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-1 (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. Davidsson (7) and associates have studied the proteonomics 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-clases 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 dysfunctionality, 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 dysfuntion process which reduces the life of the transplanted patient.

Wilma González, BS and **Pablo I. Altieri**, MD
Departments of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

References

1. Gordon J, Castelli WP, Wilson PN et al. Incidence of coronary heart disease and lipoprotein cholsterol levels. The Framingham Study: JAMA 1986;256:2835-2838.
2. Gordon J, Castelli P, H Jortland MD et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study AMJ Med 1977;62:707-714.
3. Laurila PP, Surakka AP, Sarin L et al. Transcriptomic and lipidomic profiling highlights, the role with low high density lipoprotein cholesterol. Arterioscler Tromb Vasc Biol 2013;4:847-857.
4. Jensen MK, Rimm EB, Furtado JD, Sacks FM. Apolipoprotein C-III as a Potential Modulator of the Association Between HDL-Cholesterol and Incident Coronary Heart Disease. J Am Heart Assoc 2012;1:1-10.

5. Fisher EA, Feig JE, Hewing B et al. High density lipoprotein function, dysfunction and reverse holesterol transport. Throm Vasc Biol 2013;32:2813-2820.
6. De Goma Emil, Rader DJ. High-density lipoprotein particle number. J Am Coll Cardiol 2012;60:517-520.
7. Davidsson Pia, Hulte J, Fagerberg B, Camejo G. Proteomics of Apolipoproteins and Associated Proteins From Plasma High-Density Lipoproteins. Arterioscler Tromb Vasc Biol 2010;30:153-156.
8. Yamamotos S, Yancey PG, Iklizer A et al. Dysfuntional high density lipoprotein in patients on chronic hemolyalisis. J Am Coll Cardiol 2012;60:2072-2379.
9. Rader DJ, Alexander ET, Weibel GL, Rothbalat GH. The role of reverse cholesterol transport in animals and humans and relationship to atherosclerosis. J Lipid Res 2009;50 Suppl:S189-S194.
10. Resenson RS, Brewer HB Jr, Davidson WS et al. Cholesterol efflux and athero protection: Advancing the concept of reverse cholesterol transport. Circulation 2012;125:1905-1919.
11. De Nardo Dominic, Labzin LI, Kono H et al. High density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nature Immunology 2013;15:152-160.
12. Iravedra D, Gonzalez W, Altieri P et al. Metabolic Syndrome After Heart Transplant: The Importance of HDL Elevation. Journal of Diabetes 2013; Vol. 5, Suppl S1. P-25.
13. Gonzalez W, Altieri P, Banchs HL et al. Functional and dysfunctional HDL in heart transplant: The Importance of changes post transplant. J Investig Med 2014;62:107.
14. Macpherson PA, Young IS, MacKibbeu B, MacEneny. High density lipoprotein sub fraction: Isolation composition and their duplicitous role in oxidation. J Lipid Res 2007;48:86-95.