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Review Articles

Is HDL function as important as HDL quantity in the coronary artery disease risk assessment?

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Abstract: Over the past several decades, it has been clearly established that higher plasma concentrations of high-density lipoprotein (HDL) are related to lower risk of coronary artery disease (CAD). According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, the HDL level of <40 mg/dL is considered low and is one of the CAD risk predictors. However, in the last decade, several studies have indicated the importance of the quality of HDL as another potential measure for CAD risk assessment. The loss of normal biological function of HDL particles as a result of multifactorial actions of chronic inflammation and acute phase responses has suggested a new potential pathway in the pathophysiology of atherosclerosis. The concept of "dysfunctional HDL" or "proinflammatory HDL," which exhibits chameleon-like properties of converting a positive force protecting arteries to a negative one, enhancing atherogenesis is now under active investigation. Measurements of this dysfunctional quality of HDL in cell-based or cell-free assays by analyzing anti-inflammatory functions may link these changes to in vivo assessments of vascular disease. This review provides details on functional and dysfunctional HDL and summarizes recent studies into dysfunctional HDL and its potential links to CAD.

Coronary artery disease (CAD) is the leading cause of mortality worldwide, with >4.5 million deaths occurring in the developing world.[1] In 2003, a total of 685,089 people died of heart disease (51% of them women), accounting for 28% of all of deaths in the United States (US).[2] By 2020, it is expected that CAD will be the greatest cause of disease burden worldwide, having doubled in incidence since 1990.[1,2] However, the incidence of this disease can be altered with primary prevention. In developed countries, over the last 30 years, there has been a 50% decline in CAD mortality, with mortality decreasing by 2.6% per year from 1990 to 1996 alone.[1] This decline is believed to be attributable in part to a decreasing prevalence of CAD risk factors.[1] A reduced incidence rate and an improved case-fatality rate have also contributed to improved mortality from CAD.[1] The decline is also attributable to advances in medical therapies used in both primary and secondary prevention as well as improved care for acute vascular syndromes.[3] However, despite the decline, CAD is still responsible for heavy morbidity and is the major single cause of mortality in most developed countries, with a steep increase in developing countries.

There are several risk factors that continue to contribute to CAD, including lifestyle and unhealthy behaviors such as smoking and diets rich in saturated fats. Traditional risk factors such as high blood pressure, high low-density lipoprotein (LDL) cholesterol, and type 2 diabetes (T2D) are now more aggressively treated but also remain very

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important and too often are unrecognized until late in life. Family history is an important warning sign and may reflect hidden genetic traits that are operative in atherogenesis. Among numerous genetic and lifestyle parameters, dyslipidemias are one of the most prominent risk factors for CAD.

Epidemiologic studies have identified LDL and high-density lipoprotein (HDL) as independent risk factors that modulate CAD risk.[4] Elevated LDL, reduced HDL, and often their combination with elevated triglycerides (TGs) characterize the dyslipidemias that are causative in vascular disease.[4] However, the extent of occlusive disease and CAD varies greatly between individuals with similar lipid profiles. The growing problem of obesity, associated T2D, higher blood pressure, and dyslipidemia has led to emphasis on the concomitant appearance of these disorders in the individual and the recommendation to use the diagnosis of "metabolic syndrome" as a means of identifying these high-risk patients. The criteria for this diagnosis of metabolic syndrome also recognizes that even modest elevations of several of these factors enhances risk in an additive fashion.[4]

