Diagnosis and Treatment of Lipid Disorders

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MORE THAN HALF of the coronary artery disease (CAD) in the U.S. is attributable to dyslipidemia. Some premature CAD is associated with hyperlipoproteinemias which are due to mutations in major genes involved in lipoprotein metabolism. Elevated lipoproteins in most patients with CAD, however, reflect the adverse impact of a sedentary lifestyle, excess body weight, and diets high in total and saturated fat on a less than perfect multigenic background. CAD is therefore, at least in part, a failure of preventive medicine.

Unlike other laboratory measurements, average levels of blood cholesterol are not equivalent to "normal" levels. Blood concentrations of electrolytes show little variation among different populations, whereas average serum cholesterol varies widely. The mean serum cholesterol in the U.S. (approximately 205 mg/d1) would in fact be in the upper 5th percentile (two standard deviations above the mean and hence "abnormal") in a population consuming primarily a vegetarian diet. Because such populations have an extremely low incidence of cardiovascular disease, the logical conclusion is that the statistically "average" cholesterol level in the U .S. is neither normal nor desirable.

In an attempt to have an impact on the excess CAD morbidity and mortality in the U .S., a two-pronged approach has been developed. The first approach, a population-based strategy, is aimed at lifestyle modification. Federal and private agencies have made major efforts to change the American diet. Consumers are being urged to avoid foods high in saturated fats, and to increase their intake of fresh fruits, vegetables, grains, and other low fat items. In addition, because the National Institutes of Health, American Heart Association, American Cancer Society, and American Diabetes Association all promote a similar low-fat regimen, the public is receiving a coherent dietary prescription. As a result of this major effort, we have seen a reduction in dietary fat and cholesterol intake, and a concomitant reduction in the mean plasma cholesterol of the population. That there is still much to be done is attested by the statistic that CAD is the number one cause of death in the United States.

The second component of the attack on CAD has been to target high-risk patients. The National Cholesterol Education Program (NCEP) has formulated guidelines for screening and intervention in patients with hyperlipoproteinemias. Thus, primary care providers and subspecialists need to understand the pathophysiology and available therapies for these disorders. In this review we will focus first on the known major molecular defects responsible for several well characterized hyperlipoproteinemias and then provide a practical approach for the physician as he/ she identifies, evaluates, and treats patients with increased risk of CAD.

DISORDERS OF LIPOPROTEINS

LIPOPROTEIN STRUCTURE AND METABOLISM

Lipoproteins are spherical macromolecular complexes containing a core of relatively insoluble lipids (triglycerides and cholesteryl esters) surrounded by a coat of phospholipids, unesterified cholesterol, and apoproteins. These surface molecules are amphipathic-that is, they have both hydrophilic and hydrophobic domains, which allow them to interact both with the nonpolar core lipids and the aqueous plasma. The word apo means "without"; therefore proteins separated from their normal complements of lipids are termed "apolipoproteins" or "apoproteins." Apoproteins on the surfaces of lipoprotein molecules interact with cell surface receptors and enzymes, and these interactions, in turn, lead to the metabolism and interconversion of the lipoprotein particles.

Lipoproteins are classified according to their densities. Because lipids are less dense than proteins, the larger lipoproteins, which contain a greater proportion of hydrophobic core lipids, are less dense (chylomicrons and very low density lipoproteins [VLDL]); low density lipoproteins (LDL) contain less lipid; the smallest, most protein-rich lipoproteins are high-density lipoproteins (HDL). Disorders of lipoproteins were previously classified by numbers (Fredrickson 1-5) which referred, in general, to the abnormal lipids present; currently they are more often referred to by descriptors which characterize the lipoprotein abnormalities.

TRIGLYCERIDE-RICH LIPOPROTEINS AND HYPERTRIGLYCERIDEMIA

Severe hypertriglyceridemia, with plasma triglycerides > 1000 mg/ dl, is almost always due to elevated concentrations of circulating chylomicrons. Chylomicrons are normally found only in postprandial plasma. Large amounts of chylomicrons in fasting blood produce milky white plasma and whole blood which looks like cream of tomato soup. The chylomicrons also displace the aqueous, serum components of blood and high levels of chylomicrons,therefore, cause an artifactual depression of the measured levels of sodium and other serum components. These patients may have hepatosplenomegaly, eruptive xanthomas (2-4 mm papules with a yellowish center found on the forearms, back and buttocks), and lipemia retinalis (a discoloration of the fundus due to the whitish hue of the lipemic blood). Sometimes hyperchylomicronemic patients present with pancreatitis; often the severe hypertriglyceridemia associated with increased chylomicron levels is an incidental finding on a laboratory examination.

