Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1210–1220
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Current concepts in triglyceride metabolism, pathophysiology, and treatment

Georges AbouRjaili[a], Norbert Shtaynberg[a,*], Robert Wetz[a], Thomas Costantino[a], George S. Abela[b]

[a]*Department of Medicine, Staten Island University Hospital, Staten Island, NY*
[b]*Division of Cardiology, Michigan State University, East Lansing, MI*

Received 4 March 2009; accepted 17 November 2009

Abstract

It is becoming more evident that age, gender, and race play a significant role in the metabolic profiles that are seen among individuals in a clinical setting. It is important to understand these variances in metabolic profiles; and with these variances in mind it is now possible to understand why a single diet might not decrease cardiovascular disease risk profiles uniformly for everyone. Much is now understood about triglyceride metabolism and its contribution to energy storage. In this review we will focus on triglycerides; their production, metabolism and influence on daily life, as well as the various methods for the treatment of hypertryglyceridemia and prevention of its sequelae.

1. Introduction

For the past 15 years, the public has been told to reduce total fat intake to modify risk factors for coronary artery disease (CAD) and control weight. In addition, most studies of diet and risks for CAD have been primarily interested in the effects of reducing weight and other CAD risk factors by using this approach. In response, Americans have dramatically reduced all types of fat intake; and the percentage of fat in the American diet has decreased from 45% in 1965 to 34% in 1995 (US Department of Agriculture Center for Nutrition Policy and Promotion). This nationwide decrease in fat calories has resulted in an increase in carbohydrate calories, primarily in the form of simple sugars [1].

Despite national efforts to reduce fat intake, there has been a steady increase in body weight and deleterious plasma cholesterol levels in the general population. Recent studies have shown that high-carbohydrate, low-fat diets are capable of producing high triglyceride (TG) levels, low-density lipoprotein (LDL) levels, and weight gain [2]. Accordingly, the population has become more obese and is at greater risk for developing CAD. This dietary effect on the lipid profile likely hampers physicians' endeavors in controlling cardiovascular disease (CVD) risk factors.

2. Triglyceride metabolism

In the human body, metabolic energy is mainly derived from TGs, which constitute 15% to 20% of total body weight and provide 9 kcal/g [3]. However, the preferred and first source of energy to be used is glucose (4 kcal/g), followed by TG [3]. Only a few grams of glucose (stored as glycogen) are in the liver and muscles; therefore, during starvation, glycogen will be depleted within a few hours (half a day). Humans, unlike plants, are unable to convert free fatty acids (FFAs) into glucose because of the lack of 2 important enzymes [3]. Therefore, energy production will be provided by TGs for a few weeks until fat stores are depleted, with proteins used thereafter [4]. Hence, TGs constitute the main and most reliable source of energy for the body [4]. On the other hand, when glucose is not used for energy production and when storage is saturated, all of the glucose (and carbohydrate) excess will be shifted toward the synthesis of FFA and TG [3].

* Corresponding author. 475 Seaview Ave, Staten Island, NY 10305, USA.
E-mail address: norberts@optonline.net (N. Shtaynberg).

0026-0495/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.11.014

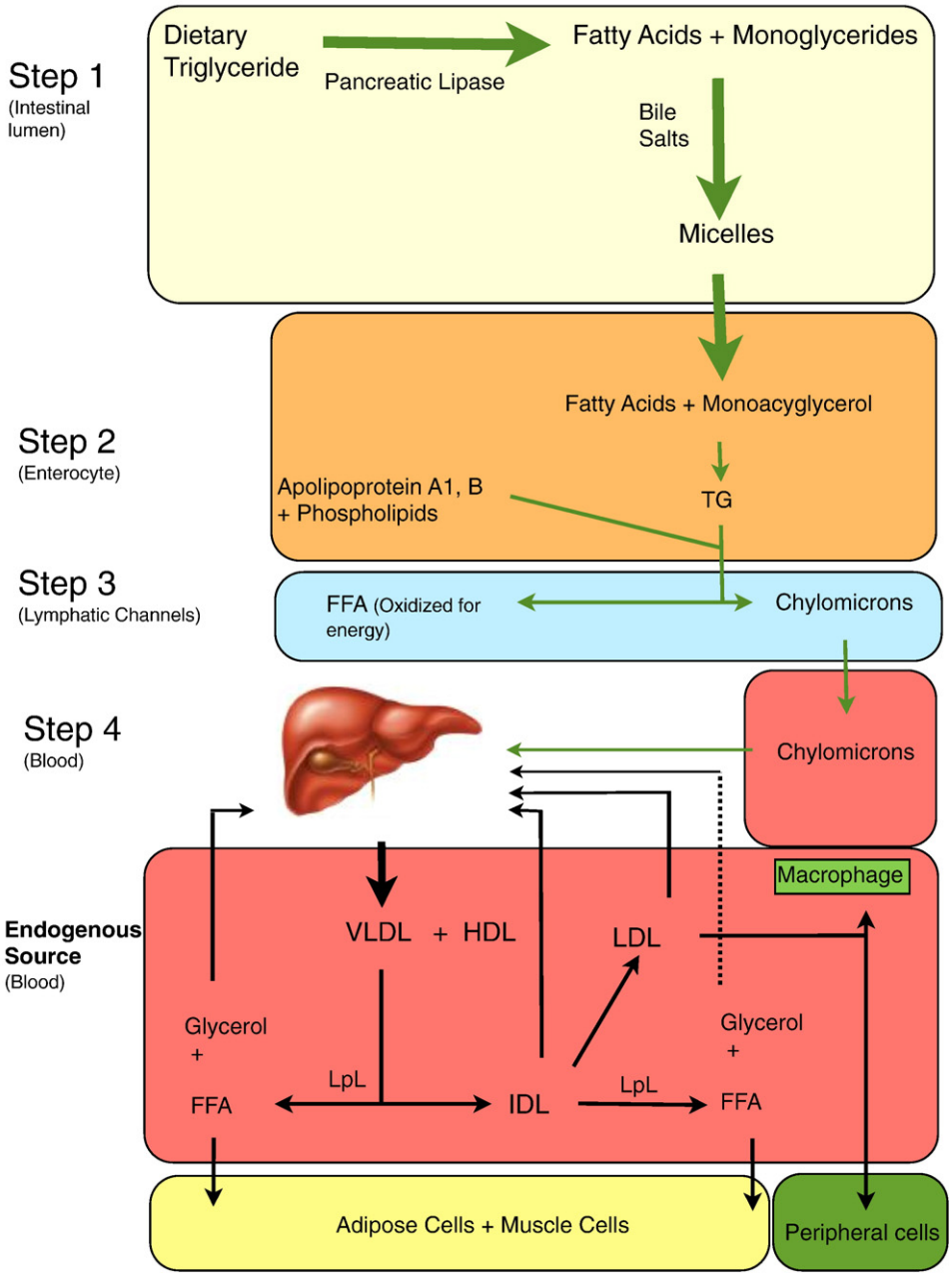

Fig. 1. Intestinal absorption (exogenous source) and synthesis of TG (endogenous source).

