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Beyond LDL-Cholesterol: New Treatments Raising HDL-Cholesterol or Enhancing Reverse Cholesterol Transport

K. Kostner

Abstract: Atherosclerotic cardiovascular disease is the worldwide leading cause of death. Atherosclerosis involves multiple pathways in which lipoprotein entry and retention, injury to the vessel wall from several stimuli and an associated long term inflammatory and immune response seem to play a key role.

Currently available treatments are aimed at reducing the high plasma lipid concentrations, most particularly LDL-cholesterol. These therapies include dietary restrictions, drugs (mainly statins) and LDL-apheresis. Unfortunately cardiovascular events continue to occur despite LDL-lowering therapy. This is probably due to the fact that there are other important risk factors in certain patients than LDL-cholesterol. Therefore there is a clear need for additional preventive and therapeutic interventions to complement the results of LDL lowering. One such target for new interventions is HDL and/or its apolipoproteins. In this review I will focus on treatments that raise HDL-cholesterol or enhance reverse cholesterol transport. Old and new drugs will be discussed as well as combination therapy and novel approaches like plasma delipidation and recombinant apolipoprotein AI.

Kurzfassung: Neue Therapiekonzepte zur Beeinflussung der HDL. Atheroskleroseassoziierte Erkrankungen sind weltweit immer noch die Todesursache Nummer 1. Heute stehen uns eine Reihe von Therapiemöglichkeiten, wie Diät, Statine oder LDL-Apherese, zur Verfügung, welche zu einer signifikanten LDL-Reduktion führen. Trotz exzellenter Risikoreduktion sowohl in der Primär- als auch in der Sekundärprävention, sind kardiovaskuläre Mortalität und Morbidität nach wie vor eine große Herausforderung für Ärzte und unser Gesundheitssystem.

Deshalb besteht ein klarer Bedarf an neuen Interventionsmöglichkeiten. High Density Lipoproteine sind ein möglicher Ansatzpunkt, und deshalb möchte ich in diesem Reviewartikel alte und neue Strategien zur Erhöhung von HDL beleuchten und 2 neue Therapieansätze, die zur Zeit klinisch getestet werden, vorstellen.
J Kardiol 2002; 9: 328–31.

■ Introduction

The clinical manifestations of atherosclerosis (cardiovascular, cerebrovascular and peripheral vascular disease) are together the major causes of death in developed countries. They are also becoming a growing problem in developing countries. Many sufferers are young and highly productive and present statistics indicate that a male child in the USA or Australia has a one in five risk of developing clinical evidence of cardiovascular disease before his 65th birthday.

Despite the tremendous progress in the achievement of lowering serum cholesterol concentrations to prevent CHD by diet, drug therapies and low density lipoprotein (LDL) apheresis, this disease remains the major cause of death. Especially statins have provided us with a potent therapeutic tool to reduce not only LDL-C, but also CAD mortality and morbidity and total mortality in our patients. A significant and clinically worthwhile relative risk reduction, ranging from 20–40 % in major cardiovascular events has been achieved with statins, without significant adverse effects or increased noncardiovascular mortality.

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. One such target for new interventions is HDL 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. I will try to summarize current options for increasing HDL-C and look at novel approaches that are being tested at the moment.

The recent availability of extractive, biosynthetic or engineered recombinant apolipoproteins have provided an innovative approach to the potential therapeutic management of atherosclerotic vascular diseases. This approach is based on an increased clearance of plasma lipids in a pathway termed reverse cholesterol transport (RCT). Another similar approach which we have taken is to remove lipids from these apolipoproteins so they can enhance this reverse cholesterol transport. But first, what are lipoproteins? And what is reverse cholesterol transport?

Apolipoproteins are the proteins that carry lipids in plasma. When they carry lipids like cholesterol, triglycerides and phospholipids they are called lipoproteins. Figure 1 shows the composition of one such lipoprotein. The apolipoproteins are named alphabetically, the most important ones are apolipoprotein A1, the main constituent of HDL and apolipoprotein B, the main constituent of LDL. The lipoproteins are named after their density during ultracentrifugation: High density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and several others.

