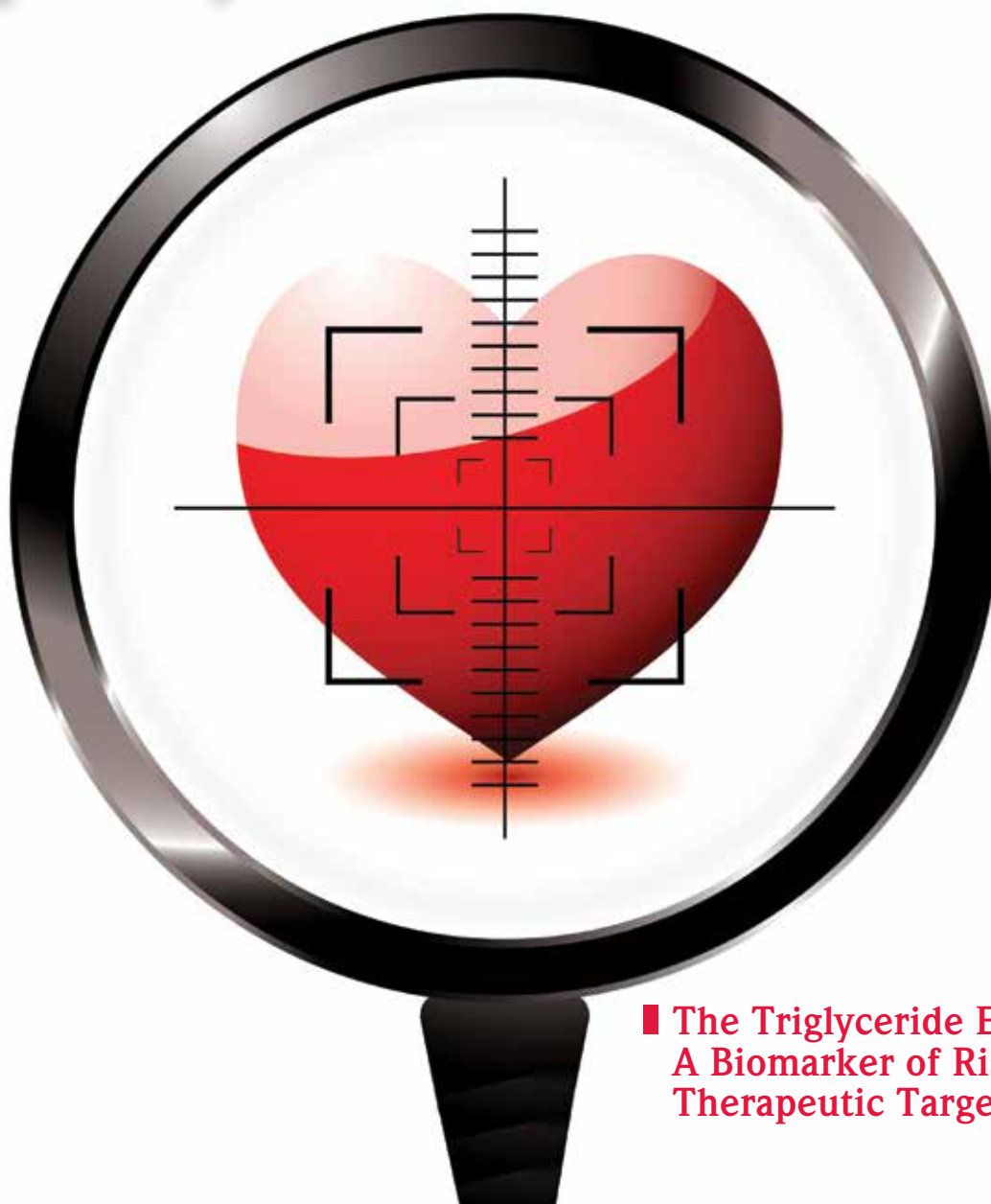


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LipidSpin



■ The Triglyceride Enigma: A Biomarker of Risk or a Therapeutic Target?

Also in this issue:

Lowering Triglycerides with Omega-3 Fatty Acids

Disorders of the Triglyceride–HDL Axis in Insulin Resistance

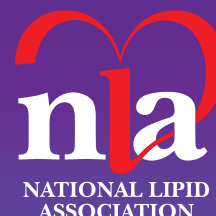
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Editors

JAMES A. UNDERBERG, MD, MS, FACPM, FACP, FNLA*
Clinical Assistant Professor of Medicine
NYU School of Medicine & NYU Center for Prevention of
Cardiovascular Disease
Director Bellevue Hospital Lipid Clinic
New York, NY

ROBERT A. WILD, MD, PhD, MPH, FNLA*
Clinical Epidemiology and Biostatistics and
Clinical Lipidology Professor
Oklahoma University Health Sciences Center
Oklahoma City, OK

Managing Editor

MELISSA HEYBOER
National Lipid Association

Executive Director

CHRISTOPHER R. SEYMOUR, MBA
National Lipid Association

Contributing Editor

KEVIN C. MAKI, PhD, CLS, FNLA

Associate Editor for Patient Education

VANESSA L. MILNE, MS, NP, CLS
Cardiac Vascular Nurse and Family Nurse Practitioner
Bellevue Hospital Lipid Clinic
New York, NY

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National Lipid Association
6816 Southpoint Parkway, Suite 1000
Jacksonville, FL 32216
Phone: 904-998-0854 | Fax: 904-998-0855

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From the NLA President: Making Waves



TERRY A. JACOBSON, MD, FACP, FNLA
National Lipid Association President
Professor of Medicine, Emory University
Atlanta, GA
Director, Lipid Clinic and Cardiovascular Risk Reduction Program
Diplomate, American Board of Clinical Lipidology



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*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*
— Johann Wolfgang von Goethe

Being a part of the National Lipid Association is about more than just raising awareness about lipid disorders — it’s about effecting change within our communities and across the country.

One of the ways the NLA has succeeded in doing this is through national campaigns geared toward promoting our organization and bringing attention to topics of great interest to healthcare providers and their patients. Since the last edition of the LipidSpin, the NLA has launched two of these successful campaigns.

To coincide with National Cholesterol Education Month in September, the NLA launched and promoted a triglyceride campaign in order to raise awareness about the significant role triglycerides play in patients’ lives. The success of this

campaign was due in large part to the participation from members who took our survey on triglyceride, knowledge, management, and practices. One thing we learned from our survey is that there is still a large gap in the use and reporting of non-HDL-C by clinical laboratories. Future, educational campaigns on high triglycerides will need to focus more on standardizing the reporting of non-HDL-C and encouraging providers to use non-HDL-C in patient management. Aiding the triglyceride educational campaign has been the Foundation of the NLA, who played a large role in the creation of patient education tools and resources. You can read more about the success of the “What’s Your Number?” campaign in the Foundation Update by Anne C. Goldberg, MD, FNLA, on page 32.

The second big initiative from the NLA leadership was the release of the Executive Summary of the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 in the September/October issue of the Journal of Clinical Lipidology. Along with the release of the Executive Summary in the Journal, was the creation of several other useful tools and

resources for clinicians including:

- Recommendations tab in the Clinical Lipidology Resource Center on lipidjournal.com
- ReachMD podcasts with NLA experts
- Infographic from the NLA Recommendations that emphasize the importance of setting cholesterol management (available on page 36)
- Lipid Insights Virtual Journal Club, a 60-minute CME Webcast, on the Recommendations
- Slide deck on the Recommendations which you can use for presentations

You can find all these tools and more on the NLA website at lipid.org/recommendations. In addition, Part 2 of these Recommendations are scheduled to be published by the time of the national meeting in June 2015.

With the creation of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia, the

leadership of the NLA felt strongly that it was time for the NLA to act. Although issuing general lipid recommendations has always been part of the NLA strategic plan, the release of the 2013 AHA ACC Guideline on the Treatment of Blood Cholesterol in Adults accelerated the process. We are very excited about the new NLA Recommendations and how they can help supplement the current AHA/ACC guidelines and also help to “fill in the gaps.” So far we have received very positive feedback by the provider community.

In the next few months, we are going to ask members to help disseminate our recommendations to the broader provider community. This could be in the form of local hospital grand rounds, presentations at medical society meetings, presentations at major subspecialty meetings, or CME

educational meetings. We look forward to member participation in disseminating the NLA Recommendations and are requesting any suggestions on how to get our message out. As to paraphrase the poet Johann Wolfgang von Goethe, “Knowing is not enough; we must apply. Willing is not enough; we must do.”

Campaigns like these are the lifeblood of the NLA and we cannot thank you enough for helping make them so successful. Whether it’s being an author on a major NLA paper or sharing a post on Facebook, your continued commitment to the NLA is invaluable.

As we move forward toward 2015, we must continue to set the bar high and find new ways to build our presence in the lipid and broader health care community.

