

Assessing And Managing Hyperlipidemia

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Abstract: Because more than one-half of adult Americans have total blood cholesterol levels that often contribute to atherosclerotic blockage of their coronary arteries, routine random screening of all adults and high-risk children for hypercholesterolemia is recommended.

Reduced intake of saturated fat and cholesterol can lower total and low-density lipoprotein (LDL) cholesterol by 10–20 percent, while several medications lower total and LDL cholesterol by 15–40 percent. A highly effective cholesterol-lowering medication, lova-

Blood cholesterol has sparked controversy for more than 2 decades. Until recently, the evidence that patients benefit from lowering their elevated blood cholesterol was not convincing to most physicians. Persuasive data are now available to support the benefit of lowering elevated blood cholesterol. The Lipid Research Clinics Coronary Primary Prevention Trial showed that when elevated total blood cholesterol was reduced 12 percent by cholestyramine treatment, the number of cases of coronary heart disease (CHD) in a large group of middle-aged men fell by 19 percent during a 7-year period.¹ In the Helsinki Heart Study, gemfibrozil (Lopid™) produced 34 percent reduction in myocardial infarction and cardiovascular death and was associated with 8 percent reduction in low-density lipoprotein cholesterol (LDL-C) and 10 percent increase in high-density lipoprotein cholesterol (HDL-C).² Two other studies showed that lowering cholesterol with medication can stabilize or regress coronary atherosclerosis in patients who have already had a heart attack and have high cholesterol. The National Heart, Lung, and Blood Institute (NHLBI) Type II Coronary Intervention Study showed that lowering cholesterol with cholestyramine slowed the progression of existing coronary lesions and prevented severe progression of lesions in most of the patients.³ The Cholesterol-Lowering Ath-

statin, has been recently marketed. The efficacy and long-term safety of ingesting large amounts of omega-3 fatty acids in fish oil supplements are unproven.

Hypercholesterolemia is a family problem transmitted between generations by various combinations of genetic factors and learned behaviors. The family physician can be most effective by working with entire families to detect and treat hypercholesterolemia early in life to prevent serious consequences of prolonged cholesterol elevation. (*J Am Bd Fam Pract* 1988; 1:175-88.)

erosclerosis Study showed similar results with a combination of colestipol and nicotinic acid (niacin).⁴

These four studies support the following recommendations:

- Perform routine screening for cholesterol elevation.
- Educate patients about lifestyle and high blood cholesterol.
- Manage hypercholesterolemia as assertively as other major risk factors for coronary disease (hypertension, smoking, and diabetes mellitus).

Hypercholesterolemia

Hyperlipidemia consists of elevated blood levels of cholesterol and/or triglycerides. Hypercholesterolemia is more important clinically than hypertriglyceridemia. Triglyceride levels are not a consistent risk predictor for CHD below about 1,000 mg/dL (11 mmol/L), but increasing levels of blood cholesterol are associated with a relatively linear increase in CHD risk at mild to moderate elevations, and there is accelerated risk at severely elevated levels. Age-adjusted cutoffs were formerly used for defining hypercholesterolemia,⁵ but recent guidelines from the National Cholesterol Education Program define borderline high cholesterol as 200–239 mg/dL (5.2–6.1 mmol/L) and high cholesterol at or above 240 mg/dL (6.2 mmol/L) in adults, regardless of age (Table 1).⁶ By these definitions, more than one-half of American

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Table 1. Total Cholesterol and LDL Cholesterol Classifications.

Total Cholesterol <200 mg/dL (5.2 mmol/L)	Desirable blood cholesterol
200–239 mg/dL (5.2–6.1 mmol/L)	Borderline-high blood cholesterol
≥240 mg/dL (6.2 mmol/L)	High blood cholesterol
LDL Cholesterol <130 mg/dL (3.4 mmol/L)	Desirable LDL-cholesterol
130–159 mg/dL (3.4–4.0 mmol/L)	Borderline–high-risk LDL-cholesterol
≥160 mg/dL (4.1 mmol/L)	High-risk LDL-cholesterol

adults have borderline high or high serum cholesterol levels.⁷

Epidemiology

Annual deaths from coronary heart disease, though on the decline in the United States since about 1968, account for 35 percent (> 500,000) of all deaths.⁸ Reasons for the abatement of CHD are multiple. Beginning in the 1960s, changes in exercise and dietary patterns reversed earlier twentieth century trends toward sedentary living and high intake of saturated fat. Although coronary care units and improved control of hypertension have helped prevent deaths from myocardial infarction, the substantial reduction in smoking by middle-aged men appears to have made the major impact on preventing heart disease.

Atherosclerosis, the underlying pathophysiologic process in CHD, often begins in the second or third decade of life and accelerates in the fourth and fifth decades. Coronary atherosclerosis becomes symptomatic, on the average, about 10 years earlier in men than in women. A cholesterol level that is at least mildly elevated for 20 or more years is a key ingredient in most patients with early coronary atherosclerosis (i.e., before the average ages of 58 in men and 68 in women).