The TGs in the body originate from 2 sources: the exogenous (or dietary) source and the endogenous source (Fig. 1) [4].

2.1. Exogenous source

Step 1: The breakdown or hydrolysis of dietary TG starts in the stomach and continues in the small intestines because of the effect of pancreatic lipases to form FFA and monoglycerides, which will subsequently form micelles with the aid of bile salts. The micelles help the monoglycerides and the FFA to attach to the intestinal brush border so they can diffuse through the lipid membrane and into the enterocytes.

Step 2: Inside the enterocytes, the FFA and the monoglycerides reassemble and reform TG.

Step 3: Triglyceride, cholesterol, apolipoproteins, and the phospholipids form the chylomicrons, which enter the lymphatic circulation. During this step, FFAs are released and oxidized for energy use.

Step 4: Chylomicrons will be targeted by the lipoprotein lipase (LPL), anchored in the capillary endothelial cells, to form chylomicron remnants, which are taken up by the liver.

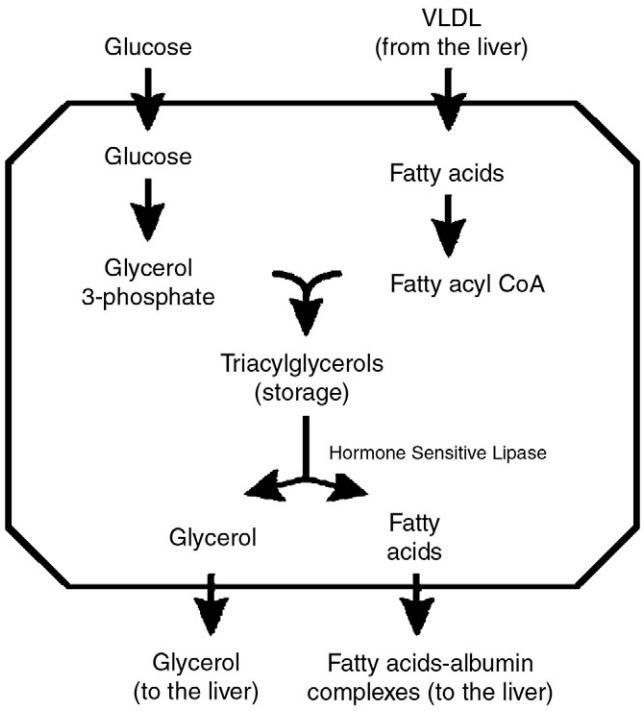

Fig. 2. Triglyceride biosynthesis at the level of adipocytes.

2.2. Endogenous source

The liver transforms the fatty acids (mainly the long chain) and monoglycerides into TG, which will be secreted into the blood as very low-density lipoprotein (VLDL) (mainly) and high-density lipoprotein (HDL). Very low-density lipoprotein is then converted to intermediate-density lipoprotein (IDL), which is further broken down into LDL, which circulates either back to the liver or to the peripheral tissue for storage.

The basic metabolic pathways of TG biosynthesis at the level of adipocytes is described in Fig. 2. Adipose cells are specialized for the esterification of FFA for biosynthesis of triacylglycerols and storage. Synthesis of triacylglycerol requires 2 components: glycerol-3-phosphate and FFA or palmitic acid. Free fatty acids, in the form of palmitate, are produced in the liver and delivered to adipose cells via the VLDL particle. When VLDL reaches adipose tissue, it is hydrolyzed into FFA and then transported into adipose cells for biosynthesis of triacylglycerol. The second component of TG synthesis is glycerol-3-phosphate, which is produced within the adipose cell from circulating glucose that the cell takes in and metabolizes. Both of these components rely on blood glucose levels for their synthesis.

3. Triglyceride and lipid profile

In the Helsinki Heart Study, elevation of TG levels was associated with low HDL levels and insulin resistance, thereby increasing the risk for CAD [5]. Very low-density lipoprotein and chylomicron remnants are the particles that make TG more atherogenic. These remnants are smaller, richer in cholesterol, and more readily taken up by macrophages, converting them to plaque-forming foam cells. As an illustrative distinction, in patients with familial chylomicronemia syndrome, where chylomicron remnants cannot be formed because of a defect in LPL and apolipoprotein (apo) C-II, the chylomicrons remain large and nonatherogenic [6].

Increases in TG and VLDL cause an increase in cholesterol ester transfer protein activity, which induces a shift in production from HDL and IDL to LDL cholesterol formation [7]. Furthermore, TGs act by shifting the LDL particle from large to small particles; these latter particles are recognized as being more atherogenic and associated with increased CAD [8].

Non–high-density lipoprotein cholesterol reflects indirectly the total apo B level, which itself is a major atherogenic lipoprotein [9]. At TG levels less than 200 mg/dL, there is no significant increase in VLDL; and hence, non-HDL cholesterol (non–HDL-c) is reflected by the LDL alone [9]. When the TG level is 200 to 499 mg/dL, there is marked increase in the VLDL fraction; and non–HDL-c represents the atherogenic lipoproteins better then LDL alone [9]. In patients with TG level of at least 500 mg/dL, non-HDL is a poorer predictor of CVD risk because of large VLDL and chylomicron particles, which are nonatherogenic [9].

