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Cardiovascular Disease Risk — Prevention by Diet

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Introduction

Coronary heart disease (CHD) is the leading cause of death in both men and women in developed countries. Mortality rates vary from ~50/100,000 in Japanese women to 436/100,000 in Scottish men.[1] In the U.S. 32% of women and 50% of men will develop CHD, and CHD is the cause of death in 31% of men and 24% of women. The current concepts of the role of the diet in the etiology of cardiovascular disease (CVD) relate components of the diet to the pathogenesis of atherosclerosis. Primarily dietary fats, especially saturated fat and cholesterol, impact on the levels of circulating lipids to raise total and low-density lipoprotein (LDL) cholesterol that increase CHD risk. Dietary factors increase triacylglycerol (TG) levels that also increase the risk of CHD and/or decrease high density lipoprotein (HDL) cholesterol the lipoprotein that lessens CHD risk. Thus, diets that lower LDL cholesterol and/or TG and/or raise (or do not lower) HDL are protective against CHD. Other dietary components such as antioxidants (carotenoids, vitamin C, vitamin E) may lessen the risk of CVD by decreasing oxidized LDL, which is more atherogenic. High blood levels of homocysteine are atherogenic, and the levels of this amino acid are decreased by intake of folate, vitamin B_6 and vitamin B_{12}. This section will review:

- The background for these hypotheses and associations
- The dietary factors that influence circulating lipids and lipoproteins (Table 51.1) and their mechanisms of atherogenesis
- The role of some nutrients in vascular biology
- The diet that may best prevent CHD in those without the disease or in individuals post-myocardial infarction

The Extended Lipid Hypothesis

The fat content and fatty acid composition of the diet were determined to be important factors in the pathogenesis of atherosclerosis as an inference from the decline in cardio-

TABLE 51.1

Foods and Nutrients that Affect Cholesterol Levels

Cholesterol-Lowering	Cholesterol-Raising
Plant sterols, 3 g/day	Saturated fatty acids
Fruits and vegetables, 5 servings/day	Trans fatty acids
Soy proteins, 25 g/day	Dietary cholesterol
Whole grains	
Soluble fiber, 30 g/day	
Psyllium	
Monounsaturated fatty acids	
The Mediterranean diet	
N-6 polyunsaturated fatty acids	

vascular mortality that was observed during the depression and with World War II.[2] Food was scarce, with a decrease in the consumption of dairy products and eggs, rich sources of saturated fat and cholesterol. The dietary fat–heart hypothesis was proposed by Keys.[3] Epidemiologic studies related CHD rates to the intake of dietary fat, especially saturated fat (Figure 51.1). A high-fat diet, enriched in saturated fats, was also related to the rise in serum cholesterol with age. The related cholesterol hypothesis proposes that increasing serum cholesterol raises the risk of CHD, and that decreasing serum cholesterol levels will reduce risk.[2]

The risk of developing CHD is continuous over the range of serum total cholesterol levels. Cholesterol levels exceeding the 75th percentile are associated with moderate risk of atherosclerosis, and at >90th percentile with high risk.[4] Low-density lipoprotein cholesterol levels similarly can be classified into low, moderate, and high risk.[5] Small, dense LDL particles are associated with a tripling of the risk of myocardial infarction (MI), compared to the larger, more buoyant LDL particle.[6] Elevated lp (a) increases the risk of

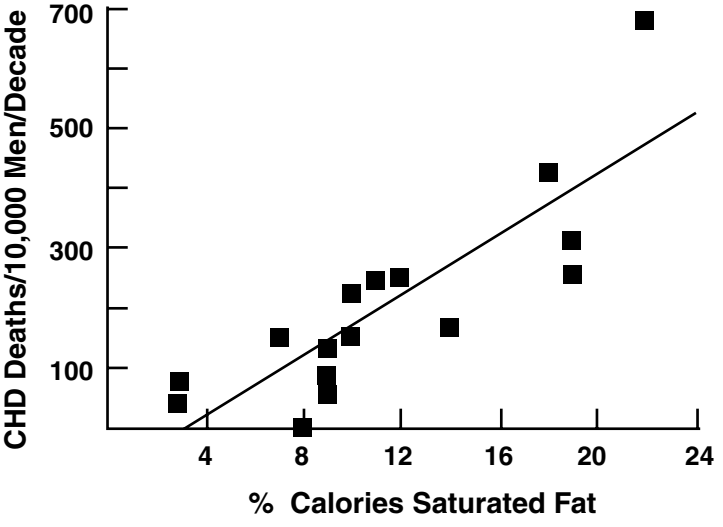

FIGURE 51.1

Death rates from CHD and the intake of saturated fat in the Seven Countries Study. The ordinate represents deaths from coronary heart disease that occurred over a 10-year period per 10,000 men enrolled in the study. The cohorts are from sites in seven countries: the U.S., Japan, Greece, Italy, Yugoslavia, the Netherlands, Finland. The regression equation is y = –83 + 25.1x, r + 0.84. Adapted from Keys A. *Seven Countries Study — A Multivariate Study of Death and Coronary Heart Disease,* Harvard University Press, Cambridge, 1980.)

