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Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association

Michael Miller, Neil J. Stone, Christie Ballantyne, Vera Bittner, Michael H. Criqui, Henry N. Ginsberg, Anne Carol Goldberg, William James Howard, Marc S. Jacobson, Penny M. Kris-Etherton, Terry A. Lennie, Moshe Levi, Theodore Mazzone, Subramanian Pennathur and on behalf of the American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular N

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Triglycerides and Cardiovascular Disease

A Scientific Statement From the American Heart Association

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Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism,
Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Nursing,
and Council on the Kidney in Cardiovascular Disease

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1. Introduction

A long-standing association exists between elevated triglyceride levels and cardiovascular disease* (CVD).^{1,2} However, the extent to which triglycerides directly promote CVD or represent a biomarker of risk has been debated for 3 decades.³ To this end, 2 National Institutes of Health consensus conferences evaluated the evidentiary role of triglycerides in cardiovascular risk assessment and provided therapeutic recommendations for hypertriglyceridemic states.^{4,5} Since 1993, additional insights have been made vis-à-vis the atherogenicity of triglyceride-rich lipoproteins (TRLs; ie, chylomicrons and very low-density lipoproteins), genetic and metabolic regulators of triglyceride metabolism, and classification and treatment of hypertriglyceridemia. It is especially disconcerting that in the United States, mean triglyceride levels have risen since 1976, in concert with the growing epidemic of obesity, insulin resistance (IR), and type 2 diabetes mellitus (T2DM).^{6,7} In contrast, mean low-density lipoprotein cholesterol (LDL-C) levels have receded.⁷ Therefore, the purpose of this scientific statement is to update clinicians on the increasingly crucial role of triglycerides in the evaluation and management of CVD risk and highlight approaches aimed at minimizing the adverse public health-related consequences associated with hypertriglyceridemic states. This statement will complement recent American Heart Association scientific statements on childhood and adolescent obesity⁸ and dietary sugar intake⁹ by emphasizing effective lifestyle strategies designed to lower triglyceride levels and improve overall cardiometabolic health. It is not intended to serve as a specific guideline but will be of value to the Adult Treatment Panel IV (ATP IV) of the National Cholesterol Education Program, from which evidence-based guidelines will ensue. Topics to be addressed include epidemiology and CVD risk, ethnic and racial differences, metabolic determinants, genetic and family determinants, risk factor correlates, and effects related to nutrition, physical activity, and lipid medications.

2. Scope of the Problem: Prevalence of Hypertriglyceridemia in the United States

In the United States, the National Health and Nutrition Examination Survey (NHANES) has monitored biomarkers of CVD risk for >3 decades. Accordingly, increases in fasting serum triglyceride levels observed between surveys conducted in 1976–1980 and 1999–2002⁶ coincided with adjustments in the classification of hypertriglyceridemia^{4,10} (Table 1). Current designations are as follows: 150 to 199 mg/dL, borderline high; 200 to 499 mg/dL, high; and ≥500 mg/dL, very high. The prevalence of hypertriglyceridemia by ethnicity in NHANES 1988–1994 and 1999–2008 according to these cut points is shown in Figure 1. Overall, 31% of the adult US population has a triglyceride level ≥150 mg/dL, with no appreciable change between NHANES 1988–1994 and 1999–2008. Among ethnicities, Mexican Americans have the highest rates (34.9%), followed by non-Hispanic whites (33%) and blacks (15.6%) in NHANES 1999–2008 (Table 2). High (≥200 mg/dL) and very high (≥500 mg/dL)

*For the purpose of this statement, CVD is inclusive of coronary heart disease and coronary artery disease.

Table 1. Triglyceride Classification Revisions Between 1984 and 2001

TG Designate	1984 NIH Consensus Panel	1993 NCEP Guidelines	2001 NCEP Guidelines
Desirable	<250	<200	<150
Borderline-high	250–499	200–399	150–199
High	500–999	400–999	200–499
Very high	>1000	>1000	≥500

TG indicates triglyceride; NIH, National Institutes of Health; and NCEP, National Cholesterol Education Program.

Values are milligrams per deciliter.

fasting triglyceride levels were observed in 16.2% and 1.1% of adults, respectively, with Mexican Americans being overrepresented at both cut points (19.5% and 1.4%, respectively). Figure 2 illustrates the sex- and age-related prevalence of triglyceride levels ≥ 150 mg/dL in NHANES 1999–2008. Within each group, the highest prevalence rates were observed in Mexican American men (50 to 59 years old, 58.8%) and Mexican American women (≥ 70 years old, 50.5%), followed by non-Hispanic white men and women (60 to 69 years old, 43.6% and 42.2%, respectively) and non-Hispanic black men (40 to 49 years old, 30.4%) and women (60 to 69 years old, 25.3%). The prevalence of triglyceride levels ≥ 200 mg/dL was also highest in Mexican American men (≥ 30 years old) and women (≥ 40 years old; 21% to 36%), followed by non-Hispanic white men (30 to 69 years old, 20% to 25%). Although the prevalence of triglyceride levels ≥ 500

mg/dL was relatively low (1% to 2%), Mexican American men 50 to 59 years of age exhibited the highest rate (9%) in NHANES 1999–2008.

Serum triglyceride levels by selected percentiles and geometric means are shown in Table 3. Because triglyceride levels are not normally distributed in the population (Section 3.1), the geometric mean, as derived by log transformation, is favored over the arithmetic mean to reduce the potential impact of outliers that might otherwise overestimate triglyceride levels.¹¹ Over the past 20 years, there were small increases in median triglyceride levels in both men (122 versus 119 mg/dL) and women (106 versus 101 mg/dL). However, the increases in triglycerides primarily were observed in younger age groups (20 to 49 years old), and overall, triglyceride levels continue to be higher than in less industrialized societies (Section 12.1). We now address the epidemiological and putative pathophysiological consequences of high triglyceride levels.

3. Epidemiology of Triglycerides in CVD Risk Assessment

The independent relationship of triglycerides to the risk of future CVD events has long been controversial. An article published in *The New England Journal of Medicine* in 1980 concluded that the evidence for an independent effect of triglycerides was “meager,”³ yet despite several decades of additional research, the controversy persists. This may in part reflect conflicting results in the quality of studies performed in the general population and in clinical samples. Second, in studies demon-

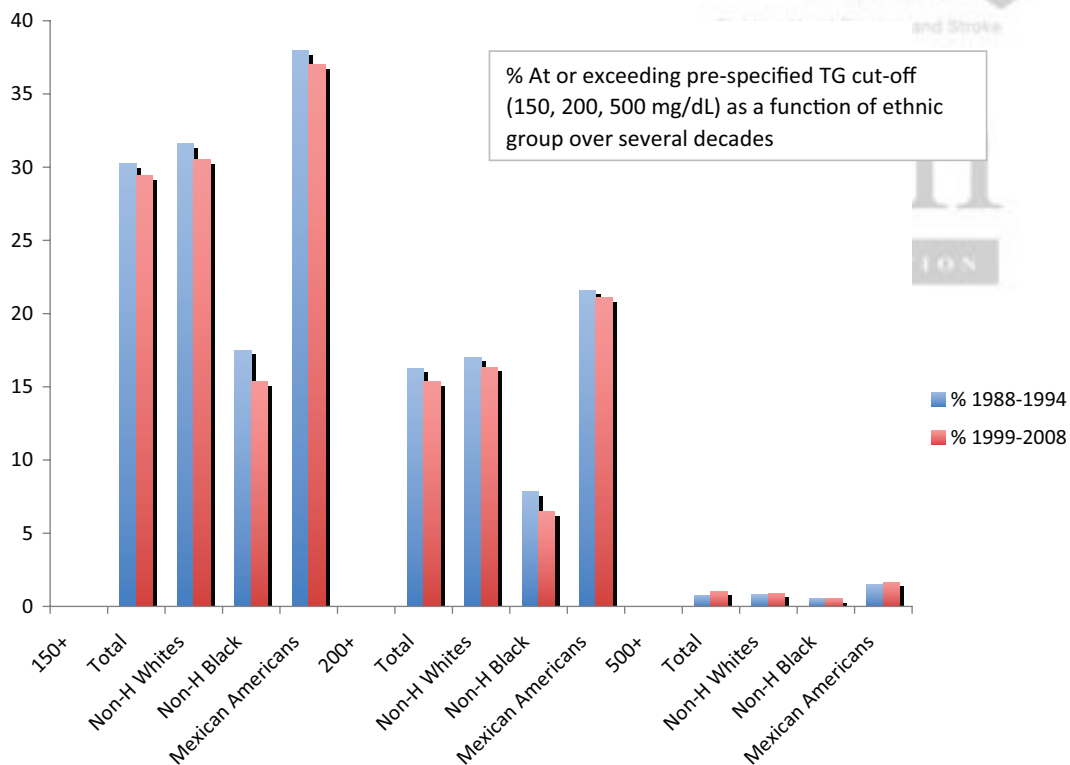


Figure 1. Prevalence of fasting triglyceride levels (≥ 150 , 200, and 500 mg/dL) in males and (non-pregnant) females ≥ 18 years of age by ethnicity in the National Health and Nutrition Examination Survey (1988–1994 and 1999–2008). TG indicates triglycerides; Non-H, non-Hispanic.

Table 2. Overall Prevalence (%) of Hypertriglyceridemia Based on 150, 200, and 500 mg/dL Cut Points by Age, Sex, and Ethnicity in US Adults, NHANES 1999–2008

Demographic	Triglyceride Cut Points, mg/dL		
	≥150	≥200	≥500
Overall (age ≥20 y)	31.0	16.2	1.1
Age, y			
20–29	20.7	9.5	0.8
30–39	25.8	14.1	0.7
40–49	32.8	16.7	1.6
50–59	36.7	20.1	1.8
60–69	41.6	22.6	1.0
≥70	34.5	17.2	0.5
Sex			
Men	35.4	19.8	1.8
Women*	26.8	12.7	0.5
Ethnicity			
Mexican American	34.9	19.5	1.4
Non-Hispanic, black	15.6	7.6	0.4
Non-Hispanic, white	33.0	17.6	1.1

NHANES indicates National Health and Nutrition Examination Survey.

Data provided by the Epidemiology Branch, National Heart, Lung, and Blood Institute.

*Excludes pregnant women.

Source: NHANES 1999–2008.

strating a significant independent relationship of triglycerides to CVD events, the effect size has typically been modest compared with standard CVD risk factors, including other lipid and lipoprotein parameters. Summarized below are methodological considerations and results from representative studies that evaluated triglycerides in CVD risk assessment.

3.1. Methodological Considerations and Effect Modification

Triglyceride has long been the most problematic lipid measure in the evaluation of cardiovascular risk. First, the distribution is markedly skewed, which necessitates categorical definitions or log transformations. Second, variability is high (Section 10) and increases with the level of triglyceride.¹² Third, the strong inverse association with high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) AI, suggests an intricate biological relationship that may not be most suitably represented by the results of multivariate analysis. Finally, evidence from prospective studies of the triglyceride association supports a stronger link with CVD risk in people with lower levels of HDL-C^{13,14} and LDL-C^{13,14} and with T2DM.^{15,16} Such an effect modification could obscure a modest but significant effect, as demonstrated recently.¹⁷

In addition to the inverse association with HDL-C, triglyceride levels are closely aligned with T2DM, even though T2DM is not always examined as a confounding factor, and when it is, the diagnosis is commonly based on history. Yet at least 25% of subjects with T2DM are undiagnosed,¹⁸ and they are often concentrated within a hypertriglyceridemic population. Similarly, many subjects with high triglyceride

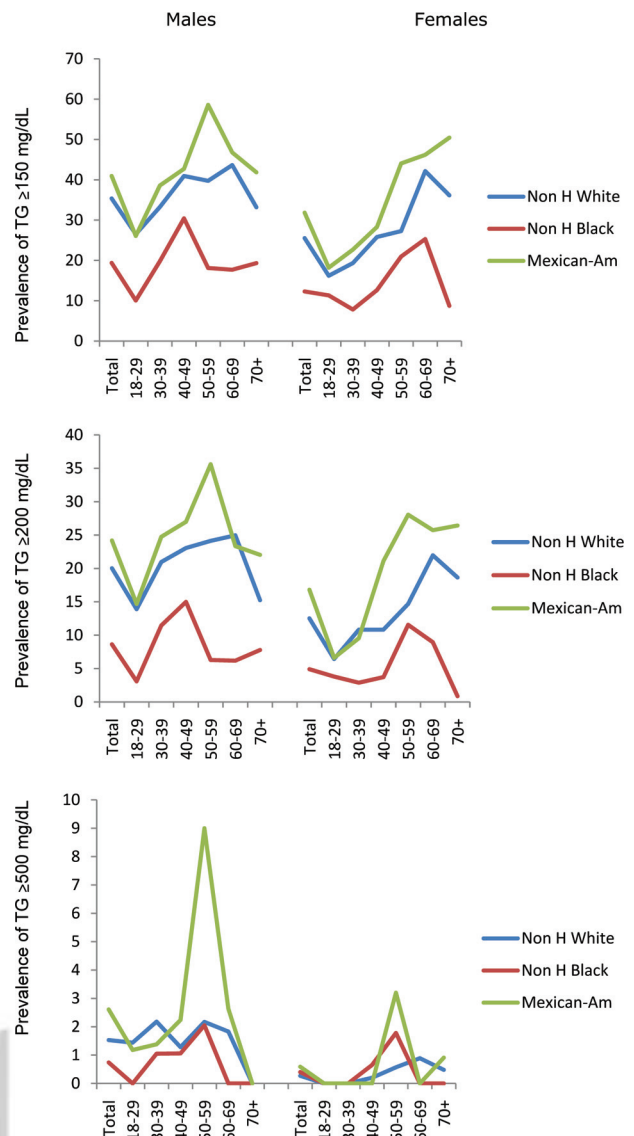


Figure 2. Prevalence of hypertriglyceridemia in males and non-pregnant females ≥18 years of age in NHANES 1999–2008. NHANES indicates National Health and Nutrition Examination Survey; TG, triglycerides; Non H, non-Hispanic; Mexican-Am, Mexican-American.

levels and impaired fasting glucose who subsequently develop T2DM are not adjusted for in multivariate analysis. Hence, these limitations restrict conclusions that support triglyceride level as an independent CVD risk factor. Compounding the aforementioned problem is the argument that an elevated triglyceride level is simply an epiphenomenon (ie, a by-product) of IR or the metabolic syndrome (MetS). However, analysis of NHANES data evaluating the association of all 5 MetS components with cardiovascular risk found the strongest association with triglycerides.¹⁹

A pivotal consideration is how triglycerides may directly impact the atherosclerotic process in view of epidemiological studies that have failed to demonstrate a strong relationship between very high triglyceride levels and increased CVD death.^{13,20} As will be described in Section 4, hydrolysis of TRLs (eg, chylomicrons, very low-density lipoproteins [VLDL]) re-

Table 3. Serum Triglyceride Levels of US Adults ≥ 20 Years of Age, 1988–1994 and 1999–2008

	1988–1994							1999–2008						
	Geometric Mean		Selected Percentile					Geometric Mean		Selected Percentile				
	Age-Specific	Age-Adjusted	5th	25th	50th	75th	95th	Age-Specific	Age-Adjusted	5th	25th	50th	75th	95th
Men														
≥20 y		127.9	53	83	119	176	321		128.3	52	85	122	182	361
20–29	95.1		45	65	88	126	237	106.2		45	70	100	150	305
30–39	118.8		52	79	113	169	298	122.1		50	80	119	175	324
40–49	138.4		58	91	133	190	349	143.8		57	94	134	201	473
50–59	146.6		61	95	137	223	394	140.6		61	93	133	197	388
60–69	146.7		64	101	140	200	378	138.2		59	96	133	196	372
≥70	134.3		64	95	131	179	306	121.5		54	87	120	168	266
Women*														
≥20 y		109.7	47	72	101	150	274		110.0	48	74	106	155	270
20–29	83.8		42	60	84	111	182	88.7		39	63	83	123	205
30–39	91.3		43	62	83	121	267	95.8		42	64	91	138	243
40–49	103.0		48	70	102	139	251	105.5		49	73	102	146	249
50–59	129.2		55	84	126	186	325	124.7		55	84	120	176	305
60–69	143.9		61	97	137	203	380	135.9		63	96	137	192	299
≥70	137.2		70	97	134	182	284	133.0		63	95	129	180	293
Race/ethnicity														
Mexican-American														
Men		138.6	53	83	120	185	387		140.8	53	89	126	196	392
Women		131.8	55	85	118	167	291		126.6	48	81	113	164	277
Non-Hispanic black														
Men		102.5	44	65	92	140	259	99.7	44	67	94	129	248	
Women		88.8	40	58	79	115	208	88.1	38	62	83	116	209	
Non-Hispanic white														
Men		131.3	55	85	123	182	323	130.3	53	87	126	188	368	
Women		110.9	48	74	102	154	276	112.1	50	77	109	161	275	

Percentile and geometric mean distribution of serum triglyceride (mg/dL).

*Excludes pregnant women.

Data provided by the Epidemiology Branch, National Heart, Lung, and Blood Institute.

Source: National Health and Nutrition Examination Survey III (1988–1994) and Concurrent National Health and Nutrition Examination Survey (1999–2008).

sults in atherogenic cholesterol-enriched remnant lipoprotein particles (RLPs). Accordingly, recent evidence suggests that nonfasting triglyceride is strongly correlated with RLPs,²¹ and in 2 recent studies, nonfasting triglyceride was a superior predictor of incident CVD compared with fasting levels.^{21,22}

3.2. Case-Control Studies, Including Angiographic Studies

Triglyceride has routinely been identified as a “risk factor” in case-control and angiographic studies, even after adjustment for total cholesterol (TC) or LDL-C^{23–34} and HDL-C.^{24,27–29,33,34} In another case-control study, case subjects were 3-fold more likely to exhibit small, dense low-density lipoprotein (LDL) particles, referred to as the “pattern B” phenotype.³⁵ However, the triglyceride level explained most of the risk of the pattern B phenotype and was a stronger covariate than LDL-C, intermediate-density lipoprotein (IDL) cholesterol, or HDL-C. Overall, data from case-control studies have supported triglyceride level as an independent CVD risk factor.

