CHOLESTEROL AND HEART DISEASE: CURRENT CONCEPTS IN PATHOGENESIS AND TREATMENT

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One of the modifiable risk factors associated with coronary heart disease (CHD) is hypercholesterolemia. This paper reviews the major plasma lipids and how they relate to coronary heart disease. Among blacks, CHD is the leading cause of death and disability. Blacks, in general, have been found to have lower low density lipoprotein (LDL), lower very low density lipoprotein (VLDL), and higher high density lipoprotein (HDL) levels than whites, but there is some evidence to suggest that lipid and lipoprotein profiles may differ in middle and upper socioeconomic subgroups of the black population from those reported for lower socioeconomic groups.

The results of the Lipid Research Clinics Coronary Primary Prevention Trial and the National Heart, Lung and Blood Institute Type II Coronary Intervention Study have shown that lowering cholesterol levels in persons with high blood cholesterol will decrease the rate of coronary heart disease events.

Diet therapy is the mainstay of treatment, and may lower blood cholesterol levels by 10 to 15 percent. For those unresponsive to diet therapy alone, a number of hypolipidemic drugs are available; some drugs (cholestyramine and colestipol) work by increasing the clearance of lipoprotein and others (clofibrate, nicotinic acid, and probucol) decrease the production of lipoproteins. The combination of diet and drugs may result in a decrease in cholesterol levels of 30 percent or more. For each 1 percent that cholesterol is decreased, there is a 2 percent decrease in coronary heart disease events.

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During the past 15 to 20 years, the mortality rate from heart disease in the United States has declined nearly 30 percent.[1,2] Even so, coronary heart disease remains the leading cause of death and disability, accounting for more than 550,000 deaths each year. Among blacks, coronary heart disease is the leading cause of death, despite a widely held belief to the contrary.[3,4] A number of risk factors have been shown to be strongly associated with the development of coronary heart disease (Table 1); the major modifiable ones are cigarette smoking, hypertension, and hypercholesterolemia. There now exists a large and convincing body of evidence that blood cholesterol is an important risk factor for coronary heart disease, that blood cholesterol levels can be lowered safely by both diet and drugs, and that lowering elevated levels of blood cholesterol reduces the risk of coronary heart disease. The supporting evidence that blood cholesterol level is an important risk factor for coronary heart disease comes from a variety of sources, including: (1) epidemiologic studies, (2) the production of atherosclerotic lesions in animals by use of a hypercholesterolemia-inducing diet, (3) the nature (components and development) of the atherosclerotic plaque, (4) the presence of hyperlipidemia in subjects with clinically manifest atherosclerosis, and (5) the occurrence of genetic diseases in which hyperlipidemia results from an inborn error of metabolism and the predisposition of patients with these diseases to develop premature atherosclerosis. In fact, the progressive development of atherosclerosis has not been identified in a population in which the serum cholesterol is low.[5]

LIPID METABOLISM

Pure cholesterol is an odorless, white, powdery substance that cannot be seen or tasted in foods. Cholesterol is present in all foods of animal origin

TABLE 1. MAJOR RISK FACTORS FOR CORONARY HEART DISEASE

Cigarette smoking
Hypertension
Hypercholesterolemia
Diabetes mellitus
Family history
Type "A" personality
Physical inactivity
Obesity
Heavy alcohol consumption
? Coffee consumption

and, in fact, is a part of every animal cell. Cholesterol and other lipids are essential constituents of cells, and are required for the synthesis of cell membranes and hormones, and for energy purposes.

Our understanding of lipid metabolism and coronary heart disease has progressed from a cholesterol era to a lipoprotein era and now into an apolipoprotein (apoprotein) era.[6] The major plasma lipids, including cholesterol and triglyceride, do not circulate freely in blood, but rather in the form of lipoprotein complexes. The lipoproteins are complexes of lipid and protein, which make the transport of plasma lipids in a stable, soluble form possible. Essentially, each lipoprotein consists of a water-soluble surface coat that contains the protein constituent and an inner core of insoluble lipid. The lipoproteins are qualitatively defined by physiochemical criteria and separated into four classes according to their density (Table 2), which is a function of the relative proportions of protein and lipid in the lipoprotein.[7]