There have been several studies showing a relationship between postprandial transient increases in TG and TG-rich

Table 1
Types of dyslipidemias and their effects [3]

Type	Defect	Lipoprotein change	Clinical findings
I (rare)	LPL deficiency Apo C-II deficiency	↑ Chylomicron ↑ TG	↑ Triacylglycerol >1000 mg/dL Lipemia retinalis Eruptive xanthomas Pancreatitis Hepatosplenomegaly
IIa	LDL receptor defect in synthesis or function	↑ LDL	Myocardial infarction before age of 20 y in homozygotes
IIb	↑ Apo B ↓ LDL receptor	↑ LDL ↑ VLDL ↑ TG	CAD
III (rare)	Abnormal apo E2 synthesis	↑ VLDL remnants ↑ Chylomicron ↑ TG	Peripheral vascular disease, premature CAD, xanthomas, ↑ risk of atherosclerosis
IV	↑ Production and ↓ elimination of VLDL	↑ VLDL ↓ HDL-c ↑ TG	Early CAD
V (rare)	LPL deficiency ↑ VLDL production	↑ VLDL ↑ Chylomicron ↑ TG	Pancreatitis Eruptive xanthomas

Table 2
Secondary causes of hypertriglyceridemia

Secondary causes of hypertriglyceridemia	Mechanism
Corticosteroids	Increase production of VLDL leading to increase in TG [18]
Hormone replacement therapy [19]	Estrogen (increases TG) replacement Progesterone Norethisterone (decreases TG) C21 progestogens (no effect on TG)
Oral contraceptives	Mainly the estrogen components are associated with high TG [20]. They increase TG by increasing synthesis rather than decreasing elimination.
Diuretics	Mainly thiazides, increase the TG by 15% to 25% [21].
β-Blockers (except those with intrinsic sympathomimetic activity)	Inhibit LPL activity leading to increased TG levels [22]
Retinoids	Stimulate the production and secretion of VLDL by the liver causing increased TG (200 up to 1000 mg/dL) [23]
Antiretroviral (mainly protease inhibitors)	Cause overproduction of VLDL by the liver causing increase in TG
Hypothyroidism	The usual dyslipidemia found in hypothyroidism is hypercholesterolemia; but hypertriglyceridemia can also be encountered, and the increase could be explained by a decrease in LPL activity [24].
Diabetes mellitus	Elevation of TG levels is due to insulin deficiency, which diminishes LPL activity, causing a TG removal defect. Insulin deficiency will lead to unopposed activity of glucagon, cortisol, and growth hormone on adipose tissue to release FFA, which will subsequently be used by the liver to synthesize VLDL, which in turn increases TG [25].
Pregnancy	Gestational hypertriglyceridemia is related to VLDL overproduction. When it occurs, it usually peaks by the third trimester and returns to normal by the 6th wk postpartum [26].
Chronic kidney disease and end-stage renal disease	The decrease in the activities of LPL and hepatic TG lipase, the large amount of glucose present in peritoneal dialysis fluid, and secondary hyperparathyroidism collectively increase the serum TG levels [27].
Nephrotic syndrome	Increased TG due to overproduction of VLDL by the liver [28].
Burns	Cause transient hypertriglyceridemia due to the reduction of TG clearance [29].
Exercise	During exercise, multiple hormones (epinephrine, norepinephrine, corticosteroid, and growth hormone) act directly on fat cells to activate hormone-sensitive TG lipase, which causes hydrolysis of TG and mobilization of FFA to be used by muscle cells as a source of energy. The excess FFA in the blood will be taken up by liver cells to synthesize VLDL and TG [3].

remnants after a high-fat meal and endothelial dysfunction (vasoreactivity), which is thought to play a role in the development of atherosclerosis and its progression [10-14]. This effect was even more pronounced in diabetic patients [13,14]. In contrast, other studies on the same subject fail to demonstrate such a relationship [15,16]. A large prospective study would be necessary to further evaluate this hypothesis.

4. Hypertriglyceridemia

Hypertriglyceridemia is defined by the National Cholesterol Education Program–Adult Treatment Panel (NCEP ATP-III) as a TG level of at least 150 mg/dL and can be divided into primary and secondary based upon the causes [9]. In primary hypertriglyceridemia, there is a genetic defect leading to flawed TG metabolism (Table 1) [17].

Many secondary etiologies of hypertriglyceridemia (Table 2) have been identified; therefore, before considering hypertriglyceridemia as a primary disease, a full and thorough history should be conducted to look for secondary causes. Left untreated and in the presence of a genetic or familial disease for high TG, these secondary conditions may lead to severe hypertriglyceridemia and life-threatening pancreatitis.

One should think of secondary causes in the following situations:

1. Marked or progressive increase of TG in the absence of a family history of hyperlipidemia.
2. Hypertriglyceridemia that is unresponsive to medical treatment.
3. Life-threatening hypertriglyceridemia in previously mild disease.

5. Triglyceride and ethnicity

Nutritional studies have shown differences in cholesterol serum levels and obesity among various ages, sexes, and ethnic groups. Specifically, in postmenopausal women, as well as in the Hispanic and Native American populations, there seems to be a predilection toward a greater risk of developing obesity and CAD [30]. This may help explain, in part, the higher incidence of diabetes and obesity noted [31].

Racial predilection toward increased TG levels has also been reported. There is a tendency for higher TG levels across Hispanic subgroups [32]. This was also associated with an increase in insulin resistance in this population group. In American Indians, there is a positive correlation between TG levels, body mass index (BMI), and waist circumference [32]. The Strong Heart Study demonstrated that obesity correlated with decreased HDL, and central obesity was more associated with abnormal lipid/lipoprotein profiles than general obesity in women [33]. However, both of these obesity distribution types were equally important in men [33].

Different studies have shown that TG levels are higher in whites compared with African American children [34, 35]. In contrast, total cholesterol levels were higher in African Americans [34,35]. The presumed cause of higher TG in

whites is not known, but the assumption is that African Americans may have an efficient TG clearing mechanism. There is evidence to suggest that African American and Mexican American children and young adults have an increased risk profile for CVD when compared with white Americans [30], which is related in part to the higher cholesterol in these populations. This trend is also seen in older African and Mexican American men and women compared with white Americans [36,37].

In African Americans, HDL-c concentrations are higher and TG concentrations are lower [36]. This lipid profile advantage, seen in African Americans, loses its significance when considering the high rate of mortality from CAD in this population, which is secondary to a higher degree of diabetes, hypertension, and obesity [30].

Another study comparing TG levels between Japanese, Koreans, and Mongolians showed that despite lower BMI values for the Japanese and Koreans compared with the Mongolians, a higher prevalence of hypertriglyceridemia was observed for both nonobese (BMI <25.0) and obese (BMI ≥25.0) Japanese and Korean subjects [38].

Finally, the apo A5 gene overexpression (APOA5∗2 and APOA5∗3) was shown to lower TG concentrations in humans. The haplotype in one study was found in 12% of white, 14% of African American, and 28% of Hispanic men and women [39].