3.3. Prospective Population-Based Cohort Studies

Although many early cohort studies found a univariate association of triglycerides with CVD, this association often became nonsignificant after adjustment for either TC or LDL-C. Most of these earlier studies did not measure HDL-C. Two meta-analyses of the triglycerides-CVD question drew similar conclusions. The first, published in 1996, considered 16 studies in men, 6 from the United States, 6 from Scandinavia, and 4 from elsewhere in Europe.³⁶ In univariate analysis, the relative risk per 1 mmol/L (88.5 mg/dL) of triglyceride for CVD in men was 1.32 (95% confidence interval 1.26 to 1.39) and 1.14 (95% confidence interval 1.05 to 1.28) after adjustment for HDL-C. In women, the association was more robust in both univariate analysis (relative risk 1.76 per mmol/L) and after adjustment for HDL-C (relative risk 1.37, 95% confidence interval 1.13 to 1.66). The second meta-analysis evaluated 262 000 subjects and found a higher relative risk (1.4) at the upper compared with the lower triglyceride tertile; this estimate improved to

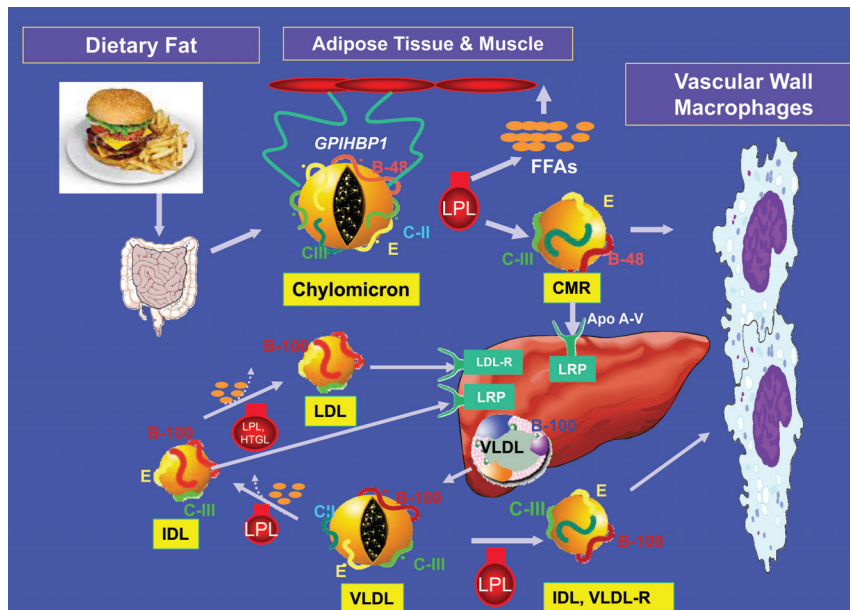


Figure 3. Overview of triglyceride metabolism. Apo A-V indicates apolipoprotein A-V; CMR, chylomicron remnant; FFAs, free fatty acids; HTGL, hepatic triglyceride lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP, LDL receptor-related protein; VLDL, very low-density lipoprotein; and VLDL-R, very low-density lipoprotein receptor.

1.72 with correction for “regression dilution bias” (intraindividual triglyceride variation).²

A recent meta-analysis from the Emerging Risk Factors Collaboration evaluated 302 430 people free of known vascular disease at baseline in 68 prospective studies.¹⁷ With adjustment for age and sex, triglycerides showed a strong, stepwise association with both CVD and ischemic stroke; however, after adjustment for standard risk factors and for HDL-C and non-HDL-C, the associations for both CVD and stroke were no longer significant. The attenuation was primarily from the adjustment for HDL-C and non-HDL-C, which led to the conclusion that “...for population-wide assessment of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-C and total cholesterol levels, although there may be separate reasons to measure triglyceride concentration (eg, prevention of pancreatitis).”¹⁷

Additional data from studies involving young men have provided new insight into the triglyceride risk status question.³⁷ In 13 953 men 26 to 45 years old who were followed up for 10.5 years, there were significant correlations between adoption of a favorable lifestyle (eg, weight loss, physical activity) and a decrease in triglyceride levels. At baseline, triglyceride levels in the top quintile were associated with a 4-fold increased risk of CVD compared with the lowest triglyceride quintile, even after adjustment for other risk factors, including HDL-C. Evaluation of the change in triglyceride levels over the first 5 years and incident CVD in the next 5 years found a direct correlation between increases in triglyceride levels and CVD risk. These observations add a dynamic element of triglyceride to CVD risk assessment based on lifestyle intervention that will be elaborated on later in this statement.

3.4. Insights From Clinical Trials

A related question is the ability of triglyceride levels to predict clinical benefit from lipid therapy in outcome trials. In many of these studies, subjects with elevated triglyceride

levels exhibited improvement in CVD risk, irrespective of drug class or targeted lipid fraction,^{38–40} primarily because elevated triglyceride level at baseline was commonly accompanied by high LDL-C and low HDL-C, and this combination (ie, the atherogenic dyslipidemic triad) was associated with the highest CVD risk. Taken together, the independence of triglyceride level as a causal factor in promoting CVD remains debatable. Rather, triglyceride levels appear to provide unique information as a biomarker of risk, especially when combined with low HDL-C and elevated LDL-C.

4. Pathophysiology of Hypertriglyceridemia

4.1. Normal Metabolism of TRLs

4.1.1. Lipoprotein Composition

Lipoproteins are macromolecular complexes that carry various lipids and proteins in plasma.⁴¹ Several major classes of lipoproteins have been defined by their physical and chemical characteristics, particularly by their flotation characteristics during ultracentrifugation. However, lipoprotein particles form a continuum, varying in composition, size, density, and function. The lipids are mainly free and esterified cholesterol, triglycerides, and phospholipids. The hydrophobic triglyceride and cholesteryl esters (CEs) compose the core of the lipoproteins, which is covered by a unilamellar surface that contains mainly the amphipathic (both hydrophobic and hydrophilic) phospholipids and smaller amounts of free cholesterol and proteins. Hundreds to thousands of triglyceride and CE molecules are carried in the core of different lipoproteins.

Apolipoproteins are the proteins on the surface of the lipoproteins. They not only participate in solubilizing core lipids but also play critical roles in the regulation of plasma lipid and lipoprotein transport. Apo B₁₀₀ is required for the secretion of hepatic-derived VLDL, IDL, and LDL. Apo B₄₈ is a truncated form of apo B₁₀₀ that is required for secretion of chylomicrons from the small intestine.

4.2. Transport of Dietary Lipids on Apo B₄₈-Containing Lipoproteins

Figure 3 provides an overview of triglyceride metabolism. After ingestion of a meal, dietary fat and cholesterol are absorbed into the cells of the small intestine and are incorporated into the core of nascent chylomicrons. Newly formed chylomicrons, representing 80% to 95% triglyceride as a percentage of composition of lipids,⁴¹ are secreted into the lymphatic system and then enter the circulation at the junction of the internal jugular and subclavian veins. In the lymph and blood, chylomicrons acquire apo CII, apo CIII, and apo E. In the capillary beds of adipose tissue and muscle, they bind to glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1),⁴² and core triglyceride is hydrolyzed by the enzyme lipoprotein lipase (LPL) after activation by apo CII.⁴³ The lipolytic products, free fatty acids (FFAs), can be taken up by fat cells and reincorporated into triglyceride or into muscle cells, where they can be used for energy. In addition to apo CII, other activators of LPL include apo AIV,⁴⁴ apo AV,⁴⁵ and lipase maturation factor 1 (LMF1),⁴⁶ whereas apo CIII⁴⁷ and angiopoietin-like (ANGPTL) proteins 3 and 4⁴⁸ inhibit LPL. Human mutations in *LPL*, *APOC2*, *GPIHBP1*, *ANGPTL3*, *ANGPTL4*, and *APOA5* have all been implicated in chylomicronemia (Section 5).

The consequence of triglyceride hydrolysis in chylomicrons is a relatively CE- and apo E-enriched chylomicron remnant (CMR). Under physiological conditions, essentially all CMRs are removed by the liver by binding to the LDL receptor, the LDL receptor-related protein, hepatic triglyceride lipase (HTGL), and cell-surface proteoglycans.^{49–51} Apo AV facilitates hepatic clearance of CMRs through direct interaction with SorLA.⁵² HTGL also plays a role in remnant removal,⁴⁹ and HTGL deficiency is associated with reduced RLP clearance. However, studies⁵³ have indicated that HTGL is elevated in T2DM (Section 6) and may be an important contributor to low HDL-C levels in this disease.

4.3. Transport of Endogenous Lipids on Apo B₁₀₀-Containing Lipoproteins

4.3.1. Very Low-Density Lipoproteins

VLDL is assembled in the endoplasmic reticulum of hepatocytes. VLDL triglyceride derives from the combination of glycerol with fatty acids that have been taken up from plasma (either as albumin-bound fatty acids or as triglyceride-fatty acids in RLPs as they return to the liver) or newly synthesized in the liver. VLDL cholesterol is either synthesized in the liver from acetate or delivered to the liver by lipoproteins, mainly CMRs. Apo B₁₀₀ and phospholipids form the surface of VLDL. Although apos CI, CII, CIII, and E are present on nascent VLDL particles as they are secreted from the hepatocyte, the majority of these molecules are probably added to VLDL after their entry into plasma. Regulation of the assembly and secretion of VLDL by the liver is complex; substrates, hormones, and neural signals all play a role. Studies in cultured liver cells^{51,54} indicate that a significant proportion of newly synthesized apo B₁₀₀ may be degraded before secretion and that this degradation is inhibited when hepatic lipids are abundant.⁵⁴

Once in the plasma, VLDL triglyceride is hydrolyzed by LPL, generating smaller and denser VLDL and subsequently IDL. IDL particles are physiologically similar to CMRs, but unlike CMRs, not all are removed by the liver. IDL particles can also undergo further catabolism to become LDL. Some LPL activity appears necessary for normal functioning of the metabolic cascade from VLDL to IDL to LDL. It also appears that apo E, HTGL, and LDL receptors play important roles in this process. Apo B₁₀₀ is essentially the sole protein on the surface of LDL, and the lifetime of LDL in plasma appears to be determined mainly by the availability of LDL receptors. Overall, ≈70% to 80% of LDL catabolism from plasma occurs via the LDL receptor pathway, whereas the remaining tissue uptake occurs by nonreceptor or alternative-receptor pathways.^{41,53}

4.4. Metabolic Consequences of Hypertriglyceridemia

Hypertriglyceridemia that results from either increased production or decreased catabolism of TRL directly influences LDL and HDL composition and metabolism. For example, the hypertriglyceridemia of IR is a consequence of adipocyte lipolysis that results in FFA flux to the liver and increased VLDL secretion. Higher VLDL triglyceride output activates cholesteryl ester transfer protein, which results in triglyceride enrichment of LDL and HDL (Figure 4). The triglyceride content within these particles is hydrolyzed by HTGL, which results in small, dense LDL and HDL particles. Experimental studies suggest that hypertriglyceridemic HDL may be dysfunctional,^{55,56} that small, dense LDL particles may be more susceptible to oxidative modification,^{57,58} and that an increased number of atherogenic particles may adversely influence CVD risk⁵⁹; however, no clinical outcome trials to date have determined whether normalization of particle composition or reduction of particle number optimizes CVD risk reduction beyond that achieved through LDL-C lowering.

An additional complication in hypertriglyceridemic states is accurate quantification of atherogenic particles in the circulation. That is, a high concentration of circulating atherogenic particles is not reliably assessed simply by measurement of TC and/or LDL-C. Moreover, as triglyceride levels increase, the proportion of triglyceride/CE in VLDL increases (ie, >5:1), which results in an underestimation of LDL-C based on the Friedewald formula.⁶⁰ Although this scientific statement will address other variables to consider in the hypertriglyceridemic patient (eg, apo B levels), it supports the quantification of non-HDL-C.^{60,61}

4.5. Atherogenicity of TRLs

In human observational studies, TRLs have been associated with measures of coronary atherosclerosis.⁶² To provide a pathophysiological underpinning for observations that relate specific lipoprotein particles to human atherosclerosis or CVD, experimental models have been developed to investigate the impact of specific lipoprotein fractions on isolated vessel wall cells. For example, in macrophage-based studies, lipoprotein particles that increase sterol delivery or reduce sterol efflux or that promote an inflammatory response are considered atherogenic. In endothelial cell models, lipopro-

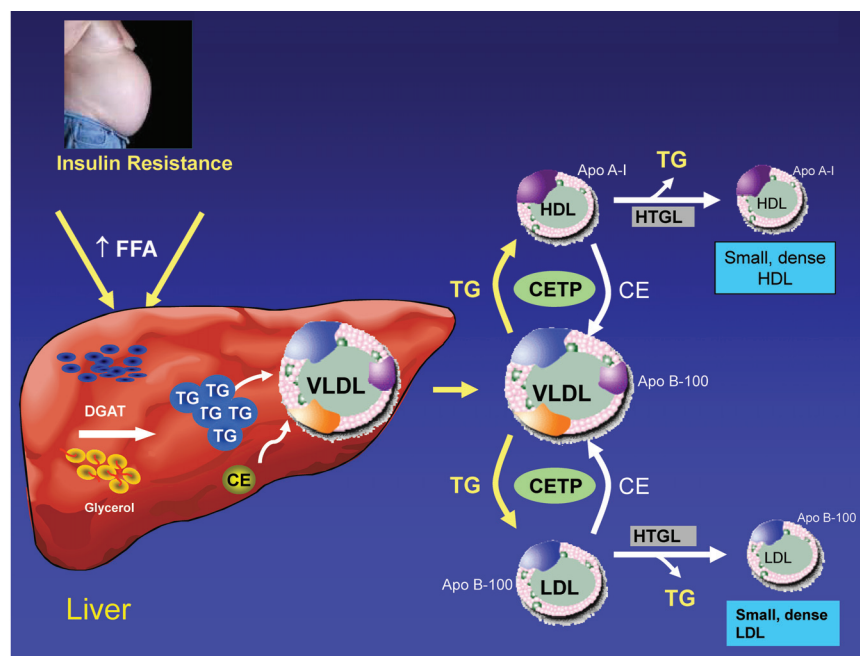


Figure 4. Metabolic consequences of hypertriglyceridemia. Apo A-I indicates apolipoprotein A-I; Apo B-100, apolipoprotein B-100; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; DGAT, diacylglycerol acyltransferase; FFA, free fatty acid; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LDL, low-density lipoprotein; TG, triglyceride; and VLDL, very low-density lipoprotein.

tein particles that promote inflammation, increase the expression of coagulation factors or leukocyte adhesion molecules, or impair responses that produce vasodilation are also considered atherogenic. These experimental systems have been used to understand the mechanisms by which modified LDL particles are associated with atherosclerosis in humans and in animals.

When one evaluates the usefulness of these systems, it is important to recognize that triglyceride overload is not a classic pathological feature of human atherosclerotic lesions, because the end product, FFA, serves as an active energy source for myocytes or as an inactive fuel reserve in adipocytes. However, the by-product of TRLs (ie, RLPs) may lead to foam cell formation⁶³ in a manner analogous to modified LDL. In addition, TRLs share a number of constituents with classic atherogenic LDL particles. They include the presence of apo B and CE. Although TRLs contain much less CE than LDL particles on a per particle basis, there are pathophysiological states (eg, poorly controlled diabetes mellitus [DM]) in which CEs can become enriched in this fraction. TRLs also possess unique constituents that may contribute to atherogenicity. For example, the action of LPL on the triglycerides contained in these particles releases fatty acid, which in microcapillary beds could be associated with pathophysiological responses in macrophages and endothelial cells. Apo CIII contained in TRLs has also been shown to promote proatherogenic responses in macrophages and endothelial cells. In the following paragraphs, we will consider selected aspects of the atherogenicity of TRL using in vitro macrophage and endothelial cell models and associated in vivo correlates.

4.5.1. Remnant Lipoprotein Particles

A number of experimental systems have demonstrated that TRLs can produce proatherogenic responses in isolated endothelial cells. RLPs are a by-product of TRL that can be

isolated from the postprandial plasma of hypertriglyceridemic subjects; they are intestinal (ie, CMRs) or liver-derived (eg, VLDL remnants) TRLs that have undergone partial hydrolysis by LPL. Liu et al⁶⁴ have shown that these particles can accelerate senescence and interfere with the function of endothelial progenitor cells; these cells play an important role in the organismal reparative response to in vivo vessel wall injury. Postprandial TRL (ppTG) has also been shown to increase the expression of proinflammatory genes (eg, interleukin-6, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and monocyte chemoattractant protein-1),⁶⁵ induce apoptosis,⁶⁶ and accentuate the inflammatory response of cultured endothelial cells to tumor necrosis factor- α .⁶⁷ After a high-fat meal, ppTG may increase the level of circulating endothelial cell microparticles, a measure of endothelial cell dysfunction in vivo.⁶⁸ That is, a high-fat diet increases the level of these particles more effectively than a low-fat diet and is correlated with ppTG levels. Moreover, Rutledge and colleagues have shown that fatty acids released by lipolysis of TRL elicit proinflammatory responses in endothelial cells.⁶⁹ TRL may also act to suppress the atheroprotective and antiinflammatory effects of HDL.^{70–72} Finally, fatty acid-binding proteins play a role in the intracellular transport of long-chain fatty acids. Recent data support a role for adipocyte- and macrophage-derived fatty acid-binding proteins in systemic inflammatory responses⁷³ that are likely amplified by high triglyceride loads provided by RLPs to the arterial macrophages.