TABLE 51.2

Factors Affecting HDL Cholesterol Levels

Increased Levels	Decreased Levels
Saturated fats	Polyunsaturated fat, high
Dietary cholesterol	Simple sugars/high carbohydrate diet (short period)
Alcohol <2 drinks/day	Some antihypertensive drugs
Long-term aerobic exercise program	Physical inactivity
Estrogens	Androgens
	Progestogens
	Anabolic steroids
Female gender	Male gender
	Obesity
	Diabetes mellitus
	Cigarette smoking

atherosclerosis,[7] although it is unknown whether decreasing levels with any intervention reduces risk. Elevated lp (a) levels are resistant to treatment other than high doses of niacin. The smaller lp (a) particles are more atherogenic, may act by promoting LDL oxidation, and may decrease endothelial-dependent vasodilatation. This additional risk factor is an indication for more aggressive management of other risk factors. Coronary events are reduced by 2 to 3% for every 1% decrease in LDL cholesterol.[1]

HDL cholesterol levels are inversely related to CVD risk.[8] Risk is appreciably higher in subjects with HDL levels < 0.92 mmol/L (35 mg/dl), and decreases when HDL levels are >1.5 mol/L (60 mg/dl). In addition, the ratio of total cholesterol to HDL cholesterol, or of LDL:HDL cholesterol, or total to non-HDL cholesterol indicate varying degrees of CVD risk. Factors influencing HDL cholesterol levels are listed in Table 51.2. Coronary events are reduced by 3% for every 1% increase in HDL cholesterol.[1]

TG levels in blood are increased by excess energy intake, fats, carbohydrates, and alcohol. Whether TG levels are independent risk factors for CHD has been debated over decades. Recent data have supported the concept that higher TG levels increase risk independent of HDL levels or other confounding factors of the dyslipidemic syndrome such as glucose intolerance, hyperinsulinism, obesity, hypertension, etc.[9] Results from one prospective study in Quebec males followed for up to five years suggest that fasting plasma insulin, apolipoprotein B levels, and LDL particle size may improve risk assessment. Identification of individuals with this cluster of abnormalities may lead to effective diet and exercise interventions.[10] This study supports conclusions from the Physicians' Health Study that elevated TG levels may help identify individuals at high risk because of the associated predominance of small, dense LDL particles.[11] Data from the Framingham Offspring Study indicate that elevated levels of fasting insulin are associated with impaired fibrinolysis and hypercoagulability in individuals with normal or abnormal glucose tolerance. This suggests that the risk factors of hyperinsulinemia and glucose intolerance may be mediated in part by enhanced potential for acute thrombosis.[12]

A meta-analysis of studies of TG levels and CVD showed that a l mmol/L increase in TG levels was associated with a 76% increase in CVD risk in women and a 31% increase in men.[13] Current data indicate that TG levels >100 mg/dl raise CVD risk, independent of the usual accompanying low HDL.[14] In the Copenhagen Male Study, fasting hypertriglyceridemia was found to be a stronger predictive risk factor than total cholesterol.[15]

Levels of circulating apoproteins may be useful in predicting the risk of CVD. Absolute levels, or changes in lipoprotein particle size or amino acid composition may be better predictors of CHD than are lipid levels.

A puzzling and as yet unanswered aspect of CHD risk is that the lipid levels of patients with various clinical symptoms or pathologic signs of atherosclerosis often fall within the "normal range." In the most recent National Health and Nutrition Examination Survey (NHANES III) (Table 26.4), the average level of total cholesterol in the U.S. was 225 mg/dl, and the average level of LDL cholesterol was 142 mg/dl.[16] Patients studied with CHD, such as in the Framingham Study, have had total cholesterol levels ranging from 200 to 250 mg/dl and LDL cholesterol ranges of 132 to 156 mg/dl.[8]

Dietary Effects on Serum Lipids and Lipoproteins

Lipids

Diets high in total fat, saturated fat, and cholesterol are atherogenic for many animal species. Long-chain saturated fatty acids (Figure 51.2) in animal or vegetable fats raise plasma cholesterol levels and decrease LDL receptor activity.[17] Paradoxically, these fats also raise HDL cholesterol levels. Predominantly monounsaturated liquid vegetable oils have a cholesterol-lowering effect, lowering LDL cholesterol, but not HDL cholesterol; some monounsaturated oils have shown a TG-lowering effect.[18,19] Polyunsaturated fats of the n-6 series in liquid vegetable oils decrease LDL cholesterol and increased amounts lower HDL cholesterol.[4] The n-3 series of polyunsaturated fatty acids found in fish (especially deep-water ocean fatty fish) and fish oil have variable effects on total LDL, and HDL cholesterol, and lower TG levels.[20] Trans-fatty acids produced from some processes of partial or complete hydrogenation of unsaturated liquid vegetable oils (in the U.S. predominantly soybean oil) raise LDL cholesterol to a somewhat lesser degree than long-chain saturated fats or butter, but in contrast, lower HDL cholesterol.[21] Investigators concluded that vegetable shortening and stick margarine have advantages over butter with respect to LDL cholesterol levels (–5 to 7%), with ingestion of liquid soybean oil or semiliquid margarine resulting in 11 to 12% lowering of LDL cholesterol in comparison