The average total blood cholesterol level for men aged 40–59 in the United States in 1972–1973 (210 mg/dL or 5.4 mmol/L)⁵ was considerably above that of countries with low rates of CHD (125 mg/dL or 3.2 mmol/L for southern Japan).⁹ In fact, the lowest cholesterol values for persons in

countries with high rates of CHD overlap very little with the highest values in countries with low rates of CHD. Populations with cholesterol levels greater than 180 mg/dL (4.7 mmol/L) have increased rates of CHD compared with populations below that level.^{10–13} The average plasma cholesterol for 35–39-year-old men in the United States in 1972–1973 was 200 mg/dL (5.2 mmol/L).⁷ The cholesterol values for 25 percent of those men were above 225 mg/dL (5.8 mmol/L); 10 percent were above 250 mg/dL (6.5 mmol/L), and 5 percent were above 270 mg/dL (6.9 mmol/L).

In many patients, the cholesterol levels that predate a heart attack or angina pectoris are not impressive at first glance. The average cholesterol value for an American before having a heart attack has been about 245 mg/dL (6.3 mmol/L).¹² This level is still reported by many laboratories as “normal.” It is normal, however, only in a statistical sense, not a physiologic one. The customary method of defining the upper limit of normal as the mean plus 2.5 standard deviations (95th percentile) is inappropriate, because more than one-half of all American adults aged 35 and greater have potentially pathophysiologic levels of blood cholesterol.

While total cholesterol level (TOTAL-C) correlates well with CHD risk, the level of low-density lipoprotein cholesterol (LDL-C) predicts CHD risk even better, up to age 50.¹⁴ LDL-C is therefore clinically more useful than TOTAL-C for evaluating a patient's risk of early heart disease. Because high-density lipoprotein cholesterol (HDL-C) correlates negatively with CHD risk in several studies, HDL-C has been acclaimed as the “good cholesterol,” with higher levels carrying a more favorable prognosis. After age 50, HDL-C is the only cholesterol measurement that correlates consistently with mortality.¹⁵ In the NHLBI Coronary Intervention Study, the ratios of HDL-C/LDL-C and HDL-C/TOTAL-C were most predictive of the stabilization versus progression of coronary lesions.³

Etiology

Blood cholesterol level is affected most strongly by heredity, diet, exercise, and stress. Primary hypercholesterolemia stems mainly from inherited variations in lipid metabolism and excess dietary intake of saturated fat and cholesterol. When a patient's blood cholesterol is elevated above the 90th percentile, with normal triglycerides, most of

the excess cholesterol is usually associated with low-density lipoprotein (LDL). Such a person may have heterozygous familial hypercholesterolemia (FHC), an autosomal dominant deficiency of LDL receptors.¹⁶ Even with stringent restriction of dietary fat, these patients (Type IIa by Frederickson classification) continue to have high cholesterol levels, usually above 300 mg/dL (7.7 mmol/L).¹⁷

"Borderline high" elevations of blood cholesterol, 200–239 mg/dL (5.2–6.1 mmol/L), stem mostly from excess production of LDL-C and high intake of saturated fat. Dietary saturated fat influences blood cholesterol much more strongly than dietary cholesterol intake.¹⁸ Stress and increased anxiety can elevate cholesterol substantially.^{19,20} Patients whose cholesterol elevations are primarily related to diet and stress appear to have a polygenic predisposition to high cholesterol and do not fit in the Frederickson classification.²¹ Their relative risk for heart disease is generally lower than FHC patients. However, because they are much more numerous, the environmentally hypercholesterolemic patients have a majority of the heart attacks, although usually at an older age than the ones with FHC.

The most common secondary causes of cholesterol elevation are iatrogenic. Most diuretics, except indapamide (Lozol™), raise LDL-C, at least temporarily, in many patients.²² Most beta-adrenergic blockers (except pindolol, acebutalol, and labetalol) elevate LDL-C or lower HDL-C,²³ as does the gallstone dissolving agent, chenodiol. Some oral contraceptive hormones with strong progestin and androgenic effects (Norlestrin 2.5/50™, Demulen™, Ovulen™, Ovral™, LoOvral™, Nordette™, and Loestrin™) decrease HDL-C, which is a theoretically undesirable lipid effect.²¹ Very low-density lipoprotein cholesterol (VLDL-C) is elevated by high-dose steroids, disulfiram (Antabuse™), and excess hyperalimentation with soybean oil (Intralipid™). Other secondary causes of hypercholesterolemia are presented in Table 2.

If both cholesterol and triglycerides are elevated, the most common causes are genetic predisposition (familial mixed hyperlipidemia), obesity, poorly controlled diabetes mellitus, excessive alcohol intake, and sedentary living. All of these conditions elevate VLDL, which is rich in triglycerides and carries some cholesterol. Frederickson categorized these hyperlipidemias as Types IIb (uncommon), IV (common), and V (uncommon), depending on the relative amounts of LDL, VLDL,

Table 2. Secondary Forms of Hypercholesterolemia.

Diabetes mellitus
Hypothyroidism
Nephrotic syndrome
Obstructive liver disease
Some progestin-containing medications (oral/depot contraceptives)
Use of anabolic steroids

and chylomicrons (fat globules) present in the blood.²¹ Types I and III are rare and are not discussed here.