According to the practice guidelines, the primary goal is to reduce LDL levels,[4] without recommending a target for HDL levels, although HDL cholesterol is among the most predictive risk factors for CAD.[4,5] Over the last decade, lowering LDL levels has been the major target in cardiovascular protection strategies, and clinical trials have clearly established that reductions in LDL are associated with a 30–45% reduction in clinical events.[5,6] There is substantial evidence from clinical trials that lowering LDL reduces cardiovascular risk. There is less evidence for the salutatory effects of raising HDL. Although LDL remains the primary target for CAD prevention according to the NCEP ATP III guidelines[4]; however, many individuals who have CAD do not have substantially elevated LDL but have derangement of other lipid fractions, most commonly low levels of HDL. In the NCEP ATP III guidelines, HDL is important in risk stratification in primary prevention, influencing the need for and intensity of treatment of LDL. Moreover, guidelines clearly define an HDL level of $<$40 mg/dL as an independent risk factor for CAD, and low HDL is often present in high-risk patients with CAD.[4] However, there is very convincing literature available from community-based studies showing the strong relationship of reduced CAD risk with concomitant measures of higher HDL cholesterol.[8,9] Epidemiologic data generally support an independent inverse association of HDL level and CAD event rates, in which CAD risk decreases by 2–3% for a 1-mg/dL increment in HDL levels.[10]

To date, a means of safely and selectively raising HDL cholesterol has not been available or has not been tested adequately in large long-term clinical trials. A growing body of experimental evidence suggests that augmenting the levels or function of HDL and its apolipoproteins could have major vascular protective effects ranging from prevention to stabilization and regression, independent of total or non-HDL cholesterol levels.[4] Recent clinical trials have stimulated tremendous interest in the structure, function, and therapeutic potentials of HDL.

Alternatively, the reduction of LDL cholesterol has been repeatedly shown to reduce clinical events. Many studies comparing drug therapy to placebo have documented reductions in CAD death and morbidity in association with reducing LDL levels.[8,9] Some of these trials also resulted in higher HDL levels.[11,12] The Scandinavian Simvastatin Survival Study (4S) evaluated the effects of lowering cholesterol with the drug simvastatin on mortality and morbidity in patients with CAD.[11] Ultimately, simvastatin produced highly significant reductions in the risk of death and morbidity in patients with CAD followed for a median 5.4 years.[10] However, it was not possible to document a relationship of the small HDL rise (8%) and event rate reduction.

Similarly, pravastatin use in patients with modest cholesterol elevations reduced total plasma cholesterol and LDL levels by 20% and 26%, respectively, and increased HDL levels by 5%, but this increase was not correlated with reduced CAD.[12] The Heart Protection Study achieved cholesterol lowering with simvastatin, aimed to help resolve some remaining uncertainties by assessing the long-term effects of cholesterol-lowering therapy on vascular and nonvascular mortality and major morbidity in a wide range of baseline cholesterol concentrations and in patients with other major risk factors such as T2D and high blood pressure.[6] The results demonstrated that the lowering of LDL with a statin produced a substantial reduction in major vascular events, benefiting not only those with CAD but also those without CAD.[6] This was true even in those patients who had LDL cholesterol $<$100 mg/dL, a value considered desirable at the time. Again, HDL cholesterol increased but no statistically significant relationship with vascular events was established.

Because of the large clinical trial evidence, LDL levels continue to be the major target in CAD preventive strategies. Reductions in LDL levels of 25–40% are associated with a 30–45% reduction in clinical events.[13,14] The Jupiter Trial, using rosuvastatin (20 mg/day) recently demonstrated a reduction of LDL cholesterol by 50% (from a mean of 110 to 55 mg/dL) with a concomitant reduction in major vascular events by 47% and myocardial infarction by 54%.[14] Lower HDL levels at baseline and during intervention in such studies remains a powerful predictor of increased vascular disease. However, despite low LDL and normal HDL levels, many patients continue to have cardiac events.[9,13] One can calculate from the published Framingham data that 44% of the CAD clinical events occurred in men with HDL cholesterol levels $>$40 mg/dL and 43% in women with HDL levels $>$50 mg/dL.[9] Because a significant number of CAD events occur in patients with normal LDL and HDL levels, there has been a continuing search for markers with better predictive value.

The ability of HDL to promote cholesterol efflux is believed to be an important mechanism explaining its