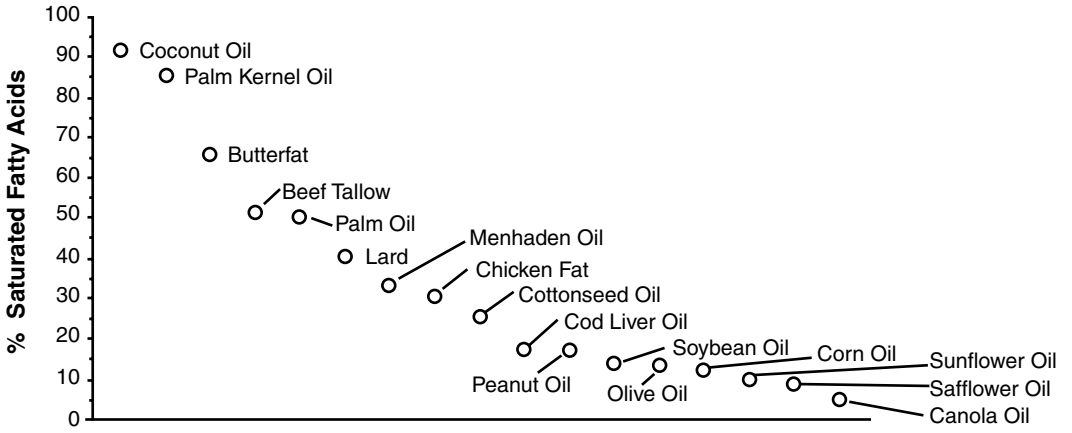

FIGURE 51.2
The saturated fatty acid content of various fats and oils.

to butter. Cholesterol is found in the diet only in animal products and is not present in any plant sources.

Atherosclerosis

Theories of Atherogenesis

Theories of atherogenesis propose that LDL cholesterol is the pathogen, delivering cholesterol to the arterial wall. Endothelial injury initiates proliferation of vascular smooth muscle cells and conversion of monocytes to macrophages (cholesterol ester-laden foam cells) and fibroblasts under the influence of growth factors and cytokines.[22] Oxidized LDL accelerates formation of foam cells, atheroma, and the fibrous plaque.[23] Plaque rupture initiates the events of myocardial infarction. CHD progression is related to levels of total and LDL cholesterol, and decreased levels of HDL cholesterol, especially HDL_2, or the ratio of HDL_2 to LDL cholesterol.[1,2] Levels of TG >2.28 mmol/L (250 mg/dl) also increase the risk of MI and warrant intervention; more recent data suggest lowering this level, perhaps to 0.91 mmol/L (100 mg/dl).[13,14] Regression of atherosclerosis occurs when cholesterol ester is mobilized from the superficial layers of plaque. Cholesterol is removed from plaque when LDL cholesterol levels are reduced to <2.5 mmol/L (95 mg/dl).[2] This level of LDL usually parallels a total cholesterol value <4.6 mmol/L (180 mg/dl).

Current theories of atherogenesis implicate plaque rupture with release of a necrotic lipid core as the precipitating factor for thrombosis at the site and MI.[22] Lipid lowering, especially of LDL cholesterol, stabilizes the plaque and reduces the risk of MI. Lower lipid levels may also decrease local concentrations of modified lipoproteins that have proinflammatory effects.[24] Evaluation of recent cholesterol-lowering clinical trials in the aggregate suggests that with treatment, CVD mortality is decreased by 25% and MI by 50%, and that a drop of 44% in LDL cholesterol halts progression of coronary atherosclerosis. The percent drop in LDL correlates 1:1 with the decrease in coronary events.[25,26]

Atherosclerosis begins in childhood and is strongly associated with LDL cholesterol levels. A lipid-lowering diet applicable to the general population can be recommended for children over the age of two years.[27]

Some mutations that predispose to atherosclerosis by affecting lipid levels and lipoprotein concentrations and composition are listed in Table 51.3.