Looking back, the 2014 Fall Clinical Lipid Update in Indianapolis was a huge success. Congratulations to the Northeast and Midwest Chapters for hosting such a popular event. If you were not able attend the meeting, you can access meeting highlights by visiting lipid.org/education/highlights.

If you haven’t already, make sure you’ve saved the date for the NLA’s upcoming meetings. The 2015 Spring Clinical Lipid Update — sponsored by the Pacific and Southwest Chapters — will take place Feb. 27– March 1, 2015, in Denver. In addition, the 2015 Annual Scientific Sessions will be hosted by the Midwest Lipid Association June 11–14, 2015, in Chicago. Please check lipid.org/conferences frequently for ongoing updates on all upcoming meetings. ■

WE NEED YOU!

Get Involved in the Dissemination of the Recommendations

The NLA Recommendations for Patient-Centered Management of Dyslipidemia was published in the *Journal of Clinical Lipidology*. As you know, these recommendations are a tool for clinicians who treat patients with dyslipidemia — and they should serve as guidance for treatment. To ensure that the NLA Recommendations are successful and reach as many clinicians as possible, we need your help and involvement!

1. As a Member of the NLA, you can help by sharing the recommendations with your colleagues and institutions. The article is accessible free of charge at lipidjournal.com.
2. Ask the press office at your institution if they would like to do an interview with you or one of the authors. We can help prepare you for an interview, or get your press office in touch with one of the authors. Contact Judith Thomas at jthomas@lipid.org for more information.
3. You can also download the slide deck and give a talk on the NLA Recommendations at your institution, hospital or County Medical Society.
4. We also encourage you to join the conversation with fellow NLA members on the NLA Recommendations forum. Also, expand awareness through social media and talk about the recommendations on Facebook and Twitter.
5. Visit lipid.org/recommendations for more information, and let us know about your success in spreading the word! In addition, more resources can be found at lipid.org or patient information at learnyourlipids.com. Flip to page 36 in this issue to view the NLA’s shareable infographic.



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From the SWLA President: Make Your Voice Heard

KRISHNASWAMI VIJAYARAGHAVAN, MD, FACC, FNLA

President, Southwest Lipid Association
Clinical Professor of Medicine, University of Arizona
Vice President, Scottsdale Cardiovascular Center
Scottsdale, AZ

Diplomate, American Board of Clinical Lipidology



Greetings! I was honored and excited to be nominated as the President of the Southwest Lipid Association (SWLA) at the National Lipid Association's (NLA) Annual Scientific Sessions in May 2014. As we acknowledge the team that have been at the executive level and performed with high energy, we would like to tap into their continued support. This year, we plan to move forward with exuberance in creating new strategies for our continued growth. We intend to implement Million Hearts in early 2015, as well as the Spring Clinical Lipid Update in Denver in February 2015. One of our goals is to initiate digital strategies to enhance awareness among non-medical communities. At SWLA, we plan to create a global presence for the NLA, thus creating an impact factor with constructive partnerships that will be exemplary.

A major goal of our association is to inform the general public and relevant healthcare professionals about lipids and other risk multipliers that lead to non-communicable diseases. To that end, the NLA and SWLA offer members the opportunity to become

engaged in activities. The most recent Recommendations for Patient-Centered Management of Dyslipidemia and the Expert Panel on Statin Safety are prime examples of effective leadership in our organization. This is your chance to get involved in councils and communities and increase your visibility. Voice your opinions on guidelines/recommendations and statements, get involved in instructing through courses and conferences, engage via social networks and the Foundation of the NLA, and inspire other organizations to team up with us for best patient outcomes. Now is the time to develop collaborative concepts and new ideas that will strengthen policies and practices to help quell cardiovascular disease. SWLA will continue to serve as a platform to recognize and provide leadership opportunities and celebrate the activities of those making an impact on people's lives through education, research, and intervention.

The theme for this *LipidSpin* issue is "The Triglyceride Enigma: A Biomarker of Risk or a Therapeutic Target?" Many authors have come together to fill the gap that is



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prevalent, and discuss fibrate therapy for high TG, triglyceride HDL axis in diabetic patients, severe hypertriglyceridemia in childhood, gene therapy in dyslipidemia, and many other topics. Hopefully, the topics will be enlightening and intriguing at the same time!

Please share your ideas, articulate your opinions, advocate your causes, increase awareness to your colleagues to become members, and show your steadfast support. I would like to invite you to find and share resources at lipid.org. Feel free to contact me at 480-945-3535 or kvijaymd@gmail.com.

Thank you and I look forward to your support. ■

Letter From the LipidSpin Editors:

Guidelines: What Are They? What Can They Do? What Can They Not Do?



ROBERT A. WILD, MD, MPH, PhD, FNLA

Clinical Epidemiology & Biostatistics and Clinical Lipid Professor
Oklahoma University Health Sciences Center
Oklahoma City, OK



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The following are some basic thoughts and information on guidelines based on my understanding.

Guidelines aim to guide decisions and criteria for diagnosis, management, and treatment. They have been around for the entire history of medicine. They are now supposed to be based on an examination of all the current evidence within the paradigm of evidenced based medicine (EBM). A healthcare provider is obliged to know the medical guidelines of his or her profession and has to decide whether or not to follow the recommendations of a guideline for an individual's treatment.

They're supposed to summarize and evaluate the highest quality evidence and the most current data about prevention, diagnosis, therapy, and prognosis. Some contain decision trees. They can integrate the identified decision points and respective courses of action to assist

experience of practitioners in clinical judgment. Often the objective is to standardize care, to raise the quality of care and to make it uniform, in hopes of reducing risk. There is little doubt that these objectives can be improved by using guidelines. National or international bodies produce them. Local healthcare providers may produce their own sets of guidelines or adapt them.

Guidelines can lose relevance as newer information becomes available. New information emerges and evolves now at an exponential rate. Some have found that as many as 20 percent of strong recommendations, especially when based on expert opinion, may be retracted.¹ Unfortunately guidelines may not be inclusive or they may be biased on information gathering and/or assessment. They may be products of conflicts of interest. They can make recommendations that are stronger than the supporting evidence.² What is more important is that more than 90 percent of the clinical decisions we have to make on a daily basis are not covered by any guidelines.

The National Lipid Association (NLA) is striving to provide clinical

recommendations that can act as a guide to all current evidence. By definition, the NLA cannot come up with best evidence for every given clinical scenario.

So what is a practitioner supposed to do? I submit that building skills to acquire best evidence is an individual learning pathway, and I believe the NLA will serve its members best by offering pathways toward this development.

What are the essential skills needed? First, basic clinical epidemiology and biostatistics. Second, point of service information access tools. Third, practice — participating in meetings that illustrate how to utilize best evidence in patient care management helps a lot. The art of finding best evidence, evaluating best evidence, and learning how to integrate the evidence within our patient value system and within the system of healthcare delivery we practice empowers us to deliver the best care available by optimizing our talents.

Nothing substitutes for clinical judgment. Evidence-based informed clinical judgment is the highest form of clinical judgment we can offer. ■

References are listed on page 33.

Clinical Feature: The Triglyceride Enigma

KRISHNASWAMI VIJAYARAGHAVAN, MD, FACC, FNLA

Scottsdale Cardiovascular Center
Clinical Professor of Medicine, University of Arizona
Scottsdale, AZ
Diplomate, American Board of Clinical Lipidology



TOM HAFHEY, DO, FACC, FNLA

President-elect, Southwest Chapter National Lipid Association
Clinical Professor, Western University/COMP
Denver, CO
Diplomate, American Board of Clinical Lipidology



*“With crown and mace and disc, a mass
of effulgence gleaming everywhere, I see
thee so dazzling to the sight, bright with
splendor of the fiery sun blazing from all
sides — incomprehensible!”*

~ Translated from Chapter 11, Verse 17,
Bhagavad Gita

Introduction

Lipidologists regard elevated triglycerides (TG) as an enigma: Are they a biomarker of risk or a target of therapy to reduce cardiovascular events? The association between elevated triglyceride levels and cardiovascular disease (CVD) remains a mystery. The magnitude to which triglycerides embody a biomarker of risk has been contested for more than three decades. Furthermore, beyond lifestyle modifications and statin therapy, pharmacological treatments aimed at lowering triglyceride levels have been

fraught with mixed results. The variables of low high-density lipoprotein (HDL), high low-density lipoprotein (LDL) and other emerging biomarkers — as well as the dynamic complexity of lipid metabolism — have confounded our treatment effects on hypertriglyceridemia. However, hypertriglyceridemia and triglyceride-rich lipoproteins seem to play a critical role in adverse global public health consequences, including atherogenesis, obesity, metabolic syndrome, diabetes, pancreatitis, and chronic kidney disease. This article will provide a brief overview of the current status of hypertriglyceridemia, not only addressing the scope of the problem but also reviewing opportunities to expand the current treatment strategies.

