Should we target HDL cholesterol level in lowering cardiovascular risk?

Peter P. Toth
Preventive Cardiology, Sterling Rock Falls Clinic, Sterling, IL, United States
University of Illinois, Peoria, IL, United States

Correspondence to: Peter P. Toth, MD, PhD, FAAFP, FNLA, FCCP, FACC, Preventive Cardiology, Sterling Rock Falls Clinic, 101 E. Miller Rd, Sterling, IL 61081, USA, phone: +1-815-632-50-93, fax: +1-815-626-59-47, e-mail: peter.toth@srfc.com
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ABSTRACT
In prospective observational studies and retrospective case control studies performed throughout the world, low serum levels of high-density lipoprotein cholesterol (HDL-C) are consistently associated with increased risk for all forms of atherosclerotic disease and its clinical sequelae, including myocardial infarction, stroke, and sudden death. In contrast, high serum levels of this lipoprotein are associated with reduced risk for these outcomes. The metabolism of high-density lipoproteins (HDLs) is complex, and a very large number of genetic polymorphisms influence the serum level of HDL particles in any given individual. A significant question in cardiovascular medicine is whether or not prospectively raising HDL in patients at risk is associated with significant reductions in cardiovascular events and rates of atherosclerotic disease progression. A recent comprehensive meta-analysis that incorporated the results of 108 prospective clinical trials suggests that the answer to this question is “no” with currently available lipid modifying therapies. However, a number of individual clinical trials and other meta-analyses suggest that, in fact, raising HDL does beneficially impact risk for cardiovascular events and slows progression or even reverses atherosclerosis. HDL appears to antagonize atherogenesis and drive a number of vasculoprotective phenomena. It has antioxidative, anti-proliferative, anti-thrombotic, and anti-inflammatory properties and potentiates reverse cholesterol transport. Under some conditions, the proteosome of HDL can change, rendering it pro-inflammatory and pro-oxidative. This paper explores many of the key questions surrounding HDL-C and why probing its efficacy may not be entirely amenable to a meta-analysis. Numerous drugs are in development which have the capacity to raise HDL-C dramatically. It is hoped that these agents will be able to provide us with a more definitive answer about the clinical efficacy of raising HDL-C, and what specific approaches will be necessary in patients with specific genetic and metabolic backgrounds in both the primary and secondary prevention settings.

Introduction  Atherosclerotic disease is widely prevalent throughout the world and predisposes patients to such clinical sequelae as myocardial infarction (MI), stroke, claudication, and sudden death. The major risk factors for developing coronary artery disease (CAD) are well characterized and include dyslipidemia, hypertension, insulin resistance and diabetes mellitus, obesity, age, family history, and cigarette smoking. The dyslipidemias are a complex group of metabolic disorders which include abnormalities in the production, trafficking, and clearance of chylomicrons, triglycerides, very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). Derangements in lipoprotein metabolism that result in elevated serum levels of atherogenic lipoproteins are unequivocally associated with increased risk for developing CAD, and aggressive reductions in the burden of these lipoproteins (especially LDLs) are correlated with significant decreases in risk for acute cardiovascular events in both the primary and secondary prevention settings.

HDLs constitute a complex group of lipoproteins. In contrast to atherogenic lipoproteins, HDLs appear to protect against the development of atherosclerosis. In a large number
of prospective epidemiologic studies and retrospective case control studies, high serum levels of HDL cholesterol (HDL-C) or of apoprotein A-I (its primary apoprotein constituent) are associated with reduced risk for CAD, while low levels are frequently observed in patients with this disease.\textsuperscript{3,11} Low serum levels of HDL-C are correlated with increased risk for ischemic stroke\textsuperscript{12}, left main coronary disease\textsuperscript{13}, sudden death\textsuperscript{14}, and recurrent infarction or death following placement of a drug eluting stent\textsuperscript{15}. Even among patients with stable CAD treated with high-dose statin therapy to an LDL-C <70mg/dl, lower HDL-C levels are associated with significantly higher risk for cardiovascular events.\textsuperscript{16} Simply lowering LDL-C more and more does not seem to constitute an adequate approach to optimally mitigating risk due to dyslipidemia, especially in its mixed forms.

