Adopted: 11/00
Revised: 09/04
Focused revision*: 07/06
To be reviewed: 09/07
Reformatted: 02/06

DYSLIPIDEMIA

Primary author: Jim Gerber, MS, DC, DACBN

Editor: Ronald LeFebvre, DC

Editorial Assistant: Anne Byrer
Original Design: Bobbie Savitz

Clinical Standards, Protocols, and Education (CSPE) Committee
Owen Conway, DC; Daniel DeLapp, DC, DABCO, ND, LAc; Lorraine Ginter, DC; Ronald LeFebvre, DC; Karen E. Petzing, DC; Ravid Raphael, DC, DABCO; Anita Roberts, DC; Cherye Roche DC

The WSCC Care Pathways provide a standardized context for clinical decision making as well as a variety of possible interventions. These pathways are not intended to replace the clinical judgment of the individual practitioner. A practitioner may vary from these guidelines, if in his or her judgment, variance is warranted to meet the healthcare needs of the patient and the variance remains within generally accepted standards of practice.

WSCC pathways are intended for use within our clinic system. They may be useful as a seed for regional guidelines or guidelines with wider application, but caution must be exercised. The following limitations would have to be addressed. 1) The literature searches employed would need to be more exhaustive; 2) inclusion criteria for published studies would need to be more stringent; 3) a wider pool of subject-matter experts would need to be tapped; 4) the participants of the consensus panel would need to be drawn from a broader cross-section of the profession and perhaps other healthcare providers as well. Although individual procedures and decision-making points within this care pathway may have established validity or reliability, the pathway as a whole is untested.

ICD-9 CODES

272.4 Hyperlipidemia

THE SCOPE OF THIS CARE PATHWAY INCLUDES SCREENING THE ADULT PATIENT POPULATION PRESENTING TO THE WSCC CLINIC SYSTEM AS WELL AS FOLLOW-UP AND INTERVENTION FOR ADULT PATIENTS WITH A VARIETY OF PROFILES OF DYSLIPIDEMIA. THE INTERPRETATION AND FOLLOW-UP FOR ATYPICALLY LOW TOTAL CHOLESTEROL LEVELS WILL NOT BE CONSIDERED.

On using this document…

Treatment interventions are divided into four protocols, based on the patient's LDL, HDL, and triglyceride levels. To aid the reader in locating this information, the footers in the management section indicate which lipid profile is covered on those pages. Treatment protocols 1-3 each also have a more aggressive version marked with a plus. For example, protocol 1+ is a more aggressive treatment approach than protocol 1 for the same dyslipidemia.

Since many of the components of treatment are the same for the various dyslipidemias, the protocols are sometimes purposely redundant and at other times refer the reader to a previous section. Syndrome X and treatment with niacin are two topics that are discussed in the appendices.

Search Strategy

An expert panel review and consensus report* and its recent update** were used to obtain background information and references on etiology, incidence, diagnosis and prognosis. The same report also provided an evaluation and conservative treatment plan that forms the backbone of this care pathway. Recent review articles and newer trials of specific conservative interventions were identified though Medline searches. These articles provided reference lists whereby additional studies could be accessed as needed. Additional conservative therapies and their references were obtained from a commercial database*** on complimentary and alternative medicine.

Focused Revision:

***** National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high cholesterol in adults (adult Treatment Panel II). National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 93-3095, September 1993.
****** National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). National Institutes Of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 01-3670, May 2001.
******* Healthnotes Online, version 6 and 7. Portland, OR: Healthnotes, Inc., 2000/2001

TABLE OF CONTENTS

NOTES

BACKGROUND

Dyslipidemia is a group of disorders of lipoprotein metabolism regarded as primary risk factors for atherosclerotic disease, especially coronary heart disease.

The components of dyslipidemia may include elevated LDL cholesterol, elevated triglycerides, and/or low HDL (protective) cholesterol. These components may occur singly or, more often, in clusters of two or all three.

These varied presentations of dyslipidemia may respond differently to the numerous therapies that may be considered for treating dyslipidemia. Therefore, this document will address the more common presentations separately. In this manner, interventions will be most effectively targeted to each patient for optimum outcome.

Pathophysiology

Dyslipidemia may have pathophysiological components that are genetic, environ-mental, or both.[1] Genetic errors of cholesterol synthesis regulation, hepatic cholesterol metabolism, cell membrane receptor function, and others are recognized, yet poorly understood. Lifestyle factors including dietary habits and activity levels are also well recognized, and their modification often constitutes initial conservative interventions in the treatment of dyslipidemia.

This benefit extends even to patients with existing coronary heart disease (CHD), where reduced recurrences of both CHD events and/or mortality have been demonstrated.[2,3]

Epidemiology

Dyslipidemia is one of the more common health disorders. About 45% of adults in the US have some degree of hyper-cholesterolemia (total cholesterol above 200, LDL cholesterol above 130).[4] Dyslipidemia involving elevated triglycerides and/or low HDL may coexist with hypercholesterolemia, or may constitute isolated syndromes in an additional number of people at high risk for premature coronary artery disease.[5]

Recently recognized is the existence of a syndrome variously referred to as atherogenic dyslipidemia, the metabolic syndrome, or syndrome X.[6-8] This syndrome, considered a significant risk factor for atherosclerotic disease, features greater deviations in triglyceride and HDL cholesterol compared to LDL cholesterol elevation. The prevalence of syndrome X has not been accurately determined at this time.

Natural History

Elevated serum LDL cholesterol or total cholesterol has a direct effect on the incidence of and mortality from coronary heart disease.[9-12] Further, the reduction of cholesterol levels, especially LDL cholesterol, is effective for reducing CHD as well as mortality, whether such cholesterol reduction is accomplished with diet, drugs, or both.[13-16]

Other lipid abnormalities, especially low HDL cholesterol and elevated serum triglycerides have been shown to contribute to CHD risk.[17] Every 1 mg/dL decrease in HDL cholesterol appears to increase CHD risk by 2-3 percent.[18]

A low HDL cholesterol (<40 mg/dL) is considered an independent risk factor for

CHD, while a high HDL level (>60 mg/dL) is considered a negative risk factor.[19,20] That is, a high HDL level appears to mitigate against the risk conferred by other risk factors (smoking, hypertension, etc.).

The direct relationship of elevated triglycerides and CHD is less clear, since it often coexists with elevated cholesterol and low HDL,[21-23] yet a recent meta-analysis has suggested a clear independent CHD risk from elevated triglycerides.[24] **Note:** Triglyceride reduction should always be addressed when it is part of a dyslipidemia syndrome that increases CHD risk.[17]

Risk Factors

Risk for dyslipidemia is increased by a variety of factors,[25] including family history, aging, weight gain, physical inactivity, menopause, insulin-resistance, diseases such as type 2 diabetes mellitus and hypothyroidism, and diets high in saturated fats, trans fats, and cholesterol. Cigarette smoking is another risk factor that contributes to low HDL cholesterol.

EVALUATION

Evaluation strategy shall conform to the recommendations of the National Cholesterol Education Program (NCEP) according to the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III),[20] with modifications based on subsequent consensus reports.[26 27]

Evaluation Steps

1. Determine serum lipid levels, preferably full lipoprotein analysis after a 12-hour fast.
2. Evaluate history for primary coronary heart disease risk factors.
3. Determine 10-year risk assessment for patients with two or more primary risk factors.
4. Determine required interventions for LDL cholesterol from Table I.
5. Evaluate for the presence of the metabolic ("insulin-resistance") syndrome.

Screening

STEP 1: Determine serum lipid levels, preferably full lipoprotein analysis after a 12-hour fast.

All adults 20 years of age and over should have a fasting lipoprotein profile, including total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride, measured at least once every five years.

Testing patients with acute illness or a recent history of major trauma, surgery, acute infection, a change in usual diet, weight loss, or pregnancy should be postponed because results may not reflect usual levels.

If only a non-fasting blood specimen is feasible, then only the values for total cholesterol and HDL will be valid. These values may be useful for determining whether a full lipoprotein analysis is essential.

A complete panel is mandatory for adults with evidence of coronary heart disease (CHD), or CHD risk equivalents that include other clinical atherosclerotic diseases (cerebrovascular disease, vascular claudication, etc.)[28,29] or diabetes mellitus.

For adults receiving the limited screening of total and HDL cholesterol, desirable values shall be considered as total cholesterol levels below 200 mg/dL and HDL cholesterol levels at or above 40 mg/dL. Patients with values above desirable levels must be strongly encouraged to return for a complete fasting lipoprotein profile.

Lipoprotein analysis includes measurement of fasting levels of total cholesterol, total triglyceride, and HDL cholesterol. Calculation of LDL cholesterol may then be done with the formula LDL cholesterol = total cholesterol - HDL cholesterol - (triglyceride/5), so long as triglycerides are below 400 mg/dL. Patients with triglyceride levels above 400 mg/dL should have lipoprotein analysis performed by ultracentrifugation.

Level of LDL	Classification
≥190 mg/dL	very high
160-189 mg/dL	high
130-159 mg/dL	borderline-high
100-129 mg/dL	near/above optimal
<100 mg/dL	optimal

Patients with optimal values are more likely to maintain those values as they age if they adopt a prudent diet. Therefore, they shall be given general educational materials about dietary modification, physical activity, and other risk-reduction activities and advised to have a repeat total cholesterol and HDL cholesterol analysis in 5 years.

STEP 2: Evaluate history for primary coronary heart disease risk factors.

These primary risk factors, according to NCEP guidelines,[20] include the following:

- Age, ≥45 years (men) and ≥ 55 years or postmenopausal in women.[30,31]
- Family history of premature CHD (definite myocardial infarction or sudden death), before age 55 in a first-degree male relative or before age 65 in a first-degree female relative.[32,33]
- Cigarette smoking.[34]
- Hypertension, 140/90 mmHg and above or taking antihypertensive medication.[35]

- A high level of HDL cholesterol (>60 mg/dL) is called a "negative" risk factor; if a patient's HDL cholesterol is high, one risk factor is subtracted.

Obesity and physical inactivity are NOT included as primary risk factors, though it is often important to treat these as targets of intervention.[36-39] For example, when excess fat is distributed primarily to the abdominal region, there appears to be a much greater risk of CHD.[40-42]

STEP 3: Determine 10-year risk assessment for patients with two or more primary risk factors.

Short-term CHD risk is an important criterion for identifying patients needing more intensive LDL-lowering therapy. This risk calculation is based on the database from the ongoing Framingham Heart Study.[43] Using age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking, risk factor points are counted and totaled. The result is converted to a risk prediction for myocardial infarction and/or CHD death within the subsequent 10 years. See Appendix I: 10-year risk assessment worksheet.

STEP 4: Determine required interventions for LDL cholesterol from Table I.

Treatment decisions are made based upon LDL cholesterol levels, evidence of established CHD and CHD risk equivalents, 10-year risk estimates, and/or presence of primary CHD risk factors. The following table shows LDL cutoff points for two levels of intervention according to severity of overall risk. In 2004, some of these cutoffs were modified to reflect new findings suggesting that further lowering of LDL levels below 100 mg/dL is beneficial for high-risk individuals.[44]

Table I. LDL Cholesterol and CHD Risk Levels Requiring Intervention[20]

Overall Risk	Conservative Intervention (See Protocol 1)	Aggressive Intervention* (See Protocol 1+)
0 or 1 Primary CHD Risk Factor	160 mg/dL	190 mg/dL
2 or more Primary CHD Risk Factors and 10 year risk <20%	100 mg/dL (10-year risk = 10-20%) 130 mg/dL (10-year risk <10%)	130 mg/dL (10-year risk =10-20%) 160 mg/dL (10-year risk <10%)
Existing Clinical Atherosclerotic Disease, Diabetes, or 10-year risk >20%**	70-100 mg/dL***	100-130 mg/dL***

*Aggressive intervention employs therapies that may increase side effects or treatment costs.
** Existing clinical atherosclerotic disease includes coronary heart disease, symptomatic carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm.
*** Lower threshold applies to patients at very high risk (i.e. clinical atherosclerotic disease coexisting with diabetes, metabolic syndrome, 10-year risk over 20%, or severe uncontrolled risk factors such as smoking). Very high-risk patients also require intervention if non-HDL cholesterol (total cholesterol minus HDL) is 100 mg/dL or greater.

When patients already have acceptable LDL cholesterol levels (below the cutoffs listed in Table I), some preventive advice is still desirable to ensure maintenance of low LDL cholesterol. Instruction on diet and physical activity should be individualized, other CHD risk factors and the metabolic syndrome, if present, should be addressed, and lipoprotein analysis repeated annually in these patients. If LDL is very low (below 100 mg/dL) in a low-risk patient (no clinical disease and less than 2 risk factors), re-testing may be postponed for 5 years.

If LDL is not at desirable levels for the patient's risk level, and this is confirmed by at least one additional measurement within eight weeks, conservative or aggressive intervention should be undertaken as described in the Management section.

STEP 5: Evaluate for the presence of the metabolic ("insulin-resistance") syndrome.

The presence of non-diabetic insulin-resistance and its metabolic consequences is suspected when any three of the following are present:

- Abdominal obesity (waist circumference > 37 in/94 cm in men, > 31 in/80 cm cm in women)
- Triglyceride levels ≥150 mg/dL or medication-treated (e.g. fibrates, nicotinic acid)
- HDL cholesterol levels <40 mg/dL in men, <50 mg/dL in women or medication-treated (e.g. fibrates, nicotinic acid)
- Blood pressure ≥130/85 mmHg or medication-treated
- Fasting glucose ≥110 mg/dL, or medication-treated

Serum triglycerides below 150 mg/dL are considered desirable by the NCEP,[20] although when other dyslipidemias or coronary artery disease exist, recent evidence indicates optimal triglyceride levels should be below 100 mg/dL.[45] HDL cholesterol less than 40 mg/dL may also be a significant risk factor for cardiovascular disease.[46] The components of the metabolic syndrome may respond to the interventions as outlined in Protocol 2.

HISTORY AND PHYSICAL EXAMINATION

Evaluate the patient clinically, especially for familial and secondary lipid disorders.[47] This clinical evaluation should include a complete history, physical examination, and basic laboratory tests (see Appendix II). The aim is to determine whether a high LDL cholesterol or triglyceride level is secondary to another disease or a drug, and whether a familial lipoprotein disorder is present.

The most common secondary causes for elevated LDL are the following:

- Diabetes mellitus
- Hypothyroidism
- Nephrotic syndrome
- Chronic renal failure
- Obstructive liver disease
- Drug side effects from progestins, corticosteroids, anabolic steroids, thiazide diuretics, etc.

The most common secondary causes for elevated triglycerides are the following:

- Diabetes mellitus (this is the most common cause of isolated elevation of triglycerides)
- Alcohol abuse (this is the second most common cause of isolated elevation of triglycerides)[48]
- Side effects of medications (e.g. thiazide diuretics)
- Kidney disease
- Pancreatic disorders

The most common secondary causes for low HDL are the following:

- Diabetes mellitus
- Syndrome X, or the atherogenic insulin resistance syndrome (see discussion in Protocol 2).
- Drug effects (beta-adrenergic blocking agents [beta-blockers], loop diuretics, anabolic steroids, and progestational agents).

Genetic disorders of lipoprotein metabolism are present in about 2.5% of the general population.[4] They are characterized by a strong family history of hyperlipidemia or early CHD death, severe elevations of LDL (>220 mg/dL) and/or triglycerides (>400 mg/dL), and sometimes the presence of subcutaneous or tendon xanthomas (cholesterol deposits).

These disorders will often require aggressive intervention, and family members should be screened to detect other candidates for intervention.

Physical examination should include some or all of the following components:

- Vitals
- Hip-waist ratio
- Inspection (to include hair, nails, feet, head, neck, and extremities)
- Ophthalmoscopic exam
- Thyroid palpation
- Heart auscultation
- Abdominal palpation
- Sensory and DTR testing (upper and lower extremity)

Special Considerations

Guidelines have been published for the assessment and management of dyslipidemias in children and adolescents.[49] However, these guidelines have been criticized and their implementation at this time may be premature.[50 51] A thorough discussion of these guidelines is beyond the scope of this document.

MANAGEMENT

Specific Therapeutic Objectives

- The primary therapeutic objective is to bring serum LDL lipoprotein levels to below cutoff points determined by the patient's risk severity as shown in Table I on Page 8.
- Addressing elevated triglycerides and low HDL is also desirable.
- Other CHD risk factors should be addressed as necessary to lower overall atherosclerotic disease risk. This is specifically indicated when the presence of the metabolic syndrome is suspected.