Pathophysiology

The pathophysiology of hypercholesterolemia and atherosclerosis is incompletely understood. The key factors appear to be the metabolism of VLDL by lipoprotein lipase, the regulation of LDL cholesterol passage into cells by LDL receptors on cell membranes, and the intracellular activity of the enzymes 3-hydroxy-3-methylglutaryl coenzyme A reductase and lecithin-cholesterol-acyltransferase.²⁴

Excess LDL in the blood initiates transformations in cells in the intima and media of susceptible arteries, leading to the formation of cholesterol-rich lesions (atheromata) in these arteries. The coronary, carotid, and iliofemoral arteries are most seriously affected. When an artery is occluded by more than 70–80 percent, the patient may become symptomatic, depending on collateral flow and the oxygen requirements of the tissue with compromised circulation.

Atherosclerosis is a complex multifactorial process involving such risk factors as smoking, hypertension, and diabetes mellitus (Table 3). Coronary-prone (Type A) behavior may play a causal role in other ways besides the known associations with elevated cholesterol and catecholamines.²⁵ A family history of atherosclerotic disease may predispose some patients to disease in unknown ways.

Clinical Manifestations

An important early clue to high cholesterol is a family history of atherosclerotic disease, especially heart attack, before age 65–70. Sudden death of unknown cause is also highly suspicious for a familial cholesterol problem. It is becoming more common for patients to report that

Table 3. Coronary Heart Disease Risk Factors.

Male sex
Hypertension
Cigarette smoking
Diabetes mellitus
Severe obesity
Family history of premature CHD

a family member has a cholesterol problem. Because of the widespread tendency to characterize only extreme elevations as high, such a history is often indicative of familial hypercholesterolemia.

Certain findings on physical examination may prompt the clinician to suspect and detect cholesterol elevation before any serious problems develop. Signs of asymptomatic hypercholesterolemia include: bruits of the carotid or iliofemoral arteries; corneal arcus before age 50; xanthomata of the Achilles tendons, upper back, elbows, palmar creases, or fingers; and xanthelasma above the eyelids nasally. Funduscopic findings include arteriovenous crossing changes (deviation, nicking, tapering, blunting) and increased arteriolar light reflex (copper or silver wiring).

The major late clinical presentations of cholesterol elevation are: intermittent claudication, impotence, transient ischemic attack, cerebrovascular accident (stroke), angina pectoris, myocardial infarction, and sudden death. All of these complications result from many years of atherosclerosis, usually accompanied by some degree of hypercholesterolemia. The patients at greatest risk are those with familial hypercholesterolemia (FHC).¹⁶ Men with this condition develop clinical coronary heart disease at an average age of 43, and women become symptomatic at an average age of 53. (Both ages are 15 years earlier than the average age of onset of CHD in the general population.) The lifetime risk of CHD for anyone with FHC is increased 25-fold.

Most lipid experts believe that an elevated triglyceride level does not pose any serious problem to health until the level exceeds 1,000 mg/dL (11 mmol/L), when there is an increased risk for acute pancreatitis.²⁶ VLDL-C elevation in the absence of LDL-C elevation is not associated with an increased CHD risk. It is unclear whether high VLDL-C worsens the adverse effects of LDL-C. An elevated triglyceride level often accompanies alcoholism, obesity, or poorly controlled diabetes mellitus.

Diagnosis

The clinician can diagnose hypercholesterolemia effectively by maintaining a high awareness and systematically screening patients. Blood cholesterol measurement is strongly indicated for any patient with signs or symptoms suspicious of hypercholesterolemia or its sequelae or with other CHD risk factors, including positive family history, smoking, hypertension, diabetes mellitus, and coronary-prone behavior pattern.

Because hypercholesterolemia is even more common than hypertension, it makes sense to screen for it initially in all new adult patients and periodically (every 3–5 years) in established adult patients.⁵ Some authorities also recommend screening all children, beginning at 6–8 years of age, to get an early start on dietary management for hypercholesterolemia.²⁷ The cost-effectiveness of such early detection and intervention is unstudied. It seems reasonable to check the blood cholesterol level of any child with hypercholesterolemic parents or with a strong family history of atherosclerotic disease in parents, grandparents, aunts, or uncles.²⁸

Routine screening for high total cholesterol can be done on a random blood sample, because blood cholesterol does not change significantly in most people after food intake^{6,29} (in contrast to triglycerides, which rise postprandially). Because HDL-C changes little after meals,¹³ it may also be checked on a random blood sample. If only TOTAL-C is checked, a few patients will be missed who have increased CHD risk because of low HDL-C levels. High-risk patients may be appropriately screened with a random TOTAL-C, LDL-C, HDL-C, and triglycerides, even though the triglyceride (TG) value may be somewhat elevated from food intake. Diffuse turbidity of the blood sample indicates elevated triglycerides. After overnight refrigeration, an oily layer on top is composed of chylomicrons.

Sometimes cholesterol is elevated transiently in association with acute or subacute stress and decreases with resolution of or improved coping with stress.²¹ In colder climates, a seasonal trend has been observed, with higher levels in the colder months possibly reflecting cyclically increased intake of saturated fat.³⁰

Laboratory Methods

An inaccurate laboratory method or poor laboratory quality control can create problems with

screening. Several recent studies have examined the validity of cholesterol analysis methods, with conflicting results that preclude making any useful generalizations about the accuracy of specific brands and models of automated cholesterol assay equipment.³¹ The best widely available assay is the cholesterol oxidase method, which is highly specific for cholesterol, as is the slower and more expensive "gold standard," the Abell-Kendall assay. A nonspecific technique, such as the Lieberman-Burchard assay often used in automated profiles, can overstate the value for TOTAL-C by as much as 100 mg/dL (2.6 mmol/L). To assess the reliability and validity of a particular laboratory cholesterol measurement, duplicate specimens can be sent to different laboratories for comparison, preferably including a regional standardization laboratory established by the Centers for Disease Control (CDC). A national campaign is underway to improve the comparative accuracy of commercially available cholesterol measurements.

