High-Density Lipoproteins: Metabolic, Clinical, Epidemiological and Therapeutic Intervention Aspects. An Update for Clinicians

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High blood concentrations of low-density lipoproteins (LDL) and low blood concentrations of high-density lipoproteins (HDL) are primary factors for the development of atherosclerotic disease, the leading cause of death in industrialized countries. A decrease of approximately 30% in the morbidity-mortality rate of the disease is attributed to the reduction of LDL-C (cholesterol linked to LDL) by the statins. To improve this rate, the focus has shifted to possibilities of increasing HDL-C (cholesterol linked to HDL), the cholesterol fraction considered protective and anti-risk factor.

In this article, we address aspects of HDL metabolism and function, conditions that affect its blood levels, its role in atherosclerotic disease, as well as current and developing therapeutic approaches aimed to increasing its levels.

METABOLIC ASPECTS

Identification

Lipoproteins (LP) consist of lipids and proteins called apoproteins (apo). They are classified according to size, density, and lipid and apoprotein composition: chylomicrons (CHY), very low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL).

HDL particles consist of 50% apoproteins (AI in larger quantity, AII, CI, CII, CIII, E, and J), 20% of free cholesterol (FC) and esterified (CE) cholesterol, 15% of phospholipids (PL), and 5% of triglycerides (TG) (Fig. 1). They are identified by lipoprotein separation using ultracentrifugation, electrophoresis, and nuclear magnetic resonance. In ultracentrifugation, HDL particles are separated at densities that range from 1.063 to 1.210, further separating into subfractions: HDL_2 at densities 1.063 to 1.125, and HDL_3 at densities 1.125 to 1.210. VHDL particles are found between densities 1.121 to 1.125. By electrophoresis, 90% to 95% of the HDL particles, i.e., virtually all those that contain more apoA-I, also known as LpA-I, present alpha mobility, and only 5% to 10% have beta mobility. By non-denaturating polyacrylamide gel electrophoresis, HDL particles, previously separated by ultracentrifugation, are classified into 5 subfractions by decreasing order of size: HDL_{2b}, HDL_{2a}, HDL_{3a}, HDL_{3b} and HDL_{3c}. Nuclear magnetic resonance provides separation into 5 classes of subparticles: H5, H4 and H3, the largest, correspond to HDL_2, and H2, H1 correspond to HDL_3. In clinical laboratory, HDL particles are indirectly determined by the cholesterol associated with them (HDL-C)[1-6].

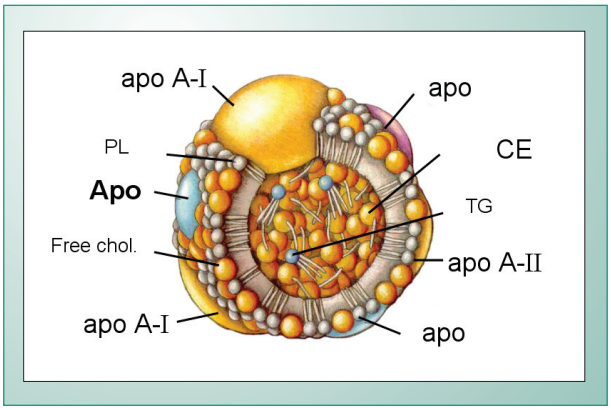

Fig. 1 - *Composition of high-density lipoprotein (HDL). Apo = apoprotein; PL= phospholipids; chol. = cholesterol; CE = esterified cholesterol; TG= triglycerides.*

According to contents of apoA-I and apoA-II, they are called LpA-I (most of them have the same density and HDL_2 load) and LpA-I + AII (most of them have the same HDL^3 density and load)[5].

HDL Formation

HDL particles are formed in plasma and in the extravascular space[7]. In order to better understand this process, it is first of all necessary to be acquainted with the secretion of the main apolipoprotein components and cholesterol efflux from peripheral cells.

