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LIPOPROTEIN SUBCLASSES AND ATHEROSCLEROSIS

H. Robert Superko

Berkeley HeartLab, Cholesterol, Genetics and Heart Disease Institute, 1875 South Grant St., San Mateo, CA 94402

TABLE OF CONTENTS

1. ABSTRACT

Differences in LDL and HDL subclass distribution contribute to increased CAD risk through a variety of mechanisms. The inherited disorder characterized by an abundance of small, dense LDL particles increased CAD risk 3-fold and is associated with rapid arteriographic progression. The metabolic milieu associated with the small LDL trait includes insulin resistance, increased IDL, increased susceptibility to oxidative damage, impaired reverse cholesterol transport, and increased post prandial lipemia. Recent evidence indicates that the LDL IIIa+b region are the LDL subclass regions most associated with atherosclerosis. Improvement in LDL subclass distribution has been associated with arteriographic improvement significantly more than LDLC change. Therapeutic treatments including diet, and many pharmacologic interventions have a differential response in subjects characterized by an abundance of either small, or large LDL particles. Individual patient information regarding LDL and HDL subclass distribution can be used to improve medical management of the CAD patient that results in improved outcomes.

2. INTRODUCTION

The role of lipoprotein particles in the atheroslcerotic process has been elucidated over several decades. Initial emphasis was placed on obvious disorders of very high total and LDL cholesterol that had a relatively clear link to coronary artery disease (CAD) (1). More recently, it has become apparent that elevated total and LDLC is not a characteristic of most individuals who suffer from CAD. Eighty percent of patients who develop CAD have the same total cholesterol value as those who do not develop CAD (2). Likewise, while total and LDLC reduction has reduced coronary events approximately 25%, a large portion of patients treated with cholesterol lowering medications continue to have clinical events (3). Part of the explanation for this apparent paradox is the fact that most of the metabolic disorders contributing to atheorsclerosis are not detected by routine tests of total and LDL cholesterol (4). The most common disorder is reflected in abnormalities of LDL and HDL lipoprotein subclass distribution (5). The clinical importance of this issue is heightened by recent studies that reveal an independent association of LDL size with coronary events, and outcome studies that reveal change in LDL size and distribution to

be the best predictors of arteriographic outcome. Many common lipoprotein therapies have different effects in patients who do, and do not, have disorders of lipoprotein subclass distribution.

3. HISTORY

The relation of lipoprotein subclasses to atherosclerosis is not a new finding. In the 1950's Dr. John Gofman and colleagues, at the Donner Laboratory, made a major contribution by investigating the effect of low-density lipoproteins (LDL) on atherosclerosis in the Framingham and Lawrence Radiation Lab at Livermore studies (6). At that time he reported the association of lipoprotein classes defined by Svedberg floatation intervals as assessed in the analytic ultracentrifuge. Intervals Sf 0-12 (LDL), Sf 12-20 (IDL), Sf(20-100) (VLDL) and Sf 100-400 (VLDL) were all noted to be associated with atherosclerosis particularly in younger males. An atherogenic index was developed that attempted to quantitate the effect of these lipoproteins on atherosclerosis although it was noted that correlation's among the subclasses prevented any statistically independent association. With a great degree of prescience, they predicted that if longevity is linked to lipoproteins, then in order to improve longevity, "… a drastic rather than moderate reduction in such parameters is required.". Due to the work of Geer and McGill, it was even suggested that alteration in lipoprotein composition might lead to the development of atherosclerosis even though no alteration in absolute lipoprotein levels occurred. Gofman and colleagues were also well ahead of their time by reporting that HDL2 (F3.5-9.0) was reduced 32.1% and HDL3 (F0-3.5) 8.4% in patients who developed CAD over 10 years. This raised the possibility of a protective role of HDL and HDL subclasses. Thus the field of lipoprotein subclasses, within the VLDL, IDL, LDL, and HDL regions, and the relation to atherosclerosis is at least 50 years old.

The Donner Laboratory, at the Lawrence Orlando Berkeley National Laboratory, University of California, extended the work of Gofman and colleagues to involve a plethora of investigations that assessed the role of lipoprotein subclasses within the entire subclass distribution and their relation to atherosclerosis (7). These investigations bridged the gap between basic science and clinical research, and most recently have involved genetics and arteriographic "regression" studies (3,8). Basic science investigations have elucidated the association of "small, dense LDL" with insulin resistance, post prandial lipemia, lipoprotein oxidative susceptibility, vessel wall LDL uptake, and genetic linkage. Clinical research has elucidated the role of the small, dense LDL trait in CAD risk, cardiovascular outcomes, and therapeutic interventions including exercise and weight loss, diet, and drugs (9).