These therapeutic objectives are presented on the following pages as

PROTOCOL 1: Conservative Intervention for Elevated LDL with or without elevated triglycerides or low HDL (P. 11)

PROTOCOL 1+: Aggressive intervention (P. 20)

PROTOCOL 2: Suspected Metabolic (Insulin Resistance) Syndrome (P. 21)

ADDENDUM: Isolated elevations of triglycerides and/or HDL cholesterol (P. 24)

PROTOCOL 1: Conservative Intervention for Elevated LDL with or without elevated triglycerides or low HDL

Elevated LDL and low HDL are defined in the evaluation section, Page 7. An elevated triglyceride level is defined by the National Cholesterol Education Program as greater than 200 mg/dL.[4] However, recent evidence suggests that coronary artery disease risk increases between 100-200 mg/dL,[45 52] and intervention may be prudent with thresholds at the lower end of this range.

For the purposes of this document, elevated triglycerides shall be defined as greater than 150 mg/dL when other dyslipidemias or coronary artery disease exist.[7] Lowering levels to below 100 mg/dL may represent an optimal target.

Triglyceride levels above 1000 mg/dL greatly increase the risk of acute pancreatitis and generally require drug therapy along with non-pharmacologic intervention.

TREATMENT SUMMARY – Protocol 1

STEP 1: Further clinical evaluations

STEP 2: Therapeutic Lifestyle Changes and Other Interventions

- Reduce saturated fat to less than 7% of dietary calories.
- Reduce dietary cholesterol to less than 200 mg/day.
- Reduce trans fats as much as possible.
- Use whole grains, fruits & vegetables as much as possible and at least 20 grams of dietary fiber per day.
- Increase aerobic physical activity up to three times weekly or more.
- Reduce weight.
- Modify diet to include additional fiber, soy, fish, and reduced alcohol.
- Use appropriate nutritional supplements.
- Treat non-lipid CHD risk factors, if indicated.

STEP 3: Monitor treatment

- Monitor lipid levels and patient compliance.

STEP 1: Further Clinical Evaluations

Review the history, physical examination, and laboratory examination for evidence of familial dyslipidemias, and for the presence of secondary lipid disorders and drug-related effects on serum lipids.

Conduct additional tests as required to rule out the following secondary causes of elevated LDL, triglycerides and/or low HDL:

- Diabetes mellitus
- Atherogenic insulin resistance syndrome
- Hypothyroidism
- Nephrotic syndrome
- Chronic renal failure
- Other kidney diseases
- Obstructive liver disease
- Pancreatic disorders
- Alcohol abuse

Review current medications for known dyslipidemic side effects.

STEP 2: Therapeutic Lifestyle Changes and Other Interventions

Therapeutic Lifestyle Changes

These changes are designed primarily to reduce LDL cholesterol, although beneficial effects on triglycerides, HDL cholesterol, and other CHD risk factors may also be realized.

- Reduce saturated fat to less than 7% of dietary calories.
- Reduce dietary cholesterol to less than 200 mg/day.
- Reduce trans fats as much as possible.
- Use whole grains, fruits & vegetables as much as possible and at least 20 grams of dietary fiber per day.
- Increase aerobic physical activity up to three times weekly or more.
- Reduce weight.

Dietary Fat Modification

Reducing dietary saturated fat and cholesterol will be accomplished by reducing consumption of the following foods:

- Milk fat (milk, cream, butter, cheese)
- Beef, pork, lamb, poultry fat
- Tropical oils (coconut, palm and palm kernel)
- Eggs and organ meats
- Foods high in partially hydrogenated oils: shortenings, some margarine, many commercially fried or baked foods and snacks, some candies and dessert foods (see Appendix IV and VI).

If weight loss is not desired, these foods may be replaced with foods high in complex carbohydrates and/or non-hydrogenated unsaturated fats with similar results.[53,54] See Appendices II-VIII for patient education tools to support these interventions.

If the metabolic ("insulin-resistance") syndrome is suspected, complex carbohydrate choices should be made with regard to the glycemic index of these foods. (See Appendix VIII.)

Rationale for Dietary Fat Modification

Reduction of dietary saturated fat and cholesterol is effective for treatment of elevated LDL cholesterol,[55 56] though it appears that the reduction of saturated fat is more important than that of dietary cholesterol.[57,58] It is important to also reduce *trans* unsaturated fats, found in foods that are high in partially hydrogenated oils, since these fats are also related to elevated LDL,[59-62] whereas other unsaturated fats are not.[53, 63] The following will often result in other benefits associated with CHD risk reduction: [64-66]

- Weight reduction,[67] which will improve lipoprotein pattern,[68] lower blood pressure,[69] and improve glucose tolerance.[70]
- Increased consumption of fruits, vegetables, grain products, and fish.
- Reduced oxidation of LDL cholesterol.[71]

Modifications to the fat content of the diet described in the "Therapeutic Lifestyle Changes" section are similar to the former NCEP Step 2 diet recommended in previous NCEP guidelines. Table II shows average percentage changes in lipid levels achieved by Step 2 diets in free-living individuals, according to a recent meta-analysis.[72]

Greater or lesser responsiveness is common, and varies with age,[73] initial serum cholesterol levels,[74] the nature of the baseline diet,[75] compliance with the new diet[76-79] and inherent biological differences.[80,81]

Table II. Percent Changes in Serum Lipid Levels in Free-Living Subjects on NCEP Step 2 Diets.[72]

Lipid Level	Reduction with Step 2 Diet
Total cholesterol (TC)	-13%
LDL	-16%
Triglyceride	-8%
HDL	-7%
TC/HDL Ratio	-7%

The Controversy Surrounding Extremely Low Fat Diets

The above finding that Step 2 type diets (which are similar to dietary recommendations in the Therapeutic Lifestyle Changes) have had a negative effect on HDL and produced no additional lowering of triglyceride levels is of concern when treating patients with combined dyslipidemias. Some investigators have suggested that diet-induced changes in HDL levels are adaptive and probably do not influence cardiovascular risk.[82,83] Nonetheless, some studies on dyslipidemic subjects,[84-87] though not all,[88] have found these effects of low fat diets are reduced or absent if weight loss is also achieved. Some reviewers have suggested that increased consumption of carbohydrates in place of dietary fat may be responsible for the dyslipidemic effects of low fat diets.[89]

However, one study found this to be true only when dietary changes were sudden and substantial,[90] and another found only hypercholesterolemic subjects, not those with combined dyslipidemias, were sensitive to changes in dietary carbohydrate.[91]

One solution to this dilemma would be to allow substitution of non-hydrogenated unsaturated fats for saturated fat in a lipid-lowering diet, which may not achieve the total dietary fat reductions recommended by the NCEP.[4] This proposal is controversial. Reduction of all fats has been advocated in many public health messages as a means for preventing CHD as well as other diseases.

These same messages recommend increased intake of plant foods, which has an overall effect of increasing dietary carbohydrate.[92] However, non-hydrogenated monounsaturated and polyunsaturated fatty acids (PUFA) are known to lower total and LDL cholesterol levels without substantial negative effects on triglycerides or HDL.[53,93-95] In addition, diets that include nuts that are high in these fats have been recently shown to have beneficial effects on serum lipids and cardiovascular risk.[96]

Lipid-lowering diets could allow the incorporation of appropriate vegetable oils or nuts and seeds containing these oils into the daily diet. This may have advantages over substituting complex carbohydrates for saturated fat in diets for some people with combined dyslipidemias, as long as reduced total energy intake is not a priority.[89] Preliminary research suggests that substitution of lean protein for dietary carbohydrate in a low fat diet is another feasible option that may also lower levels of undesirable blood lipids while increasing HDL.[97-99]

A program combining extreme restriction of dietary fat, sugar, and alcohol along with aerobic exercise, yoga and stress management has been shown effective in reducing LDL as well as many symptoms and signs of existing CHD.[3] However, similarly extreme dietary fat restrictions have been shown to add no more benefit over traditional lipid-lowering diets.[88,100]

Lifestyle Interventions

A program of regular aerobic exercise should be prescribed, typically defined as at least 20 minutes of exercise sufficient to elevate heart rate to at least 60% of maximum (maximum = 220-age) repeated three times weekly. **Cautions:** See Appendix X for guidelines on pre-exercise evaluation.

Weight reduction in the overweight may occur naturally from a lower fat diet combined with increased physical activity. Rapid weight-loss programs should be avoided since they rarely result in long-term weight control.

For purposes of compliance and preserving patient morale, those who need to stop smoking as well as lose weight may find it a less overwhelming task to try smoking cessation first, which will likely have the bigger impact on heart disease risk.

Rationale for Lifestyle Interventions

Increased physical activity will not always affect LDL levels specifically, but it should benefit triglycerides and HDL,[37,101] especially at higher exercise intensities,[102] and will result in other benefits associated with CHD risk reduction.[38] One recent study found a diet similar to that recommended in Therapeutic Lifestyle Changes did not lower elevated LDL unless it was combined with aerobic exercise.[103]

Weight reduction has benefits relevant to many heart disease risk factors. When the dietary changes outlined above are applied along with beginning a regular exercise program, weight loss usually results, which appears to contribute to reductions in LDL cholesterol,[104-106] triglycerides,[37,104,107] as well as increased HDL.[104,108]

Additional Dietary Interventions

Specific foods or food components may be emphasized to take advantage of their ability to help lower serum total and LDL cholesterol while substituting for high-fat foods as well.

- Dietary fiber, several daily servings of fruit, vegetables and whole-grain products. High-fiber food supplements can be incorporated into the diet by using breakfast cereals and other foods that contain oat bran, or are fortified with psyllium, or by adding to meals several grams daily of flaxseed, psyllium seed husk, glucomannan, or mixed soluble fiber supplements. See Appendix VII for dietary soluble fiber recommendations. **Cautions:** One full glass of plain water should be consumed immediately after each use of a fiber supplement, and daily water intake should total 8 cups per day when fiber supplements are used. Dietary fiber is rarely contraindicated, except in cases of bowel obstruction.

- Plant stanol containing margarines, providing 2 grams/day stanols. **Cautions:** *None.*

- Soybean products, 2 or more servings/day or soy protein supplement, 30-45 grams/day. **Cautions:** *May occasionally trigger severe allergic reactions.*

- Fish up to 2-3 times/week. **Cautions:** *May occasionally trigger severe allergic reactions.*

- Alcohol may be permitted, when serum triglycerides are normal, up to two drinks per day (one drink equals 12 oz. beer, 4 oz. wine, and1 oz. distilled spirits). When elevated serum triglycerides are present, alcohol intake should be restricted to no more than two drinks per week. **Cautions:** *Should not be recommended to abstainers or patients with alcohol-related health risks.*

Rationale for Additional Dietary Interventions

Dietary fiber, especially soluble fiber,[109-111] can produce a decrease in total cholesterol of about 10%, though sometimes the effects of this intervention alone may be more modest.[112] Supplemental flaxseed (15-50 g/day),[113-115] psyllium seed husk (10 g/d or 3 tsp/day), [116-121] breakfast cereals enriched with psyllium or pectin (1 serving/day),[122,123] glucomannan (4-13 g/day),[124,125,126,127] or mixed soluble fiber supplements (15-20 g/day) [128,129] have significantly reduced total and LDL cholesterol.

Plant stanol containing margarine has recently been introduced into the U.S. marketplace. Plant stanols belong to the phytosterol family of molecules that resemble cholesterol and occur in the typical Western diet at levels of 200-400 mg/day. Phytosterols are capable of inhibiting the absorption of dietary cholesterol[130] and, in quantities of 1.5-3.3 grams/day supplied to adults in margarine or other foods, have been shown to lower LDL cholesterol from 8-20%.[131-135] However, plant stanols were not effective in one study in which dietary cholesterol intake was kept below 200 mg/day.[136] Effects on HDL and triglycerides are inconsistent, but some studies report average HDL increases as high as 11% and average triglyceride reductions as much as 12%.[193]

Soybeans and soy protein,[137-140] which in generous amounts (31-47 grams protein/day), lowers serum cholesterol an average of 9%, LDL 12.9% and serum triglycerides by an average of 10.5%.

Increased consumption of fish has been shown to raise HDL levels,[141] and fish consumption is associated with reduced CHD risk.[142,143] Fish oil supplementation is discussed below.

Moderate alcohol intake increases HDL and provides other cardiovascular benefits at levels of two drinks or less per day.[144] However, alcohol raises triglycerides in many individuals.[145,146] Additionally, it is not wise to recommend alcohol to non-drinkers, due to the possibility of alcoholic dependency, or to women at high risk of breast cancer.[147]

Additional Lifestyle Interventions

- Smoking cessation, especially when HDL cholesterol is low.

Rationale for Additional Lifestyle Interventions

Cigarette smoking significantly raises overall risk of CHD,[148] and smoking cessation lowers these risks.[149,150] One mechanism for the deleterious effects of smoking is a reduction of cardioprotective HDL cholesterol.[151]

Nutritional Supplements

Certain nutrition and botanical supplements have been shown effective for treatment of elevated serum cholesterol, triglycerides, and/or low HDL. See the rationale section and the Treatment Summary for help deciding whether some or all are appropriate for each individual case. See Appendix IX for relative costs of dyslipidemia supplements.

- Powdered garlic supplement standardized to provide at least 5,000 mcg/day allicin. **Cautions:** *Contra-indicated prior to elective surgery.*

- Inositol hexaniacinate, 1600-4000 mg/day of the total compound in divided doses including a nighttime dose. **Cautions:** *Mild cutaneous vasodilation side effects may occur.*
- Fish oil supplements, containing 3000-7000 mg/day total omega-3 fatty acids. **Cautions:** *May raise LDL levels in some patients and raise blood sugar in some diabetics; may cause nosebleeds in some patients.*
- Phytosterols (e.g. beta-sitosterol), 1.5-3.3 grams/day supplied by supplement or in commercially available margarine. **Cautions:** *None.*
- Chromium, 200 mcg/day. **Cautions:** *Supplements in excess of 500 mcg/day may be unsafe for long-term use.*
- Vitamin C, 500 mg/day, if marginal vitamin C status is suspected. **Cautions:** *None.*

The following supplements are recently available but more costly, and may be considered as second-line choices.

- Pantethine, 300 mg three times daily. **Cautions:** *None.*
- Guggul, 75-100 mg guggulsterones per day or 500 mg of the total extract three times daily. **Cautions:** *Mild abdominal discomfort has been reported with long-term use. Guggul should be used with caution by persons with liver disease and in cases of inflammatory bowel disease and diarrhea.*
- Policosanol, 10-20 mg daily. **Cautions:** *None.*

Rationale for Nutritional Supplements

Garlic powder, standardized for 1.3% allicin, at 900 mg/day has reduced serum total cholesterol from 9-12% in many controlled trials,[152-154] though several recent studies have shown no benefit.[155-159] LDL cholesterol has not been measured in many of these trials, but reduction of 11% has been reported.[160] Triglyceride levels have been lowered by 8-27% in several studies.[161-163] Other studies have reported no benefit.[155-158]

Garlic supplementation provides additional benefits for cardiovascular disease prevention, including lowered blood pressure and reduced platelet aggregation.[164,165] Garlic tablets are available with enteric-coating, which minimizes odor.

Note: Patients should be advised to discontinue garlic before elective surgery due to the risk of increased post-operative bleeding.[166,167]

Inositol hexaniacinate. Niacin supplements in crystalline or sustained-release form are not appropriate for conservative intervention due to the high probability of side effects (see under aggressive intervention). However, inositol hexaniacinate has been used successfully in the treatment of vascular diseases with milder to no significant side effects,[168-177] and is considered safer to use than niacin by alternative health practitioners.[178] The hypolipidemic effect of this form of niacin has only received brief mention in the scientific literature, however.[179-184]

Therapeutic doses range from 1600-4000 mg/day of the total compound in divided doses. Reductions of total cholesterol by 5-25% and of serum triglycerides by 15-27% have been reported. A nighttime dose may be effective in reducing nocturnal lipolysis (release of fat from adipose cells during sleep) which, in turn, may further help in reducing serum triglycerides.[185]

Fish oil supplements, containing 3000-7000 mg/day total omega-3 fatty acids, have lowered serum triglycerides by 25-30% in several controlled studies.[186,187] One of these omega-3 fatty acids, docosahexaenoic acid (DHA), given alone at 1.25 grams/day reduced triglycerides 17-21% in one controlled study.[188] Fish oils have little effect on LDL or HDL cholesterol.