4.5.2. Apo CIII

Apo CIII is a 79-amino acid glycoprotein that is a major component of circulating TRL and is correlated with triglyceride levels.⁷⁴ Recently, a mutation in *APOC3* was identified in association with low triglyceride levels, reduced coronary artery calcification, and suggestion of familial longevity.⁷⁵ Emerging evidence from a number of in vitro studies has shown that apo CIII, alone or as an integral component of

TRL, can produce proatherogenic responses in cultured endothelial and monocytic cells.^{74,76} These include activation of adhesion and proinflammatory molecule expression and impairment of endothelial nitric oxide production and insulin signaling pathways.^{74,76–80}

4.5.3. Macrophage LPL

Macrophages are a rich source of LPL in the vessel wall,⁸¹ and expression of LPL by macrophages could play a role in accelerating atherogenesis by a mechanism that depends on interaction with circulating TRL.⁸² For example, direct incubation of mouse peritoneal macrophages with TRL increases macrophage cell triglyceride and fatty acid content; more importantly, this incubation increases expression of macrophage inflammatory proteins, including tumor necrosis factor- α , interleukin-1 β , monocyte chemotactic protein-1, intercellular adhesion molecule-1, and matrix metalloproteinase-3.^{83,84} Lipolytic products of TRL have also been shown to produce cytotoxicity and apoptosis in isolated macrophages.⁸⁵ Macrophage apoptosis is considered an important event that impacts the in vivo atherogenic process.⁸⁶

In summary, in vitro experimental models examining the response of isolated endothelial cells or monocytes and macrophages to TRL have produced results consistent with atherogenicity of this class of particles. These particles, or their lipolytic degradation products, can increase the expression of inflammatory proteins, adhesion molecules, and coagulation factors in endothelial cells or monocytes and macrophages. TRLs may interfere with the ability of HDL to suppress inflammatory responses in cultured endothelial cells and the capacity of apo AI or HDL to promote sterol efflux from monocytes or macrophages. TRLs also impair endothelial cell-dependent vasodilation, enhance the recruitment and attachment of monocytes to endothelium, may be directly cytotoxic, and produce apoptosis in isolated vessel wall cells. However, although the results from in vitro studies provide important pathophysiological context and proof of concept, final conclusions about atherogenicity and clinical significance of lowering triglyceride levels as a surrogate of TRL particles must be based on in vivo studies that use appropriate models of human dyslipidemia in randomized controlled trials (RCTs), as will be elaborated on in Section 15.

5. Causes of Hypertriglyceridemia

5.1. Familial Disorders With High Triglyceride Levels

Familial syndromes with triglyceride levels above the 95th percentile by age and sex may be associated with an increased risk of premature CVD, as in familial combined hyperlipidemia (FCHL).^{87–90} Alternatively, when triglyceride elevation is very severe (ie, >1000 mg/dL), fasting chylomicronemia may be the consequence of rare but recognizable single gene mutations.^{91–93} The persistence of fasting chylomicronemia leads to a syndrome characterized by eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly and is associated, although not invariably, with acute pancreatitis.^{94,95} Because the latter can lead to chronic pancreatitis or death, effective treatment is of paramount importance. Nonetheless, there can

be no question that prevention of the markedly elevated triglyceride levels seen in those with genetic syndromes of triglyceride metabolism is an important therapeutic goal.

To understand these disorders, one must focus on LPL regulation, because LPL is needed for the hydrolysis of plasma triglyceride to FFA.⁹⁶ The generation of FFA by LPL is regulated by cofactors such as insulin and thyroid hormone. Factors that reduce VLDL clearance can raise triglyceride concentrations in those with high baseline levels (eg, usually >500 mg/dL, because of the competition of VLDL and chylomicrons for a common saturable removal mechanism).⁹⁷

Table 4 lists syndromes of genetic hypertriglyceridemia. The rare but monogenic disorders that cause a marked impairment of LPL activity have clinical expression in childhood. These young patients present with the chylomicronemia syndrome and an increased risk for pancreatitis and may be homozygous for either LPL deficiency, apo CII deficiency, or the more recently described *APOA5* and *GPIHBP1* loss-of-function mutations.^{91–93,102,103} In some populations, such as French Canadians, as many as 70% of cases can be traced to a single founder.¹⁰⁴

For those with less severe genetic disorders of triglyceride metabolism, complex interactions between genetic and environmental factors may lead to the type V phenotype (fasting chylomicronemia and increased VLDL). In these cases, triglyceride concentrations exceed 1000 mg/dL, and when exacerbated by weight gain, certain medications (Table 5) or metabolic perturbations can lead to the chylomicronemia syndrome and increased risk of pancreatitis. Patients with heterozygous LPL deficiency present with elevated triglyceride levels and low HDL-C, but in association with excess alcohol, steroids, estrogens, poorly controlled DM, hypothyroidism, renal disease, or the third trimester of pregnancy, triglyceride levels can rapidly exceed 2000 mg/dL and produce the clinical sequelae of the chylomicronemia syndrome. Although there is no single threshold of triglyceride concentration above which pancreatitis may occur, increased risk is defined arbitrarily by levels exceeding 1000 mg/L. Overall, alcohol abuse and gallstone disease account for at least 80% of all cases of acute pancreatitis, with hypertriglyceridemia contributing \approx 10% of cases.^{105,134} A history of 2 predisposing factors in the same individual may cause confusion about the proper diagnosis. If elevated triglyceride level persists after the removal of exacerbating causes through diet modification, discontinuation of drugs (Table 5), and/or provision of insulin therapy for patients with poorly treated DM,¹³⁵ one must consider rare disorders that are resistant to traditional therapies, such as autoantibodies against LPL.¹³⁶

Additional genetic syndromes in the differential diagnosis of hypertriglyceridemia include mixed or familial combined hyperlipidemia (FCHL), type III dysbetalipoproteinemia, and familial hypertriglyceridemia (FHTG). FCHL is characterized by multiple lipoprotein abnormalities due to hepatic overproduction of apo B-containing VLDL, IDL, and LDL, whereby apo B levels exceed the 90th percentile.^{87,88} It is observed in affected relatives in successive generations, and the diagnosis is made when in the face of increased levels of cholesterol, triglyceride, or apo B, at least 2 of the lipid abnormalities identified in the patient also segregate among the patient's first-degree relatives.¹³⁷ The variable clinical

Table 4. Familial Forms of High Triglycerides

	Inheritance/Population Frequency	Pathogenesis	Typical Lipid/Lipoprotein Profiles	Comments
Rare genetic syndromes presenting as chylomicronemia syndrome				
LPL deficiency (also known as familial type I)	Autosomal recessive; rare (1 in 10 ⁶)	Increased chylomicrons due to very low or undetectable levels of LPL; circulating inhibitor to LPL has been reported	Homozygotes: TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons	Homozygous mutations cause lipemia retinalis, hepatosplenomegaly, eruptive xanthomas accompanying very high TG. CAD believed uncommon, but cases reported
Apo CII deficiency	Autosomal recessive; rare	Increased chylomicrons due to absence of needed cofactor, Apo CII	Homozygotes TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons Obligate heterozygotes with normal TG despite apo CII levels ≈30% to 50% of normal	Attacks of pancreatitis in homozygotes can be reversed by plasmapheresis; xanthomas and hepatomegaly much less common than in LPL deficiency
Apo AIV homozygosity	Rare	Mutations in the <i>APOA5</i> gene, which lead to truncated apo AIV devoid of lipid-binding domains located in the carboxy-terminal end of the protein	Homozygotes: TG-to-cholesterol ratio 10:1; TG >1000 mg/dL; increased chylomicrons	Apo A5 disorders can form familial hyperchylomicronemia with vertical transmission, late onset, incomplete penetrance, and an unusual resistance to conventional treatment
GPIHBP1	Rare; expressed in childhood	Mutations in <i>GPIHBP1</i> may reduce binding to LPL and hydrolysis of chylomicron triglycerides	TG-to-cholesterol ratio 7:1; TG >500 mg/dL; increased chylomicrons partially responsive to low-fat diet	May have lipemia retinalis and pancreatitis; eruptive xanthomas not reported
Other genetic syndromes with hypertriglyceridemia*				
Heterozygous apo AIV	Rare	A heterozygous loss-of-function mutation in 1 of several genes encoding proteins involved in TG metabolism. More than half of type V patients carried 1 of the 2 apo A5 variants compared with only 1 in 6 normolipidemic controls ⁹⁸	TG 200-1000 mg/dL until secondary trigger occurs; then TG can exceed 1000 mg/dL; increased VLDL and chylomicrons	The promoter polymorphism –1131T>C is associated with increased TG and CVD risk ⁹⁸
Heterozygous LPL deficiency	Rare, but carrier frequency higher in areas with founder effect (eg, Quebec)	Decrease in LPL	TG 200-1000 mg/dL until secondary trigger occurs; then TG can exceed 1000 mg/dL; increased VLDL and chylomicrons	Premature atherosclerosis can be seen ⁹⁹ (or increased atherosclerosis risk in familial hypercholesterolemia heterozygotes with elevated TG, low HDL ¹⁰⁰)
Familial hypertriglyceridemia	Common; ≈5% to 10%; likely polygenic, often not expressed until adulthood because of environmental factors, obesity, stress	VLDL overproduction and reduced VLDL catabolism result in saturation of LPL; secondary causes exacerbate the hypertriglyceridemia	TG 200-1000 mg/dL; apo B levels are not elevated as in FCHL	Usually not associated with CHD unless MetS features are seen or baseline TG levels are high (eg, >200 mg/dL) ¹⁰¹ ; then increased CHD may be present
FCHL	Genetically complex disorder; common (1% to 2% in white populations)	Increased production of apo B lipoproteins; FCHL diagnosed with combinations of increased cholesterol, TG, and/or apo B levels in patients and their first-degree relatives. See interaction of multiple genes and environmental factors such as adiposity and the degree of exercise	Elevated cholesterol, TG, or both; elevated apo B; small dense LDL is seen	Obesity as indicated by increased waist-to-hip ratio can greatly increase apo B production in these patients; usually onset is in adulthood, but pediatric obesity may allow for earlier diagnosis
Dysbetalipoproteinemia (also known as familial type III)	Autosomal recessive; rare; requires an acquired second "hit" for clinical expression	Defective apo E (usually apo EII/EIII phenotype); commonest mutation Apo EII, Arg158Cys, causes chylomicrons and VLDL remnants to build up in plasma	TG and cholesterol levels elevated and approximately similar should raise clinical suspicion; non-HDL-C is a better risk target than apo B levels, which are low because these are cholesterol-rich VLDL; see increased intermediate-density particles with ratio of directly measured VLDL-C to plasma TG of >0.3	Acquired second "hits" include exogenous estrogen, alcohol, obesity, insulin resistance, hypothyroidism, renal disease, or aging; may be very carbohydrate sensitive

LPL indicates lipoprotein lipase; TG, triglyceride; CAD, coronary artery disease; apo, apolipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; VLDL, very low-density lipoprotein; CVD, cardiovascular disease; HDL, high-density lipoprotein; CHD, coronary heart disease; MetS, metabolic syndrome; FCHL, familial combined hyperlipidemia; LDL, low-density lipoprotein; HDL-C, HDL cholesterol; and VLDL-C, VLDL cholesterol.

*Genetic syndromes that usually require an acquired cause to raise TG to high levels and present with either the type IV (increased VLDL) or type V (increased VLDL and fasting chylomicronemia) phenotypes.

Table 5. Causes of Very High Triglycerides That May Be Associated With Pancreatitis**Genetic^{91–95,105–107}**

Lipoprotein lipase deficiency
 Apolipoprotein CII deficiency
 Apolipoprotein AV deficiency
 GPIHBP1 deficiency
 Marinesco-Sjögren syndrome
 Chylomicron retention (Anderson) disease
 Familial hypertriglyceridemia (in combination with acquired causes)

Acquired disorders of metabolism*

Hypothyroidism¹⁰⁸
 Pregnancy, especially in the third trimester†^{109–111}
 Poorly controlled insulinopenic diabetes^{112,113}

Drugs (medications)*

α-Interferon¹¹⁴
 Antipsychotics (atypical)¹¹⁵
 β-blockers such as atenolol‡¹¹⁶
 Bile acid resins§¹¹⁷
 L-Asparaginase¹¹⁸
 Estrogens|| (oral, not transcutaneous)¹¹⁹
 Protease inhibitors¹²⁰
 Raloxifene¶¹²¹
 Retinoic acid drugs¹²²
 Sirolimus¹²³
 Steroids¹⁰⁸
 Tamoxifen¹²⁴
 Thiazides¹²⁵

Diet*

Alcohol excess, especially with a high saturated-fat diet^{126,127}

Diseases*

Autoimmune chylomicronemia (eg, antibodies to LPL,¹²⁸ SLE¹²⁹)
 Chronic idiopathic urticaria¹³⁰
 Renal disease¹³¹

GPIHBP1 indicates glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LPL, lipoprotein lipase; and SLE, systemic lupus erythematosus.

*These factors are especially concerning in the patient with preexisting known hypertriglyceridemia, often on a genetic basis.

†Triglyceride increase with each trimester, but invariably, it is the third trimester when hypertriglyceridemia in susceptible patients becomes symptomatic.

‡Carvedilol is preferred in diabetic patients and those with hypertriglyceridemia who are receiving β-blockers.¹³²

§Bile acid resins should not be used with preexisting hypertriglyceridemia.

||Estrogens in oral contraceptives or in postmenopausal hormone therapy; hypertriglyceridemia can occur when the progestin component is stopped.¹³³

¶In women who experienced hypertriglyceridemia with estrogen therapy.

expression of the lipid phenotypes makes identification difficult, and the combination of both family screening and upper 10th percentile apo B levels is often needed for diagnostic confirmation. A nomogram is available to calculate the probability that a patient is likely to be affected by FCHL.¹³⁸ In the absence of age- and sex-adjusted values for a population, it has been further suggested that FCHL may be

present if hypertriglyceridemia (>133 mg/dL) and hyperapo B (>120 mg/dL) are present.⁵⁸ The important role of weight gain in the clinical expression of the phenotype is underscored by the observation that as adiposity (assessed by an elevated waist-to-hip ratio) increases, FCHL subjects express higher plasma apo B concentrations than matched control subjects. Genetic studies that used ultrasound findings and alanine aminotransferase as surrogates for fatty liver have shown that fatty liver is a heritable aspect of FCHL.¹³⁹ The molecular basis underlying FCHL is largely unknown; genetic variants in the APOA1/C3/A4/A5 cluster and the upstream stimulatory factor 1 (*USF1*) gene may play a role.^{140–142} Importantly, FCHL is strongly represented in studies of survivors of myocardial infarction,⁸⁷ especially those survivors <40 years of age.¹⁴³

The increased frequency with which FCHL is seen may relate in part to the observation¹⁴⁴ that in addition to multiple genes that upregulate apo B secretion, the worldwide trend of energy excess and associated weight gain exaggerates the baseline abnormalities in apo B secretion. Although the phenotypic expression of FCHL is delayed until young adulthood, as childhood obesity rates increase, the higher adipose tissue mass that drives apo B secretion accelerates the number of cases of FCHL diagnosed in the young adult population.¹⁴⁵

Familial type III hyperlipoproteinemia or dysbetalipoproteinemia is due to the accumulation of cholesterol-rich VLDL,^{146,147} which results in a higher ratio of core CE to triglyceride (>0.3) than in normal VLDL (0.2). The type III phenotype is often characterized by near-equivalent cholesterol and triglyceride values due to impaired receptor-mediated clearance, whereas the hypertriglyceridemia of type III reflects the impaired processing of remnants and increased VLDL hepatic production associated with increased levels of apo E. In this disorder, apo B is not a useful marker of overall atherogenicity, as in FCHL; non-HDL-C would be a more appropriate target.¹⁴⁸ Homozygosity for the rare apo E2 isoform, which displays defective binding to the LDL receptor compared with the most common apo E3 isoform, is necessary for the expression of type III, but it is not sufficient. Rather, additional factors (eg, obesity, T2DM, or hypothyroidism) are generally required for expression of the type III phenotype, which includes the characteristic palmar or tuberoeruptive xanthomas and increased cardiovascular and peripheral vascular disease risk. Affected individuals may be extraordinarily responsive to a low-carbohydrate (CHO) diet.¹⁴⁹

FHTG has a population prevalence of ≈5% to 10% and is defined by the familial occurrence of isolated high VLDL levels with triglyceride values most commonly in the 200 to 500 mg/dL range. It is genetically heterogeneous, and its expression is accentuated by the presence of a secondary factor such as obesity or IR. Initially, it was thought that FHTG was not associated with an increased risk of CVD, as contrasted with FCHL.⁸⁷ However, this was reexamined in the National Heart, Lung, and Blood Institute's Family Heart Study, which studied 5381 subjects from 1245 families.⁹⁰ FCHL and FHTG were diagnosed in 10.2% and 12.3% of 334 random control families, respectively, and in 16.7% and 20.5% of 293 families with at least 1 case of premature CVD. MetS was identified in 65% of FCHL and 71% of FHTG patients compared with 19% of control subjects without

Table 6. Association Between BMI and Hypertriglyceridemic Status (≥ 150 mg/dL or ≥ 200 mg/dL)*

BMI, kg/m ²	TG Concentration, mg/dL		TG Concentration, mg/dL	
	≥ 150 (n=1744)	<150 (n=3250)	≥ 200 (n=937)	<200 (n=4057)
<25	20.1	42.7	17.5	39.0
25 to <30	39.9	31.6	39.6	33.3
≥ 30	39.9	25.6	42.9	27.7

BMI indicates body mass index; TG, triglyceride.

*Values come from National Health and Nutrition Examination Survey 1999–2004. Values are percent of participants within a TG category as a function of BMI status.

FCHL or FHTG. The increased prevalence of the MetS alone could account for the elevated CVD risk associated with both FCHL and FHTG. Thus, the increasing prevalence of both obesity and MetS appears to increase the frequency, onset of expression, and severity of genetic triglyceride syndromes.

