprandial TG levels and has patients return fasting, the remnants will be gone. So please never discount postprandial TG elevations.

Therapeutic Actions to reduce chylomicrons: Simple: Diet and exercise. If not dealing with Type I: fibrates first, and niacin second are the main drugs.

References of the Week

1) Associations Between Baseline Risk Factors and Vertebral Fracture Risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study: J Bone Miner Res 2004;19:764 –772.

In the univariate analysis, significant interactions were observed between raloxifene treatment and age (p 0.04), **serum triglycerides** (p 0.03), LS BMD (p 0.08), and diabetes mellitus p 0.04). In the multivariate analysis, the effectiveness of raloxifene was independent of almost all risk factors, with the exception of baseline serum triglyceride level and LS BMD, suggesting an increased efficacy of raloxifene in patients with increased triglyceride levels (p 0.06) and lower LS BMD values (p 0.008) at baseline. These data suggest that the efficacy of raloxifene in reducing vertebral fractures is largely independent of the presence of clinical risk factors for osteoporotic fractures.

2) Effect of the Combination of Methyltestosterone and Esterified Estrogens Compared with Esterified Estrogens Alone on Apolipoprotein CIII and Other Apolipoproteins in Very Low Density, Low Density, and High Density Lipoproteins in Surgically Postmenopausal (J Clin Endocrinol Metab 89: 2207–2213, 2004)

In conclusion, methyltestosterone, when administered to surgically postmenopausal women taking esterified estrogen, has a selective effect to reduce the apoCIII concentration in VLDL and LDL, a predictor of CHD. Methyltestosterone may lower plasma triglycerides through a reduction in apoCIII.

3) Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults A Prospective Study of Parents and Offspring JAMA. 2004;291:2204-2211

Conclusions Using validated events, we found that parental cardiovascular disease independently predicted future offspring events in middle-aged adults. Addition of parental information may help clinicians and patients with primary prevention of cardiovascular disease.

NEWS ITEM OF THE WEEK Good news for Metformin users and patients

Metformin HI (Glucophage) and Metformin HI Extended Release (Glucophage XR) Tablets Not Associated With Lactic Acidosis

The FDA approved a revision on March 19 to the warnings section of labeling for metformin HI (Glucophage), and metformin HI extended release tablets (Glucophage XR), both of which are made by Bristol-Myers Squibb, to reflect that there were no reports of lactic acidosis during more than 20,000 patient-years of exposure to metformin in clinical trials.

DAYSRING TRAVELS

Mountain Lakes, NJ

Dallas - Fort Worth and Tyler TX (last week May)

Kansas City AFP Annual Meeting June 3

San Francisco, Walnut Creek, Pleasanton, Fresno, Sacramento

Morristown, Edgewater and Clinton NJ

Bridgeport, CT

Manhattan

Greensboro, NC

We will return to lipid cases next week. Prayers and blessings for our troops.

Happy Lipiding,

Tom

Thomas Dayspring MD

North Jersey Institute of Menopausal Lipidology

516 Hamburg Turnpike

Wayne, NJ 07470

Tele: 973-790-8604

Fax: 973-790-1488