Flaxseed oil, a rich source of another omega-3 fatty acid, alpha-linolenic acid, is not as effective in lowering serum triglycerides. In fact, its effects are not different from those of other vegetable oils.[187] HDL cholesterol levels are not significantly affected, but LDL cholesterol tends to rise 5-10% with fish oil therapy,[187] although this effect may be avoided with a increased soluble fiber intake[189] or garlic supplementation.[190]

While older studies reported that fish oil supplementation in diabetics could worsen glucose tolerance,[191] a recent meta-analysis could find no long-term effects of fish oil on glycemic control in diabetes.[192]

Phytosterols are plant molecules resembling cholesterol that occur in the typical Western diet at levels of 200-400 mg/day. Plant stanols are semisynthetic phytosterols used in certain lipid-lowering margarines (see Additional Dietary Interventions above). Natural phytosterols include beta-sitosterol, and are also capable of inhibiting the absorption of dietary cholesterol.[193] These are available in supplements that, in quantities of 1.5-3.3 grams/day, have been shown to lower LDL cholesterol from 8-20%.[194-190]

However, phytosterols were not effective in one study in which dietary cholesterol intake was kept below 200 mg/day.[198] Effects on HDL and triglycerides are inconsistent, but some studies report average HDL increases as high as 11% and average triglyceride reductions as much as 12%.[193]

Chromium supplementation, at least 200 mcg/day, has been shown to reduce total and/or LDL cholesterol in some controlled studies,[199-205] but not others.[206-208] The magnitude of change in positive studies ranged from 7-18% reduction in total cholesterol and 10-11% reduction in LDL cholesterol.

Response may depend upon the chromium status of the patient, those with marginal deficiencies being more likely to respond.[209] Unfortunately, there does not exist a reliable assessment tool for chromium nutrition. Chromium has reduced serum triglycerides by as much as 17%-20% in both diabetic [202,210,211] and non-diabetic[212,213] patients, though its effects are not consistent.[214]

Chromium has increased HDL 9-38% in most controlled studies.[215-218] Other studies have shown no effects of chromium on HDL, perhaps because chromium is only effective in patients with marginal deficiency or who are glucose intolerant.[219] Three unrelated cases of possible toxic reactions to large doses of chromium (600 mcg/day) have been recently reported.[220-222]

Vitamin C may have hypocholesterolemic effects in some individuals.[223] Although research is conflicting, vitamin C at 500 mg/day or more has demonstrated effectiveness more consistently in hypercholesterolemic individuals having marginal vitamin C status.[224,225]

However, long-term intake of gram doses of vitamin C has produced evidence of impaired copper status,[226] which is of concern since marginal copper deficiency has been linked to hypercholesterolemia.[227-229]

Vitamin C intake in hypercholesterolemic patients should therefore be maintained at

less than 1000 mg/day or be accompanied by supplementary copper (2-3 mg/day).

Pantethine is a derivative of pantothenic acid (vitamin B5) that has reduced cholesterol levels in numerous uncontrolled[230-235] and a few controlled[236,237] studies, with one report of no effect in a controlled trial of patients resistant to diet and drug therapy.[238] Usual dose recommendations are 300 mg tid, and no significant adverse effects have been reported. Typical reductions of 14-17% total cholesterol and 14% LDL have been reported. Serum triglycerides have been lowered 30-48% in controlled studies.[236-237, 239] Treatment of dyslipidemic patients with pantethine has occasionally resulted in increased HDL cholesterol.[231,237]

Gugulipid is a mixture of substances taken from the plant *Commiphora mukul*, which is a mainstay in Ayurvedic medicine for the treatment of hyperlipidemia. Effective reduction of cholesterol by gugulipid has been shown in both uncontrolled [240,241] and controlled studies[242-245] using daily doses of 75-100 mg guggulsterones per day or 500 mg of the total extract three times daily. Reductions achieved in total cholesterol levels using gugulipid average 11-24%, while LDL has declined an average of 13%. Reduction of triglyceride levels averaging 12-27% has been reported using gugulipid in controlled studies.[242-244] Gugulipid has increased HDL in most,[241-244] but not all,[242] studies. Average reported improvement of HDL in one study was 36%.[244] In contrast to the above studies, which were all carried out in East Indian populations, a recent trial conducted in a Western population found no significant benefit of gugulipid, even at doses of 150 mg guggulsterones per day.[246]

Policosanol is a mixture of long-chain aliphatic alcohols, primarily octacosanol, extracted from sugar cane, beeswax, or other natural sources. This mixture appears to inhibit cholesterol production by the liver.[247] Extensive research in Cuba has reported that small amounts of policosanol (10-20 mg/day) lead to large reductions in total cholesterol (17-21%), LDL cholesterol (21-29%) and/or increased HDL (7-29%).[248,249,250,251,252,253,254,255] Effects on serum triglycerides has been inconsistent.[248,250,251,256,257,258] In contrast, no effects on any measure of blood lipids were reported in two trials conducted outside of Cuba.[259 260]

Table III. Reported Percentage Changes in Blood Lipids for Natural Supplements

Supplement	Total Cholesterol	LDL-C	HDL-C	Triglycerides
Garlic	– 0-12%	– 0-11%	0	– 0-27%
Inositol hexaniacinate	– 5-25%	N/A	N/A	– 15-27%
Fish oils	0	+ 5-10%	0	– 25-30%
Phytosterols	– 6-15%	– 8-20%	+ 0-11%	+ 1 to -0-12%
Chromium	– 0-18%	– 0-11%	+ 0-38%	– 0–20%
Pantethine	– 14-17%	– 14%	+ 0-10%	– 30-48%
Gugulipid	– 11-24%	– 13%	+ 0-36%	– 12-27%
Policosanol	– 17-21%	–21-29%	+ 7-29%	– 0–14%
Red yeast rice	– 11-32%	– 22%	0	– 0-19%

Source: See references under Rationale for Nutritional Supplements
See also Appendix IX for relative costs of dyslipidemia supplements.

Treat non-lipid CHD risk factors, if indicated.

Non-lipid CHD risk factors include the following and should be addressed as noted:

- Hypertension (see Hypertension care pathway)
- Use aspirin or other antiplatelet therapies to reduce prothrombotic state (see antiplatelet protocol, when available)
- Insulin resistance (see Protocol 2)

STEP 3: Monitoring Treatment

Measure serum total cholesterol (if more convenient) or LDL, along with triglycerides and HDL, and evaluate dietary compliance at 4-6 weeks and 3 months. For most patients, serum total cholesterol levels of 240 and 200 mg/dL correspond roughly to LDL cholesterol levels of 160 and 130 mg/dL. If total cholesterol appears to normalize, then LDL should be measured to confirm that the LDL goal has been achieved.

Triglyceride levels between 400-1000 mg/dL are considered high, though not necessarily a certain CHD risk factor when no other risk factors exist. However, these patients should be monitored closely while conservative intervention is attempted, as some of them may be labile and prone to further elevations necessitating drug therapy.[4]

After successful treatment, long-term monitoring should be done. Schedule follow-up visits every three months for the first year and twice yearly thereafter.

- Measure total cholesterol and re-evaluate risk factors.

- Reinforce dietary, nutritional and physical activity recommendations.

Failure to respond to conservative intervention after 3 months indicates a trial of aggressive intervention, which may or may not include medication.

PROTOCOL 1+: Aggressive Intervention for Elevated LDL with or without elevated Triglycerides and/or Low HDL

Treatment Summary

- Increase compliance
- Niacin therapy
- Chinese Red Yeast Rice, 10 mg/day monacolins

Increase Compliance

Ensure dietary and physical activity compliance and consider increased restriction.

- Refer patient to qualified professional, such as a registered dietitian and/or personal trainer.
- Introduce Step 2 diet or further restrictions of saturated fat, total fat and cholesterol.
- A 6-month minimum of intensive dietary therapy and counseling generally should be carried out in primary prevention before initiating drug therapy; shorter periods can be considered for patients with severe elevations of LDL cholesterol (>220 mg/dL). Drug therapy should be added to dietary therapy, and not substituted for it.

Niacin (nicotinic acid) Therapy

Niacin therapy can be recommended if there are no contraindications and there is an excellent likelihood of regular patient follow-up for purposes of monitoring side effects. (See Appendix XI: Niacin Therapy.)

Chinese Red Yeast Rice

Red yeast rice is a traditional Chinese remedy produced by fermenting cooked rice with the yeast *Monascus purpureus*. Its lipid-lowering activity is attributed to constituents called monacolins that appear to inhibit hepatic cholesterol synthesis in a manner similar to statin drugs, although other active constituents may also be present.[261,262,263] In the only placebo-controlled study to date, a dose delivering 10 mg/day total monacolins lowered total cholesterol (16%), LDL cholesterol (22%), and serum triglycerides (6.5%), but did not affect HDL cholesterol.[261] Prior studies in China using similar red yeast rice products reported even larger effects, including elevated HDL cholesterol.[264,265,266]

Anaphylactic reactions to *Monascus purpureus* have been reported.[267 268] Precautions and contraindications relevant to the use of statin drugs should also be observed for red yeast rice. These include avoiding use by patients with a history of liver disorders, and monitoring for liver function and muscle pain, the latter of which may indicate myopathy.[269] Lastly, there are concerns regarding statin-induced depletion of coenzyme Q_{10} (CoQ_{10}, ubiquinone), a mitochondrial energy metabolism cofactor, suggesting that either CoQ_{10} blood levels be monitored, or that CoQ_{10} be supplemented along with red yeast rice.[270,271]

PROTOCOL 2: Conservative Intervention for the Metabolic (Insulin-Resistance) Syndrome

According to the NCEP guidelines, [20] the presence of non-diabetic insulin-resistance and its metabolic consequences is suspected when any *three* of the following are present:

A. Abdominal obesity (waist circumference >40 in/102 cm in men, >35 in/88 cm in women)
B. Triglyceride levels 150 mg/dL or over
C. HDL cholesterol levels <40 mg/dL in men, <50 mg/dL in women
D. Blood pressure 130/85 mmHg or over
E. Fasting glucose 110 mg/dL or over

Additional indicators that suggest the presence of this syndrome include: [6,7,272]

F. Family history of diabetes mellitus
G. Hyperinsulinemia, (fasting plasma insulin 13.0 mU/l or above).

The metabolic syndrome represents a collection of risk factors that predict significant cardiovascular risk. The NCEP recommends considering treatment for the metabolic syndrome after an adequate trial (usually 3 months) of conservative LDL-lowering therapy,[20] which may itself improve many of the components of the metabolic syndrome. At that time, either LDL-lowering therapy will have achieved its primary LDL goal, or aggressive LDL intervention will be considered. In this context, additional interventions to address the causes or components of the metabolic syndrome may also be considered.

Greater emphasis on weight loss and regular aerobic exercise is the primary intervention recommended by the NCEP when the metabolic syndrome is suspected.[20] Additionally, each risk factor present could be addressed by proven or promising interventions. Interventions

indicated for elevated triglycerides and/or low HDL are presented in Protocol 3. Hypertension may be treated according to the WSCC Care Pathway for that disorder. Impaired fasting glucose may respond to interventions targeting insulin resistance as described below.

Lifestyle Interventions for the Metabolic Syndrome

- Smoking cessation
- Weight loss
- Regular exercise, including aerobic exercise

Dietary Interventions for the Metabolic Syndrome

The low-fat, high fiber diet recommended in the Therapeutic Lifestyle Changes section, starting on Page 12, may be effective intervention for the metabolic syndrome. However it may be necessary to consider dietary modifications to specifically address carbohydrate intolerance, if overall lipid levels (triglycerides, LDL and HDL) did not optimally respond to the Therapeutic Lifestyle Changes diet.

- Lower carbohydrate, moderate fat diet emphasizing non-atherogenic fats (primarily non-hydrogenated monounsaturated and polyunsaturated fatty acids) and low glycemic index carbohydrates.
- Dietary restrictions would include most refined sugars and other high glycemic index carbohydrates.
- See Appendices II, III, VI and VII for non-atherogenic fat foods and low and high glycemic index foods.
- Substituting carbohydrate with protein using low-fat protein foods is another conceivable choice, but there is little clinical evidence to predict the long-term results of this option.

Rationale for Lifestyle and Dietary Interventions

Smoking cessation. Insulin resistance has been associated with cigarette smoking,[273,274] secondhand smoke,[275] and even nicotine replacement products.[276,277] Moreover, smoking cessation has resulted in increased insulin sensitivity.[278]

Weight loss. Obesity, especially in the abdominal region, increases the severity of insulin resistance.[279,280] Weight loss improves insulin sensitivity,[281,282] and has been shown to do so specifically in patients with the metabolic syndrome.[283] Weight reduction can lower an elevated triglyceride level,[37,104,107] and can affect other problems associated with CHD and the insulin resistance syndrome, such as overall lipoprotein pattern[37,68,104-108] and blood pressure.[69]

Exercise. Both aerobic and strength training exercise improves insulin sensitivity.[284,285] In a recent controlled study, insulin resistance in patients with the metabolic syndrome responded more consistently to an exercise program when it was complemented by dietary changes targeted to heart disease risk reduction.[283] Aerobic physical activity can lower an elevated triglyceride level,[101,102] and can affect many additional problems associated with CHD and the insulin resistance syndrome,[36,38] including overall lipoprotein pattern,[37,101] and blood pressure.[286,287]

Low-fat, high carbohydrate diets. Diets similar to those recommended in the Therapeutic Lifestyle Changes section have been found to improve insulin sensitivity, and to improve many of the cardiovascular risk factors that are part of the metabolic syndrome, including insulin resistance,[283] elevated triglycerides,[17,72,90 288-290] impaired glucose tolerance,[291,292]

and hypertension.[293,294] A healthy balanced diet with a frequent intake of raw and salad vegetables, fruits in both summer and winter, fish, pasta and rice and low intake of fried foods, sausages, fried fish, and potatoes was found to correlate with low incidence of several components of the metabolic syndrome.[295]

Moderate fat, lower carbohydrate diets. In some patients the reduction of dietary fat, if it results in a higher carbohydrate intake, may cause an increase in triglyceride levels and/or decreased HDL,[296-299] especially when there is coexisting insulin resistance.[300] However, one study found this to be true only when dietary changes were sudden and substantial;[90] another found that hypercholesterolemic subjects, but not those with combined dyslipidemias, were sensitive to changes in dietary carbohydrate.[91] Nonetheless, increasing non-atherogenic fats (primarily non-hydrogenated monounsaturated and polyunsaturated fatty acids) may improve insulin sensitivity[301] and overall lipoprotein pattern in many patients.[53,56,89]

The value of this diet compared to the Therapeutic Lifestyles Diet may depend primarily on which diet leads to greater weight loss.[301] Saturated fat should remain restricted, due to its well-known atherogenic effects as well as evidence suggesting detrimental effects on insulin sensitivity.[302]

Restriction of refined sugars and high-glycemic index foods. Refined sugars in large amounts have been shown, in animal studies, to worsen insulin sensitivity and other components of the metabolic syndrome, but human research is conflicting.[303-305] Restricting carbohydrate intake to low-glycemic index foods, which may include several types of starchy foods (e.g. processed refined wheat flour products) and only certain sugars (e.g. glucose, sucrose), may be more effective for improving components of the metabolic syndrome than restricting only sugars.[306]

High protein diets. Preliminary research suggests that substitution of lean protein for dietary carbohydrate in a low fat diet is another feasible option that may improve the overall lipoprotein risk profile.[99] One controlled study found a high protein weight-loss diet equally effective for improving insulin sensitivity as a high carbohydrate weight-loss diet.[307] However, a preliminary report suggested that high protein diets that do not restrict atherogenic fats might have detrimental effects on cardiovascular risk.[308]

Nutritional Supplements

Specific supplements may directly improve insulin sensitivity.

- Chromium, 200-1000 mcg/day. **Cautions:** *Chromium intake above 500 mcg/day has been linked to kidney dysfunction and other side effects in a few case reports.*
- Water-soluble fiber supplement: glucomannan, 8-13 grams/day or guar gum, 30 grams/day. **Cautions:** *None.*

Rationale for Nutritional Supplements

Chromium. Chromium plays a metabolic role in promoting insulin sensitivity.[309,310] While chromium supplements have not been tested specifically on patients with the metabolic syndrome, numerous controlled studies have shown 200-1000 mcg/day improves glucose tolerance and overall lipoprotein patterns in diabetics.[311,312]

Water-soluble fiber supplement. Both glucomannan[313,314] and guar gum[315,316] have demonstrated beneficial effects on glycemic control in diabetics in some studies. Glucomannan, 8-13 grams/day, improved some measures of glycemic control and lipoprotein pattern in a controlled study of patients with the metabolic syndrome.[317] Guar gum, in large amounts of 30 grams/day,[318] but not 8-16 grams/day,[319] has improved several components of the metabolic syndrome in non-diabetics, but has not been tested specifically in cases of the metabolic syndrome.