The liver secretes A-I and A-II apolipoproteins, whereas the intestine only secretes A-I. Free cholesterol present in peripheral cells generates oxysterols that are endogenous ligands for nuclear liver receptors (LXR) and retinoid receptors (RXR). These are also affected by the peroxisome proliferator-activated receptors (PPARs) alpha and gamma. The LXR/RXR

Key words

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receptors and the cholesterol-regulating protein (SREBP) control the transcription of the cholesterol-transporter carrier gene (ABCAI) existing on the surface of macrophages in the artery wall. The ABCAI transporter promotes the exit of free cholesterol from the cell, which will be captured by apoA-I by the influence of the plasma phospholipid transfer protein (PLTP). There are also the ABCG1 transporters, expressed in macrophages and in endothelial cells, and the ABCG4 which is expressed in the brain. These transporters also promote cholesterol efflux[1,3,5,8-13].

Apolipoprotein A-I (apo A-I) participate in HDL formation through 3 pathways (Fig. 2)[3]: 1) capturing free cholesterol and phospholipids from peripheral cells, and forming pre-beta HDL. Influenced by lecithin-cholesterol acyltransferase (LCAT), free cholesterol is esterified, forming the round, mature, esterified-cholesterol-rich HDL particles. Still by influence of LCAT, the "mature" HDL particles are converted into HDL_3 particles (denser, even richer in esterified cholesterol), and later, also by PLTP action, acquire phospholipids and are converted into HDL_2 (less dense). It is worth mentioning that the interconversion between HDL_2 and HDL_3 takes place in arterial wall and in plasma (Fig. 3): PLTP and LCAT participate in converting HDL_3 into HDL_2; hepatic lipase (HL) and cholesteryl ester transfer protein (CETP, glycoprotein produced by the liver) participate in converting HDL_2 into HDL_3[11,13]; 2) discoid particles containing apoA-I, phospholipids and free cholesterol are secreted by liver and intestine and are transformed, by the action of the LCAT enzyme, into mature HDL particles; 3) TG-rich lipoproteins (CHY, IDL, VLDL) undergo lipoprotein lipase (LLP) action, releasing fragments containing phospholipids, free cholesterol, and small apoproteins. These fragments go into the HDL pool.

Reverse Cholesterol Transport

After being formed, HDL particles are captured by liver via the SRB1 receptors (Scavenger receptor B, class 1) and apoE receptors[8,14,15] (also present in adrenal glands and ovaries), that selectively remove esterified cholesterol from liver. Hepatic cholesterol is then excreted in bile, mediated by ABCG5/ABCG8 transporters[7,11,14].

Additionally, there is exchange of cholesterol linked to HDL with TG of VLDL, IDL, and LDL, and this exchange is mediated by CETP whose expression is regulated by SREBP and LXR/RXR. Therefore, HDL becomes richer in TG, and cholesterol bound to LDL, IDL, and LDL is captured by B/E hepatic receptors[1,5].

The reverse cholesterol transport, therefore, consist of two pathways: 1) 50% directly, by the uptake of HDL-free cholesterol involving SRB1; 2) 50% indirectly, involving CETP[1].

Catabolism

Hepatic lipase (HL) acts on TG-rich HDL particles hydrolyzing phospholipids and TG, and facilitating interaction with SRB1 receptors. HDLs then return to the interstitium proportionally with more and smaller proteins, reinitiating the cholesterol removal cycle[1]. Some authors consider that apoA-I is broken down via SRB1, while others believe that apoA-1 and/or TG-rich HDLs are catabolized in the kidneys by endocytosis in proximal tube with participation of cubilin-megalin proteic complex[1,5,7,16,17].

HDL Actions

Several different actions are attributed to HDLs, which taken all together, have an anti-atherogenic effect. The primary action is the reverse cholesterol transport, mentioned above. Other actions have been described *in vitro* and in animals, such as: antioxidant, anti-inflammatory, platelet antiaggregant, anticoagulant, profibrinolytic, and endothelial protection effects[2,3,5,8,18].