4. PATHOPHYSIOLOGY

4.1. Lipoprotein heterogeneity

The lipoproteins are a diverse group of particles that are separated into various categories based historically on their density. The regions include triglyceride rich, very low-density lipoproteins (VLDL) and intermediate density lipoproteins (IDL), and the relatively cholesterol rich low density lipoproteins (LDL). High-density lipoprotein (HDL) particles may play a role in what has been termed "reverse cholesterol transport".

The transport role appears to follow a path of large particles rich in triglycerols and relatively poor in cholesterol that undergo a series of metabolic interactions. These interactions result in more dense particles that are relatively rich in cholesterol and poor in triglycerols. The large triglyceride rich transport particles, derived from an intestinal source, are termed chylomicrons. The somewhat smaller, triglyceride rich particles, derived from a hepatic source, are termed very low density lipoproteins (VLDL).

After a series of interactions with the enzyme lipoprotein lipase, the particles become more dense and relatively cholesterol rich. An intermediate density lipoprotein (IDL) precedes the appearance of low density lipoprotein (LDL), which is normally the greatest source of cholesterol transport among the lipoproteins. Further metabolism involves the interaction of lecithin–cholesterol acyltransferase (LCAT), apoproteins, and neutral exchange factors (10,11). VLDL particles are produced in both large, and smaller forms and through different pathways, that involve lipoprotein and hepatic lipase, and develop into either large, or small LDL particles (Figure 1) (7).

4.1.1.IDL

Intermediate density lipoprotein (IDL) is defined as the lipoprotein mass in the svedberg floatation intervals Sf 12-20. The most common laboratory method of determing LDLC involves precipitation of apo B containing lipoprotein particles, measurement of the cholesterol content of the remaining plasma (HDLC) and then calculation of LDLC with the Friedawald equation (12). When using this method. IDLC is included in the LDLC number. Thus, part of the ahterogenicity, or response to treatment, attributed to the LDLC value may, in part, be due to IDL.

In the natural history progression of CAD, it has been reported that IDL and inversely HDL are associated with CAD progression while LDL (determined in an ultracentrifuge) is not (13). Most recently, work using the analytic ultracentrifuge at the Donner Laboratory has discovered that IDL is significantly associated with atherosclerosis progression as determined by carotid wall intima medial thickness (14).

4.1.2. LDL

LDL is not a homogeneous category of lipoproteins but consists of a set of discrete subspecies with distinct molecular properties, including size and density (15,16). In normal subjects, at least four major LDL subspecies can be identified: LDL-I is the largest and least dense, and, the smallest, LDL-IV, is the most dense. Analysis of LDL subspecies is made possible by numerous techniques, including gradient gel electrophoresis, which separates LDL particles into seven regions on the basis of