Reverse cholesterol transport (RCT) is a pathway where cholesterol is transported from atherosclerotic plaques or other lipid deposits back to the liver to be excreted into the faeces via bile. Even though a lot of enzymes, proteins and cells are involved in RCT, HDL seems to be the most important player (Figure 2).

■ Cholesterol Metabolism of Atherosclerotic Plaques and Reverse Cholesterol Transport

The accumulation of cholesterol within atherosclerotic lesions occurs when the influx of cholesterol (carried by apoB-containing lipoproteins) into the arterial wall exceeds cholesterol efflux [1]. Increased influx of cholesterol is accompanied by an increased influx of monocyte/macrophages, which take up cholesterol-rich lipoproteins and store the cholesterol constituent as cholesterol esters. In contrast to parenchymal cells, cholesterol uptake by macrophages is not regulated by a sterol-mediated feedback mechanism. This results in a continuing cholesterol uptake by macrophages and their eventual

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conversion into lipid-laden, atherosclerotic foam cells. To reduce the cholesterol influx and, thus, to prevent or retard coronary artery disease, the current therapeutic modalities are aimed at reducing the concentrations of cholesterol-rich apoB-containing lipoproteins by dietary means, hypolipidaemic drugs, or extracorporeal removal of plasma lipoproteins as previously presented and discussed. However, the discovery and partial characterization of the so-called reverse cholesterol transport has opened up the possibility of an additional therapeutic modality, the goal of which is to increase the efflux of cholesterol from the arterial wall and, possibly, from already developed atherosclerotic lesions. It is thought that in the reverse cholesterol transport the peripheral cholesterol is moved from plasma membranes to a high density lipoprotein acceptor followed by its esterification in a reaction catalyzed by lecithin-cholesterol acyl transferase (LCAT); in the presence of cholesterol ester transfer protein (CETP) a greater portion of cholesterol esters is then transferred to apoB-containing lipoproteins (in exchange for triglycerides) and ultimately returned to the liver through the LDL-receptor pathway. The physiologic acceptor for peripheral cholesterol *in vivo* seems to be nascent discoidal, pre-beta-migrating complexes of apoA-I and phospholipids. When incorporated cholesterol is esterified by LCAT, the nascent apoA-I/phospholipid complexes are converted into spherical, "-migrating Lp-A-I particles, which in turn serve as donors of cholesterol esters for apoB-containing lipoproteins. These findings have suggested, among others that increased concentrations of apoA-I/phospholipid complexes may enhance the rate of cholesterol efflux from peripheral tissues including native arteries and atherosclerotic lesions. One of the major problems for testing such possibility (in *in vivo* experiments) has been the preparation of large quantities of artificial apoA-I/phospholipid complexes [2].

■ Clinical Evidence for the Benefits of Raising HDL-C Levels

The relationship between low levels of HDL-C and the development of CHD can be inferred from epidemiological studies, were even small differences in the level of HDL-C are associated with substantial variations in the risk of major coronary events. Data from the Framingham population indicated that at any given level of total cholesterol, the relative risk of CAD increases with decreasing levels of HDL-C [3].

In addition, prospective clinical studies have demonstrated a link between low HDL-C and an increased risk of atherosclerosis. In the PROCAM-study low levels of HDL-C were associated with a high incidence of atherosclerotic CAD. The relationship between HDL-C and the incidence of CHD in the Framingham Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial control group and the Multiple Risk Factor Intervention Trial control group was examined by Gordon et al. Analysis of these studies demonstrated that for every 1 mg/dl rise in HDL-C, the risk of CHD decreased by 2 % in men and 3 % in women, and this was independent of LDL-C [4].

