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REFLECTION

# Danger of very high HDL levels

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High Density Lipoprotein (HDL) (Fig. 1) is known as the "good cholesterol" because of its role in reverse cholesterol transport, or the process, by which cholesterol is transported from the tissues to the liver for excretion via bile.

On the other side, low density lipoproteins (LDL) are evidently atherogenic (1). There is a strong association between high HDL cholesterol in plasma and protection against heart disease. In addition to its well-known role in the reverse cholesterol transport, HDL also plays an important role as the immune/inflammatory aspects of heart disease.

The aim of this short review is to show that there exist a danger of extremely high HDL levels.

Elevated HDL levels are associated with low levels of very low-density lipoprotein cholesterol (VLDL) and triglyceride (TG) levels. LDL-C levels may be within the reference range or elevated. HDL is more tightly controlled by genetic factors than are the other lipoproteins (ie, LDL, VLDL, intermediate-density lipoprotein (IDL), and chylomicrons). For example, in certain families, especially some families with Japanese ancestry, a genetic deficiency of cholesteryl ester transfer protein (CETP) is associated with strikingly elevated HDL cholesterol levels.

However, environmental factors also have a significant impact on HDL levels. Factors that elevate HDL concentrations include chronic alcoholism, treatment with oral estrogen replacement therapy, extensive aerobic exercise, and treatment with niacin, statins, or fibrates. On the other hand, smoking reduces levels of HDL cholesterol, while quitting smoking leads to a rise in the plasma HDL level. Measuring HDL-cholesterol levels provides information about the size of the HDL pool, but does not predict HDL composition or function. Similarly as LDL, HDL can be damaged by oxidation. The main component of HDL, apolipoprotein A-I (apo A-I), is largely responsible for the reverse cholesterol transport. Apo A-I can be damaged by oxidative mechanisms, which render the protein less able to promote cholesterol efflux (Fig. 1). HDL also contains a number of other proteins that are affected by the oxidative environment of the acute-phase response. Modification of the protein components of HDL can convert it from an anti-inflammatory to a proinflammatory particle (4, 5). Very high

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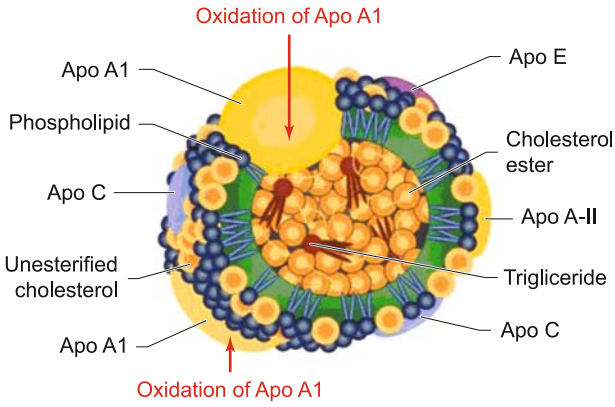


**Fig. 1. Structure of HDL particle according to http://www.hdlforum.org.**

levels of HDL and oxidized HDL cholesterol (ox-HDL) have been reported to be atherogenic. The mechanism of this paradoxical effect is not entirely clear. Robust assays to evaluate the function of high HDL and ox-HDL are needed.

Apo A-I can be damaged by oxidative mechanisms, which render the protein less able to promote cholesterol efflux. HDL also contains a number of other proteins that are affected by the oxidative environment of the acute-phase response. Modification of the protein components of HDL can convert it from an anti-inflammatory to a proinflammatory particle. Small peptides that mimic some of the properties of apo A-I have been shown in preclinical models to improve HDL function and reduce atherosclerosis without altering HDL-cholesterol levels. Robust assays to evaluate the function of HDL are needed to supplement the measurement of HDL-cholesterol levels in the clinic.

Lp(a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells. This impairs plasminogen activation, plasmin generation, and fibrinolysis. Lp(a) also binds to macrophages via a high-affinity receptor that promotes foam cell formation and the deposition of cholesterol in atherosclerotic plaques.

## Conclusion

Extremely high levels of Lp(a) and Lp(a)-ox bind to macrophages. This promotes foam cell formation and the deposition

of cholesterol in atherosclerotic plaques. A genetic mutation that raises HDL cholesterol levels rather than protecting against heart disease, actually increases the risk of it.

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