ADDENDUM: Interventions for Isolated Elevations of Triglycerides or HDL Cholesterol

Occasionally, a patient may present with acceptable LDL cholesterol levels and less than three of the indicators required for presumption of the metabolic syndrome, yet may exhibit undesirable levels of serum triglycerides (200 mg/dL or greater) and/or HDL cholesterol (less than 40 mg/dL). In such cases, interventions described in Protocols 1, 1+, and/or 2 may be considered. See the *Rationales for Dietary and Lifestyle Interventions* and *Nutritional Supplements*, and *Table III* for more information about the effects of these interventions on serum triglyceride and HDL cholesterol levels. Note that triglyceride levels above 1000 mg/dL greatly increase the risk of acute pancreatitis and generally require drug therapy along with nonpharmacologic intervention.

APPENDICES on next page.

Appendix I. 10-year risk assessment worksheet

Add up the points from each category and see the 10-year risk for developing cardiovascular disease.

Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Age 20-29	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
>280	11	8	5	3	1

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
>60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
>160	2	3

Point Total	10 Year Risk %	Point Total	10 Year Risk %
0	1	9	5
1	1	10	6
2	1	11	8
3	1	12	10
4	1	13	12
5	2	14	16
6	2	15	20
7	3	16	25
8	4	≥17	≥30

10-Year Risk _____%

Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Age 20-29	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	8	6	4	2	1
240-279	11	8	5	3	2
>280	13	10	7	4	2

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
>60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
>160	4	6

Point Total	10 Year Risk %	Point Total	10 Year Risk %
<9	<1	17	5
9	1	18	6
10	1	19	8
11	1	20	11
12	1	21	14
13	2	22	17
14	2	23	22
15	3	24	27
16	4	≥25	≥30

10-Year Risk _____%

Appendix II. Evaluating secondary causes and complications of dyslipidemias [320,321]

A. Patients with elevated LDL must be screened for secondary causes by searching for the following indicators:

1. **Diabetes mellitus**
   a) History: family history of diabetes
   b) Physical: obesity
   c) Lab: fasting plasma glucose above 126 mg/dL

2. **Hypothyroidism**
   a) History: easy fatigability, lethargy, cold intolerance, muscle aches, stiffness, hair loss, constipation
   b) Physical: dry, scaly skin; sparse eyebrows, delayed relaxation of Achilles' tendon reflex
   c) Lab: elevated TSH, low T4

3. **Nephrotic syndrome**

4. **Chronic renal failure**
   a) History: acute kidney disease, hypertension
   b) Physical: hypertension
   c) Lab: elevated serum BUN, creatinine; proteinuria, hematuria

5. **Obstructive liver disease**
   a) History: pruritus, dark urine, light stools
   b) Physical: jaundice
   c) Lab: elevated serum alkaline phosphatase, bilirubin

6. **Drug side effects**
   a) Collect information on all currently prescribed medications.
   b) Consult drug reference for potential interactions with blood lipids.
   c) Commonly involved with high LDL are progestins, corticosteroids, anabolic steroids, and thiazide diuretics.

7. **Genetic lipoprotein disorders**
   a) History: Family history of high cholesterol
   b) Physical: xanthomas (usually small, often multiple, firm or soft masses, sometimes pigmented yellow, orange or brown) below skin or tendons of extensor surfaces of extremities, palms, buttocks, or eyelids.
   c) Lab: serum cholesterol over 400 mg/dL, LDL over 220 mg/dL.

B. Patients with elevated triglycerides must be screened for secondary causes by searching for the following indicators:

1. **Diabetes mellitus**
   a) History: family history of diabetes
   b) Physical: obesity
   c) Lab: fasting plasma glucose above 126 mg/dL

2. **Side effects of medications**
   a) Collect information on all currently prescribed medications.
   b) Consult drug reference for potential interactions with blood lipids
   c) Commonly involved in high triglycerides are thiazide diuretics.

3. **Alcohol abuse**
   a) History: alcoholism, alcoholic hepatitis, cirrhosis, pancreatitis, DWI record
   b) Physical: alcohol breath odor, parotid gland enlargement, spider nevi or angioma, tremulousness, hepatomegaly
   c) Lab: abnormal liver function tests, elevated serum amylase

4. **Kidney disorders**
   a) History: acute kidney disease, dialysis, kidney transplantation, diabetes, hypertension
   b) Physical: hypertension, edema, ascites, pleural effusion
   c) Lab: elevated serum BUN, creatinine, low serum albumin; proteinuria, hematuria

5. **Pancreatic disorders**
   a) History: alcoholism
   b) Physical: epigastric tenderness, guarding, distention
   c) Lab: elevated serum amylase or lipase, leukocytosis

6. **Genetic lipoprotein disorders**
   a) History: Family history of high triglycerides; personal history of recurrent abdominal pain
   b) Physical: xanthomas, hepatosplenomegaly
   c) Lab: Serum triglycerides over 400 mg/dL

C. Patients with low HDL must be screened for secondary causes by searching for the following indicators:

1. Diabetes mellitus

a) History: family history of diabetes
b) Physical: obesity
c) Lab: fasting plasma glucose above 126 mg/dL

2. Syndrome X, or the atherogenic insulin resistance syndrome

a) History: Personal or family history for impaired glucose tolerance or diabetes (elevated fasting plasma glucose or abnormal 2-hour post-glucose test)
b) Physical exam: Severe obesity (Body Mass Index ≥30); BMI = body weight in kilograms/(height in meters)^2; elevated waist/hip ratio (1.0 or above for men and 0.9 or above for women). Waist and hip circumferences are measured at the largest circumferences of the abdomen and buttocks, respectively. Hypertension (140/90 mmHg or greater)
c) Laboratory: Hyperinsulinemia, (fasting plasma insulin 13.0 mU/l or above); hypertriglyceridemia (fasting serum triglycerides over 200 mg/dL); low serum HDL cholesterol (less than 35 mg/dL)
d) Criteria: There are no established criteria for confirming the diagnosis of syndrome X. Several of the above indicators should be present before considering intervention.

3. Drug side effects

a) Collect information on all currently prescribed medications.
b) Consult drug reference for potential interactions with blood lipids
c) Commonly involved in low HDL are beta-adrenergic blocking agents (beta-blockers), probucol, loop diuretics, anabolic steroids, and progestational agents

Appendix III. Case management outline

A. Evaluate patient's current diet for foods high in saturated fat and cholesterol. Also evaluate the methods of cooking at home and the frequency and pattern of eating outside the home.

B. Emphasize the need to modify eating behavior and outline strategies:

1. Increase consumption of vegetables; fruits; breads, cereals, rice, legumes and pasta; skim milk and skim milk products; and lean meat, poultry and fish.

    a) Breads, cereals, pasta, potatoes, rice, dry peas and beans (6 or more servings per day)
    b) Fruits and vegetables (5 or more servings per day)
    c) Low-fat dairy products (2-3 servings per day)
    d) Lean meats, poultry, and fish (up to 5-6 oz per day)
    e) Fats and oils (no more than 6-8 teaspoons per day, including fats and oils used in food preparation). Choose from products containing non-hydrogenated canola oil, corn oil, olive oil, safflower oil, soybean oil, sunflower oil, rice bran oil, or peanut oil.
    f) Conversions: one teaspoon of fats and oils equals 1/3 tablespoon equals 1/6 fluid ounce, equals approximately 5 grams of fat.

2. Reduce or eliminate use of non-lean* ground beef, processed meats (hot dogs, sausage, bacon), luncheon meats and poultry skin; whole and 2% milk, butter, cheese, ice cream; egg yolks; organ meats; pizza and other high-fat fast foods; any fried foods, baked foods or other products with over 1 gram of saturated fat per serving.

C. Consider, with patient, the desirability and availability of individual or group diet counseling.

D. Monitor response.

---

*Ground beef and other meats are often labeled according to percentage of fat-free meat by weight. Therefore, 80% lean ground beef is 20% fat by weight, and a one-quarter pound serving (about 100 grams) contains about 20% X 100 or 20 grams of fat. Acceptable leanness is no less than 90% lean before cooking.

Appendix IV. Saturated fat and cholesterol containing foods with suggested substitutions

Saturated fat/cholesterol-dense foods	Alternatives
Meat, poultry, seafood - organ meats, most beef, pork and lamb products, most lunch meats, frankfurters, poultry with skin, duck, goose, ground turkey, fried seafood and chicken	Lean beef (round, sirloin flank, tenderloin), wild game, ham, Canadian bacon, pork tenderloin, veal chops/roasts, 95+% lean lunch meat, low fat vegetarian meat substitutes, skinless chicken, turkey, cornish hen, non-fried seafood, canned fish
Dairy products - most cheeses, whole milk/yogurt, cream, regular and premium dairy desserts, cheese/cream sauces, dressings, etc.	Cottage cheese, parmesan cheese, low/nonfat cheeses, low/nonfat milk/yogurt, low/nonfat dairy desserts, sauces and dressings made with low/nonfat cheese
Eggs and egg dishes	Egg whites only or low-calorie egg substitutes
Fats - butter, hard margarine, mayonnaise, coconut oil, palm oil, shortening, cream products, non-dairy creamer, rich sauces/gravies/salad dressings, coconut	Margarine low in trans or hydrogenated fat, low-calorie mayonnaise, spray oil for cooking, low fat/condensed nonfat milk, low fat sauces/gravies/salad dressings
Breakfast breads and cereals - Doughnuts, pastries, croissants, gourmet muffins, high-fat cereals and granola, pancakes, waffles, French toast	Toast/bagel/English muffin, low/nonfat muffins and pastries, cooked cereals, low/nonfat breakfast cereals and granola, low/nonfat recipe pancakes and waffles
Lunch/dinner entrees - casseroles/noodle dishes/stews/soups with meat/cheese/ cream/eggs, many fast food sandwiches, many Mexican/Asian/Italian dishes, fried foods	Tomato-based or other dishes without meat/cheese/rich sauces, low-calorie salad entrees, broth soups, lean meat sandwiches w/o cheese, low-fat international dishes, broiled/baked/steamed foods
Starchy snacks - Fried chips, rich crackers, regular popcorn, French fries, onion rings	Pretzels, bread sticks, low/non-fat crackers, chips and popcorn
Sweet snacks - Rich cookies, cakes, pies, high-fat frozen desserts, most granola bars, most candy bars, creamy candy	Fresh fruit, flavored nonfat yogurt, nonfat frozen desserts, sherbet/fruit ices, gelatin desserts, angel food cake, animal crackers, fig/fruit Newtons, nonfat cookies/cakes, hard candy

Appendix V. "Checkbook" method of tracking fat grams

This method is based on managing your fat intake as you might manage a checkbook. You budget yourself a certain number of fat grams per day. Follow the steps outlined below and consult with the chart on the next page. Your intern will help you with the calculations and in deciding what dietary targets would be appropriate for you.

Step 1: Determine your **ideal weight** based on your height.

These numbers are probably lower than the weight you will attain with your new eating style, and they don't take in consideration your natural build. However, they are useful for calculating your targeted calorie intake. (See chart, "Calories needed daily to sustain weight.")

Step 2: Choose your **current activity level** and find your target daily calorie intake number.

Let us say that you are a 6 foot male who works a computer job and who rarely exercises. Your ideal daily calorie intake would be 1,958.

Step 3: Choose the **percentage of fat intake** that is your goal.

Step 1 diet should be at least 30%. Patients with proven heart disease should consider limiting fat to 20% or lower.

Step 4: Look up your **daily "fat budget."**

Look up the number of fat grams that you can eat each day. (See chart, "Grams of Fat Allowed.") In our example, the 6-foot computer programmer would not eat more than 44 grams of fat per day.

Step 5: Decide how much **saturated fat** you can allow yourself.

Try to limit yourself to between 7-10% of your total calorie intake. 1,958 x .10 = 196 calories. Each gram of fat supplies 9 calories. 196 divided by 9 ≈ 22 grams of saturated fat. So our programmer could eat 44 grams of fat per day of which up to 22 could be saturated. Even better would be 7% saturated fat diet which would equal about 15 grams of saturated fat per day. After a month or so, it may be easier to just track your saturated fat intake.

Remember, every gram of partially hydrogenated fat would count the same as a saturated gram. If partially hydrogenated fats are present in a food, they will appear in fine print in the ingredient list, but they will NOT be cited in grams on the package. It would be better to avoid foods which contain them (see Appendix IV), or eat these foods only sparingly. The closer to the beginning of the listed ingredients, the more of the substance is present; the closer to the end of the list, the less is present.

Name _____
DATE _____
Daily fat grams _____
Daily saturated fat grams _____

CALORIES NEEDED DAILY BY MEN TO SUSTAIN WEIGHT

Height	Ideal Weight	Extremely Inactive	Moderately Active	Active	Extremely Active
5’2”	118	1,298	1,534	1,770	2,124
5’3”	124	1,364	1,612	1,860	2,232
5’4”	130	1,430	1,690	1,950	2,340
5’5”	136	1,496	1,768	2,040	2,448
5’6”	142	1,562	1,846	2,130	2,556
5’7”	148	1,628	1,924	2,220	2,664
5’8”	154	1,694	2,002	2,310	2,772
5’9”	160	1,760	2,080	2,400	2,880
5’10”	166	1,826	2,158	2,490	2,988
5’11”	172	1,892	2,236	2,580	3,096
6’0”	178	1,958	2,314	2,670	3,204
6’1”	184	2,024	2,392	2,760	3,312
6’2”	190	2,090	2,470	2,850	3,420
6’3”	196	2,156	2,548	2,940	3,528
6’4”	202	2,222	2,626	3,030	3,636

CALORIES NEEDED DAILY BY WOMEN TO SUSTAIN WEIGHT

Height	Ideal Weight	Extremely Inactive	Moderately Active	Active	Extremely Active
4’11”	95	1,045	1,235	1,425	1,710
5’0”	100	1,100	1,300	1,500	1,800
5’1”	105	1,155	1,365	1,575	1,890
5’2”	110	1,210	1,430	1,650	1,980
5’3”	115	1,265	1,495	1,725	2,070
5’4”	120	1,320	1,560	1,800	2,160
5’5”	125	1,375	1,625	1,875	2,250
5’6”	130	1,430	1,690	1,950	2,340
5’7”	135	1,485	1,755	2,025	2,430
5’8”	140	1,540	1,820	2,100	2,520
5’9”	145	1,595	1,885	2,175	2,610
5’10”	150	1,650	1,950	2,250	2,700
5’11”	155	1,705	2,015	2,325	2,790
6’0”	160	1,760	2,080	2,400	2,880

Grams of Fat Allowed

Daily Caloric Intake	Percentage of Calories from Fat			
	15%	20%	25%	30%
1,200	20	27	33	30
1,300	22	29	36	43
1,400	23	31	39	47
1,500	25	33	42	50
1,600	26	36	44	53
1,700	28	38	47	57
1,800	30	40	50	60
1,900	31	42	53	63
2,000	33	44	56	67
2,100	35	47	58	70
2,200	36	49	61	73
2,300	38	51	64	77
2,400	40	53	67	80
2,500	41	56	69	83
2,600	43	58	72	87
2,700	45	60	75	90
2,800	46	62	77	93
2,900	48	64	80	96
3,000	50	67	83	100

This table presents *maximum* grams of fat in a day. Only in unusual circumstances would a person need more than 60 grams of fat per day. The higher values are in the chart for reference only.

Appendix VI. Trans fatty acid containing foods[322]

Hydrogenated or partially-hydrogenated vegetable oils

Margarines and shortenings containing the above fats and oils

Commercial products baked or fried in the above fats and oils

Included are most fried fast foods, potato and tortilla chips, donuts, crackers, cookies and other bakery items.

Package labels will indicate the presence of hydrogenated or partially-hydrogenated fats, but amounts of *trans* fats are not required by current labeling laws.

