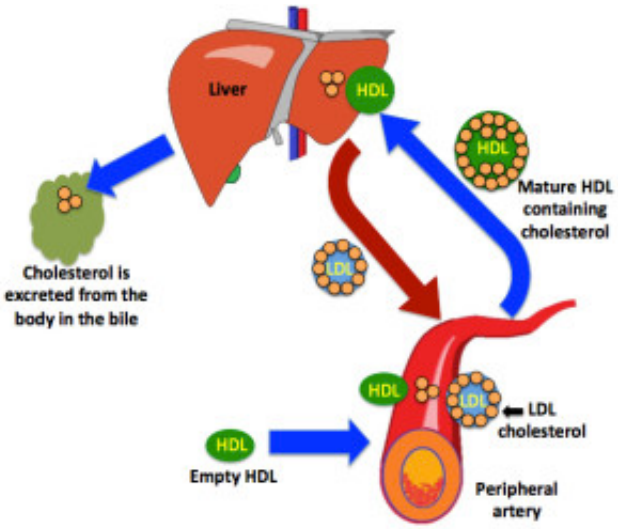
HDL cholesterol: sometimes more is not necessarily better

Lipoproteins are complex particles that are responsible for transporting the water insoluble molecule, cholesterol, through the blood stream. Cholesterol is transported from the liver to peripheral tissues. Excess cholesterol in low-density lipoprotein (LDL) is deposited in the arterial wall, which can cause a heart attack. The main function of high-density lipoprotein (HDL) is to remove excess cholesterol from the artery and transport it to the liver to be excreted from the body in the bile. This process is known as reverse cholesterol transport.



Reverse cholesterol transport pathway HDL picks up cholesterol deposited in peripheral tissues and transports it to the liver to be excreted from the body in the bile

Given its role in reverse cholesterol transport, it has been thought that higher levels of HDL cholesterol would lead to the removal of more cholesterol from the coronary arteries and be more protective against heart disease. In fact, prior studies have demonstrated that higher levels of HDL cholesterol are associated with a lower risk for heart disease.

Interestingly, we identified a number of individuals with very high levels of HDL cholesterol that developed heart disease, even in the absence of major risk factors. We asked the question ‘why did some individuals with high levels of HDL cholesterol develop heart disease while most others seemed to be protected?’ We sought to determine what might be different in the HDL from disease susceptible and resistant individuals. We hypothesized that there would be a difference in the ability of HDL in the patients who develop heart disease to remove arterial cholesterol. Therefore, we decided to look more closely at the function of HDL in a part of the reverse cholesterol transport pathway in both of these groups of patients.

Our research group had previously devised an *in vitro* assay to measure how efficiently HDL can remove cholesterol from macrophages that simulate the environment of the cells in the coronary arteries. We ran this assay with the HDL from the patients with high HDL cholesterol and heart disease and compared it to those with high HDL cholesterol without heart disease.

We found that HDL from the patients with heart disease was less efficient in the removal of cellular cholesterol in our simulated *in vitro* assay as compared to those without heart disease. These findings suggest that there is a difference in the functionality of HDL between patients who have heart disease and those who do not. Additionally, we demonstrated that the composition of the HDL particle in susceptible individuals was different from those protected from heart disease. This difference in the HDL particle composition may reflect its inability to function optimally in reverse cholesterol transport.

In this study we challenged the existing paradigm that higher levels of HDL always confer greater protection against heart disease. These findings are important because they suggest that the quality of HDL is more important than the quantity. A clear understanding of HDL function may help identify individuals at risk for developing heart disease even though they have high levels of HDL cholesterol.

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