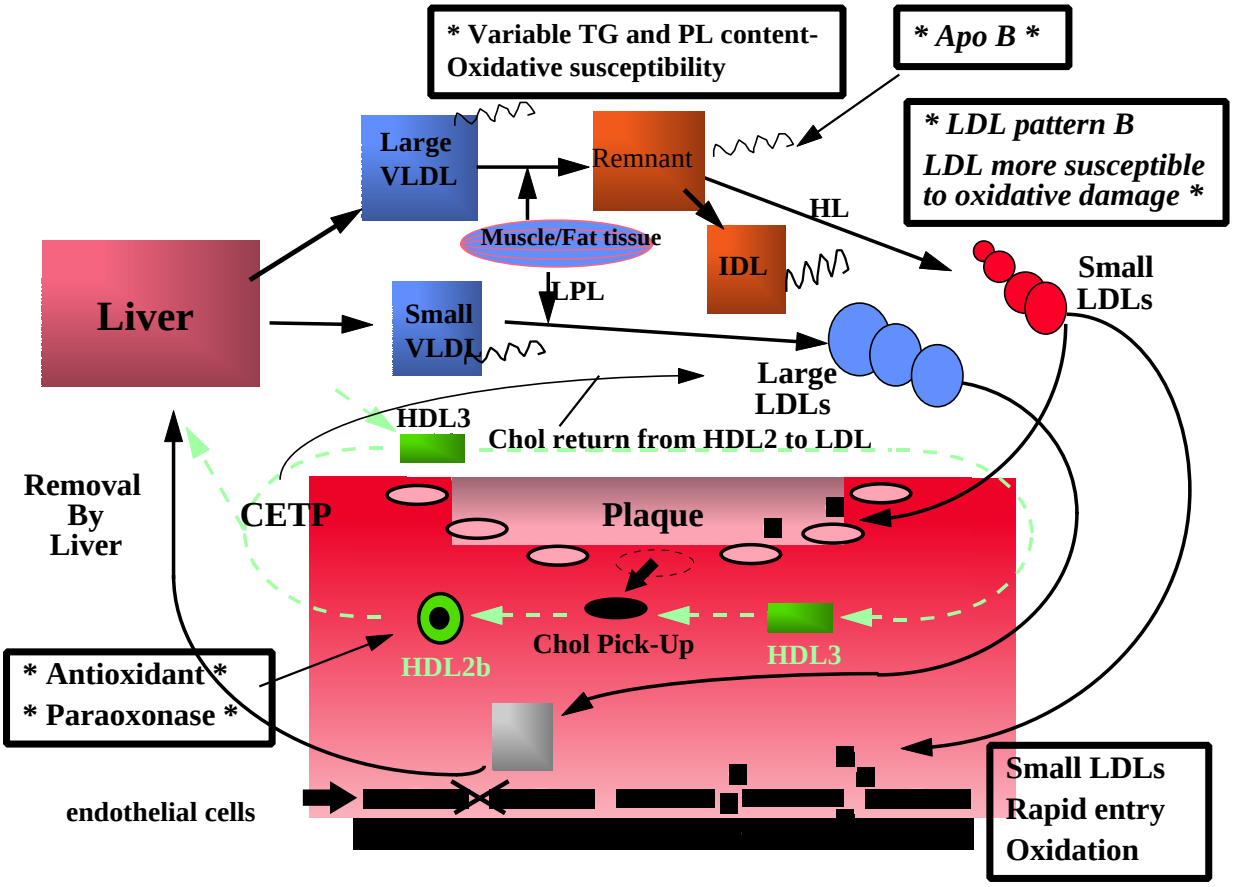

Figure 1. Metabolic pathway of lipoproteins including lipoprotein heterogeneity.

their differing size, and ultra-centrifugation, which separates the particles into 12 regions on the basis of their differing density (17,18). In most healthy people, the major subspecies are large or buoyant, whereas the smaller denser LDL subspecies are generally present in small amounts.

LDL subclass distribution and pattern is determined by two different methods, Analytic ultracentrifugation (ANUC) and gradient gel electrophoresis. ANUC is a complex ultracentrifugation method, which provides separation of particles based on density and svedberg flotation intervals (17). This method is available only in a few research laboratories around the world. Work by Dr. John Gofman and colleagues in the 1950 first elucidated lipoprotein heterogeneity with this method at the University of California, Berkeley (6). Gradient gel electrophoresis (GGE) is the second method that has been used in parallel with ANUC at the University of California, Berkeley, and determines multiple LDL peaks and the diameter of each peak in angstroms, position of peaks, and percent distribution in seven LDL regions (17). By analyzing samples from clinical trials in parallel with these two techniques, the GGE methodology, as developed at Berkeley, can now be used as an accurate and relatively inexpensive clinical tool to determine LDL subclass distribution, LDL subclass pattern, and response to treatment. Multiple studies at the University of California, Berkeley, and Stanford University, have revealed significant changes in LDL subclass distribution, seen as a reduction in small LDL balanced by an increase in large LDL, despite no change in total LDL mass or LDLC (9). Examples of LDL subclass distribution, as determined by GGE are illustrated in Figure 2. The presence of more than one LDL subclass in an individual patient is illustrated by Figure 3.

4.1.3. HDL

High-density lipoprotein is derived from both intestinal and hepatic sources. Hepatic HDL in a nascent, or new form, appears as a disk-shaped structure. Intestinally derived HDL is more spherical and varies in its protein composition. Both of these HDL particles are relatively small and cholesterol-poor and can be classified as HDL3 based on analytic ultracentrifugation (ANUC) or GGE. Following interaction with LCAT and lipoprotein lipase in both adipose and muscle tissue, cholesterol ester content is increased and the particle becomes less dense, larger, and classified as HDL2.

