The high-density lipoprotein cholesterol / apolipoprotein A1 ratio: an indicator of cardiovascular disease

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Abstract

Purpose of review

In multiple studies, the high-density lipoprotein cholesterol (HDL-C) concentration has been shown to be inversely associated with cardiovascular disease (CVD) and CVD risk. Based on this observation, increasing the plasma HDL-C concentration is thought to be a desirable strategy, in the 21st century, for decreasing the burden of CVD.

Recent findings

Recent studies have shown that powerful HDL-C concentration-increasing drugs are ineffective for decreasing CVD. Increasing evidence now shows that HDL is an unstable and heterogeneous particle, and that "HDL particle functionality" is far more important in atheroprotection than is the HDL-C level, alone. Apolipoprotein A-I (ApoA-I) is the major protein component of HDL and increasing evidence suggests that the ratio of HDL-C to apoA-I may give additional insight as a risk marker not just for CVD but also for all-cause and cancer mortality.

Summary

In this review, we discuss the importance of HDL composition, apoA-I levels, and the HDL-C/apoA-I ratio for predicting CVD and mortality outcomes.

Keywords

High-density lipoprotein cholesterol / apolipoprotein A-I ratio, cardiovascular disease

Introduction

Numerous studies have shown an inverse relationship between the concentration of high-density lipoprotein cholesterol (HDL-C) and the risk of coronary heart disease [1-3]. Based on these observations, raising plasma HDL-C levels may protect against cardiovascular disease (CVD): the increase in HDL-C concentration may reflect the body's capacity to return peripheral tissue cholesterol to the liver for elimination. However, recent studies have questioned this association; these studies showed that agents that inhibit the cholesterol ester transfer protein (CETP) markedly increase HDL-C concentrations, but fail to show any decrease in cardiovascular events [4,5]. The reason for the failure of these agents to reduce cardiovascular events is uncertain, but these results have focused attention on identifying the key component or function of HDL that confers cardiovascular protection. In attempting to address this issue, recent studies have suggested that the HDL lipoprotein is an unstable and heterogeneous particle, and that "HDL particle functionality" is far more important in atheroprotection than the HDL-C level, alone [6].

The protein component of HDL is 70% apolipoprotein A-I (apoA-I) and 20% apolipoprotein A-II (apoA-II) [7]. HDL lipoprotein particles are heterogenous in size, charge, lipid and proteomic composition, metabolism and function. Consequently, alternative indices of the lipoprotein besides HDL-C, such as HDL function, size or composition of HDL particles may be better clinical markers of the physiological role of HDL particles. Recently, the HDL-C/apoA-I ratio was shown to be associated with preclinical atherosclerosis and mortality [8,9]. In this review, we discuss recent evidence obtained from intervention studies that have tested the effect of increasing HDL-C levels on clinical outcomes. We also discuss the relationship between HDL composition and CVD, and the clinical implications of the HDL-C/apoA-I ratio on CVD risk prediction.

Dysfunctional HDL and atherosclerosis

HDL comprises a heterogenous group of particles that differ in size, density, composition of lipids and apolipoproteins and electrophoretic mobility. α-HDL is the most abundant HDL in human plasma, whereas pre-β-HDL represents only 2-14% of the apoA-I population [10,11]. HDL metabolism involves at least 5 important steps. First, apoA-I, secreted by the liver and intestine, combines with phospholipids to form small, discoidal pre-β-1-HDL that can bind to cholesterol. Second, pre-β-HDL is converted into small, discoidal α-4-HDL by the efflux of cellular free cholesterol from macrophages into the arterial wall via ATP-binding cassette (ABC)A1 and ABCG1 transporters. Third, lecithin-cholesterol acyl transferase (LCAT) esterifies the cholesterol. Fourth, the triglyceride (TG) from TG-rich lipoprotein is exchanged for the HDL cholesterol ester (CE) through the functioning of CETP,

resulting in the formation of pre-α-HDL (reverse cholesterol transfer). Lastly, the liver takes up CE from HDL and apoA-I and the remaining pre-β-HDL is catabolized and excreted by the kidney [12].