Chylomicrons (the largest of the lipoproteins) and VLDL transport triglyceride, the storage form of energy, around the body. The metabolic pathway for chylomi-

crons is illustrated in Figure 1. (1) Chylomicrons are assembled in enterocytes from dietary triglycerides, cholesterol, fat-soluble vitamins, and apoB48. (2) They are initially transported in the lymph, eventually entering the circulation via the thoracic duct. (3) Much of the triglyceride within these lipoproteins is hydrolyzed by lipoprotein lipase (LPL). LPL is synthesized within adipose tissue and muscle and interacts with

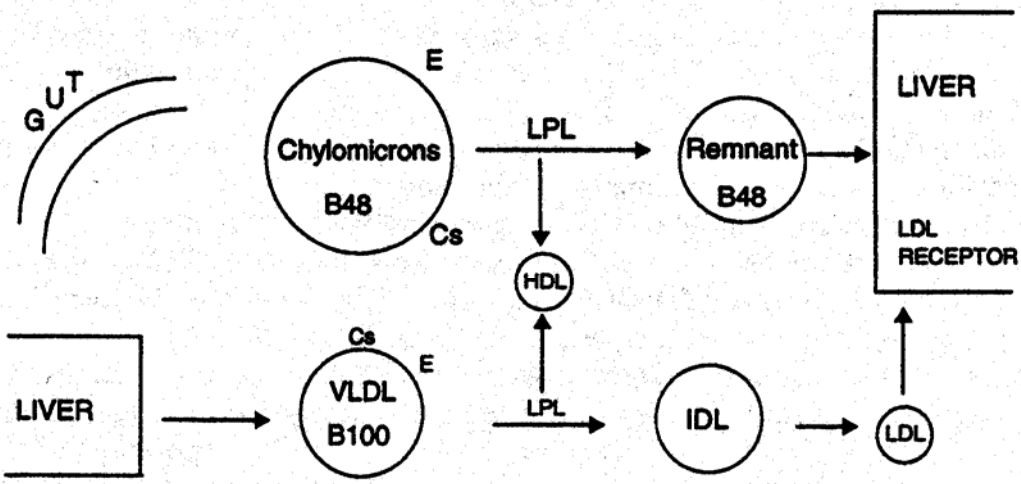

Fig. 1. Lipoprotein metabolic pathways. Chylomicrons, containing dietary triglycerides, are converted to remnant lipoproteins via the actions of LPL (lipoprotein lipase). VLDL (very low density lipoproteins) are secreted by the liver. The major structural protein in VLDL is apoB100; chylomicrons contain the amino terminal 48% of apoB, i.e., apoB48. VLDL triglyceride is also hydrolyzed by LPL, converting it to intermediate-density lipoproteins (IDL), and eventually to LDL (low-density lipoproteins). The LDL receptor removes LDL from the plasma. ApoB100 and apoE are ligands for the LDL receptor which, by removing LDL from the bloodstream, controls LDL concentrations. HDL are synthesized in the gut and the liver and, while in the bloodstream, acquire lipids during hydrolysis of VLDL and chylomicrons.

lipoproteins while attached to the luminal surface of capillary endothelial cells. The free fatty acids produced during hydrolysis of triglyceride are used as energy by muscles or are stored within the fat tissues after re-esterification to triglycerides. (4) The triglyceride-depleted chylomicron remnants containing apoE are then removed by the liver. Hepatic receptors for these remnants include the LDL receptor and the LDL receptor-related protein (LRP). LRP may also be responsible for removal of a number of proteolytic proteins from the circulation.

A homozygous genetic deficiency in LPL or its activator-apoCll-leads to an inability to catabolyze dietary triglyceride (type 1 hyperlipoproteinemia). Patients with this deficiency have severe hypertriglyceridemia and hyperchylomicronemia, often presenting with multiple episodes of pancreatitis starting in childhood. They do not typically have an increased risk of CAD. Heterozygous LPL deficiency causes milder forms of fasting hypertriglyceridemia and may be associated with increased postprandial lipemia. Cases of severe chylomicronemia may appear during pregnancy or diabetes mellitus. Rarely, hyperchylomicronemia occurs with autoimmune disorders and antibodies to apoproteins, LPL, or heparin. VLDL have a metabolic pathway which is similar to that of chylomicrons. (1) VLDL are assembled within the liver; the triglyceride

is derived from circulating fatty acids or synthesized *de novo* from carbohydrates or amino acids. (2) Within the circulation VLDL triglycerides are broken down into fatty acids which are taken-up by peripheral tissues. (3) VLDL remnants (also called intermediate density lipoproteins IDL) are either removed by the liver or converted into cholesterol-rich, denser, LDL.

