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Cholesterol, Triglycerides, and the Treatment of Hyperlipidemias

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Prior to the discovery of antibiotics in the mid twentieth century, the number one cause of death involved infectious diseases. After the discovery of penicillin by Sir Alexander Fleming and the development of newer antibiotics, coronary artery disease (CAD) became the number one cause of death among North Americans and Europeans alike. In the United States, CAD kills more people than all other diseases combined. In 1998, CAD killed more people *worldwide* than any other illness or cause of death.

The initial relationship between dietary cholesterol and CAD can be traced back to the early 1900s, if not before. Approximately 30 years ago, research into atherosclerotic plaques began first with rhesus and cynomolgus monkeys[1-10] and showed that cholesterol plaqueing occurred when animals were placed on diets high in cholesterol. These studies also showed that the disease could be reversed if the animals where later placed on diets low in cholesterol.

Beginning in the late 1970s, epidemiologic data began to accumulate[11-14] that showed a positive correlation between dietary intake of cholesterol and the subsequent development of atherosclerosis. During the same period of time,[15-29] studies were conducted to determine the impact of various medications designed to reduce cholesterol (antihyperlipemics and hypolipemics), with little if any attention being paid to the effect of dietary modification. Some of these studies are listed in Table 30.1, representing more than 70,000 people.

Attempts to document changes in atherosclerotic plaques by coronary arteriography (cardiac catheterization) began during the 1970s. Some of these studies[30-38] demonstrated improvement (regression), whereas others did not. Multiple reasons exist for the discrepancy in these results, including but not limited to (1) inadequate changes in dietary restriction of cholesterol, triglycerides (fat), and total calorie intake; (2) inadequate methods for determining changes in cholesterol plaques; and (3) problems with various medications used for the treatment of hyperlipidemia and hypertension.

Most of the studies to date[39-58] have not differentiated between the effect obtained with dietary modification and that obtained with hypolipemic medications. Distinction between the effects obtained with dietary restriction, hypolipemic medications, and the combination of both waited until the early 1990s[59-69] and has included studies on both older (> 65 years of age) and younger (< 65 years of age) individuals. In this chapter we review the screening of hyperlipidemia and the importance of both dietary and medical management.

Routine Screening of Hyperlipidemia

Beginning in the late 1980s the American Heart Association proposed routine screening of cholesterol levels in an attempt to identify individuals at increased risk for CAD and begin treatment to reduce elevated lipid levels. Multiple algorithms exist, including the one shown in Figure 30.1. The initial screening of cholesterol levels does not require that the patient fast, however, fasting is necessary if the cholesterol is to be fractionated to determine the levels of low-density lipoprotein (LDL-C) cholesterol, high-density lipoprotein (HDL-C) cholesterol, triglycerides, and total cholesterol (TC). Although opinions vary, a TC level exceeding 240 mg/dL is considered to place a person at increased risk for CAD. However, if we look at populations of people[11-14] who live relatively long life spans and are healthy and active, we discover that their TC levels are below 150 mg/dL, with relatively low HDL-C levels. It now appears that TC levels ≥ 150 mg/dL, LDL-C levels ≥ 100 mg/dL (and probably ≥ 80 mg/dL), or triglyceride levels ≥ 150 mg/dL increase a person's risk for heart disease and stroke. An in-depth review of cholesterol is beyond the scope of this chapter and can be found elsewhere.[70,71]

Individuals with TC levels between 200 and 239 mg/dL are particularly at increased risk for CAD if they have two or more additional risk factors for atherosclero-

TABLE 30.1. Examples of studies looking at morbidity and mortality.

Reference	Number of patients	Age range	Sex
Dewar et al.[15]	497	<65 yr	Both
Alstead et al.[16]	717	40–69 yr	Both
Coronary Drug Project Research Group[17]	8341	30–64 yr	Male
Puska et al.[18]	1683	25–59 yr	Both
Kornitzer et al.[19]	19,390	40–59 yr	Male
Shekelle et al.[20]	1900	40–55 yr	Male
Kjelsberg[21]	12,866	35–57 yr	Male
Lipids Research Clinics Program[22]	3806	35–59 yr	Male
Goldbourt et al.[23]	10,059	>40 yr	Male
Miettinen et al.[24]	1825	50–65 yr	Male
Brunner et al.[25]	2992	35–64 yr	Both
Frick et al.[26]	4081	40–55 yr	Male
Carlson and Rosenhamer[27]	555	<70 yr	Both
Assmann et al.[28]	2754	40–65 yr	Male
Alderman et al.[29]	101	36–73 yr	Both