Chylomicrons

The chylomicrons are the lightest (and largest) particles of all, being composed predominantly (90 percent) of triglyceride of dietary (exogenous) origin. Chylomicrons are formed in the intestines from ingested fat, and taken by intestinal lymphatics to peripheral blood, and then to adipose and other tissues. Most of the triglyceride is acted upon by the enzyme, lipoprotein lipase (adherent to capillary walls in muscle and adipose tissue). This enzyme hydrolyzes the triglycerides of the chylomicrons; the resultant liberated of fatty acid and monoglyceride are transported across the cell membrane, resynthesized into triglyceride, and stored.[7,8] When required, the intracellular triglyceride can undergo lipolysis, the released fatty acid being transported out of the cell and bound to albumin for transport in the plasma. Following lipolysis by lipoprotein lipase, a chylomicron "remnant" is transported to the liver and catabolized. Also, a portion of the surface of the chylomicron particle containing apolipoproteins (apo A group), free cholesterol, and phospholipid is transferred to nascent high-density lipoprotein particles that have been formed in the liver. After 12 to 14 hours of fasting, chylomicrons are usually absent from plasma, and their presence in fasting plasma should always be considered abnormal. After standing for 12 to 24 hours in a cold test tube, these large particles cause lactescence, and a creamy layer forms at the top of the tube. Chylomicronemia, even when marked, has not been associated with premature coronary disease.

Very Low Density Lipoproteins

The very low density lipoproteins (VLDLs) are also triglyceride rich (65 percent), but not to the same extent as chylomicrons. Synthesized by the liver and intestines, VLDLs transport lipid from there to peripheral tissues. The triglyceride in VLDL is removed through the action of lipoprotein lipase (in a manner similar to chylomicrons). The remaining remnant from this process is intermediate density lipoprotein (IDL), which represents a transition between VLDL and low density lipoprotein (LDL); IDL contains approximately 40 percent triglyceride and 30 percent cholesterol. Intermediate density lipoprotein appears to be transported to the liver where more triglyceride is removed (by the enzyme hepatic triglyceride lipase) and converted to LDL. Sometimes classified as a fifth lipoprotein class, IDL is perhaps best thought of as a transition between VLDL and LDL; it is not normally detectable in plasma.

The atherogenicity of VLDL is an unresolved issue. Many patients with coronary heart disease have elevated triglyceride levels and VLDLs. In some of these patients the high levels are due to genetic hyperlipidemias, whereas in others it is caused by the presence of obesity or diabetes mellitus. A high percentage of patients with coronary heart disease have hypertriglyceridemia, but this appears to reflect other lipoprotein abnormalities that are the real atherogenic factors.[9]

TABLE 2. PLASMA LIPOPROTEIN CLASSES BY DENSITY AND COMPOSITION

Lipoprotein Class	Density (g/mL)	Composition (%)			
		Cholesterol	Triglyceride	Protein	Phospholipid
Chylomicron	0.95	5	90	1	4
VLDL*	0.95-1.006	13	65	10	12
LDL**	1.019-1.063	43	10	25	22
HDL***	1.063-1.21	18	2	50	30

*VLDL, Very low density lipoprotein
**LDL, Low density lipoprotein
***HDL, High density lipoprotein

Low Density Lipoprotein (LDL)

The low density lipoproteins are cholesterol rich and normally account for 60 to 70 percent of the total plasma cholesterol. Low density lipoprotein is the final product of VLDL degradation, is the major carrier of cholesterol in plasma, and is also the most closely linked to atherogenesis. LDL is removed from plasma by binding to specific receptors located in the liver and many other tissues. Following binding and uptake, LDL is metabolized to free cholesterol and other products. Within cells, cholesterol is stored as the ester. Saturation of the LDL receptors inhibits intracellular cholesterol synthesis by inhibiting the rate-limiting enzyme in cholesterol synthesis (HMG-coA-reductase). A negative feedback system is therefore present, such that intracellular cholesterol synthesis varies inversely with the availability of extracellular LDL-cholesterol.[8] Factors that increase LDL receptor binding will decrease circulating LDL levels by enhancing LDL catabolism. In familial hypercholesterolemia, there is a deficiency of LDL receptors. Impaired LDL catabolism and clearance results in severe hypercholesterolemia. This disorder is characterized by severe hypercholesterolemia, tendon xanthomata, and premature atherosclerosis, which often develop in these patients in their teens and twenties. Total plasma cholesterol is usually in the 350 to 500 mg/dL range, most of the increase being LDL. Very low density lipoprotein (VLDL) and HDL levels are normal or low. This disorder is relatively common, occurring with a population frequency of 1 in 500.