Finally, genome-wide association studies have uncovered multiple loci associated with high levels of triglyceride.¹⁵⁰ Specifically, common variants in *APOA5*, glucose kinase regulatory protein (*GCKR*), *LPL*, and *APOB* have been identified, thereby supporting a role for both common and rare variants responsible for hypertriglyceridemia.¹⁵¹ Efforts are ongoing to identify genetic variants that influence the response to drugs, which may be used to tailor drug selection and dosing to the profile of the individual patient.¹⁵²

5.2. Obesity and Sedentary Lifestyle

Evidence from epidemiological and controlled clinical trials has demonstrated that triglyceride levels are markedly affected by body weight status and body fat distribution. Data from 5610 participants ≥ 20 years of age from NHANES between 1999 and 2004 reported a relationship between body mass index (BMI) and triglyceride concentration.¹⁵³ Approximately 80% of participants classified as overweight (BMI 25 to 30 kg/m²) and obese (BMI ≥ 30 kg/m²) had triglyceride levels ≥ 150 mg/dL. When the triglyceride cut point was ≥ 200 mg/dL, $\approx 83\%$ of participants were classified as overweight or obese (Table 6). Participants with a normal BMI (<25 kg/m²) were more likely to have triglyceride levels <150 mg/dL (43%) and <200 mg/dL (39%). A similar trend was reported recently for youths in the NHANES Survey 1999–2006¹⁵⁴; only 5.9% of participants in the normal-weight category had high triglyceride levels (≥ 150 mg/dL), whereas 13.8% and 24% of overweight or obese individuals had elevated triglyceride levels.¹⁵⁴

In addition to the association between triglyceride levels and BMI, the Framingham Heart Study¹⁵⁵ reported strong associations of triglyceride levels with both subcutaneous abdominal adipose tissue and visceral adipose tissue in men and women (mean age 50 years). For visceral adipose tissue, the multivariable-adjusted residual effect was approximately twice that for subcutaneous abdominal adipose tissue for both women and men ($P<0.0001$ for both). Thus, although it is clear that excess adiposity is associated with elevated triglyceride levels, visceral adiposity is a greater contributor than subcutaneous adipose

tissue.^{155,156} Excess visceral fat in patients with IR may further expose the liver to higher levels of FFAs via the portal circulation, and increased flux of FFAs to the liver contributes to increased secretion of VLDL. A consequence of excessive fat combined with impaired clearance or storage of triglycerides in subcutaneous fat is ectopic fat deposition in skeletal muscle, liver, and myocardium, which may result in IR, nonalcoholic fatty liver disease, and pericardial fat.^{157,158} A disproportionate amount of visceral versus subcutaneous adipose tissue may also reflect a lack of adipocyte storage capacity, with saturation of the normal sites of fat deposition. Subcutaneous fat may serve as a protective factor with regard to the metabolic consequences of obesity¹⁵⁹; a relative paucity (ie, lipodystrophy) is associated with hypertriglyceridemia.

5.3. Lipodystrophic Disorders

5.3.1. Genetic Disorders

Lipodystrophy can be inherited or acquired. The inherited lipodystrophies are rare disorders that are characterized by loss of adipose tissue. These disorders may be inherited in either autosomal recessive or dominant patterns. The loss of adipose tissue is selective and variable and may be partial or complete. Some forms manifest at birth, whereas others become evident later in life, with loss of fat beginning in childhood and puberty.¹⁶⁰

Hypertriglyceridemia is seen in many lipodystrophic disorders, often in association with low HDL-C. The severity of hypertriglyceridemia is related to the extent of the loss of fat,¹⁶¹ and mechanisms include decreased storage capacity of fat, with delayed clearance of TRLs and increased hepatic lipid synthesis. Fat accumulation in insulin target organs may cause lipotoxicity and IR. One of the most severe forms is congenital generalized lipodystrophy, a rare autosomal recessive disorder that presents at birth with a nearly complete absence of subcutaneous adipose tissue. Affected children may present with metabolic derangements, including severe hypertriglyceridemia, with eruptive xanthomas and pancreatitis.¹⁶² At least 3 molecular variants have been described that involve genes whose products are necessary for the formation and maturation of lipid droplets in adipocytes.¹⁶⁰ Varieties of familial partial lipodystrophy, which are rare autosomal dominant disorders, involve fat loss from the extremities more than the trunk. Hypertriglyceridemia is most severe in the Dunnigan variety, which is caused by a defect in the gene for lamin A and tends to be more severe in women than in men.^{162,163}

5.3.2. Acquired Disorders

HIV-associated dyslipidemic lipodystrophy is characterized by increased content of triglycerides in VLDL, LDL, and HDL due to reduced clearance of TRL.¹⁶⁴ The fat distribution abnormalities appear in 1 of 3 prevalent forms: (1) Generalized or localized lipoatrophy, which usually involves the extremities, buttocks, and face; (2) lipohypertrophy with generalized or local fat deposition that involves the abdomen, breasts, dorsocervical region, and supraclavicular area; or (3) a mixed pattern with central adiposity with peripheral lipoatrophy. Factors that influence the development of lipodystrophy include increased duration of HIV infection, high viral load, low CD4 counts before highly active antiretroviral

therapies, and prolonged survival and duration of highly active antiretroviral therapies. Several antiretroviral drugs used to treat HIV infection can cause hypertriglyceridemia, including the protease inhibitors lopinavir and ritonavir.¹⁶⁵

Other acquired forms of lipodystrophy occur with autoimmune diseases such as juvenile dermatomyositis.¹⁶¹ Patients with acquired generalized lipodystrophy lose fat from large areas of the body during childhood and adolescence, and this is often accompanied by hepatic steatosis.¹⁶²

6. Diabetes Mellitus

High triglyceride levels that accompany either normal or impaired fasting glucose predict the development of T2DM,^{166,167} and therefore, hypertriglyceridemic states should prompt surveillance to rule out T2DM. In addition, $\approx 35\%$ of T2DM adults have fasting triglyceride levels ≥ 200 mg/dL¹⁶⁸ associated with decreased HDL-C and small, dense LDL particles.^{41,53,112,113,169,170} Patients with poorly controlled type 1 diabetes mellitus (T1DM) may exhibit a similar pattern of dyslipidemia. Causes of hypertriglyceridemia in DM include increased hepatic VLDL production and defective removal of chylomicrons and CMRs, which often reflects poor glycemic control.¹⁷¹

6.1. Type 1 Diabetes Mellitus

6.1.1. Chylomicron Metabolism

In general, chylomicron and CMR metabolism can be altered significantly in DM.^{49,53} In untreated or poorly controlled T1DM, LPL activity will be low, and ppTG levels will in turn be increased. Insulin therapy rapidly reverses this condition, which results in improved clearance of chylomicron triglyceride from plasma. In chronically treated T1DM, LPL measured in postheparin plasma, as well as adipose tissue LPL, may be normal or increased, and chylomicron triglyceride clearance may also be normal. Other hepatic and intestinally derived proteins that modulate chylomicron production and intestinal lipoprotein secretion (eg, microsomal transfer protein and glucagon-like peptides 1 and 2) have been studied in T1DM-induced rodents, but their clinical relevance vis-à-vis chylomicron metabolism in human T1DM has yet to be established.^{172–174}

6.1.2. VLDL Metabolism

Individuals with DM frequently have elevated levels of VLDL triglyceride. In T1DM, triglycerides correlate closely with glycemic control, and marked hyperlipidemia can be found in patients with DM and ketoacidosis. The basis for increased VLDL in subjects with poorly controlled but nonketotic T1DM is usually overproduction of these lipoproteins.¹¹³ Specifically, insulin deficiency results in increased adipocyte lipolysis, with FFA mobilization driving hepatic VLDL apo B secretion. Reduced clearance of VLDL apo B also contributes to triglyceride elevation in severe cases of uncontrolled DM. This results from a reduction of LPL, which returns to normal with adequate insulinization. In fact, plasma triglycerides may be low-normal with intensive insulin treatment in T1DM, with lower than average production rates of VLDL being observed in such instances.

6.2. Type 2 Diabetes Mellitus

6.2.1. Chylomicron Metabolism

In T2DM, metabolism of dietary lipids is complicated by coexistent obesity and the hypertriglyceridemia associated with IR. Defective removal of chylomicrons and CMRs has been observed in T2DM⁴⁹; however, LPL is normal or only slightly reduced in untreated patients.^{49,112} Because both fasting hypertriglyceridemia and reduced HDL-C are common in T2DM and are correlated with increased ppTG levels, it is difficult to identify a direct effect of T2DM on chylomicron metabolism. Recently, studies have indicated that IR can result in increased assembly and secretion of chylomicrons.¹⁷⁵ This parallels the central defect of increased hepatic VLDL secretion in IR and T2DM (section 6.2.2) and clearly contributes to increased postprandial lipid levels with T2DM.

6.2.2. VLDL Metabolism

Overproduction of VLDL, with increased secretion of both triglycerides and apo B₁₀₀, appears to be the central cause of increased plasma VLDL levels in patients with T2DM.¹⁷⁶ Increased assembly and secretion of VLDL is probably a direct result of both IR (with loss of insulin's action to stimulate degradation of newly synthesized apo B) and increases in FFA flux to the liver and de novo hepatic lipogenesis (with increased triglyceride synthesis). LPL levels have been reported to be reduced¹¹² in T2DM, and this may contribute significantly to elevated triglyceride levels, particularly in severely hyperglycemic patients. Because obesity, IR, and concomitant familial forms of hyperlipidemia are common in T2DM, study of the pathophysiology is difficult. The interaction of these overlapping traits also makes therapy less effective. In contrast to T1DM, in which intensive insulin therapy normalizes (or even "supernormalizes") VLDL levels and metabolism, insulin or oral agents only partly correct VLDL abnormalities in the majority of individuals with T2DM.¹¹³ Therapies such as metformin and the thiazolidinediones can lower plasma triglyceride concentrations 10% to 15% and 15% to 25%, respectively.¹⁷⁷ The thiazolidinediones appear to improve peripheral insulin sensitivity, and this leads to inhibition of lipolysis in adipose tissue. Plasma levels of FFAs fall $\approx 25\%$ at the highest dose of both of the presently available thiazolidinediones, and such changes should lead to lower hepatic triglyceride synthesis and reduced VLDL secretion. However, pioglitazone lowers triglyceride levels by increasing LPL-mediated lipolysis, whereas VLDL secretion remains unchanged.¹⁷⁸ Rosiglitazone does not affect triglyceride levels, although the basis for this difference is unclear.¹⁷⁹

6.2.3. Small LDL Particles

LDL particles in patients with DM may be atherogenic even at normal LDL-C concentrations. For example, glycosylated LDL can be taken up by macrophage scavenger receptors in an unregulated manner, thereby contributing to foam cell formation.¹⁸⁰ In addition, hypertriglyceridemia is associated with small, dense, and CE-depleted LDL particles. Thus, individuals with T2DM and mild to moderate hypertriglyceridemia exhibit the pattern B profile of LDL (smaller, denser particles) described by Austin and Krauss¹⁸⁰; these particles

Table 7. Cardiovascular Risk Components of the Metabolic Syndrome*

Increased waist circumference	>40 inches in men (>35 inches for Asian men); >35 inches in women (>31 inches for Asian women) or population- and country-specific definitions
High triglycerides	≥150 mg/dL, or taking medication for high triglycerides
Low HDL-C (good cholesterol)	<40 mg/dL in men; <50 mg/dL in women, or taking medication for low HDL-C
Elevated blood pressure	≥130 mm Hg systolic ≥85 mm Hg diastolic, or taking antihypertensive medication in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or taking medication to control blood sugar

HDL-C indicates high-density lipoprotein cholesterol.

*The metabolic syndrome is diagnosed when a person has ≥3 of these risk factors.

Adapted from Huang¹⁸² and NCEP ATP III.^{182a}

may be more susceptible to oxidative modification and catabolism via macrophage scavenger receptors than pattern A LDL particles. Overproduction of LDL apo B₁₀₀ may also occur with T2DM even with mild degrees of hyperglycemia, especially if there is concomitant elevation of VLDL, resulting in the atherogenic dyslipidemic triad, mixed hyperlipidemia, or FCHL.

6.2.4. Reduced HDL-C

In T1DM, HDL-C levels are often normal; however, in decompensated T1DM with hypertriglyceridemia, CE transfer protein-mediated exchange will result in low HDL-C concentrations. Similarly, in T2DM, especially in the presence of increased secretion of apo B-containing lipoproteins and concomitant hyperlipidemia, CE transfer protein-mediated transfer of HDL CE to those lipoproteins results in lower levels of HDL-C (and increased HDL triglycerides). Fractional catabolism of apo AI is increased in T2DM with low HDL-C, as it is in nondiabetic subjects with similar lipoprotein profiles. Although apo AI levels are reduced consistently, correction of hypertriglyceridemia does not usually alter apo AI levels.^{53,181}

6.2.5. Summary

In summary, T1DM may be associated with elevations of VLDL triglyceride and LDL-C if glycemic control is poor or if the patient is ketotic. In contrast, T2DM is often accompanied by high triglyceride levels, reduced HDL-C, and the presence of smaller CE-depleted LDL particles. Treatment with hypoglycemic agents has a variable drug-dependent effect on plasma lipid levels.

7. Metabolic Syndrome

Elevated triglyceride levels, along with increased waist circumference, elevated fasting glucose, elevated blood pressure, or reduced HDL-C levels, are MetS risk factors, with a tally of 3 needed for the diagnosis (Table 7). The prevalence

of MetS in the United States is currently estimated at 35% in both men and women¹⁸³ and is higher in CVD patients; in NHANES III, MetS was present in >40% versus 28% of subjects with or without CVD, respectively.¹⁹

7.1. Prevalence of Elevated Triglyceride in MetS

The prevalence of triglyceride levels ≥150 mg/dL is nearly twice as high in subjects with MetS as in those without MetS.^{184,185} Among individual components of MetS, high triglyceride level was the second most common (74%), after elevated blood pressure.¹⁸⁶ A high prevalence of triglyceride levels ≥150 mg/dL (72%) was also observed in patients with MetS and CVD.¹⁸⁷ In contrast, a low prevalence of hypertriglyceridemia was reported in MetS patients with advanced heart failure owing in part to hepatic congestion and cachexia.¹⁸⁸

7.2. Prognostic Significance of Triglyceride in MetS

Longitudinal and cross-sectional studies have suggested that high triglyceride level may be a predictor of CVD risk. For example, a “hypertriglyceridemic waist,” as defined by elevated triglyceride and increased waist circumference, was associated with arteriographic CVD¹⁸⁹; elevated triglyceride level was also associated with myocardial infarction and stroke risk in NHANES III.¹⁹ Nonetheless, clinical outcome studies have failed to demonstrate the prognostic significance of triglyceride levels in MetS. Rather, other factors (eg, low HDL-C, elevated glucose, or elevated blood pressure) independently predicted CVD and all-cause mortality in RCTs.^{184–187} Thus, although elevated triglyceride is highly prevalent in subjects with MetS, it is less predictive of CVD outcomes than other MetS components, thus relegating triglyceride level as an important biomarker rather than a prognosticator of CVD.

8. Chronic Kidney Disease

Dyslipidemia is commonly present in patients with chronic kidney disease (CKD) and occurs at all stages. It occurs in both children and adults,¹⁹⁰ in those with nephrotic syndrome, in patients undergoing dialysis, and after renal transplantation. A triglyceride level >200 mg/dL is present in ≈50% of those with CKD, often in association with low HDL-C. In addition, several risk factors that alter lipoprotein metabolism, such as T2DM, obesity, IR, and MetS, frequently are also found in CKD subjects,¹⁹¹ which results in qualitative lipoprotein abnormalities that include increased RLPs and small, dense LDL particles. Patients with nephrotic syndrome or undergoing peritoneal dialysis are especially likely to exhibit a proatherogenic lipid profile.¹⁹² In renal transplant recipients, hyperlipidemia is a frequent finding, affecting 80% to 90% of adult recipients despite normal renal function.¹⁹³

The primary abnormality in CKD subjects is reduced catabolism of TRL,¹³¹ which results in elevated levels of RLPs and prolonged ppTG that begins during the early stages of CKD.¹⁹⁴ The diminished clearance of TRL results from reduction in activity of both LPL and HTGL. Alterations in

the composition of circulating triglycerides associated with increases in the LPL inhibitor, apo CIII, and decreases in the LPL activator, apo CII, may exacerbate this defect.¹⁹⁴ Other factors such as increased parathyroid hormone levels,¹³⁵ increased calcium accumulation in liver and adipose tissue,¹⁹⁵ and a putative circulating lipase inhibitor (ie, CE-poor pre- β -HDL¹⁹⁶) have also been shown to downregulate LPL in the plasma of uremic patients. In renal transplant recipients, immunosuppressive agents such as corticosteroids, calcineurin inhibitors, and rapamycin may significantly worsen dyslipidemia. Finally, other factors that accompany CKD, such as DM, MetS, hypothyroidism, obesity, excessive alcohol intake, marked proteinuria, and chronic liver disease, may potentiate hypertriglyceridemia.

Although the beneficial effects of lipid-lowering therapy in both primary and secondary prevention of CVD in the general population are well established, there is a paucity of RCTs addressing the role of treatment of dyslipidemia, particularly hypertriglyceridemia, in the CKD population. In fact, a number of studies have shown a paradoxical effect of low serum cholesterol in CKD and dialysis populations to be an adverse predictor of mortality.^{197–200} This might reflect an adverse outcome of chronic inflammation and malnutrition that results in risk reversal. Of 2 clinical outcome trials completed recently, neither demonstrated benefits of LDL-C and lowering triglyceride levels in hemodialysis patients.^{201,202} Results from RCTs to date cannot be extrapolated to milder forms of CKD, and therefore, an RCT is warranted in this subgroup. Until then, the benefit of lowering triglyceride levels in CKD remains unproven.