6. Triglyceride, sex, and age

Postmenopausal women have a higher level of remnant lipoprotein-cholesterol levels [31]. In addition, it is well recognized that hormone replacement in postmenopausal women lowers LDL and increases HDL significantly, mainly HDL2 [40]. Although total TG levels did not change significantly, the remnant lipoprotein-cholesterol levels decreased with estrogen and estrogen-progestin therapy ($P < .05$) [40].

There is some evidence that suggests that both women and men have different metabolic profiles because of sex influences and age. One study has suggested that the redistribution of body fat is associated with the differences in triacylglycerol and cholesterol levels of older women [41]. Other evidence suggests that these metabolic changes might be attributed to the different hormonal levels seen in postmenopausal and premenopausal women [42]. For some time, estrogen has been attributed to the cardioprotective effects that women have during their childbearing years [43]. There is an obvious difference in fat distribution between men and women that has been linked to the differences in TG and lipid levels between sexes [44].

With regards to age, older men may reportedly have a less favorable lipid profile independent of fat distribution or BMI [45]. In addition, age was shown to be an independent factor in determining TG levels [46]. In the Prospective Cardiovascular Munster study [47], a large observational study, it was shown that men (18.6%) more than women (4.2%) have mild increases in TG (TG >200 mg/dL) [47]. Triglyceride levels in men increase up to the age of 45 years and then decrease slightly, whereas in women, they continue to increase with age [47].

7. Diet, lipid profile, and CVD

Several studies have shown, in both men and women, that overfeeding of equivalent isoenergetic diets that are sugar rich vs fat rich resulted in the same amount of fat storage. This is most likely due to the conversion of carbohydrates to fat via hepatic and extrahepatic lipogenesis [1,2,48].

Various studies have shown an increase in hepatic secretion of the VLDL-particle–containing palmitate in response to high-carbohydrate diets fed to humans [31,49]. Studies of high-carbohydrate, low-fat diets have also shown a decrease in fat oxidation in humans [31,49]. These 2 mechanisms are strong stimuli for the de novo synthesis and storage of TG. Furthermore, these metabolic trends can be helpful in understanding why low-fat diets are not producing long-term decreases in weight and/or significant decreases in cholesterol serum levels.

Although fruits and vegetables are rich in carbohydrates, multiple studies have shown that they do not exert any effect on TG levels [49-52]. In a study where healthy men and women were randomized either to continue their current diet of fruit and vegetables or to an intervention group, which increased consumption to 8 servings per day, there was no effect by the high fruit and vegetable arm on lipid or lipoprotein levels [51]. However, 2 studies have shown that fruits rich in fiber and antioxidants (eg, guava) have a TG-lowering effect [53,54].

The chief concern about dietary fats is their role in promoting CAD, and some studies have shown that the total

Table 3
Contribution of fatty acids on lipid profile [3]

Type	Source	Effect
trans-Fatty acids	Industrial hydrogenation of polyunsaturated fatty acids	Increase: 1. TG
Saturated fatty acids	1. Animal products: especially dairy products and red meats 2. Cocoa butter	2. LDL 3. Total cholesterol Decrease: 1. HDL
Monounsaturated fatty acids	Mediterranean diet	Decrease: 1. TG
Polyunsaturated fatty acids	1. The N-6 family found in safflower, sunflower, and corn oils 2. The N-3 family or α-linolenic acid found in fish oils	2. Platelet aggregation 3. Fibrinogen 4. Total cholesterol 5. LDL Increase: 1. HDL

Table 4
Modes of action and adverse effects of the different antihyperlipidemic medications

Drug class	Mode of action	Lipid effects [69]	Adverse effects [69]	Drug examples
HMG-CoA reductase inhibitors	↓ Cholesterol biosynthesis, by inhibiting the enzyme responsible for the rate-limiting step of cholesterol formation, which ↑ LDL receptor activity and clears LDL from the circulation [9]. Activate PPAR-α expression, which increases APOAV expression and ↓ TG	↓ LDL ↓ TG (7%-30%) ↑ HDL ↓ VLDL	Skin—rash NS—peripheral neuropathy Liver—weight loss, decrease appetite, increase transaminases GI—abdominal pain, nausea, diarrhea Muscle—myositis, pain, rhabdomyolysis Immune—lupus-like syndrome Protein binding—decrease binding of warfarin	Lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin
Fibric acid derivatives (fibrates)	Activates PPAR-α stimulating LPL in plasma and adipose tissue causing VLDL catabolism [70] ↑ Apo A-I genes ↓ Apo C-III production	↓ TG (20%-50%) ↑ HDL ↑ LDL	Skin—rash GI–abdominal pain, cholesterol-saturated bile with increase gallstone incidence (1%-2%) GU—erectile dysfunction (mainly clofibrate) Muscle—myositis with impaired renal function Plasma proteins—interference with binding of warfarin Liver—increase serum aminotransferases	Gemfibrozil, fenofibrate, clofibrate
Nicotinic acid (niacin)	↓ Mobilization of FFA from peripheral adipose tissue ↓ HDL catabolism Reduces hepatic synthesis of TG and secretion of VLDL Shifts LDL from small dense to large buoyant particles and lowers lipoprotein concentrations by 30% [70]	↓ VLDL ↓ TG (20%-50%) ↑ HDL ↓ LDL ↓ Lp(a)	Skin—flushing, dry skin, pruritis, ichthyosis, acanthosis nigricans Eyes—conjunctivitis, cystoid macular edema, retinal detachment Respiratory tract—nasal stuffiness Heart—supraventricular arrhythmias GI—heartburn, loose bowel movement or diarrhea Liver—mild increase transaminases, nausea, and fatigue Muscle—myositis Metabolic—hyperglycemia (5%), increase in serum uric acid levels by 10%	Extended-release niacin, crystalline niacin, polygel controlled-release niacin
Cholesterol absorption inhibitors	Inhibits intestinal cholesterol absorption, but does not affect absorption of bile acids, fat soluble vitamins, or TG. It has been shown to ↓ TG 7% in monotherapy and 14% in combination with a statin [70, 71]. ↓ Cholesterol content of chylomicrons	↓ TG ↔ HDL ↓ LDL	GI—diarrhea, abdominal pain	Ezetimibe
Bile acid sequestrants (resins)	Interrupt enterohepatic recirculation of bile acids ↑ Hepatic conversion of cholesterol to bile ↑ Hepatic LDL receptor activity	↓ LDL ↑ HDL ↑ TG	GI—abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissures. Liver—mild increase transaminases Metabolic—increase TG ~10% Electrolyte—hyperchloremic acidosis	Cholestyramine, colestipol, colesevelam HCl
ω-3-Acid ethyl esters	↓ TG synthesis by reducing substrate availability, which could be secondary to an increase in β-oxidation, a decrease in FFA delivery to the liver, a decrease in	↓ TG (45%) ↓ VLDL	Skin—alopecia, eczema, pruritus, and sweating Eyes—cataracts Respiratory tract—asthma, bronchitis, increased cough, dyspnea,	ω-3-Acid ethyl esters (Lovaza)