Based on the relative density obtained in the analytic ultracentrifuge (ANUC), the more dense, relatively

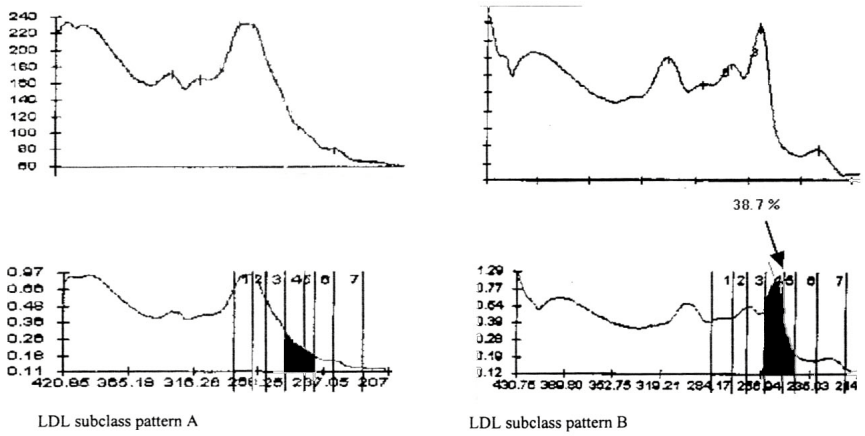

Figure 2. LDL subclass pattern A compared to pattern B. Gradient gel electrophoresis representing multiple LDL peaks, peak particle diameter, and percent distribution in 7 LDL regions (1,2,3,4,5,6,7, or, I, IIa, IIb, IIIa, IIIb, IVa, IVb). In the pattern A subject there are two LDL peaks at 277 and 270 angstroms. 10.2% of the LDLs are in the atherogenic region IIIa+b. Region IIIa and IIIb are the same as regions 4 and 5. Lp(a) can be seen at 331 angstroms. In the LDL pattern B subject, there are two LDL peaks. The predominant peak is at 250.9 A and 38.7% of the LDLs are in the IIIa+b (4+5) region. The LDLC value in these two subjects is the same and does not reflect the 3-fold increased CAD risk present in the LDL subclass pattern B subject. The extent of expression of pattern B can be appreciated by the percent distribution in the small regions 4,5,6,7.

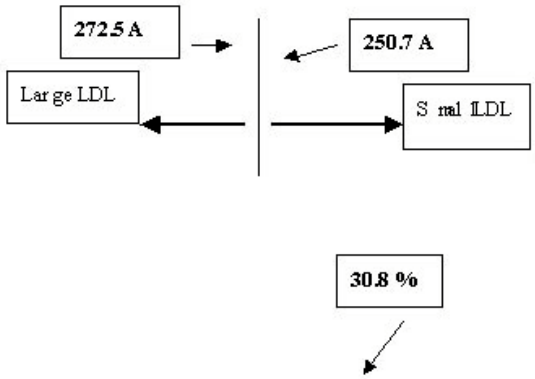

Figure 3. LDL gradient gel electrophoresis with 2 LDL peaks of almost equal height. One peak is clearly in the large region (272.5 A) and the second is clearly in the small region (250.7 A). 30.8% is in region 4+5. Approximately 40% of patients exhibit 2 or more LDL peaks in which the "minor" peak is > half the amount as the primary peak.

cholesterol-poor form is termed HDL3 (1.125 to 1.21 G per ml) and the less dense, relatively cholesterol-rich form is termed HDL2 (1.062 to 1.125 G per ml) (18,19). In studies performed at the University of California, Berkeley that determined HDL subclass distribution in parallel with both ANUC and gradient gel electrophoresis (GGE), it was determined that HDL2b as determined on GGE correlates significantly ($r=0.92$, $p<0.0001$) with HDL2 as determined by ANUC. Following interaction or enhancement with specific lipoproteins and neutral exchange factors, cholesterol esters are transferred to a modified VLDL, which eventually is identified as LDL-cholesterol. The function and result of this change in cholesterol content may be to play a role in what has been termed "reverse cholesterol transport". After interaction with hepatic lipase, HDL reappears as the relatively cholesterol-poor form HDL3. While total HDLC is an established CAD risk factor in epidemiological investigations, differences in HDL subclasses exist within the "normal" HDLC range and may contribute to CAD risk in individuals with "normal" HDLC values. Low HDL2b has been linked to both arteriographically assessed CAD severity, and arteriographic progression of CAD (20). The presence of low HDL2b (determined by GGE), and the effect of nicotinic acid is illustrated in Figure 4.