Patients without known heart disease risk factors can be screened most cost effectively with a random total blood cholesterol. If a random total cholesterol is elevated above 200 mg/dL (5.2 mmol/L), a fasting blood sample may then be obtained to confirm the elevation and determine LDL-C and HDL-C levels. Although the diagnosis of hypercholesterolemia, like that of hypertension, is ideally based on three measurements,¹⁸ two elevated values are sufficient to initiate dietary management. If acute stress or seasonal fluctuation is thought to contribute to the elevation, the measurements should be made 4 to 12 weeks apart.

Blood samples for diagnostic and management purposes should be analyzed by the cholesterol oxidase method for total cholesterol and by a reliable technique for HDL-C (e.g., the ferric chloride assay). From these values and the triglyceride level, the LDL cholesterol can be easily calculated by the following formula: $LDL-C = TOTAL-C - HDL-C - TG/5$. This formula works well as long as TGs are below 400, because TG/5 is a good approximation of VLDL-C up to that point. Although a separate assay for LDL-C is more accurate than estimates, it is rarely performed in clinical laboratories because it is expensive, tedious, and time consuming.

LDL-C elevation is the harmful feature of high cholesterol. LDL-C levels of 130–159 mg/dL (3.4–4.0 mmol/L) are characterized as border-

line-high-risk, and 160 mg/dL (4.1 mmol/L) or above as high-risk for CHD. Diagnosis of familial hypercholesterolemia (FHC) is made by tissue culture techniques for research purposes.³² In clinical practice, FHC is diagnosed presumptively and is based on a markedly elevated level of LDL-C and the absence of other possible etiologies.

HDL-C levels below 35 mg/dL (0.9 mmol/L) are an independent high-risk factor. The clinical significance of having a low HDL-C level without high LDL-C is unclear at this point, because the correlation between low HDL-C and poor prognosis has not been confirmed. Common causes of low HDL-C are hereditary predisposition, cigarette smoking,³³ and a sedentary lifestyle.

Ratios of cholesterol distribution in blood may be useful for summarizing risk in patients with mid-range values. A ratio of LDL-C to HDL-C of greater than 4.0 is markedly abnormal, as is a ratio of TOTAL-C to HDL-C of more than 5.0 and a

Table 4. Reference Cholesterol Ratios for American Adults.

	Ideal*	Mean	Markedly Abnormal
LDL-C/HDL-C	1.5	3.0	>4.0
TOTAL-C/HDL-C	2.7	4.0	>5.0
TOTAL-C/LDL-C	1.8	1.5	<1.4
HDL-C/LDL-C	0.67	0.33	<0.25
HDL-C/TOTAL-C	0.40	0.25	<0.20
LDL-C/TOTAL-C	0.55	0.67	<0.70

*Based on TOTAL-C = 160, HDL-C = 60, TG = 50, LDL-C = 90.

ratio of TOTAL-C to LDL-C of less than 1.4. Ideal and abnormal average cholesterol ratios for American adults are shown in Table 4. Ratios involving HDL-C must be interpreted carefully, because they may be disproportionately affected by small changes in HDL-C.

Measurements of apolipoprotein B (found primarily in LDL) and apolipoprotein A-I (mainly in HDL) are the most accurate prognostic indicators for CHD, but they are not widely available and may be too expensive for routine clinical use.³⁴ Lipoprotein electrophoresis rarely contributes useful information to the assessment of hyperlipidemia.

Differential Diagnosis

Although cholesterol elevation is seldom due to other disease, the more common secondary causes may be briefly considered while interviewing and examining the patient with hypercholesterolemia. One or more of the following laboratory tests may be indicated to exclude secondary causes:

- Serum thyroxine (T4)—to detect hypothyroidism.
- Liver function tests—to detect biliary tract obstruction.
- Serum creatinine and blood urea nitrogen (BUN)—to detect renal insufficiency.

Testing for other more unusual causes of high cholesterol is not needed unless the history or physical examination raises suspicion.

Medications frequently contribute to cholesterol abnormalities, especially thiazide diuretics, most beta blockers, and some oral contraceptives. Alternative antihypertensive medications that do not adversely affect lipids include indapamide, acebutalol, prazosin, terazosin, enalapril, captopril, and verapamil. To investigate iatrogenic possibility, discontinue any suspect medication for several weeks before retesting cholesterol.

To distinguish combined hyperlipidemia from hypercholesterolemia, a fasting blood sample for TOTAL-C, LDL-C, HDL-C, and triglycerides provides sufficient information. Combined hyperlipidemia is characterized by a triglyceride level greater than 250 mg/dL (2.75 mmol/L). A 4–8-week trial of a diet low in saturated fat and cholesterol identifies diet-sensitive hypercholesterolemia, if the patient follows the diet closely.

