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EDITORIAL

Beyond LDL Cholesterol: the Role of LDL Particles and HDL

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ABSTRACT

Currently available hypolipidemic treatments aim at reducing low density lipoprotein (LDL)-cholesterol. Unfortunately, cardiovascular events continue to occur despite LDL-lowering therapy with use of statins. Recent evidence has revealed that having increased concentrations of *small LDL particles*, though common, is an unhealthy pattern; high concentrations of small LDL particles correlate with much faster growth of atheroma, progression of atherosclerosis and earlier and more severe cardiovascular events and death. In addition, at any given level of total cholesterol, the relative risk of coronary artery disease increases with decreasing levels of high density lipoprotein (*HDL)-cholesterol*. Thus, the target for new interventions would be to reduce small LDL particles and increase HDL and/or its apolipoproteins, which are recognized to have major vascular protective effects ranging from prevention to stabilization and regression of atherosclerosis.

KEY WORDS: *LDL cholesterol; LDL particles; HDL cholesterol; coronary heart disease; statins; niacin; fibrates; ezetimibe*

List of Abbreviations:
CHD = coronary heart disease
HDL = high density lipoprotein
LDL = low density lipoprotein

LDL CHOLESTEROL AND LDL PARTICLES

Atherosclerotic cardiovascular disease is the worldwide leading cause of death, which involves multiple pathways in which lipoprotein entry and retention, injury to the vessel wall from several stimuli, and inflammation seem to play a key role. Currently available treatments are aimed at reducing the high plasma lipid concentrations, most particularly low density lipoprotein (LDL)-cholesterol. Increasing evidence has revealed that the concentration and size of the *LDL particles* are powerfully related to the degree of atherosclerosis progression than the concentration of cholesterol contained within all the LDL particles.[1-3] The LDL particles actually vary in size and density, and studies have shown that a pattern that has more small dense LDL particles—called "Pattern B"—equates to a higher risk factor for coronary heart disease (CHD) than does a pattern with more of the larger and less dense LDL particles ("Pattern A"). This is because the smaller particles are more easily able to penetrate the endothelium. "Pattern I," meaning "intermediate," indicates that most LDL particles are very close in size to the normal gaps in the endothelium (26 nm). The healthiest pattern, though relatively rare, is to have small numbers of large LDL particles and no small particles. Having *small LDL particles*, though common, is an unhealthy pattern; high concentrations of small LDL particles (even though potentially carrying the same total

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cholesterol content as a low concentration of large particles) correlates with much faster growth of atheroma, progression of atherosclerosis and earlier and more severe cardiovascular disease events and death.

HDL CHOLESTEROL

Statin therapy has improved event-free survival by lowering LDL-cholesterol and controlling inflammation. Unfortunately, cardiovascular events continue to occur despite LDL-lowering therapy. This is probably due to the fact that there are risk factors that are important in certain patients other than LDL-cholesterol. Therefore, there is a clear need for additional preventive and therapeutic interventions to complement the results of LDL lowering. Among others increased level of high density lipoprotein-cholesterol (*HDL-cholesterol*)[4,5] is thought to protect against atherosclerosis by promoting the efflux of excess cholesterol from cells and returning that cholesterol to the liver for secretion into the bile, but depends on the repeated transfer of cholesteryl esters among lipoproteins before finally the excretion occurs through the liver. Interestingly, during the last several years investigators have explored the effect of inflammatory stimuli on the formation of a phenotype of HDL with reduced anti-atherogenicity, suggesting a link between inflammation and HDL functionality. One such target for new interventions is HDL[4-6] and/or its apolipoproteins. HDL and/or its apolipoproteins have been recognized to have major vascular protective effects ranging from prevention to stabilization and regression of atherosclerosis. The relationship between low levels of HDL-cholesterol and the development of coronary heart disease can be inferred from epidemiological studies, where even small differences in the level of HDL-cholesterol are associated with substantial variations in the risk of major coronary events. Data from the Framingham population[7] indicated that at any given level of total cholesterol, the relative risk of coronary artery disease increases with decreasing levels of HDL-cholesterol. Low HDL-cholesterol is commonly found in the general population. For example, 18% of men and 4% of women in the Framingham Offspring study[8] had HDL-cholesterol equal or below 35 mg/dl.

The Veterans Affairs cooperative studies program High density Intervention Trial (VA-HIT)[9] assessed the effect of raising HDL-cholesterol levels on CHD-risk in patients with low levels of both LDL-cholesterol and HDL-cholesterol. After 1-year with gemfibrozil treatment there was a significant effect on HDL-cholesterol and total cholesterol but not LDL-cholesterol, which was associated with a reduction of 22 % in non-fatal myocardial infarction or death due to coronary heart disease, compared to placebo therapy. For every 5 mg increase in HDL-cholesterol, there was a decrease in CHD-death or myocardial infarction by 11 %. Furthermore, the PROCAM[10] and the Helsinki Heart studies[11] suggest that a high ratio of triglyceridemia/HDL cholesterol constitutes a powerful risk factor for fatal or non-fatal myocardial infarction that would escape attention if LDL cholesterol levels alone were determined. Dietary and exercise modifications can lead to improvement in HDL-cholesterol concentrations, which may be associated with greater anti-oxidative role of HDL-cholesterol. Kesteloot et al,[12] in a Belgian population group, investigated the relationship between dietary fat intake and serum total and HDL-cholesterol and revealed that polyunsaturated fat and the polyunsaturated/saturated fat ratio decrease the HDL-cholesterol value, while dietary cholesterol increased the HDL-cholesterol level in women only, alcohol consumption increased and cigarette smoking decreased HDL-cholesterol levels, demonstrating the importance of dietary fat as a determinant of the serum lipid level within a population. The key lifestyle changes to increase HDL-cholesterol are weight loss in the case of obesity, increased physical activity, smoking cessation and alcohol consumption in moderate amounts. With smoking cessation for example, HDL-cholesterol increases on average 6–8 mg/dl.

DRUG INTERVENTION

Ezetimibe[13] is a new selective cholesterol absorption inhibitor that blocks the uptake of dietary and biliary cholesterol by preventing its transport through the intestinal wall, without affecting the passage of other fat-soluble nutrients. Ezetimibe can reduce LDL-cholesterol levels by up to 19% and moderately increases HDL-cholesterol by 3.5%, while it is well tolerated when administered with a statin or fibrate with additive effects. A combination of simvastatin plus extended release niacin,[14] currently in clinical development, has been demonstrated to produce greater effects on LDL-cholesterol, HDL-cholesterol and triglyceride levels than either of the two drugs alone; HDL-cholesterol levels were increased by 30 %, LDL-cholesterol decreased by 47%. However, cutaneous flushing resulted in the withdrawal of 7% of patients from the study. Another very interesting therapeutic approach is the infusion of apolipoprotein A-I,[15] the main apolipoprotein of HDL. This approach seems to lead also to an increase of reverse cholesterol transport and regression of atherosclerosis in animal models.

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