HDL particles serve several functions, one of which is as an antioxidant. Paraoxonase is an enzyme associated primarily with the AI containing HDL particle, which is the HDL2b region, and has the ability to retard the accumulation of lipid peroxides in LDL (21,22). It initially was described as an enzyme that can play a role in neutralizing organophosphate

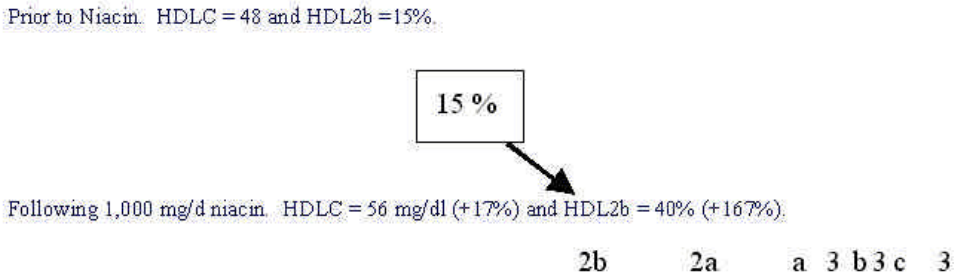

Figure 4. Example of an individual's HDL subclass distribution prior to, and following 1,000 mg/d niacin. HDL2b is the region most associated with cardiovascular protection and reflects "reverse cholesterol transport". HDL2b has been artificially darkened for illustration purposes.

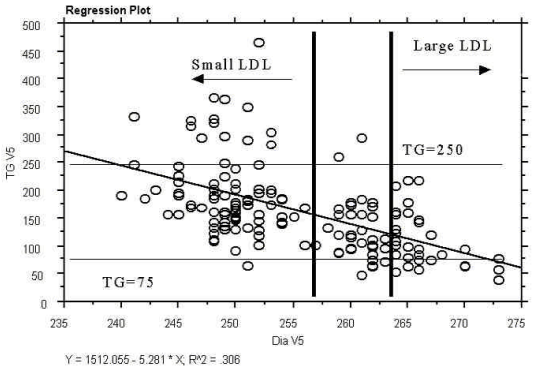

Figure 5. Fasting triglycerides and LDL peak particle diameter by GGE (r=0.55, p=0.0001).

compounds (23). The gene for paraoxanase has been located to chromosome #7 and isoforms have been identified that affect paraoxonase activity (24).

4.2. Metabolic Milieu

The small LDL pattern B trait is linked to several metabolic issues that help explain it's atherogenicity and has been termed the Atherogenic Lipoprotein Profile (ALP) (25). Pattern B is a term used to describe individuals with a predominance of small LDL particles compared to pattern A, which describes individuals with predominately large LDL particles. Small LDLs are able to infiltrate the arterial wall approximately 40 to 50% faster than large LDL particles, these particles are more susceptible to oxidative damage, and the HDL subclass that plays the most powerful role as an antioxidant, HDL2b, is reduced in LDL pattern B subjects. Further, this trait is associated with significantly increased blood fats following a meal, increased PAI-I, increased insulin resistance and an increased risk for the development of Type 2 diabetes. This trait is inherited in a dominant fashion and has been linked to a position on chromosome #19, although, at least 4 other genes impact expression. Hypertriglyceridemia is often, but not always, associated with LDL pattern B and epidemiological analysis has now identified elevated triglycerides as an independent coronary heart disease (CHD) risk factor but it is the association of moderately elevated triglycerides with ALP that create the atherogenic milieu (26,27). The pattern B trait is also associated with insulin resistance, low HDL2b, enhanced postprandial lipemia, low vitamin E lipoprotein particle content and increased susceptibility to oxidation, and elevated IDL (28,29)