Information about a person's life stress often raises the possibility that anxiety is contributing to cholesterol elevation. For patients in whom the blood cholesterol level falls following spontaneous resolution of transient stress, the primary management may emphasize preventing and managing anxiety behaviorally or through counseling or psychotherapy. Persons who are chronically stressed, some of whom fit the Type A pattern, may have cholesterol elevations that are just as resistant to hygienic interventions as the familial hypercholesterolemia (FHC) patients. Their cholesterol levels may be difficult to lower unless they can be encouraged to moderate their over-stressed patterns.²⁶

When a patient is found to have a severely elevated blood cholesterol, screening first-degree rel-

atives (parents, siblings, children) may be the most reliable way to diagnose or rule out heterozygous FHC. Accurate identification of these persons is very important because of their grim prognosis without intervention and the presence of others in the family who are at risk but unaware of their condition.

Radiographs of the Achilles tendons can detect subclinical tendon xanthomas, which are strongly indicative of FHC.³⁵

Dietary Recommendations

The American Heart Association recommends to the general public the following dietary guidelines to prevent the emergence of hypercholesterolemia³⁶:

- A reduction in total fat intake from the previous American average of 40 percent to a new level of 30 percent of total calories;
- An even mix of saturated, monounsaturated, and polyunsaturated fat, each contributing 10 percent of total calories; and
- Limitation of cholesterol intake to less than 300 mg a day.

The primary approach to lowering elevated blood cholesterol is to reduce intake of foods high in saturated fat:

- Fatty cuts of beef and pork;
- Meat products such as sausage and beef and pork lunch meats; and
- Whole milk and whole milk dairy products such as cheese, butter, cream, ice cream, and sour cream.

These foods are also high in cholesterol. The hydrogenated oils in many margarines, dairy substitute products, cooking oils, and salad dressings are less obvious sources of saturated fat in home cooking and in many convenience foods.

To be able to serve "heart-healthy" foods (Table 5), patients need guidelines for reading food labels to select products intelligently when shopping. For any oil-containing item, such as margarine, the three keys are:

- The first ingredient on the label (the one present in the largest amount) should be a liquid oil (preferably corn or safflower), not a "partially hydrogenated" oil.

Table 5. Recommendations for a Heart-Healthy Diet.

Eat minimal amounts of
Fatty cuts of beef and pork (trim visible fat)
Meat products such as sausage, beef and pork lunch meats
Whole milk and whole milk dairy products such as cheese, butter, cream, sour cream, ice cream
Hydrogenated oils in shortening, margarine, salad dressings, dairy substitute products (some creamers)
Liver and other organ meats like sweetbread
Egg yolks
In place of the above foods, eat
Fish, especially cold water varieties
Poultry (chicken, turkey) with the skin removed
Non-fat or low-fat milk
Dairy products made from non-fat or low-fat milk (ice milk, cottage cheese, yogurt) or dairy substitutes made from polyunsaturated oils
Polyunsaturated oil products with a polyunsaturated/saturated (P/S) fatty acid ratio greater than 1.5 (first listed label ingredient should be "liquid safflower, corn, sesame, sunflower or soybean oil")
Monounsaturated oil (olive oil may be healthier than peanut oil)
Egg whites (2 egg whites = 1 whole egg in cooking)

- The ratio of polyunsaturated (P) to saturated (S) fat should be at least 1.5. If this information is not on the label, the ratio is almost certainly below 1.
- Many products high in saturated fat have vague, misleading labels like "pure vegetable oil" or "cholesterol free."

Major ways to minimize intake of dietary-saturated fat and cholesterol are: trim all visible fat from meats; limit protein sources mostly to chicken, fish, and vegetables; and use low-fat or non-fat dairy products. Avoiding foods high in cholesterol such as eggs, organ meats, and shellfish is helpful to a few patients but may not benefit the majority. Eating several eggs a day does not significantly affect most people's cholesterol level,³⁷ but high cholesterol intake may induce clinically detrimental qualitative alterations in lipoprotein structure and properties.³⁸

A mild increase in polyunsaturated fat (to a maximum of 10 percent of total calories) will help lower cholesterol and is appropriate for slender patients who need caloric replacement of the eliminated saturated fat. Higher levels of polyunsaturated fat intake are not advised due to uncer-

tainty about the long-term safety of such a dietary pattern. The influence of dietary monounsaturated fats is unclear. Peanut oil, high in monounsaturates, has been particularly atherogenic in some animal studies.³⁹ Replacing saturated fat calories with olive oil (also high in monounsaturated oleic acid) has been recently shown to have a more beneficial impact on blood lipids than carbohydrate calorie replacement.⁴⁰

While dietary change usually lowers blood cholesterol, the amount of change varies widely among persons, partly because of variations in adherence to dietary guidelines. A thorough reduction in saturated fat and cholesterol intake produces an average reduction in total cholesterol of 10–20 percent of the baseline value.⁴¹ Usually, most of the change comes from a desirable reduction in LDL-C, but HDL-C is sometimes lowered as well, especially with a high-carbohydrate diet.⁴⁰

Other dietary manipulations have been tested or promoted for their effects on cholesterol. Although high intake of wheat fiber (bran) has no consistent lowering effect on cholesterol,⁴² oat fiber may have a beneficial effect.⁴³ A large amount of either pectin (fruit fiber)⁴⁴ or garlic⁴⁵ does lower cholesterol significantly, but neither of these is likely to gain widespread favor with the public. The excessive intake of simple carbohydrates and alcohol raises triglycerides but not cholesterol, except in alcoholism and poorly controlled diabetes mellitus. The HDL-elevating effect of one to two drinks of alcohol a day is of unclear clinical significance, because it affects a different substituent of HDL-C than does exercise.⁴⁶ Lecithin has no consistent effect on lipids.⁴⁷