Milder hypertriglyceridemia, with triglyceride levels of 200-500 mg/ dl, is asymptomatic and primarily due to VLDL overproduction. Elevated VLDL concentrations occur with primary hypertriglyceridemia (type 4 hyperlipoproteinemia) or familial combined hyperlipidemia (elevated VLDL and LDL, type 2B hyperlipoproteinemia). Obesity is a very common concomitant of hypertriglyceridemia and increased VLDL levels. Renal failure, diabetes mellitus, consumption of alcohol, and treatment with estrogens are associated with increased VLDL production. Reduced blood HDL concentrations are associated with most hypertriglyceridemias except those due to alcohol and estrogens.

Most instances of adult-onset severe hypertriglyceridemia (e.g., that in patients with type 2 diabetes) are associated with both increased VLDL production and decreased VLDL catabolism. LPL activity, which is regulated by insulin, is usually depressed in patients with type 2 diabetes mellitus. This defect in LPL synthesis and secretion may derive from either absolute insulin deficiency, or more usually, from insulin resistance. Since LPL is saturated at triglyceride concentrations >500 mg/ dl, both VLDL and chylomicron catabolism can be abnormal above such levels. The acute signs and symptoms of elevated VLDL and chylomicron levels (type 5 hyperlipoproteinemia) are the same as with elevated levels of chylomicrons alone. These patients, however, often develop CAD, probably because VLDL levels are increased along with chylomicrons.

CHOLESTEROL-RICH LIPOPROTEINS AND HYPERCHOLESTEROLEMIA

All lipoproteins contain cholesterol. Therefore, a marked elevation of even the triglyceride-rich lipoproteins (VLDL and chylomicrons) will cause increased blood cholesterol levels. Elevated concentrations of LDL, and less commonly HDL, usually present as hypercholesterolemia without hypertriglyceridemia. The most dramatic forms of elevated levels of LDL are seen in patients with familial hypercholesterolemia (type 2A hyperlipoproteinemia), a disorder associated with mutations in the gene for the LDL receptor. Heterozygous carriers of this disorder present with LDL levels in excess of 250 mg/ dl and often have a family history of CAD in the third to fifth decades of life. Although the diagnosis is usually made using laboratory results, patients often have tendon xanthomas which are best appreciated as diffuse or nodular thickenings of the Achilles tendons. Familial hypercholesterolemia occurs in approximately 1/500 people and is present in 5% of patients with CAD under the age of 60. Thus, it is one of the most common genetic disorders. The diagnosis of familial hypercholesterolemia requires cholesterol screening of family members, or DNA sequencing of the gene.

Most plasma LDL is derived from plasma metabolism of VLDL (see Figure 1). Elevated LDL levels may result from increased production of VLDL, decreased LDL catabolism, or both. The catabolic pathway for LDL requires its interaction with a cell surface receptor. Apo Bl00 is the ligand for the LDL receptor. As noted above, most cases of familial hypercholesterolemia are due to a defect in this receptor. A defect in

apoB which prevents its interaction with the receptor has also been described. It is caused by a mutation in the LDL binding region of the protein, and its prevalence appears to be similar to that of mutations in the LDL receptor gene. However, it is very important to note that most hypercholesterolemia is not associated with either of these genetic defects, but is presumably polygenetic. All disorders of increased LDL are exacerbated by a lifestyle which includes diets high in saturated fat and cholesterol, obesity, and decreased physical activity.

Elevated plasma concentrations of HDL occasionally cause hypercholesterolemia but are not associated with disease. Low HDL concentrations are associated with increased risk for CAD in U.S. and Western European populations. The HDL class of lipoproteins can be further subdivided, e.g., into HDL2 and HDL3. Although each of these subfractions may relate to CAD risk, most large population studies have only assessed total HDL cholesterol. Therefore, total HDL is used for clinical decisions.

HDL concentrations are modulated by the synthesis rate of HDL proteins, the catabolism of those proteins, and addition and subtraction of lipid from the HDL. HDL lipid includes (1) lipid (mainly phospholipid) associated with newly synthesized HDL particles, (2) cell membrane cholesterol which is converted to cholesteryl ester in the blood by lecithin cholesteryl acyl transferase (LCAT), and (3) lipid from triglyceride-rich lipoproteins which transfers to HDL during lipolysis. Cholesteryl ester transfer protein (CETP) mediates an exchange of HDL cholesteryl ester for VLDL (and chylomicron) triglyceride in plasma and modulates the core lipid composition of HDL. Familial deficiency of CETP, a genetic defect, is associated with very high plasma levels of HDL cholesterol.