Taken in aggregate, it should be relatively straightforward to conclude that decreasing LDL-C and increasing HDL-C should together constitute important goals for reducing risk for CAD. While this may ultimately turn out to be true, this approach is not widely accepted, despite the fact that in both Europe and the United States, recommendations on this have been advanced for higher risk patients.\textsuperscript{17,18} It is acknowledged in cardiovascular medicine that, when it comes to LDL-C, lower is better.\textsuperscript{19,20} The clinical importance and utility of raising HDL-C in order to potentiate reductions in risk for cardiovascular morbidity and mortality is a much more controversial therapeutic goal. There are a plethora of reasons for this.

Meta-analyses of clinical trials Meta regression analyses are an important tool with which to try to explore relationships among variables with much larger numbers of subjects than might be encountered in a single clinical trial. In an analysis of 14 prospective randomized statin trials by the Cholesterol Treatment Trialists Collaboration, for every 1 mmol/l reduction in serum LDL-C with statin therapy over a mean 5-year follow-up, there was a 12% reduction in all cause mortality, a 19% reduction in coronary mortality, a 24% reduction in MI or coronary death, a 24% reduction in need for revascularization, and a 17% reduction in fatal/nonfatal stroke.\textsuperscript{21} A number of meta-analyses have also been performed on studies which measured changes in HDL-C in response to different therapies.

The largest meta-analysis to date of randomized, controlled clinical trials showed no benefit by intention to treat, etc.) were also performed. None of these adjustments altered the final conclusion. There was a preponderance of statin trials (62), followed by trials using fibrates (9), combinations of drugs with niacin (6), diet/surgery (5), and others. Of note, the average HDL-C elevation in the statin trials was 1.6 mg/dl, in the fibrate trials 2.6 mg/dl, and in the groups given combinations with niacin 12 mg/dl. In the diet/surgery group, HDL-C changed 0.1 mg/dl and with glitazones 3.1 mg/dl. With the exception of the niacin combination treatments, these constitute modest changes in HDL-C at best. Any signal resulting from the niacin trials would likely be drowned out as there were only 779 randomized subjects in this group. The meta-analysis is heavily weighted toward statin intervention trials (157,101 subjects). In the meta-analysis as a whole, the mean change in HDL-C was 1.7 mg/dl. This may be a size effect that is below the biological threshold necessary to detect a beneficial effect of HDL-C on cardiovascular morbidity and mortality. Given the fact that this is a meta-analysis, the lack of effect of HDL-C on cardiovascular outcomes must be considered hypothesis generating only. Consistent with this, had there been a positive result, it would have been suggestive of benefit, not demonstrative of one. Consistent with other meta-analyses, the study did show a statistically significant effect of LDL-C reduction on cardiovascular events.

Three other recent meta-analyses leave the door open for HDL and its possible beneficial impact on both the progression of CAD and reduction in risk for cardiovascular events. A meta-analysis of four statin based coronary intravascular ultrasonography studies which included 1455 patients showed significant coronary atheroma regression when an LDL-C reduction below 87.5 mg/dl is coupled with at least a 7.5% elevation in HDL-C.\textsuperscript{23} In this study, HDL-C increased from a mean of 42.5 to 45.1 mg/dl, a change of 2.6 mg/dl. None of the trials in this meta-analysis were powered to evaluate impact on cardiovascular events. An analysis by Brown et al. of 23 randomized controlled trials supported the importance of coupling aggressive elevations in HDL-C with reductions in LDL-C.\textsuperscript{24} After adjustment for placebo, the sum of the % HDL increase and % LDL reduction correlated linearly with reduction in cardiovascular morbidity and mortality as well as change from baseline in mean proximal percent stenosis on quantitative coronary angiography. Importantly, the combination of statins with bile acid binding resins and niacin combination therapies yielded the largest benefit in both of these endpoints. Another analysis of 11 statin trials shows that as HDL-C levels on treatment increase, rates of atherosclerosis disease progression decrease linearly.\textsuperscript{25} While it makes clinical sense to try to regress atherosclerotic plaque, it is not yet clear whether or not plaque regression correlates with reductions in cardiovascular events.
What have individual clinical trials taught us about HDL-C elevation? Although niacin combination therapies in the above meta-analyses yield the largest effects on HDL-C and some of the most compelling reductions in both cardiovascular events and rates of coronary atherosclerotic disease progression, clinical trials with fibric acid derivatives (i.e., “fibrates”) in both the primary and secondary prevention settings have also provided insight into the importance of managing HDL-C. In the Veterans Affairs HDL-C Intervention Trial (VA-HIT), 2531 men with coronary heart disease (CHD) and HDL-C >40 mg/dl (mean baseline 31 mg/dl) were treated with 600 mg of gemfibrozil twice daily. Risk for CAD-related events was reduced by 11% for each 5-mg/dl increase in HDL-C. Neither baseline nor on-treatment LDL-C nor triglycerides correlated with event reduction. Similar results were found in patients without CHD in the Helsinki Heart Study. Reduction in CHD risk was not due to the 35% decrease in triglyceride levels; rather, it was significantly associated with changes in LDL-C (~11%) and HDL-C (~11%) levels. In the Bezafibrate Infarction Prevention (BIP) Study, 3122 subjects with stable CAD or previous MI and HDL-C <45 mg/dl, triglycerides <300 mg/dl, and LDL-C <180 mg/dl were treated with 400 mg/d of bezafibrate. Bezafibrate therapy increased HDL-C by 18% and reduced triglycerides by 21%, resulting in a frequency of the primary endpoint of 13.6% on bezafibrate therapy vs. 15% on placebo (p = 0.26). However, the reduction in the primary endpoint with bezafibrate treatment was 39.5% (p = 0.02) in a subgroup with triglycerides >200 mg/dl. The relationship between on-treatment increments in HDL-C levels and cardiac mortality was subsequently assessed in 3026 BIP trial participants. Over a median of 7.9-years follow-up, the risk of cardiac mortality decreased by 27% for every 5-mg/dl increase in on-treatment HDL-C (p <0.001).