Scope of the Problem

Hypertriglyceridemia levels are classified as: 150 to 199 mg/dL (borderline high);

200 to 499 mg/dL (high); and ≥ 500 mg/dL (very high).¹ From the National Health and Nutrition Examination Survey (NHANES) data set, 31 percent of the adult U.S. population has a triglyceride level ≥ 150 mg/dL, a level unchanged since 1988. Among the various ethnic groups, Mexican Americans have the highest rates (34.9 percent), followed by non-Hispanic whites (33 percent), and blacks (15.6 percent), the lowest. In addition to the high prevalence, there are other factors that contribute to the degree of concern regarding hypertriglyceridemia.



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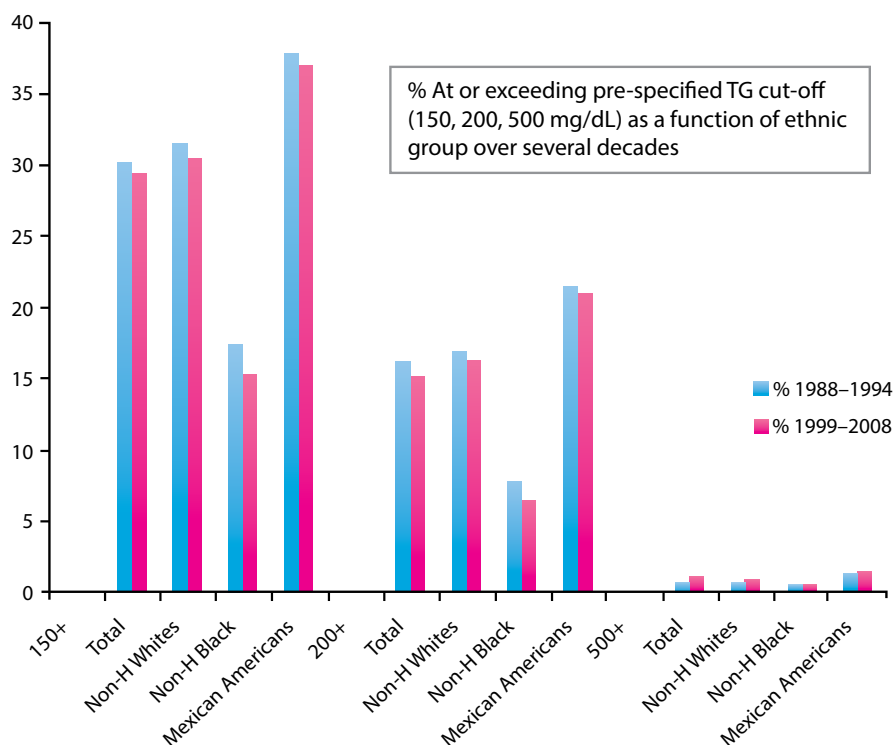


Figure 1. Prevalence of fasting triglyceride levels (≥ 150 , 200, and 500 mg/dL) in males and (non-pregnant) females ≥ 18 years of age by ethnicity in the National Health and Nutrition Examination Survey (1988–1994 and 1999–2008).

First, measuring TG itself is an issue. Triglyceride levels are not normally distributed; hence, log transformation is favored over the arithmetic mean to reduce the potential impact of outliers. In addition, there is a strong inverse association with high-density lipoprotein cholesterol (HDL-C) and apolipoprotein AI (Apo AI), suggesting a complex biological relationship that may not reflect the effects in a multivariate analysis.

Secondly, in many case-control and angiographic studies, TG has been identified as a “risk factor” even after adjustment for total cholesterol, low-density lipoprotein cholesterol (LDL-C) and HDL-C.

Thirdly, prospective cohort studies demonstrate a univariate association of triglycerides with CVD that became non-significant after adjustment for either total cholesterol (TC) or LDL-C. Meta-analysis

from the U.S. and Europe — including the Emerging Risk Factors Collaboration that evaluated 302,430 people free of known vascular disease at baseline in 68 prospective studies — demonstrated a strong, stepwise association with both CVD and ischemic stroke in univariate analysis; 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. Additional data from studies involving young men have provided new insight into the triglyceride risk status question. In 13,953 men ages 26 to 45 years old followed for more than 10 years, there were significant correlations between adoption of a favorable lifestyle, TG level, and CVD reduction.

Fourth, while the landmark randomized controlled trials with statins to reduce LDL-C have remained the principle treatment target for cardiovascular

prevention, the Veterans Affairs HDL-C Intervention Trial (VA-HIT) showed that treatment using a fibric-acid derivative — with more marked effects on triglycerides (-31 percent) and HDL-C ($+6$ percent) and no effects on LDL-C — significantly reduced the relative risk of recurrent coronary heart disease in men ages ≤ 74 years without profoundly elevated LDL-C (mean = 111 mg/dl).

Fifth, there is a convincing case for targeting non HDL-C (a measure of atherogenic lipids that incorporates TG levels elevated in subjects with residual risk) to impede atherosclerotic progression and prevent cardiovascular events in patients with diabetic dyslipidemia.

In the analysis of the Get With the Guidelines database and United Kingdom General Practice Research Database, subjects with low HDL-C (< 40 mg/dl in men and < 46 mg/dl in women) and elevated triglycerides (≥ 150 mg/dl) had a 39 percent higher relative risk of cerebrovascular and cardiovascular events. In the Treating to New Targets (TNT) study, maximum-dose atorvastatin lowered the relative risk of major cardiovascular events by 22 percent ($p < 0.001$); however, statin recipients still had a 17.4 percent 10-year absolute risk of a first event. In addition, even among patients who achieved LDL-C levels < 70 mg/dl with high-dose statin therapy, those with the lowest HDL-C levels still had high residual cardiovascular risk.

In the European Prospective Investigation of Cancer (EPIC-Norfolk) study, the Women’s Health Study and the Strong Heart Study (SHS), non-HDL-C seems to play a bigger role. However, both the Heart Protection Study 2 — Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and AIM – HIGH studies did not show benefits of niacin in improving CV events in subjects

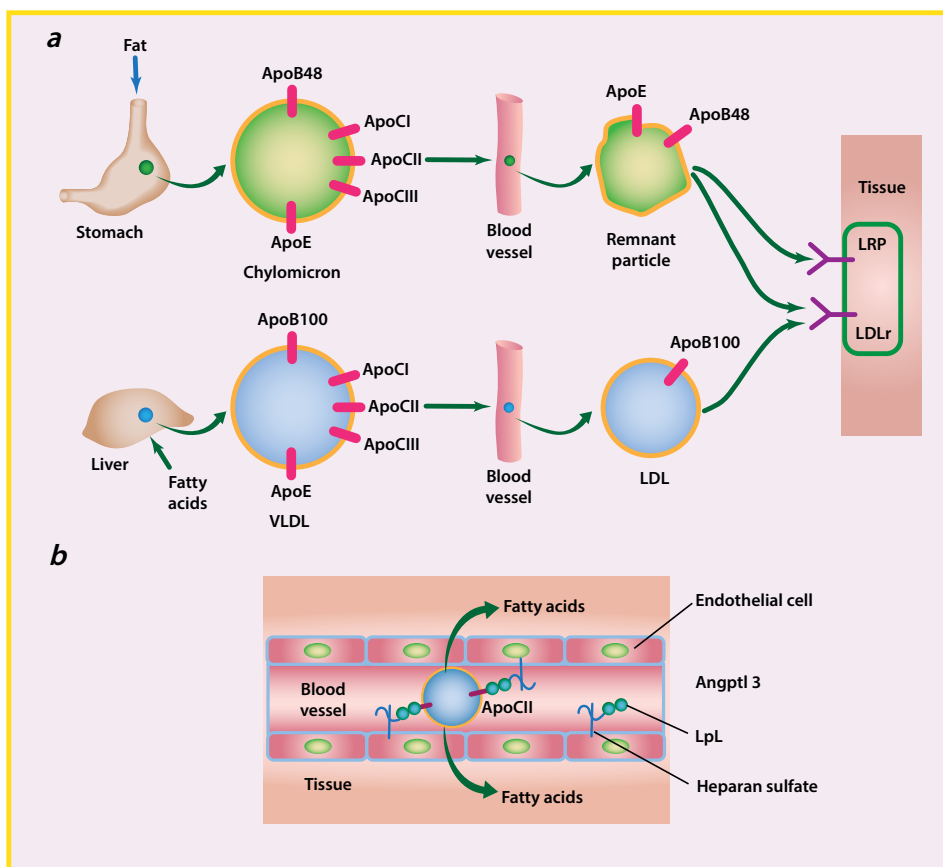


Figure 2. Triglyceride Metabolism

a. Metabolism of Triglyceride rich proteins

b. Lipolysis of Triglyceride rich proteins

For details, refer to the section "Triglyceride Metabolism" in the article

with low HDL. Finally, in the Expert Panel in the recent American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines, no recommendations are made for or against specific LDL-C or non-HDL-C goals for the primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD). These recommendations will be discussed further in this theme issue.