9. Interrelated Measurements and Factors That Affect Triglycerides

9.1. Non-HDL-C, Apo B, and Ratio of Triglycerides to HDL-C

As discussed previously in this statement, TRLs and RLPs in particular are atherogenic. Therefore, when a high-triglyceride profile is assessed, it is important to assess the overall atherogenicity of plasma. Both non-HDL-C (non-HDL-C = TC – HDL-C), which is a summary measure of all the cholesterol carried in apo B-containing particles, and directly measured apo B levels can be used for this purpose.

9.1.1. Non-HDL-C

The value of non-HDL-C in CVD risk assessment was first proposed by Frost and Havel in 1998,⁶¹ and this relationship has now been confirmed in many studies.^{203–216} In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study, an autopsy study of 15- to 34-year-old individuals who died of non-CVD causes, non-HDL-C was correlated with fatty streaks and raised lesions in the right coronary artery.²⁰⁴ In adults, non-HDL-C correlates with coronary calcification^{205,206} and CVD progression.²⁰⁷ Although the relationship between non-HDL-C and CVD outcomes has been studied less extensively than the relationship between LDL-C, myocardial infarction, and cardiovascular death, there are prospective studies that have demonstrated strong relationships between non-HDL-C levels and CVD events in the ab-

sence^{208–210} or presence^{211,212} of preexisting CVD or acute coronary syndrome. Long-term data from the Lipid Research Clinics Follow-Up Study demonstrated that non-HDL-C levels were strongly predictive of CVD mortality after 19 years of follow-up.²¹³ In the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study, non-HDL-C predicted 10-year CVD mortality only among those with impaired fasting glucose, not among those with normal fasting glucose.²¹⁴ Non-HDL-C levels also predicted ischemic stroke,^{215,216} and its predictive value has been further demonstrated in both men and women, across all age and ethnic groups, and with or without CVD or associated risk factors.

Non-HDL-C can be assessed in the nonfasting state^{22,217} and is more accurately determined because it does not depend on fasting triglyceride concentrations, as calculated LDL-C does.⁶¹ Data on the distribution of non-HDL-C in the US population are available for children (Bogalusa cohort²¹⁸) and adults (NHANES III²¹⁹), and non-HDL-C levels in childhood strongly predict such levels in adulthood.^{219,220} Among adults, age-adjusted non-HDL-C concentrations are lower among women than men, increase with age through age 65 years (to a greater degree in women than in men), and decline in individuals >65 years of age (more so in men than in women).²⁰⁹ Non-Hispanic black women and men have the lowest non-HDL-C levels, whites are intermediate, and Mexican Americans have the highest level. Among women, non-HDL-C levels were inversely related to education.²¹⁹

The ATP III guidelines recommended that non-HDL-C serve as a secondary treatment target if elevated levels of triglyceride (≥ 200 mg/dL) persisted after LDL-C target levels had been achieved.^{10,221} The non-HDL-C target was set 30 mg/dL higher than LDL-C, based on the fact that a triglyceride level of 150 mg/dL corresponds to a VLDL cholesterol level of 30 mg/dL.²²¹ A meta-analysis of clinical trial data supports a 1:1 relationship between the percent of non-HDL-C lowering and the percent of cardiovascular reduction.²²² Yet recent data indicate that non-HDL-C remains undertreated in the United States. For example, in the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey, the proportion of individuals with triglyceride levels ≥ 200 mg/dL who had achieved their non-HDL-C goal ranged from 64% with 0 to 1 risk factor to 52% with ≥ 2 risk factors and only 27% with CVD risk equivalents.²²³ Data from NHANES also showed that only a modest proportion (37%) of high-risk individuals were at their non-HDL-C goal.²²⁴ Finally, in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) study of men and women with CVD and DM, the mean non-HDL-C level (131 ± 40 mg/dL) was above the recommended goal of <130 mg/dL.²²⁵

9.1.2. Apo B

Apo B is contained within all potentially atherogenic lipoproteins, including lipoprotein(a), LDL, IDL, VLDL, and TRL remnants. Moreover, because each of these lipoprotein particles contains 1 apo B molecule, apo B provides a direct measure of the number of atherogenic particles present in the circulation.^{58,226} A direct link between apo B and severity of

CVD in patients undergoing diagnostic cardiac catheterization²²⁷ was followed by numerous studies that supported apo B as being highly predictive of CVD and, in some cases, more closely linked to CVD outcomes than LDL-C.^{58,228,229} In contrast, findings of studies that compared apo B with non-HDL-C have been more heterogeneous. Although apo B and non-HDL-C are highly correlated, their interrelationship varies depending on the underlying lipid disorder and treatment status.^{148,230} As reviewed recently,²³¹ many epidemiological studies have compared the predictive value of apo B with non-HDL-C for CVD outcomes and have more commonly identified apo B to be either superior or equivalent to non-HDL-C, whereas non-HDL-C has only been more predictive in limited cases.¹⁴³ Yet in studies that demonstrated statistically significant differences between apo B and non-HDL-C, the differences in point estimates were often quite small and therefore unlikely to have a major impact in day-to-day clinical practice.²³¹ Consequently, the ATP III guidelines favored use of non-HDL-C rather than apo B; this was related in part to the limited availability of apo B assays in clinical laboratories, compounded by the relative lack of standardization of the apo B assay and higher cost than for non-HDL-C.²²¹ Nevertheless, in view of additional data and in the presence of standardization that has accrued since ATP III was released in 2001, a panel of international experts has recommended a revision of this assessment.²²⁹

9.1.3. Ratio of Triglycerides to HDL-C

The joint occurrence of high triglyceride level and low HDL-C characterizes the dyslipidemia of MetS. It strongly predicts CVD in observational studies, and post hoc analyses of clinical trials suggest that patients who have both adverse markers tend to benefit more from treatment than those who do not.^{39,40,232} The ratio of triglycerides to HDL-C serves as a summary measure for either elevated triglyceride level, low HDL-C, or both. It is linked to IR in whites^{233,234} (but not in blacks) and to small, dense LDL particles and higher LDL particle numbers.^{233,235} The link between IR and the ratio of triglycerides to HDL-C is already apparent in youth.²³⁶ In recent years, case-control and prospective studies have linked the ratio of triglycerides to HDL-C to CVD incidence, outcomes, and all-cause mortality,^{237–242} with improved predictive power in some studies compared with LDL-C or non-HDL-C.^{238,239,242}

10. Factors That Influence Triglyceride Measurements

Considerable biological and, to a lesser extent, analytic variability exists in the measurement of triglycerides, with a median variation of 23.5% compared with 4.9% for TC, 6.9% for HDL-C, and 6.5% for calculated LDL-C.²⁴³ Although biological variability as a consequence of lifestyle, medications, and metabolic abnormalities accounts for most of the intraindividual variation in triglycerides, other considerations that affect triglyceride measurements include postural effects, phlebotomy-related issues, and fasting versus nonfasting state. These latter considerations become more critical in the design of clinical trials aimed at evaluating the role of

triglyceride levels in CVD risk assessment. In this regard, it has been suggested that in addition to the recommendations listed below (ie, posture- and phlebotomy-related issues), an average of 3 fasting serial samples be drawn at least 1 week apart and within a 2-month time frame to provide a more accurate estimate of baseline triglyceride levels.²⁴³

10.1. Postural Effects

Because TRLs do not readily diffuse between vascular and extravascular compartments, the increase in plasma volume that accompanies movement from a standing to a supine position also results in a temporary decrease in triglyceride concentrations.²⁴⁴ As a result of these positional changes, triglyceride levels are reduced by $\approx 12\%$ after 20 to 30 minutes and by 15% to 20% by 40 minutes, with more modest decreases when a person changes from standing to sitting (ie, 8% and 10%, respectively).^{245,246} Thus, it is recommended that standardization of blood sampling conditions be instituted on each occasion (eg, 5 minutes in sitting position) to minimize variability in triglyceride measurements.²⁴³

10.2. Phlebotomy-Related Issues

The 2 relevant phlebotomy-related issues that impact triglyceride levels are the venous occlusion time and differences between serum- and plasma-containing tubes. Because increases of as much as 10% to 15% in triglyceride levels have been reported with prolonged venous occlusion times, the National Cholesterol Education Program Working Group on Lipoprotein Measurement has recommended that a tourniquet not be applied for >1 minute before blood withdrawal.²⁴³ Moreover, plasma tubes contain ethylenediaminetetraacetic acid and reduce triglyceride levels by 3% compared with serum because of the relative dilution of nondiffusible components in plasma.²⁴⁷ Therefore, reliability in triglyceride measurements will be enhanced when either serum or plasma is used consistently.

10.3. Fasting Versus Nonfasting Levels

Although an overnight fast has been the traditional method for assessment of triglyceride levels, there are several lines of evidence that support a nonfasting measurement to screen for hypertriglyceridemia. First, the fasting state only represents a small proportion of time spent each day and therefore understates levels that are attained in the postprandial state. From a pathophysiological standpoint, a postprandial state enriched in dietary fat (eg, 70 to 100 g) may affect saturation parameters and impede hepatic removal of circulating CMRs,²⁴⁸ thereby permitting their uptake and incorporation by macrophages.^{63,249,250} Supportive observational studies have recently identified nonfasting triglyceride levels to be a superior predictor of CVD risk compared with fasting levels.^{21,22}

The relationship between fasting and ppTG levels and factors that influence the response to dietary fat in healthy normolipidemic subjects were reviewed in 39 studies approximating 1500 ppTG measurements.^{68,251–288} Although baseline dietary characteristics, fat content, and composition of test meals often varied between studies, a graded association

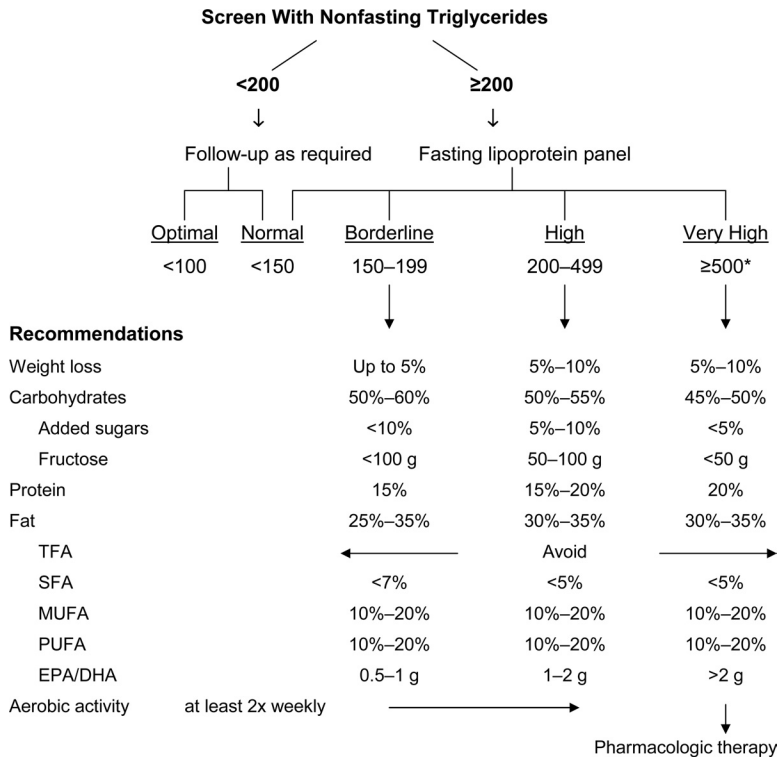


Figure 5. Practical algorithm for screening and management of elevated triglycerides. TFA indicates *trans* fatty acid; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; and EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid.

*When patients present with abdominal pain due to hypertriglyceridemic pancreatitis, removal of all fat from the diet is required (with the possible exception of medium chain triglycerides [MCTs]) until appropriate therapies lower triglyceride levels substantially.

existed between the amount of dietary fat in the test meal and the ppTG response. For example, a meal that contained up to 15 g of fat was associated with minimal (20%) increases in peak ppTG levels,²⁷⁶ whereas high-fat meals (eg, 50 g), including those served in popular fast-food restaurants, increased triglyceride levels by at least 50% beyond fasting levels.^{68,273,275,279} Because median triglyceride levels in US adults range between 106 (women) and 122 (men) mg/dL, measurement of nonfasting triglyceride levels in the absence of a high-fat meal (eg, <15 g) would be expected to eliminate the requirement for a fasting lipid panel in a sizeable proportion of otherwise healthy adults.

A practical algorithm for screening triglyceride measurements is suggested in Figure 5. In normotriglyceridemic subjects (ie, fasting triglyceride levels <150 mg/dL), consumption of a low-fat breakfast (ie, <15 g) before blood sampling would not be expected to raise ppTG levels above 200 mg/dL. In these cases, no further testing for hypertriglyceridemia is indicated, although further discussion of lifestyle measures may be advocated on the basis of that individual's level of risk. However, if nonfasting triglyceride levels equal or exceed 200 mg/dL, a fasting lipid panel is recommended within a reasonable (eg, 2 to 4 weeks) time frame.

11. Special Populations

11.1. Children and Adolescent Obesity

Although the consequences of atherosclerotic CVD are seen only rarely in children, the early pathophysiological changes in arteries begin soon after birth and accelerate during adolescence.²⁸⁹ The same risk factors associated with disease severity and progression in adults are present in the pediatric population, and the degree to which these risk factors are present in childhood is predictive of their prevalence in adulthood.^{290,291} Therefore, it is clear that primary prevention of CVD should begin in childhood, as has been the established policy of the American Heart Association, the American Academy of Pediatrics, and the National Heart, Lung, and Blood Institute.^{292,293} The National Heart, Lung, and Blood Institute's Pediatric Cardiovascular Risk Reduction Initiative panel has completed its work, and a full report was anticipated in 2011. Table 8 presents the pediatric cut points for hypertriglyceridemia, although these reference values are based on data from the 1981 Lipid Research Clinics prevalence study.²⁹³ More recent data from NHANES 1999–2006 identified a triglyceride level ≥150 mg/dL in 11.4% of boys and 8.8% of girls 12 to 19 years of age, with the highest rate (16.4%) in the 18- to 19-year-old group.¹⁵⁴

Table 8. Age- and Sex-Based Reference for Plasma Triglycerides in Children

Triglyceride Percentile	Boys, by Age Group			Girls, by Age Group		
	5–9 y	10–14 y	15–19 y	5–9 y	10–14 y	15–19 y
75th: Acceptable	58	74	88	74	85	85
90th: Borderline	70	94	125	103	104	112
95th: High	85	111	143	120	120	126

Values are milligrams per deciliter.

11.1.1. Risk Factors for Hypertriglyceridemia in Childhood

The genetic abnormalities of triglyceride metabolism (notably, *LPL*, *APOC2*, and, most recently, *APOA5* and *GPIHBP1*) that may be identified in childhood are rare and generally diagnosed soon after birth. More commonly identified are milder triglyceride level elevations (ie, 100 to 500 mg/dL) associated with environmental triggers such as poor diet, lack of exercise, obesity, DM, and MetS.

11.1.2. Obesity and High Triglyceride Levels in Childhood

At least one third of American children and adolescents are overweight, and childhood obesity represents the major cause of pediatric hypertriglyceridemia. Approximately 1 in 5 children with a BMI above the 95th percentile are hypertriglyceridemic, a rate that is 7-fold higher than for nonobese children 6 to 10 years of age.^{294,295} Obese children are also more prone to have other CVD risk factors such as IR, high LDL-C, low HDL-C, and hypertension. In 2006, the American Heart Association convened the Childhood Obesity Research Summit to highlight the significance of pediatric obesity in CVD and to set research priorities for prevention and treatment.²⁹⁵

11.1.3. IR and T2DM in Childhood

Studies in children, including the Cardiovascular Risk in Young Finns Study²⁹⁶ and a Pima Indian population study,²⁹⁷ indicate that IR precedes the development of other risk factors, including obesity, hypertension, and hypertriglyceridemia. There are some impediments to the study of IR in youth, namely, lack of consensus for serum insulin norms and the well-documented physiological IR of puberty. Despite ongoing controversy in this area, 1 recent study identified IR (measured by fasting insulin) as being associated with failure to respond to therapeutic lifestyle change in obese adolescents.²⁹⁸ In fact, recent data from NHANES III found a 7% prevalence of impaired fasting glucose in US adolescents. However, Mexican Americans and overweight adolescents had the highest rates (13% and 17.8% respectively) of impaired fasting glucose, which was associated with significantly higher fasting insulin, dyslipidemia, and hypertension.²⁹⁹

Impaired glucose tolerance is also associated with an increased incidence of hypertriglyceridemia. For example, in the NHANES cohort of 1999–2000, Williams et al²⁹⁹ found that mean triglyceride levels were 28% higher in adolescents with impaired glucose tolerance than in those with normal fasting glucose concentrations. Triglyceride levels were independently associated with physical activity levels and sugar-sweetened beverage intake in the NHANES 1999–2004 studies of adolescents (n=6967) 12 to 19 years of age. Each additional daily serving of sugar-sweetened beverages was associated with a 2.25-mg/dL increase in triglyceride levels, as well as increases in IR, LDL-C, and systolic blood pressure and a decrease in HDL-C. In boys but not in girls, the combination of a high level of physical activity coupled with low intake of sugar-sweetened beverages was significantly associated with lower triglyceride levels, higher HDL-C, and reduced IR.³⁰⁰

11.2. Triglycerides as a Cardiovascular Risk Factor in Women

The Framingham Heart Study was among the first observational studies to recognize elevated triglyceride level as a predictor of CVD in women,³⁰¹ and the Lipid Research Clinics Follow-Up Study found a triglyceride level >200 mg/dL to be strongly predictive of cardiovascular death.³⁰² Triglyceride level is also a significant predictor in older women; in the Cardiovascular Study in the Elderly,³⁰³ a 12-year longitudinal epidemiological study among Italian men and women ≥65 years of age at entry, women in the highest triglyceride quintile had a 2.5-fold greater risk of CVD mortality than women in the lowest quintile, even after adjustment for preexisting CVD, T2DM, obesity, and alcohol consumption. When low HDL-C was also present, risk increased 3.8-fold. Current guidelines for CVD prevention in women encourage fasting triglyceride levels <150 mg/dL and non-HDL-C <130 mg/dL through TLC.³⁰⁴