sis, as listed in Table 30.2. In fact, for each 1% increase in serum cholesterol, there is a 2% increased risk for CAD. Although most algorithms advise that dietary changes should be initiated first and then hypolipemic medications, there is little if any useful information in the medical literature regarding the appropriate dietary changes necessary to reduce elevated cholesterol levels. In many cases both the patient and doctor are confused about what constitutes an appropriate diet. Many individuals are inclined to be too liberal in their saturated fat, calorie, and cholesterol intake. This can be like trying to put out a fire (cholesterol) with gasoline. If you see a fire and you add a pint of gasoline (less cholesterol in the diet), as opposed to a gallon of gasoline (regular diet), you are not going to put out the fire. In fact you will just have added more fuel.

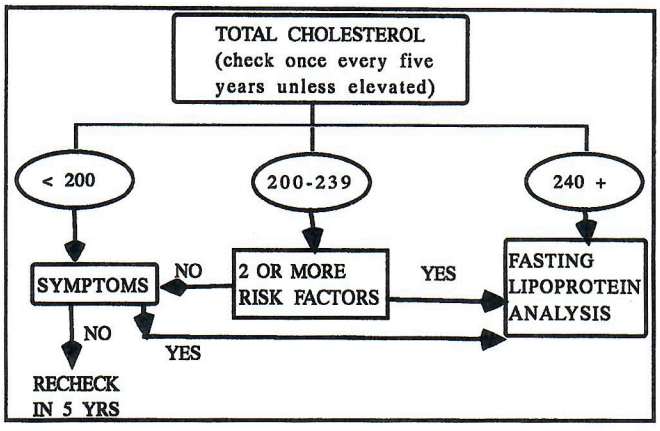

FIGURE 30.1. *Old algorithm* for cholesterol screening. Patients with no prior history of heart disease or who have never had their cholesterol checked should undergo testing at least every 5 years. Further determinations concerning the need for fasting lipoprotein profiles should be based on the total cholesterol level, presence of other risk factors, and the presence or absence of symptoms.

Two books recently published for the lay public[70,71] are excellent references for patients, physicians, and other health care providers as they seek to understand and lower cholesterol levels. Table 30.3 lists the recommended dietary guidelines according to the American Heart Association, however, as we discuss later, patients who modify their diets by eliminating cholesterol and reducing calories and saturated fat are able to achieve dramatic reductions in their TC levels, with few exceptions. The Fleming guidelines[68–71] are also shown in Table 30.3, with the major difference being that the total caloric need for an individual is calculated first, and then the amount of protein, fat, and carbohydrate needed is determined, making the dietary guidelines useful for people with high cholesterol and triglyceride levels, high blood pressure, and excess weight, as well as people with diabetes mellitus. As noted in Chapter 29 on atherosclerosis, the successful reduction of percent diameter stenosis by regression of cholesterol plaques can produce a significant improvement in exercise tolerance and other symptoms.

TABLE 30.2. Independent risk factors for coronary artery disease.

Prior heart attack
Angina pectoris
Men or postmenopausal women
Family history
Smoking
Hypertension
Diabetes mellitus
Severe obesity

TABLE 30.3. Comparison of the current US diet, the American Heart Association (AHA) guidelines, and the Fleming guidelines.

Nutrient	Current US diet	Step 1 AHA diet	Step 2 AHA diet	Fleming guidelines
Cholesterol	500 mg	<300 mg	<200 mg	<200 mg
Total fat	~42%	<30%	<30%	15%
Saturated fat	~17%	<10%	<7%	<5%
Carbohydrates	—	50%–60%	50%–60%	70%
Protein	—	15%–20%	15%–20%	15%