High Density Lipoprotein (HDL)

The high density lipoproteins are the heaviest class of lipoproteins, reflecting their higher protein content. These are a heterogeneous group of proteins, derived from both hepatic and intestinal synthesis and from the catabolism of VLDL. The major protein constituent is apolipoprotein A-I. Various ultracentrifugation and electrophoretic techniques have identified several subclasses of HDL and several subspecies. The major subclasses are HDL-2 and HDL-3. A third and minor subclass is HDL-1. Particles of HDL-2 are larger than HDL-3 and contain more lipid-rich particles, whereas HDL-3 are relatively protein rich, lipid poor, and dense. The inverse relationship between HDL and coronary heart disease is closely related to the HDL-2 subfractions.

Several mechanisms have been proposed to explain the cardio-protective effect of HDL.[10-12] One hypothesis is that HDL facilitates the removal of excess cholesterol from tissues and returns to the liver for metabolism. This process has been called "reverse cholesterol transport." Another mechanism is that HDL (or a subclass of HDL containing apoprotein E) inhibits the delivery of cholesterol to tissue by competing with LDL for receptor-mediated binding and uptake into cells. Other proposed protective mechanisms include a counteracting of the damaging effects of LDL on endothelial cells[13] and stimulation of prostacyclin synthesis by endothelial cells conferring a potential protective effect by inhibiting platelet aggregation. The increase in HDL levels associated with moderate ethanol intake is due to an increase

in HDL-3 levels, a subclass of HDL that has not been shown to have an inverse relationship with the development of atherosclerosis. Ethanol does not affect HDL-2 levels.[14]

Apolipoproteins

The apolipoproteins (apoproteins) are the protein components of lipoproteins. They play an important role in the maintenance of the structure of the lipoproteins and in the regulation of their function and metabolism. Apolipoprotein binds with phospholipid on the surface of the lipoprotein particle, making it a stable, soluble complex. The apolipoproteins are divided into five major subgroups designated A,B,C,D, and E. For each apolipoprotein there are subgroups. For example, A-I, A-II, and A-IV are all present in chylomicrons and HDL. The apolipoproteins present in LDL[15] are B-100 (74 percent), C-111 (17 percent) and E (9 percent). High density lipoprotein differs from atherogenic lipoprotein in that HDL contains no apolipoprotein B.

According to some investigators, apolipoprotein levels may be more important determinants and markers of coronary heart disease than cholesterol levels.[16-17] Increased LDL apolipoprotein B may predispose to coronary heart disease in the presence of normal LDL cholesterol; thus, the absence of hyperlipidemia in patients with atherosclerosis does not mean that lipid risk factors are absent. A recent study by Brunzell[18] (in which apolipoprotein B, triglyceride, LDL cholesterol, and total cholesterol levels were measured in a series of patients undergoing coronary angiography) revealed that the apolipoprotein B level was the best determinant for separating patients with angiographically normal coronary arteries from those with coronary artery disease. In some patients with diseased arteries, LDL levels were normal, whereas apolipoprotein B levels were elevated. This suggests the presence of abnormal LDL, even though the LDL cholesterol level is normal. Patients with elevated apolipoprotein B levels and normal LDL levels appear to have a higher number of LDL particles that are more dense than usual. The inner cores of these particles are low in cholesterol, whereas the outer cores are rich in apolipoprotein B. In patients with hypertriglyceridemia, elevated levels of apolipoprotein B appear to be markers for the presence of significant coronary artery disease whether LDL levels are elevated or not.[18]