11.2.1. Triglyceride Levels During the Lifespan in Women

Although higher triglyceride levels among female newborns than among male newborns have been reported,³⁰⁵ triglyceride levels in girls and boys are generally similar during early childhood. In adolescence, girls experience a decrease in triglycerides, whereas boys experience an increase, likely due to a greater degree of IR among males.³⁰⁶ Population-based data in US adults indicate that compared with men triglyceride levels are lower in young and middle-aged females and among non-Hispanic whites, blacks, and Mexican Americans; in contrast, older women have higher levels than men in all ethnic groups.⁶ Mexican American women have the highest triglyceride levels, whereas non-Hispanic white women have intermediate levels, and black women have the lowest levels.⁶ Triglyceride levels in the 1999–2002 NHANES survey were higher than those documented in earlier NHANES surveys in 1976–1980 and 1988–1994. This increase occurred despite the fact that the use of lipid-lowering medications among adult women ≥20 years of age increased from 3.5% to 8% between the 1988–1994 and the 1999–2002 surveys.⁶

11.2.2. Prevalence of Hypertriglyceridemia in Women

The prevalence of triglyceride levels ≥150 mg/dL has increased among US women ≥20 years of age from 24.6% in 1988–1994 to 29.9% in 1999–2000,³⁰⁷ with stabilization at 26.8% (1999–2008; Table 2). Prevalence is highest among Mexican American women, intermediate among non-Hispanic white women, and lowest among black women,^{308,309} but data are lacking in other Hispanic and non-Hispanic subgroups (Figure 2). Women who develop DM experience a greater rise in triglyceride levels and have an overall more adverse lipid profile than men who develop DM.³¹⁰

11.2.3. Hormonal Influences

Triglyceride levels in women are significantly impacted by the endogenous hormonal environment and by exogenously administered reproductive hormones. The impact of cyclic hormonal fluctuations on lipoprotein levels during the menstrual cycle in premenopausal women is controversial.³¹¹

Recent studies have reported no change in basal VLDL triglyceride and apo B₁₀₀ kinetics³¹² and triglyceride levels,³¹³ whereas other studies have shown small changes in triglyceride levels during the cycle but with overall coefficients of variation similar to those of postmenopausal women and men.³¹⁴ These findings suggest that screening and risk assessment in premenopausal women can be performed without standardization of lipoprotein measurements to the phase of the menstrual cycle. Women with polycystic ovarian syndrome have higher triglyceride levels than women with normal premenopausal physiology, even after correction for BMI.^{315,316} This difference is present in women as young as 18 to 24 years of age and persists thereafter.³¹⁵

Lipid metabolic effects of oral contraceptives vary on the basis of their estrogen and progestin content.^{317,318} In the CARDIA study (Coronary Artery Risk Development in Young Adults), which did not distinguish between various formulations, oral contraceptive users had higher triglyceride levels than nonusers, despite their use being associated with lower fasting glucose levels and reduced odds of DM.³¹⁹ Higher triglyceride levels among oral contraceptive users were also found in a population-based survey in Canada.³²⁰ Although most studies suggest increases in the 20% to 30% range, triglyceride level increases of as much as 57% (and decreases in LDL particle size) have been reported in some populations.³²¹

In pregnancy, women experience a “physiological hyperlipidemia” due to enhanced lipolytic activity in adipose tissue, with >2-fold increases in circulating triglyceride levels during the third trimester.^{109,110} As is the case in the nonpregnant state, non-Hispanic black women have lower triglyceride levels during pregnancy than their white counterparts.³²² Although some studies find a hypertriglyceridemia-associated shift toward smaller, denser LDL particle size,^{323,324} others have shown a shift toward larger, buoyant LDL particles in late pregnancy.³²⁵ Both IR³²⁶ and hyperestrogenemia³²⁷ represent causative factors for the development or amplification of hypertriglyceridemia during pregnancy and may present a therapeutic challenge, especially if pancreatitis develops.¹⁰⁵ Maternal hypertriglyceridemia in gestational DM also predicts babies that are large for their gestational age.³²⁸ In contrast, endothelial function is not adversely affected as a result of pregnancy-induced hyperlipidemia.³²⁹

As women transition through menopause in middle age, triglyceride levels increase, but it is not clear how much of this increase is mediated by aging and accompanying lifestyle changes (eg, reduced physical activity) versus a consequence of menopausal hormonal transition.^{330–334} In the Study of Women’s Health Across the Nation (SWAN), the triglyceride increase peaked during late perimenopause/early postmenopause. The magnitude of change attributable to aging was similar to that associated with the menopausal transition; both were substantially greater than changes directly attributable to decreases in estradiol or increases in follicle stimulating hormone.³³⁵

Orally administered exogenous estrogens increase triglyceride levels, whereas exogenously administered progestins tend to ameliorate this estrogen-induced hypertriglyceridemia

to varying degrees depending on dose and type of progestin.^{336,337} Triglyceride levels vary substantially over time in women who are receiving cyclic hormone regimens.³³⁸ It is assumed, but not well documented, that the increase in triglyceride levels induced by oral estrogens is enhanced among women with preexisting hypertriglyceridemia; therefore, hypertriglyceridemia has often been an exclusionary criteria in hormone-based RCTs.^{339,340} Triglyceride elevations are not usually observed with transdermally administered estrogens.^{337,341,342} Selective estrogen-receptor modulators have less impact on the lipid profile than oral hormone therapy in the absence of hypertriglyceridemia with estrogen therapy.¹²¹ Raloxifene, for example, increased triglyceride levels by 8% in a 3-year study among healthy women but only by 1.5% in the much larger Multiple Outcomes of Raloxifene Evaluation trial, which included women with and without CVD.^{343,344} Finally, tamoxifen has been reported to cause marked elevation in triglyceride levels,¹²⁴ with rare reports of pancreatitis (Table 5).

11.3. Triglycerides in Ethnic Minorities

Populations from South Asia, including India, Pakistan, Sri Lanka, Bangladesh, and Nepal, have an increased prevalence of MetS and T2DM compared with Europeans.³⁴⁵ Several factors have been suggested to explain the propensity of South Asians to develop these metabolic risk factors for CVD. For example, South Asians have increased fat compared with muscle tissue, with a more central distribution of body fat, which has been attributed to the “adipose tissue overflow hypothesis.”³⁴⁶ This often occurs without a sufficient increase in waist circumference that meets the criteria of MetS as defined by ATP III, thereby resulting in a lower threshold for abnormal waist circumference for South Asians and several other ethnic groups; a BMI of 23 kg/m² in South Asians corresponds to a BMI of 25 kg/m² in whites.³⁴⁷ Other hypotheses include genetic or phenotypic adaptations of the metabolism of South Asians to enable improved survival in the face of inadequate caloric intake.^{345,346} In South Asians and other minorities (eg, Mexican Americans, Native Hawaiians, and American Indians), MetS is uniformly accompanied by an increase in atherogenic TRLs, thereby contributing to increased CVD risk in these populations.

Studies in American Indians have provided valuable information with regard to the influence of MetS and T2DM on triglyceride levels. Specifically, the Strong Heart Study, a cross-sectional prospective observational study of 4600 American Indians,³⁴⁸ found a moderate elevation in triglyceride levels and a significantly increased prevalence of T2DM to have contributed to incident CVD.³⁴⁹ Additional data from the Strong Heart Study have identified non-HDL-C as an important predictor of CVD in this subgroup.²⁰⁸

In contrast to ethnicities who have elevated levels of triglycerides, non-Hispanic blacks often possess lower levels of triglycerides; the mechanism for this inherent difference may be increased LPL activity.³⁵⁰ A study of 185 blacks in whom IR was documented by the euglycemic-hyperinsulinemic clamp procedure demonstrated mean triglyceride levels (109 mg/dL) below the cut point for elevated triglyceride used in MetS, although they were higher than in the

insulin-sensitive cohort (mean 77 mg/dL).³⁵¹ Thus, blacks with MetS or T2DM may not possess high triglyceride levels as commonly as observed in other ethnic groups, thereby attenuating the predictive value of triglycerides or triglycerides-to-HDL ratios in this subgroup to identify IR.^{234,350,352}

12. Classification of Hypertriglyceridemia

12.1. Defining Levels of Risk per the National Cholesterol Education Program ATP Guidelines

As described in Section 2: Scope of the Problem, triglyceride levels are classified as normal (<150 mg/dL), borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), or very high (\geq 500 mg/dL) based on measurements after a 12-hour fast. The most clinically relevant complication of hypertriglyceridemia is acute pancreatitis, yet only 10% of cases are a direct consequence of triglyceride levels. Because documentation for a specific threshold in triglyceride-induced pancreatitis is lacking, levels associated with increased risk are arbitrarily defined as triglyceride levels \geq 1000 mg/dL^{105,353}; however, because only 20% of subjects presenting with these extremely high levels develop pancreatitis,³⁵⁴ it is often difficult to identify a high-risk subject on the basis of triglyceride levels alone. Table 5 lists genetic and secondary causes (disorders of metabolism, diet, drugs, and diseases that cause hypertriglyceridemia-induced pancreatitis^{91–95,105–131,355,356}). Even when a secondary cause is identified, family screening to uncover a genetic lipid disorder is also in order.³⁵⁷ In addition to pancreatitis, other potentially adverse clinical manifestations of chylomicronemia include retinal thrombosis³⁵⁸ and, in rare cases, blindness. Therefore, very high triglyceride levels often require both therapeutic lifestyle change and pharmacological therapy as outlined in ATP III.¹⁰

Although borderline-high and high triglyceride levels (150 to 500 mg/dL) are not associated with pancreatitis, they are correlated with atherogenic RLPs and apo CIII-enriched particles.⁷⁴ The elevations in triglyceride levels serve as a biomarker for visceral adiposity, IR, DM, and nonalcoholic hepatic steatosis (fatty liver).^{156,157,360} It is important to recognize that individuals with values in this range may remain at risk for pancreatitis, especially if they are placed on triglyceride-lowering treatment for very high levels (ie, \geq 500 mg/dL) and experience an exacerbation due to secondary factors or interruption of treatment.

A low fasting triglyceride level (ie, <100 mg/dL) is commonly found in underdeveloped societies and countries at low CVD risk (eg, Africa, China, Greece, and Japan),^{361–373} as contrasted with the United States, where mean levels are \approx 15% to 30% higher.⁶ Consistent with a reduced likelihood of abnormal metabolic parameters (eg, IR) are observational studies and clinical trials^{3,232,367,374–380} that have consistently demonstrated the lowest risk of incident and recurrent CVD in association with the lowest fasting triglyceride levels. Taken together, these data raise the possibility that an optimal fasting triglyceride level may be <100 mg/dL; similarly, an optimal nonfasting triglyceride level may be <150 mg/dL because of the <50% anticipated increase in ppTG levels after a fat load (Section 10.3., Fasting Versus Nonfasting Levels).

An “optimal” triglyceride cut point is only intended to define one physiological parameter of cardiometabolic health. It does not represent a therapeutic target, because there is insufficient evidence that lowering triglyceride levels improves CVD risk prediction beyond LDL-C and non-HDL-C target goal recommendations. Nevertheless, the \approx 25% rise in triglyceride levels in US adults during the past several decades⁶ that has coincided with higher caloric intake⁹ and higher rates of juvenile obesity and T2DM⁸ is of great concern. These developments have provided the impetus for intensification of efforts aimed at therapeutic lifestyle change to halt and potentially reverse an alarming trend that, if not proactively addressed, may eradicate the considerable progress in CVD risk reduction that has been achieved in recent years.³⁸¹

13. Dietary Management of Hypertriglyceridemia

13.1. Dietary and Weight-Losing Strategies

Nutrition measurements that affect triglyceride levels include body weight status; body fat distribution (Section 5.2., Obesity and Sedentary Lifestyle); weight loss; the macronutrient profile of the diet, including type and amount of dietary CHO and fat; and alcohol consumption. Importantly, multiple interventions can yield additive triglyceride-lowering effects that result in significant reductions in triglyceride levels. One intervention is to eliminate dietary *trans* fatty acids, which increase triglycerides and atherogenic lipoproteins (ie, lipoprotein[a], LDL-C)³⁸² and are linked to increased cardiovascular risk.³⁸³ Although *trans* fatty acid consumption represents a small proportion of total caloric intake, certain food products, such as bakery shortening and stick margarine, contain high *trans* fatty acid concentrations (ie, 30% to 50%), and each 1% replacement of *trans* fatty acids for monounsaturated fat (MUFA) or polyunsaturated fat (PUFA) lowers triglyceride levels by \approx 1%.³⁸⁴

13.1.1. Weight Status, Body Fat Distribution, and Weight Loss

Weight loss has a beneficial effect on lipids and lipoproteins.³⁸⁵ A weight loss of 5% to 10% results in a 20% decrease in triglycerides, approximately a 15% reduction in LDL-C, and an 8% to 10% increase in HDL-C.³⁸⁶ The magnitude of decrease in triglycerides is directly related to the amount of weight loss.³⁸⁷ Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease \approx 1.9%, or 1.5 mg/dL.^{388,389}

13.2. Macronutrients

13.2.1. Total Fat, CHO, and Protein

The relationship between percent of total fat intake and change in triglyceride and HDL-C concentrations was reported in a meta-analysis of 19 studies published by the Institute of Medicine.³⁹⁰ In this analysis comparing low-fat, high-CHO diets versus higher-fat diets, for every 5% decrease in total fat, triglyceride level was predicted to increase by 6% and HDL-C to decrease by 2.2%. In a subsequent meta-analysis of 30 controlled feeding studies in patients with

or without T2DM ($n=1213$), a moderate-fat diet (32.5% to 50% of calories from fat) versus a lower-fat diet (18% to 30% of calories from fat) resulted in a decrease in triglyceride level of 9.4 mg/dL (range from -6.1 to -12.2 mg/dL, $P<0.00001$) in those without T2DM³⁹¹; however, in those with T2DM, the moderate-fat diet resulted in greater triglyceride reduction (-24.8 mg/dL, $P<0.05$) than seen with the low-fat diet.³⁹¹ Lastly, in a large meta-analysis of 60 controlled feeding studies,³⁹² replacement of any fatty acid class with a mixture of dietary CHOs increased fasting triglyceride levels. Specifically, for each 1% isoenergetic replacement of CHOs, decreases in triglyceride levels resulted with saturated fat (SFA; 1.9 mg/dL), MUFA (1.7 mg/dL), or PUFA (2.3 mg/dL) interchange (all $P<0.001$), which translated into an approximate 1% to 2% decrease in triglyceride levels.

The evidence statement from ATP III relative to dietary CHOs conveyed the following message: "... [V]ery high intakes of carbohydrate (>60 percent of total calories) are accompanied by a reduction in HDL cholesterol and a rise in triglyceride These latter responses are sometimes reduced when carbohydrate is consumed with viscous fiber ...; however, it has not been demonstrated convincingly that viscous fiber can fully negate the triglyceride-raising or HDL-lowering actions of very high intakes of carbohydrates."²²¹ Accordingly, the recommendation by ATP III for dietary CHO was, "Carbohydrate intakes should be limited to 60 percent of total calories. Lower intakes (eg, 50 percent of calories) should be considered for persons with the metabolic syndrome who have elevated triglycerides or low HDL cholesterol."²²¹

As a follow-up to the recommendation from ATP III that high-CHO diets be avoided in individuals with elevated triglyceride levels, Berglund et al³⁹³ evaluated a high-CHO (54% of calories) and low-fat (8% SFA) diet versus a high-MUFA (37% of calories from fat; 22% MUFA, 8% SFA) and average American (37% of calories from fat; 16% SFA) diet in individuals with any combination of HDL-C ≤ 30 th percentile, triglyceride levels ≥ 70 th percentile, or insulin ≥ 70 th percentile. Although triglyceride levels were not affected by the MUFA diet compared with the average American diet, they were higher on the CHO diet than with either the average American diet or the MUFA diet (7.4% and 12%, respectively; $P<0.01$ for both).

Since ATP III, several large clinical trials have reported no increase in triglycerides in response to a reduction in total fat and a concurrent increase in dietary CHOs. In the DASH (Dietary Approaches to Stop Hypertension) trial, the effects of 3 dietary patterns on blood pressure, lipids, and lipoproteins were evaluated.^{394,395} DASH emphasizes fruits and vegetables (8 to 10 servings per day) and low-fat dairy products (2 to 3 servings per day), including whole grains, legumes, fish, and poultry, and limits added sugars and fats. The DASH diet is high in dietary fiber (≈ 30 g/d) and provides 27% of calories from total fat, <7% of total calories from SFA, 150 mg of cholesterol per day, and 18% of calories from protein. In the DASH study, 436 adults with mildly elevated blood pressure (systolic blood pressure <160 mm Hg and diastolic blood pressure 80 to 95 mm Hg) were randomized to consume either a Western diet (control

diet; 48% CHO, 15% protein, 37% total fat, 16% SFA), a fruits and vegetables diet (which provided more fruits and vegetables and fewer snacks and sweets than the control diet but otherwise had a similar macronutrient distribution), or the DASH diet for 8 weeks. Compared with a Western diet, the DASH diet reduced TC (-9.5%), LDL-C (-9.1%), and HDL-C (-9.2%) but did not adversely affect triglycerides. TC, LDL-C, HDL-C, and triglyceride levels did not change with the fruits and vegetables diet.