(continued on next page)

Table 4 (*continued*)

Drug class	Mode of action	Lipid effects [69]	Adverse effects [69]	Drug examples
	hepatic fatty acids synthesis, increased phospholipid synthesis, or decreased activity of TG-synthesizing enzymes [72]		Heart—arrhythmia, hypertension, tachycardia GI—anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, pancreatitis Lymphatic—lymphadenopathy Muscle—arthralgia, arthritis, myalgia Metabolic system—edema, hyperglycemia, increased transaminases	

HMG-CoA indicates hydroxymethylglutaryl–coenzyme A; PPAR, peroxisome proliferator-activator receptor; APOAV, apolipoprotein AV; NS, neurological system; GI, gastrointestinal; GU, genitourinary; Lp(a), lipoprotein (a). Lovaza is manufactured by GlaxoSmithKline, Clifton, NJ.

fat is less important than the type of fat [55-57]. The FFA can be subdivided into 4 types (Table 3).

In summary, saturated and *trans*-fatty acids play an important role in the genesis of heart disease, contrary to monounsaturated and polyunsaturated fatty acids, which confer a protective role. Despite their positive and negative effects on the heart, there was no association between FFA and stroke in a large prospective study of 43,732 men participating in the Health Professionals Follow-up Study [58].

8. Triglycerides and alcohol

Just one drink of alcohol could increase TG in susceptible people. In one study where 630 calories of alcohol were administered to 12 individuals, obese individuals were more susceptible to the hyperlipidemic effects of alcohol and had increased TG and VLDL-TG concentrations compared with lean individuals [59]. In one meta-analysis, consuming 30 g of alcohol daily increases TG level by 5.69 mg/dL and HDL-c by 3.99 mg/dL [60].

High-density lipoprotein cholesterol increases mostly in individuals with the slow oxidizing allele of alcohol dehydrogenase type 3, leading to the hypothesis that genetics play an important role in the effect of alcohol [61]. In addition, the alcohol-induced elevation in serum HDL-c may also, in part, involve a reduction in cholesteryl ester transfer protein activity [62], which facilitates the exchange of neutral lipids, particularly cholesteryl esters (but also TG and to some degree phospholipids), from HDL to TG-enriched lipoproteins in exchange for TG [58,63,64]. Low cholesteryl ester transfer protein activity will reduce the redistribution of cholesterol from HDL, thereby increasing serum HDL-c concentrations (mainly HDL-3) [58,63,64]; but this finding needs further investigation. Lastly, a study by Hartung et al [65] showed that levels of HDL_3C and HDL_2C, the latter being protective against heart disease, increased significantly with moderate alcohol intake.

The cardioprotective role of moderate alcohol consumption is attributed to its effects on the lipid metabolism, but this benefit needs to be weighed carefully against alcohol's considerable adverse effects and potential for abuse.

9. Triglycerides and the metabolic syndrome

According to the NCEP ATP-III criteria, the *metabolic syndrome* was defined by the presence of 3 of the 5 following criteria [9]:

- Waist circumference (men, >40 in; women >35 in)
- TG of at least 150 mg/dL
- Blood pressure of at least 130/85 mm Hg
- HDL (men, <40; women, <50)
- Fasting blood glucose of at least 110 mg/dL

The prevalence of this syndrome ranges from 20% to 40% (among individuals >60 years of age) and confers a risk for CAD [9,66,67], especially in the Hispanic and African American populations [68]. The treatment of hypertriglyceridemia constitutes a cornerstone in the management of the metabolic syndrome because TG and HDL are inversely related and the treatment of one leads to the normalization of the second.

10. Therapeutic approaches

10.1. Diet

The major focus of treatment and prevention of hypertriglyceridemia and adverse lipid serum levels seems to be found in manipulating quality and quantity of diet intake (Table 4). A variety of diets with different percentages of fat, protein, and carbohydrates have been recommended to lower lipid profiles. There is the low-fat (11%-19%) and very low-fat (<10%), very high carbohydrate, moderate-protein diets by Dr Dean Ornish's *Program for Reversing Heart Disease* [73], *Eat More Weigh Less* [74], and *The New Pritkin Program* [75]. There has been the moderate-fat (20%-30%), high-carbohydrate, and moderate-protein diet recommended by the US Department of Agriculture Food Guide Pyramid, DASH (Dietary Approaches to Stop

Hypertension) diet, and Weight Watchers [76]. A third version is the high-fat (55%-65%), low-carbohydrate (<100 g/d), high-protein diet supported *Dr Atkin's New Diet Revolution* [77], *Protein Power* [78], and *Life Without Bread* [79].

There are currently only a limited number of ways in which we know that HDL levels can be raised. These are exercise, weight loss (through diets containing high mono- and polyunsaturated FFA substituted for saturated fat), and moderate amounts of alcohol intake. Drugs such as niacin and fibrates are also able to increase HDL levels, but only modestly [9].

The American Heart Association (AHA) released a "Dietary Guideline Revision" in 2000, which takes into consideration the recent evidence of the benefits of ω-3 fatty acids and mono- and polyunsaturated fatty acids [80]. Research has shown that monounsaturated and polyunsaturated fats, common in the Mediterranean diet, have beneficial effects in lowering atherogenic lipid profiles, specifically by reducing TG and small dense LDL particles while maintaining appropriate HDL levels [81]. The Mediterranean diet consists of mostly vegetables, fruits, nuts, grains, and legumes. The diet contains a moderate amount of fat, nearly all in the form of olive oils, nut and seed oils, and fish oils.

A study comparing the AHA step II diet [80] and a diet high in monounsaturated fat has shown that monounsaturated fatty acids produce superior lipid profiles [82]. The study showed that replacement of saturated fats in the AHA step II diet with foods high in monounsaturated fatty acids lowered total cholesterol and TG levels while maintaining HDL cholesterol levels [82]. This had an overall effect of decreasing CVD risk by up to 25% as compared with the 12% reduction with the AHA step II diet [82].