ELEVATED CHOLESTEROL AND TRIGLYCERIDE CONCENTRATIONS

Elevations of both VLDL and LDL occur in familial combined hyperlipidemia (type 2B hyperlipoproteinemia). Both the patients and their family members can have elevated plasma concentrations of cholesterol, triglyceride, or both. Isolated hypertriglyceridemia and isolated hypercholesterolemia can occur in the same person at different times in their lives. In this disorder the liver overproduces apoB-containing lipoproteins. The ability of the patient to hydrolyze triglycerides and convert VLDL to LDL will detemine the proportion of VLDL and LDL in the blood. Thus, when lipolysis is increased by weight loss or fibric acid medications, VLDL may decrease while LDL increases. In contrast, when lipolysis is decreased-for example, during periods of poor glycemic control of diabetes- VLDL increases and LDL decreases. Familial combined hyperlipidemia is associated with an increased risk of CAD and may be an indication to treat hypertriglyceridemia more aggressively.

A less common cause of combined increased blood triglyceride and cholesterol concentrations is dysbetalipoproteinemia (type 3 hyperlipoproteinemia). This disorder is due to elevated concentrations of remnant lipoproteins, also termed beta- VLDL or IDL. Dysbetalipoproteinemia, which is found in 1/10,000 individuals, is associated with the homozygous state for an abnormal form of apoE (called apoE2), the protein required for removal of remnant particles. Signs of this disease include pa1mar xanthoma (yellow-orange discolorations in the creases of the palms) and tuberous xanthomas. The diagnosis is made by isolation of the VLDL, measurement of cholesterol and triglyceride

in this fraction, and demonstration that it is enriched in cholesterol (ratio of cholesterol/triglyceride >0.3). Increased concentrations of beta-VLDL also occur in hypothyroidism and nephrotic syndrome. Dysbetalipoproteinemia increases the risk for CAD and peripheral vascular disease.

Table 1: Common Hyperlipoproteinemias

	Lipoprotein Increased	*Pathophysiology*
Familial hypercholesterolemia	**LDL**	**Defective or lack of LDL receptors**
Familial defective apoB	**LDL**	**ApoB with altered LDL receptor binding**
Familial combined hyperlipoproteinemia	**VLDL & LDL**	**Overproduction of apoB-containing lipoproteins**
Dysbetalipoproteinemia	**Remnants**	**Abnormal apoE**
Hypertriglyceridemia	**Moderate – VLDL Severe – VLDL and Chylomicrons**	**Overproduction of triglycerides; defective catabolism**
Genetic lipoprotein lipase or apo Cll deficiency	**Chylomicrons**	**Defective catabolism**

FACTORS ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS

APPROACH TO THE PATIENT

Measurement of blood lipoproteins

Although the initial indication of an abnormality in lipoprotein metabolism is via blood measurements of lipids, the disorders are abnormalities of specific lipoproteins. Thus, lipoprotein analysis should assess VLDL, LDL, and HDL concentrations. HDL cholesterol is the cholesterol remaining in the plasma after precipitation of the apo B-containing lipoproteins, i.e., LDL, IDL, and VLDL. In the past, direct measurements of plasma LDL has required laborious centrifugation or chromatographic techniques. Instead, LDL cholesterol concentrations are usually estimated by subtracting the HDL and VLDL cholesterol from the total plasma cholesterol. Because VLDL has approximately 5 times as much triglyceride as cholesterol, VLDL cholesterol is estimated to be the plasma triglyceride level/5. Therefore:

LDL cholesterol (estimate) =total cholesterol- [HDL cholesterol + Triglyceride/5]

Hypertriglyceridemia greater than 500 mg/ dl increases the ratio of triglyceride

to cholesterol because of an accumulation of larger VLDL or chylomicrons. For this reason, LDL estimates are not accurate in this situation. Recently, commercial laboratories have developed direct LDL cholesterol measurements.