TABLE 51.3

Mutations that Predispose to Atherosclerosis

Heterozygous LPL gene mutation
(May be associated with pattern B LDL)
LDL subclass pattern B (small dense)
Increased apo C-II, C-III or A-II on TG-rich lipoproteins
(Delays clearance and increases atherogenic remnant particles)
? Subtle polymorphisms in ABC-1 gene contribute to reduction in HDL levels

Risk Factors for Atherosclerotic CVD

In addition to the composition and concentration of serum lipids and lipoproteins that have been associated with risk of CVD, i.e., hypercholesterolemia, high lp (a), other factors modify risk and may interact with the lipids. These risk factors include:[28,29]

TABLE 51.4

National Cholesterol Education Program Guidelines, Adult Treatment Panel III, mg/dl[a]

Factor	Optimal	Near/Above Optimal	Borderline High	High	Very High
LDL cholesterol	<100	100-129	130-159	160-189	>190
Non-HDL cholesterol	<130	<160	<190		
Total cholesterol	***Desirable*** <200		200-239	>240	
HDL cholesterol	***Low*** <40 men <50 women			>60	
Triglycerides	***Normal*** <150		150-199	200-499	>500

[a] Full report available on the NHLBI Web site: http//www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

Adapted from expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA* 285: 2486, 2001.

- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Obesity, especially truncal; weight gain 5 kg+ after age 18 (women)
- A sedentary lifestyle (physical inactivity)
- Gender (males at increased risk, females at lower risk)
- Increasing age
- Excessive alcohol
- (Low socioeconomic status)

Obviously, optimal prevention should aim at modifying any or all of these factors that can be manipulated.

NCEP and Dietary Guidelines

The National Cholesterol Education Program Adult Treatment Plan (NCEP ATP) recommends strategies for identifying and managing subjects at risk for CHD, either primary prevention in healthy people, or secondary prevention for those with CHD[5] (Table 51.4). Dietary and lifestyle modification is the first intervention, with lipid-lowering drugs added if target goals are not reached. Diet is more aggressive when lipid levels are higher. The more potent drug intervention is introduced earlier when lipid levels are very high, when there are multiple risk factors, or in patients who already have CVD (MI, unstable angina, stroke).

Diet modifications and the strategies proposed to lessen the risk of CVD and optimize the lipid and lipoprotein risk factors include:

- Lower total fat from the usual 35% in the American diet to 30% (low fat), or to <20% (very low fat)

TABLE 51.5

Selected Foods High in Monounsaturated Fatty Acids

Food	g/30 g Portion
Canola oil	16.4
Olive oil	20.0
High oleic safflower oil	20.4
High oleic sunflower oil	23.4
Hazelnuts	14.7
Macadamia nuts	16.5
Pistachios	10.1
Pecans	11.4

- Emphasize that the decrease in fat content should mainly reduce saturated fat (+trans) intake to <10%, or to <7% (Figure 51.1 shows the saturated fatty acid content of some common fats and oils)
- Decrease saturated fat similarly but not total fat by substituting monounsaturated fat for saturated fat (Mediterranean diet)
- Concentrate on the ratio of saturated, monounsaturated, and polyunsaturated fats to decrease saturates, increase polyunsaturates, and result in a l:l:l proportion of the three types of long-chain fatty acids
- Consume primarily a plant-based diet and limit meat and dairy products
- Increase whole grains and soluble fiber and limit refined sugars and foods with a high glycemic index. Dietary fiber has been estimated to lower LDL cholesterol from 3 to 10%.[1,2] Fiber sources include oats, barley, beans, psyllium, pectin, and guar gum. Gastrointestinal side effects are common. The AHA recommends a total dietary fiber intake of 25 to 30 g/day from food, about double the current intake in the U.S.
- Balance energy intake with energy expenditure to prevent or treat obesity which contributes to the atherogenic lipid pattern

Food sources of saturated fat, monounsaturated fat, and cholesterol are listed in Tables 51.5 through 51.7. The AHA Step 1 and Step 2 diets are described in Table 51.8.

Maximal dietary therapy typically reduced LDL cholesterol by 15 to 25 mg/dL, or about 5 to 10%.[5,30,31] Addition of a vigorous exercise program (10 miles/week of brisk walking or jogging) doubled LDL lowering in contrast to the Step 2 diet while preserving HDL cholesterol levels.[32]

Other proposals emphasize increasing the intake of fish and n-3 oils like flaxseed, in part because of their favorable action on eicosanoids.[33-35] Recently, commercial food products have been developed that add cholesterol-lowering plant sterols or their derivatives (sitosterol, sitostanol) to fats and salad dressings. Studies have shown a reduction in total cholesterol of 6 to 13% and a 9 to 20% reduction of LDL cholesterol with 3 g/day of stanol ester in margarine.[36] Other dietary components that lower cholesterol or reduce oxidized cholesterol include 25 g/day of soy protein, perhaps 35 mg/day of the soy isoflavones,[37] and antioxidant vitamins (E, C, and carotenoids).[38] The amount and type of dietary protein can affect levels of total and LDL cholesterol, i.e., animal proteins are hypercholesterolemic, and plant proteins are cholesterol-lowering. This may be attributable to the content of amino acids lysine and methionine in animal proteins, and arginine in plant proteins.[39] Some additional foods that may favorably influence CV risk and lipid/lipoprotein levels and atherogenicity include garlic (putative lipid lowering) or green tea (antioxidant).[40] In