More recent studies also suggest a positive relationship between elevating HDL-C and reducing rates of atherosclerosis disease progression. Prospective controlled trials with the thiazolidinedione pioglitazone in subjects with type 2 diabetes mellitus show that raising HDL-C stabilizes both carotid intima media thickness and coronary atheromatous plaque. Torcetrapib is a cholesteryl ester transfer protein (CETP) inhibitor. CETP catalyzes a 1 for 1 stoichiometric exchange of cholesteryl esters from HDL particles for triglycerides in apoB100-containing particles, such as VLDL. By reducing the loading of HDL particles with triglycerides, the particle is rendered less vulnerable to lipolysis and catabolism by hepatic lipase. This therapeutic approach is designed to preserve HDL. Torcetrapib has been removed from development because it induced a number of off-target toxicities, including hypertension, hypokalemia, elevations in aldosterone secretion, and significant elevations in serum bicarbonate. It is believed that these changes account for its association with increased mortality. In the ILLUSTRATE trial (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation), a post hoc analysis reveals that among patients who experienced a 56% or more elevation in HDL-C, there was a significant regression in percent atheroma volume among target coronary plaques. Other CETP inhibitors, such as dalcetrapib and anacetrapib, that do not stimulate aldosterone production and elevate blood pressure are in development and will hopefully provide greater insight into how to manipulate this pathway of HDL metabolism in a clinically favorable manner.

Why is sorting HDL out so complicated? Low serum levels of HDL-C are widely prevalent and are a defining feature of familial combined hyperlipidemia, familial hypoalphalipoproteinemia, insulin resistance and metabolic syndrome, and Tangier’s disease. A large number of genetic polymorphisms in cell surface receptors, serum lipases and intracellular enzymes, and apoproteins regulate serum HDL-C levels. The proteome of HDL particles is complex, with up to 75 different proteins evaluable by shotgun proteomics. The protein cargo of HDL can change rapidly in response to both acute and chronic changes in metabolic background. HDL particles are comprised of a variety of apoproteins (apo A-I, apo A-II, apo C-I, apo C-II, apo C-III, apo E, apo J), antioxidative enzymes (paraoxonase, platelet activating factor acetylhydrolase, glutathione peroxidase), enzymes involved in lipid metabolism (lecithin cholesteryl acyl transferase, CETP), and components of the complement pathway.