Dietary Changes

When making changes in an individual's dietary habits, several factors must be kept in mind. First, if the serum cholesterol level is elevated, the person is at increased risk for heart disease. Failure to understand that prior eating habits have led to elevated lipids is the first problem you and the patient must overcome. As mentioned in Chapter 29 on atherosclerosis, the progression of atherosclerosis from 40% to 80% diameter stenosis results in significant reductions in the flow reserve of the heart. Cholesterol is not the patient's friend, and like anything else that threatens the patient's life, it should be avoided like the plague. Good reference sources for fat, calorie, and cholesterol contents of foods, along with recipes, are now available[70,71] for patients and doctors alike. For an individual who is less likely to adhere to changes in their diet, the physician should (with the assistance of a registered dietitian and/or nutritionist) strive to have the patient change his or her diet to either the step I or step II American Heart Association diet. The general guidelines for this diet are listed in Table 30.3. However, remember that this diet merely pours a pint of gasoline on the fire instead of a gallon of gasoline. Obviously there is less fuel for the fire, but the fire is not likely to go out. Later we review what happens when patients adhere to either the AHA step II or Fleming guidelines.

Second, the overall fat intake must be reduced to control cholesterol level and body weight. Triglycerides, which are part of the overall lipid component, are made from fats. When dietary fat is increased there is an increase in triglyceride levels and, subsequently, an increase in cholesterol, regardless of whether any cholesterol is consumed in the diet. Particularly alarming is the amount of saturated (animal and processed foods) fat eaten by most people. One of the major problems with most dietary regimens, once the patient adheres to eliminating cholesterol in the diet, is a failure to watch the amount of fat and calories in the diet. As noted in Figure 30.2, adequate reductions in cholesterol levels require control of cholesterol, fats, and calories.

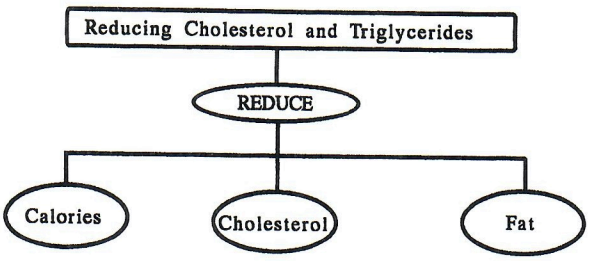

FIGURE 30.2. Control of hyperlipidemia means reducing calories and cholesterol, and saturated fat intake. Adequate reduction of serum lipids (cholesterol and triglycerides) is dependent on the modification of dietary calorie, cholesterol, and saturated fat intake.

Third, the number of calories the patient eats in a day should not exceed his or her caloric needs.[70,71] When this amount is exceeded, the excess calories will be stored as glycogen, cholesterol, and triglycerides for future needs. Of course, if one does not draw on these stored calories, they will continue to accumulate. Adipose tissue is one area where excess calories are stored. Another area is the coronary arteries, where this stored energy can be rapidly broken down and supplied to the heart during emergencies. This makes perfect sense when preparing for fight-or-flight situations, but most individuals do not tap into these stores. So the stored energy continues to accumulate, eventually leading to problems with atherosclerosis.

Finally, the time of day the patient eats is also important.[68–70] If one eats the required number of calories per day and no more, one might assume there will be no problem. However, this is not so. Eating just before going to bed, or eating a major meal within a few hours of going to bed, will not give the body enough time to use those calories before going to sleep. As the metabolism slows for sleep, the body perceives the additional calories as excessive and store them as glycogen, cholesterol, and triglycerides. Although some of these calories may be catabolized by the body the following day, it is unlikely that all of these calories will be used, and the slow but steady accumulation of cholesterol and triglycerides continues, leading to increased risk of atherosclerotic heart disease and other potential health problems.

Hypolipemic Medications

Over the last 30 years a variety of medications have been developed and utilized in an attempt to reduce serum

TABLE 30.4. Commonly available hypolipemic medications.

Group of medications	Medication	Dosage per day
Bile acid sequestrants	Colestid	5–30 g
	Questran	4–24 g (1–6 scoops)
Fibric acid derivatives	Atromid-S	2 g
	Lopid	600–1200 mg
	Tricor	67–201 mg
3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors	Lescol	20–40 mg
	Mevacor	20–80 mg
	Pravachol	10–40 mg
	Zocor	5–40 mg
	Lipitor	5–40 mg
	Baycol	0.2–0.3 mg
Nicotinic acid	Nicobid	250–1000 mg
	Nicolar	1–6 g
Other	Lorelco	500–1000 mg

cholesterol and triglyceride levels. A list of many of the currently available medications for the treatment of elevated cholesterol and triglyceride levels is shown in Table 30.4.