Currently, there is some evidence that reversal of the metabolic syndrome abnormalities has been produced with replacement of a high saturated fat intake with that of a diet consisting of polyunsaturated fats [83]. An explanatory model has been proposed that diets that contain at least 5% of energy from polyunsaturated fatty acids can inhibit sterol regulatory element gene expression [84]. Sterol regulatory elements are segments of DNA that contain genes responsible for activating lipogenic enzymes; hence, inhibition will lead to a decrease in fatty acid synthesis [84]. This model parallels studies that have shown increased plasma TG levels with low-fat diets and decreased TG levels with diets high in mono- and polyunsaturated fatty acids.

Clinical studies have provided evidence that ω-3 fatty acids lower TG levels and decrease blood coagulation states [85,86]. A 45% reduction in TG level is associated with intake of foods rich in ω-3 fatty acids such as fish, canola oil, flaxseed oil, soybean oil, and nuts. Currently, the AHA recommends a minimum of 2 servings of cold-water fish per week [80].

According to the Nurses' Health Study, the risk of CAD can be reduced by 42% if energy from saturated fat was replaced by energy from unsaturated fats and by 53% if energy from *trans* fat was replaced by energy from unhydrogenated, unsaturated fat [87].

10.1.1. Fish oil (ω-3)

ω-3 Fatty acids are usually divided into eicosapentaenoic acid and docosahexaenoic acid, which are found in various fish including salmon, mackerel, lake trout, tuna, and herring. High doses (>6 g/d) can inhibit the synthesis of VLDL-TG and apo B, thus reducing levels of TG [88]. At higher levels, 15 g/d could yield a 50% reduction in TG levels [89]. However, at this dose, adverse effects of fish oil are seen, like an increase in the level of cholesterol; therefore, this amount is not recommended. In a randomized trial of 223 patients, dietary fish oil supplementation with approximately 1.5 g/d for 2 years, compared with placebo, reduced the progression and enhanced the regression of angiographically determined coronary atherosclerosis [90].

In another cohort study, the Nurses' Health Study, there was a positive correlation between lower risk of CAD and CAD deaths and a higher consumption of fish and ω-3 fatty acids [91]. This association was also described in a second study, with α-linolenic acid, the metabolic precursor of the fish oils [92]. Fish oils are also associated with a variety of clinical benefits including reductions in blood pressure, arrhythmias, and coagulability and improvement in endothelial function [93], in addition to all the benefits on the lipid profile mentioned above. The usual indication for prescribing ω-3 fatty acids is TG levels that are greater than 500 mg/dL.

10.1.2. Soy protein

In one meta-analysis, the average intake of 47 g/d (compared with a control diet) lowered TG by 10.5%, total serum cholesterol by 9.3%, and LDL cholesterol (LDL-c) by 12.9%, whereas HDL-c concentration increased by 2.4% [94].

As per the advisory from the Nutrition Committee of the AHA, 25 to 50 g/d of soy protein was found to be safe and effective for reducing TG and LDL levels and promoting heart health [95].

10.1.3. Garlic

Over time, garlic has become an important part of the human diet. Its benefits have been described by Hippocrates, the ancient Egyptians, and many others; but despite this historical perspective, data are still conflicting regarding its effects on the lipid profile. Multiple studies have shown that garlic supplementation significantly decreased both total cholesterol and TG concentrations [96-101], but others failed in confirming this relationship [102-104]. Hence, the need for further controlled human studies with standardized preparations of this herb.

10.1.4. Fiber

It is known that a high-fiber diet exerts a cardioprotective role and that intake of 1 g of soluble fiber reduces LDL-c by 2.2 mg/dL, as well as TG levels [105,106]. This effect was similar with various soluble fibers [106].

Table 5
NCEP ATP-III TG treatment guidelines [9]

TG level	Treatment option
<150 mg/dL (normal)	None
150-199 mg/dL (borderline high)	Weight reduction, physical activity, achieve LDL goal (as per ATP-III recommendations)
200-499 mg/dL (high)	Weight reduction, physical activity, achieve LDL goal Use of LDL-lowering drugs or nicotinic acid or fibrates to achieve non-HDL goal (30 mg/dL higher than LDL goal)
≥500 mg/dL (very high)	TG lowering as primary goal, then LDL goal. Very low fat diet, weight reduction, and physical activity Use nicotinic acid or fibrates as first-line medication

10.1.5. Walnut

Substituting walnut for monounsaturated fats in a diet can achieve a 4% to 12% reduction in serum total cholesterol and a 6% to 12% reduction in serum LDL-c [107]. Another small randomized trial suggested that, in addition to lowering total and LDL-c levels, consumption of walnuts may improve endothelial function in patients with elevated cholesterol [107]. In a review from the prospective Adventist Health Study, individuals who consumed nuts more than 4 times per week had significant reductions in mortality from CAD (relative risk, 0.52) and in nonfatal infarctions (relative risk, 0.49) compared with those who consumed nuts less than once per week [108].

10.1.6. Red yeast rice

Red yeast rice may have cholesterol-lowering ability due to the presence of monacolins that have hydroxymethylglutaryl–coenzyme A reductase inhibitor activity and possibly other active substances. It has been shown to decrease TG levels by 34.1% after 8 weeks of use vs placebo at 12.8% [109].

10.2. Therapy guidelines

The NCEP ATP-III guidelines (Table 5) for treatment of hypertriglyceridemia include the use of lifestyle modification as well as the use of medication based upon the level of TG [9].