TABLE 51.6

Dietary Sources of Cholesterol[a]

Food[b]	Cholesterol
Fruits, grains, vegetables	0 mg LOW
Scallops (cooked)	53 mg
Oysters (cooked)	45 mg
Clams (cooked)	65 mg
Fish, lean	65 mg
Chicken, turkey, light meat (without skin)	80 mg
Lobster	85 mg
Beef, lean	90 mg
Chicken, turkey, dark meat (without skin)	95 mg
Crab	100 mg
Shrimp	150 mg
Egg yolk	270 mg
Beef liver	440 mg
Beef kidney	700 mg

[a] From National Heart, Lung, and Blood Institute, NIH Publication No. 85-2606, January 1985.

[b] Seafood, fish, poultry, and meat are cooked, and portion size is about 3 1/2 oz.

TABLE 51.7

Selected Foods High in Saturated Fatty Acids

Food	g/100 g Edible Portion
Beef, roast, chuck, cooked	11.2
Beef, steak, prime rib, cooked	12.8
Ground beef, cooked	9.9
Bologna, beef, regular	13.8
Frankfurter, all beef, Kosher, regular	13.6
Frankfurter, regular, beef and pork	13.7
Salami, hard or dry, pork	16.0
Bacon, regular cut	23.7
Egg, yolk only, cooked	9.6
Cream, half-and-half	32.6
Cream, light, coffee cream	12.0
Parmesan cheese, dry	19.1
American cheese, processed	18.7
Cream cheese, Neufchatel	13.8
Cheddar cheese, natural	21.1
Cheddar cheese, low fat	10.9
Swiss cheese, natural	17.8
Monterey Jack cheese, natural	19.1
Mozzarella cheese, part skim milk	10.9
Brie cheese	15.3
American flavor cheese, low fat	9.8
Coconut oil	86.5
Palm oil	49.3
Palm kernel oil	71.5
Lard	39.2
Butter, regular, salted	50.5
Coconut, fresh	29.7

Adapted from Table A 21-a in *Modern Nutrition in Health and Disease*, Shils M.E., Olson J.A., Shike M., Ross, A.C., Eds, 9th ed, Williams & Wilkins, Baltimore, 1999, p A-121.

TABLE 51.8

Step I and Step II Diets

Nutrient	Step I Recommend	Step II Recommend
Total fat	<30 % of kcalories	<30% of kcalories
Saturated fat	8%-10% of kcalories	<7% of kcalories
Polyunsaturated fat	Up to 10% of kcalories	Up to 10% of kcalories
Monounsaturated fat	Up to 15% of kcalories	Up to 15% of kcalories
Carbohydrate	>55% of kcalories	>55% of kcalories
Protein	~15% of kcalories	~15% of kcalories
Cholesterol	<300 mg/day	<200 mg/day
Kcalories	Achieve, maintain desirable weight	Achieve, maintain desirable weight

addition to effects on blood lipids and LDL oxidation, these nutrients also may influence factors involved in vascular reactivity, such as nitric oxide and thrombus formation.[41] Chinese red yeast rice is another traditional herbal remedy that may be lipid lowering because of its content of statins and precursors.[42]

HDL cholesterol levels are raised by moderate intake of alcoholic beverages;[43] red wine, grapes, and grapeseed oil also may contain favorable antioxidants.[44] Short-term replacement of usual dietary oil with grapeseed oil in subjects with moderate elevations of LDL cholesterol and low HDL cholesterol resulted in a 7% lowering and 8% increment respectively (personal communication, D.T. Nash). Similar antioxidants are found in rice bran oil.[45] Ingestion of rice bran oil has resulted in decreases in LDL and increases in HDL comparable to effects of canola oil. Components of fats and oils that are not the fatty acids, but perhaps the tocotrienols, plant sterols, or flavonoids may be partially responsible for an antiatherogenic effect. As vascular biologists derive more scientific data, foods may influence atherogenesis by mechanisms less dependent on lipid/lipoprotein levels.

Nutritionists debate the importance of limiting dietary cholesterol intake (see Table 51.7 for sources), especially in relation to the established merit of decreased saturated fat. Examples of some menus and foods for lipid-lowering diets are provided in Table 51.9.

Diet Trials

There has been no large scale long-term trial of the effects of diet on serum lipids and lipoproteins, or most importantly on cardiovascular risk (morbidity, mortality). Dietary recommendations are derived by consensus and are modified as new scientific information is obtained, usually from epidemiologic or animal studies.

