The Mysterious HDL

The importance of lipoproteins in heart disease is well known. Total cholesterol and LDL (bad cholesterol) levels are highly correlated to a higher incidence of coronary artery disease. High levels of HDL-C (good cholesterol) lower the incidence of coronary obstructive disease (1-2). Some investigators have brought new ideas of HDL-C function, related to coronary artery disease. We will discuss them:

HDL is a heterogeneous particle with a density of 1.063-1.21 gm/ml showing a complex function of its role in heart diseases. The overwhelming majority of HDL contains apolipoprotein A-I (Apo A-I). HDL also contains apolipoprotein A-II (Apo A-II). Apo A-I is the most abundant apolipoprotein in normal human plasma. Apo A-I forms in the liver and intestine interacts with ABCA1 gene to form HDL. HDL remodeling by plasma and cell surface enzymes (ABCG I, hepatic lipase, phospholipid transfer produces HDL-C. This is known (HDL-C) as good cholesterol, because high levels are generally associated with low incidence of coronary artery disease. At present some investigators question this correlation. New observations have suggested that levels of HDL-C is not the ideal indicator of coronary disease risk. They suggest that probably HDL-C function is a better indicator. This brings the possibility of separate and distinct mechanistic pathways for different functions of HDL-C, that may involve compositional changes in specific HDLs (3-5).

HDL particles as opposed to total HDL-C is a better indicator of coronary heart disease. Investigators discovered that measuring HDL particles (HDL-P) as opposed to HDL-C is a better indicator of coronary artery disease (6). This suggests that it is important not only to measure total HDL-C, but the particles such as HDL-P. Davidson (7) and associates have studied the proteomics of apolipoprotein and associated proteins from plasma HDL-C. They have found subclass specific function of HDL-C (small-large HDL), each with specific characteristics and functions. They suggest that quantitative proteonomic studies helps to assigns specific roles to the sub-classes of HDL.

Some HDL may not protect against heart disease. Some investigators have shown that small protein (Apo C-III) which sometimes (13%) resides in the surface of HDL-C may increase the risk of heart disease and that HDL-C without this protein may be cardiac protective (4).

The concept of functional and dysfunctional HDL-C (8-9) has been brought to the scientific lipidology world. Most of this work has been done in patients with chronic renal disease. Investigators have found a markedly impaired capacity to licit cholesterol efflux while increasing inflammation in macrophages compared to patients with similar clinical characteristics, but without renal failure (10). This will produce deposition of cholesterol in tissues, especially in the aorta and coronaries, producing an accelerated atherosclerotic process. Statins doesn’t affect this abnormality. De Nardo and Lanza from the University of Bonn have shown that probably a gene from regulated genes is involved (11). This gene is found in phagocytes and through Toll-like receptors (TLR) releases inflammatory substances, which may cause organ failure.

Our experience (12-13) with functional and dysfunctional HDL-C comes from our heart transplant patients. We found that HDL-C increased from 38 ± 16mg/dl to 52 ± 17mg/dl in the total group, but a sub group of patients with rejected hearts, the HDL-C level increased from 47 ± 22mg/dl to 71 ± 40mg/dl. This elevation was observed immediately after transplantation and remained elevated until the death of the patients. The autopsies of the rejected hearts showed severe atherosclerosis of the aorta and coronary arteries. The transplanted heart age was 21 years. We consider these findings a result of dysfunctional HDL-C. This dysfunctional HDL-C (8-9) will produce abnormal efflux of cholesterol producing accumulation of cholesterol in the aorta and coronary arteries. We think that probably this marked elevation of HDL-C in rejected hearts can be considered a biomarker of rejection. At present, we are considering changes in the rejection protocol to try to stop this process. What causes this dysfunctional, is not known, but probably is related to the effect of inflammation in the HDL-C sub fractions genes producing changes in the protein composition of HDL or changes in the HDL associated lipids or Apo A-1 Studies are in process to clarify this (14). Proteonomic studies are in process to fractionate this abnormal serum of patients with heart transplant, especially the rejected sub group and clarify which particles of HDL-C are involved in this dysfunction process which reduces the life of the transplanted patient.

References