To summarize the scope of TG as target for therapy, the independence of triglyceride levels as a causal factor in promoting CVD remains contentious. Rather, triglyceride levels appear to provide distinctive information as a biomarker of risk, especially when combined with low HDL-C and elevated LDL-C. (Figure 1)

Triglyceride Metabolism

Chylomicrons and very low-density

lipoproteins (VLDL) are the two classes of lipoproteins whose major lipid is triglyceride. Chylomicrons are formed in the intestine and their triglyceride is mainly derived from dietary fat. These particles initially are secreted into the lymphatics. Once in the bloodstream, much of the triglyceride is hydrolyzed into free fatty acid (FFA). The smaller, remnant particles are removed from the bloodstream by low-density lipoprotein receptor (LDLr) and lipid-rich plaque (LRP). Apolipoprotein E (Apo E) and Apo B are the ligands for these receptors. VLDL contains triglycerides assembled in the liver from the FFA or de novo-synthesized fatty acids. Some of these fatty acids are derived from adipose tissue when hormone-sensitive lipase is activated. VLDL triglyceride also is lipolyzed within the bloodstream and the remaining lipid — primarily cholesterol and cholesteryl ester — circulates as LDL.

Apo B100, the major structural protein of LDL, contains a LDL receptor-binding region; apolipoprotein CI (Apo CI) and apolipoprotein CIII (Apo CIII) are smaller proteins that modulate lipolysis and interaction of triglyceride-rich lipoproteins (TRL) with receptors. The conversion of triglyceride to FFA occurs primarily within the capillaries. The fatty acids are then internalized and used for muscle energy or stored primarily within the adipose. The particles must interact with lipoprotein lipase (LpL) that is associated with heparan sulfate proteoglycans on the luminal surface of endothelial cells. LpL requires a co-enzyme, apolipoprotein CII (Apo CII), which is a component of both VLDL and chylomicrons. Apo CIII and perhaps other apolipoproteins inhibit the lipolysis reaction. ApoCIII containing TRLs contribute to atherogenesis. (Figure 2)

Factors Causing Hypertriglyceridemia

Multiple factors contribute to hypertriglyceridemia. Causes can include familial and inherited disorders, hypothyroidism, third-trimester pregnancy and poorly controlled diabetes with insulin deficiency. Medications such as interferon, antipsychotics, beta blockers, bile acid resins, estrogens, protease inhibitors, raloxifene, thiazide diuretics, retinoic acid, steroids, sirolimus, and tamoxifen also raise TG. Obesity, sedentary habits, diabetes, metabolic syndrome, alcohol excess, idiopathic urticarial, and chronic kidney disease also can be considered causes.

Treatment Strategies in Hypertriglyceridemia

Optimization of nutrition can result in a marked triglyceride-lowering effect that ranges between 20 and 50 percent. Strategies including weight loss, reducing simple carbohydrates (CHO), increasing dietary fiber, eliminating *trans* fatty acids, restricting fructose, and saturated fatty acids (SFA), implementing a Mediterranean-style diet and consuming

Clinical trials	Drug used	Inclusion criteria	Primary outcomes	RRR vs placebo
HHS	Gemfibrozil 600 mg twice a day	Men and women with non-HDL-C ≥ 200 mg/dL (5.2 mmol/L)	Cardiac death or fatal/non-fatal MI	34%
VA-HIT	Gemfibrozil 1200 mg daily	Men with CHD (LDL-C ≤ 140 mg/dL; HDL-C ≤ 40 mg/dL)	CHD death or non-fatal MI	22%
BIP	Bezafibrate 400 mg daily	Men and women with previous MI (HDL-C ≤ 45 mg/dL; LDL-C ≤ 180 mg/dL; TGs > 200 mg/dL)	Sudden cardiac death or fatal/nonfatal-MI	7.3%
FIELD	Fenofibrate 200 mg daily	Men and women with diabetes type 2 not taking statin therapy at entry	CHD death or non-fatal MI	11%
ACCORD	Fenofibrate + Simvastatin vs Simvastatin alone	Men and women with diabetes type 2 and a glycated hemoglobin $\geq 7.5\%$	CHD death, nonfatal MI, nonfatal stroke	20%
FATS	Colestipol + Niacin	Men < 62 years of age with elevated apo B levels, coronary atherosclerosis and family history of CHD	Change in stenosis in 1 out of 9 proximal coronary artery segments	11%
HATS	Simvastatin + Niacin	Men and women with clinical CAD and with at least 3 stenoses of at least 30% of luminal diameter and/or 1 stenosis of at least 50% (HDL-C < 35 mg/dL; LDL-C < 145 mg/dL; TG < 400 mg/dL)	Mean change from initial arteriogram to final arteriogram in % stenosis caused by the most severe lesion in each of the nine proximal coronary segments	68%
CDP	Niacin 3 gram/day	Men with a history of MI	5-year total mortality	NS *
AIM-HIGH	Simvastatin 40-80 mg daily + extended release niacin 1500-2000 mg daily	Men and women with established CV disease and atherogenic dyslipidemia	CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, symptom-driven coronary or cerebral revascularization	NS
GISSI	Omega-3 polyunsaturated fatty acid	Men and women with history of MI (< 3 months)	Nonfatal MI, nonfatal stroke	15%
HPS 2 THRIVE	ER Niacin plus laropiprant versus placebo on background statin therapy	Men and women in China and 5 European countries with history of vascular events	Recurrent major vascular events	NS Increased risk with niacin
JELLIS	EPA 1800 mg plus statin vs. statin alone	Men and women 40-75 years with and without CAD	Non-fatal Coronary events	19 % reduction

Table 1. Clinical trials on hypertriglyceridemia

marine-derived omega-3 polyunsaturated fatty acids (PUFA) have proved successful.

However, dietary interventions also depend on the diagnosis. Inherited LPL and related disorders require fat restriction while many of the secondary causes require CHO restriction. Factors 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.

Published clinical trials so far have not been designed specifically to examine the effect of triglyceride reduction on CVD event rate. But secondary analyses from major trials of lipid intervention 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.

As monotherapy, fibrates offer the most triglyceride reduction, followed

by immediate-release niacin, omega-3 FA, extended-release niacin, statins and ezetimibe. In statin trials, subgroups with increased baseline triglyceride levels were reported to have increased CVD risk in the Scandinavian Simvastatin Survival Study (4S), Cardiac Angiography in Renally Impaired Patients (CARE), West of Scotland Coronary Prevention Study (WOSCOPS),

“Hypertriglyceridemia is highly prevalent in patients with metabolic syndrome and studies have shown this to be an independent risk factor for developing CVD.”

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) and Treating to New Targets (TNT) studies and to have greater CVD risk reduction with lipid therapy in 4S and CARE. Thus, in patients with hypertriglyceridemia, statin therapy may be beneficial in the setting of high LDL-C levels. In addition, high-risk subgroups with high TG benefited in the Helsinki Heart Study, the Bezafibrate Infarction Prevention study, and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.

In the VA-HIT, 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 type 2 diabetes mellitus (T2DM), did show benefit in the subgroup with elevated triglyceride levels (>204 mg/dL) and low HDL-C (<34 mg/dL).

In summary, aggregate data suggest that statin or fibrate monotherapy may be beneficial in patients with high triglyceride levels, low HDL-C, or both. In the Pravastatin or Atorvastatin Elevation and Infection Therapy trial (PROVE-IT/TIMI 22) and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial, we have learned that 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.

In the Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS), patients who received a statin plus eicosapentaenoic acid (EPA) compared to statin alone reduced their CVD risk by 53 percent, even though the dose of EPA (up to 1.8 g/d) translated to minimal triglyceride reduction (5 percent between groups). However, subgroup analysis of primary prevention patients in JELIS indicated that patients with baseline triglyceride levels at or exceeding 150 mg/dL and HDL-C <40 mg/dL had significantly increased CVD risk. CVD risk reduction with combination therapy was not statistically significant in either baseline triglyceride subgroup (<151 or ≥ 151 mg/dL). Consequently, the cardiovascular benefit in JELIS was not a primary triglyceride-mediated effect. Also, trials that used statin plus niacin in AIM HIGH and HPS2 have not shown reduction in CV outcomes. (Table 1)

Summary

Hypertriglyceridemia is highly prevalent in patients with metabolic syndrome and studies have shown this to be an independent risk factor for developing CVD. The initial approach to treating hypertriglyceridemia is lifestyle and dietary changes and treating secondary causes of elevated TGs. When TG levels are still above 200 mg/dL but less than 500 mg/dL after conventional treatment, the first-line pharmacological treatment is a statin to normalize LDL-C. Those patients with residual lipid abnormality may benefit from the addition of fibrates, especially gemfibrozil, niacin or omega-3 fatty acids. In addition to intensive therapeutic lifestyle change, utilizing triglyceride-lowering medications to prevent pancreatitis in those with triglyceride levels >500 mg/dL is reasonable. Whether these modalities favorably influence CVD outcomes beyond proven therapies (e.g., statins) remains an unproven hypothesis. Therefore, additional clinical outcome trials are necessary. ■

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References are listed on page 33.