In the OmniHeart (Optimal Macronutrient Intake) Trial, the effects of substituting SFA with CHO, protein, or unsaturated fat were evaluated in a 3-period, 6-week crossover feeding study that involved 164 prehypertensive or stage 1 hypertensive subjects.³⁹⁶ Each diet period emphasized 1 macronutrient: High CHO (58% of total calories), moderate/high protein (25% of total calories, 50% of which were from plant proteins), or high unsaturated fat (37% of total calories, of which 21% came from MUFA and 10% from PUFA). All test diets provided 6% of calories from SFA and were high in dietary fiber (>30 g/d). Compared with baseline levels, triglyceride levels decreased significantly after the high-unsaturated-fat and high-protein diets (-9.3 and -16.4 mg/dL, respectively) but not after the high-CHO diet (increase of 0.1 mg/dL). Another major clinical trial, the Women's Health Initiative (WHI) Dietary Modification Trial of 48 835 postmenopausal women, found no differences in triglyceride levels (142 versus 145 mg/dL) between the low-fat dietary intervention and a higher-fat comparator group after 3 years of follow-up.³⁹⁷ Thus, although many studies of high-CHO diets have shown increases in triglyceride levels, others (eg, DASH, OmniHeart, and WHI) have shown no effect. This discrepancy may reflect higher fiber intake (≈ 30 g/d; DASH, OmniHeart), higher protein intake (>15% of energy; DASH, OmniHeart, WHI), or a combined effect. Notably, the dietary patterns in DASH, OmniHeart, and WHI were high in fruits and vegetables, as well as grains (including whole grains). Results also suggest that moderate intake of predominately unsaturated fat (30% to 35% of energy or more) and plant-based proteins (17% to 25% of energy) may produce a triglyceride-lowering effect.

13.2.2. Mediterranean-Style Dietary Pattern

Epidemiological and clinical trial evidence suggests that the Mediterranean-style dietary pattern^{398,399} is associated with decreased triglyceride levels. In the Framingham Heart Study Offspring Cohort ($n=2730$), subjects in the highest quintile for Mediterranean-style dietary pattern score had the lowest triglyceride levels (103 versus 114 mg/dL, $P<0.001$) over a 7-year follow-up.³⁹⁸ Several clinical trials have reported beneficial effects of a Mediterranean-style diet on triglycerides compared with a lower-fat diet. Esposito et al⁴⁰⁰ compared the effects of a Mediterranean-style diet with a control diet over a 2-year period on markers of CVD risk in patients ($n=180$) with MetS. The Mediterranean-style diet comprised more foods rich in MUFA, PUFA, and dietary fiber. Total fruit, vegetables, nuts, whole grains, and olive oil were higher in the intervention group. The intervention diet provided 28% of calories from total fat, with 8%, 12%, and 8% of calories from SFA, MUFA, and PUFA, respectively. The control diet

provided 30% of calories from total fat, with 14%, 10%, and 7% of calories from SFA, MUFA, and PUFA, respectively. After 2 years, triglyceride levels decreased 12% in the intervention group ($P=0.001$ versus the control diet). In addition, subjects on the intervention diet decreased body weight by 6.2 lb or 2.8 kg ($P<0.001$) and waist circumference by 0.8 inches or 2 cm ($P=0.01$) compared with the control group. Similarly, reduced triglyceride levels were reported in the Mediterranean Diet, Cardiovascular Risks and Gene Polymorphisms (Medi-RIVAGE) Study.⁴⁰¹ Finally, the PREDIMED (Prevención con Dieta Mediterránea) Study evaluated the effects of a Mediterranean diet plus virgin olive oil (1 L per week) and a Mediterranean diet plus mixed nuts (30 g/d; walnuts, hazelnuts, and almonds) versus a low-fat diet (control diet) in subjects ($n=1224$) at increased risk for CVD.⁴⁰² Both Mediterranean-style diets provided higher energy intake from fat than the control diet (41% to 43% versus 38% of calories) and were higher in MUFA content (21% to 22% versus 19.4% of calories). After 1 year, hypertriglyceridemia was less prevalent in both Mediterranean-style diet groups (12.3% and 13.6%) than in those eating the control diet (21.3%). With few exceptions, such as the Lyon Diet Heart Study,⁴⁰³ which found no significant change in triglyceride levels on a MUFA-enriched versus low-fat, high-n-6 PUFA diet, implementation of a Mediterranean-style diet versus a low-fat diet is more commonly associated with an approximately 10% to 15% lowering of triglycerides and a reduced prevalence of hypertriglyceridemia.

13.3. Type of Dietary CHO

13.3.1. Dietary Fiber

The role of fiber in CVD risk has been reviewed by Erkkila and Lichtenstein,⁴⁰⁴ and the evidence specifically for associations or effects on triglycerides is limited, especially in the absence of T2DM. In contrast, data exist related to fiber intake and triglycerides in individuals with or at increased risk for T2DM. The Botnia Dietary Study, a population study of 248 male and 304 female adult nondiabetic relatives of patients with T2DM from West Finland, reported an inverse association between serum triglycerides and total dietary fiber, water-insoluble fiber, and water-soluble fiber.⁴⁰⁵ Anderson et al⁴⁰⁶ conducted meta-analyses of T2DM to evaluate the lipid, lipoprotein, and glycemic effects of diets low (<10 g/1000 kcal) or high (>20 g/1000 kcal) in dietary fiber and with moderate (30% to 59.9% of energy) or high ($>60\%$ of energy) CHO intake. In 7 studies ($n=98$) that compared moderate CHO and high fiber versus moderate CHO and low fiber, triglyceride levels decreased by 8% in the high-fiber groups. Similarly, in 9 studies ($n=119$) that compared high CHO and high fiber versus moderate CHO and low fiber, triglyceride levels decreased 13% in the high-fiber group. Therefore, these data support a triglyceride-lowering effect for dietary fiber in individuals with T2DM.

13.3.2. Added Sugars

Consumption of added sugars has increased markedly in the United States from 1977–1978, when it was 10.6% of calories, to the current intake of 15.8% of calories.^{407,408} The American Heart Association recommends limiting added

sugars to fewer than 100 calories daily (ie, 6 tsp) for women and 150 calories daily (9 tsp) for men ($\approx 5\%$ of total energy).⁹ The association of added sugars with increased obesity, T2DM, dental caries, and decreased diet quality is evident, which is part of the evidence base for recommendations made by other organizations to limit added sugars.^{409,410} Recently, the association between added sugars and lipid measures was evaluated in a cross-sectional study of US adults ($n=6113$) that used NHANES 1999–2006 data.⁴⁰⁸ The lowest triglyceride levels were observed when added sugar represented $<10\%$ of total energy. Conversely, higher triglyceride levels (5% to 10%) were observed when added sugar represented a greater proportion of energy intake.

13.3.3. Glycemic Index/Load

The glycemic index (GI) is defined as the ratio of the blood glucose response to a specific food and the glucose response to a standard food (ie, white bread). By comparison, the glycemic load (GL) of a food is calculated by multiplying the GI by CHO intake (in grams) and dividing by 100. In general, most refined starchy foods in the American diet have a high GI, whereas nonstarchy vegetables, fruit, and legumes typically have a low GI.

The role of GI and GL in CVD risk assessment remains controversial.^{411–413} Two epidemiological studies, the Nurses' Health Study and the Women's Health Study, reported a positive association between GL and/or GI and fasting triglyceride levels.^{414,415} A positive correlation between GI/GL and triglyceride levels was also reported in a cohort of Japanese women.⁴¹⁶ In terms of race/ethnicity, GL was positively associated with triglyceride levels in whites but not in blacks or Hispanics.⁴¹⁷ In an elderly population, however, there was no association between GI and triglyceride levels.⁴¹⁸ Other studies have reported mixed results. For example, the Insulin Resistance Atherosclerosis Study⁴¹⁹ found GL but not GI to be positively associated with triglycerides, whereas in the Whitehall II Study, GI but not GL correlated with triglyceride levels.⁴²⁰ A Cochrane review of 15 RCTs from 1982 to 2003 assessing the relationship between low-GI diets and lipids found no evidence that low-GI diets affected plasma triglycerides⁴²¹; however, 2 subsequent studies reported lower triglyceride levels with low-GI diets.^{422,423} The relationship between GI/GL and triglycerides also remains unresolved in patients with T2DM, with 1 meta-analysis having identified a 6% reduction in triglyceride level in low- versus high-GI diets⁴⁰⁶ but another study finding no appreciable differences in triglyceride levels in 162 subjects with T2DM assigned to a low- or high-GI diet.⁴²⁴

13.3.4. Fructose

Americans consume fructose in large quantities (up to 150 g/d). Fructose enhances lipogenesis and triglyceride synthesis. In contrast to glucose metabolism, which is regulated in part by phosphofructokinase, fructose metabolism is relatively unregulated.⁴²⁵ In the past 4 decades, fructose consumption has increased appreciably because it is used in many beverages and foods sweetened with sucrose or "table sugar," the content of which is 50% fructose, or high-fructose

Table 9. Fructose Content in Selected Foods and Beverages From the USDA Nutrient Database*

Item	Amount, g
Cola with HFCS (12 oz)	22.5
Lemon-lime soda with HFCS (12 oz)	21.7
Ginger ale with HFCS (12 oz)	13.5
Raisins, seedless (1.5-oz box)	13
Power bar (chocolate)	10.9
Agave nectar (tbsp)†	8.9
Honey (tbsp)	8.6
Applesauce, sweetened (3.5 oz)	8
Fruit (apple, pear)	4–10
Molasses (tbsp)	2.6
Table sugar (tsp)	2

USDA indicates US Department of Agriculture; HFCS, high-fructose corn syrup; tbsp, tablespoon; and tsp, teaspoon.

*Available at <http://www.nal.usda.gov/fnic/foodcomp/search/> and derived from the Association of Official Analytical Chemists method of analysis (http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR23/sr23_doc.pdf).

†Data obtained from Patzold and Bruckner.⁴²⁹

corn syrup, which comprises 42% to 55% fructose.⁴²⁶ Recent data suggest that dietary supplementation with fructose increases ppTG and CMRs compared with glucose.⁴²⁷ In an extensive meta-analysis of 60 studies that evaluated the effects of fructose consumption on triglyceride levels, intakes ≤ 100 g/d had no significant effects on fasting plasma triglycerides. The lack of effect was demonstrated irrespective of whether fructose replaced starch, sucrose, or glucose. In contrast, intakes of fructose that exceeded 100 g/d revealed a dose-related increase in plasma triglycerides.⁴²⁸ Similarly, in the 12 studies that monitored ppTG, a dose-dependent increase was observed above the 50-g fructose dose.⁴²⁸ These data support limiting fructose in men and women with borderline or elevated triglyceride levels (Figure 5). A list of fructose-containing products is provided in Table 9.

Mechanistically, high CHO intake triggers pancreatic insulin release in response to increased blood glucose. Insulin, in turn, activates sterol regulatory element-binding protein, (SREBP-1c), a transcription factor that regulates fatty acid and triglyceride synthesis.⁴³⁰ Recently, 2 additional transcription factors, X-box binding protein 1 (XBP1) and CHO response element-binding protein (ChREBP), have been identified as inducers of hepatic lipogenesis in response to ingested CHOs (eg, fructose and glucose) that is independent of insulin.^{431,432} In contrast, unsaturated fatty acids reduce or inhibit SREBP-1c transcription, thereby reducing hepatic fatty acid synthesis⁴³⁰ and plasma triglycerides.

13.4. Weight Loss and Macronutrient Profile of the Diet

Historically, there has been an interest in evaluating the effect of the macronutrient profile of the diet on weight loss and accompanying effects on lipids and lipoproteins. The Preventing Obesity Using Novel Dietary Strategies (POUNDS LOST) trial evaluated 4 weight loss diets that varied in

macronutrient composition.⁴³³ After 2 years, weight loss was similar in participants assigned to low and high protein (15% versus 25%), low and high fat (20% versus 40%), or low and high CHO (65% versus 35%). Irrespective of macronutrient composition, all diets decreased triglyceride levels similarly (12% to 17%).⁴³³ Another popular weight loss alternative is a very low-CHO diet, defined as intake of <35 g of CHO per day.⁴³⁴ A meta-analysis of RCTs that evaluated low-CHO versus low-fat ($<30\%$ of energy) diets found greater reductions in triglyceride levels on the low-CHO diet.⁴³⁵ Consistent with these findings, Bonow and Eckel⁴³⁴ concluded that low-CHO diets produced a more robust triglyceride-lowering effect than low-fat diets despite a similar magnitude of weight loss after 1 year.

The effect of a reduced-fat weight loss diet intervention was also evaluated in the Diabetes Prevention Program, a program comparing the effects of intensive therapeutic lifestyle change versus metformin on the development of T2DM in patients with impaired glucose tolerance. After 2.8 years, the intensively treated group lost weight (mean 5.6 kg) in association with a reduction in triglyceride levels (22 mg/dL).⁴³⁶ Another analysis of the Diabetes Prevention Program that evaluated subjects with MetS reported a downward shift in the prevalence of triglyceride levels ≥ 150 mg/dL from 73% to 60% in the intensive-lifestyle versus placebo group.⁴³⁷ Similar results were reported in the Look AHEAD (Action for Health in Diabetes) Trial,⁴³⁸ in which weight reduction also translated into appreciable triglyceride lowering. The effects of a Mediterranean-style weight loss diet were compared with low-CHO and low-fat energy-restricted diets.⁴³⁹ After 6 months, triglyceride levels were reduced the most in the low-CHO group (22%), but after 12 months, similar reductions were observed in both the low-CHO and Mediterranean-style groups, with minimal change in the low-fat group. Two additional studies evaluated 4 popular weight loss diets^{440,441} in free-living subjects for 1 year. Dansinger et al⁴⁴⁰ studied the effects of the Atkins diet, the Zone diet, the Weight Watchers diet, and the very low-fat Ornish diet on weight loss and CVD risk factors. Weight loss was similar after 12 months (4.8 to 7.3 kg) for all 4 diets. Although significant reductions in triglycerides occurred after 2 months on the Atkins and Zone diets, these effects were no longer significant after 12 months. In the study by Gardner et al,⁴⁴¹ which compared the Atkins, Zone, LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition) and Ornish diets, weight loss was greatest on the Atkins diet (4.7 kg) followed by LEARN (2.6 kg), Ornish (2.2 kg), and Zone (1.6 kg), with corresponding reductions in triglyceride levels (3% to 23%). Thus, diets that produce significant and sustained weight loss offer the most favorable reductions in triglyceride levels.

13.5. Alcohol

Prospective studies have demonstrated an inverse relationship between moderate alcohol consumption (ie, up to 1 oz daily) and CVD.⁴⁴² In evaluating the relationship between alcohol consumption and triglycerides, some studies have shown no association,^{443–445} whereas others found modestly lower triglyceride levels in women who consumed up to 0.6 oz

daily.⁴⁴⁶ At higher intakes, triglyceride levels increase,^{447,448} and Rimm et al⁴⁴⁹ estimated that ingestion of 1 oz/d would correspond to a 5% to 10% higher triglyceride concentration than found in nondrinkers.

In contrast, alcohol abuse may be associated with hypertriglyceridemia; nearly 1 in 5 hospitalized alcoholics have triglyceride levels exceeding 250 mg/dL.⁴⁵⁰ An exaggerated rise in triglycerides occurs in the setting of excess alcohol intake combined with a meal high in saturated fat. Ethanol-induced lipemia may be due to inhibition of LPL-mediated hydrolysis of chylomicrons.^{126,451,452} Therefore, in subjects with very high triglyceride levels, complete abstinence is strongly recommended in concert with reduced saturated fat intake to reduce the likelihood of pancreatitis.¹⁰⁵

13.6. Marine-Derived Omega-3 PUFA

The American Heart Association recommends 2 to 4 g of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) per day, provided as capsules under a physician's care, for patients who need to lower their triglyceride level.⁴⁵³ This recommendation is based on a large body of evidence showing triglyceride-lowering effects of marine-derived omega-3 PUFA. In a comprehensive review of human studies, Harris⁴⁵⁴ reported that ≈ 4 g of marine-derived omega-3 PUFA per day decreased serum triglyceride concentrations by 25% to 30%, with accompanying increases of 5% to 10% in LDL-C and 1% to 3% in HDL-C. A dose-response relationship exists between marine-derived omega-3 PUFA and triglyceride lowering, with an approximate 5% to 10% reduction in triglycerides for every 1 g of EPA/DHA consumed⁴⁵⁵; efficacy is greater in individuals with higher triglyceride levels before treatment.^{455–457} Skulas-Ray et al⁴⁵⁸ reviewed studies that evaluated baseline triglyceride levels and the response to EPA plus DHA dose and found that the response was curvilinear, with individuals at lower baseline triglyceride levels having less of a triglyceride-lowering effect ($\approx 20\%$ versus 30% for higher triglyceride levels).

Mechanistically, decreased VLDL triglyceride secretion results from preferential shunting of omega-3 PUFA into phospholipid cellular synthesis, reduced expression of SREBP-1, and enhanced peroxisomal β -oxidation. In addition, upregulation of LPL facilitates VLDL triglyceride clearance.^{459,460} Individually, EPA or DHA may reduce triglyceride,⁴⁶¹ ppTG,⁴⁶² or CMR⁴⁶³ levels. However, marine-derived dietary sources contain both EPA and DHA in varying proportions. Table 10 lists foods enriched in marine-derived omega-3 PUFA. Because the amount needed for significant triglyceride lowering (2 to 4 g) is difficult to attain through diet alone on a daily basis, supplementation with capsules may be needed. The content of EPA/DHA per capsule is highly variable and ranges from 300 mg to ≈ 850 mg. Although marine-derived omega-3 PUFA capsules have been shown to be free of contaminants, their clinical efficacy at high doses (2 to 4 g/d) has yet to be established. Therefore, a well-designed RCT will be important to determine the extent to which triglyceride and non-HDL-C lowering through supplementation with marine-derived omega-3 PUFA improves CVD outcomes beyond standard-of-care therapy.