Machines which measure blood cholesterol on fingerstick samples of blood give reasonably accurate measurements if properly maintained and standardized. Newer machines can measure total cholesterol, triglyceride and HDL cholesterol from a drop of blood. In the absence of severe hypertriglyceridemia, non-fasting blood samples can be used for cholesterol screening. However, after a fat-containing meal, plasma triglycerides rise and both HDL and LDL cholesterol levels fall modestly (by the action of CETP). The ratio of triglyceride to cholesterol in VLDL also increases postprandially. Estimations of LDL are, therefore, best done on fasting samples. Screening with only cholesterol levels will not detect individuals with isolated low HDL. Thus, screening for CAD should include an HDL (can be measured on non-fasting blood although it is likely to be lower than it would be fasting) or lipoprotein profile (i.e., triglyceride, cholesterol, HDL, and LDL estimate).

Cholesterol concentrations in both LDL and HDL are decreased after myocardial infarctions or during acute inflammatory conditions. Lipoprotein analyses on cardiac patients may be falsely reduced if taken more than 24 hours after an acute event, but if abnormal they may alert the physician to an underlying lipid disorder. Since serum lipids vary, several measurements taken a few weeks apart should be obtained prior to initiating costly and time-consuming therapies. A minimum of two values should be obtained before any treatment decisions are made.

GUIDELINES FOR LDL TREATMENT

The current national guidelines for treatment of lipoprotein abnormalities are based on blood concentrations of lipoprotein lipids. Although research and c1inical laboratories often offer measurements of individual apoproteins, e.g., apoB and apoAI, these measurements are generally not used in practice. Except for the diagnosis of dysbetalipoproteinemia, which is usually made using ultracentrifugation methods, lipoprotein electrophoresis is also not useful. Recently, genotyping of apoE has become available in research laboratories; it is the optimal way to determine if someone has dysbetalipoproteinemia.

An overwhelming body of clinical and experimental data shows that LDL cholesterol reduction alters the incidence and progression of CAD. In addition, LDL can be reduced in most patients by life-style changes and medications. Some experts advocate the use of cholesterol/HDL ratios as a better assessment of individual risk. This is a reasonable approach provided both the patient and the physician are aware that treatment goals are to reduce LDL. In addition, physicians must be aware of the absolute values of each because rare patients with very high or very low levels of both LDL and HDL will have ratios that are not evaluable based on population studies.

The NCEP Adult Treatment Panel recommends more aggressive therapy for those patients with multiple risk factors. Risk factors include family history of premature CAD (below the age of 55 years in a male parent or sibling, or below 65 in female relatives), hypertension (even if it is treated with medications), cigarette smoking (more than 10 cigarettes per day), and low HDL (<40 mg/ dl). In addition, since CAD is more prevalent in older individuals, age (males >45 years and females >55 years or younger with

premature menopause without estrogen replacement) is also a risk factor. HDL concentrations >60 mg/dl have been assigned a negative risk factor status, i.e. one other risk factor is subtracted.

Patients with CAD, CAD equivalents (peripheral or cerebrovascular disease), or diabetes mellitus

Historically, the treatment of CAD has focused on palliation of symptoms like angina and CHF. It is now established that dietary and pharmacologic treatments of hypercholesterolemia slow progression and, in some cases, cause regression of atherosclerotic lesions. Moreover, because elevated levels of LDL inhibit nitric oxide (the endothelium-derived relaxation factor) and prevent vasodilitation of vessels, LDL-lowering therapy has the potential to acutely alter ischemic symptoms. CAD patients should be screened for lipid abnormalities during and after their initial diagnoses. A goal of lowering plasma LDL concentrations to <100 mg/ dl is now advocated for patients with known CAD. Because other forms of atherosclerotic disease and diabetes carry very high risks for CAD, patients with these diseases are treated as if CAD was present.

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL Level at Which To Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)
2+ Risk Factors (10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk < 10% ≥160 mg/dL
0-1 Risk Factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

In a recent statement, NCEP's ATP said that lowering LDL cholesterol to <70 mg/dl is an option in patients at "very high risk". Such patients have CAD and multiple risk factors, including diabetes.

High triglycerides and low HDL

The evidence that treatments which reduce plasma triglyceride levels or increase plasma concentrations of HDL cholesterol lead to long-term health benefits is less compelling than that for LDL. It is clear that efforts should be made to reduce triglycerides if they may precipitate pancreatitis. Thus, triglycerides >500 mg/dl are generally treated. Lower levels (200-500 mg/ dl) are commonly treated, especially in individuals with other CAD risk factors. A key question is "what is the reason for the inverse correlation between HDL cholesterol and CHD?" Its answer is unknown. Several

theories have been proposed, among them these: HDL removes cholesterol from arteries via a process known as reverse cholesterol transport (i.e., reversing the flow of cholesterol from into, to out of the vessel); HDL is a marker for the rate of triglyceride catabolism (i.e., higher HDL levels are markers of more efficient catabolism of remnants); and HDL prevents oxidative conversion of LDL into more atherogenic lipoproteins.