Foods Containing a High Percentage of Trans Fats*[1]

40%-50% of fat as trans:	**Danish pastry, popcorn, cheese snacks, crackers, potato nuggets, chicken nuggets, French fries**
25%-35% of fat as trans:	**Donuts, cake mixes, pancakes, waffles, chicken and fish burgers (if breaded or battered)**
15%-25% of fat as trans:	**Croissants**
5%-15% of fat as trans:	**Potato and corn chips, granola bars, hamburgers**

***Average content of typical examples**

[1] Elias SL, Innis SM. Bakery foods are the major dietary source of trans-fatty acids among pregnant women with diets providing 30 percent energy from fat. J Am Diet Assoc 2002;102:46-51.

Appendix VII. Foods high in soluble fiber

3 or more grams per serving

- black-eyed peas

2-3 grams per serving

- kidney beans
- garbanzos
- pinto beans
- 100% oat bran cereal
- whole kernel corn
- dried fruit

1-2 grams per serving

- all-bran cereal
- oatmeal
- split peas
- lima beans
- lentils
- kale
- cabbage
- Brussels sprouts
- garden peas
- carrots
- yams
- zucchini
- squash

Appendix VIII. Low glycemic index diet

(This chart should be followed when choosing carbohydrate-containing foods to support normal insulin secretion and sensitivity. *Individual responses to foods may vary.)

Food Category	Avoid as much as possible (GI>80)**	Use in moderation (GI<80, >55)	Use freely (GI<55)
Breads	French bread (not sourdough)	Sourdough bread	Pumpernickel bread
		Most other white breads	Heavy mixed grain bread
		Most other whole grain breads	Oat bran bread
Breakfast cereals	Most made with refined grains	Most made with whole grains or bran	Unsweetened whole grain cereals
		Cream of wheat	Oatmeal, low-sugar oat cereals
			100% bran cereals
			Psyllium fortified cereals
Rice	Most regular white or brown rice	White or brown basmati rice	
		Parboiled rice	
Other starches	Most potatoes	Yams, sweet potatoes	Barley, buckwheat, bulgar wheat
	Most milled corn products	Sweet corn	Rye kernels, wheat kernels
	Millet	Most pasta	
Legumes		Green peas	Most legumes
Dairy foods		Most sweetened dairy	Most unsweetened dairy
			Most cultured dairy
Fruits	Watermelon	Banana, pineapple, raisins	Apple, orange and these juices
			Peach
Sweets	Most candy	Fructose sweetened products	Artificially-sweetened products
	Most cookies	Oatmeal cookies	
	Sugar (sucrose), honey, maltose		
	Corn/malt/rice syrup, corn sweetener		

****If these foods must be used, they should be combined with low glycemic index foods or protein foods.**

Appendix IX. Relative costs of dyslipidemia supplements

Supplement	Minimum Monthly Cost*	Minimum Daily Pills*
Garlic	$14.45	1
Inositol hexaniacinate	$33.00/26.25	3
Fish oils	$39.00	6
Phytosterols	$28.00	6
Chromium	$2.65	1
Pantethine	$60.00	3
Gugulipid	$73.00	6
Policosanol	$20.00	1
Niacin	$5.85	6
Chinese Red Yeast Rice	$30.00	4

*Approximate retail cost at minimum recommended dosage

Source: January 2000 Price List. PhytoPharmica: Green Bay, Wisconsin.
February 2000 Price List. Metagenics: Eugene, Oregon.
February 1999 Price List. Thorne Research: Dover, Idaho.
October 1999 Price List. Nature's Life: Garden Grove, California.
Internet Search, July 2002.

Appendix X. Prescribing an exercise program

Guidelines for exercise stress testing

Patients with known or suspected cardiac, pulmonary, or metabolic disease should be considered for exercise stress testing if moderate exercise* is considered. If a vigorous exercise* program is contemplated, consider exercise stress testing for patients over 40 years old, who have never exercised before, or have at least one of the following major coronary risk factors: history of blood pressure above 145/95 mmHg, cigarette smoking, abnormal ECG, family history of coronary or other atherosclerotic disease prior to the age of 50, or diabetes mellitus. If stress testing is not a viable option, then a slow introduction of low intensity exercises can be introduced and gradually increased based on the patient's tolerance.

Possible contraindications to exercise outside of a monitored environment include MI within 6 months, angina, physical signs and symptoms of congestive heart failure (e.g., bilateral rales, shortness of breath with or without pedal edema), or a resting systolic pressure of 200 mmHg or higher or diastolic of 110 or higher.

In elderly patients, cardiac reserves can be tested in the office by getting up and down from the examination table, walking 15 meters, climbing one flight of stairs, and/or cycling in the air for 1 minute. A patient who develops chest pain or substantial shortness of breath would not be a good candidate for exercise outside of a controlled environment. Patients over the age of 75 should have their resting ECG reviewed for new Q-waves, ST-segment depressions, or T-wave inversions.

Starting a program

Patients should start slowly with activities that they can tolerate, like walking. For elderly patients, start with low intensity exercises such as self-paced walking, gait training, balance exercises, tai chi, or lower extremity resistance training with elastic tubing or ankle weights.

In the case of elderly patients, consider supervising a brief 5-10 minute session (for example, the patient could walk a circuit through the building).

Most patients and even some elderly patients will progress onto more intensive programs such as strength training using weight machines, fast walking, swimming or bicycling. Except in young, healthy adults, it is prudent to monitor blood pressure and heart rate at the start of more intensive exercise programs. Patients who have an abnormal cardiac response such as a decrease in systolic pressure of more than 20 mmHg, an increase to 250 mm systolic or 120 mm diastolic, or a repeated increase to 90% or more of age specific maximum, would be poor candidates for a moderate program.

---

* The American Heart Association (1995) and American College of Sports Medicine (1995) while not identical in their definitions suggest that moderate exercise is between 40-60% of maximal oxygen consumption or well within a person's current capacity (i.e., one which could be comfortably sustained for an hour), has a gradual initiation and progression and is generally non-competitive.

Vigorous exercise represents a substantial cardiorespiratory challenge and results in fatigue within 20 minutes, such as running and jogging.

Frequency
4 times a week or more

Duration
30-40 minutes, even broken into 10-15 minute sessions within the same day. Sedentary patients should start out with brief sessions, as little as 5-10 minutes. Try not to progress too quickly.

Intensity
For a low intensity program, the patient should exercise hard enough to breathe faster, but still be able to carry on a conversation. Heart rate can also be monitored for specific training targets. Elevate heart rate to at least 60% of maximum (maximum = 220-age).

Type
The patient should choose an activity that s/he will enjoy and have ready access to. Walking briskly is safe. Benefits increase especially after one mile. The distance may be more important than the speed. Patients should wear appropriate shoes Other activities that are also suitable, even for the elderly, include low impact aerobic exercises, cycling, jogging and swimming.

Structure
The patient should be encouraged to keep a record. Exercise programs should include warm-up period (5-10 minutes) at a rate lower than the exercise rate. Likewise, a cool down period should be included, usually 5-10 minutes.

Precautions
Dress warmly and keep hydrated (especially for patients over 65 years old). Never take an extremely hot bath or shower after exercising (especially older patients). Stop immediately if in case of the following:

- Tightness or severe pain in chest, arms or legs
- Severe breathlessness (can only speak one or two word at a time)
- Lightheadedness or dizziness
- Nausea or vomiting.

Note: Some shortness of breath is expected after exercise. Within 10 minutes breathing should be comfortable again, at a rate of 12-16 breaths per minute.

Relapse prevention

- Regular follow-up and modification are critical to the long-term success.
- Emphasize the specific benefits to the patient.
- Clearly outline the commitment required of the patient.
- If possible, provide both group and individual support.

References

Gill, TM, DiPietro L, Krumholz HM. Role of exercise stress testing and safety monitoring for older persons starting an exercise program. JAMA 2000;284(3):342-9.

Appendix XI. Niacin (nicotinic acid) therapy

Niacin therapy can be recommended if there are no contraindications and there is an excellent likelihood of regular patient follow-up for purposes of monitoring side effects.

Niacinamide, another form of vitamin B_3, is ineffective for treating dyslipidemia. Two forms of niacin are available, immediate release (crystalline) niacin and extended (sustained, timed) release niacin. Extended release has the advantage of reduced flushing, but may increase the risk of liver toxicity. Therefore, an attempt to successfully implement therapy with immediate release niacin is recommended.

Niacin therapy is effective beginning at 1500 mg/day. However, this high dose must be achieved gradually to minimize side effects. The following dose schedule is typical, but smaller and slower dose increments may be necessary in patients who experience side effects.

- First week: 125 mg twice daily with or immediately after meals
- Second week: 250 mg twice daily with or immediately after meals
- Third week: 500 mg twice daily with or immediately after meals
- Fourth week: 500 mg twice daily with or immediately after meals
- Fifth week: 1,000 mg twice daily with or immediately after meals
- Sixth week: 1,500 mg twice daily with or immediately after meals

Three times daily dosing is also permissible. Some patients will find it helpful for reducing flushing symptoms to take a single morning dose of aspirin (325 mg) or ibuprofen (200 mg) 30 minutes before the morning dose of niacin. This should only be necessary for the first 14 days of starting or restarting therapy, and also on the first day of increasing the dose. With time and consistent use, the body should develop a tolerance to the flushing symptoms.

Relative contraindications include:

- Diabetes mellitus or impaired glucose tolerance
- Liver disease
- Cardiac dysrhythmias
- Gout or hyperuricemia
- Peptic ulcer

Side Effects

Patients should be monitored regularly for side effects. Harmless, but uncomfortable side effects may include tingling, warm feelings, headaches, nausea, gas, heartburn, itching and rash. These symptoms should subside with the development of tolerance and can be minimized with daily aspirin or ibuprofen, temporarily reducing the daily dose, or distributing the daily amount over several smaller doses. More serious side effects involve liver toxicity, impaired glucose tolerance, gastritis or ulcer, increased uric acid leading to attacks of gout.

Screening for these conditions should be performed before beginning niacin therapy, every 12 weeks for the first year of therapy, and periodically thereafter. The following laboratory tests will be useful for monitoring purposes.

- Serum transaminases (AST, ALT)
- Serum uric acid
- Plasma glucose

Severe elevations of serum transaminases (over three times upper limit of normal) require immediate cessation of niacin therapy.[323] Otherwise, elevations above normal reference ranges of any of these tests should be verified in one month. Persistent elevations require either reducing niacin dosage and retesting within 3 months, or referral for medical consultation.

Niacin therapy has been shown to increase plasma levels of homocysteine, a suspected cardiovascular risk factor.[324] Since this may reduce the overall effectiveness of niacin therapy for reducing heart disease risk, consideration should be given to interventions that can reduce homocysteine levels. These include the following B-vitamin supplements: folic acid, 400-1000 mcg/day; vitamin B_{12}, 50-300 mcg/day; and vitamin B_6, 10-50 mg/day.[325,326]

Rationale for Niacin Therapy

Niacin has been recognized for decades as an effective hypolipidemic agent that reduces clinical outcomes such as recurrent myocardial infarction, cerebrovascular events, and total mortality.[327-330] A dose-response effect is typically seen beginning at 1500 mg/day that ranges from 10-30% reduction of LDL cholesterol levels,[331-333] 25-50% reduction of triglycerides, [331,332,334] and 10-40% increases in HDL.[331,332,335 ,336]

Side effects

Side effects are common with niacin therapy, especially at higher doses.[337-340] Sustained-release preparations have been shown to produce more frequent toxic side effects in some,[341] but not all,[342,343] studies.

- Liver dysfunction – elevated liver enzymes, often accompanied by symptoms such as fatigue, nausea and anorexia
- Hyperuricemia, leading to attacks of gout or uric acid renal stone formation
- Abnormal glucose tolerance and worsened diabetes mellitus[344]
- Cardiac dysrhythmias
- Peptic ulcer

The most common side effect of niacin therapy is rapid subcutaneous vasodilation, causing a flushing sensation, tingling, headache, and occasionally hypotension, itching and skin rash. This can be minimized by taking niacin with meals, taking one adult aspirin or one OTC ibuprofen 30 minutes before each dose,[4,345] or taking sustained-release niacin during the daytime or before sleeping.[346] Sustained-release niacin usually produces less of this effect, which often results in better compliance.[347]

REFERENCES

[1] Semenkovich CF. Chapter 74. Nutrient and genetic regulation of lipoprotein metabolism. In: Shils ME, Olson JA, Shike M, et al. Modern Nutrition in Health and Disease, 9th ed. Baltimore, MD: Williams & Wilkins, 1999:1191-97.

[2] Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. N Engl J Med 1990;323:1112-9.

[3] Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease: the Lifestyle Heart Trial. Lancet 1990;336:129-33.

[4] National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994;89:1333-445.

[5] Genest J Jr, McNamara JR, Ordovas JM, et al. Lipoprotein cholesterol, apolipoprotein A-I and B and lipoprotein (a) abnormalities in men with premature coronary artery disease. J Am Coll Cardiol 1992;19:792-802.

[6] Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. Am J Cardiol 1999;83(9B):25F-29F.

[7] Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. Circulation 1997;95:1-4.

[8] Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev 1995;75:473-86.

[9] Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. JAMA 1986;256:2835-8.

[10] Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986;256:2823-8.

[11] Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham Study. JAMA 1987;257:2176-80.

[12] Jacobs D, Blackburn H, Higgins M, et al. Report of the conference on low blood cholesterol: mortality associations. Circulation 1992;86:1046-60.

[13] Mann JI, Marr JW. Coronary heart disease prevention: trials of diets to control hyperlipidemia. In: Miller NE, Lewis B, editors. Lipoproteins, atherosclerosis and coronary heart disease. Amsterdam: Elsevier/North-Holland Biomedical Press; 1981: 197-210.

[14] Holme I. An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. Circulation 1990;82:1916-24.

[15] Rossouw JE. Clinical trials of lipid-lowering drugs. In: Rifkind BM, editor. Drug treatment of hyperlipidemia. New York: Marcel Dekker, Inc.; 1991: 67-88.

[16] Law MR, Wald NJ, Thompson SM. By how much and how quickly does reduction serum cholesterol concentration lower risk of ischemic heart disease? BMJ 1994;308:367-73.

[17] NIH Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease. Triglyceride, high-density lipoprotein, and coronary heart disease. JAMA 1993;269:505-10.

[18] Gordon DJ, Probstfeld JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. Circulation 1989;79:8-15.

[19] Wilson PWF, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality: the Framingham Heart Study. Arteriosclerosis 1988;8:737-41.

[20] National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Executive Summary. National Institutes Of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 01-3670, May, 2001.

[21] Avins AL, Haber RJ, Hulley SB. The status of hypertriglyceridemia as a risk factor for coronary heart disease. Clin Lab Med 1989;9:153-68.

[22] Hulley SB, Avins, AL. Asymptomatic hypertriglyceridemia: insufficient evidence to treat. Br Med J 1992;304:394-6.

[23] Grundy SM, Vega GL. Two different views of the relationship of hypertriglyceridemia to coronary heart disease. Arch Intern Med 1992;152:28-34.

[24] Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213-9.
[25] Grundy SM. Chapter 75: Management of hyperlipidemia and atherosclerosis. In: Shils ME, Olson JA, Shike M, et al. Modern Nutrition in Health and Disease, 9th ed. Baltimore, Maryland: Williams & Wilkins, 1999:1199-1216.
[26] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
[27] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
[28] Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.
[29] Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
[30] Castelli WP, Garrison RJ, Wilson PWF, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. JAMA 1986;256:2835-8.
[31] Thom TJ. Cardiovascular disease mortality among United States women. In: Eaker ED, Packard B, Wenger NK, Clarkson TB, Tyroler HA, editors. Coronary heart disease in women. New York: Haymarket Doyma; 1987: 33-41.
[32] Shea S, Ottman R, Gabrieli C, Stein Z, Nichols A. Family history as an independent risk factor for coronary artery disease. J Am Coll Cardiol 1984;4:793-801.
[33] Jorde LB, Williams RR. Relation between family history of coronary artery disease and coronary risk variables. Am J Cardiol 1988;62:708-13.
[34] U.S. Surgeon General. Cardiovascular disease: the health consequences of smoking. Washington (DC): U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health; 1983. DHHS Publication No. (PHS) 84-50204. 384 p.
[35] Joint National Committee. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1993. NIH Publication No. 93-1088. 49 p.
[36] Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol 1990;132:612-28.
[37] Wood PD, Stefanick ML, Williams PT, Haskell WL. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. N Engl J Med 1991;325:461-6.
[38] Fletcher GF, Blair SN, Blumenthal J, et al. Benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation 1992;86(1):340-4.
[39] Denke MA, Sempos CT, Grundy SM. Excess body weight: an underrecognized contributor to high blood cholesterol levels in white American men. Arch Intern Med 1993;153:1093-103.
[40] Larsson B. Regional obesity as a health hazard in men: prospective studies. Acta Med Scand 1988;723:45-51.
[41] Larsson B, Bengtsson C, Bjorntorp P, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women. Am J Epidemiol 1992;135:266-73.
[42] VanItallie TB. Waist circumference: a useful index in clinical care and health promotion. Nutr Rev 1998;56:300-13 [review].
[43] Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
[44] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circulation 2004;110:227-39.
[45] Miller M. The epidemiology of triglycerides as a coronary artery disease risk factor. Clin Cardiol 1999;22(Suppl II):II-1—II-6.