The Veterans Affairs cooperative studies program High-density Intervention Trial (VA-HIT) assessed the effect of raising HDL-C levels on CHD-risk in patients with low levels of both LDL-C and HDL-C. After 1-year, gemfibrozil treatment in comparison with placebo had significant effects on HDL-C and total cholesterol but not LDL-C and was associated with a reduction of 22 % in non-fatal MI or death due to CHD. For every 5 mg increase in HDL-C, CHD-death or MI decreased by 11 % [5]. However, further studies are required to confirm these findings, even though, owing to the complexity of lipid metabolism, it is difficult to isolate the effect of HDL-C on CHD.

■ Enhancing HDL-C Levels With Lifestyle Changes

Since HDL is generally little affected by changes in the type of dietary fatty acids and substitution of carbohydrates for fat can lower HDL-C-concentrations, the key lifestyle changes to increase HDL are weight loss in the case of obesity, increased physical activity, smoking cessation and alcohol in moderate amounts. With smoking cessation for example, HDL-C increases on average 6–8 mg/dl.

■ Enhancing HDL-C-Levels With Drugs

In addition to the dose-dependant reduction of LDL-C levels, statins exert beneficial effects across the lipid profile; however they differ in their ability to raise HDL-C. A direct comparison of the lipid modifying effects of atorvastatin, pravastatin, lovastatin, fluvastatin and simvastatin was performed in the CURVES study [6]. Simvastatin and rosuvastatin seem to have the most beneficial effects on HDL-C. However, if the primary objective is to raise HDL-C, statins are not the drugs of first choice.

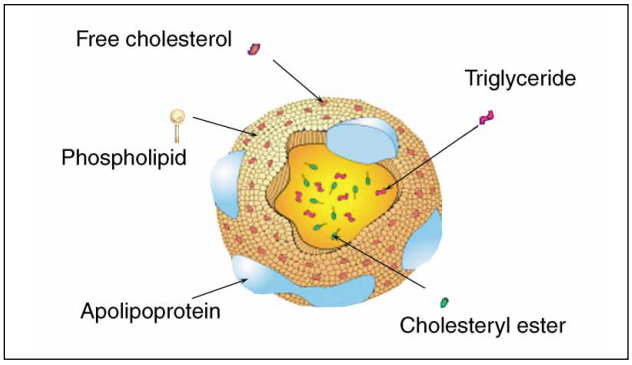

Figure 1: Structure of lipoproteins

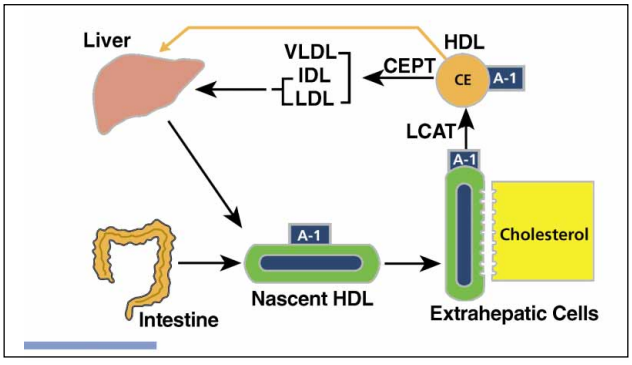

Figure 2: Reverse cholesterol transport

Of the lipid-modifying agents available, niacin and fibrates are the most effective at increasing HDL-C-levels, but they produce only modest LDL-C-lowering. Niacin raises HDL-C-levels by up to 30 % and increases of 10–15 % have been reported with fibrates.

Ezetimibe 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-C-levels by up to 19 % and moderately increases HDL-C by 3.5 %. It is well tolerated when administered with a statin or fibrate with additive effects [7].

Statin-fibrate combinations have only been studied in small trials. Such combination therapy does improve the entire lipid profile, clotting factors, insulin resistance and blood pressure [8]. However high incidences of myalgia and rhabdomyolysis have consistently been reported with combination therapies involving gemfibrozil and an excess of these adverse events precipitated the withdrawal of cerivastatin in 2001.

