This article reviews the beneficial role of high density lipoproteins, or HDLs, to cardiovascular health. HDLs are vital to removing excess fatty acids and lipids via the reverse cholesterol transport pathway. Beyond this, HDL proteins possess anti-inflammatory and anti-oxidant activities that protect against cardiovascular disease.

HDL’s beneficial health profile has clinical relevance as well. Small and macromolecular treatments that increase HDL levels have been investigated as therapeutics for cardiovascular disease. Treatments like Apo A-I Milano, statins and fibrates can increase circulating HDL levels in the blood and improve cardiovascular health, while others, such as CETP inhibitors, increase circulating HDL levels in the blood but don’t show expected improvements to cardiac health.

**The Highly Desirable Lipoprotein**
Lipoproteins are macromolecular complexes that transport lipids, fatty acids and cholesterol through the body.

Of all the lipoprotein particles, high density lipoprotein or HDL, is the smallest and most protein-rich. In a process called reverse cholesterol transport (RCT), HDL particles remove excess fats and cholesterol from cells and arteries and transport them to the liver for disposal. This unique function gives HDL a protective role against cardiovascular diseases, especially atherosclerosis. So while other lipoproteins like low density lipoprotein or LDL, have negative impacts on the cardiovascular system, HDL generally has a favorable influence on cardiovascular health unless it has been modified pathologically. For this reason it is often referred to as “good” cholesterol. Indeed, research finds that higher circulating levels of HDL are associated with a lower risk of atherosclerotic diseases.²

Several properties help HDL convey protective effects against atherosclerosis. HDLs primary function is promoting cholesterol efflux from cells and delivering it to the liver and other tissues for reuse or excretion.
This action prevents the build-up of harmful LDL species in blood vessels and reduces the likelihood of atherosclerotic plaque formation. In addition to this function, other actions, most notably anti-oxidant and anti-inflammatory activity carried out by HDL proteins are also important for atherosclerosis prevention. Apo A-I, which is the most abundant protein in HDL accounting for nearly 70% of protein mass, appears to be particularly important for the particle’s anti-oxidant actions. Apo A-I removes oxidized phospholipids from oxidized LDLs and also from cells. As the major HDL associated protein, it triggers cholesterol efflux by activating transport mechanisms that remove oxidant LDLs from the bloodstream. In addition, the protein stabilizes antioxidant enzymes such as serum paraoxonase (PON1) that are carried by HDL. And in human HDL, Apo A-I directly reduces cholesteryl ester and phosphatidylcholine hydroperoxides via methionine residues 112 and 148.

These antioxidant behaviors are essential protection mechanisms as oxidized phospholipids and LDLs contribute to atherosclerotic plaque formation and progression.

Apo A-II, which is the second most abundant protein in HDL particles, makes up another 20% of the particle’s protein mass. Its role is more elusive than that of Apo A-I, but recent research provides evidences that it too has anti-oxidant properties. HDL complexes enriched with Apo A-II protect very low density lipoproteins from oxidation. Moreover, particles enriched with human Apo A-II are able to promote effective reverse cholesterol transport from macrophage cells. Though much of Apo A-II’s function remains unknown, these actions indicate the importance of Apo A-II for HDLs anti-oxidant properties.

In addition to antioxidant behavior, HDL also promotes anti-inflammatory responses. HDL appears to neutralize the effects of the inflammation associated C-reactive protein (CRP).

In vivo experiments involving administration of Apo A-I in small animals show a reduction in inflammatory indicators such as chemokine production and monocyte activation in endothelial cells. HDL limits expression of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 that induce endothelial cell apoptosis and mediate the upregulation of cell adhesion molecules. And in one more piece of supporting evidence, peptide mimics of Apo A-I have proven effective in promoting clearance of pro-inflammatory lipids. These anti-inflammatory actions are particularly important given that atherosclerosis involves an ongoing inflammatory response within artery walls.

Clinical Relevance
Given the association between HDL levels and the lower risk for cardiovascular disease, HDL targeting therapies have been popular clinical interventions with varying degrees of success. For example, reconstituted HDL has been considered as a treatment for atherosclerosis, with very limited success.

Reconstituted HDLs are crude lipoprotein particles, consisting of phospholipids and apolipoproteins like Apo A-I and Apo E. The apoproteins are inserted into phospholipid vesicles to form bilayers containing the apolipoproteins. Reconstituted HDL therapies have been effective at increasing plasma HDL levels. Treatment with these particles diminishes the release of pro-inflammatory cytokines and also reduces the expression of adhesion molecules that would find their way into atherosclerotic plaques. Unfortunately, reconstituted HDL on its own has not yet proven an effective tool in reducing the occurrence of coronary events, nor has it proven to be effective at reducing the plaque burden of atherosclerotic patients.