[46] Miller M, Kwiterovich PO Jr. Isolated low HDL-cholesterol as an important risk factor for coronary heart disease. Eur Heart J 1990;11(Suppl H):9-14.
[47] Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am 1994;78:117-41 [review].
[48] Steinberg D, Pearson TA, Kuller LH. Alcohol and atherosclerosis. Ann Intern Med 1991;114:967–76.
[49] Anonymous. Highlights of the report of the expert panel on blood cholesterol levels in children and adolescents. National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Am Fam Physician 1992;45:2127-36.
[50] Newman TB, Garber AM, Holtzman NA, et al. Problems with the report of the Expert Panel on blood cholesterol levels in children and adolescents. Arch Pediatr Adolesc Med 1995;149:241-7.
[51] Dennison BA, Jenkins PL, Pearson TA. Challenges to implementing the current pediatric cholesterol screening guidelines into practice. Pediatrics 1994;94:296-302.
[52] Miller M, Seidler A, Moalemi A, et al. Normal triglyceride levels and coronary artery disease events: the Baltimore Coronary Observational Long-Term Study. J Am Coll Cardiol 1998;31:1252-7.
[53] Mensink RP, Katan MB. Effects of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. Arterioscler Thromb 1992;12:911-9.
[54] Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. Br Med J 1997;314:112-7.
[55] Chait A, Brunzell JD, Denke MA, et al. Rationale of the diet-heart statement of the American Heart Association: report of the Nutrition Committee. Circulation 1993;88:3008-29.
[56] Howell WH, McNamara DJ, Tosca MA, et al. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr 1997;65:1747-64.
[57] Grundy SM, Barrett-Connor E, Rudel LL, Miettinen T, Spector AA. Workshop on the impact of dietary cholesterol on plasma lipoproteins and atherogenesis. Arteriosclerosis 1988;8:95-101.
[58] Grundy SM, Denke MA. Dietary influences on serum lipids and lipoproteins. J Lipid Res 1990;31:1149-72.
[59] Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. N Engl J Med 1999;340:1933-40.
[60] Khosla P, Hayes KC. Dietary trans-monounsaturated fatty acids negatively impact plasma lipids in humans: critical review of the evidence. J Am Coll Nutr 1996;15:235-9.
[61] Katan MB, Sock PL. Trans fatty acids and their effects on lipoproteins in humans. Ann Rev Nutr 1995;345:278-82.
[62] Lichtenstein AH. *Trans* fatty acids, plasma lipid levels, and risk of developing cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1997;95:2588-90.
[63] Grundy SM. The optimal ratio of fat-to-carbohydrate in the diet. Annu Rev Nutr 1999;19:325-41.
[64] Chait A, Brunzell JD, Denke MA, et al. Rationale of the diet-heart statement of the American Heart Association: report of the Nutrition Committee. Circulation 1993;88:3008-29.
[65] .Nelson GJ. Dietary fat, trans fatty acids, and risk of coronary heart disease. Nutr Rev 1998;56(8):250-2.
[66] Ascherio A, Willett WC. Health effects of trans fatty acids. Am J Clin Nutr 1997;66(suppl):1006S-10S [review].
[67] NIH Technology Assessment Conference Panel. Methods for voluntary weight loss and control. Ann Intern Med 1992;116:942-9.
[68] Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992;56:320-8.
[69] Alderman MH. Nonpharmacologic approaches to the treatment of hypertension. Lancet 1994;334:307-11 [review].
[70] Pi-Sunyer FX. Weight and non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1996;63(suppl):426S-9S.
[71] Levy Y, Maor I, Presser D, Aviram M. Consumption of eggs with meals increases the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. Ann Nutr Metabol 1996;40:243-51.
[72] Yu-Poth S, Zhao G, Etherton T, et al. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. Am J Clin Nutr 1999;69:632-46.

[73] Schaefer EJ, Lamon-Fava S, Ausman LM, et al. Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. Am J Clin Nutr 1997;65:823-30.
[74] Denke MA, Frantz ID Jr. Response to a cholesterol-lowering diet: efficacy is greater in hypercholesterolemic subjects even after adjustment for regression to the mean. Am J Med 1993;4:626-31.
[75] Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. Metabolism 1965;14:776-87.
[76] Tang JL, Armitage JM, Lancaster T, et al. Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects. BMJ 1998;316:1213-20.
[77] Henkin Y, Garber DW, Osterlund LC, Darnell BE. Saturated fats, cholesterol, and dietary compliance. Arch Intern Med 1992;152:1167-74.
[78] Grundy SM. Adherence to cholesterol-lowering diets. Arch Intern Med 1992;152:1139.
[79] National Diet-Heart Study Research Group. The national diet-heart study final report. Circulation 1968;37(Suppl 1):I1-428.
[80] Katan MB, van Gastel AC, de Rover CM, van Montfort MA, Knuiman JT. Differences in individual responsiveness of serum cholesterol to fat-modified diets in man. Eur J Clin Invest 1988;18:644-7.
[81] Grundy SM, Vega GL. Plasma cholesterol responsiveness to saturated fatty acids. Am J Clin Nutr 1988;47:822-4.
[82] Wolf G. High-fat, high-cholesterol diet raises plasma HDL cholesterol: studies on the mechanism of this effect. Nutr Rev 1996;54:34-5.
[83] Brinton EA, Eisenberg S, Breslow JL. A low-fat diet decreases high density lipoprotein (HDL) cholesterol levels by decreasing HDL apolipoprotein transport rates J Clin Invest 1990;85:144-51.
[84] Turley ML, Skeaff CM, Mann JI, Cox B. The effect of a low-fat, high-carbohydrate diet on serum high density lipoprotein cholesterol and triglyceride. Eur J Clin Nutr 1998;52:728-32.
[85] Schaefer EJ, Lichtenstein AH, Lamon-Fava S, et al. Body weight and low-density lipoprotein cholesterol changes after consumption of a low-fat ad libitum diet. JAMA 1995;274:1450-5.
[86] Katzel LI, Coon PJ, Dengel J, Goldberg AP. Effects of an American Heart Association step I diet and weight loss on lipoprotein lipid levels in obese men with silent myocardial ischemia and reduced high-density lipoprotein cholesterol. Metabolism 1995;44:307-14.
[87] Lichtenstein AH, Ausman LM, Carrasco W, et al. Short-term consumption of a low-fat diet beneficially affects plasma lipid concentrations only when accompanied by weight loss. Hypercholesterolemia, low-fat diet, and plasma lipids. Arterioscler Thromb 1994;14:1751-60.
[88] Knopp RH, Walden CE, Retzlaff BM, et al. Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men: the Dietary Alternatives Study. JAMA 1997;278(18): 1509-15.
[89] Katan MB, Grundy SM, Willett WC. Beyond low-fat diets. N Engl J Med 1997;337:563-6.
[90] Ullmann D, Connor WE, Hatcher LF, et al. Will a high-carbohydrate, low-fat diet lower plasma lipids and lipoproteins without producing hypertriglyceridemia? Arterioscler Thromb 1991;11:1059-67.
[91] Retzlaff BM, Walden CE, Dowdy AA, et al. Changes in plasma triacylglycerol concentrations among free-living hyperlipidemic men adopting different carbohydrate intakes over 2 y: the Dietary Alternatives Study. Am J Clin Nutr 1995;62:988-95.
[92] Connor WE, Connor SL. The case for a low-fat, high-carbohydrate diet. N Engl J Med 1997;337:562-3.
[93] Howell WH, McNamara DJ, Tosca MA, et al. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr 1997;65:1747-64.
[94] Truswell AS, Choudhury N. Monounsaturated oils do not all have the same effect on plasma cholesterol. Eur J Clin Nutr 1998;52:312-5.
[95] Howard BV, Hannah JS, Heiser CC, et al. Polyunsaturated fatty acids result in greater cholesterol lowering and less triacylglycerol elevation than do monounsaturated fatty acids in a dose-response comparison in a multiracial study group. Am J Clin Nutr 1995;62:392-402.
[96] Fraser GE. Nut consumption, lipids, and risk of a coronary event. Clin Cardiol 1999;22(Suppl III):III-11-5 [review].
[97] Wolfe BM, Giovannetti PM. Short-term effects of substituting protein for carbohydrate in the diets of moderately hypercholesterolemic human subjects. Metabolism 1991 Apr;40(4):338-43.

[98] Wolfe BM, Giovannetti PM. High protein diet complements resin therapy of familial hypercholesterolemia. Clin Invest Med 1992;15:349-59.
[99] Wolfe BM. Potential role of raising dietary protein intake for reducing risk of atherosclerosis. Can J Cardiol 1995;11:127G-131G.
[100] Brown GD, Whyte L, Gee MI, et al. Effects of two "lipid-lowering" diets on plasma lipid levels of patients with peripheral vascular disease. J Am Diet Assoc 1984;84:546-50.
[101] Tran ZV, Weltman A. Differential effects of exercise on serum lipid and lipoprotein levels seen with changes in body weight: a meta-analysis. JAMA 1985;254:919-24.
[102] Marrugat J, Elosua R, Covas M, et al. Amount and intensity of physical activity, physical fitness, and serum lipids in men. Am J Epidemiol 1996;143:562-9.
[103] Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. N Engl J Med 1998;339:12-20.
[104] Caggiula AW, Christakis G, Farrand M, et al. The multiple risk factor intervention trial (MRFIT). IV: Intervention on blood lipids. Prev Med 1981;10:443-75.
[105] Gordon DJ, Salz KM, Roggenkamp KJ, Franklin FA Jr. Dietary determinants of plasma cholesterol change in the recruitment phase of the Lipid Research Clinics Primary Prevention Trial. Arteriosclerosis 1982;2:537-48.
[106] National Diet-Heart Study Research Group. The national diet-heart study final report. Circulation 1968;37(Suppl 1):I1-428.
[107] Wood PD, Stefanick ML, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. N Engl J Med 1988;319:1173-9.
[108] Wolf RN, Grundy SM. Influence of weight reduction on plasma lipoproteins in obese patients. Arteriosclerosis 1983;3:160-9.
[109] Anderson JW, Garrity TF, Wood CL, Whitis SE, Smith BM, Oeltgen PR. Prospective, randomized, controlled comparison of the effects of low-fat and low-fat plus high-fiber diets on serum lipid concentrations. Am J Clin Nutr 1992;56:887-94.
[110] Ripsin CM, Keenan JM, Jacobs DR Jr, et al. Oat products and lipid lowering: a meta-analysis. JAMA 1992;267(24):3317-25. Erratum. JAMA 1992;268:3074.
[111] Glore SR, Van Treeck D, Knehans AW, et al. Soluble fiber and serum lipids: a literature review. J Am Diet Assoc 1994;94:425-436.
[112] Brown L, Rosner B, Willett WW, et al. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 1999;69:30-42.
[113] Bierenbaum ML, Reichstein R, Watkins TR. Reducing atherogenic risk in hyperlipemic humans with flaxseed supplementation: a preliminary report. J Am Coll Nutr 1993;12:501-4.
[114] Arjmandi BH, Khan DA, Juma S, et al. Whole flaxseed consumption lowers serum LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. Nutr Res 1998;18:1203-14.
[115] Jenkins DJA, Kendall CWC, Vidgen E, et al. Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: a controlled crossover trial. Am J Clin Nutr 1999;69:395-402.
[116] Abraham ZD, Mehta T. Three-week psyllium-husk supplementation: effect on plasma cholesterol concentrations, fecal steroid excretion, and carbohydrate absorption in men. Am J Clin Nutr 1988;47:67-74.
[117] Anderson JW, Zettwoch N, Feldman T, Tietyen-Clark J, Oeltgen P, Bishop CW. Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. Arch Intern Med 1988;148:292-6.
[118] Bell LP, Hectorne K, Reynolds H, Balm TK, Hunninghake DB. Cholesterol-lowering effects of psyllium hydrophilic mucilloid. JAMA 1989;261:3419-23.
[119] Levin EG, Miller VT, Muesing RA, Stoy DB, Balm TK, LaRosa JC. Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. Arch Intern Med 1990;150:1822-7.
[120] Everson GT, Daggy BP, McKinley C, Story JA. Effects of psyllium hydrophilic mucilloid on LDL-cholesterol and bile acid synthesis in hyper-cholesterolemic men. J Lipid Res 1992;33:1183-92.

[121] Sprecher DL, Harris BV, Goldberg AC. Efficacy of psyllium in reducing serum cholesterol levels in hypercholesterolemic patients on high- or low-fat diet. Ann Intern Med 1993;119:545-54.
[122] Bell LP, Hectorn KJ, Reynolds H, Hunninghake DB. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia. Am J Clin Nutr 1990;52:1020-6.
[123] Olson BH, Anderson SM, Becker MP, et al. Psyllium-enriched cereals lower blood total cholesterol and LDL cholesterol, but not HDL cholesterol, in hypercholesterolemic adults: Results of a meta-analysis. J Nutr 1997; 127:1973-80.
[124] Vuksan V, Jenkins DJ, Spadafora P, et al. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial. Diabetes Care 1999;22:913-9.
[125] Zhang MY, Huang CY, Wang X, et al. The effect of foods containing refined Konjac meal on human lipid metabolism. Biomed Environ Sci 1990;3:99-105.
[126] Arvill A, Bodin L. Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men. Am J Clin Nutr 1995;61:585-9.
[127] Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes 1984;8:289-93.
[128] Jensen CD, Haskell W, Whittam JH. Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. Am J Cardiol 1997;79:34-7.
[129] Knopp RH, Superko HR, Davidson M, et al. Long-term blood cholesterol-lowering effects of a dietary fiber supplement. Am J Prev Med 1999;17:18-23.
[130] Jones PJ, MacDougall DE, Ntanios F, et al. Dietary phytosterols as cholesterol-lowering agents in humans. Can J Physiol Pharmacol 1997;75:217-27.
[131] Jones PJ, Ntanios FY, Raeini-Sarjaz M, et al. Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men. Am J Clin Nutr 1999;69:1144-50.
[132] Gylling H, Miettinen TA. Cholesterol reduction by different plant stanol mixtures and with variable fat intake. Metabolism 1999;48:575-80.
[133] Hallikainen MA, Uusitupa MI. Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. Am J Clin Nutr 1999;69:403-10.
[134] Weststrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. Eur J Clin Nutr 1998;52:334-43.
[135] Gylling H, Radhakrishnan R, Miettinen TA. Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine: women and dietary sitostanol. Circulation 1997;96:4226-31.
[136] Denke MA. Lack of efficacy of low-dose sitostanol therapy as an adjunct to a cholesterol-lowering diet in men with moderate hypercholesterolemia. Am J Clin Nutr 1995;61:392-6.
[137] Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Eng J Med 1995;333:276-82.
[138] Potter SM, Baum JA, Teng H, et al. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. Am J Clin Nutr 1998;68:1375S-79S.
[139] Wong WW, Smith EO, Stuff JE, et al. Cholesterol-lowering effect of soy protein in normocholesterolemic and hypercholesterolemic men. Am J Clin Nutr 1998;68:1385S-89S.
[140] Wang MF, Yamamoto S, Chung HM, et al. Antihypercholesterol-emic effect of undigested fraction of soybean protein in young female volunteers. J Nutr Sci Vitaminol 1995;41:187-95.
[141] Santos MJ, Lopez-Jurado M, Llopis J, et al. Influence of dietary supplementation with fish on plasma total cholesterol and lipoprotein cholesterol fractions in patients with coronary heart disease. J Nutr Med 1992;3:107-15.
[142] Kromhout D, Bosschieter EB, De Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205-9.
[143] Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23-8.