References

[1] Willett WC. Is dietary fat a major determinant of body fat? Am J Clin Nutr 1998;67(Supplement):556S-62S.
[2] Lammert O. Macronutrient Metabolism Group Symposium on Dietary fat: how low should we go?' Changes in fat synthesis influenced by dietary macronutrient content. Br J Nutr 2000;84:233-45.
[3] Stryer L, editor. Biochemistry. 3rd ed. New York: WH Freeman and Co; 1988.
[4] Guyton, editor. Textbook of medical physiology. 10th ed. W.B. Saunders Company; 2000. p. 1064.
[5] Tenkanen L, et al. The triglyceride issue revisited. Findings from the Helsinki Heart Study. Arch Intern Med 1994;154:2714-20.
[6] Kingsbury KJ, Bondy G. Understanding the essentials of blood lipid metabolism. Prog Cardiovasc Nurs 2003;18:13-8.
[7] Mann CJ, et al. Mechanism of plasma cholesteryl ester transfer in hypertriglyceridemia. J Clin Invest 1991;88:2059-66.
[8] Roheim PS, Asztalos BF. Clinical significance of lipoprotein size and risk for coronary atherosclerosis. Clin Chem 1995;41:147-52.
[9] Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
[10] Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. Am J Cardiol 1997;79:350-4.
[11] Plotnick GD, Corretti MC, Vogel RA. Effect of antioxidant vitamins on the transient impairment of endothelium-dependent brachial artery vasoactivity following a single high-fat meal. JAMA 1997;278:1682-6.
[12] Groot PH, et al. Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. Arterioscler Thromb 1991;11:653-62.
[13] Anderson RA, et al. The relationships between post-prandial lipaemia, endothelial function and oxidative stress in healthy individuals and patients with type 2 diabetes. Atherosclerosis 2001;154:475-83.
[14] Nappo F, et al. Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. J Am Coll Cardiol 2002;39:1145-50.
[15] Djousse L, et al. Acute effects of a high-fat meal with and without red wine on endothelial function in healthy subjects. Am J Cardiol 1999;84:660-4.
[16] Gudmundsson GS, et al. Resistance vessel endothelial function in healthy humans during transient postprandial hypertriglyceridemia. Am J Cardiol 2000;85:381-5.
[17] Jeppesen J, et al. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. Circulation 1998;97:1029-36.
[18] Ettinger Jr WH, Hazzard WR. Prednisone increases very low density lipoprotein and high density lipoprotein in healthy men. Metabolism 1988;37:1055-8.
[19] Hormones and cardiovascular diseases: oral contraceptives and hormonal replacement therapy: differential effects on coronary heart disease, deep venous thrombosis and stroke. The ESHRE Capri Workshop Group. Hum Reprod 1998;13:2325-33.
[20] Godsland IF, et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990;323:1375-81.
[21] Grimm Jr RH, Hunninghake DB. Lipids and hypertension. Implications of new guidelines for cholesterol management in the treatment of hypertension. Am J Med 1986;80:56-63.
[22] Day JL, et al. Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. Br Med J 1979;1:77-80.
[23] O'Leary TJ, et al. Changes in serum lipoproteins and high-density lipoprotein composition during isotretinoin therapy. Clin Invest Med 1987;10:355-60.
[24] Michalopoulou G, et al. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol 1998;138:141-5.
[25] Taskinen MR. Insulin resistance and lipoprotein metabolism. Curr Opin Lipidol 1995;6:153-60.
[26] Montes A, et al. Physiologic and supraphysiologic increases in lipoprotein lipids and apoproteins in late pregnancy and postpartum. Possible markers for the diagnosis of "prelipemia". Arteriosclerosis 1984;4:407-17.

[27] Rader DJ, Rosas S. Management of selected lipid abnormalities. Hypertriglyceridemia, low HDL cholesterol, lipoprotein(a), in thyroid and renal diseases, and post-transplantation. Med Clin North Am 2000;84:43-61.
[28] Joven J, Vilella E. Hyperlipidaemia of the nephrotic syndrome—the search for a nephrotic factor. Nephrol Dial Transplant 1995;10:314-6.
[29] Vega GL, et al. Levels of cofactors for lipoprotein lipase and lecithin-cholesterol acyltransferase in plasma patients with severe thermal injury. J Burn Care Rehabil 1988;9:18-21.
[30] Winkleby MA, et al. Ethnic variation in cardiovascular disease risk factors among children and young adults: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. JAMA 1999;281:1006-13.
[31] Jeppesen J, 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.
[32] Kato M, et al. Comparison of the lipid profiles of Cubans and other Hispanics with non-Hispanics. Arch Intern Med 1991;151:1613-6.
[33] Hu D, et al. Effects of obesity and body fat distribution on lipids and lipoproteins in nondiabetic American Indians: the Strong Heart Study. Obes Res 2000;8:411-21.
[34] Frerichs RR, et al. Serum cholesterol and triglyceride levels in 3,446 children from a biracial community: the Bogalusa Heart Study. Circulation 1976;54:302-9.
[35] Christensen B, et al. Plasma cholesterol and triglyceride distributions in 13,665 children and adolescents: the Prevalence Study of the Lipid Research Clinics Program. Pediatr Res 1980;14:194-202.
[36] Sundquist J, Winkleby MA, Pudaric S. Cardiovascular disease risk factors among older black, Mexican-American, and white women and men: an analysis of NHANES III, 1988-1994. Third National Health and Nutrition Examination Survey. J Am Geriatr Soc 2001;49:109-16.
[37] Gardner CD, Winkleby MA, Fortmann SP. Population frequency distribution of non-high-density lipoprotein cholesterol (Third National Health and Nutrition Examination Survey [NHANES III], 1988-1994). Am J Cardiol 2000;86:299-304.
[38] Shiwaku K, et al. Triglyceride levels are ethnic-specifically associated with an index of stearoyl-CoA desaturase activity and n-3 PUFA levels in Asians. J Lipid Res 2004;45:914-22.
[39] Pennacchio LA, et al. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. Hum Mol Genet 2002;11: 3031-8.
[40] Sanada M, et al. The effect of hormone replacement therapy on metabolism of lipoprotein remnants in postmenopausal women. Maturitas 2000;34:75-82.
[41] Zamboni M, Armellini F, Harris T, Turcato E, Micclolo R, Bergamo-Andreis IA, et al. Effects of age on body fat distribution and cardiovascular risk factors in women. Am J Clin Nutr 1997;66:111-5.
[42] Peters HW, et al. Menopausal status and risk factors for cardiovascular disease. J Intern Med 1999;246:521-8.
[43] Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA 1995;273:199-208.
[44] Freedman DS, et al. Body fat distribution and male/female differences in lipids and lipoproteins. Circulation 1990;81:1498-506.
[45] Bonora E, et al. Cardiovascular risk profile in 38-year- and 18-year-old men. Contribution of body fat content and regional fat distribution. Int J Obes Relat Metab Disord 1996;20:28-36.
[46] Greenfield MS, et al. Effect of age on plasma triglyceride concentrations in man. Metabolism 1980;29:1095-9.
[47] Cullen P, Schulte H, Assmann G. The Munster Heart Study (PROCAM): total mortality in middle-aged men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. Circulation 1997;96:2128-36.
[48] McDevitt RM, et al. Macronutrient disposal during controlled overfeeding with glucose, fructose, surcrose, or fat in lean and obese women. Am J Clin Nutr 2000;72:369-77.
[49] Mittendorfer B, Sidossis LS. Mechanism for increase in plasma triacylglycerol concentrations after consumption of short-term, high-carbohydrate diets. Am J Clin Nutr 2001;73:892-9.
[50] Maskarinec G, et al. Exploring the feasibility and effects of a high-fruit and -vegetable diet in healthy women. Cancer Epidemiol Biomarkers Prev 1999;8:919-24.
[51] Zino S, et al. Randomised controlled trial of effect of fruit and vegetable consumption on plasma concentrations of lipids and antioxidants. BMJ 1997;314:1787-91.
[52] Smith-Warner SA, et al. Increasing vegetable and fruit intake: randomized intervention and monitoring in an at-risk population. Cancer Epidemiol Biomarkers Prev 2000;9:307-17.
[53] Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. Int J Epidemiol 1997;26:1-13.
[54] Lampe JW. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am J Clin Nutr 1999;70(3 Suppl):475S-90S.
[55] Oh K, et al. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. Am J Epidemiol 2005;161:672-9.
[56] Reaven P, et al. Effects of oleate-rich and linoleate-rich diets on the susceptibility of low density lipoprotein to oxidative modification in mildly hypercholesterolemic subjects. J Clin Invest 1993;91:668-76.
[57] Phillipson BE, et al. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. N Engl J Med 1985;312:1210-6.
[58] He K, et al. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. BMJ 2003;327: 777-82.
[59] Crouse JR, Grundy SM. Effects of alcohol on plasma lipoproteins and cholesterol and triglyceride metabolism in man. J Lipid Res 1984;25: 486-96.
[60] Rimm EB, et al. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999;319:1523-8.
[61] Hines LM, et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. N Engl J Med 2001;344:549-55.
[62] De Oliveira ESER, et al. Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. Circulation 2000;102:2347-52.
[63] Branchi A, et al. Association of alcohol consumption with HDL subpopulations defined by apolipoprotein A-I and apolipoprotein A-II content. Eur J Clin Nutr 1997;51:362-5.
[64] Puchois P, et al. Effect of alcohol intake on human apolipoprotein A-I–containing lipoprotein subfractions. Arch Intern Med 1990;150: 1638-41.
[65] Hartung GH, et al. Effect of alcohol dose on plasma lipoprotein subfractions and lipolytic enzyme activity in active and inactive men. Metabolism 1990;39:81-6.
[66] Lakka HM, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002; 288:2709-16.
[67] Isomaa B, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
[68] Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. Circulation 2002;105:2696-8.
[69] Physician desk reference, Vol. 63. Montvale: Thompson Reuters; 2009.
[70] Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999; 341:498-511.
[71] Gagne C, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1084-91.
[72] McKenney JM, Sica D. Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia. Pharmacotherapy 2007;27: 715-28.