Guest Editorial:

Current ACC/AHA Guidelines Regarding Hypertriglyceridemia



RAJASREE PAI RAMACHANDRA PAI, MD

Endocrinologist
Eureka, CA



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The American College of Cardiology (ACC) and the American Heart Association (AHA) — in collaboration with the National Heart, Lung and Blood Institute (NHLBI) — published their evidence-based hyperlipidemia guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular diseases (ASCVD). Even though this major guideline revision after the Adult Treatment Panel III report in 2002 has some unique aspects, such as including stroke as a cardiovascular outcome and removing low-density lipoprotein (LDL) targets, it does not add much new information regarding the management of hypertriglyceridemia.¹

By definition, hypertriglyceridemia occurs when the level of triglyceride reaches ≥ 150 (150-199 is borderline high, 200-499 is high, and ≥ 500 is very high).² An elevated triglyceride level is

not a target for therapy, per se, unless when ≥ 500 (especially if $\geq 1,000$) and the recommendation is to reduce the levels to <500 with a goal of preventing pancreatitis with drugs (fibrates, high-dose omega-3 fatty acids, and nicotinic acid).^{1,2} When combined with a statin, though fenofibrate is considered safer than gemfibrozil, the guidelines recommend “against use of non-statins in any statin-tolerant patient for preventing cardiovascular outcomes” and that “the combination of a statin with any fibrate should be avoided because of an increased risk of toxicity.”^{1,2}

Controversy on Hypertriglyceridemia Management — the Data Behind the Guidelines

The treatment of asymptomatic hypertriglyceridemia is controversial. No strong evidence exists for a direct causal relationship between cardiovascular disease and hypertriglyceridemia.³ The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High

Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial showed that the addition of niacin to statins did not improve major vascular events when the LDL cholesterol levels were controlled.^{4,5} The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial did not show any significant reduction in fatal cardiovascular events with fenofibrate, but a possible benefit for patients with high-baseline triglycerides and low high-density lipoprotein (HDL) was observed.⁶

High Triglycerides — a Neglected Topic for Cardiovascular Prevention?

The guidelines rightfully support statin use while recommending against use of non-statins, mostly based on randomized control trials. To a primary care provider assessing a patient for the first time, the risk assessment tool might be handy. But do the same rules apply to an endocrinologist for whom most patients are either insulin resistant or diabetic?

In patients with metabolic syndrome, insulin resistance, or diabetes, lipid metabolism is altered and hypertriglyceridemia occurs in conjunction

with low HDL and high LDL, increasing the risk of atherogenesis.⁷ Although hypertriglyceridemia has not yet been shown to be an independent risk factor in the general population, it is an integral part of atherogenic dyslipidemia in high-risk patients with diabetes (type 1 or 2).⁷ Similar mechanisms operate in patients with lipodystrophy, in which a deficiency in adipose tissue impairs fat storage and adipose tissue function, making those patients vulnerable to cardiovascular diseases. Therefore, these groups of patients might require special consideration in terms of hypertriglyceridemia.

The expert panel mentioned that “non-statin therapies do not provide acceptable ASCVD risk reduction compared to their potential for adverse effects in the routine prevention of ASCVD” and did not provide clear recommendations for diabetics.

Why Avoiding Non-Statins May Help in Some Ways

One major argument to support the new lipid guidelines is that adjuvant use of fibrates or niacin along with statins may prompt physicians to reduce statin doses in an attempt to lower the risk of side effects such as myopathy and could, as a result, lower statin efficacy. Avoiding non-statins can, therefore, be beneficial in maximizing statin dose.

Another positive note is the emphasis on the role of lifestyle and controlling risk factors such as diabetes, lack of exercise and hypertension in reducing cardiovascular events instead of adding a non-statin.

Is There Evidence to Support Treating Pancreatitis as a Primary Goal?

The National Institutes of Health consensus development conference in 1983 concluded that the risk of pancreatitis is present in triglyceride

levels > 500 in spite of lacking evidence to support the same.² There are no studies excluding the role of alcohol and gallstones in assessing the risk of hypertriglyceridemia in pancreatitis, and there is very limited data to suggest that treatment of triglyceridemia $\geq$ 500 improves susceptibility to pancreatitis.^{8,9,10}

With lack of proper evidence, is it advisable to treat hypertriglyceridemia $\geq$ 500 with non-statins to try to prevent pancreatitis instead of with statins to prevent cardiovascular outcomes, especially in those with derangement of glucose metabolism?

“We need randomized control trials to evaluate alternate therapies for cardiovascular risk reduction which may be difficult to implement in this statin era.”

Which Non-Statins to Use?

Evidence from the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) for gemfibrozil showed a 24-percent reduction in relative risk of cardiovascular events compared to placebo,¹¹ but the current guidelines recommend “gemfibrozil should not be initiated with statin therapy due to increased risk for muscle symptoms and rhabdomyolysis” and that “fenofibrate may be considered along with a low or moderate intensity statin only if benefits from ASCVD risk or triglycerides above 500 outweighs risks.”

This is in contradiction to the results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which showed no significant improvement in major cardiovascular outcomes with use of fenofibrate, the effects of which could have been masked by concomitant statin use.¹²

How Do the New Guidelines Change our Practice?

Some hospitals and formularies are considering changing drug policies for non-statins. Patients with active cardiac disease who were on fibrates or niacin in addition to statins are being taken off the non-statins by some physicians, while other physicians — after discussing with their patients the lack of supporting data on outcomes — have taken a cautious approach because of possible favorable lipid changes in dyslipidemic groups in the ACCORD and AIM-HIGH trials.^{5,6}

Future Research

We need randomized control trials to evaluate alternate therapies for cardiovascular risk reduction which may be difficult to implement in this statin era. We also need studies to compare the use of non-statins with lower doses of statins and to look at the role of statins versus non-statins in isolated hypertriglyceridemia $\geq$ 500 in cardiovascular risk reduction. ■

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References are listed on page 33.

EBM Tools for Practice:

Triglyceride and Atherogenic Dyslipidemia in Adolescence



PIERS R. BLACKETT, MD, FNLA

Department of Pediatrics
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Diplomate, American Board of Clinical Lipidology



CATHERINE MCNEAL, MD, PhD, FNLA

Department of Pediatrics
Department of Internal Medicine, Division of Cardiology
Scott & White Healthcare
Temple, TX

Diplomate, American Board of Clinical Lipidology



DON P. WILSON, MD, FNLA

Department of Pediatrics,
Pediatric Endocrinology and Diabetes
Cook Children's Medical Center
Fort Worth, TX

Diplomate, American Board of Clinical Lipidology



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Moderate elevation in triglyceride in the <500 mg/dl range frequently presents in children and adolescents,¹ and is among risk factors associated with autopsy-proven atherosclerosis,² whereas severe hypertriglyceridemia leading to pancreatitis is less common than in adults. Children with moderately high triglyceride levels have a characteristic clinical presentation — with obesity, a family history of type

2 diabetes, or the metabolic syndrome — and represent a therapeutic challenge. Since atherosclerosis rarely advances to overt disease in children or adolescents, surrogate end-points have been used in longitudinal studies designed to determine whether childhood risk markers predict intima-media thickening (IMT) in adulthood. Triglyceride, non-high-density lipoprotein cholesterol (non-HDL-C), apoB, and apoB:apoA-I ratio predict IMT after more than 20 years of follow-up,^{3,4} and non-HDL-C is known to be superior to triglyceride as a predictor.⁴ Similar to findings in adult meta-analyses,⁵ adjustment for established risk factors attenuated the association of triglyceride

with early cardiovascular disease (CVD) evident as young adult IMT thickening.⁴

Association of lifetime triglyceride lowering on protection from CVD is evident in recent studies on loss of function apo C-III mutations⁶ supporting maintenance of low triglyceride levels beginning at early ages. Also, triglyceride's lifetime role in atherogenic particle formation^{7,8} is evident from the association of gene variants with classic hypertriglyceridemic phenotypes (IIb, III, IV and V) supporting shared genetic architecture^{7,9} and a common genetic background for the triglyceride-containing lipid phenotypes.¹⁰ Furthermore, expression is increased

by insulin resistance and hepatic fat deposition.¹¹ Thus, the combined effects of genetic and environmental factors beginning before birth promote insulin resistance and associated dyslipidemia,^{12,13} leading to early adult disease.³ (Figure 1)

“Reversal by lifestyle interventions for children have not met with the expected success...”

