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Review

New Insights into the High-Density Lipoprotein Dilemma

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Although high-density lipoprotein-cholesterol (HDL-C) concentration is a negative risk factor for atherosclerotic cardiovascular disease (CVD), efforts to reduce CVD risk by raising HDL-C have not been uniformly successful. Many studies have shown that alcohol consumption, that increases plasma HDL-C concentration, reduces CVD incidence. However, recent genetic studies in large populations have not only removed HDL-C from the causal link between plasma HDL-C concentration and reduced CVD risk, but also suggest that the association is weak. We propose here that the cardioprotective effects of alcohol are mediated by the interaction of its terminal metabolite, acetate, with the adipocyte free fatty acid receptor 2 (FFAR2), which elicits a profound antilipolytic effect that may increase insulin sensitivity without necessarily raising plasma HDL-C concentration.

Trends

A large body of epidemiological evidence shows that plasma HDL-C concentrations are negatively correlated with the incidence of atherosclerosis.

CETP inhibitors and HDL alleles that increase plasma HDL-C concentrations do not cardioprotect.

The functional qualities of HDL are more relevant to cardioprotection than plasma HDL-C concentrations.

Alcohol consumption is associated with reduced cardiovascular disease without a profound increase in plasma HDL-C concentrations.

Alcohol is converted to acetate, which elicits an antilipolytic effect via a G-protein coupled receptor (FFAR2).

New interventions that improve HDL functionality without necessarily increasing its concentration should be identified and validated.

Introduction

The underlying cause for most CVD is atherosclerosis, which begins with the transfer of low-density lipoproteins (LDL) to the subendothelial space of the arterial wall where they undergo oxidative modification. Blood monocyte-derived macrophages within the subendothelium take up oxidized LDL and acquire a foamy aspect owing to the intracellular accumulation of LDL-cholesteryl esters. High plasma LDL-cholesterol (LDL-C) levels and low plasma levels of HDL-C and major CVD lipid risk factors. Statins, which reduce plasma LDL-C concentrations, reduce CVD events in men and women with a range of plasma LDL-C concentrations and with other risk factors – diabetes, hypercholesterolemia, normocholesterolemia, angina, previous myocardial infarction (MI), and high-sensitivity C-reactive protein, an inflammatory marker [1]. There is a consensus that reducing plasma LDL-C levels is beneficial; the value of raising plasma HDL-C concentrations is under increasing scrutiny.

Raising Plasma HDL-C Concentrations Is Cardioprotective

The French physician-scientist Michel-Alexandre Macheboeuf is the father of plasma lipoproteins. In his doctoral thesis, *Recherches sur les lipides, les stérols et les protéides du sérum et du plasma sanguins*, he described the coprecipitation of lipids and proteins from horse serum [2]; the precipitate was later revealed to be HDL. Nearly 30 years passed until Gofman and colleagues began the first prospective study to relate HDL subfractions to heart disease risk. After 10 years follow-up they reported that ischemic heart disease was elevated in those with low plasma HDL concentrations, especially the larger, more cholesteryl ester-rich fraction, HDL_2 [3]. This observation was confirmed by a 29 year follow-up of the study [4]. Later investigations of HDL shifted away from the tedious method of analytical ultracentrifugation used by Gofman to measuring plasma HDL-C concentrations. An early study showed that mean HDL-C levels were inversely associated with coronary heart disease (CHD), even after adjusting for LDL-C and

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triglyceride (TG) levels [5]. This association was confirmed by the Framingham Heart Study [6]. Given the compelling cross-sectional and prospective data, tests were begun with the fibrate gemfibrozil, a peroxisome proliferator-activated receptor ∝ (PPAR∝) agonist that profoundly lowers plasma TG concentrations, while modestly increasing plasma HDL-C concentrations. Over a period of 5 years, gemfibrozil versus placebo reduced plasma levels of total cholesterol (10%), non-HDL-C (14%), LDL-C (11%), and TG (35%), and increased mean HDL-C (11%). These changes were associated with a reduction (34%) in the incidence of coronary heart disease [7], a finding that was confirmed by the Veterans Affairs HDL Intervention Trial [8], an important study because it included patients with type 2 diabetes and metabolic syndrome. However, the cardiovascular benefit was more strongly correlated with insulin resistance than with HDL-C. Moderate exercise and regular, moderate alcohol consumption increase the plasma HDL-C concentration nearly equally; however, addition of regular alcohol consumption does not add to the HDL-C-raising effect of moderate exercise [9]. Regular, moderate alcohol consumption is also associated with reduced CVD incidence and mortality [10], an effect initially assigned to attendant increased HDL-C [11]. Collectively, these studies revealed an inverse association between CVD and plasma HDL and HDL-C concentrations, and provided support for plasma HDL-C reduction as a cardioprotective measure.

Raising Plasma HDL-C Concentrations Is Not Cardioprotective

There is now a growing body of evidence that raising plasma HDL-C levels is not uniformly cardioprotective. Various studies, including genetic studies of several large cohorts, have put the 'higher-HDL-is-better' hypothesis in doubt. For example, some patients with genetically elevated plasma levels of apolipoprotein A1 (APOA1), the major protein component of HDL, and of HDL-C, did not have a reduced risk for ischemic heart disease or MI [12]; an HDL-C–raising endothelial lipase variant was not associated with reduced MI [13]; controlling for HDL-C does not affect the magnitude of the negative relationship between alcohol intake and death from CVD [14]. According to these data, HDL is not mechanistically linked to the atheroprotective effects of alcohol ingestion.

Other studies have also failed to support the 'higher HDL-C is better' hypothesis. Many patients with low HDL-C do not develop CVD, and vice versa. For example, the very high plasma HDL-C concentrations found in patients with cholesteryl ester transfer protein (CETP) deficiency do not commensurately reduce CVD incidence [15] and, to date, tests of CETP inhibitors, which profoundly increase HDL-C levels [16,17], have not reduced CVD events [17–19]. The CETP inhibitor torcetrapib disappointed because of unexpected toxicity and mortality [16], and dalcetrapib also failed due to a lack of clinically meaningful efficacy [17], perhaps scuttling the higher-HDL-is-better hypothesis. Mechanisms underlying the potential benefits of CETP inhibitors are difficult to sort out because of their concurrent LDL-C lowering effects.

Although niacin (also known as nicotinic acid or vitamin B3), which increases HDL-C levels, reduces CVD events and all-cause mortality [20], addition of niacin to a statin did not reduce CVD events [21]. In the AIM-HIGH Trial, niacin increased HDL-C and lowered TGs and LDL-C concentrations, but after 3 years the trial was stopped for futility [22]. There was no difference with respect primary composite end-points at the end of 3 years. Thus, it appears doubtful that addition of niacin to a statin adds any benefit. Despite these findings, other niacin analogs and formulations are in various stages of development. Although other niacin analogs that do not cause flushing are in development, the disappointing results of niacin trials with statins put their futures in doubt.

HDL Function

Given the failure of some interventions that raise plasma HDL-C concentrations to prevent atherosclerosis, other mechanistic strategies based on lipoprotein quality and function have