Bile Acid Sequestrants

The bile acid sequestrants, which consist primarily of colestipol hydrochloride and cholestyramine, have been available for approximately 20 years. As shown in Figure 30.3, these drugs, which are bile acid resins, work in the intestines and absorb bile salts, including cholesterol. Several forms of these medicines have been available, including mixes and bar forms. Because they are active only while passing through the intestines, they must be taken two or three times each day and have been associated with gastrointestinal bloating. Additionally, medications (e.g., digoxin) that are taken within a couple hours of these drugs may be bound by the bile acid sequestrant and not absorbed as they should be.

As shown in Figure 30.3, once ingested (step 1), these resin drugs bind with available bile salts that are also in the intestine (step 2), resulting in less LDL-C in the liver. The liver is then able to receive more LDL-C from the blood (step 3). As a result of increased uptake of LDL-C by the liver from the blood, the liver may actually increase its production of very low density lipoprotein cholesterol (VLDL-C), causing as much as a 20% percent increase in TC.

Other potential problems include gastrointestinal problems such as gallstones, constipation, and hemorrhoid exacerbation, in addition to dizziness, headaches, myalgias, weakness, and other symptoms. In addition, patients with phenylketonuria should not use colestipol hydrochloride because it contains phenyalanine.

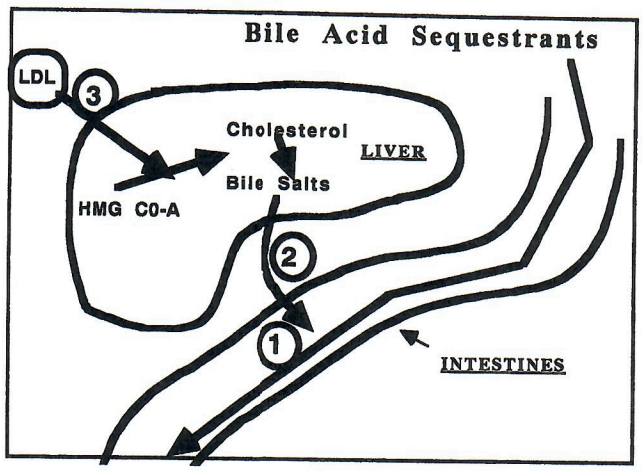

FIGURE 30.3. How bile acid sequestrants work: Once ingested, bile acid sequestrants bind bile salts (including cholesterol). This causes further production of bile salts by the liver and release of these bile salts from the gallbladder into the gastrointestinal tract. Once this occurs, LDL-C can be removed from the bloodstream by the liver, which may then increase its production of cholesterol. HMG Co-A, 3-hydroxy-3-methylglutaryl-coenzyme A.

Fibric Acid Derivatives

There are three principal fibric acid medications available for prescription by most physicians: clofibrate, gemfibrozil, and fenofibrate. These medications are used for the treatment of elevated triglyceride levels, although there have been intermittent reports that some beneficial reduction in LDL-C may also occur. As shown in Figure 30.4, these medications work by increasing the activity of the enzyme lipoprotein lipase, which converts VLDL-C to intermediate lipoprotein cholesterol, which is then converted to LDL-C.

Clofibrate and gemfibrozil, like the bile acid sequestrants, must be taken more than once a day to have an ef-

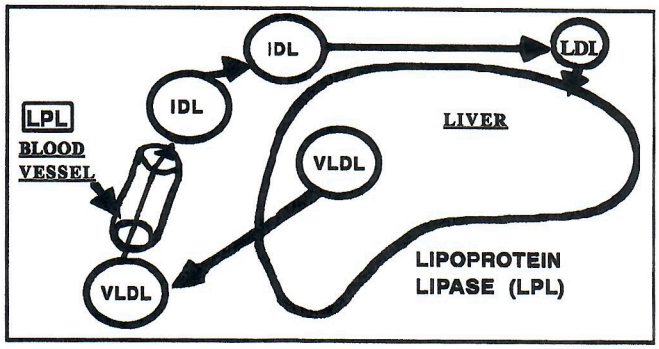

FIGURE 30.4. How fibric acid derivatives work: fibric acid derivatives increase the activity of lipoprotein lipase, which increases the catabolism of VLDL cholesterol to intermediate lipoprotein (IDL) cholesterol, and finally to LDL cholesterol.