HDL particles can exert a variety of antiatherogenic functions. Among the most important of these is their ability to drive the process of reverse cholesterol transport (RCT), a series of reactions by which HDL particles interact with cell surface receptors on macrophages (ATP binding membrane cassette transports A1 and G1 [ABCA1, ABCG1], scavenger receptor BI), promote the externalization and esterification of cholesterol, and transport this cholesterol back to the liver for elimination as either bile acids or biliary cholesterol. The process of RCT has been confirmed in both animal and human models. HDL particles also have the capacity to reduce oxidized acyl chains in LDL, inhibit endothelial cell adhesion molecule expression, stimulate vasodilatation and endothelial nitric oxide production, promote endothelial progenitor cell migration and repair, inhibit endothelial apoptosis, inhibit platelet activation, and participate in immunity, among other possible functions. Unlike other lipoproteins which are generally viewed as inducers of endothelial cell dysfunction and atherogenesis, HDL particles are seen as potentially capable of maintaining normal endothelial function and as antagonizing lipid deposition and atherogenesis in the vessel wall.
It is unique among lipoproteins, not only in its range of function, but also in its constitutional complexity. In general, all HDL particle species (nascent discoidal HDL, HDL₃, HDL₄) are seen as antiatherogenic and beneficial. Is a low serum HDL-C always associated with increased risk? No. Examples of low serum levels of HDL-C associated with longevity are seen in patients who are carriers of apo A-Iₐₙₐₙ and apo A-Iₜₜₜ. These apo A-I variants compensate for low serum availability by having increased functionality, with greater capacity for RCT and vascular-protective functions. A reconstituted, infusible form of apo A-Iₐₙₐₙ was induced to show significant human coronary atheromatous plaque regression in only 5 weeks relative to placebo. Unfortunately, development of this therapeutic approach was halted due to risk for anaphylactic reactions. Is HDL always beneficial and vascular-protective? The answer here appears to be no. Under proinflammatory systemic conditions, the proteosome of HDL particles can change, leading to loss of vasoprotection and increased potential for pro-inflammatory and pro-oxidative activity. Key apoproteins and antioxidative enzymes can be replaced by acute phase reactants and other mediators of injury. Treatment of patients with CAD and pro-inflammatory HDL with such drugs as statins and niacin helps to restore appropriate HDL functionality and phenotype. Do patients with high HDL-C also develop CAD? Yes, but much depends on their genetic and metabolic background, the burden of concomitant risk factors, and the functionality of their HDL particles. Sweeping generalizations do not apply to HDL. It is both ontically and teleonomically a complex polymolecular assembly prone to reorganization and adjusting its functionality depending upon the prevailing metabolic milieu.

Where do we go from here? Clearly, HDL metabolism is fascinating and, in many ways, perplexing. We speak in common parlance of HDL-C being protective, yet this is not true. It is the HDL particle, not the cholesterol transported in HDL, that exerts antiatherogenic efficacy. A large variety of drugs are being developed to further explore the clinical utility and benefit of HDL raising in patients at risk for cardiovascular events. Based on the studies summarized above, we have every reason to pursue these approaches. Unlike the current use of statins, fibrates, bile acid binding resins, and other lipid modifying drugs, it is possible that future HDL therapies will have to be much more tailored to patients with specific genetic and metabolic characteristics. Sorting this out will require an enormous amount of additional investigation. It is unlikely to be a simple one size fits all approach to metabolic modification. It is possible that specific types of patients may require complex combinations of drugs based on the presence or absence of specific genetic polymorphisms. Much more attention will also have to be devoted to how established and emerging therapies impact not only the production but also the functionality of HDL particles, and what impact this has on disease progression as well as cardiovascular morbidity and mortality in both the primary and secondary prevention settings.

As a preventive cardiologist and clinical lipido-ologist, do I treat low serum levels of HDL-C in patients at risk in the year 2009? Absolutely. Many studies that have looked at this issue and have been able to raise HDL-C significantly do suggest that this is an important therapeutic maneuver and impacts rates of disease progression as well as cardiovascular events. Is there a serum level we need to raise it to? We need more information about functionality and whether or not there is a true identifiable threshold. While we have surmised such thresholds for LDL-C stratified by risk, I do not expect that there will be one for HDL-C. While the study by Briel is rigorous and quite well done, given the number of metabolic pathways and nuclear transcription factors that impact HDL, the number of factors that regulate HDL serum concentration and functionality, the heterogeneity of different drugs on HDL metabolism (e.g., stimulating hepatic apo A-I expression, reducing triglyceride loading of HDL and decreasing its catabolism, stimulating intravascular HDL biosynthesis by upregulating ABCA1 expression, etc.), is this lipoprotein species truly amenable to meta-analysis? I do not believe so. Future prospective, randomized studies will help us to more effectively ascertain how and under what circumstances to raise HDL-C. In the meantime, it is important to treat patients with currently available pharmacologic and lifestyle approaches to raise HDL-C.