Fish oil supplement is the most recently advocated dietary approach to lowering cholesterol. Epidemiologic⁴⁸ and clinical⁴⁹ studies suggest that two omega-3 fatty acids, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), have several beneficial effects on blood lipids, coagulability, and platelet aggregation that may reduce the risk of myocardial infarction. The epidemiologic evidence suggests a protective benefit may be derived from eating one average-sized serving a day of cold water fish high in EPA and DHA, such as mackerel, herring, bluefish, salmon, tuna, and sardines. The amounts of EPA and DHA used in the clinical studies have been at a pharmacologic level that is much higher than the amounts normally consumed by any human population groups. Because the long-term safety of such high

amounts is unknown, recommending or condoning high-level supplementation appears to be inadvisable until data are available on adverse effects associated with chronic use. Commercially marketed preparations of EPA and DHA advise a daily intake comparable to the regular intake of cold water fish. Because the efficacy of lowering blood cholesterol is minimal at the low dose, taking the recommended amount of fish oil supplement is probably benign but ineffective.

Weight Control and Exercise

Overweight patients are advised to lose weight and maintain it as close to ideal as possible. Although losing weight without changing dietary saturated fat intake does not effect major changes in cholesterol level in most patients, weight loss does bring about desirable changes in the LDL-C/HDL-C ratio.⁵⁰

Physical activity does not consistently affect total cholesterol. Regular aerobic exercise does, however, raise HDL-C and lower VLDL-C, decreasing the LDL-C/HDL-C ratio favorably. Running or jogging 10 or more miles a week raises HDL-C significantly in most patients.⁵¹ Any aerobic exercise done at least 20 minutes at a time, three or more times a week, will probably have a similar beneficial effect. Keeping the heart rate above 70 percent of the maximal rate produces optimal cardiovascular benefit from the exercise (e.g., 130 with a maximum rate of 185).

Stress Management

The effects of relaxation techniques and behavior modification (for Type A behavior pattern) on cholesterol levels have not been studied. From the

literature on hypertension, some potential reduction of cholesterol or prevention of cholesterol elevation by mental hygienic approaches might be anticipated.⁵² Useful patient education materials are now available to help patients modify their coronary-prone behavior.^{53,54}

Management Goals

Depending on the patient's other risk factors, a satisfactory total cholesterol level would be below 200–220 mg/dL (5.2–5.7 mmol/L). An ideal physiologic level is thought to be 160 +/- 20 mg/dL (4.1 +/- 0.5 mmol/L).⁵⁵ Some large epidemiologic studies have found a correlation between total cholesterol below 160 mg/dL (4.1 mmol/L) and gastrointestinal cancer, but most studies have not corroborated this association.⁵⁶ In the absence of any disease that causes low total blood cholesterol, values below 160 mg/dL (4.1 mmol/L) do not appear to constitute a risk to long-term health. The National Cholesterol Education Program recommends using LDL-C for deciding which patients to treat and for evaluating treatment response.⁶ Dietary treatment is recommended for LDL-C at or above 130 mg/dL (3.4 mmol/L) (Table 6).

Drug Treatment

Some patients, including most with FHC, will not lower their cholesterol levels satisfactorily with the approaches above. Diet, exercise, and other nonmedical approaches should be tried for 6–12 months before medical management is considered. If LDL-C stays at or above 190 mg/dL (4.8 mmol/L) after dietary modification, pharmacologic treatment is recommended.⁶ For patients with

Table 6. Recommended Guidelines for Making Treatment Decisions.

	Initiate Treatment: LDL-Cholesterol Above	Treatment Goal: LDL-Cholesterol Below
Dietary treatment		
Without definite CHD or 2 other CHD risk factors	160 mg/dL (4.1 mmol/L)	160 mg/dL (4.1 mmol/L)
With definite CHD or 2 other CHD risk factors	130 mg/dL (3.4 mmol/L)	130 mg/dL (3.4 mmol/L)
Drug Treatment		
Without definite CHD or 2 other CHD risk factors	190 mg/dL (4.9 mmol/L)	160 mg/dL (4.1 mmol/L)
With definite CHD or 2 other CHD risk factors	160 mg/dL (4.1 mmol/L)	130 mg/dL (3.4 mmol/L)

Table 7. FDA-Approved Lipid-Lowering Medications.

