HDL- The Anti-Atherogenic Lipoprotein

Kenneth Feingold
Professor of Medicine- UCSF
Chief Endocrine Clinic- SFVAMC

Two Dimensional Gel Electrophoresis

Proteins Associated With HDL
Low HDL-C Is Very Common

According to NHANES III
• 35% adult men have HDL-C <40 mg/dL
• 39% of adult women have HDL-C <50 mg/dL

• Epidemic of obesity/metabolic syndrome/type 2 diabetes is leading to increased prevalence of low HDLc

HDL-C Is an Independent Risk Factor for CHD:
• A low HDL-C level is strongly and inversely associated with CHD risk
• Independent relationship holds after correction for other risk variables in multivariate analysis
• A low HDL-C level often correlates with elevations of serum triglycerides and remnant lipoproteins

CHD Risk According to HDL-C Levels
Prospective Cardiovascular Münster Study

HDL-C Is a Modifier of Risk at All Levels of LDL-C
The Framingham Study*

*N = 4467 men

*Men 50 to 70 years of age
Low HDL-C Increases CVD Risk Even if LDL-C Levels Are Well-Controlled
Treating to New Targets (TNT) Study

Patients With LDL-C ≤80 mg/dL on Atorvastatin 80 mg

n = 4874

*On-treatment level (3 months)

P<.0001 for Inverse Relationship


Potential Antiatherogenic Actions of HDL-C

HDL-C inhibits expression of endothelial cell adhesion molecules and MCP-1

Monocyte

Adhesion molecule

Cytokines

MCP-1

LDL-C

HDL-C

Intima

Vessel Lumen

Endothelium

Foam cell

Macrophage

CD36

SR-A


Development of an Atheroma


Monocyte

Induction of adhesion molecules and chemotaxis

VCAM-1

ICAM-1

P-selectin

E-selectin

Migration

MCP-1

CCR-2

oxLDL

Differentiation (GM-CSF)

Macrophage

Foam cell

Monocyte macrophage

Cytokines

MMPs

Endothelin-1

Endothelial cells

Intima

Lumen

CD40

IFN-gamma

LDL-C, β-VLDL, Lp(a)

HDL-C inhibits expression of endothelial cell adhesion molecules and MCP-1

HDL-C inhibits oxidation of LDL-C

HDL-C promotes efflux of cholesterol from foam cells

Risk of Atherosclerosis Does Not Always Correlate with HDL Levels

• SR-B1 transgenic mice have decreased HDL levels but are resistant to the development of atherosclerosis due to increased reverse cholesterol transport.
• SR-B1 KO mice have increased HDL levels but have an increase in atherosclerosis due to a decrease in reverse cholesterol transport.

HDL Can Be Dysfunctional

Nonpharmacologic Treatment of Low HDL-C

• Physical activity
• Smoking cessation
• Weight loss
• ETOH

Note – low fat diet can lower HDL
Effects of Lipid-Modifying Drugs on HDL-C Levels

- Nicotinic acid: ↑ 15%–35%
- Fibrates: ↑ 10%–15%
- Estrogens: ↑ 10%–15%
- Statins: ↑ 5%–10%
- TZDs: ↑ 5%–15%

Drugs in Development

- Glitazars (PPARα and PPARδ activators)
- CETP inhibitors
- Reconstituted HDL/Apo A1 Milano
- Apolipoprotein A1 mimetics
- Apolipoprotein A1 up-regulators

Key Question

Will these changes in lipid levels reduce cardiovascular disease?