QUALITY AS WELL AS QUANTITY IN HDL-C. INTRODUCING: THE ATHEROSCLEROTIC KITCHEN SINK AND THE ATHEROSCLEROTIC RISK EQUATION

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Most primary care clinicians are aware of the quantity risk of low high density lipoprotein cholesterol (HDL-C), whether it is isolated low HDL-C, low HDL-C, high total cholesterol/HDL-C ratio, or an elevated non-HDL-C. However, the quality of HDL-C is rapidly emerging. The anti-atherosclerotic roles of reverse cholesterol transport and the pleiotropic anti-oxidant-anti-inflammatory mechanistic effects of HDL-C are undergoing rapid exponential growth (Table 1 and Figure 1).

In 1977 the Tromso Heart Study demonstrated that coronary artery disease (CAD) patients have HDL-C levels 35% lower than controls and those patients with low HDL-C are three times more likely to develop CAD than those with elevated LDL-C. These early views certainly support the concept that low HDL-C is a common antecedent of clinical coronary heart disease (CHD), as well as being important in accelerating the progression of atherosclerosis.

The inverse relation of HDL-C to CHD events has been widely discussed since the original publication of data from the Framingham study in 1986. Castelli and colleagues were able to show an inverse association of high HDL-C and low coronary risk was as statically as strong as the direct association of high LDL-C and high coronary risk in a cohort of men and women age 40-82 followed for 12 years who were free from CAD at study entry.

At Any Level of Cholesterol Low HDL-C Increases the Rate of CHD

The NCEP ATP III guidelines clearly define a level < 40 mg/dL as an independent risk factor for CHD. Raising HDL-C is not a target for either primary or secondary prevention at this time; however, its importance as a tertiary target is rapidly emerging.

Michael Miller has stated: “Low HDL-C is the most common lipoprotein abnormality in patients with CHD and is predictive of CHD events, even when total cholesterol levels are normal.” NHANES data has shown that 1 out of 3 males and 1 out of 6 females have low HDL-C in the U.S. (these figures would be even higher in the postmenopausal female). With the emerging epidemic of obesity – diabesity, metabolic syndrome (47 million strong and growing), prediabetes, and overt type 2 diabetes mellitus we can expect to see even a larger percentage of patients with low HDL-C.

While we have many available therapeutic medications at our disposal, the treatment of low HDL-C can often be a daunting experience for both the patient and the clinician (Table 2). The metabolic syndrome and type 2 diabetes mellitus frequently require combination therapy to get HDL-C to the normal range and bring the secondary treatment goal of non-HDL-C to NCEP ATP guideline goals. Even so, this time-consuming team effort approach in global risk reduction is well worth the effort.

There exists a “sink” of atherogenic beta lipoproteins (non-HDL-C, modified LDL-C, VLDL-C, and atherogenic remnant lipoproteins) within the intima of the arterial vessel wall (AVW). This sink may be referred to as the Atherogenic Kitchen Sink (Figure 2) and recently a simple equation has been proposed by the author, which incorporates the following:

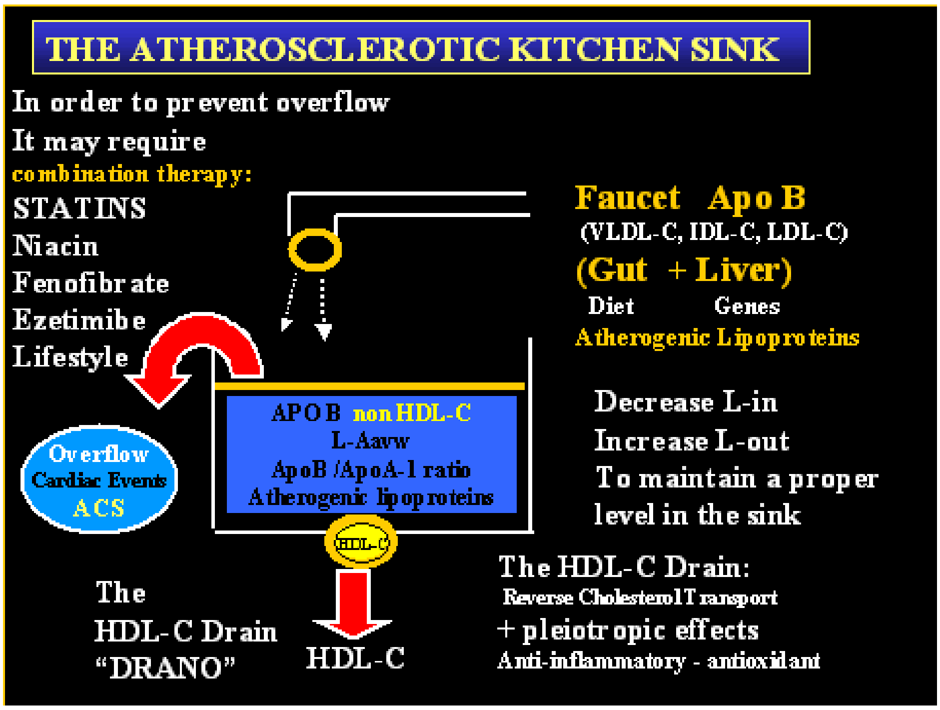

Figure 2. Atherogenic Kitchen Sink

Lipoprotein Accumulation (retention) in the arterial vessel wall = Lipoproteins in minus lipoproteins out.