LIPIDS AND BLACK POPULATIONS

Several studies have compared blood lipids and lipoproteins in various populations and racial groups. In general, blacks have been found to have lower LDL, lower VLDL, and higher HDL cholesterol levels than whites.[19-23] The Framingham Heart Study Cohort is one of the most important ongoing epidemiologic studies. This study cohort included only six black participants.[24] Wilson et al[24] recently reported on various lipoprotein cholesterol measurements made on a random sample of 100 highly educated, middle and upper socioeconomic level black adult residents of Framingham, Massachusetts. The plasma lipid determinations were performed by the Framingham Heart Study Lipoprotein Laboratory, and results were compared with the values previously obtained from the Framingham Cohort and their offspring (age-matched). The mean age of participants was 42 years for both male and female (range: 20 to 69 years). The total cholesterol values for blacks were consistently lower than the values for whites in each age group and sex. A similar pattern was found for plasma triglycerides. The mean HDL cholesterol values, however, were also lower in blacks compared with whites. These findings differ from those of several other studies,[19,25] and appear to suggest that lipid and lipoprotein profiles may differ in middle and upper socioeconomic subgroups of the black population from those reported for lower socioeconomic subgroups. Social and economic upward mobility may be associated with a less desirable lipoprotein, thus changing the coronary heart disease risk profile. In black populations outside the United States (Africa, the Caribbean Islands, and Latin America), coronary heart disease is less prevalent, although recent evidence suggests that the incidence may be increasing in some of these populations as socioeconomic change occurs. Watkins[26] recently reviewed the English language literature on morbidity and mortality from coronary heart disease in black populations in underdeveloped countries. He found that hypercholesterolemia was uncommon, but even when relatively high cholesterol levels

occurred, coronary heart disease was rare. The latter finding he attributed to the occurrence of relatively high levels of HDL cholesterol.

LIPIDS AND ATHEROSCLEROSIS

Coronary heart disease (CHD) results from atherosclerosis. This is a slowly progressive disease of the large arteries that begins early in life and develops over a period of many years. The early plaques begin as fatty streaks with variable amounts of smooth muscle cell proliferation, lipid accumulation, fibrous proliferation, and progression to a fibrous plaque.[27] During plaque development, there may be periods of quiescence and regression interspersed with progression. Clinical disease results from progressive narrowing of the lumen of the affected vessel, hemorrhage into the plaque, or embolism-thrombus formation at the site of the plaque with vessel occlusion. Disease may go undetected until the first heart attack, and the first heart attack is often fatal.

Epidemiologic, genetic, experimental, and clinical studies have provided a wealth of data supporting a causal relationship between high blood cholesterol levels and coronary heart disease. It must be kept in mind, however, that elevated blood cholesterol is only one of several important risk factors contributing to an increased predisposition to CHD (Table 1). It has now been established with certainty that the reduction of elevated cholesterol levels will decrease the rate of CHD. Two clinical studies are important to note in this regard. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) showed that a 9 percent reduction of total cholesterol was associated with 19 percent reduction in the combined rate of fatal and nonfatal coronary events.[27,28] The National Heart, Lung, and Blood Institute Type II Coronary Intervention Study showed a 25 percent reduction in cholesterol and a decrease in the progression of coronary disease (as seen through angiography) in cholestyramine-treated patients with type II hyperlipidemia.[29,30] These trials do not permit conclusions about the effect of lowering blood cholesterol on mortality. However, they do permit the conclusion that lowering cholesterol levels in persons with high blood cholesterol will decrease the rate of coronary heart disease events.

The Lipid Research Clinics Coronary Primary Prevention Trial

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)[27,28] has now provided conclusive evidence that the risks of coronary heart disease can be reduced by lowering blood cholesterol. The LRC-CPPT was a double-blind, placebo-controlled clinical trial that tested the efficacy of lowering plasma cholesterol levels for primary prevention of coronary heart disease. The study began in 1976, and included 3,806 asymptomatic middle-aged men with primary hypercholesterolemia (type II hyperlipoproteinemia), who were recruited through 12 participating research clinics located throughout the United States and in Canada. Both placebo and treated groups followed a moderate cholesterol-lowering diet. The treatment group received the bile acid sequestrant, cholestyramine resin, and the control group received placebo. Patients were followed for an average of 7.4 years. All patients had plasma cholesterol levels of greater than or equal to 265 mg/dL (95th percentile) and low density lipoprotein cholesterol levels greater than 190 mg/dL. Subjects with triglyceride levels greater than 300 mg/dL or type III hyperlipoproteinemia, those with conditions associated with secondary hyperlipoproteinemia (diabetes melitus, hypothyroidism, hepatic disease, hyperuricemia, nephrotic syndrome) were excluded. Patients who had a history of previous myocardial infarction, angina pectoris during exercise electrocardiography, electrocardiographic abnormalities, or congestive heart failure were also excluded.