Generic Name (Trade Name)	Dose	Effect	Adverse Effects	Patient Monthly Cost	Compliance Potential	
	Form	Usual				
Cholestyramine (Questran™)	Powder 9gm pk 60pk/ct or 378 gm/can	1-2 pk/scp tid-qid mix in liquid	↓ LDL 15-25%	Constipation; nausea; abd.cramps; vitamin/mineral deficiencies	(2pk, tid) \$175 (PKS) \$90 (CN) (2 scoops, tid)	Low
Colestipol (Colestid™)	Powder 5gm/pk 30pk/bx or 500gm/btl	1-2pk/scp tid mix in liquid	↓ LDL 15-25%	Same as choles- tyramine	\$90 (2, tid)	Low
Gemfibrozil (Lopid™)	Cap 300 mg	2,bid	↓ VLDL 15-30% ↑ HDL 10-25% Inconsistent LDL change	Myalgias & anemia (rare)	\$45 (2,bid)	High
Lovastatin (Mevacor™) (formerly mevinolin)	Tab 20 mg	1-2, qd/bid	↓ LDL 30-40%	Well-tolerated; hepatitis, myo- sitis	\$85 (1,bid)	Medium
Nicotinic acid (Nicobid™, Nicolar™)	500 mg SR cap; 500 mg tab	2,bid	↓ LDL 10-15% ↑ HDL 10-50%	Flushing and itch- ing (usual); arrhyth- mias (rare); hyper- glycemia (rare)	\$50 (SR) (2,bid) \$40 (tab)	Low
Probuco (Lorelco™)	Tab 250 mg	2,bid	↓ LDL 15-25% ↓ HDL 10-25%	Diarrhea (rare); flatulence (unusual)	\$45 (2,bid)	High

LDL-C of 160-189 mg/dL (4.1-4.7 mmol/L) and two or more other CHD risk factors, drug therapy would be indicated (Table 6). Patients with CHD or multiple risk factors may benefit from drug treatment at LDL-C of 130-159 mg/dL (3.4-4.0 mmol/L). Several medications lower cholesterol effectively in most patients who fail to respond adequately to dietary management. Available medications yield average reductions of 20-30 percent of the total cholesterol level attained after dietary modification. Characteristics of these medications are given in Table 7.

Bile Acid Binders

Cholestyramine (Questran™) and colestipol (Colestid™) bind cholesterol bile salts in the small intestine, preventing their reabsorption into the enterohepatic circulation. They must be mixed into a liquid or food and taken 2-3 times a day to be effective. They frequently cause constipation and are quite expensive. For these reasons, good

long-term compliance with these preparations is only likely with highly motivated patients who have abundant financial resources. In the Lipid Research Clinics Primary Prevention Trial, a full dose of cholestyramine lowered blood cholesterol by 25 percent and was associated with a calculated 50 percent reduction in CHD risk.⁵⁷

Probuco

Of the available medications, probucon (Lorelco™) has the most favorable compliance profile. It offers a simple, convenient regimen at a low cost. Probucon lowers cholesterol by changing the LDL structure and increasing the rate of LDL degradation. Its tendency to lower HDL-C does not appear to detract from its benefit to patients, because tendon xanthoma regression correlates more strongly with HDL-C decrease than with LDL-C decrease.⁵⁸ Its considerable advantages appear to outweigh the potential drawbacks of its systemic absorption.⁵⁹ Through its antioxidant ac-

tion, it prevents oxidation of LDL into its more atherogenic form⁶⁰ and prevents the transformation of macrophages into foam cells, the initiating cells of fatty streaks and atheromata.⁶¹

Nicotinic Acid

Another effective medication, nicotinic acid (niacin), has an adverse effect that limits its acceptability by some patients. The initial itching and flushing sensation may be minimized by starting at a low dose and increasing gradually or by taking aspirin before each dose. The intensity of the sensations usually diminishes after the first few weeks. Nicotinic acid may be used as a primary or an adjunctive medication for the patient who has not responded adequately to diet.⁶² Besides lowering LDL-C, it also elevates HDL-C. Cardiac arrhythmias, hyperglycemia, or hepatitis are precipitated in some patients.

Lovastatin

The most effective medication for lowering LDL-C, lovastatin (Mevacor™), formerly called mevinolin, was recently released. Lovastatin lowers TOTAL-C by 30–35 percent and LDL-C by 35–40 percent, on the average, in patients with either familial or polygenic hypercholesterolemia.^{63,64} It is convenient to take either once or twice a day⁶⁵ and is well tolerated. If its long-term safety is acceptable and its high cost is reduced, it may become the drug of choice for hypercholesterolemia.

Older Drugs and Combinations

Two medications, clofibrate (Atromid-S™) and gemfibrozil (Lopid™), lower VLDL-C more than LDL-C and are useful primarily in lowering triglycerides in patients with familial, combined hyperlipidemia.⁶⁶ They both lower LDL-C inconsistently and elevate HDL-C more predictably. Clofibrate is no longer used because of such occasional serious adverse effects as cholelithiasis and hepatoma. Another effective medication not approved by the FDA for use in lowering cholesterol is neomycin. The main obstacles to its use are nephrotoxicity and ototoxicity.⁶⁷

As with severe or refractory hypertension, some patients with severe hypercholesterolemia require multiple drug therapy to lower cholesterol to a level where the risk of CHD is markedly reduced. Either of the bile salt binders works well with pro-

bucol⁶⁸ or nicotinic acid.⁴ Probuco! and nicotinic acid work well together, because their mechanisms of action are different. Multiple drug therapy often lowers TOTAL-C and LDL-C by as much as 50 percent.