Apo A-I Milano, a mutant of Apo A-I, has drawn considerable interest as a potential therapeutic due to anti-atherogenic effects observed when administered to small animal models. Administering Apo A-I intravenously to rats prevented platelet aggregation and delayed formation of blood clots.

Intravenous administration of Apo A-I Milano also reduced the number of atherosclerotic lesions in cholesterol fed rabbits and led to a regression of pre-existing plaques. These results encouraged consideration of reconstituted HDLs containing Apo A-I Milano mutants as a treatment in humans, with at least one study yielding favorable results, including rapid and significant reductions in plaques when assessed by intravascular ultrasound.

Gene therapies for both Apo A-I and Apo A-I Milano have demonstrated enormous therapeutic potential in mice models. Transgenic insertion of Apo A-I into Apo E deficient...
The highly desirable lipoprotein, HDL, is a macromolecular complex that transports lipids in the blood and improves cardiovascular health, while other lipoproteins, such as LDL, have negative impacts on the cardiovascular system. HDL's beneficial health profile has clinical relevance as well. This article reviews the beneficial role of high density lipoprotein (HDL) in cardiovascular health.

HDL plays an important protective role for cardiovascular health due to its function in reverse cholesterol transport. HDL possesses antioxidant and anti-inflammatory properties thought to be beneficial to cardiovascular health. Current treatments increase HDL and to various extents protect patients from the persistent inflammation associated with cardiovascular diseases. Furthermore, clinical studies repeatedly show an association with increased plasma HDL levels and reduction in cardiovascular events, however, more definitive research is needed to elucidate the nature of HDL's role in reducing cardiovascular risk and improving clinical outcomes.

Small molecule treatments that increase HDL concentration have also been considered. Inhibitors of cholesteryl ester transfer protein (CETP) have been thoroughly investigated for their potential as therapeutics. Deficient CETP is associated with increased plasma HDL levels and decreased LDL. Similarly, inhibition of CETP by small molecules increases plasma HDL levels, while decreasing plasma LDL concentrations. Several CETP inhibitors have been investigated clinically. The most well-known is torcetrapib, which increased HDL levels, improved Apo A-I and –II concentrations, and also proved beneficial to lipid metabolism. However, in clinical trials the treatment was associated with increased morbidity and mortality and the study was terminated. Other CETP inhibitors include anacetrabip, dalcetrapib, and evacetrapip all of which are associated with improved HDL levels and function, but have not proven beneficial in preventing disease progression.

Anacetrapip, which has been shown to increase HDL by as much as 138% in one study, is expected to remain in clinical trials through 2017.

Trials of dalcetrapib were halted in 2012 after failing to show any clinical efficacy and development of evacetrapip was stopped in October of 2015 after it, too, failed to improve clinical outcomes.

Other small molecule therapies improve HDL concentration and function and also reduce cardiac events. Statins, which are a widely prescribed treatment for patients with elevated LDL, raise the levels of HDL slightly - typically in the range of 5-10% - during treatment. Fibrates are another treatment for patients at risk of cardiovascular diseases. This class of agents target peroxisome proliferator-activated receptors (PPARs), which regulate lipid metabolism and can raise HDL by 5-20% depending on a patient’s baseline level of HDL expression. Fenofibrate has been shown to also increase Apo A-I.

Niacin has proven the most effective treatment when it comes to boosting HDL metabolism and structure. Niacin, also known as Vitamin B3 or nicotinic acid, increases HDL in the range of 15-35%. Niacin also improves HDL quality. It increases the Apo A-I residence time in HDL particles, causing protein concentrations to rise. It also increases HDL particle size and promotes retention of cholesteryl esters in HDL, both of which could improve its cholesterol efflux efficiency. Although improvements in HDL cholesterol is well documented with niacin, there is little clinical evidence suggesting that it also reduces the frequency of coronary events such as heart attacks or strokes. One study suggests that niacin resulted in rates reduced coronary events, while another more recent study shows no improvement in rates of cardiovascular events after a 3 year treatment period.

Conclusion

HDL plays an important protective role for cardiovascular health due to its function in reverse cholesterol transport. HDL possesses antioxidant and anti-inflammatory properties thought to be beneficial to cardiovascular health. Current treatments increase HDL and to various extents protect patients from the persistent inflammation associated with cardiovascular diseases. Furthermore, clinical studies repeatedly show an association with increased plasma HDL levels and reduction in cardiovascular events, however, more definitive research is needed to elucidate the nature of HDL's role in reducing cardiovascular risk and improving clinical outcomes.
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