HDL particles contain the paraoxonase enzyme that is capable of hydrolyzing lipid peroxides by catalyzing the reaction of oxidized phospholipids into LDL[5,19]. They eliminate the products of LDL oxidation (lipoperoxides and lysophosphatidylcholine)[3,20]. Anticoagulant and profibrinolytic

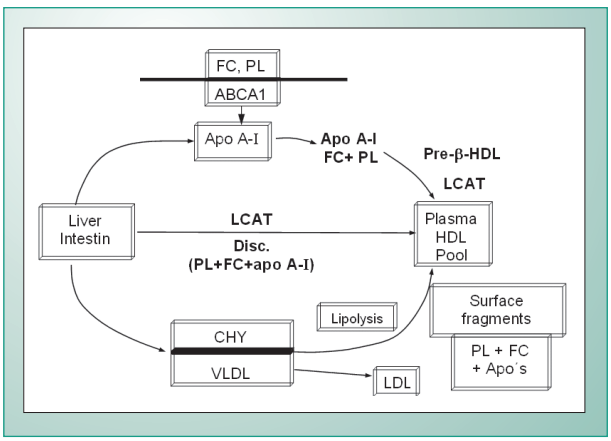

Fig. 2 - HDL Formation: role of A-I3 apolipoprotein. FC = Free cholesterol; PL = phospholipid; ABCA1 = ABCA1 transporter; Apo = apoprotein; HDL = high-density lipoprotein; LCAT = lecithin-cholestrol acyltransferase; CHY = chylomicron; VLDL = very low-density lipoprotein; LDL = low-density lipoprotein; Disc. = discoid particle.

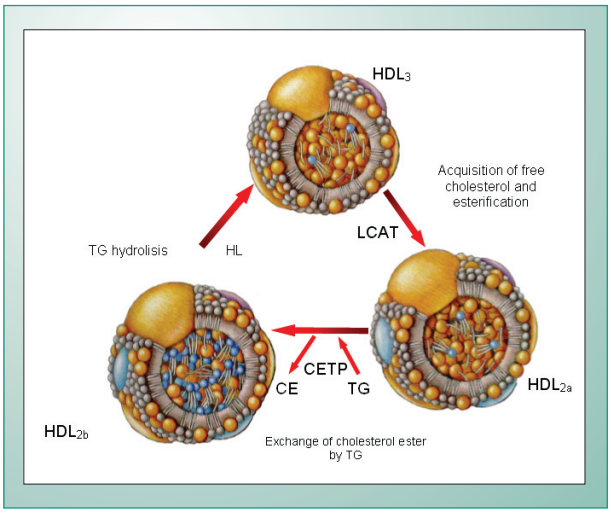

Fig. 3 - Interconversion of HDL2 and HDL3 fractions. HDL = high-density lipoprotein; HL = hepatic lipase; LCAT = lecithin-cholesterol acyltransferase; CETP = cholesteryl ester transfer protein; CE = cholesterol ester; TG = triglycerides.

effects are based on inhibition of X-factor and platelet activation, tPA secretion (tissue plasminogen activator), and PAI (plasminogen activator inhibitor)[2,3,5,21]. They stimulate C-reactive protein activity[2].

Endothelial protection takes place by: 1) inhibition of oxidized LDL infiltration and consequent protection against acetylcholine-mediated vasodilation and antagonism of vasodilation inhibition caused by lysophosphatidylcholine[20]; 2) inhibition of adhesion of monocytes to the endothelium by inhibiting adhesion molecules to be expressed on the endothelial surface: VCAM1 (vascular cell adhesion molecule), ICAM1 (intracellular adhesion molecule), and E-selectin. Interleukins 1 (IL1) and 8 (IL8) are also reduced. The HDL_2 particles, in particular, can completely eliminate the adhesion of monocytes to endothelial cells[22]; 3) smaller production of endothelin-1 by the endothelial cells[23]; 4) stimulation of prostacyclin synthesis and longer half-life, improving muscle relaxation[24]; 5) modulation of C-type natriuretic peptide production, which causes vasodilation[25]; 6) activation of eNOS (endothelial nitric oxide synthesis), releasing NO[26,27]; 7) stimulation of smooth muscle cell production, which may facilitate the recovery of cells lost after the rupture of the atherosclerotic lesion fibrous cap[2,28]; 8) prevention of cell injury and necrosis resulting from activation of the complement system[29].