As has been proposed for diabetes-related genotypes,¹⁴ the “thrifty” gene variants may not express without nutritional excess. Increased consumption of sugar and sugared drinks, especially when containing high-fructose corn syrup, have profound effects on production of very-low-density lipoprotein (VLDL) and liver fat content.^{15,16,17} Reversal by lifestyle interventions for children have not met with the expected success,¹⁸ but randomized controlled trials on aerobic exercise for those ages 5 to 19 years have been more encouraging.¹⁹ Ideally, lifestyle change needs to be sustained as a structured program involving motivational strategies such as those adopted by the Yale pediatric program, which serves as a model.²⁰ Outcomes are ideally dependent on commitment and financial support for a team approach and being aware that the consequences of multiple childhood factors include increased circulating triglyceride-rich particle production leading to long-term and potentially fatal consequences (Figure 1).

When lifestyle measures fail, medications are an option; however, there is limited trial information or Food and Drug

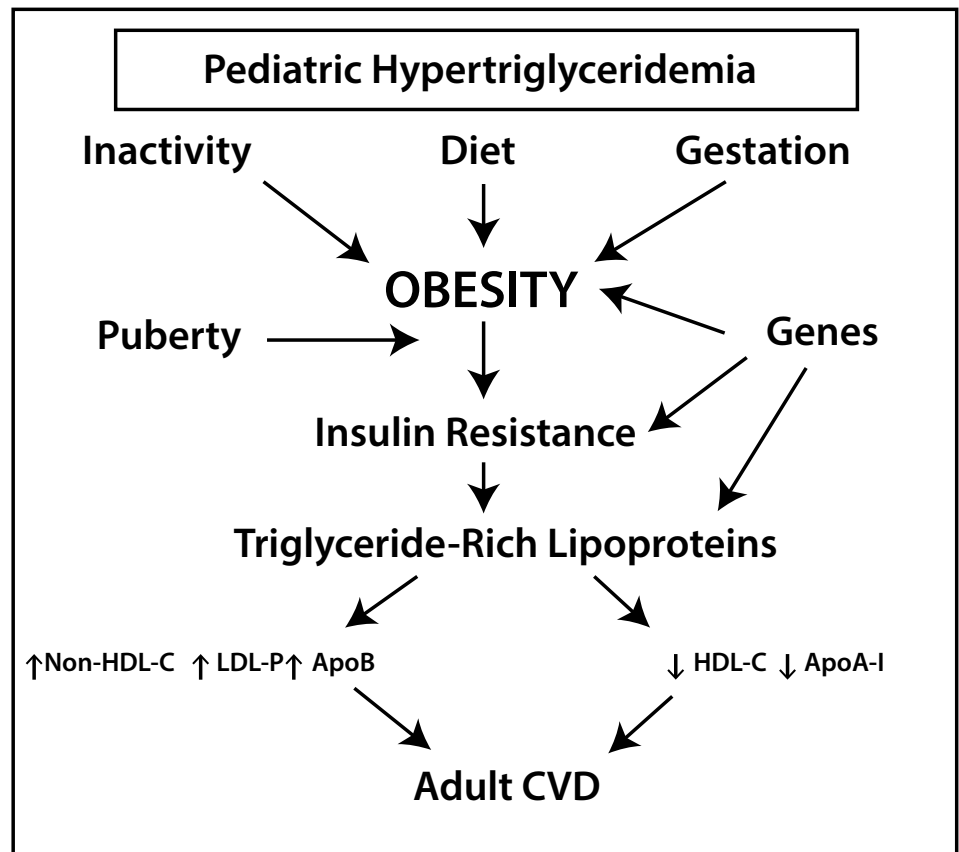


Figure 1. The role of hypertriglyceridemia in CVD

Administration (FDA) approval for use of triglyceride-lowering agents such as fibrates or prescription omega-3s for those under 18 years of age.^{21,22}

The 2011 NHLBI’s pediatric guidelines and American Heart Association (AHA) statement both recommend non-HDL-C as the treatment target in cases with elevated triglyceride, providing better treatment options for children and adolescents.^{23,24} The way forward is to present such evidence to those who are in a position to initiate, implement, and sustain substantial changes in health beginning at early ages. ■

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References are listed on page 33.

Non-HDL-C = non-high-density lipoprotein cholesterol
 LDL-P = low density lipoprotein particle number
 Apo B = apolipoprotein B
 HDL-C = high density lipoprotein cholesterol
 Apo A-1 = apolipoprotein A-1

Lipid Luminations: Whither Fibrates?



SCOTT SHURMUR, MD, FNLA

Cardiology Division Chief
Texas Tech University Health Sciences Center
Lubbock, TX

Diplomate, American Board of Clinical Lipidology



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The role of fibrates in treating patients with hyperlipidemia remains controversial.¹⁻³ Recent randomized clinical trials of fibrates, alone or in combination with statins, have been inconclusive.^{4,5}

Fibric acid derivatives exert favorable lipid effects through the ligand-dependent transcription factor PPAR α , which can regulate multiple target genes.⁶ Mechanistically, fibrates have been shown to induce lipoprotein lipase transcription^{7,8} and reduce hepatic apo-CIII production.⁹⁻¹¹ Fibrates also increase synthesis of the HDL apolipoproteins A-1 and A-II via stabilization of mRNA transcription,¹²⁻¹⁴ which likely increases HDL “functionality.” This class of agents has also been shown to increase LDL particle size and decrease LDL particle triglyceride content, thereby increasing affinity of LDL particles for the

apo B/E hepatic LDL receptor.¹⁵⁻¹⁸

Despite what appears to be very favorable lipid effects, randomized clinical trial results have been disappointing. Trials comparing gemfibrozil to placebo did show favorable results.^{19,20} However, these trials did not employ standard-of-care “background” statin therapy, and the interference of gemfibrozil with statin glucucoridation and subsequent increased myopathy risk makes combining these agents untenable.²¹⁻²⁴

Thus there was great promise with fenofibrate, which does not interact unfavorably with statins.²¹ In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial — designed as a fibrate monotherapy trial — more than 9,000 subjects were randomized to placebo or fenofibrate, 200mg/day. Median baseline triglyceride level in each group was 154mg/dl, with median HDL level of 43mg/dl. The trial failed to meet its primary endpoint, with no reduction in total CHD events with fenofibrate. However, in the analysis of

the subgroup with lipid characteristics of the metabolic syndrome, a statistically significant 14-percent reduction in the primary endpoint was achieved with fenofibrate. Additionally, statin “drop-ins” were greater in the placebo arm, with 40 percent of placebo group patients taking a statin by year five of the study.⁵

In the Accord Lipid Study, more than 5,000 patients with type II diabetes mellitus were treated with simvastatin therapy, and were randomized to placebo or fenofibrate. Again, the primary endpoint of a reduction in myocardial infarction, stroke, or death was not achieved with fenofibrate in the trial. However, in the prespecified analysis of subjects in the highest tertile of baseline triglyceride level (>204mg/dl) and lowest tertile of baseline HDL (<34mg/dl), a borderline statistically significant reduction in primary endpoint was achieved with the addition of fenofibrate. (12.4 percent fenofibrate group; 17.3 percent placebo group; $p=.06$).⁴

Similar “lipid-dependent” results have

been seen in trials of other fibrates. Bezafibrate, available in Europe, was evaluated compared to placebo in the randomized Bezafibrate Infarction Prevention (BIP) Study. In this study, more than 3,000 patients with coronary artery disease were randomized to 400mg bezafibrate per day or placebo. Subjects with triglyceride levels >300mg/dl were excluded, but all had HDL cholesterol levels <45mg/dl. Insulin-dependent diabetes was also excluded. Open-label use of additional lipid-modifying therapy was almost twice as common in the placebo group (237 subjects) as in the bezafibrate group (136 subjects). Again, the primary endpoint of MI or sudden death failed to be reduced in the bezafibrate group. Post-hoc analysis of events, based upon triglyceride levels, revealed no benefit of bezafibrate in subjects with baseline triglyceride <200mg/dl, but a nearly 40 percent reduction in primary endpoint was achieved in subjects with triglyceride levels ≥ 200 mg/dl ($p=.02$).²⁵

The gemfibrozil monotherapy trials, referred to earlier, yielded similar results. Though the overall trial results were positive with gemfibrozil in the Helsinki Heart Study, the benefit was most striking in subjects with LDL/HDL ratio >5.0, and triglyceride levels > 200mg/dl. In this group, gemfibrozil reduced ischemic coronary events by 71 percent.¹⁹ Similarly, a benefit of gemfibrozil was seen overall in the VA-HIT Study, but was most pronounced in those subjects with the most severe insulin resistance. In subjects with diabetes (25 percent of the entire study population) the combined ischemic endpoint of nonfatal MI, CHD death, or stroke, was reduced by 32 percent with gemfibrozil ($p=.004$), whereas in the larger nondiabetic study population, a statistically significant reduction was not achieved (18 percent; $p=.07$). Furthermore, the benefits of gemfibrozil increased with each quartile

of fasting plasma insulin levels. In the lowest quartile, no reduction in events was noted, while in the highest quartile of fasting insulin level (≥ 39 uU/ml) a 35-percent reduction in events was seen with gemfibrozil.