Partial Ileal Bypass Surgery

For patients who do not respond to dietary and multiple drug management, another option, partial ileal bypass surgery, is available in a few medical centers. This procedure produces sustained reduction of both total and LDL cholesterol of 30–40 percent, in addition to that attained by diet. Together with dietary change, a partial ileal bypass usually reduces TOTAL-C and LDL-C by up to 50 percent.⁶⁹

Prognosis and Complications

The outlook for the untreated patient with hypercholesterolemia is worrisome, with many patients in the prime of life developing disabling, life-threatening, and fatal outcomes. Recent studies have shown conclusively that medical treatment produces an improved prognosis for middle-aged males with hypercholesterolemia. From these and previous studies, it seems reasonable to infer a likely benefit from medical treatment for middle-aged hypercholesterolemic females.⁷⁰ Taking epidemiologic evidence into account, a strong case can also be made for dietary reduction of elevated cholesterol and for dietary prevention of hypercholesterolemia in children and adults.⁵

No data are available on pharmacologic treatment of hypercholesterolemia in the elderly. Quality of life may be improved for some patients by postponing the occurrence of heart attack or stroke or by preventing the progression of disabling peripheral vascular disease.⁷¹⁻⁷³ Limited information is available on the safety and efficacy of pharmacologic treatment of children and adolescents with hypercholesterolemia.^{74,75}

Long-term treatment with available medications may entail unknown risks. At the present time, however, the benefits appear to outweigh the overall costs of medical management of patients with total cholesterol levels that remain above 240 mg/dL (6.2 mmol/L) and LDL-C levels that remain above 160 mg/dL (4.1 mmol/L) despite sustained dietary changes.

Table 8. Recommended Follow-up Assessment.

Total cholesterol <200 mg/dL (5.2 mmol/L)	Repeat within 5 years
Total cholesterol 200–239 mg/dL (5.2–6.1 mmol/L) Without definite CHD or 2 other CHD risk factors (one of which can be male sex)	
With definite CHD or 2 other CHD risk factors (one of which can be male sex)	
Total Cholesterol >240 mg/dL (6.2 mmol/L)	Fasting blood sample Recheck total cholesterol Get HDL-C, LDL-C, and TG

Patient and Family Education

Many patients are much more willing and able to change their diet to lower their cholesterol levels than health care providers believe them to be. To be successful, patients need specific information about what is expected and regular follow-up visits to sustain motivation and check results. Involving spouses and children in the educational process can be crucial to long-lasting changes in diet and exercise patterns. Printed materials are useful adjuncts to verbal patient education,^{76,77} but they lack the vital ingredients of caring and concern that physicians can provide so well when they take the time to do so. Free pamphlets and excellent audiovisual materials are available from the American Heart Association.

Physicians who have reduced their own intakes of saturated fat and cholesterol and who exercise regularly are more effective patient educators than those who advocate lifestyle changes from an armchair viewpoint. Those who practice what they prescribe can answer patients' questions better, and they have greater credibility as positive role models.

Monitoring Therapy

Follow-up visits should be closely spaced every 4–6 weeks initially and then spread out to every 3–6 months, depending on the patient's status and stage of management (Table 8). Conducting periodic follow-up by having office personnel mail out educational and motivational materials and by talking with patients and spouses by telephone can be as effective as office visits⁷⁸ and may be more convenient and cost-effective. Fasting measurement of total cholesterol (to minimize variation) is adequate for assessing management success, unless VLDL or HDL elevation confuses

the picture. Occasional measurements of LDL-C, HDL-C, and TGs may be desirable to monitor effects of various management.

Indications for Referral and Hospitalization

The well-informed family physician can manage most hyperlipidemic patients without any need for consultation or referral. The primary indications for referral are resistance to dietary and medical management and atherosclerotic problems outside one's range of clinical competence and confidence. Hospitalization is indicated only for atherosclerotic or hyperlipidemic complications such as unstable angina or acute pancreatitis. Good preventive management can allow many patients to avoid or defer the serious consequences of hypercholesterolemia and atherosclerosis.

Management of Hypertriglyceridemia

For the patient with severely elevated triglycerides (above 1,000 mg/dL or 11 mmol/L), dietary changes are one key to control. Eliminating excess alcohol and excess simple carbohydrates (mainly sucrose) often lowers triglycerides dramatically. Weight control is crucial to successful management in most patients with severe hypertriglyceridemia. Improved control of diabetes mellitus can be the most important treatment step. Regular physical activity can lower TGs by helping with weight reduction and enhancing the metabolism of VLDL by lipoprotein lipase. Reducing saturated fat and cholesterol intake is recommended when the LDL-C level is elevated.

For persistent, severe hypertriglyceridemia, gemfibrozil is the preferred medication.⁶⁸ Although its chemical similarity to clofibrate sug-

gests a potential for similar serious adverse effects, early experience indicates that gemfibrozil is probably a safer drug, with comparable efficacy in lowering TGs. Nicotinic acid or pharmacologic doses of omega-3 fish oil supplements can also be very effective in lowering high triglyceride levels.⁷⁹

The Larger Perspective

The authors of recent cost-effectiveness analyses concluded that successful interventions with hypercholesterolemia are likely to have less beneficial impact on life expectancy than successful interventions with hypertension and smoking.^{80,81} While this may be a valid conclusion, the analysis disregards the quality-of-life benefit derived by people whose myocardial infarctions would be prevented or postponed by lowering elevated cholesterol levels.

To realize their full potential, heart disease prevention efforts require attention to all reversible risk factors whenever patients are willing and able to modify them. For optimal impact, continued societal efforts are needed to reduce the atherogenicity of the modern lifestyle and family environment.⁸² Although family physicians have been somewhat slow to take the initiative in detecting and managing hypercholesterolemia,⁸³ progress has been made,⁸⁴ and family medicine still has an opportunity to assume a leadership role in this area.

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