HDL Levels

Based on epidemiologic studies, HDL-C levels < 35 mg/dl are considered low for men, and < 45 mg/dl low for women[30,31]. Updated guidelines established that values < 40 mg/dl are undesirable and increase risk for coronary atherosclerotic disease (CAD), whereas values > 60 mg/dl are "protective"[32-34]. To characterize the metabolic syndrome, along with other abnormalities, HDL-C values < 40 mg/dl are established for men, < 50 mg/dl for women[32,33]. In recent publication, values < 50 mg/dl were established as risk for women.

Low or high HDL values result from rare genetic causes or are associated with other risk factors and/or medications.

Low HDL Levels

Genetic causes for low levels of HDL include: 1) total deficiency or mutations of apolipoprotein A-I. ApoA-I Milano and apoA-I Paris are mutations in which cysteine is replaced by arginine at locus 173 and 151, respectively. Despite low levels of HDL-c, patients with these mutations have no atherosclerotic involvement. In experiments, these variants were found to be more effective than the original apoA-I in preventing lipid oxidation, and they are also capable of mediating cholesterol efflux from macrophage cells by interacting with ABCAI[36-38]; 2) complete or partial LCAT deficiency. Fish-eye disease is one form of latter in which patients exhibit low HDL and apoA-I levels, accelerated apoA-I and apo-AII catabolism, remarkable lipid corneal arc, but rarely develop premature atherosclerosis[39]; 3) genetic disorders related to the ABCAI carrier, such as Tangier disease and familial hypoalphalipoproteinemia. In Tangier disease, HDL levels are extremely low, as are those of apoA-I and apoA-II; lipid deposits are formed in lymphoid organs, such as the tonsils, that become orange-colored, hepatosplenomegaly, and peripheral neuropathy[40]; 4) poorly explained disorders, such as cases of familial hypoalphalipoproteinemia, familial combined hyperlipidemia, and metabolic syndrome[41].

Low HDL levels are clinical findings commonly associated with smoking (due to LCAT deficiency), visceral obesity (due to decreased LCAT and LLP), very low-fat diets, hypertriglyceridemia, and use of certain drugs (such as beta-adrenergic blocking agents, steroids, and androgenic progestogens)[42-45].

Elevated HDL Levels

High HDL levels are rarely associated to genetic disorders, such as CETP or HL deficiency. In CEPT deficiency, HDL is very rich in esterified cholesterol, although there is no evidence that it has a protective effect against atherosclerosis[13].

They are generally associated with the regular practice of aerobic exercises (by increasing LCAT and LLP, and reducing HL), diets rich in saturated fat and cholesterol (by delaying apoA-I clearance), regular alcohol consumption (by inhibiting HL and increasing apoA-I and apoA-II synthesis), and use of some medications such as estrogens (by increasing apoA-I production and inhibiting HL) and phenytoin[42,46-50].

HDL Role in the Atherosclerotic Disease

Experimental, epidemiologic, clinical, and therapeutic intervention investigations have shown that there is an inverse relationship between HDL-C and atherosclerotic disease. To date, there are no reports of anatomical and pathological studies conducted on human subjects or animals showing the direct association of HDL and lesion progression. HDL atherogenicity may be influenced by non-measurable variables, including genetic and acquired factors, or by subclass concentration, metabolic kinetics, and not by absolute quantities of HDL[5,51,52]. Studies conducted with different populations showed that risk for CAD, if HDL-C is low, is accompanied by other lipid alterations, such as hypertriglyceridemia (specially if the TC/HDL-C is high), an increased concentration of remnant lipoproteins, and small and dense LDL particles. These alterations may be associated with the metabolic syndrome[5,53-57].