Three months prior to randomization, all such subjects were placed on a diet designed to provide 400 mg of cholesterol (a polyunsaturated-to-saturated fat ratio of approximately 0.8) and to lower cholesterol by 3 to 5 percent. Those patients whose LDL levels fell to less than 175 mg/dL on diet therapy alone were excluded from further study.

Following randomization, the treatment group received 24 g/d of cholestyramine taken in two to four equal doses daily. The primary endpoints of the study were definite coronary heart disease death, definite nonfatal myocardial infarction, or both. Other endpoints included death from all

TABLE 3. BLOOD CHOLESTEROL RISK GROUPS

Age Group	Measurement
Age 20-29	
Moderate Risk	Greater than 200 mg/dL
High Risk	Greater than 220 mg/dL
Age 30-39	
Moderate Risk	Greater than 220 mg/dL
High Risk	Greater than 240 mg/dL
Age 40 and older	
Moderate Risk	Greater than 240 mg/dL
High Risk	Greater than 260 mg/dL

other causes, the development of an ischemic electrocardiographic response to exercise, angina pectoris, atherothrombotic brain infarction, arterial peripheral vascular disease, and transient cerebral ischemic attacks.

The cholestyramine-treated group had an average plasma total and low density lipoprotein cholesterol reductions of 13.4 and 20.3 percent, respectively, which were 8.5 and 12.6 percent greater reductions than in the placebo group. The occurrence of primary endpoints was documented in 155 cases in the treated group compared with 187 cases in the placebo group, representing a 19 percent reduction in risk. This reflected a 24 percent reduction in definite coronary heart disease death rate and a 19 percent reduction in nonfatal myocardial infarction. The reductions in incidence of other endpoints included a 25 percent lower incidence of developing a new positive exercise test, 20 percent less angina, and a 21 percent lower incidence of the need for coronary bypass surgery.

The LRC-CPPT results permit the conclusion that each 1 percent reduction in blood cholesterol yields approximately a 2 percent reduction in CHD rates. Thus, a 10 percent reduction in cholesterol would decrease CHD rates by 20 percent, and a reduction in cholesterol by 25 percent would reduce CHD rates by 50 percent.

TREATMENT OF HYPERCHOLESTEROLEMIA

Hyperlipidemia is defined on the basis of measurements of serum or plasma levels of lipids and comparison between age- and sex-matched population norms. An abnormally high level of a biologic substance is usually considered to be that level above the upper 5 percent of the population (95th percentile). The use of this criterion to define normal cholesterol levels in the United States is considered unreasonable because a large fraction of the population probably has levels of blood cholesterol that are too high, especially in view of the fact that CHD is the major cause of death.

The average blood cholesterol level for middle-aged adults in the United States is about 215 mg/dL. The NIH Consensus Development Conference Statement on Lowering Blood Cholesterol to Prevent Heart Disease[31] recommends treatment of individuals with blood cholesterol levels above the 75th percentile (upper 25 percent of values). The consensus panel defined two levels of hypercholesterolemia (Table 3): "high risk" and "moderate risk." The high risk (severe hypercholesterolemia) category is defined as the upper 10 percent (90th percentile) as determined by the Lipid Research Clinics Prevalence Study. This group includes individuals with hereditary forms of high blood cholesterol, which require the most aggressive treatment. The moderate risk (moderate hypercholesterolemia) category is defined as between the 75th and 90th percentiles. This group includes a large number of individuals whose elevated blood cholesterol is due, in part, to their diet. The intensity of treatment is determined by the cholesterol level, clinical history, family history, and the presence of other coronary risk factors.

Both the genetic and acquired forms of hyperlipidemia usually occur because of defects in one of the four sites of physiologic regulations[10]: (1) increased hepatic triglyceride and VLDL production, (2) decreased VLDL and chylomicron catabolism due to deficient lipoprotein lipase activity, (3) decreased removal of remnants and catabolism, and (4) impaired catabolism of LDL because of a deficiency in key LDL receptors.