Atherosclerotic Risk Equation

LAr = L(in) – L(out)

L(in), or the faucet, would represent the net accumulation of beta lipoproteins and L(out) would represent the antiatherosclerotic alpha lipoproteins, which could be directly applied to the lipoprotein profile currently in use. This would represent the total cholesterol – HDL-C ratio and the newer atherogenic (apoB)/antiatherogenic (apoA-1) ratio used in the INTERHEART study as well. The atherogenic lipoprotein ratio ApoB/ApoA-1 was found to be the best predictor of CHD (odds ratio of 3.25 for the top verses the lowest quintile) as compared to the other eight risk factors.

L(in), would be comparable to the faucet (GI tract and liver) delivering the atherogenic apoB lipoproteins, while the kitchen sink would represent the accumulation of atherogenic lipoproteins within the arterial vessel wall or LAr. In a like manner, the drain would represent L(out) or the HDL-C - apoA-1 lipoproteins. From this analogy it can easily be seen that if there is inadequate HDL-C or apoA-1 the atherogenic kitchen sink will overflow and result in acute coronary syndromes as occurs in so many patients with low HDL-C (Figure 2).

Quality of HDL-C

Modifications of HDL-C resulting in dysfunctional HDL-C such as those seen with oxidation of HDL-C from reactive oxygen species, myeloperoxidase modification from inflammation, and the glycation-glycoxidation from glucotoxicity could certainly impair its positive-protective roles in the intima of atherosclerosis. This alteration of quality and quantity view of modified HDL-C and low HDL-C could help us to understand why there is such an increase in vascular calcification and acute coronary events in the metabolic syndrome, prediabetes, and type 2 diabetic patients.

Recently, the discovery of Apo A-1_{Milano} and Apo A-1_{Paris} protein isoforms (gene polymorphisms), have resulted in a marked increase in research interests for the HDL-C lipoprotein particle and its future manipulation. In the near future we may be utilizing gene transfer utilizing variations of the Milano and Paris isoforms, as well as the newer apoA-1 mimetics such as L-4F and other bioengineered HDLs in development.

Currently, increased interest in CETP inhibitors is ongoing and Phase II studies are underway with torcetrapib and the combination of torcetrapib and atorvastatin.

Additional attention to the antiatherosclerotic effects of nuclear receptor (PPAR), the liver X receptor alpha (LXR alpha), and the hepatic scavenger receptor B-1 agonists is being employed at the present and the positive dual effects on HDL-C (apoA-1 protein) and atherosclerosis is being actively investigated. This dual agonism of PPAR alpha, gamma, and possible delta, as well as the dual effects of PPAR alpha and LXR alpha are quite exciting and we will learn a great deal regarding their effects on atherosclerosis and HDL-C in the near future.

At the University of Missouri we are currently studying the parallel mechanisms between vascular calcification in atherosclerosis, the accelerated atherosclerosis (atheroscleropathy) associated with metabolic syndrome and type 2 diabetes mellitus, and calciphylaxis (calcific uremic arterolopathy). It is exciting to implicate low HDL-C with vascular calcification. Parhami F and Demer LL have been able to demonstrate that HDL-C clearly regulates early and late events in osteogenic differentiation and the *in vitro* calcification of vascular cells. Oxidized HDL-C was found to be pro-osteogenic thus reflecting again the quality of HDL-C.

John Snow, M.D. (1813-1858), a legendary figure in the field of epidemiology, of London, England was recently honored. He hypothesized that cholera was transmitted by water rather than miasma (bad air). He correctly hypothesized the water from the Broad Street pump was the source of the disease and subsequently had the pump handle removed in 1854 (150 years ago). Could low HDL-C be the “pump handle” of atherosclerosis and CVD?

As more and more research help us to better understand the important roles of HDL-C, we will undoubtedly have more tools to treat this devastating complex disease process. HDL-C is commonly referred to as “good cholesterol” and in a like manner these lipoproteins could be compared to the popular children’s toy known as the Rescue Heroes. These rescue heroes play such an important role in preventing the development and progression of atherosclerosis and it is now time to examine not only their quantity as in the past but also their quality and their future role in prevention of the atherosclerotic disease process.