REFERENCES

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Sacks FM. The role of high-density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: expert group recommendations. Am J Cardiol. 2002; 90: 139-143.


Toth PP. When high is low: raising low levels of high-density lipoprotein cholesterol. Curr Cardiol Rep. 2008; 10: 488-496.
ARTYKUŁ POGŁĄDOWY

Czy powinniśmy wpływać na stężenie cholesterolu HDL w celu zmniejszenia ryzyka sercowo-naczyniowego?

Peter P. Toth
Preventive Cardiology, Sterling Rock Falls Clinic, Sterling, IL, Stany Zjednoczone
University of Illinois, Peoria, IL, Stany Zjednoczone

Adres do korespondencji:
Peter P. Toth, MD, PhD, FAAP, FNLA, FCCP FAHA, FACC,
Preventive Cardiology, Sterling, Rock Falls Clinic, 101 E. Miller Rd, Sterling, IL 61081, USA,
etl. +1 815 632 59 93,
tax +1 815 626 59 47,
e-mail peter.toth@srfc.com

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STRESZCZENIE

W prospektywnych badaniach obserwacyjnych i retrospektywnych badaniach kliniczno-kontrolnych przeprowadzonych na całym świecie małe stężenie w surowicy cholesterolu frakcji lipoprotein o dużej gęstości (high-density lipoprotein cholesterol – HDL-C) wiąże się spójnie ze zwiększym ryzykiem wszystkich postaci choroby mijażdyżcowej i jej następstw klinicznych, w tym zawalu serca, udaru mózgu i naglej śmierci sercowej. Natomiast duże stężenie tej lipoproteiny w surowicy wiąże się ze zmniejszonym ryzykiem wystąpienia tych zdarzeń. Metabolizm lipoprotein o dużej gęstości (high-density lipoprotein – HDL) jest złożony, a na stężenie cząstek HDL w surowicy u poszczególnych osób wpływa wiele polimorfizmów genetycznych. Ważnym pytaniem w leczeniu chorób sercowo-naczyniowych jest: czy zwiększenie stężenia HDL u chorych z grupy ryzyka spowoduje istotne zmniejszenie częstości zdarzeń sercowo-naczyniowych i prędkości progressji choroby mijażdyżcowej. Niedawna obszerna metaanaliza obejmująca wyniki 108 prospektywnych badań klinicznych sugeruje, że odpowiedź na to pytanie jest przecząca, przy obecnie dostępnych metodach leczenia modyfikującego stężenia lipidów. Niemniej jednak szereg indywidualnych badań klinicznych i inne metaanalizy sugerują, że w rzeczywistości zwiększenie stężenia HDL wpływa korzystnie na ryzyko zdarzeń sercowo-naczyniowych i zwalnia progresję lub nawet cofa mijażdyżcję. HDL wydają się przeciwdziałać rozwojowi mijażdyżicy i brać udział w mechanizmach chroniących naczynia. Mają właściwości antyoksydacyjne, antyproliferacyjne, przeciwkrzepłiwie i przeciwpalne oraz zwiększają zwrotny transport cholesterolu. W pewnych sytuacjach proteosom HDL może się zmienić, zmieniając działanie cząstki na prozapalne i prooksydacyjne. W niniejszej pracy omówiono wiele kluczowych pytań dotyczących HDL-C oraz wyjaśniono, dlaczego metaanaliza nie jest wystarczająco dobrą metodą oceny jego efektów. Trwają prace nad wieloma lekami umożliwiającymi znaczne zwiększenie stężenia HDL-C. Jest nadzieja, że ich zastosowanie może dostarczyć bardziej jednoznacznej odpowiedzi na temat klinicznej skuteczności zwiększania stężenia HDL-C oraz jakie swoiste podejście będzie niezbędne u chorych z określonymi zaburzeniami genetycznymi i metabolicznymi w warunkach prewencji pierwotnej i wtórnej.

SŁOWA KLUCZOWE

cholesterol, lipoproteiny o dużej gęstości, metaanaliza, mijażdyżca, odwrotny transport cholesterolu

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