Once the presence of high-risk or moderate-risk blood cholesterol levels has been demonstrated, this should be confirmed by repeat analysis. The repeat analysis should be performed after an overnight fast so that a valid triglyceride level can also be determined. One should exclude secondary causes of hypercholesterolemia (hypothy-

roidism, nephrotic syndrome, dysproteinemias, diabetes mellitus, and obstructive liver disease). If there is no secondary cause identified, the primary cause should be evaluated, including family screening to detect hereditary forms of hypercholesterolemia as well as to identify other family members who need treatment. High density lipoprotein levels should be measured to determine whether the elevated blood cholesterol is due to high HDL levels. A high HDL level is associated with a lower risk of CHD, and a low HDL cholesterol is an independent risk factor for CHD.

Diet Therapy

Diet therapy is the mainstay of treatment of patients with all forms of hyperlipidemia. The dietary prescription must be formulated on an individual basis and is dependent on the clinical situation. In the United States, mild to moderate hypercholesterolemia with an elevated level of LDL is often related to dietary habits with excesses in the ingestion of cholesterol and saturated fats. Thus, it is extremely important that the first step in evaluating and managing patients with hyperlipoproteinemia include a careful dietary history and that patients receive careful detailed dietary instructions, preferably from a dietition. In many patients with primary hyperlipoproteinemia, blood lipid levels will return to normal on a dietary regimen alone.

The average American man consumes about 500 mg of cholesterol daily. About 40 percent of calories in the average American diet come from fat, and 42 percent of this fraction is saturated fat. The American Heart Association and the Atherosclerosis Study Group of the Inter-Society Commission for Heart Disease recommend a three-phase dietary approach. The initial phase (phase I) is a prudent diet for the general population at large. It consists of (1) caloric reduction to attain ideal body weight, (2) reduction of total cholesterol intake to 250 to 300 mg/d, (3) a reduction in total fat intake to 30 percent of total calories, and a reduction in saturated fat intake to 10 percent or less of total calories to achieve a dietary polyunsaturated-to-saturated fat ratio of 1.0 rather than the usual 0.3. Fifty-five percent of calories should be eaten as carbohydrate and 15 percent as protein.

Patients with insufficient response to phase I and/or who have family histories of hyperlipidemia should move to phase II. The phase II diet restricts fat to 25 percent of total calories and cholesterol consumption to 200 to 250 mg/d. Carbohydrate intake is increased to 60 percent and protein intake is kept at 15 percent. Egg yolks should be eliminated, and a major meal without red meat should be eaten at least three times a week. Foods such as fish, skinless chicken, and fresh fruit and vegetables are recommended in place of red meat.

The phase III diet is specifically targeted for individuals with severe hypercholesterolemia (levels above the 95th percentile). Fats are restricted to 20 percent of total calories and cholesterol limited to 100 to 150 mg/d. Only three ounces of meat, fish, or poultry are allowed each day, supplemented by selections from meatless alternatives. These include low-fat cheeses, dried beans, peas or lentils, egg substitutes, peanut butter, and tofu (soybean curd). Each of the three phases can be modified for patients who are hypertensive, diabetic, or pregnant.

Exercise

Exercise is frequently recommended as a means of modifying plasma lipid levels, although definitive answers await further investigation. On the basis of present evidence from cross-sectional and longitudinal studies, it appears that an exercise threshold needs to be surpassed before changes are realized. The level at which HDL cholesterol increases appears to be more than 8 to 15 miles of jogging each week, and up to nine months may be required before the effects become apparent on clinically available tests.[32] Thus, an absolute amount of additional energy expenditure (1,000 kcal/wk) appears necessary, and changes in HDL levels appear unlikely to occur in patients who do not achieve this level of activity. Elevated HDL, low LDL, and high HDL-to-total-cholesterol ratios have been found in men and women who habitually engage in endurance-type exercise.

Drug Therapy

Patients who are unresponsive to dietary treatment may require additional aid with specific drug

therapy.[33-35] The hypolipidemic effects of currently available drugs are usually achieved through one of two mechanisms: (1) increased clearance of lipoproteins, or (2) decreased production of lipoproteins. Cholestyramine resin and colestipol hydrochloride increase lipid clearance, whereas clofibrate, nicotinic acid, and probucol decrease lipoprotein reduction.