Among the two membrane transporters implicated in cholesterol transport from macrophages, that is, ABCA1 and ABCG1, ABCA1 exports cholesterol to lipid-free apoA-I, whereas ABCG1 mediates cholesterol efflux to mature HDL, but not to lipid-free apoA-I [13,14]. ABCA1 and ABCG1 function cooperatively to remove cholesterol from cells in vitro, and dysfunction of these two transporters impairs reverse cholesterol transport and increases macrophage cholesterol accumulation in vivo [15] In a study by Du et al.,using reconstituted HDL particles of defined size and composition, they showed that ABCA1 is the major mediator of macrophage cholesterol efflux to HDL, demonstrating most marked efficiency with small, dense HDL subfrations (HDL3b and HDL3c) [16].

Nearly 20 years ago, the conversion of HDL from an anti-inflammatory particle to a proinflammatory particle was suggested to occur during the acute-phase response [17]. The data used to make this suggestion were obtained by measuring the capacity of a 'test' HDL to inhibit monocyte chemotaxis induced by oxidized LDL. Patients with coronary heart disease (CHD) showed significantly higher levels of this 'inflammatory index' than did control patients [18]. In contrast to the anti-inflammatory HDL particle, the proinflammatory particle was characterized by an altered protein composition that contained increased levels of ceruloplasmin and serum amyloid A (SAA), and decreased levels of apoA-I, PON, and PAF-AH [17].

Overexpression of LCAT, in a mouse model, increased the risk of atherosclerosis despite increased plasma HDL-C and apoA-I levels [19]. A subsequent report showed that in the absence of CETP and LCAT-generated HDL cholesterol esters cannot be transferred to TG-rich lipoproteins, resulting in the formation of HDL particles with altered composition and function [20]. Thus, distinguishing between loss of HDL function and increased HDL dysfunction may be important.

The anti-inflammatory and antioxidative activities of HDL can be impaired due to the accumulation of HDL particles containing oxidized phospholipids, which possess proinflammatory properties. In a proteomics study involving patients with acute coronary syndrome (ACS), HDL particles had higher levels of SAA, complement C3, and other inflammatory proteins, compared with HDL particles from individuals without ACS [21]. In an analysis of the Nurses' Health and Health Professionals Follow-Up Studies, the presence or absence of apoC-III in an HDL subfraction identified patients with and without a risk of future CHD [22]. Therefore, these results suggest that the alteration of HDL composition may be key to HDL's atheroprotective role.

HDL/apoA-I oxidation and composition in inflammation

Myeloperoxidase (MPO), a heme protein highly expressed in human atherosclerotic tissue, is able to modify lipids, proteins, and lipoproteins [23,24]. Oxidation of apoA-I by MPO, results in increased oxidation of multiple residues. In turn, oxidative damage to HDL-associated lipid-poor apoA-I in the arterial wall might decrease the capacity of HDL/apoA-I to mediate cholesterol efflux from macrophages, thus promoting atherosclerosis development [25,26]. In addition to MPO-induced oxidation of apoA-I, HDL also undergoes substantial modification during the inflammatory response. Further, the circulating levels of HDL and apoA-I are markedly decreased during the inflammatory acute-phase response; HDL particles become enriched in TG and depleted of cholesteryl esters [27].

During the acute-phase response, SAA might associate with spherical HDL particles, resulting in the displacement of apoA-I [28]. SAA might also reduce the levels of HDL-C by inhibiting the formation of nascent HDL [29]. Cytokines are known to increase hepatic SAA expression, and the secreted SAA is associated with HDL, thereby comprising the major protein of HDL [30]. SAA and apoA-I levels seem to be reciprocally regulated in the liver by inflammatory cytokines, suggesting the substitution of apoA-I by SAA during the acute-phase response.

Other mechanisms that affect HDL composition during inflammation are suggested by the loss of HDL-associated PON and PAF-AH, reduced HDL function, and an increased rate of apoA-I catabolism via phospholipase A2 [17,31].

Clinical implications of the HDL-C/apoA-I ratio

Decreased HDL-C and apoA-I concentrations are known to be associated with an increased risk of CVD. The association between low HDL-C concentrations and increased CVD risk being mediated through other factors, such as insulin sensitivity, HDL particle size, apoA-I content, or the ratio of lipid to apoA-I within the HDL particle, and affecting HDL function is plausible [32]. Pre-β-HDL and lipid-poor apoA-I particles are synthesized and secreted from both the liver and intestine, and pre-β-HDL particles can bind to the hepatic and enterocyte ABCA1 transporters and modulate intracellular cholesterol levels in the liver and intestine [33]. These results support data showing that the ratio of lipid to apoA-I within the HDL particle may affect HDL function [34]. High TG and low HDL-C levels are well-known to increase CVD risk; however, data are limited from studies describing the association of HDL-C levels with CVD risk after adjusting for other CV risk factors, such as levels of apoA-I or other atherogenic lipoproteins [35]. In addition, functional studies that have dynamically assessed HDL function and CVD are very limited.