Experimental Studies

ApoA-I administration to transgenic mice delays formation of atherosclerotic lesions[7,58]. In rabbits, injection of HDL-VHDL promoted the regression of fatty streak and lipid deposits caused by diets very rich in cholesterol. Injection of apoA-I in hyperlipidemic rabbits lead to reduction in intima thickness and in contents of macrophage cells after balloon injury [18,59-61]. In rats with apo-E deficiency, administration of apoA-I was associated to increase of HDL-C (2 to 3x) and lower susceptibility (6x) to atherosclerosis, and also reduced neointimal formation after endothelial denudation[18,62,63].

Epidemiological studies

Several epidemiological studies have shown that there is an inverse relationship between HDL-C blood levels and the

risk for atherosclerotic disease in coronary arteries[5,11,18]. We call attention for:

1) World Health Organization study[64], analysed data from 19 countries and showed an inverse correlation between HDL-C values and mortality due to CAD; 2) Framingham study[65], in which an inverse correlation between HDL-C levels and CAD was observed in men and women of different age groups, and also that the risk is greater with HDL-C are < 40 mg/dl, regardless of LDL-C values. HDL-C > 65 mg/dL conferred protection against coronary events, even if LDL-c >160 mg/dl. The relationship was maintained after other risk factors had been controlled, such as diabetes mellitus, hyperglycemia, age, arterial hypertension, smoking, and obesity; 3) Prospective Cardiovascular Munster Study (PROCAM) [54], in which men with HDL-C < 35 mg/dL had a greater risk for CAD relative to those with HDL-C > 35 mg/dL; 4) control groups of the Multiple Risk Factor Intervention Trial (MRFIT)[66] and of the Lipids Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)[67], in which the incidence of CAD was greater at HDL-C levels < 40 mg/dL; 5) Lipid Research Clinics Prevalence Mortality Follow-up Study[68] shows an increase of 1 mg/dL in HDL-C associated to a 3.5% reduction in the risk for CAD, a mortality rate of 3.7% in men and 4.7% in women for HDL-C < 35 mg/dL, and the risk for cardiovascular disease (CVD) 6 times higher if HDL-C < 35 mg/dL.

Combined analysis of the Framingham, Lipid Research Clinics Prevalence Mortality Follow-up Study, and the LRC-CPPT and MRFIT control groups revealed that, after the adjustment for other risk factors, for each 1 mg/dl reduction in HDL-C, the risk for CAD increases 3% in women and 2% in men[69].

It is worth mentioning that elevated HDL-C levels do not necessarily confer protection against atherosclerotic disease and, sometimes, are associated to an excessive cardiovascular risk. This situation was observed in PROCAM and Copenhagen City Heart studies in hypertriglyceridemic patients. In PROCAM and in a Belgium population sample, there was excessive mortality in the 5th quintile of HDL-C in comparison with intermediate levels[4,54,70-72].

Clinical and therapeutic intervention studies

The inverse relationship between HDL-C blood concentrations and atherosclerotic lesions in coronary arteries has been demonstrated by several clinical and therapeutic intervention studies.

Atherosclerotic impairment and lipid deposits in different organs were observed in individuals with low levels of HDL-C of unknown etiology. In clinical setting, coronary artery injuries are linked to low levels of HDL-C associated to smoking, obesity, hypertriglyceridemia, and metabolic syndrome.

Drexel et al[73] observed that the number of coronary atherosclerotic lesions was inversely proportional to HDL_2 values, and this fraction is a better "predictor" of lesion extension. In a study conducted in 80 males with coronary disease, aged 27 to 55 years, smokers, sedentary, non-diabetic and non-obese, Giannini et al[74] did not observe a significant relationship between mean HDL-C values and the intensity of damage to the coronary arteries, even though lower values had been found when the injury was more pronounced. Shah and Amin[75], in a study conducted with patients who had undergone coronary angioplasty, observed that low HDL-C levels can be considered "predictive" of intimal proliferation, which leads to early restenosis.