There have been no intervention trials in which only increases in HDL cholesterol concentrations have been achieved. However, treatment of hypercholesterolemic patients with gemfibrozil led to a decrease in CAD events which was greater than that expected with the observed LDL decreases. In a recent study, gemfibrozil treatment was beneficial in men with CAD and LDL levels near 100 mg/dl, suggesting that increasing HDL and/or lowering triglycerides reduced CAD events. Beneficial effects of niacin have been attributed, in part, to the triglyceride-lowering and HDL-raising actions of this medication. HDL levels are primarily genetically determined, are sometimes decreased by a heart-healthy diet, and often show little response to drugs. Alcohol will often increase HDL. However, the many adverse effects of alcohol preclude its general use as a therapeutic measure. For these reasons hygienic approaches-low saturated fat diets, maintenance of ideal body weight, and participation in regular exercise-are usually recommended for patients with low HDL.

Aside from the "classic" risk factors listed above, a number of other clinical and biochemical factors are being appreciated as co-determinants of atherosclerotic risk and are under active study.

Insulin Resistance

Individuals with a syndrome, sometimes referred to as syndrome X, which includes central obesity, insulin resistance, hyperinsulinemia, hypertension and hypertriglyceridemia with low HDL cholesterol are at greater risk for the development of CAD. The obesity is central (apple-shaped body habitus) rather than peripheral (pear-shaped body habitus). The central obesity can be assessed by determining the waste-hip ratio to be >0.85. Many of the individuals meet the criteria for the “metabolic syndrome” which has been defined by ATP III as a high risk syndrome for CAD.

Lipoprotein oxidation

The atherosclerotic lesion contains both intracellular and extracellular cholesterol, much of which is derived from LDL. Cholesterol-rich macrophages, termed foam cells, cannot be produced by incubating human macrophages with LDL. LDL which has been oxidatively modified-with changes in its charge, it aggregability, its association with proteoglycans and other extracellular proteins, and its interaction with cell surface receptors-can load macrophages with cholesterol. Some altered LDL are internalized by the macrophage scavenger receptor. Oxidized LDL have been found within atherosclerotic lesions. Beta-carotene and vitamins C and E can prevent LDL oxidation in vitro, and in animal models of severe hypercholesterolemia and atherosclerosis. Moreover, LDL-vitamin E content and a history of vitamin E intake were associated with less CAD in some studies. However, clinical trials with pharmacologic doses of antioxidants have not reduced the incidence of CAD. In a recent study, large doses of antioxidants seem to reduce the HDL-raising effects of niacin.

Lipoprotein (a) [lp(a)]

Lp(a) concentrations in the blood are correlated with the incidence of CAD in Caucasian, but not black, populations. However, recent studies indicate that smaller molecular weight isoforms of Lp(a) are atherogenic in both blacks and whites. Lp(a) is a LDL associated with apo(a), a high-molecular-weight protein. Apo(a) has homology with plasminogen: thus apo(a) may affect thombotic events. Lp(a) levels in blood do not respond to dietary maneuvers that lower LDL cholesterol; nor do Lp(a) levels respond to most lipid-altering medications, although treatment with niacin does produce modest reductions in Lp(a) concentrations. Estrogen treatment in post-menopausal females reduces Lp(a) levels by about 30%. There is now a standardized test to measure lp(a), and elevated concentrations are sometimes used as an additional risk factor for CAD.

Estrogen deficiency

Postmenopausal replacement therapy with estrogen appeared to have protective effect against development of CAD in population studies. The decrease in CAD events in women who have taken postmenopausal hormone is much greater than would be expected from the decreases in LDL and increases in HDL which occur with this treatment. However, in the HERS trial, women with documented coronary disease who received estrogen-replacement therapy had higher death rates during a two-year follow up compared to placebo-treated women. In the Women's Health Initiative, estrogen-replacement therapy (with or without progestin) was associated with increased CHD in women without prior disease. Estrogen is no longer recommended for cardio-protection in postmenopausal women.

TREATMENTS

LIFE-STYLE

Physicians play an important role in initiating and monitoring dietary therapy. The importance of dietary approaches should be emphasized by taking a dietary history and having the patient bring in food diaries. Many patients who are informed of hyperlipidemias will change their diets with little or no assistance from health professionals. Dietary therapy for patients with genetic hyperlipoproteinemia or atypical life-styles is often best performed by a trained nutritionist, with the physician playing a supportive role.