Table 10. EPA/DHA Content in Selected Foods (per 3.5-oz Serving)

Fish	Omega-3 PUFA, g
Anchovy (canned)	2.1
Herring, Atlantic (kippered)	2.1
Salmon, Atlantic (farmed)	2.1
Salmon, Atlantic (wild)	1.8
Herring, Atlantic (pickled)	1.4
Sardines, canned in tomato sauce	1.4
Salmon, coho	1.3
Trout, rainbow (farmed)	1.2
Halibut, Greenland	1.2
Salmon, sockeye	1.2
Salmon, pink or red (canned)	1.1
Sardines, canned in oil	1.0
Trout, rainbow (wild)	1.0
Tuna, white (canned in water)	0.9
Halibut, Atlantic or Pacific	0.5
Crabs	0.5
Lobster	0.5
Salmon, smoked (lox)	0.5
Shrimp	0.5
Tuna, light (canned in water)	0.3
Tuna, white (canned in oil)	0.2

EPA indicates eicosapentaenoic acid; DHA, docosahexaenoic acid; and PUFA, polyunsaturated fatty acid.

13.7. Nonmarine Omega-3 PUFA

Dietary marine-derived omega-3 PUFA intake is very low, at <0.2 g of the ≈ 1.4 g of total omega-3 PUFA consumed daily in the United States.^{464,465} Non-marine-based omega-3 PUFA is derived from α -linolenic acid, a plant-based PUFA found in canola, chia, flaxseed, perilla, rapeseed, soybeans, walnuts, and purslane.^{465,466} Yet non-marine-based PUFAs have not demonstrated consistent reductions in triglycerides⁴⁶⁷; this may reflect very low conversion rates of α -linolenic acid and its intermediary, stearidonic acid,⁴⁶⁸ to the active triglyceride-lowering omega-3 compounds EPA and DHA.⁴⁶⁹ Therefore, if omega 3 PUFAs are used for triglyceride lowering, they should be exclusively marine-derived EPA and/or DHA.

13.8. Dietary Summary

Overall, optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%. These practices include weight loss, reducing simple CHO at the expense of increasing dietary fiber, eliminating industrial-produced *trans* fatty acids, restricting fructose and SFA, implementing a Mediterranean-style diet, and consuming marine-derived omega-3 PUFA (Table 11). Dietary practices or factors that are associated with elevated triglyceride levels include excess body weight, especially visceral adiposity; simple CHOs, including added sugars and fructose; a high glycemic load; and alcohol.

14. Physical Activity and Hypertriglyceridemia

The high triglyceride levels observed with sedentary living, high SFA intake, visceral obesity, and IR commonly are

Table 11. Effects of Nutrition Practices on Triglyceride Lowering

Nutrition Practice	TG-Lowering Response, %
Weight loss (5% to 10% of body weight)	20
Implement a Mediterranean-style diet vs a low-fat diet	10–15
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10
Decrease carbohydrates	
1% Energy replacement with MUFA/PUFA	1–2
Eliminate <i>trans</i> fats	
1% Energy replacement with MUFA/PUFA	1

TG indicates triglyceride; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and MUFA, monounsaturated fatty acid.

accompanied by an increased content of intramyocellular triglyceride that largely reflects ineffective utilization of fat (ie, reduced muscle fatty acid oxidation).^{470–472} In contrast, aerobic activity enhances lipid oxidation, thereby facilitating the hydrolysis and utilization of triglycerides in skeletal muscle.⁴⁷³ The effect of physical activity on triglyceride levels varies depending on baseline triglyceride, level of intensity, caloric expenditure, and duration of activity. For example, an optimal fasting triglyceride level (eg, <100 mg/dL) was associated with minimal (ie, <5%) reductions in postexercise triglyceride levels compared with greater (ie, 15% to 20%) reductions if baseline triglyceride levels exceeded 150 mg/dL.⁴⁷⁴ Moreover, in a study of 2906 middle-aged men, moderately intensive activity (ie, jogging 10 miles weekly) versus no activity was associated with a 20% lower fasting triglyceride level; the highest activity level (>20 miles weekly) was also accompanied by the lowest mean fasting triglyceride level (86 mg/dL).⁴⁷⁵ Higher baseline triglyceride levels (mean 197 mg/dL) also translated into significant triglyceride reductions (26%) in a 6-month trial of overweight subjects who walked 12 miles weekly at 40% to 55% of peak oxygen consumption.⁴⁷⁶ However, other studies evaluating walking duration, frequency, and intensity (30 minutes daily at a maximum 65% to 75% of age-predicted heart rate) in the absence of weight loss did not demonstrate differences in postexercise triglyceride levels.⁴⁷⁷ Similarly, increasing energy expenditure through physical activity without changing energy intake did not result in lower triglyceride levels if baseline levels were relatively normal (ie, mean 110 mg/dL). However, a reduction in energy intake (300 kcal/d) resulted in a 23% reduction in fasting triglyceride levels during the 1-year trial.⁴⁷⁸ Additional benefits of exercise include reduction in the ppTG response and attenuation of the triglyceride elevations observed after consumption of a low-fat, high-CHO diet.⁴⁷⁹ In fact, 60 minutes of aerobic exercise daily abolishes the CHO-induced increases in TRL.⁴⁸⁰ Overall, exercise is most effective in lowering triglycerides (eg, 20% to 30%) when baseline levels are elevated (ie, >150 mg/dL), activity is moderate to intensive, and total caloric intake is reduced.⁴⁸¹

15. Pharmacological Therapy in Patients With Elevated Triglyceride Levels

The association of elevated triglycerides with increased CVD risk and clustered metabolic abnormalities (as discussed in

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction^{504,480a–480d}

Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

other sections of this scientific statement) has led to research and clinical interest in the potential protective benefit of reducing high levels of triglycerides. Although no published clinical trials have been designed specifically to examine the effect of triglyceride reduction on CVD event rate, secondary analyses from major trials of lipid-regulating therapy have assessed CVD risk in subgroups with high triglyceride levels. Unfortunately, most clinical trials limited entry triglyceride level to <400 mg/dL, and no known triglyceride-specific data from trials of diet and other lifestyle modifications are available. With the noted limitations of the published trial data, we attempt to address the following 3 questions:

1. Do patients with elevated triglyceride levels at baseline benefit from pharmacological monotherapy?

The triglyceride-lowering effects of lipid-altering agents are shown in Table 12. As monotherapy, fibrates offer the most triglyceride reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe. In contrast, bile acid resins may raise triglyceride levels (Table 5). A number of trials of statin or fibrate monotherapy have examined the potential role of baseline triglyceride level, categorized by various criteria (eg, cut points, MetS, combined with low HDL-C), on CVD risk. To date, similar analyses are not available for ezetimibe or niacin. In statin trials, subgroups with increased baseline triglyceride levels were reported to have increased CVD risk in the Scandinavian Simvastatin Survival Study (4S),^{40,482,483} the Cholesterol and Recurrent Events (CARE) Trial,⁴⁸⁴ the West of Scotland Coronary Prevention Study (WOSCOPS),⁴⁸⁵ the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),⁴⁸² and the Treating to New Targets (TNT) study⁴⁸⁶ and to have greater CVD risk reduction with lipid therapy in 4S^{482,483} and CARE.⁴⁸⁷ However, CVD event reductions were similar across categories of baseline triglycerides in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID),⁴⁸⁸ the Heart Protection Study,⁴⁸⁹ and WOSCOPS,⁴⁹⁰ and CVD event reduction was greater in patients without MetS in the Anglo-Scandinavian Cardiac Outcome Trial.⁴⁹¹ Thus, in patients with hypertriglyceridemia, statin therapy may be beneficial in the setting of an LDL-C level that merits treatment.

Although statins have consistently shown benefit in subgroups with or without high triglyceride levels, fibrates have more commonly been shown to provide greater benefit in subgroups with increased triglyceride levels. These high-cardiovascular-risk subgroups benefited in the Helsinki Heart

Study,³⁹ the Bezafibrate Infarction Prevention study,^{492,493} and the Fenofibrate Intervention and Event Lowering in Diabetes study.^{494,495} In the Veterans Affairs HDL Intervention Trial (VA-HIT),^{496,497} fibrate therapy reduced cardiovascular risk across all categories of baseline triglycerides. The recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which did not show an overall benefit for fibrate therapy added to statin therapy in T2DM, did show benefit in the subgroup with elevated triglyceride levels (>204 mg/dL) and low HDL-C (<34 mg/dL).⁴⁹⁸ In summary, the aggregate data suggest that statin or fibrate monotherapy may be beneficial in patients with high triglyceride levels, low HDL-C, or both.

2. *Is a high triglyceride level in individuals receiving pharmacological monotherapy associated with increased CVD risk?*

Fewer trials have reported the potential effect of on-treatment triglyceride levels on CVD risk, even in secondary analyses. On-treatment triglyceride level was not associated with CVD risk in AFCAPS/TexCAPS⁴⁹⁹ and was not predictive of CVD event rate or risk reduction in VA-HIT.⁴⁹⁷ However, in LIPID, although baseline triglyceride level was not significantly associated with CVD risk in patients given placebo, each 89-mg/dL decrease in on-treatment triglyceride level in patients given pravastatin significantly decreased CVD risk by 11%, as well as by 14% after adjustment for nonlipid risk factors. However, the lipid-related parameters most strongly associated with CVD risk in LIPID were apo B, LDL-C, and the ratio of TC to HDL-C.⁵⁰⁰ In the PROVE IT-TIMI 22 trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction), achievement of an on-treatment triglyceride level <150 mg/dL was associated with a 27% reduction in CVD risk compared with higher levels; each 10-mg/dL decrease in on-treatment triglyceride level was associated with CVD risk reductions of 1.8% in the unadjusted estimate and 1.4% in the fully adjusted model.³⁷⁸ In a post hoc analysis of combined data from IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid lowering) and TNT, CVD risk was ≈30% higher in patients with on-treatment triglyceride levels >150 mg/dL than in patients with lower on-treatment levels and 63% higher in patients in the top quintile for on-treatment triglyceride than for those in the lowest quintile in age- and sex-adjusted analysis. However, additional adjustment for HDL-C and the ratio of apo B to apo AI decreased the predictive ability of on-treatment triglyceride levels, and further adjustment for baseline glucose, BMI, hypertension, T2DM, and smoking eliminated the association.⁵⁰¹ Thus, high-risk statin-treated patients who continue to have elevated triglyceride levels display an increased risk for CVD, but these patients also have other metabolic abnormalities, and adjustment for measures of these associated abnormalities, such as non-HDL-C and apo B, decreases the predictive effect of triglycerides.

3. *Do patients with elevated triglyceride levels while undergoing statin therapy receive additional cardiovascular risk reduction by the addition of a second drug that targets triglycerides or TRL?*

In the Japan EPA Lipid Intervention Study (JELIS), in which patients received a statin plus either EPA or a placebo, CVD risk reduction with combination therapy was not statistically significant in either baseline triglyceride subgroup (<151 or ≥151 mg/dL).⁵⁰² However, subgroup analysis of primary prevention patients in JELIS (80% of the study population) indicated that patients with baseline triglyceride levels at or exceeding 150 mg/dL and HDL-C <40 mg/dL had significantly increased CVD risk. Moreover, combination therapy with statin plus EPA in this high-risk subgroup reduced CVD risk by 53% compared with statin monotherapy,⁵⁰³ even though the dose of EPA (up to 1.8 g/d) translated into minimal triglyceride reduction (5% between groups). Consequently, the cardiovascular benefit in JELIS was not a primary triglyceride-mediated effect.

Trials that used statin plus niacin (or in some cases bile acid resin) combination therapy have shown a reduction in coronary arteriographic progression and regression, as well as regression of carotid artery intima-media thickness.^{504,505} Reduction in CVD outcomes were observed in several of these studies, although event rates were low, a statin placebo group was not used, and the studies were neither powered nor prespecified to address CVD events as a primary outcome measure. Nevertheless, they set the stage for the statin-niacin outcome trials listed below.

Unfortunately, there are limited data on the potential benefit of adding a second drug in high-risk patients treated with a statin who continue to have high triglyceride levels. As noted above, the ACCORD trial⁴⁹⁸ did not find that fibrate therapy added to statin reduced cardiovascular events in DM patients (median triglyceride level of 162 mg/dL) except in the subgroup in the upper triglyceride tertile and lowest HDL-C tertile ($P=0.06$). Although ongoing clinical trials are not specifically designed to examine this issue, secondary analyses of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH),⁵⁰⁶ Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),⁵⁰⁷ and the ezetimibe-statin trial, IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT),⁵⁰⁸ may provide useful information.

16. Preventive Strategies Aimed at Reducing High Triglyceride Levels

The rise in triglyceride levels coinciding with the current epidemic of juvenile obesity, IR, and DM^{509–511} has created new opportunities for establishing and disseminating CVD health promotion efforts aimed at maximizing primordial prevention. For example, resolutions have now been adopted in all 50 states targeting obesity, including the elimination of high caloric sugared sodas and *trans* fatty acid products from public school vending machines and increasing the number of walking and bicycle paths.^{512,513} Initiatives such as reducing access to low-nutrient, energy-dense foods in school cafeterias serve as other adjunctive measures for controlling high triglyceride and obesity rates.⁵¹⁴ Among the most comprehensive national programs has been Healthy People 2010, the

initiative established by the Centers for Disease Control and Prevention in 1998 for health promotion and disease prevention.⁵¹⁵ The principal objectives are to improve the quality of healthy living and eliminate health disparities through interventions aimed at heart disease and stroke prevention.^{515,516} In addition to community-based outreach programs, nutrition education beginning in elementary school may yield considerable dividends toward reducing obesity rates, because dietary behaviors are often established in childhood.⁵¹⁷ Prototypical pilot studies demonstrate a greater understanding of healthy food choices, which in turn may also improve academic performance.^{518,519} Strategies to attenuate hypertriglyceridemia and its associated metabolic complications include increasing physical activity during school and after-school sessions,^{520,521} incentivizing schools committed to fostering nutrition education,⁵²² and offering a variety of fresh fruits and vegetables daily to school cafeterias.⁵²³ Overall, identification of the most successful pilot programs for implementation on a national level will require coordinated efforts by clinicians, policymakers, and advocacy groups focused on reducing hypertriglyceridemia, obesity, and IR through a greater emphasis on and implementation of intensive lifestyle interventions.

17. Statement Summary and Recommendations

This scientific statement reviews the pivotal role of triglycerides in lipid metabolism and reaffirms that triglyceride is not directly atherogenic but represents an important biomarker of CVD risk because of its association with atherogenic remnant particles and apo CIII. Although some familial disorders of triglyceride metabolism are associated with increased risk for pancreatitis when fasting triglyceride level exceeds 1000 mg/dL, others are associated with increased atherosclerotic risk. Moreover, IR, obesity, and sedentary lifestyle can all lead to or aggravate metabolic syndrome risk factors, which should urgently prompt clinicians to focus first on improving the patient's lifestyle. Knowledge of the metabolic pathways of triglyceride-rich particles and the consequences of hypertriglyceridemia is crucial in understanding the characteristic lipid alterations in DM, lipodystrophic disorders including those seen with HIV, and chronic renal disease. Measurements of non-HDL-C, apo B, or both may be especially useful in those with prominent triglyceride/HDL abnormalities in which LDL-C measurements may underestimate true atherosclerotic vascular risk.

This statement suggests the following new designations: (1) Optimal fasting triglyceride levels, defined as <100 mg/dL, as a parameter of metabolic health, and (2) nonfasting triglyceride levels, to screen for those with high fasting triglyceride levels. A suggested practical algorithm for screening and management of elevated triglyceride levels is outlined in Figure 5. A nonfasting level of <200 mg/dL is commensurate with a normal (<150 mg/dL) or optimal

(<100 mg/dL) fasting triglyceride level and requires no further testing. Fasting samples are used to designate borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), and very high (≥ 500 mg/dL) triglyceride levels. Nonfasting triglyceride levels are not used in the definition of MetS and should not be used in the calculation of LDL-C by the Friedewald formula.

Overall, the treatment of elevated triglyceride levels focuses on intensive therapeutic lifestyle change. For example, a 5% to 10% reduction in body weight anticipates a triglyceride-lowering response of 20%. Further offsets in CHO calories by reducing added sugars and fructose while increasing unsaturated fat intake may contribute an additional 10% to 20% reduction in triglyceride levels. Elimination of *trans* fats, restriction of SFA,^{524–527} and increasing consumption of marine-based omega-3 products, coupled with aerobic activity, will further optimize triglyceride-lowering efforts. Taken together, reductions of 50% or more in triglyceride levels may be attained through intensive therapeutic lifestyle change.

In subjects with very high triglyceride levels or a history of triglyceride-induced pancreatitis, additional dietary considerations include complete abstinence from alcohol, the nutrition practices listed above, the possible use of MCTs⁵²⁸ and pharmacological therapies (see also Tables 11 and 12). The subject of medication and triglycerides is still lacking crucial clinical trial evidence. Nonetheless, several points should be made. First, clinicians should rule out medications as a potential cause of an elevated triglyceride value. For example, hormone therapy (Table 5) can greatly influence triglyceride levels; in women of reproductive age who develop hypertriglyceridemia while taking oral contraceptive therapy, lower estrogen-containing preparations or other forms of contraception should be considered. For postmenopausal women with hypertriglyceridemia who require postmenopausal hormone preparations, switching to transdermal preparations may blunt the triglyceride increases observed with oral compounds. Second, utilizing triglyceride-lowering medications to prevent pancreatitis in those with triglyceride levels >500 mg/dL is reasonable in addition to intensive therapeutic lifestyle change. In those with a history of triglyceride-induced pancreatitis, it is especially important to keep triglyceride levels well controlled, and this will require both lifestyle and pharmacological approaches. What remains to be established is whether these modalities favorably influence CVD outcomes beyond proven therapies (eg, statins). Therefore, additional clinical outcome trials are necessary.

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*Modest.

†Significant.

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