“Without a recent positive trial with contemporary fibrate therapy, we are left without an evidence-basis for our lipid-subgroup-driven beliefs.”

So, where does this leave us? Clearly, fibrates exert many beneficial effects in atherogenic dyslipidemias,⁶ and many trials of fibrates have clearly shown differential “lipid-dependent” beneficial effects of fibrate therapy.^{4,5,19,25,26} Yet, without a recent positive trial with contemporary fibrate therapy, we are left without an evidence-basis for our lipid-subgroup-driven beliefs. Of course, no large fibrate trial has ever studied a population with baseline median triglyceride levels >200mg/dl, despite strong evidence that it is only in this group that fibrates have benefit. Let us hope that the planned VA FIT trial, a randomized trial of fenofibrate with triglyceride levels <200mg/dl an exclusion criterion, in fact commences and proceeds to completion. Without such much-needed evidence, very relevant clinical questions may remain unanswered, and the role for fibrates in hyperlipidemia treatment and event reduction may remain undefined. ■

Disclosure statement: Dr. Shurmur has no disclosures to report.

References are listed on page 34.

Specialty Corner:

Disorders of the Triglyceride-HDL Axis in Insulin Resistance



JOSEPH L. LILLO, DO, FNLA, CPI

Adjunct Professor, Midwestern University
Glendale, AZ
Private Practice
Scottsdale, AZ



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Disorders of the triglyceride-high-density lipoprotein (TG-HDL) axis, i.e. high TGs and low HDL cholesterol (HDL-C), are well documented in the medical literature,¹ and are of particular importance to clinicians treating patients who are insulin resistant (IR) or who have diabetes mellitus (diabetes). We all see this in clinic every day, because there are now approximately 115 million Americans who are IR or who have diabetes.²

As I speak to colleagues in my community, I realize that TG-HDL axis disorders are underappreciated and undertreated. Even worse, many choose to focus on the issue of low HDL-C, which is really just a biomarker of the condition, and ignore the real villain, high TGs. The American Heart Association (AHA) scientific statement on TGs and cardiovascular disease states that during the past three to four decades,

mean TG levels have increased in the U.S. while mean low-density lipoprotein cholesterol (LDL-C) levels have decreased.³

A recently published analysis of the Copenhagen City Heart Study and the Copenhagen General Population Study suggested that elevated TG levels should be a potential therapeutic target. This analysis examined non-fasting TGs and the risk of ischemic vascular disease and ischemic heart disease in more than 75,000 individuals during a median follow-up of 34 years. There was a clear increase in risk for ischemic cardiovascular disease in patients with elevated TGs. In addition, the incidence of diabetes rose with each increasing quintile of TG levels.⁴

TG-HDL Axis in Insulin Resistance

Insulin resistance induces many physiologic changes in those affected, and it is these changes that confer the increased cardiovascular risk. Insulin-resistant patients, who are often overweight or obese, have elevated TGs as a result of reduced visceral adipocyte sensitivity to endogenous circulating insulin as adiponectin levels decrease. This results

in increased activity of hormone-sensitive lipase, which induces hydrolysis of TGs and release of fatty acids. In turn, these fatty acids travel via the portal circulation to the liver where they have a negative impact on circulating lipids. Within the liver they are reincorporated into atherogenic, TG-rich apolipoprotein (Apo) B-containing, very-low-density lipoprotein (VLDL) particles. These particles ultimately are converted into other atherogenic Apo B-containing lipoproteins — intermediate-density lipoproteins (IDLs) and then LDLs. However, as the VLDL load accumulates, cholesterol ester transfer protein (CETP) facilitates an exchange of TG for cholesterol ester within HDL particles. These newly TG-laden HDL particles are now a substrate for multiple lipases. The action of the lipases ultimately helps reduce serum HDL-C concentration as particles lose triglyceride content and become smaller. As these particles remodel, they become so small that they are excreted via the megalin-cubilin complex in the kidney. Thus the low HDL-C and high TG concentrations of the TG-HDL axis is created. Further insults to the system include the down-regulation

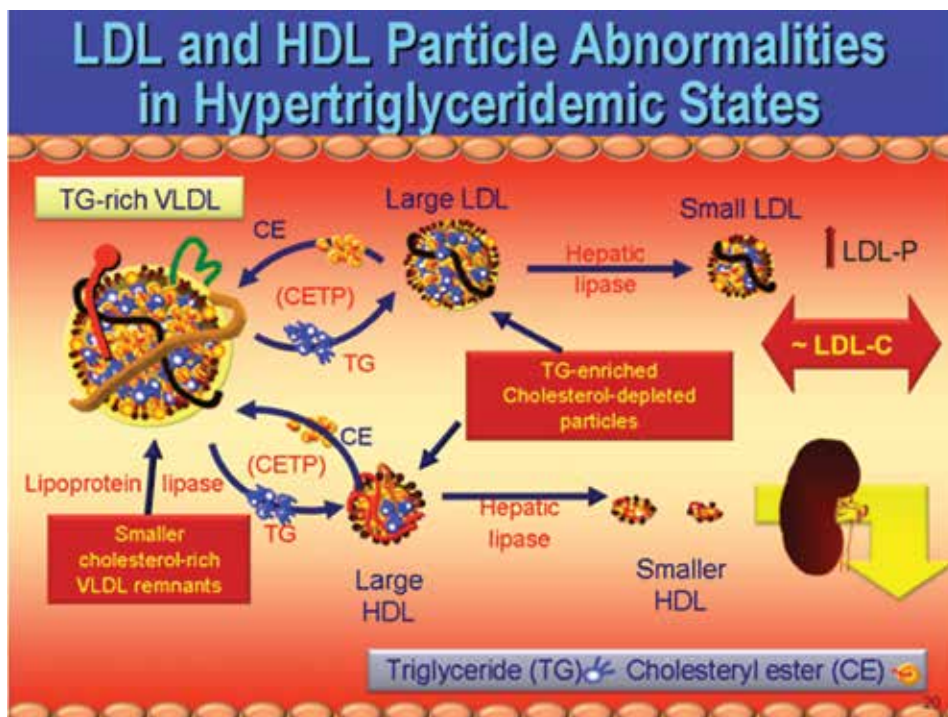


Figure 1. Used with permission, Tom Dayspring, MD, FNLA

of scavenger receptor B1, which results in less cholesterol being trafficked back to hepatocytes by HDL particles, as well as reduced macrophage cholesterol transport due to the inflamed adipocytes' down-regulation of ATP binding cassette transporter-A1. This reduces the lipidation of HDL particles in what is possibly their most cardioprotective role, both lowering HDL-C and impairing removal of atherogenic cholesterol from lipid-laden macrophages in the endothelium. (Figure 1)

To complete this biochemical assault on the vasculature, the prolonged exposure of elevated serum glucose seen in IR results in increased TG production as the glucose enters hepatic cells and fuels lipogenesis. I outlined these biochemical pathways in an article in an earlier edition of *LipidSpin*.⁵

Clinical Management of Insulin Resistance

There are biomarker abnormalities unique to the IR patient that can help us to more effectively treat them. LDL-C has been shown to be less accurate for

cardiovascular risk prediction than Apo B or low-density lipoprotein particle number (LDL-P) measurements, particularly in this group. IR patients exhibit the highest degree of discordance between the standard lipid panel and the atherogenic particle load.⁶ Indeed, the National Lipid Association has endorsed testing this patient population as a reasonable measure with advanced biomarkers including Apo B and LDL-P.⁷ As early as 2008, the American College of Cardiology/American Diabetes Association (ACC/ADA) joint position paper opined that the IR patient population is best served with measurement of Apo B or LDL-P both for diagnosis and to assist achievement of therapeutic goals. As my own clinical practice experience has documented, it is quite common to see Apo B or LDL-P elevations even when the LDL-C concentration is at a level that many clinicians would consider to be at goal in IR patients.⁶

Insulin-resistant patients are "diabetics in training." As the severity of IR progresses over time, they generally display a disorder

of the TG-HDL axis during laboratory evaluation. I believe we should treat the IR and resultant TG-HDL axis disorder early and aggressively to help prevent cardiovascular events. This thought has, of course, become a little more challenging with the release last year of the National Heart, Lung & Blood Institute (NHLBI)-funded ACC/AHA treatment guidelines. I certainly do not believe that these guidelines represent genuine help to clinicians who intend to provide comprehensive therapy for lipid disorders, including those of the TG-HDL axis. However, this discussion has already been aired in the medical literature, and I will only register my opinion.