4.3. Genetics

The dense LDL subclass pattern, (ALP or LDL pattern B), is a heritable trait determined by a single major dominant gene (the *alp* locus) (30,31). The gene for this trait has been localized to chromosome # 19, near the LDL receptor, and expression is affected by at least three other loci, the apo AI/CIII/AIV gene cluster on chromosome #11, the manganese superoxide dismutase gene on chromosome #6, and the cholesteryl ester transfer protein gene on chromosome #16 (32,33). There is no linkage between the LDL receptor gene. The full expression of this trait occurs following puberty in men and after menopause in women. Based on Hardy-Weinberg equilibrium, 30% to 35% of people are heterozygous for *alp*, and another 5% are homozygous. ALP, or the dense LDL subspecies, is a marker for a common genetic trait that affects lipoprotein metabolism and increases CAD risk.

4. PROSPECTIVE INVESTIGATIONS

Low density lipoprotein subclass distribution determination contributes information to CAD risk determination that is independent of TC and LDLC. The *Boston Area Health Study, the Physicians Health Survey,*

The Stanford Five City Project, and the Quebec Cardiovascular Study all confirmed that the presence of an abundance of small, dense LDL particles signifies an approximate 3-fold increased risk for cardiovascular events (33-36). This is clinically important because this common genetically determined CAD risk factor is not reflected by measurement of LDLC. It may help explain the high incidence of CAD in the majority of patients who do not have classic hypercholesterolemia.

While the small LDL trait has been associated with elevations in fasting triglycerides, many patients with fasting triglycerides between 70-250 mg/dl can exhibit either small or large LDL particles. In this triglyceride group, fasting triglycerides are unreliable in determining individual LDL subclass distribution (Figure 5).

6. VASCULAR IMAGING INVESTIGATIONS

6.1. Carotid ultrasound

B-mode carotid ultrasound has the ability to determine intima-media thickness (IMT). The IMT thickness has been correlated with atherosclerosis as defined by coronary arteriography and change in IMT thickness correlates well with change in arteriographically determined CAD (37). In the Monitored Atherosclerosis Regression Study (MARS) IMT change was correlated with coronary arteriographic change and clinical events. The National Cardiovascular Health Study followed 5,201 men and women for 6.2 years and assessed the ability of near and far wall, common and internal carotid artery IMT to predict cardiovascular events (39). The subjects were greater than 65 years of age and the mean LDLC was 130 mg/dl. There was a significant relation ($p<0.001$) between IMT thickness and both cardiac events and stroke so that subjects in the highest IMT thickness quintile had a relative risk of 6.3 and adjusted relative risk of 3.6 compared to the lowest quintile. Carotid IMT has also been correlated with small LDL III as determined by gradient gel electrophoresis. Investigators in Stockholm reported the relationship of LDL-III to IMT progression in a group of healthy middle aged male subjects (39). Importantly, it was reported that LDL III had a significant relationship to IMT thickness ($r=0.44$, $p<0.001$) while LDLC did not.

6.2. Arteriographic investigations

Evidence that LDL heterogeneity is clinically important in determining arteriographic change over time comes from several investigations. The NHLBI-II was the first investigation to report significantly less arteriographic progression in subjects with reduction in IDL and dense LDL (40). The Monitored Atherosclerosis Regression Study reported that significant arteriographic benefit was evident in CAD patients with mid-density LDLs but despite an equal LDLC reduction, patients with predominately dense, or buoyant LDLs revealed no significant arteriographic benefit (41). The Stanford Coronary Risk Intervention Project has revealed that individuals with predominantly dense LDLs in the control group, had an approximate 2-fold greater rate of arteriographic progression, but with multifactorial risk intervention, they did significantly better than patients with predominantly buoyant LDL in regard to arteriographic benefit (42). The benefit appears to be linked to reductions in LDL IIIa and IIIb (unpublished data). The Familial Atherosclerosis Treatment Study reported that change in LDL buoyancy was the best predictor of arteriographic outcome in this investigation that used resin + niacin, or resin + statin as treatment modalities (46).

6.3. EBT investigations

Electron Beam Tomography (EBT) is a method that detects coronary calcification and is a reflection of coronary atherosclerosis. Subjects with coronary calcification on EBT can be defined as having coronary atherosclerosis (47). The use of EBT offers an alternative classification for patients with CAD (presence of coronary calcification) or no CAD (no coronary calcification). Using EBT as the definition of the presence of coronary atherosclerosis, it has been reported that in asymptomatic individuals, LDLC < 160 mg/dl has no significant statistical relationship to coronary calcium score (48). In patients with coronary calcification 99% had either small LDL, elevated Lp(a), or elevated tHcy that was not detected by routine lipid analysis recommended by the National Cholesterol Educational Program Guidelines II (49).