Patients with hyperlipidemia are encouraged to eat a diet lower in cholesterol and saturated fat than the typical American diet. Because weight reduction is often recommended, decreased total as well as saturated fat intake is advisable. Whole-mi1k dairy products, egg yolks, meats, and tropical oils should be replaced with fresh fruits and vegetables, complex carbohydrates (especially whole grain products) and low-fat dairy products. Shellfish have very low fat content and except for shrimp, also have low cholesterol content. Shrimp, in moderation, are acceptable too. Portion size needs to be stressed; the protein and fat-rich portion of a meat-containing meal should be less than 4 ounces, the size of a deck of cards. Substitutions with any low saturated fat food such as bran, nuts, and olive oil will have similar positive effects on LDL. Hydrogenation of vegetables oils increases the saturation of the fatty acids and is not advantageous. In particular, recent studies have demonstrated that trans-fatty acids, mainly found in

commercially hydrogenated vegetable oils, raise LDL and can lower HDL cholesterol levels.

Severe hyperchylomicronemia requires very low fat diets, avoidance of free sugars, and decreased alcohol intake. Patients with genetic LPL deficiency are instructed to prepare their food using medium chain triglyceride oils which are not incorporated into chylomicrons. Fish oil-containing capsules decrease triglyceride synthesis and in high doses may be used as treatment for severe hypertriglyceridemia.

Changing a patient's diet and exercise program requires the successful physician to be conversant with basic principles of behavior modification, such as (1) getting an accurate picture of the patient's current behavior, (2) assessing previous successes and failure, (3) using experience as a guide, (4) setting attainable goals and a specific plan to allow the patient to derive some positive reinforcement for behavior change, and (5) arranging for follow-up.

DRUGS

In general, lipid-lowering medications are an adjunct or secondary therapy which follows attempts to modify lipid parameters with lifestyle changes. Although a trial of diet therapy of several months is usually attempted before addition of medications is advocated, the length of this trial requires clinical judgment. For example, a young, otherwise healthy, person with moderately elevated LDL might be given a more prolonged diet trial. In contrast, patients with genetic familial hypercholesterolemia who are likely to require several lipid-lowering drugs or patients with established CAD should have shorter trials of diet alone before moving onto medications. Indeed, evidence from several secondary prevention trials has led some physicians to start patients on cholesterol-lowering medications at the time of their heart attack. Recent studies in patients with acute coronary syndrome support immediate cholesterol-lowering treatment. The physician should be aware that some patients who have achieved a substantial amount of lipid lowering from medication discontinue their diets, thus negating some of the beneficial effects of the drugs.

As listed in Table 2, lipid-lowering medications primarily affect VLDL and chylomicrons (triglyceride) or LDL cholesterol. Only niacin is an effective, first-line therapy for both elevated VLDL and LDL. Bile acid-binding resins decrease LDL but may exacerbate hypertriglyceridemia. Fibric acid drugs are primarily effective in reducing triglyceride-rich lipoprotein concentrations, whereas hydroxymethylgluteryl CoA (HMG-CoA) reductase inhibitors (statins) lower LDL but are less effective for treatment of hypertriglyceridemia.

Several lipid-lowering drugs are difficult to tolerate. Resins can cause constipation. To avoid this problem, patients should add a source of fiber (e.g., bran or metamucil) to their diets prior to beginning resins. The resin dose should then be slowly titrated to find the maximum dose that is well tolerated by the patient.

Ezetimibe is a newly approved agent that blocks the absorption of dietary and biliary cholesterol at the brush-border of small intestinal cells. It is absorbed and recirculates between the liver and the intestine. It appears safe and effective as an LDL cholesterol lowering agent.