Recently, Kuvin et al [76] showed that in coronary disease patients, the endothelium-mediated vasodilation was: 1) greater if LDL-C values were < 80 mg/dl, in comparison with HDL-C ≥ 80 mg/dL and < 100 mg/dL, but this difference was significant only when HDL-C were < 40 mg/dL; 2) greater in individuals with LDL-C < 75 mg/dL and HDL-C ≤ 36 mg/dL treated with niacin in comparison with no treated.

Studies of therapeutic intervention in patients with hyperlipidemia or in individuals with low blood concentrations of HDL-C showed, as explained below, that increase in HDL-C values is associated to a decrease in mortality and risks of new coronary events, as well possibility of lesion regression[5,18,46,76-78].

Therapeutic measures to increase HDL-C

With regard to measures used to reduce morbidity-mortality due to CAD, over the past few years the focus has been shifted to those capable of increasing blood HDL-C concentrations, by changes in lifestyle or medication.

Lifestyle measures

Lifestyle measures include an adequate diet, physical exercise, smoking cessation, and lowering body weight for individuals who are overweight or obese.

Dietary habits

Specific diets intended to modify HDL-C levels require not only medical orientation, but also and attendance by a nutritionist[8,46,79]:

1) Saturated fatty acids raise HDL-C levels by delaying apoA-I clearance. Restriction of saturated fatty acids reduces TC and LDL-C, as well as HDL-C, and the latter is effective especially in women[80-83]; 2) omega 3 polyunsaturated fatty acids inhibit the hepatic secretion of VLDL and, thus, increase HDL-C. Omega 6 fatty acids reduce these levels by reducing apoA-I production and by increasing HDL catabolism; 3) monounsaturated fatty acids induce HDL-C elevation by reducing VLDL secretion; 4) unsaturated fatty acids, in trans-form, enhance apoA-I catabolism and, thus, reduce HDL-C[84]; 5) carbohydrates reduce HDL-C by increasing its catabolism as well as the secretion of VLDL. Recently, Aude et al[85]; showed that reduced ingestion of simple carbohydrates and an increased ingestion of complex carbohydrates, associated to an increase of mono-unsaturated fatty acids, result in a less marked reduction of HDL-C in comparison with the Phase 1 diet recommended by NCEP[31]. Westman et al[86], in contrast, showed that increased HDL-C levels, induced by carbohydrate restriction, accompanied body weight loss; 6) alcohol consumption increasing HDL-C by inhibiting hepatic lipase and increasing apoA-I and A-II synthesis. This increase is dose-dependent: in normal individuals, the consumption of half a bottle of wine per day (39 g of alcohol) after six weeks increased HDL-C by 7 mg/dl, whereas one beer per day

(13,5 g of alcohol) caused an increase of only 2 mg/dl[87,88]; 7) coffee reduces HDL-C by reducing LCAT and increasing CETP activities; 8) besides reducing lipid oxidation, cocoa polifenoles raise HDL-C by a mechanism not yet fully explained[89].

Adoption of diet intended for lowering body weight is of greater importance. Caloric restriction increases HDL-C values. For each 3 kg of body weight lost, there is a corresponding 1 mg/dL elevation in HDL-C. Increase in LCAT and LLP activities is observed after a sustained six-week weight loss[42,90,91]. It should be emphasized that weight loss should be the main focus in metabolic syndrome, helping to control glycidic and lipidic disorders and arterial pressure[92].

Smoking cessation

Smoking cessation increases LCAT activity and HDL-C concentrations return to previous levels within 30 to 60 days[44,93].