fect. Typically they are taken twice a day before meals. Fenofibrate is taken once daily. The most common problems reported with these medications include hepatobiliary (e.g., cholelithiasis) problems and myalgias. Frequent checking of liver function tests and creatine kinase levels is recommended to detect problems with muscle and liver irritation. This is particularly important because of the increased rate of deaths from cancers and pancreatitis among patients taking clofibrate. Fibric acid medications can be particularly problematic if taken with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG Co-A) reductase inhibitors. Other problems include elevation of blood sugar and blurry vision, particularly in diabetic individuals. Patients taking coumadin should be monitored closely because the combination of fibric acid medications and coumadin has been associated with an increased tendency to bleed.

HMG Co-A Reductase Inhibitors (Statins)

The HMG Co-A reductase inhibitors have been shown not only to improve LDL-C levels but also to improve total triglyceride and HDL-C levels. The drugs in this newest class of hypolipemic medicines include fluvastatin, lovastatin, pravastatin sodium, simvastatin, atorvastatin, and cerivastatin. Each works by slowing down but not stopping the production of cholesterol in the liver by inhibiting the enzyme HMG Co-A. This enzyme is the rate limiting step in the production of cholesterol by the liver. Figure 30.5 shows the site of action of these drugs in the liver. Many of these medications are taken with the evening meal or at bedtime. By taking these medications at this time of day, they have their maximum impact on cholesterol synthesis while the patient is sleeping. Because the majority of cholesterol synthesized by the liver is made during sleep, taking the medications earlier in the day has less effect on cholesterol production, although some physicians prescribe these medicines twice a day.

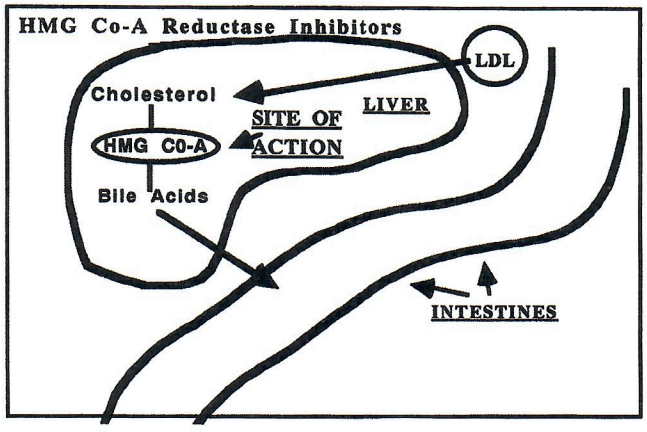

FIGURE 30.5. How HMG Co-A reductase inhibitors work: HMG Co-A reductase inhibitors work by reducing the rate at which cholesterol is synthesized in the liver by slowing the rate-limiting enzyme HMG Co-A.

As mentioned earlier, the combined use of these medications with fibric acid derivatives has been associated with increased myalgias and liver abnormalities. The combination has, however, demonstrated greater reductions in cholesterol than either group of medicines alone. Caution should be used when these medicines are taken with other drugs that are metabolized in the liver, such as erythromycin (macrolide antibiotics), niacin, cyclosporine, and FK-506 (tacrolimus), to name a few. Frequent monitoring of liver function tests and creatine kinase levels is recommended.

Nicotinic Acid

Neither of the two medications (niacin and timed-release niacin) in this class of drugs contains nicotine. Instead they both contain niacin, whose primary effect is to increase HDL-C levels up to 25%. Little if any effect on the other lipid components is seen. The most frequent side effect is skin flushing, which is caused by the release of prostaglandins and can be blocked by taking an aspirin one-half hour before the niacin. Because of the associated stomach irritation, niacin should be taken with food, although caution needs to be exercised in diabetic patients because of niacin's tendency to increase blood glucose. Patients with gout should be cautioned about an increased tendency to precipitate gouty episodes. Although most of the problems associated with these medicines are minor, fatal dysrhythmias have been reported, and caution should be exercised in any patient with cardiac dysrhythmias, as well as in patients with liver disease or inflammatory bowel disease. Patients should be carefully monitored while taking these drugs.