[144] Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? BMJ 1996;312:731-36 [review].
[145] Ginsberg H, Olefsky J, Farquhar JW, Reaven GM. Moderate ethanol ingestion and plasma triglyceride levels: a study in normal and hypertriglyceridemic persons. Ann Intern Med 1974;80:143-9.
[146] Crouse JR, Grundy SM. Effects of alcohol on plasma lipoproteins and cholesterol and triglyceride metabolism in man. J Lipid Res 1984:25;486-96.
[147] Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women. A pooled analysis of cohort studies. JAMA 1998;279:535-40.
[148] Michael Pittilo R. Cigarette smoking, endothelial injury and cardiovascular disease. Int J Exp Pathol 2000;81:219-30.
[149] Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000;160:939-44 [review].
[150] Nyboe J, Jensen G, Appleyard M, Schnohr P. Smoking and the risk of first acute myocardial infarction. Am Heart J 1991;122:438.
[151] Eagles CJ, Martin U. Non-pharmacological modification of cardiac risk factors: Part 3. Smoking cessation and alcohol consumption. J Clin Pharm Ther 1998;23:1-9.
[152] Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. Ann Intern Med 1993;119(7 Pt 1):599-605.
[153] Silagy C, Neil A. Garlic as a lipid lowering agent--a meta-analysis. J R Coll Physicians Lond 1994;28(1):39-45.
[154] Steiner M, Khan AH, Holbert D. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. Am J Clin Nutr 1996;64:866-70.
[155] Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. Atherosclerosis 1995;113(2):219-225.
[156] Neil HA, Silagy CA, Lancaster T, et al. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. J R Coll Physicians Lond 1996;30(4):329-34.
[157] McCrindle BW, Helden E, Conner WT. Garlic extract therapy in children with hypercholesterolemia. Arch Pediatr Adolesc Med 1998;152:1089-94.
[158] Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins. Arch Intern Med 1998;158:1189-94.
[159] Berthold HK, Sudhop T, von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism. JAMA 1998;279:1900-2.
[160] Jain AK, Vargas R, Gotzkowsky S, McMahon FG. Can garlic reduce levels of serum lipids? A controlled clinical study. Am J Med 1993;94:632-5.
[161] Silagy C, Neil A. Garlic as a lipid lowering agent--a meta-analysis. J R Coll Physicians Lond 1994;28(1):39-45.
[162] Mader FH. Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study. Arzneimittelforschung 1990;40(10):
1111-6.
[163] Holzgartner J, Schmidt U, Kuhn U. Comparison of the efficacy of a garlic preparation vs. bezafibrate. Arzneim-Forsch Drug Res 1992;42:1473-77.
[164] Mansell P, Reckless JPD. Garlic—effects on serum lipids, blood pressure, coagulation, platelet aggregation, and vasodilatation. BMJ 1991;303:379-80 [editorial].
[165] Lawson LD, Ransom DK, Hughes BG. Inhibition of whole blood platelet-aggregation by compounds in garlic clove extracts and commercial garlic products. Thrombosis Res 1992;65:141-56.
[166] German K, Kumar U, Blackford HN. Garlic and the risk of TURP bleeding (case report). Br J Urol 1995;76:518.
[167] Petry JJ. Garlic and postoperative bleeding. Plast Reconstr Surg 1995;96:483-84.
[168] O'Hara J, Jolly PN, Nicol CG. The therapeutic efficacy of inositol nicotinate (Hexopal) in intermittent claudication: a controlled trial. Br J Clin Pract 1988;42:377-83.

[169] Kiff RS, Quick CRG. Does inositol nicotinate (Hexopal) influence intermittent claudication? – a controlled trial. Br J Clin Pract 1988;42:141-45.
[170] Head A. Treatment of intermittent claudication with inositol nicotinate. Practitioner 1986;230:49-54.
[171] Hotz W. Nicotinic acid and its derivatives: a short survey. Adv Lipid Res 1983;20:195-217.
[172] Ring EF, Porto LO, Bacon PA. Quantitative thermal imaging to assess inositol nicotinate treatment for Raynaud's syndrome. J Int Med Res 1981;9:393-400.
[173] Ring EFJ, Bacon PA. Quantitative thermographic assessment of inositol nicotinate therapy in Raynaud's phenomena. J Int Med Res 1977;5:217-22.
[174] Holti G. An experimentally controlled evaluation of the effect of inositol nicotinate upon the digital blood flow in patients with Raynaud's phenomenon. J Int Med Res 1979;7:473-83.
[175] Aylward M. Hexopal in Raynaud's disease. J Int Med Res 1979;7:484-91.
[176] Sunderland GT, Belch JJF, Sturrock RD, Forbes CD, McKay AJ. A double-blind randomised placebo controlled trial of hexopal in primary Raynaud's disease. Clin Rheumatol 1988;7:46-49.
[177] Seckfort H. Treating circulatory problems with inositol nicotinic acid ester. Med Klin 1959;10:416-18. 1800 mg/d
[178] Head KA. Inositol hexaniacinate: A safer alternative to niacin. Alt Med Rev 1996;1:176-84 [review].
[179] Holti G. An experimentally controlled evaluation of the effect of inositol nicotinate upon the digital blood flow in patients with Raynaud's phenomenon. J Int Med Res. 1979;7:473-483.
[180] Aylward M. Hexopal in Raynaud's disease. J Int Med Res 1979;7:484-491.
[181] Hutt V, Wechsler JG, Klor HU, Ditschuneit H. Changes in lipids and lipoproteins in patients with hyperlipidemia type Iib, IV and V treated with different lipid-lowering drugs. Artery 1980;8:113-9.
[182] Wechsler JG, Hutt V, Klor HU, Ditschuneit H. Lipids and lipoproteins in hyperlipidemia type IIa during treatment with different lipid lowering drugs. Artery 1980;8:519-29.
[183] Dorner Von G, Fisher FW, Zur Beinflussung der Serumlipide und -lipoproteine durch den Hexanicotinsaureester des m- Inositol. Arzneimittel Forschung 1961;11:110-13 [German].
[184] Welsh AL, Ede M. Inositol hexanicotinate for improved nicotinic acid therapy. Int Record Med 1961;174(1):9-15.
[185] Kruse W , Kruse W, Raetzer H, et al. Nocturnal inhibition of lipolysis in man by nicotinic acid and derivatives. Eur J Clin Pharmacol 1979;16:11-15.
[186] Prichard BN, Smith CCT, Ling KLE, Betteridge DJ. Fish oils and cardiovascular disease. BMJ 1995;310:819–20 [editorial/review].
[187] Harris WS. n-3 Fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;65:1645S-54S.
[188] Davidson MH, Maki KC, Kalkowski J, et al. Effects of docosahexaenoic acid on serum lipoproteins in patients with combined hyperlipidemia: a randomized, double-blind, placebo-controlled trial. J Am Coll Nutr 1997;16:236-43.
[189] Sheehan JP, Wei IW, Ulchaker M, Tserng K-Y. Effect of high fiber intake in fish oil-treated patients with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1997;66:1183-7.
[190] Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. Am J Clin Nutr 1997;65:445-50.
[191] Schectman G, Kaul S, Kassebah AH. Effect of fish oil concentrate on lipoprotein composition in NIDDM. Diabetes 1988; 37:1567-73.
[192] Friedberg CE, Janssen MJ, Heine RJ, et al. Fish oil and glycemic control in diabetes. A meta-analysis. Diabetes Care 1998;21:494-500.
[193] Jones PJ, MacDougall DE, Ntanios F, et al. Dietary phytosterols as cholesterol-lowering agents in humans. Can J Physiol Pharmacol 1997;75:217-27.
[194] Lees AM, Mok HY, Lees RS, et al. Plant sterols as cholesterol-lowering agents: Clinical trials in patients with hypercholesterolemia and studies of sterol balance. Atheroscler 1977;28:325-38.
[195] Pelletier X, Belbraouet S, Mirabel D, et al. A diet moderately enriched in phytosterols lowers plasma cholesterol concentrations in normocholesterolemic humans. Ann Nutr Metab 1995;39:291-5.
[196] Grundy SM, Ahrens EH Jr, Davignon J. The interaction of cholesterol absorption and cholesterol synthesis in man. J Lipid Res 1969;10:304-15 [review].
[197] Hendriks HF, Weststrate JA, van Vliet T, Meijer GW. Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects. Eur J Clin Nutr 1999;53:319-27.

[198] Denke MA. Lack of efficacy of low-dose sitostanol therapy as an adjunct to a cholesterol-lowering diet in men with moderate hypercholesterolemia. Am J Clin Nutr 1995;61:392-6.
[199] Boyd SG, Boone BE, Smith AR, et al. Combined dietary chromium picolinate supplementation and an exercise program leads to a reduction of serum cholesterol and insulin in college-aged subjects. J Nutr Biochem 1998;9:471-5.
[200] Lefavi R. Lipid-lowering effects of a dietary nicotinic acid-chromium (III) complex in male athletes. FASEB J 1991;5(6):A1645 [abstract].
[201] Press RI, Geller J, Evans GW. The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. West J Med 1990;152:41-5.
[202] Anderson RA, Cheng N, Bryden NA, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 1997;46:1786-91.
[203] Offenbacher EG, Pi-Sunyer FX. Beneficial effect of chromium-rich yeast on glucose tolerance and blood lipids in elderly subjects. Diabetes 1980;29:919-25.
[204] Elwood JC, Nash DT, Streeten DH. Effect of high-chromium brewer's yeast on human serum lipids. J Am Coll Nutr 1982;1:263-74.
[205] Anderson RA. Chromium metabolism and its role in disease processes in man. Clin Physiol Biochem 1986;4:31-41 [review].
[206] Wilson BE, Gondy A. Effects of chromium supplementation on fasting insulin levels and lipid parameters in healthy, non-obese young subjects. Diabetes Res Clin Pract 1995;28:179-84.
[207] Uusitupa MI, Kumpulainen JT, Voutilainen E, et al. Effect of inorganic chromium supplementation on glucose tolerance, insulin response, and serum lipids in noninsulin-dependent diabetics. Am J Clin Nutr 1983;38:404-10.
[208] Uusitupa MI, Mykkanen L, Siitonen O, et al. Chromium supplementation in impaired glucose tolerance of elderly: effects on blood glucose, plasma insulin, C-peptide and lipid levels. Br J Nutr 1992;68:209-16.
[209] Mertz W. Chromium in human nutrition: a review. J Nutr 1993;123:626-33.
[210] Lee NA, Reasner CA. Beneficial effect of chromium supplementation on serum triglyceride levels in NIDDM. Diabetes Care 1994;17:1449-52.
[211] Fox GN, Sabovic Z. Chromium picolinate supplementation for diabetes mellitus. J Fam Pract 1998;46:83-6.
[212] Riales R, Albrink MJ. Effect of chromium chloride supplementation on glucose tolerance and serum lipids including high-density lipoprotein of adult men. Am J Clin Nutr 1981;34:2670-8.
[213] Abraham AS, Brooks BA, Eylath U. The effects of chromium supplementation on serum glucose and lipids in patients with and without non-insulin-dependent diabetes. Metabolism 1992;41:768-71.
[214] Mooradian AD, Failla M, Hoogwerf B, et al. Selected vitamins and minerals in diabetes. Diabetes Care 1994;17:464-79.
[215] Abraham AS, Brooks BA, Eylath U. The effects of chromium supplementation on serum glucose and lipids in patients with and without non-insulin-dependent diabetes. Metabolism 1992;41:768-71.
[216] Roeback JR, Hla KM, Chambless LE, Fletcher RH. Effects of chromium supplementation on serum high-density lipoprotein cholesterol levels in men taking beta-blockers. Ann Intern Med 1991;115:917-24.
[217] Riales R, Albrink MJ. Effect of chromium chloride supplementation on glucose tolerance and serum lipids including high-density lipoprotein of adult men. Am J Clin Nutr 1981;34:2670-78.
[218] Mossop RT. Effects of chromium (III) on fasting glucose, cholesterol and cholesterol HDL levels in diabetics. Cent Afr J Med 1983;29:80-2.
[219] Anderson RA. Chromium, glucose tolerance, diabetes and lipid metabolism. J Adv Med 1995;8:37-50.
[220] Wasser WG, Feldman NS. Chronic renal failure after ingestion of over-the-counter chromium picolinate. Ann Intern Med 1997;126:410 [letter].
[221] Cerulli J, Grabe DW, Gauthier I, et al. Chromium picolinate toxicity. Ann Pharmacother 1998;32:428-31.
[222] Martin WR, Fuller RE. Suspected chromium picolinate-induced rhabdomyolysis. Pharmacotherapy 1998;18:860-2.

[223] Jacques PF, Sulsky SI, Perrone GE, Jenner J, Schaefer EJ. Effect of vitamin C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations. Ann Epidemiol 1995;5(1):52-9.
[224] Simon JA. Vitamin C and cardiovascular disease: a review. J Am Coll Nutr 1992;11:107-25.
[225] Ginter E, Bobek P. The influence of vitamin C on lipid metabolism. In: Counsell JN & Hornig DH (eds). Vitamin C (Ascorbic Acid). NJ: Appl Sci Pubs; 1981: 299-348.
[226] Finley EB, Cerklewski FL. Influence of ascorbic acid supplementation on copper status in young adult men. Am J Clin Nutr 1983;37:553-6.
[227] Reiser S, et al. Effect of copper intake on blood cholesterol and its lipoprotein distribution in men. Nutr Rep Int 1987;36:641-50.
[228] Davis GK, Mertz W. Copper. In: Mertz W, ed. Trace elements in human and animal nutrition, vol. 1, 5th ed. San Diego: Academic Press; 1987:301-64.
[229] Klevay LM. Dietary copper: a powerful determinant of cholesterolemia. Med Hypotheses. 1987;24:111-9 [review].
[230] Coronel F, Tornero F, Torrente J, et al. Treatment of hyperlipemia in diabetic patients on dialysis with a physiological substance. Am J Nephrol 1991;11:32-6.
[231] Arsenio L, Bodria P, Magnati G, et al. Effectiveness of long-term treatment with pantethine in patients with dyslipidemia. Clin Ther 1986;8:537-45.
[232] Miccoli R, Marchetti P, Sampietro T, et al. Effects of pantethine on lipids and apolipoproteins in hypercholesterolemic diabetic and non diabetic patients. Curr Ther Res 1984;36:545-49.
[233] Avogaro P, Bon B, Fusello M. Effect of pantethine on lipids, lipoproteins and apolipoproteins in man. Curr Ther Res 1983;33;488-93.
[234] Galeone F, Scalabrino A, Giuntoli F, et al. The lipid-lowering effect of pantethine in hyperlipidemic patients: a clinical investigation. Curr Ther Res 1983;34:383-90.
[235] Donati C, Bertieri RS, Barbi G. Pantethine, diabetes mellitus and atherosclerosis. Clinical study of 1045 patients. Clin Ter 1989;128:411-22 [Italian].
[236] Prisco D, Rogasi PG, Matucci M, et al. Effect of oral treatment with pantethine on platelet and plasma phospholipids in IIa hyperlipoproteinemia. Angiology 1987;38:241-7.
[237] Gaddi A, Descovich GC, Noseda G, et al. Controlled evaluation of pantethine, a natural hypolipidemic compound, in patients with different forms of hyperlipoproteinemia. Atherosclerosis 1984;50:73-83.
[238] Da Col PG, et al. Pantethine in the treatment of hyper-cholesterolemia: a randomized double-blind trial versus tiadenol. Curr Ther Res 1984;36:314.
[239] Tonutti L, Taboga C, Noacco C. Comparison of the efficacy of pantethine, acipimox, and bezafibrate on plasma lipids and index of cardiovascular risk in diabetics with dyslipidemia. Minerva Med 1991;82:657-63 [Italian].
[240] Agarwal RC, Singh SP, Saran RK, et al. Clinical trial of gugulipid new hypolipidemic agent of plant origin in primary hyperlipidemia. Indian J Med Res 1986;84:626-34.
[241] Gopal K, Saran RK, Nityanand S, et al. Clinical trial of ethyl acetate extract of gum gugulu (gugulipid) in primary hyperlipidemia. J Assoc Physicians India 1986;34:249-51.
[242] Gaur SPS, Garg RK, Kar AM, et al. Gugulipid, a new hypolipidemic agent in patients of acute ischemic stroke: effect on clinical outcome, platelet function and serum lipids. Asia Pacific J Pharm 1997;12:65-9.
[243] Singh RB, Niaz MA, Ghosh S. Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia. Cardiovasc Drugs Ther 1994;8:659-64.
[244] Nityanand S, Srivastava JS, Asthana OP. Clinical trials with Gugulipid—A new hypolipidemic agent. J Assoc Phys India 1989;37:323-8.
[245] Verma SK, Bordia A. Effect of *Commiphora mukul* (gum guggulu) in patients of hyperlipidemia with special reference to HDL-cholesterol. Indian J Med Res 1988;87:356-60.
[246] Szapary PO, Wolfe ML, Bloedon LT, et al. Guggulipid for treatment of hypercholesterolemia: a randomized controlled trial. JAMA 2003;290:765-72.
[247] Menendez R, Arruzazabala L, Más R, et al. Cholesterol-lowering effect of policosanol on rabbits with hypercholesterolaemia induced by a wheat starch-casein diet. Br J Nutr 1997;77:923–32.