Improve physical exercise

Physical exercise increases LCAT and LLP activity and reduces HL[42,47] activity, resulting in increased HDL levels**:** 1) in both normal individuals and those with different types of dyslipidemia (hypercholesterolemia, isolated hypertriglyceridemia or associated with low levels of HDL-C, isolated low HDL-C)[94,95]; 2) in obese and non-obese individuals[96]; 3) particularly when associated to diet orientation. Compared to women, men have more significant HDL-C elevations when they adopt an adequate diet combined with physical exercises[97]; 4) success depends on quantity and not on intensity of the exercise[98].

Over the period of one year, the association of physical exercise with fat and cholesterol restriction raised HDL-C values by 2% and reduced those of LDL-C (8%) and TG (21%). In comparison to control group, there was greater regression (29% x 6%) and lower progression (10% x 45%) of coronary lesions[99].

Drug Therapy

Hypolipidemic agents (lipid lowering drugs – lld) in clinical practice

Fibrates, nicotinic acid, and statins increase HDL-C 10%, 20%, and 5 to 10% respectively. Fibrates activate PPARs alpha in the liver, increasing apoA-I production; they also reduce the regulation of SRB1, lowering HDL clearance. Nicotinic acid reduces apoA-I catabolism. Statins reduce CETP activity and increase apoA-I synthesis; reduction in CETP mass has been observed with the use of atorvastatin and sinvastatin[5,11,77].

In a metanalysis of randomized studies conducted from 1966 to 2004 with fibrates and nicotinic acid, Birjmohum et al[100] showed that, despite a more marked elevation of HDL-C with nicotinic acid (16% x 10%), the decline in events was similar (27% x 25%). But this reduction was significantly associated to elevations in HDL-C levels induced by gemfibrozil in primary and secondary prevention studies[4,5,18]. In the Helsinki Heart Study – HHS[101], elevations in HDL-C (10%) and reductions in LDL-C (10%) and TG (43%) were observed. Increases of HDL-C and the HDL-C/TC ratio were related to risk of CAD. In Veterans Affairs High-Density Lipoprotein Intervention Trial - VAHIT[102,103] (mean initial value of HDL-C was equal to 32 mg/dL), after one year the 6% increase in HDL-C levels was accompanied by a 22% reduction in the death rates due to CAD or non-fatal MI. For each 5 mg/dL increase in HDL-C, the risk of coronary events fell by 11%. This did not occur in the Bezafibrate Infarction Prevention study[104,105] in which HDL-C were high and increased 18%; the conclusion was that an increase in low HDL-C translates into greater protection.

In primary prevention studies (Air Force/Texas Coronary Atherosclerosis Prevention Study – AFCAPS/Tex CAPS)[106] and West of Scotland Prevastatin Study – WOS)[107] or secondary prevention trials (Cholesterol and Recurrent Events Trial – CARE[108], Scandinavian Sinvastatin Survival Study – 4S[109], The Long–Term Intervention with Provastatin in Ischaemic Disease – LIPID[110]), statins also reduced cardiovascular events, even more significantly so when HDL-C values were lower. However, this correlation was not significant[4]. In the AFCAPS study[106], reductions were 45%, 44%, and 15% respectively if HDL-C was < 34, 35 to 39, or > 40 mg/dL. The combined analysis of WOS, CARE, and LIPID (Prospective Pravastatin Pooling Project [111]) studies showed a similar reduction in cardiac events (27% to 28%) in both placebo and treatment groups, considering the more elevated HDL-C percentile in relation to the lowest[18]. In the 4S study, a 1% increase in HDL-C was associated with a 0.80% reduction in risk, regardless of the decline in LDL-C levels[112]. More distinct angiographic and clinical benefits were also observed in the Lipoprotein and Coronary Atherosclerosis Study – LCAS[5,18,113]. Combination of simvastatin and niacin, administered for 3 years, reduced the risk of events by 90% and each 1% increase in HDL-C corresponded to a 1% reduction in cardiovascular risk (HDL – Atherosclerosis Treatment Study – HATS)[5,18,114]. In 167 cardiac patients (x = 67 years of age) treated with statins, addition of niacin after 12 months, increased HDL-C (21%), but no modifications were observed in carotid intima-media thickness (increased in the placebo group)[115].