Some relevant diet and lifestyle trials include the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell Infarto [Miocardico]) trial that evaluated dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E in patients after MI.[33] Patients who took 1 g daily of n-3 PUFA (equivalent to about 100 g/day of fatty fish), but not those who took 300 mg/day of vitamin E, had significant benefit attributable to the 20 to 30% decrease in risk for overall and cardiovascular mortality. The fish oil capsule contained 375 mg DHA ethyl ester and 465 mg EPA ethyl ester. All of these study patients in Italy were also ingesting a Mediterranean diet and were taking cardiac medications. The investigators propose the benefit of n-3 PUFA on arrhythmogenesis over the 3 1/2 years of treatment. A similar protective effect of fatty fish in the secondary prevention of CHD (29% reduction in overall mortality) has been reported in the Diet and Reinfarction Trial

TABLE 51.9

Step I AHA — Meal Plan

Food	Total Kcal	Goals: Fat (g)	<30% Fat <10% Sat. Fat <300 mg Chol. Sat. Fat (g)	Chol. (mg)
Breakfast				
Cantaloupe, pieces, 1 c	56	0.4	0.1	0
Toast, whole wheat, 2 sl	130	2	0.4	0
Margarine, Promise Extra Lite soft, 1 Tb	50	5.6	0.9	0
Milk, 1% Fat, 8 fl. oz	102	2.6	1.6	10
Breakfast subtotal	338	10.6	3	10
Lunch				
Grilled chicken sandwich:				
Chicken breast w/o skin, boneless, 2 oz	95	2.1	0.6	47
Bun, 1	133	2.2	0.2	0
Mayonnaise, light, 1 Tb	50	5	1	0
Lettuce, 1 leaf	2	0	0	0
Carrot, raw, 1 med	31	0.1	0	0
Pretzels, 1 oz	108	1	0.2	0
Apple, raw w/peel, 1 med	81	0.5	0.1	0
Lunch subtotal	500	10.9	2.1	47
Dinner				
Grouper, baked, 4 oz	133	1.4	0.4	52
Rice, 1/2 c cooked	100	0.5	0.1	0
Green peas, 1/2 c	59	0.3	0.1	0
Margarine, Promise Extra Lite, soft, 1 Tb	50	5.6	0.9	0
Dinner roll, 1	85	2.1	0.5	0
Sherbert, 1/2 c	132	1.9	1.1	5
Pineapple, raw, pieces, 1/2 c	37	0.4	0	0
Dinner subtotal	596	12.2	3.1	57
Snacks				
Oatbran muffin, 1 med	154	4.2	0.5	0
Milk, 1%, 8 fl. oz	102	2.6	1.6	10
Snacks subtotal	256	6.8	2.1	10
Daily Total	1690	40.5	10.3	124
		22%	5%	
20% Protein				
58% Carbohydrate				

(DART).[46] The protective effect of fish also was reported in the observational Health Professionals Study[34] and the U.S. Physicians Health Study.[35] Diet recommendations developed and updated by the American Heart Association and the federal government will be modified in 2000.

Since TG levels are raised by diets high in carbohydrate, especially refined sugars, and also are sensitive to alcohol and excess kcalories, TG-lowering diets limit sugars, alcohol, and kcalories, and increase energy expenditure.[47]

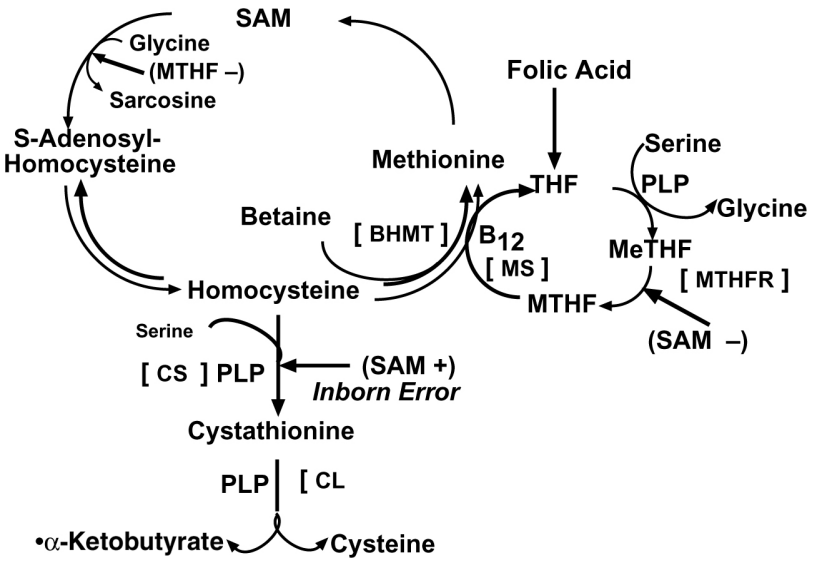

FIGURE 51.3
Homocysteine metabolism is regulated by enzymes dependent on folate and vitamins B_6 and B_{12}. + = activation, – = inhibition. Abbreviations: THF = tetrayhydrofolate; MeTHF = methylene tetrahydrofolate; MTHF = methyl-tetrahydrofolate; SAM = S-adenosylmethionine; PLP = pyridoxalphosphate (biological active form of vitamin B_6); CS + cystathionine synthase; CL = cystathionine lyase; MS = methionine synthase; MTHFR = methylene tetrahydrofolate reductase; BHMT = betaine homocysteine methyl transferase.