[248] Gouni-Berthold I, Berthold HK. Policosanol: clinical pharmacology and therapeutic significance of a new lipid-lowering agent. Am Heart J 2002;143:356-65.
[249] Mirkin A, Mas R, Martinto M, et al. Efficacy and tolerability of policosanol in hypercholesterolemic postmenopausal women. Int J Clin Pharmacol Res 2001;21:31-41.
[250] Castano G, Mas R, Fernandez JC, et al. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. J Gerontol A Biol Sci Med Sci 2001;56:M186-92.
[251] Castano G, Mas R, Fernandez L, et al. Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: A 6-month double-blind study. Int J Clin Pharm Res 2001;1:43-57.
[252] Castano G, Tula L, Canetti M, et al. Effects of policosanol in hypertensive patients with type II hypercholesterolemia. Curr Ther Res 1996;57:691-5.
[253] Castano G, Canetti M, Moreira M, et al. Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: a 12-month study. Curr Ther Res 1995;56:819-23.
[254] Aneiros E, Calderson B, Más R, et al. Effect of successive dose increases of policosanol on the lipid profile and tolerability of treatment. Curr Ther Res 1993;54:304-12.
[255] Pons P, Rodríquez M, Más R, et al. One-year efficacy and safety of policosanol in patients with type II hypercholesterolemia. Curr Ther Res 1994;55:1084-92.
[256] Mas R, Castano G, Illnait J, et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. Clin Pharmacol Ther 1999;65:439-47.
[257] Torres O, Agramonte AJ, Illnait J, et al. Treatment of hypercholesterolemia in NIDDM with policosanol. Diabetes Care 1995;18:393-7.
[258] Canetti M, Moreira M, Mas R, et al. A two-year study on the efficacy and tolerability of policosanol in patients with type II hyperlipoproteinaemia. Int J Clin Pharmacol Res 1995;15:159-65.
[259] Berthold HK, Unverdorben S, Degenhardt R, et al. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia. JAMA 2006;295:2262-69.
[260] Lin Y, Rudrum M, van der Wielen RPJ, et al. Wheat germ policosanol failed to lower plasma cholesterol in subjects with normal to mildly elevated cholesterol concentrations. Metabolism 2004;53:1309-14.
[261] Heber D, Yip I, Ashley JM, et al. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr 1999;69:231-6.
[262] Ma J, Li Y, Ye Q, et al. Constituents of red yeast rice, a traditional Chinese food and medicine. J Agric Food Chem 2000;48:5220-5.
[263] Endo A, Komagata D, Shimada H. Monacolin M, a new inhibitor of cholesterol biosynthesis. J Antibiot (Tokyo) 1986;39:1670-3.
[264] Wang J, Su M, Lu Z, et al. Clinical trial of extract of Monascus purpureus (red yeast) in the treatment of hyperlipidemia. Chin J Exp Ther Prep Chin Med 1995;12:1-5.
[265] Shen Z, Yu P, Su M, et al. A prospective study on Zhitai capsule in the treatment of primary hyperlipidemia. Nat Med J China 1996;76:156-7.
[266] Wang J, Lu Z, Chi J, et al. Multicenter clinical trial of the serum lipid-lowering effects of a Monascus purpureus (red yeast) rice preparation from traditional Chinese medicine. Curr Ther Res 1997;58:964-78.
[267] Hipler UC, Wigger-Alberti W, Bauer A, Elsner P. Case Report. Monascus purpureus-a new fungus of allergologic relevance. Mycoses 2002;45:58-60.
[268] Wigger-Alberti W, Bauer A, Hipler UC, Elsner P. Anaphylaxis due to Monascus purpureus-fermented rice (red yeast rice). Allergy 1999;54:1330-1.
[269] Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: two-efficacy and safety follow-up. Am J Cardiol 1994;74:667-73.
[270] Bliznakov EG. More on the Chinese red-yeast-rice supplement and its cholesterol-lowering effect. Am J Clin Nutr 2000;71:152-4.
[271] Bliznakov EG, Wilkins DJ. Biochemical and clinical consequences of inhibiting coenzyme Q_{10} biosynthesis by lipid-lowering HMG-CoA reductase inhibitors (statins): a critical overview. Adv Ther 1998;15:218-28.
[272] Opara JU, Levine JH. The deadly quartet--the insulin resistance syndrome. South Med J 1997;90:1162-8.

[273] Tahtinen TM, Vanhala MJ, Oikarinen JA, Keinanen-Kiukaanniemi SM. Effect of smoking on the prevalence of insulin resistance-associated cardiovascular risk factors among Finnish men in military service. J Cardiovasc Risk 1998;5:319-23.
[274] Mikhailidis DP, Papadakis JA, Ganotakis ES. Smoking, diabetes and hyperlipidaemia. J R Soc Health 1998;118:91-3 [review].
[275] Henkin L, Zaccaro D, Haffner S, et al. Cigarette smoking, environmental tobacco smoke exposure and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. Ann Epidemiol 1999;9:290-6.
[276] Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 1996;94:878-81.
[277] Assali AR, Beigel Y, Schreibman R, et al. Weight gain and insulin resistance during nicotine replacement therapy. Clin Cardiol 1999;22:357-60.
[278] Eliasson B, Attvall S, Taskinen MR, Smith U. Smoking cessation improves insulin sensitivity in healthy middle-aged men. Eur J Clin Invest 1997;27:450-6.
[279] Frayn KN. Visceral fat and insulin resistance—causative or correlative? Br J Nutr 2000;83:S71-7 [review].
[280] Belfiore F, Iannello S. Insulin resistance in obesity: metabolic mechanisms and measurement methods. Mol Genet Metab 1998;65:121-8.
[281] Ross R, Dagnone D, Jones PJ, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. Ann Intern Med 2000;133:92-103.
[282] Bessesen DH. Obesity as a factor. Nutr Rev 2000;58:S12-S15 [review].
[283] Torjesen PA, Birkeland KI, Anderssen SA, et al. Lifestyle changes may reverse development of the insulin resistance syndrome. The Oslo Diet and Exercise Study: a randomized trial. Diabetes Care 1997;20:26-31.
[284] van Baak MA, Borghouts LB. Relationships with physical activity. Nutr Rev 2000;58:S16-S18 [review].
[285] Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. Int J Sports Med 2000;21:1-12 [review].
[286] Kukkonen K, Rauramaa R, Voutilainene E, Lansimies E. Physical training of middle-aged men with borderline hypertension. Ann Clin Res 1982;14(Suppl 34):139-45.
[287] Young DR, Appel LG, Jee SH, Miller ER III. The effect of aerobic exercise and T'ai Chi on blood pressure in older people: results of a randomized trial. J Am Geriatr Soc 1999;47:277-84.
[288] Cominacini L, Zocca I, Garbin U, et al. Long-term effect of a low-fat, high carbohydrate diet on plasma lipids of patients affected by familial endogenous hypertriglyceridemia. Am J Clin Nutr 1988;48:57-65.
[289] Anderson JW, Gustafson NJ. High-carbohydrate, high-fiber diet. Postgrad Med 1987;82:40-55 [review].
[290] Consensus Development Panel. Treatment of hypertriglyceridemia. JAMA 1984;251:1196-200.
[291] Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.
[292] Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. Diabetes Care 2001;24:619-24.
[293] Appel LJ, Moore TJ, Boarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336:1117-24.
[294] Svetkey LP, Simons-Morton D, Vollmer WM, et al. Effects of dietary patterns on blood pressure: a subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. Arch Intern Med 1999;159:285-93.
[295] Williams DE, Prevost AT, Whichelow MJ, et al. A cross-sectional study of dietary patterns with glucose intolerance and other features of the metabolic syndrome. Br J Nutr 2000;83:257-66.
[296] Flynn MM, Zmuda JM, Milosavljevic D, et al. Lipoprotein response to a National Cholesterol Education Program step II diet with and without energy restriction. Metabolism 1999;48:822-6.
[297] Hunninghake DB, Stein EA, Dujovne CA, et al. The efficacy of intensive dietary therapy alone or combined with lovastatin in outpatients with hypercholesterolemia. N Engl J Med 1993;328:1213-9.

[298] Schaefer EJ, Lichtenstein AH, Lamon-Fava S, et al. Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. Arterioscler Thromb Vasc Biol 1995;15:1079-85.
[299] Jeppeson J, Schaaf P, Jones C, et al. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997;65:1027-33.
[300] Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) of syndrome X? A viewpoint strongly against. Curr Opin Lipidol 1997;8:23-7.
[301] Riccardi G, Rivellese AA. Dietary treatment of the metabolic syndrome—the optimal diet. Br J Nutr 2000;83:S143-S148.
[302] Storlien LH, Kriketos AD, Calvert GD, et al. Fatty acids, triglycerides and syndromes of insulin resistance. Prostaglandins Leukot Essent Fatty Acids 1997;57:379–85.
[303] Bessesen DH. The role of carbohydrates in insulin resistance. J Nutr 2001;131:2782S-86S.
[304] Daly ME, Vale C, Walker M, et al. Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. Am J Clin Nutr 1997;66:1072-85.
[305] Wolever TMS, Brand Miller J. Sugars and blood glucose control. Am J Clin Nutr 1995;62:212S-17S [review].
[306] Wolever TM. Dietary carbohydrates and insulin action in humans. Br J Nutr 2000;83:S97-S102.
[307] Baba NH, Sawaya S, Torbay N, et al. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. Int J Obes Relat Metab Disord 1999;23:1202-6.
[308] Fleming RM. The effect of high-protein diets on coronary blood flow. Angiology 2000;51:817-26.
[309] Vincent JB. Mechanisms of chromium action: low-molecular-weight chromium-binding substance. J Am Coll Nutr 1999;18:6-12.
[310] Anderson RA. Nutritional factors influencing the glucose/insulin system: chromium. J Am Coll Nutr 1997;16:404-10.
[311] Anderson RA. Chromium, glucose intolerance and diabetes. J Am Coll Nutr 1998;17:548-55.
[312] Anderson RA. Chromium in the prevention and control of diabetes. Diabetes Metab 2000;26:22-7.
[313] Vuksan V, Jenkins DJ, Spadafora P, et al. Konjac-mannan (glucomannan) improves glycemia and other associated risk factors for coronary heart disease in type 2 diabetes. A randomized controlled metabolic trial.
Diabetes Care 1999;22:913-9.
[314] Vorster HH, Lotter AP, Odendaal I, et al. Benefits from supplementation of the current recommended diabetic diet with gel fibre. Int Clin Nutr Rev 1988;8:140-6.
[315] Groop PH, Aro A, Stenman S, Groop L. Long-term effects of guar gum in subjects with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1993;58:513-8.
[316] Nuttall FQ. Dietary fiber in the management of diabetes. Diabetes 1993;42:503-8.
[317] Vuksan V, Sievenpiper JL, Owen R, et al. Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial. Diabetes Care 2000;23:9–14.
[318] Landin K, Holm G, Tengborn L, Smith U. Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men. Am J Clin Nutr 1992;56:1061-5.
[319] Cavallo-Perin P, Bruno A, Nuccio P, et al. Dietary guar gum supplementation does not modify insulin resistance in gross obesity. Acta Diabetol Lat 1985;22:139-42.
[320] Barker LR, Burton JR, Zieve PD, eds. Principles of ambulatory medicine, 4th ed. Baltimore, MD: Williams & Wilkins; 1995.
[321] Tilkian SM, Conover MB, Tilkian AG. Clinical implications of laboratory tests, 3rd ed. St. Louis, MO: CV Mosby; 1983.
[322] Litin L, Sack F. *Trans*-fatty acid content of some common foods. N Eng J Med 1993;329:1969-70.
[323] No author listed. ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. Am J Health-Syst Pharm 1997;54:2815-9.
[324] Garg R, Malinow M, Pettinger M, Upson B, Hunninghake D. Niacin treatment increases plasma homocyst(e)ine levels. Am Heart J 1999;138(6 Pt 1):1082-7.
[325] Taylor BV, Oudit GY, Evans M. Homocysteine, vitamins, and coronary artery disease. Comprehensive review of the literature. Can Fam Physician 2000;46:2236-45.
[326] Lobo A, Naso A, Arheart K, et al. Reduction of homocysteine levels in coronary artery disease by low-dose folic acid combined with vitamins B_6 and B_{12}. Am J Cardiol 1999;83:821-5.

[327] Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360-81.
[328] Kudchodkar BJ, Sodhi HS, Horlick L, Mason DT. Mechanisms of hypolipidemic action of nicotinic acid. Clin Pharmacol Ther 1978;24:354-73.
[329] Drood JM, Zimetbaum PJ, Frishman WH. Nicotinic acid for the treatment of hyperlipoproteinemia. J Clin Pharmacol 1991;31:641-50.
[330] Guyton JR. Effect of niacin on atherosclerotic cardiovascular disease. Am J Cardiol 1998;82(12A):18U-23U.
[331] Yovos JG, Patel ST, Falko JM, Newman HA, Hill DS. Effects of nicotinic acid therapy on plasma lipoproteins and very low density lipoprotein apoprotein C subspecies in hyperlipo-proteinemia. J Clin Endocrinol Metab 1982;54:1210-5.
[332] Wahlberg G, Walldius G, Olsson AG, Kirstein P. Effects of nicotinic acid on serum cholesterol concentrations of high density lipoprotein subfractions HDL2 and HDL3 in hyperlipo-proteinemia. J Intern Med 1990;228:151-7.
[333] Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang Z, Ripsin CM. Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991;151:1424-32.
[334] Brown WV. Niacin for lipid disorders. Postgrad Med 1995;98:183-93 [review].
[335]Alderman JD, Pasternak RC, Sacks FM, Smith HS, Monrad S, Grossman W. Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. Am J Cardiol 1989;64:725-9.
[336] Henkin Y, Oberman A, Hurst DC, Segrest JP. Niacin revisited: clinical observations on an important but underutilized drug. Am J Med 1991;91:239-46.
[337] Henkin Y, Oberman A, Hurst DC, Segrest JP. Niacin revisited: clinical observations on an important but underutilized drug. Am J Med 1991;91:239-46.
[338] Drood JM, Zimetbaum PJ, Frishman WH. Nicotinic acid for the treatment of hyperlipoproteinemia. J Clin Pharmacol 1991;31:641-50.
[339] Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 1985;34:642-50.
[340] Charmon RC, Matthews LB, Braeuler C. Nicotinic acid in the treatment of hypercholesterolemia. A long term study. Angiology 1972;23(1):29-35.
[341] McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs. immediate-release niacin in hypercholesterolemic patients. JAMA 1994;271:672-7.
[342] Gibbons LW, Gonzalez V, Gordon N, Grundy S. The prevalence of side effects with regular and sustained-release nicotinic acid. Am J Med 1995;99:378-85.
[343] Morgan JM, Capuzzi DM, Guyton JR. A new extended-release niacin (Niaspan): efficacy, tolerability, and safety in hypercholesterolemic patients. Am J Cardiol 1998;82:29U-34U.
[344] Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. JAMA 1990;264:723-6.
[345] Jungnickel PW, Maloley PA, Vander Tuin EL. Peddicord TE. Campbell JR. Effect of two aspirin pretreatment regimens on niacin-induced cutaneous reactions. J General Intern Med 1997;12(10):591-6.
[346] Knopp RH. Clinical profiles of plain versus sustained-release niacin (Niaspan) and the physiologic rationale for nighttime dosing. Am J Cardiol 1998;82(12A):24U-28U; discussion 39U-41U.
[347] Brown BG, Bardsley J, Poulin D, et al. Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-density lipoprotein cholesterol <100 mg/dL in patients with hyperlipidemia and coronary artery disease. [Clinical Trial. Journal Article. Randomized Controlled Trial] Am J Cardiol 1997;80(2):111-5.