Whitney et al[115] recently published the results of an angiographic placebo-controlled study designed for individuals with low levels of HDL-C. After 6 months of a Phase 2 diet of the American Heart Association and regular physical exercises, patients (HDL-C = 34 ± 6 mg/dL, LDL-C = 128 ± 27 mg/dL, and TC = 196 ± 31 mg/dL), were randomized to receive placebo combined with gemfibrozil (1200 mg/dL), nicotinic acid (250 to 3000 mg/day from the 3rd month) and cholestyramine (16 g/day from the 6th month). Reductions in TC (20%), LDL-C (26%), and TG (50%), as well as an increase in HDL-C levels (36%) were observed. After 3 years, treated group had a greater reduction in coronary obstructive processes (↓ 0.8% x ↑ 1.4%) and in cardiovascular events (12.7% x 26.4%).

CETP inhibitors

Elevation of blood HDL-C levels is more pronounced due to the action of CETP inhibitors, drugs not yet available for clinical use[5,11,18]. Two of these are JTT-705 and torcetrapib.

Administration of JTT-705 to rabbits doubled HDL-C values, markedly reducing (70%) the size of the atherosclerotic lesion[117]. Healthy individuals, with HDL-C < 45 mg/dL, had HDL-C levels increased 37% after treated with JTT-705 for 4 weeks[118].

In rabbits, torcetrapib significantly reduced atherosclerosis[119]. In human subjects with HDL-C < 40 mg/dL (x = 33 mg/dL) receiving 120 mg/day, the drug increased HDL-C levels 46% after 4 weeks and 106% after 8 weeks. When associated to 20 mg/day of atorvastatin, after 4 weeks the increase was 61%[120].

Drugs in development

Currently, there are studies underway with drugs capable of raising HDL-C by different mechanisms of action**:** PPARs alpha and gamma agonists, apoA-I synthesis inducers, selective LXR activators or modulators, FXR activators (farnesoid X receptor / biliary bile acid receptor), endothelial and hepatic lipase inhibitors, SRB1 modulators, and –mimetics of sphingolipids[11].

Other possibilities

In an effort to increase HLD-C levels, CETP inhibition was induced in rabbits by a "vaccine" (a synthetic peptide homologous to the sequence of peptides in catalytic CETP site), which reduced the aortic lesions by 39.6%[121]. In human subjects, HDL-C increase was small[122].

Infusion of apoA-I increases the ABCAI-mediated cholesterol efflux. In rabbits, repeated infusions of apoA-I inhibited the progression of atherosclerosis and reduced lesion size[123]. Recently, Nissen et al[124] showed that patients in acute phase of myocardial infarction had a reduction in atheroma volume due to endovenous administration of recombinant apoA-I Milano.

Summary

High density lipoproteins (HDL) constitute a class of heterogeneous lipoproteins with a complex, not fully understood metabolism, particularly concerning cholesteryl ester transfer protein (CETP) action and catabolism. HDLs are anti-atherogenic due to reverse cholesterol transport and to antioxidant, anti-inflammatory, anticoagulant, profibrinolytic and endothelial protection properties, (shown *in vitro* and in animals). Experimental, clinical, epidemiologic, and therapeutic intervention studies have shown that there is an inverse relationship between blood levels of these lipoproteins and the development of atherosclerotic disease in coronary arteries.

Measures to increase plasma HDL-C levels, besides changes in lifestyle habits (an adequate selection of diet components, smoking cessation, regular practice of aerobic exercises) include lipid lowering drugs (LLDs). Drugs capable of inhibiting CETP are currently in advanced stages of development. Research is also being conducted with other drugs that act on different points of lipid metabolism.

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