Borja et al recently developed a rapid and precise assay employing electron paramagnetic resonance spectroscopy that measures the relative rate of HDL-apoA-I exchange (HAE). HAE provides a

measure of the ability of HDL to remodel and release lipid-poor apoA-I [36,37]. The ratio of lipid-free to lipid-bound apoA-I measured by this assay provides a measure of the relative exchangeability of endogenous apoA-I and the dynamic nature of HDL particles. HAE is known to be impaired in patients with CVD [37]. In this study, they found that HAE was highly correlated with both total and ABCA1-specific cholesterol efflux capacity, and this relationship remained significant after adjustment for HDL-C or apoA-I in 77 subjects, concluding that the ability of HDL to exchange apoA-I and remodel is a significant contributor to serum HDL efflux capacity, independent of HDL-C and apoA-I *per se* [38].

In our previous studies investigating the association between HDL-C concentrations and coronary artery calcium scores (CACs) (marker of pre-clinical atherosclerosis) and all-cause mortality, we evaluated associations with the HDL-C/apo A-I ratio [8,9]. The purpose of controlling for apoA-I levels was to investigate the influence of varying the HDL-C to apoA-I ratio. In a cross-sectional study of 12,031 men from an occupational cohort, computed tomographic estimations of their CAC score (CACS) resulted in the stratification of the men into four groups according to their HDL-C levels [8]. The proportion of men with CACS > 0 decreased linearly from the 1st to 4th HDL-C quartile groups (13.9, 11.1, 10.4, and 9.7%; $p < 0.001$). When regression analyses were undertaken with CAC as the dependent variable, the odds ratio (OR) for CAC were significantly lower in the 2nd to 4th quartile groups, compared with the lowest quartile group. However, when apoA-I was included in the model, there was a marked change in the direction of the relationship, with a positive association between HDL-C concentration and CACS > 0. When the OR for CACS > 0 was analyzed according HDL-C/apoA-I ratio quartile groups, those in the highest HDL-C/apoA-I quartile showed an increased OR of CACS > 0 (1.21; 95% confidence interval, 1.06-1.63). In contrast, when the OR for CACS > 0 was analyzed by apoA-I quartile group, those in the highest quartile group showed a significantly decreased OR compared with the lowest quartile group, and the results were not materially altered by adjusting for HDL-C level.

In another study by our group, involving 263,340 people (2002-2009), the association between risk of CVD-related, cancer-related, and all-cause mortality was analyzed according to HDL-C levels, apoA-I levels, and HDL-C/apoA-I ratios [9]. Although HDL-C level did not show a significant association with mortality risk, the apoA-I level was inversely associated with cancer mortality, after adjusting for risk factors. In addition, in the highest HDL-C/apoA-I quartile a significantly increased risk for CVD-related, cancer-related, and all-cause deaths was observed.

These results suggest that the apoA-I level, rather than the HDL-C level, is important in affecting subclinical atherosclerosis and mortality. Furthermore, we suggest that an increased HDL-C/apoA-I ratio may be a surrogate marker for subclinical atherosclerosis and an increased mortality risk. The

conceptual model of dividing the HDL-C concentration by the apoA-I concentration may reflect a variation in the amount of cholesterol per HDL particle. Our findings suggest that individuals with cholesterol-rich HDL particles (those with high HDL-C/apoA-I ratios) have an increased risk of subclinical atherosclerosis and mortality (Figure 1). In contrast, individuals with lipid-poor HDL particles (a low HDL-C/apoA-I ratio) have a lower prevalence of subclinical atherosclerosis and mortality. This suggests that cholesterol-poor HDL particles have a better capacity to accept cholesterol from peripheral tissues than do cholesterol-rich HDL particles, which have a limited capacity to accept more cholesterol and thereby increasing the risk of atherogenesis. These suggestions are supported by other data showing that HDL quality, rather than quantity, is important. In addition, lifestyle modifications and strategies for improving metabolic abnormalities may be great options for altering the HDL-C/apoA-I ratio (Figure 1). Also, studies have shown that selective delipidation procedures convert large HDL particles into small particles resembling small α, pre-β-1, and other pre-β forms, increasing the efficacy of plasma to stimulate cholesterol transfer from monocytes to HDL particles [39]. These studies also showed that selective HDL delipidation activates reverse cholesterol transport and tends to reduce diet-induced aortic atherosclerosis in monkeys, as assessed by intravascular ultrasound (IVUS).