7. TREATMENT IMPLICATIONS

7.1. Diet

Low fat diets have been recommended as the foundation for treating lipid disorders (NCEP). However, when diets are reduced in fat, without reducing total calories, the fat calories are frequently replaced by simple carbohydrate calories. The effect of such diets has been investigated in regard to LDL and HDL subclass distribution change (50). With reduction of percent calories from fat from 46% to 20%, a significant reduction in LDLC and Apo B was reported in LDL pattern B subjects but unexpectantly, 40% of the subjects classified as LDL pattern A on the 46% fat diet converted to LDL pattern B on the 20% fat diet. Reduction of total calories from 20 to 10% can significantly increase small LDL and reduce HDL2b (51).

7.2. Exercise/weight loss

Exercise and associated weight loss can have a significant effect on reducing small, dense LDL and increasing HDL2b (52). This effect appears to be linked to the exercise induced loss of excess body fat (53).

7.3. Medications

7.3.1. Nicotinic acid

Nicotinic acid has been reported to have a differential effect on LDL subclass distribution in subjects classified as LDL pattern A or B (54). The reduction in small, dense LDL is counterbalanced by an increase in large, buoyant LDL, which results in a LDLC reduction that does not reflect the significantly greater reduction in small LDL (55). Nicotinic acid has a significant effect on increasing HDL2b that is greater than appreciated from the change in HDLC. For example, 1,000 mg/day niacin may

Table 1. Clinical trails associating differences in lipoprotein subclass distribution with increased CAD risk.

Study	Type	Lipoprotein Subclass Finding
Livermore (6)	Prospective	Triglyceride rich Sf(20-100) lipoproteins associated with CAD risk. Lower HDL2 and HDL3 mass found in DeNova CAD subjects.
Framingham (6)	Prospective	Triglyceride rich Sf(20-400) lipoproteins associated with CAD risk.
Boston Heart (33)	Case Control	LDL pattern B associated with 3-fold increased CAD risk.
Physicians Health (34)	Prospective	LDL pattern B associated with a 3.4-fold increased CAD risk independent of total and HDL cholesterol, and Apo B. Not statistically independent of TC/HDLC ratio.
Stanford FCP (35)	Prospective	LDL size is best predictor of CAD risk by conditional logistic regression. Not statistically independent of nonfasting triglycerides.
Quebec CV (36)	Prospective	LDL size independent predictor of CAD risk.

Table 2. Arteriographic investigations that contribute to the knowledge base regarding lipoprotein subclass distribution and arteriographic outcome.

Montreal (13)	Arteriographic	IDL and HDL related to CAD progression but not LDLC.
NHLBI-II (40)	Arteriographic	Reduction in LDL, IDL, and small LDL mass related to atherosclerosis stability.
CLAS (44)	Arteriographic	Subjects with lower triglycerides benefited the least from niacin and resin treatment.
MARS (41)	Arteriographic	In treated subjects with LDLC < 85 mg/dl, triglyceride rich lipoproteins were correlated with disease progression.
SCRIP (42,43)	Arteriogarphic	Despite identical LDLC reduction, subjects with a predominance of small LDL (pattern B) had significantly slower CAD progression compared to control subjects while those with a predominance of large LDL (pattern A) revealed no arteriogrpahic effect of treatment compared to control subjects.
STARS (45)	Arteriographic	Change in dense LDL was the best predictor of arteriographic outcome.
FATS (46)	Arteriographic	Change in LDL buoyancy (inverse of density) was the best predictor of arteriographic outcome.

induce a 17% increase in HDLC, but a 167% increase in HDL2b.

7.3.2. Gemfibrozil

In general, fibrates reduce small LDL particularly when elevated triglycerides are reduced, and they may increase HDL2b. However, different fibrates can have different effects on HDL subclass distribution. Gemfibrozil has been shown to reduce small, dense LDL significantly in LDL pattern B subjects but have little to no effect on small LDL in pattern A subjects (55,57). This effect of fibrates on LDL and HDL subclass distribution may have implications for the interpretation of the VA-HIT study that associated an increase in HDLC, attributed to gemfibrozil treatment, with fewer cardiovascular events (58).