Other Nutritional Factors and CVD Risk

Homocysteine

An important nutritional risk factor for CVD is the blood homocysteine level, which increases in relation to deficient intake or metabolism of folate, and vitamins B_6 and B_{12} (see Figure 51.3). Elevated levels of homocysteine may be due to defects in enzymes catalyzing transsulfuration or remethylation pathways caused by drugs (methotrexate, phenytoin, theophylline, carbamazepine), deficiency of cofactors or cosubstrates (folate, B_{12}, B_6), impaired renal clearance, hypothyroidism, ovarian, pancreatic or breast cancer, or increasing age impairing vitamin absorption.

In recent years evidence has accumulated concerning the efficacy of folate (folic acid) in preventing heart disease. It is arguable whether folate from food sources (polyglutamates) is as effective as folic acid supplements (monoglutamate) in risk reduction. Folate bioavailability from food is 50%, whereas bioavailability from synthetic folic acid approaches 85% (1.7×).

Dietary folate or folic acid supplements may reduce the risk of cardiovascular disease in individuals with hyperhomocysteinemia resulting from genetic disorders of methionine metabolism and/or subclinical deficiencies of the B vitamins folate, B_{12}, and B_6. The genetic disorder is associated with premature cerebral, peripheral, and possibly coronary vascular disease. Homocyst(e)ine has been proposed as a risk factor for atherosclerotic CHD for more than 30 years.[48] Recent studies have concluded that homocyst(e)ine is an independent risk factor for coronary heart disease equivalent in importance to hyperlipidemia and

smoking.[49,50] It promotes prothrombotic changes in the vascular environment, arterial narrowing and endothelial cell toxicity, affects platelets and clotting control mechanisms, and stimulates smooth muscle cell proliferation. Investigators have linked hyperhomocysteinemia with premature vascular occlusive diseases: carotid occlusive disease, cerebrovascular disease, CHD, peripheral arterial occlusive disease, and veno-occlusive disease. Homocysteine may be synergistic for thromboembolic disease with other risk factors, e.g., diabetes mellitus, hyperlipidemia, smoking, deficient antithrombin II, protein C, protein S, or Factor V Leiden.

Normal fasting levels are slightly lower in women (6 to 10 μmol/L) than in men (8 to 12 μmol/L). Risk of CVD is significantly increased when homocysteine levels exceed the 95th percentile (~15.8 nmol/ml). There appears to be a graded effect of the homocysteine level on risk of CVD, and homocysteine level is a strong predictor of cardiovascular mortality. Elevated homocysteine may account for 10% of the attributable risk of CHD.

Importantly, elevated blood levels of homocysteine can be normalized with vitamin supplements (0.2 to 1 mg folic acid, with or without 0.4 mg cyanocobalamin, 10 mg pyridoxal), potentially decreasing cardiovascular risk. Results of such intervention have not yet been reported in any prospective large scale randomized placebo-controlled clinical prevention trial. Whether reduction of plasma homocysteine by diet and/or vitamin therapy will reduce CVD risk is not known. Thus, at the present time emphasis should be placed on meeting requirements for folate and vitamins B_6 and B_{12}. Screening for fasting plasma homocysteine may be indicated in patients with premature CVD or with a family history of premature CVD.

Vitamins and Minerals

Other nutrients that have been associated with CVD risk include niacin that is lipid lowering only in pharmacologic doses at minimum 50 times the daily requirement for the vitamin,[51] copper (cholesterol and LDL-lowering),[52] and zinc (increasing cholesterol and LDL).[53] Vitamin D may be atherogenic, and retinoids have been shown to raise TG levels.

The possible role of antioxidant vitamins (beta-carotene and carotenoids, vitamin C, vitamin E) and dietary supplements in reducing CVD risk is under investigation. At present the dose of vitamin E that may be effective and safe, and the minimum duration of treatment for protection are unknown. The Canadian Heart Outcome Prevention Evaluation Study in patients at high risk for CV events found that treatment with 400 IU daily of vitamin E for 4.5 years had no apparent effect on cardiovascular outcomes.[54]