Previously reported studies show results similar to ours. The Prospective Epidemiological Study of Myocardial Infarction reported the absence of an association between HDL-C concentration and myocardial infarction, after adjusting for apoA-I, LDL-C, and TG levels [40]. In the Atherosclerosis Risk in Communities study, HDL-C levels were negatively associated with CVD risk following adjustment for apoA-I and apoB levels [41]. In another study, a post-hoc analysis of two prospective studies suggested that when apoA-I levels were kept constant in statistical models, a high HDL-C concentration and an increased HDL particle size conferred increased CVD risk [42].

As for the implications of HDL-C/apoA-I ratio on clinical outcome, in 2,566 statin-treated patients with angiographic coronary artery disease who underwent serial evaluation of atheroma burden with IVUS, increasing ratio of HDL-C/apoA-I, but not HDL-C or apoA-I, showed association with less progression of percent atheroma volume and total atheroma volume [43]. In another study performed in 2,529 Chinese patients who underwent elective percutaneous coronary intervention (PCI), U-shaped association was seen between quintiles of postprocedural peak cardiac troponin I elevation and HDL-C/apoA-I ratio, showing the lowest risk in the middle quintile of HDL-C/apoA-I ratio, although the mechanism for this association is still unclear [44].

Recently, a mechanism for apoA-I-mediated atheroprotection was proposed, suggesting that apoA-I stimulates CETP and apoE secretion from lipid-loaded macrophages. ApoA-I has been shown to attenuate palmitate-mediated NF-κB activation by reducing Toll-like receptor-4 recruitment into lipid

rafts. Therefore, targeting apoA-I overexpression might be a useful tool for combatting vascular inflammation [45]. A recently published results from AEGIS-I, a phase 2b clinical which evaluated the safety profile of CSL112, a reconstituted infusible formulation of apoA-I among subjects with acute myocardial infarction (AMI) [46]. Among 1,258 patients with AMI, 4 weekly infusions of CSL112 were feasible, well tolerated, and not associated with any significant alterations in liver of kidney function of other safety concern. The ability of CSL112 to acutely enhance cholesterol efflux was confirmed. Together with our results, these results emphasize that the apoA-I concentration is a better surrogate marker of CVD risk; we suggest that strategies for increasing apoA-I levels would reduce CVD risk and prevent CVD. In addition, HDL-C/apoA-I ratio could be considered as the novel surrogate marker for the prediction of the subjects with high CVD risk.

Conclusion

In conclusion, our data and those of others suggest that the HDL-C/apoA-I ratio may be a novel surrogate marker for an increased risk of CVD, and all-cause and cancer mortality. Further work is needed to test the effect of this ratio in risk prediction studies. We suggest that an increased HDL-C/apoA-I ratio may reflect cholesterol-rich HDL particles that have an impaired capacity to accept additional excess cholesterol from peripheral tissues and developing atherosclerotic plaques.

Key points

- Increasing evidence now shows “HDL particle functionality” is far more important in atheroprotection than is the HDL-C level, alone.
- Apolipoprotein A-I (ApoA-I) is the major protein component of HDL
- HDL-C to apoA-I ratio may give additional insight as a risk marker not just for CVD but also for all-cause and cancer mortality.

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Conflicts of interest

None.

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**The estimated HRs mortality according to quartiles of HDL-C/ApoA-I ratio were analyzed from an occupational cohort of 263,340 Korean adults. During the median follow-up of 4.2 years, there was a positive trend for the association across HDL-C/ApoA-I ratio quartiles and mortality from CVD,

cancer and all-cause. The adjusted HRs for mortality in the highest HDL-C/ApoA-I ratio quartile versus the lowest were 2.37 (95% CI 0.89 to 6.37)(CVD); 2.32 (95% CI 1.34 to 4.03)(cancer) and 1.87 (95% CI 1.32 to 2.66)(all-cause). These data show for the first time that an increased HDL-C/ApoA-I ratio may be a shared risk factor for CVD, cancer and all-cause mortality.

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*** This study examines the safety and tolerability of CSL112, a reconstituted, infusible, plasma-derived ApoA-I in patients with AMI. CSL112 was well-tolerated and were not associated with alterations in either kidney or liver function.

Figure 1. The clinical implication of HDL-C/ApoA-I ratio