Other Hypolipemics

Probucol has been shown to decrease LDL-C levels via its antioxidation effect. However, it also decreases HDL-C levels. Because of this effect and its potential for fatal dysrhythmias, it is seldom used. Any patient who is considered for this drug should have a resting electrocardiogram to determine if there is QT prolongation. Probucol should not be given to people taking tricyclic antidepressants because of potential problems with QT prolongation and rhythm abnormalities. Patients with low potassium and magnesium levels also should not be placed on this drug. In general, patients who have bradycardia or conduction problems, are taking digoxin, or have recently had a myocardial infarction should find alternative treatment. Other problems include syncope and lightheadedness.

Other medications that have been associated with reductions in TC levels but are not primarily designed to

treat hyperlipidemia include the angiotensin-converting enzyme inhibitors. Some but not all of these drugs reduce TC levels by a pathway not yet elucidated.

Comparing Dietary Change and Hypolipemic Drugs in the Management of Hyperlipidemia

Beginning in 1992 our group began investigating both dietary and drug effects in the treatment of hyperlipidemia.[59–70] Throughout the 18-month study and since, 70 individuals were enrolled into one of four treatment groups designed to determine the effect of diet, diet and drug, drug only, and no treatment. The first group received routine suggestions to reduce their dietary intake of fats and cholesterol, and to control the total number of calories they were eating to maintain an ideal body weight. Reading material was available but no additional counseling or medications were provided. Over the following 18 months, these patients increased their TC levels by 15%, which represented a 30% increased risk for CAD.

During this same time interval, the second group of subjects received dietary counseling with specific instructions to assist in reducing or eliminating foods with cholesterol and saturated fats. Additionally, patients were counseled regarding their caloric intake. By the completion of the study all patients had attained a step II (see Table 30.3) diet or better despite their original belief that they could not make the necessary changes in their diet. As a result the average TC level dropped by 13% during the first 6 months, and 30% by the end of the study. This represents a 26% and 60% reduction in the risk of heart disease at 6 and 18 months, respectively.

The third group of individuals received 6 months of dietary counseling identical to that received by the second group. However, after the first 6 months of the study, these patients stopped receiving dietary counseling and subsequently returned to their prior eating habits. Additionally, this group also received hypolipemic medications at the beginning of the study, with increased dosages as determined by the primary care physician. During the first 6 months these people not only showed an average reduction in their TC levels of 27%, representing a 54% reduced risk for heart disease, but many were able to discontinue antianginal medications. This undoubtedly represents an improvement in flow reserve as explained in Chapter 29 on atherosclerosis. Unfortunately, after the dietary counseling was discontinued, the overall TC levels increased from the 6-month level. The TC levels demonstrated an overall reduction of 12% by the end of the study as compared with the beginning of the study. This 12% reduction is typical of what is seen and reported in the literature when patients receive medications but do not change their diet. The results during the first 6 months of the study suggest, however, that even greater strides could have been made if dietary counseling and improved dietary habits had been maintained.

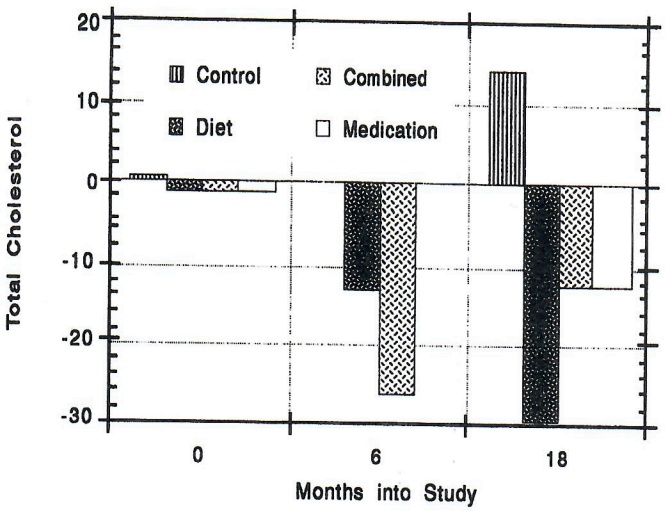

FIGURE 30.6. The effect of changed diet, hypolipemic medications, and the combination of diet and medication. Reductions in TC levels can be achieved either by dietary changes, hypolipemic medications, or a combined approach. When dietary modification to either a step 2 American Heart Association diet or Fleming guidelines occured, cholesterol levels were decreased by 30%. Hypolipemic medications resulted in a 12% reduction, whereas the combined approach yielded even greater reductions (in as little as 3 to 6 months) than either approach used alone.