[73] Orniish D. Program for reversing heart disease. New York: Ballantine Books; 1991. p. 672.
[74] Orniish D. Eat more, weigh less. 1 ed. New York: Harpertorch; 1993. p. 480.
[75] Pritkin N. The new Pritkin program for diet and exercise. New York: Simon and Schuster Inc; 1990.
[76] Freedman MR, King J, Kennedy E. Popular diets: a scientific review. Obes Res 2001;9(Suppl 1):1S-40S.
[77] Atkins RC. Dr Atkins' new diet revolution. New York: Haroer Collins; 2002. p. 560.
[78] Eades MR, Eades MD. Protein power. New York: Bantam; 1996.
[79] Allan CB, Lutz W. Life without bread. New York: McGraw-Hill; 2000. p. 235.
[80] Krauss RM, et al. AHA dietary guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000;102:2284-99.
[81] Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. Am J Cardiol 1999;83:25F-9F.
[82] Kris-Etherton PM, et al. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. Am J Clin Nutr 1999;70:1009-15.
[83] Riccardi G, Rivellese A. Dietary treatment of the metabolic syndrome —the optimal diet. Br J Nutr 2000;83(Supplement):1S143-8S143.
[84] Xu J, et al. Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. A mechanism for the coordinate suppression of lipogenic genes by polyunsaturated fats. J Biol Chem 1999;274:23577-83.
[85] Harris WS. N-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;64:1645S-54S.
[86] Mori TA, et al. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. Arterioscler Thromb Vasc Biol 1997;17:279-86.
[87] Hu FB, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491-9.
[88] Nestel PJ, et al. Suppression by diets rich in fish oil of very low density lipoprotein production in man. J Clin Invest 1984;74:82-9.
[89] Harris WS, et al. Effects of fish oil on VLDL triglyceride kinetics in humans. J Lipid Res 1990;31:1549-58.
[90] von Schacky C, et al. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;130:554-62.
[91] Hu FB, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002;287:1815-21.
[92] Baylin A, et al. Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica. Circulation 2003;107:1586-91.
[93] Goodfellow J, et al. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol 2000;35: 265-70.
[94] Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995; 333:276-82.
[95] Erdman Jr JW. AHA Science Advisory: soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. Circulation 2000;102:2555-9.
[96] Silagy C, Neil A. Garlic as a lipid lowering agent—a meta-analysis. J R Coll Physicians Lond 1994;28:39-45.
[97] Reuter HD. *Allium sativum* and *Allium ursinum*, part 2: pharmacology and medicinal application. Phytomedicine 1995;2:51-63.
[98] Keys A, et al. The diet and 15-year death rate in the seven countries study. Am J Epidemiol 1986;124:903-15.
[99] Bordia A, Verma SK. Effect of garlic feeding on regression of experimental atherosclerosis in rabbits. Artery 1980;7:428-37.
[100] Agarwal KC. Therapeutic actions of garlic constituents. Med Res Rev 1996;16:111-24.
[101] Reuter HD, Koch HP, Lawson LD. Garlic. Therapeutic effects of garlic and its preparations. 2nd ed. London: Williams and Wilkins; 1996. p. 135-62.
[102] Isaacsohn JL, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Intern Med 1998;158:1189-94.
[103] Simons LA, et al. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. Atherosclerosis 1995; 113:219-25.
[104] Berthold HK, Sudhop T, von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. JAMA 1998;279:1900-2.
[105] Anderson JW. Dietary fiber prevents carbohydrate-induced hypertriglyceridemia. Curr Atheroscler Rep 2000;2:536-41.
[106] Brown L, et al. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr 1999;69:30-42.
[107] Ros E, et al. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation 2004;109:1609-14.
[108] Fraser GE, et al. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. Arch Intern Med 1992;152:1416-24.
[109] Wanga 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.