A combination of lovastatin plus extended release niacin, currently in clinical development, has been demonstrated to produce greater effects on LDL-C, HDL-C and TG levels than either of the two drugs alone; HDL-C-levels were increased by 30 %, LDL-C decreased by 47 % [9]. However, cutaneous flushing resulted in the withdrawal of 7 % of patients from the study.

■ Novel Treatments Increasing Reverse Cholesterol Transport

The Plasma Delipidation Process (PDP)

We recently developed a plasma delipidation process, a novel extracorporeal solvent extraction procedure that removes essentially all cholesterol and triglyceride from treated plasma while not affecting important blood constituents including apolipoproteins. PDP is a novel procedure for the potential removal of cholesterol deposited in arterial atherosclerotic lesions (Figure 3). This procedure involves three major steps including:

a) partial delipididation of plasma lipoproteins (formation of phospholipid-protein complexes) by a mixture of n-butanol and diisopropyl ether;
b) reintroduction of partially delipidated lipoproteins into the plasma compartment of autologous recipients; and
c) recombination of partially delipidated lipoproteins with plasma neutral lipids and cholesterol mobilized from fixed tissues including arteries and arterial atherosclerotic lesions. The delipidated plasma, free of solvent, containing the apolipoproteins is returned/reinfused back to the same subject [10–14].

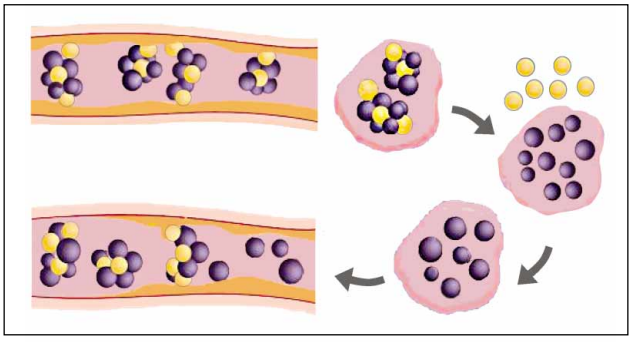

Figure 3: Vascular lipid removal mechanism (for explanation see text)

Some of the results of animal studies that we performed in Brisbane several years ago are summarized below:

1. PDP results in acute reduction of circulating plasma lipids. A readily available extravascular cholesterol pool in the hypercholesterolaemic animals was mobilized following infusion of delipidated plasma. PDP does not affect any of the studied haematological and biochemical parameters.
2. PDP caused *in vivo* changes of lipoprotein electrophoretic patterns. The observed changes were more pronounced in hypercholesterolaemic animals. A novel pre-alpha-lipoprotein band and a pre-beta HDL band were observed soon after PDP. These complexes are known to be anti-atherogenic lipid-protein conjugates and are involved with recruitment of membrane cholesterol and thus play a major role in reverse cholesterol transport.
3. PDP results in immediate reduction of plasma unesterified cholesterol concentration, which was sustained for 2.5 h after PDP. The extent of the relative reduction of unesterified cholesterol concentration in the normocholesterolaemic animals was much higher when compared to the hypercholesterolaemic animals induced changes in the ratio of unesterified to total cholesterol in the plasma of the normocholesterolaemic animals but not in the hypercholesterolaemic animals. In the hypercholesterolaemic animals the lecithin-cholesterol acyl transferase activity was not affected by PDP, whereas, in the normocholesterolaemic animals the lecithin-cholesterol acyl transferase activity was acutely reduced and this reduction in activity was sustained for up to 2.5 h. Saturated lecithin-cholesterol acyl transferase kinetics occurred in the hypercholesterolaemic animals but not in the normocholesterolaemic animals. Lecithin-cholesterol acyl transferase obeyed the Michaelis-Menten relationship. These results indicate that after PDP there was a more available pool of unesterified cholesterol, which served as substrate for lecithin-cholesterol acyl transferase in the hypercholesterolaemic animals relative to normocholesterolaemic animals. These events may be of considerable importance in the overall regulation of cholesterol transport from peripheral tissues through the plasma. PDP-triggers these events, which may have implications in reverse cholesterol transport.
4. Multiple PDP-treatments resulted in mobilization of body fat. One enzyme (LCAT) that is known to be involved with reverse cholesterol transport and thus with regression of atherosclerosis is activated.
5. The concentration of the anti-atherogenic apolipoprotein A1 is increased by multiple treatments.
6. With multiple treatments it was shown that mobilization of fat (adipose tissue) from the abdomen occurred in roosters. Histological analyses of the aorta revealed regression of atherosclerosis. Haematological and biochemical parameters were not affected by multiple PDP treatments.