The final group consisted only of people receiving medications to treat hyperlipidemia. There was no dietary counseling. By the completion of the study, the average reduction in TC levles was 12%. This is identical to the results obtained by group 3 after dietary counseling had ceased and patients had returned to their prior dietary habits. The results of this study are graphically shown in Figure 30.6.

Conclusion

Atherosclerotic CAD is the number one killer of people worldwide. More people die each year in the United States from heart disease and strokes than would have died in 20 Vietnam Wars. This means that each day more than 8000 people (one every 10 s) will die from heart disease in the United States (more than half will be women), with one third to one half having no prior symptoms or warning signs. Additionally, one American has a stroke every minute, and every 4 min a person dies

from a stroke-related problem. The current recommendations are to reduce total serum cholesterol levels to less than 150 mg/dL, or LDL-C levels to less than 100 mg/dL. Likewise, triglyceride levels should be reduced to 150 mg/dL or less. Studies over the past 30 years have shown that hyperlipidemia can and should be treated and that CAD can be reversed, at least to some extent, depending on the severity of the disease, when it is detected, and the motivation of the patient and doctor. Until recently, little information has been available to assist with the dietary changes necessary to significantly reduce elevated cholesterol and triglyceride levels. We now know that diet or diet and drug therapy can dramatically reduce elevated lipids and reduce the risk of CAD and stroke. This information[70,71] is now available for the general public and the clinician to assist them in better understanding the diagnosis and treatment of hyperlipidemia.

Although cholesterol and calcium (atherosclerosis) are two factors involved in CAD, the Fleming theory[71–73] (as explained in Chapter 64) proposes that other factors may be important in individual cases. The first of these is the inflammatory process that is initiated with damage to coronary endothelium. This can occur as a result of cholesterol deposition, ulceration of plaques, interventional procedures, and oxidative stress. A second is bacterial involvement, including *Streptococcus pneumoniae, Chlamydia pneumoniae,* and *Helicobactor pylori.* Once these bacteria infiltrate a coronary plaque they may precipitate further damage and ulceration in addition to increasing the inflammatory process. Once the initial screening for hyperlipidemia is completed it is important that repeat evaluations continue to monitor the patient's progress and, when appropriate, markers of inflammation and bacterial involvement, including fibrinogen, lipoprotein (a), C-reactive protein, interleukins, and homocysteine.

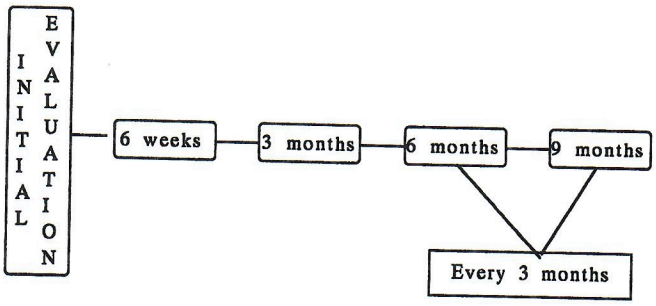

FIGURE 30.7. Recommended follow-up evaluations for patients with hyperlipidemia. Once patients undergo dietary and/or hypolipemic drug management for hyperlipidemia, close monitoring of results with dietary and drug modifications is necessary to optimize results. Patients should have fasting lipoprotein analysis (LDL-C, HDL-C, TC, and total triglycerides) performed at each visit, along with appropriate liver function tests, monitoring of creatine kinase (if taking hypolipemic medications), and other tests as outlined in Chapter 64.

Adjustments in dietary habits and medications can be made during these visits, along with monitoring of the effects of the medications on the liver and muscles. The recommended schedule for office visits and blood work is shown in Figure 30.7.

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