Table 2: Lipid-lowering Medications

LDL-lowering agents

- Bile-binding resins: cholestyramine, cholestipol
  - Action: Interruption of bile, decreases LDL, increases VLDL synthesis
  - Principal Side effects: Decreased absorption of medications, bloating, and constipation
  - Contraindications: GI obstruction, chronic constipation. May exacerbate hypertriglyceridemia
  - Colestipol dose- 23-30 gm divided into 2-3 doses per day
  - Cholestyramine dose: 16-26 grams divided into 2 or 3 doses per day
    Supplied in packets and bulk cans (the cans are usually less expensive);
    Should be taken 2-3 hours apart from other medications
  - Colesevelam dose: 625 mg tablet- 6 tablets daily in one or divided doses.
- Ezetimibe
  - Action: Inhibits absorption of dietary and biliary cholesterol
  - Side effects: Minimal
  - Contraindications: Hypersensitivity to any component of this medication. The combination of ZETIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.
  - Dose: 10 mg once daily
- Nicotinic acid (Niacin)
  - Action: Decreases VLDL and LDL production, increases HDL
  - Side effects: Flushing, atrial tachycardia, puritus, dry skin and mucous membranes, Hyperuricemia, glucose intolerance, GI distress and peptic ulcer disease, Diarrhea, and hepatitis.
  - Contraindications: Peptic ulcer disease, cardiac arrhythmia, liver disease. Relatively Contraindicated in diabetes and puritic skin disorders.
  - Dose: 1-7 gm per day, divided into 2-3 doses; begin at low doses, e.g., 100 mg/dose taken with meals, and gradually increase dose.
  - An intermediate release niacin preparation is now available: 1-2 gm taken at bedtime.
- HMGCoA Reductase Inhibitors
  - Action: Inhibits HMGCoA reductase, the rate-limiting enzyme for cholesterol biosynthesis; increases LDL receptors; LDL decreases.
  - Side effects: Occasional elevations of LFTs, myositis.
  - Contraindications: cyclosporin, fibric acid drugs, niacin, and erythromycin increase risk for myositis
  - Dose: Lovastatin 20 mg OD- 40 mg BID, taken with meals, esp. dinner
    Pravastatin 10 mg OD- 40 mg taken as an evening dose before bed
    Simvastatin 10-80 mg OD taken with meals
    Atorvastatin 10-80 mg taken anytime
    Rosuvastatin 5-40 mg taken anytime
  - Fibric acid medications (see below)

Triglyceride-lowering agents

- Nicotinic acid (Niacin; see above)
- Fibric Acids
  - Action: Increases triglyceride lipolysis by increasing LPL activity, decreases secretion of VLDL. Decreases triglyceride, decreases Beta VLDL-remnants, increases HDL, some decrease in LDL.
  - Side effects: Clofibrate increases gallstones. Occasional nausea, abnormal LFTs, and rarely, myositis.
  - Contraindications: Hepatic or biliary disease. Reduce dose with renal failure. Relative, HMG CoA reductase inhibitors
- Dose: Gemfibrozil: 600 mg BID; Fenofibrate: 48-145mg OD with a meal.

Niacin (nicotinic acid) has been used as a lipid-lowering medication since the 1950s. Patients treated with niacin in a secondary prevention trial, the Coronary Drug Project, had less CAD, decreased overall mortality, and less atherosclerosis progression. Only niacin, not niacinamide, is effective for lipid lowering. Because niacin is a vitamin available over-the-counter, it is relatively inexpensive and is a good first-line drug for patients whose compliance might be affected by the price of the medication. In addition, because niacin reduces both triglycerides and LDL, it is an especially good medication for patients with familial combined hyperlipidemia. Niacin is the best medicine for raising HDL cholesterol concentrations.

Although niacin has a number of side effects, the major impediment to successful niacin therapy is the flushing which occurs approximately 30 minutes after taking the drug. The flush feels more like a sunburn than a postmenopausal hotflash. It occurs transiently, primarily when patients begin the drug or increase the dose. Beginning niacin at a low dose and gradually increasing it, taking niacin along with food, and also taking aspirin or non-steroidal anti-inflammatory agents decreases the severity of the flushing. The incidence of flushing is less using slow-release niacin preparations, but slow-release niacin tablets are less effective, may have more liver toxicity, and are more expensive. A new intermediate release niacin can be taken once daily at bedtime and seems to be as safe and as effective as regular niacin.

Several HMG-CoA reductase inhibitors are currently available. These agents have been used in successful clinical trials to lower CAD rates and mortality. There appears to be no significant difference in efficacy or side effect profile of these agents. HMG-CoA reductase inhibitors are generally well-tolerated and very effective LDL-lowering agents. A significant, fortunately unusual side effect is myositis, which occurs more frequently in patients who are also taking fibric acids, cyclosporin, niacin, erythromycin, and some antifungal medications.

Several lipid-lowering agents may be used in combination either to produce more LDL lowering than can be obtained with only one drug or to decrease both LDL cholesterol and plasma triglyceride levels. Resins combined with niacin or HMG CoA reductase inhibitors give additive reductions in LDL; resins and niacin or gemfibrozil can be used for familial combined hyperlipidemia. High-risk patients can be cautiously treated with low doses of HMG CoA reductase inhibitors and fibric acids or reductase inhibitors and niacin. Both of these combinations have been associated with an increased risk of myositis. Ezetimibe can be added to HMGCoA reductase inhibitor to have an additive effect on LDL lowering.

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