Cholestyramine is a bile acid sequestrant that is effective in reducing total cholesterol and LDL cholesterol levels. It is nonabsorbable from the gastrointestinal tract, has few systemic effects and and a low level of significant toxicity. It is the treatment of choice for patients with familial hypercholesterolemia. The usual dosage is 12 to 24 g/d. The most frequent side effects are gastrointestinal, which are usually ameliorated by a reduction in dose.

Colestipol is also a bile acid sequestrant with an effect on plasma cholesterol and LDL similar to that of cholestyramine. It is also indicated for the treatment of familial hypercholesterolemia. The average dosage is 5 g orally three times daily with a maximum dose of 30 grams.

Probucol is effective in patients with mild to moderate elevations of LDL. Its mechanism of action is unclear and may be related to a lowering of LDL synthesis. When used in combination with colestipol, probucol has been reported to be effective in treating heterozygous familial hypercholesterolemia. Because probucol also lowers HDL levels, its usefulness in the prevention or control of coronary disease must be considered limited.

Gemfibrozil is structurally similar to clofibrate and has a similar effect on lipoprotein metabolism. It decreases plasma levels of total cholesterol, LDL, and VLDL, but increases HDL concentration. The most common side effects are minor gastrointestinal symptoms and transient elevations in hepatic enzymes. Gemfibrozil potentiates the effects of warfarin and is contraindicated in patients with liver or kidney disease. It appears to be less lithogenic than clofibrate. There is considerable enthusiasm about the effects of gemfibrozil on increasing HDL, but the clinical significance of this and its effects on atherogenesis remain to be established.

Nicotinic acid is indicated for the treatment of those disorders characterized by increased VLDL. It also lowers IDL and LDL while increasing HDL. It is contraindicated in patients with liver disease or active peptic ulcers. It may elevate serum glucose, uric acid, and liver enzymes. The drug may also cause flushing, pruritis, eye irritation, and skin dryness. Because of frequent and often severe side effects, this agent is of limited utility and should probably be avoided in patients with liver disease, diabetes, or gout.

Clofibrate is useful in the treatment of disorders characterized by increased VLDL and IDL. Its usefulness is limited in controlling elevations of LDL, and in some patients, it may increase levels of this lipid. In the Coronary Drug Project, this drug was associated with an increase in cholelithiasis, arrhythmias, angina, thromboembolism, and intermittent claudication in patients who had myocardial infarctions.[29] A recent primary prevention trial in which clofibrate was used showed a significant decline in suspected and proven myocardial infarction, but there was an increase in the overall mortality rate. In spite of these problems, clofibrate may be a useful agent for the long-term management of patients with marked elevations of triglycerides in order to help prevent life-threatening episodes of acute pancreatitis.

Experimental Drugs: Many other drugs are currently being tested as lipid lowering agents.[36] Among these are oral neomycin, compactin, and mevinolin. At a dose of 1 g twice daily, oral neomycin appears to be a safe, well-tolerated, and efficacious drug for lowering LDL cholesterol. Compactin is an agent that inhibits the activity of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase. It has been reported to be very effective in patients with heterozygous familial hypercholesterolemia with 20 to 35 percent lowering of LDL-cholesterol. Mevinolin, another experimental agent, is very similar in its effect and mechanism of action as compactin.

CONCLUSIONS

As with smoking and hypertension, high blood cholesterol has been clearly established as one of the major modifiable risk factors associated with CHD. The recent evidence from the Lipid Research Clinics Coronary Primary Prevention Trial and the National Heart, Lung and Blood Institute Type II Coronary Intervention Study has shown that lowering cholesterol levels lowers CHD risk

and decreases the progression of atherosclerosis. Diet therapy alone may lower blood cholesterol levels by 10 to 15 percent and the combination of diet and drugs may result in a decrease of 30 percent or more. Furthermore, for each 1 percent that cholesterol is decreased, there is a 2 percent decrease in CHD risk. Thus, it is important that patients be advised about the risks of high blood cholesterol and the benefits of reducing it. A much more aggressive posture (as has occurred with hypertension) needs to be taken by physicians, a position important not only for the care of individual patients but for the general public as well.

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