HDLs: Do we have a clue?? The following on-going discussion on HDL complexities was prepared for the National Lipid Association web site (www.lipid.org click on blogs or groups). I want to challenge some long upheld beliefs about high density lipoproteins. In reality, we still are pretty clueless on how they function, how they are related to atherosclerosis and what if anything we have to do to them therapeutically to reduce clinical atherothrombotic events.

A recent on line prepublication article in Atherosclerosis called HDL Biogenesis: Quality and Quantity [Atherosclerosis (2009), doi:10.1016/j.atherosclerosis.2009.05.034] is great reading The authors state: "While reviewing the literature, it also becomes clear that despite the vast amount of existing knowledge on HDL, more studies are needed to determine the interrelation of the atheroprotective properties of HDL to each other, as well as their individual significance and contribution towards the prevention of atherosclerosis and CHD. Furthermore, the development of laboratory tests that will provide an easy, reproducible and accurate quantization of all antiatherogenic properties of HDL may provide a more precise assessment of cardiovascular risk in the future."

Being the son of a fireman I like to compare HDL particles to fire engines. Normally, when a fire apparatus shows up at a house afire, the firefighters use axes, hoses, extinguishers, and water in the booster tank to combat the fire. Theoretically HDLs are thought to have cardioprotective properties and atherosclerosis is a disease where the arterial wall is on fire. The HDL must not only be capable of inducing macrophage RCT (delipidation of arterial wall sterol-laden macrophages called foam cells) but release several cardioprotective proteins they carry (traffic) which possess antithrombotic, profibrinolytic, antioxidative, anti-inflammatory proteins as well as others that induce NO, and suppress ICAMs and selectins. So if an HDL that shows up in plaque and it lacks those proteins or has lost its the ability to attach to and delipidate foam cells that is sort of like a fire engine showing up at a fire scene and realizing that they forgot the hoses and water! I'd call that a pretty useless fire engine and I likewise call that a pretty useless HDL particle. A better scientific term would be dysfunctional or even proatherogenic HDL. Just like looking at a fire engine speeding down the street does not tell you if it is fully equipped, a serum HDL-C has no relationship at all to the functionality of the HDL particle. I think of you read the authors conclusion above it appears they are saying HDL-P is far more important than HDL-C.

Let's take a close look at HDL-C – an everyday measurement – however few realize it is the least accurate of standard lipid measurements. In the best large labs, never mind physician office labs its accuracy is plus or minus 10%. So in reality an HDL-C level of 40 is actually somewhere between 36 and 44 mg/dL. One is a risk factor, one is normal and a man with a 44 is typically told he is in good shape. HDL-C is defined as the cholesterol trafficked in all of the HDL particles in a deciliter (dL) of plasma. HDL-P is the number of alpha HDLs per liter of plasma. HDL-P does not include the unlipidated apoA-I or prebeta HDL species (usually less than 5% of total HDL-P). Just like LDL geometrics it takes less numbers of large HDLs to traffic a given amount of cholesterol than small HDLs (volume of a spherical particle is a third power of the radius). As HDL-C rises from 20 to 40 mg/dL there is a tremendous increase in total HDL-P, with almost all being small particles. As the HDL-C goes from 40-80 mg/dL there is very little additional increase in HDL-P, but rather disappearance of small HDLs and appearance of large HDL particles. About 80% of the total HDL-C is trafficked in the large HDL species. Thus a rise in HDL-C > 40 is occurring because the particles are maturing, not increasing in number. If

HDL-P is the more important factor related to CHD risk, then seemingly there is little benefit raising HDL-C beyond 40 mg/dL. Indeed in TNT trial, high risk patients with LDL-C less than 70 on a statin had significant residual risk if the HDL-C was < 40 mg, but that risk disappeared at an HDL-C of 42 and was identical at much higher HDL-C levels. If raising HDL-C was important, risk should have continued to drop as the HDL-C went higher and higher. It did not.

HDL Lipidation: If HDL particles fill up (lipidate) with cholesterol they have to get it somewhere. The basic HDL structural protein or apolipoprotein A-I (apoA-I) is a helical protein with stereospecific surface charges that make it a powerful acceptor of cholesterol. Thus HDLs will accept cholesterol from any cell that is willing to export it to the apoA-I protein. All cells need cholesterol, mostly for cell membranes but for specific functions in certain cells (steroid, bile acid production, etc.). Any extra accumulation of cholesterol causes it to potentially crystallize and become toxic to the cell. Thus cells must get rid of unneeded cholesterol. Some of this excess can simply diffuse through cell membranes into larger HDL species. This is a minor way HDLs acquire cholesterol. Cells can also upregulate sterol exporter proteins belonging to the ABC (ATP Binding Cassette) family of membrane transporters, specifically ABCA1. In an energy driven process cholesterol is transferred through ABCA1into unlipidated apoA-I, very small prebeta HDL species or the very, very small alpha HDL species. Large HDL species do not bind to ABCA1. As the free cholesterol is esterified, changing to the very hydrophobic cholesteryl ester, it seeks the core of the HDL and the HDL particles become spherical and larger. Scavenger receptors B1 (SR-B1) are a bidirectional membrane proteins than can facilitate cholesteryl ester entry into cells from delipidation of large HDL species or they can also export cholesteryl ester from cells, especially arterial wall sterol-laden macrophages, to large HDL species. Finally the ABCG4 transporter (also found in arterial macrophages) can export sterols, including oxysterols to large HDL species. Via any or all of the above mechanisms smaller HDLs acquire cholesterol or cholesteryl ester and become large mature HDL species. Amazingly the makeup of the HDL cholesterol content is:

~30% enterocyte origin

~60-70 % hepatocyte origin

~ 5-10% peripheral origin

Amount delipidated from sterol laden macrophages (macrophage RCT): very little

In other words the amount of cholesterol HDLs pull out of arteries, although crucial to arterial health, has no clinical effect on serum HDL-C levels. The amount of cholesterol that exists in arterial plaque is a miniscule percentage of total body cholesterol. Thus nothing an HDL does to plaque has any influence on HDL-C. When clinicians look at HDL-C they are basically looking at hepatic and enterocyte derived cholesterol.

Next blog will look at HDL mediated forward and reverse cholesterol transport.