CVD Risk Prevention by Non-Lifestyle Modifications

In recent years successful primary and secondary prevention as well as documented slowing of progression or regression of atherosclerotic lesions have been achieved by a variety of modalities established by sound randomized, often double-blind, intervention trials that have been carried out in the U.S. and abroad.[25] Most trials address the lipid risk factors by use of lipid-lowering medications or ileal bypass. Other modalities include LDL plasmapheresis.[55] Chelation therapy with EDTA is unorthodox therapy that is generally not recognized as effective or safe. Low-dose aspirin has been shown to reduce the risk of MI in men, and oral anticoagulants continue to be proposed to reduce the risk of MI and stroke.[41] Some studies have shown a reduction in the risk of stroke as well as cardiovascular events with the use of statin drugs.[56] Of interest and debate is whether the favorable

response is proportional to lowering of cholesterol and LDL, or raising of HDL, or whether a threshold is achieved for optimal prevention. In some trials, favorable results decreasing morbidity and mortality occurred too soon to expect them to be related to the degree of atherosclerosis but were more likely associated with stabilization of plaque. These trials also have demonstrated favorable effects in patients with lipid levels within the normal or average range, which is the level found in many patients with CHD. In fact, 20 to 25% of MIs occur in people with LDL cholesterol levels between 100 and 129 mg/dl.[8,57]

The first effective and safe cholesterol-lowering drugs were the bile acid-binding resins cholestyramine and colestipol. The efficacy of resins and the newer statin drugs (HMG Co A reductase inhibitors) and fibric acid derivatives on lipids and lipoproteins is depicted in Figure 52.9 of the Hyperlipidemia section. High-dose niacin therapy has also been administered for several decades, and is included as well. Often these drugs are used in combination to aggressively treat resistant forms of hyperlipidemia. Adverse effects of lipid-lowering drugs are observed on the gastrointestinal tract, liver, and muscles. The diet modifications initiated prior to drug therapy are usually continued during drug treatment in order to minimize the drug dosage, thereby decreasing adverse events and cost. If the diet, however, has been shown to be ineffective, then emphasis during drug treatment might better be placed on controlling body weight and eating a balanced diet.

Clinical Trials, Lifestyle

The studies of the effects on circulating lipids of changes in the content and composition of the diet are too numerous to cite in this section. Rather, more recent multicenter or large scale diet trials and three randomized controlled lifestyle intervention trials that address disease outcomes and/or angiographic endpoints over five years will be discussed.

The Lifestyle Heart Trial in patients with moderate to severe CHD demonstrated that intensive lifestyle changes lead to regression of coronary atherosclerosis.[58,59] The diet prescribed was a 10% fat, vegetarian diet and moderate aerobic exercise, stress management training, smoking cessation, and group support.

The St. Thomas' Atherosclerosis Regression Study (STARS) in patients with CHD included one arm of a 27% fat, weight reduction diet supervised by dietitians.[60] Dietary change retarded overall progression and induced regression of CHD.

The diet and exercise trial from Heidelberg in high-risk young men included rigorous exercise and a 20% fat diet.[28] A significant slowing of progression of coronary lesions was demonstrated.

Despite the demonstrated benefits of the Ornish regimen, other investigators have reported no benefit in lowering fat some 3 to 5% below the Step 1 diet in hypercholesterolemic men with and without hypertriglyceridemia followed for one year.[61] The Diet Effects on Lipoproteins and Thrombogenic Activity (DELTA) study at four sites included women, minorities, and older subjects in a comparison of eight weeks of the Step 1 diet (6% lower in total fat and saturated fat) and a 3% even lower-fat and saturated fatty acid diet in contrast to the average American diet (34% fat, 15% saturated fat).[31] Confirming other studies, the significant results were that with the Step 1 diet there was a drop in total (5%), LDL and HDL cholesterol (7%), apo B (–3%), and apo A-1 (5%), with a 9% increase in TG and 10% increase in lp (a). Further fat reduction resulted in a significant 4 to 5% fall in total, LDL, and HDL cholesterol and apo A-1, and a 7% increase in lp (a). The increase in negative risk factors lp (a) and TG raised questions about benefit in lowering CHD risk. The degree of lipid lowering with diet was similar to that observed

in the earlier diet-lovastatin study[30] and continue to be less than earlier predictions from Keys-Hegsted.[1]

Lessons from Large-Scale Clinical Trials of Lipid-Lowering Therapy[25,26,65]

Many studies using effective lipid-lowering drugs, primarily statins, in primary and secondary prevention of CHD have yielded an overwhelming body of evidence to confirm that significant risk reduction can be achieved in about five years of treatment. Interestingly, the benefit is beyond the change in plaque in angiographic studies, but extends to symptoms of unstable angina and precipitation of acute MI from plaque rupture. Thus, the conclusion is that lesions are stabilized as a result of effective lipid-lowering treatments that may affect a number of inflammatory and thrombotic mechanisms. More aggressive treatment with LDL cholesterol lowered to <100 mg/dl reduces progression still more. The implication is that all patients with CHD should be treated to lower their cholesterol. This recommendation also may apply to individuals with very high LDL (>220 mg/dl) or with LDL levels >160 mg/dl and other risk factors, especially diabetes mellitus.

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