A phase I-study to test the safety of this procedure in humans is under way in Australia.

Recombinant Apolipoprotein A-I/HDL

Another very interesting approach is the infusion of apolipoprotein A-I, 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.

Two recent reports provide substantial support for the feasibility of apoA-I-infusions in human subjects. In the first of these studies, apoA-I/phosphatidyl choline discs were infused over 4 hours into 7 healthy men [15]. The rise of plasma apoA-I was greatest in small pre-beta-migrating lipoproteins not present in the infusate; there was a simultaneous increase in the levels of HDL-unesterified cholesterol. After stopping the infusion, the concentrations of HDL-unesterified cholesterol, apoA-I and small pre-beta-HDL particles decreased and those of HDL-cholesterol esters and large "-migrating HDL increased. ApoB-containing lipoproteins became enriched in cholesterol esters. The authors have concluded that the infusion of apoA-I/phosphatidyl complexes resulted in an increased intravascular production of small pre-beta-HDL *in vivo* and that this was associated with an increase in the efflux and esterification of unesterified cholesterol from fixed tissues. However, it was not possible to determine which fixed tissues (liver, spleen, aorta) were the sources of the new cholesterol in plasma HDL.

In the second study, Ericksson et al. explored the effect of pro-apoA-I/phospholipid complexes on the fecal sterol excretion as the final step in the reverse cholesterol transport pathway [16]. After intravenous infusion of recombinant pro-apoA-I/phospholipid complexes into four subjects with heterozygous familial hypercholesterolaemia, there was a 30 % increase in fecal bile salt excretion and a 39 % increase in neutral sterol excretion, corresponding to the removal of approximately 500 mg/dL excess of cholesterol after infusion. Control infusion with only liposomes in two patients had no effect on the cholesterol excretion. Equally important was the observation that serum lathosterol, a marker for the rate of cholesterol synthesis *in vivo*, was unchanged, suggesting that the net increase in cholesterol excretion reflected an enhanced reverse cholesterol transport. Although it was not possible to identify the precise source of the excess excreted cholesterol, authors speculated that repeated treatments with pro-apoA-I/phospholipid complexes might reduce cholesterol in the arterial wall to some extent. They have suggested that clinical trials will be necessary to evaluate the anti-atherogenic potential of such therapy. Finding a way to increase the efflux of cholesterol from foam cells within the arterial wall and delivering this cholesterol to the liver for excretion may be the key to achieving timely regression of atherosclerotic lesions.

Both of these studies have shown that the infusion of apoA-I/phospholipid complexes into human subjects is a clinically safe procedure that may enhance the efflux of cholesterol from the arterial wall and, possibly, lead to the regression of atherosclerotic lesions. The advantage of the PDP-procedure would be in providing a relatively simple means of preparing apoA-I/phospholipid complexes and, thus, making it applicable to a larger number of subjects in comparison with procedures dependent on a limited supply of artificially prepared apoA-I or pro-apoA-I liposomes.

■ Conclusion

While reducing LDL-C-levels is the priority for the treatment of dyslipidaemia, not all coronary events are prevented despite aggressive LDL-C-lowering. Of the lipid-modifying drugs available, statins are generally accepted as the therapy of choice, however new treatments with beneficial effects upon HDL-C are emerging and may provide additional benefit for the reduction of CHD-risk.

The pleiotropic biological effects of HDL and some of its constituents provide an excellent rationale for finding new treatments for atherosclerosis.

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