Addendum (28 February 2005): Nobécourt E and colleagues have just demonstrated the *Quality* issue in their recent publication in *Diabetologia* [7]. They were able to demonstrate a deficient antioxidative activity of small dense HDL-C in T2DM and that this is linked to oxidative stress, hyperglycemia, and hypertriglyceridemia. They conclude that the impaired antioxidative activity of small dense HDL-C reflects abnormal intrinsic physicochemical properties of HDL-C particles (or an altered *Quality* of HDL-C).

References

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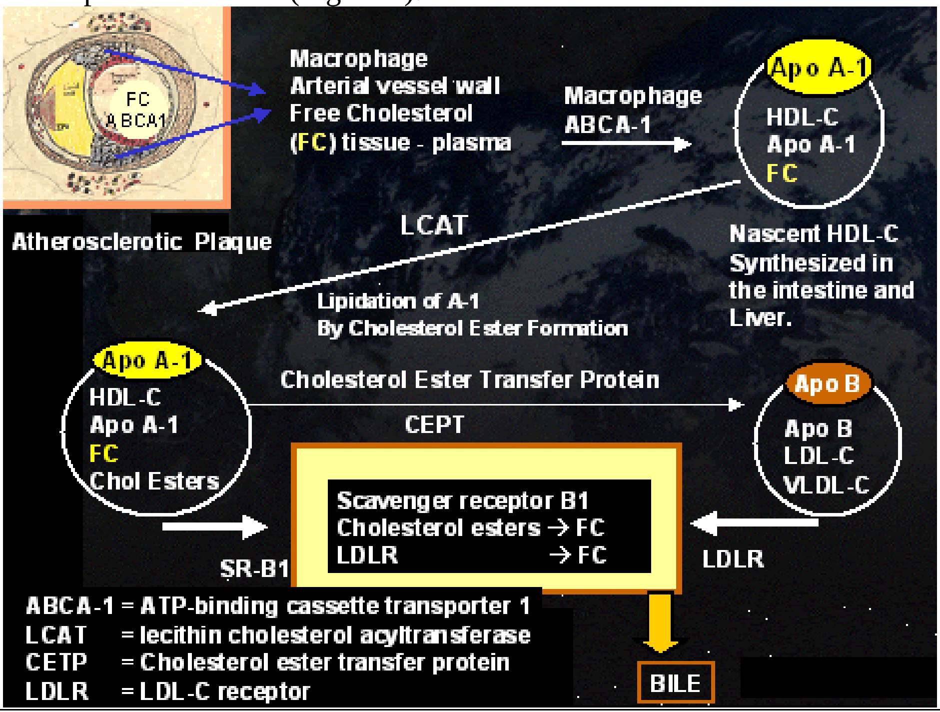
Table 1. Beneficial Effects Of HDL-C

<table>
<tr><td>REVERSE CHOLESTEROL TRANSPORT</td></tr>
<tr><td>Accepts cholesterol from the macrophage and tissues and transports it back to the liver for disposal in the bile (Figure 1).



</td></tr>
<tr><td>Acts as an apoprotein donor to the other lipoproteins</td></tr>
<tr><td>ANTIOXIDANT</td></tr>
<tr><td>Antioxidant activity (through intimal paraoxonase, and redox –sensitive methionine residues of apo A-1)</td></tr>
<tr><td>Increases eNOS and endothelial nitric oxide</td></tr>
<tr><td>ANTIINFLAMMATORY</td></tr>
<tr><td>Downregulates adhesion molecule expression on endothelium: (I-CAM, V-CAM and MCP-1)</td></tr>
<tr><td>Inhibits neutrophil degranulation</td></tr>
<tr><td>ANTITHROMBOTIC</td></tr>
<tr><td>Antithrombotic activity via its ability to block TxA_2 and potentiates activity of proteins: C and S.</td></tr>
<tr><td>Stimulates prostacyclin production (antithrombotic and vasodilitory).</td></tr>
<tr><td>ENDOTHELIAL PROTECTION PROTERTIES</td></tr>
<tr><td>Acts as an endothelial mitogen and inhibits endothelial cell apoptosis: This would help to decrease the incidence of plaque erosion and promote plaque stabilization</td></tr>
<tr><td>Stimulates endothelial nitric oxide (eNO and its enzyme eNOS) and prostacyclin production with vasodilatation, antioxidant, and anti-inflammatory properties.</td></tr>
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Table 2. Effects of Drugs on HDL-C Levels

DRUG Keep in mind the Quality issue	PERCENT INCREASE HDL-C Keep in mind the Quality issue
Nicotinic acid (niacin)	15% - 35%
Fibrates	10% - 15%
Estrogens	10% - 15%
Statins Coupled Dual Effect Associated with potent LDL-C reduction, which make the statins “shine”	5% - 10%
Alpha blockers	10% - 20%
Alcohol (in moderation)	10%
Ezetimibe	3%