7.3.3. HMGCoA reductase inhibitors

The effect of HMGCoA reductase inhibitors including pravastatin, lovastatin, simvastatin, and fluvastatin have been investigated using gradient gel electrophoresis and no significant differential effect on LDL subclass distribution was reported (41,59-63).

7.3.4. Alpha and beta blockers

Selective and nonselective beta blocker medications are known to be associated with an increase in trilycerides and reduction in HDLC (64). The generalized effect is associated with increased small, dense LDL distribution counterbalanced by a reduction in large, buoyant LDL particles (65). The alpha blocker prazosin is associated with mild reductions in triglycerides and increases in HDLC which are further associated with reductions in small, dense LDL counter balanced by increases in large, buoyant LDL distribution. The reduction in HDLC induced by non-selective beta blockade is also associated with reductions in the HDL2 distribution (66).

7.3.5. Hormone replacement therapy

The hormonal components of oral contraceptives exert major effects on plasma lipoprotein metabolism that suggests hormone replacement therapy in post menopausal women may impact lipoprotein metabolism as well (67). Hormone replacement therapy (HRT) may be beneficial in postmenopausal women for a variety of reasons (68). Treatment with 0.625 mg/d conjugated equine estrogen and 2.5 mg/d medroxyprogesterone in post menopausal women was recently reported to have a significantly greater effect on reducing LDLC and Apo B in LDL pattern B postmenopausal women compared to LDL pattern A women (69). This reduction in LDLC was accompanied by a significant reduction in small dense LDL (%IIIa+b, or Sf5-7), increase in HDL2b, and increase in lipoprotein lipase. For postmenopausal women with the LDL pattern B disorder, HRT may be considered as a possible therapeutic maneuver.

7.3.6. Combination

Combination drug therapy can produce dramatic improvement in the lipoprotein abnormalities associated with combined hyperlipidemia (70). In regard to LDL

subclass distribution, combinations of lipid lowering medications that have been reported to have a beneficial effect on LDL subclass distribution include, pravastatin + niacin, niacin+ resin, and niacin+gemfibrozil (71-73).

8. REIMBURSEMENT ISSUES

New laboratory tests need to fulfill three general requirements prior to acceptance for payment by third party agencies. These requirements include, 1) evidence that the new test results are not provided by existing tests, 2) that the results of the new test indicate a clear treatment decision, and, 3) the results of treatment, based on the new test results, will provide the patient with significantly better medical outcome. In January 1999, Medicare approved payment of the Berkeley LDL GGE for patients with appropriate diagnostic codes which include 43 codes associated with atherosclerosis conditions (74).

9. PERSPECTIVE

Lipoprotein heterogeneity is a clinically important issue that has been investigated for 50 years. In the past two decades an abundance of evidence indicates that the presence of predominantly small, dense LDL particles identifies a group of individuals who have a three-fold increased risk for CAD that is independent of standard cardiovascular risk factors including total, LDL, and HDL cholesterol, as well as triglycerides and body mass index (75). In patients with established CAD, the presence of small LDL identifies patients with approximately 2-fold greater rate of arteriographic progression, but, with treatment, these patients have a better arteriographic outcome than similarly treated patients with predominantly large LDL particles. This arteriographic improvement has been linked to change in LDL density and distribution as determined by gradient gel electrophoresis. Treatments including low fat diets, exercise, weight loss, HRT, nicotinic acid, bile acid binding resins, gemfibrozil, statins, and combination therapies have been investigated in patients classified as LDL pattern A, B, or I by analytic ultracentrifugation or gradient gel electrophoresis and differential effects of treatment reported in these groups.

This plethora of scientific investigations indicates that the ALP trait is one of the most important risk factors for accurately determining CAD risk and progression of existing disease. Equally important, specific treatment selection, based on knowledge of LDL subclass distribution has been demonstrated and this knowledge can be used to individualize patient treatment programs to achieve the optimal individual cardiovascular outcome.

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Send corrspondence to: H. Robert Superko, MD. FACC, Berkeley HeartLab, Cholesterol, Genetics and Heart Disease Institute, 1875 South Grant St., San Mateo, CA 94402, Tel:650-372-1960, Fax 650-372-1948, E-mail: superko@best.com