Since the new ACC/AHA guidelines are not rules, I believe we must use human physiology and every shred of data we find credible to treat patients for which no Level 1 evidence-based medicine exists. I urge clinicians to treat IR, and disorders of the TG-HDL axis, and not to ignore it while waiting for more evidence.

Of course, first-line therapy remains diet, exercise, and weight loss where appropriate. This cannot be emphasized enough or just taken as "lip service" before the first prescription is written.

The pharmacologic options to treat IR are well known. Treating every facet of IR is critical, in my opinion. Normalizing glucose levels is important to reduce lipogenesis. I believe metformin to be baseline therapy, but reviewing all other glucose-lowering agents is beyond the scope of this article. Note that, to date, it has been difficult to prove that just lowering glycated hemoglobin (HBA1c) will prevent any macrovascular events. It is my opinion this is because of the contributions of the TG-HDL axis to this patient type.

Much the same can be said for treating

elevated blood pressures. With new guidelines for blood pressure as well, the clinician is obligated to apply them to each patient, considering all the individual characteristics that unique patient exhibits.⁸

From a lipid perspective, there are multiple agents that may be utilized after baseline statin therapy is in place. These agents include primarily fibrates, n-3 fatty acids, and niacin. Yes, niacin, not to raise HDL-C but to reduce TGs and further reduce the atherogenic particle concentration. The evidence on lowering TGs to prevent cardiovascular events is not yet “iron clad.” However, I believe that treating high TGs in the IR patient population is justified based on the physiology and data noted above. It is my clinical goal to minimize risk by treating every risk factor I can with the smallest number of pharmacologic

interventions. This truly is a difficult balance to achieve. I believe every patient deserves an individualized approach based on the totality of the evidence that we have viewed through the lens of best clinical judgment. ■

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Practical Pearls:

Lowering Triglycerides with Omega-3 Fatty Acids

DONALD G. LAMPRECHT, PharmD, BCPS, FNLA, CLS

Clinical Pharmacy Specialist, Clinical Pharmacy Cardiac Risk Service (CPCRS)

Kaiser Permanente of Colorado

Clinical Assistant Professor,

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Aurora, CO

Diplomate, Accreditation Council of Clinical Lipidology



LISA J. SCHWELLENBACH, PharmD, BCPS

Clinical Pharmacy Specialist, Clinical Pharmacy Cardiac Risk Service (CPCRS)

Kaiser Permanente of Colorado

Clinical Instructor,

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Aurora, CO



Approximately 27 percent of adult Americans have elevated (≥ 150 mg/dL) fasting triglycerides (TG).¹ This commonly encountered dyslipidemia is an important indicator of the presence of atherogenic lipoprotein particles and may be considered a modifiable risk factor for cardiovascular disease.² While genetic defects are responsible for familial forms of hypertriglyceridemia, secondary causes of hypertriglyceridemia often can be attributed to dietary factors (e.g. very low-fat diets, overconsumption of simple carbohydrates, excessive alcohol intake), medications (e.g. oral estrogen, glucocorticoids, protease inhibitors) and certain disease states that alter lipid metabolism (e.g. nephrotic syndrome, metabolic syndrome, uncontrolled diabetes, hypothyroidism, obesity).³ These secondary causes should be addressed prior to or in conjunction with the implementation of corrective therapy (e.g.

omega-3 fatty acids (n-3 FA), fibrates, niacin).

Marine-derived n-3 FA (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), otherwise known as “fish oil,” generally is devoid of clinically important drug interactions and represents an effective means to help correct alterations in TG production and metabolism.^{4,5} Two prescription versions of n-3 FA are currently available in the U.S. and have been shown to lower TG by 27 to 45 percent.^{6,7} In situations in which cost or drug formulary restrictions preclude their use, over-the-counter (OTC) formulations may be used⁸ under the supervision of a lipid specialist.

In general, a total daily dose of 1 gram of EPA and/or DHA can be expected to result in a 5 to 10 percent lowering of TG.² Several manufacturers market OTC

fish oil supplements of varying quality, so clinicians should encourage patients to use United States Pharmacopeia (USP) verified formulations that assure purity and potency. In the past, the most commonly marketed dose of OTC fish oil contained only 300 mg of combined DHA plus EPA per capsule,⁹ thus requiring in excess of nine capsules a day to achieve clinically meaningful results. Fortunately, highly concentrated “double- or triple-strength” formulations are now widely available, generally contain 684–900 mg of combined DHA plus EPA per capsule, and sell in the range of \$10 to \$15 per bottle. (Table 1) It may be helpful to initiate



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Omega-3 Fish Oil Formulation	DHA content per capsule (mg)	EPA content per capsule (mg)	Number of capsules (per day) to lower TG by 25%–45%
OTC - standard	120	180	9–13
OTC - double strength	274	410	4–5
OTC - triple strength	253	647	3–4
Rx: DHA + EPA	375	465	4
Rx: EPA	---	1000	4

Table 1. Comparison of DHA/EPA Content of Omega-3 FA Products

therapy at two capsules daily and titrate to effect as tolerated. For patients who have difficulty swallowing large capsules, highly concentrated liquid formulations are available, albeit at an increased cost.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol recommends that clinicians evaluate patients for gastrointestinal disturbances when EPA and/or DHA are used for the management of severe hypertriglyceridemia.³ Eructation, with a fishy aftertaste, and dyspepsia are common side effects reported by patients taking fish oil supplements. Fishy aftertaste may be minimized by storing capsules in the freezer or using enteric-coated formulations¹⁰ to help prevent capsule dissolution in the esophagus and stomach, thereby minimizing belches. Of note, the manufacturers of prescription formulations recommend storage at room temperature.^{6,7} Other strategies to help improve tolerability include taking fish oil prior to meals or at bedtime or using flavored formulations.

Patients may inquire about krill oil because of the reported lack of fishy aftertaste, smaller capsule size and potential for lower pill burden since krill oil may have better bioavailability than fish oil.¹¹ Unfortunately, few studies have compared krill oil to fish oil for TG lowering. A single study compared varying doses (1–3 gm/d) of a specific krill oil formulation

(unspecified amount of DHA/EPA) to standard fish oil (900 mg/d of DHA/EPA). A significant reduction in TG (~28 percent) was reported with 2–3 gm/d of krill oil as compared to a non-significant 3.2 percent reduction with fish oil.¹² Alternatively, Ulven et al. reported comparable TG lowering between krill oil (543 mg/d DHA/EPA) and fish oil (864 mg/d DHA/EPA).¹³

“Fortunately, highly concentrated ‘double- or triplestrength’ formulations are now widely available, generally contain 684–900 mg of combined DHA plus EPA per capsule, and sell in the range of \$10 to \$15 per bottle.”

More studies are needed to determine how krill oil compares to fish oil, especially when administered in equipotent doses.

Shellfish allergies do not preclude the use of fish oil, although safety in this patient

population has not been established. Our experience has been that such patients tend to be hesitant out of fear of experiencing allergic reactions. One option clinicians have is to consider n-3 FA products derived from algae sources. Disadvantages are that these products are not as readily available and tend to be costly. Krill oil should be avoided in those with shellfish allergies, because it contains a shellfish allergen.¹⁴

The collective clinical experience of our practice has been that omega-3 fish oil is a cost-effective means by which to treat elevated triglycerides. Educating patients on how to read product labels, focusing on the amount of EPA and/or DHA content per capsule rather than the amount of fish oil concentrate, helps to ensure that adequate doses of omega-3 fatty acids are employed. Adherence to therapy should be assessed at each lipid panel review and verification of appropriate dose/formulation should be documented whenever feasible.

Disclosure statement: There are no disclosures to report.

References are listed on page 34.

Case Study:

Type III Hyperlipidemia Unmasked by Biliary Cirrhosis

Amita Maturu, MD

Endocrinologist
OhioHealth Endocrinology Physicians
Columbus, OH



Lisa Forman, MD, MSCE

Associate Professor of Medicine, Division of Gastroenterology
University of Colorado
Aurora, CO



James M. Falko, MD, FNLA

Clinical Professor, Division of Endocrinology Diabetes and Metabolism
University of Colorado
Aurora, CO

Diplomate, American Board of Clinical Lipidology



Introduction

Many causes of hypertriglyceridemia are either acquired or genetic. One uncommon genetic cause is broad-beta disease, or dysbetalipoproteinemia (type III hyperlipidemia). This disease is associated with the apolipoprotein E2/E2 or, occasionally, the E2/E3 phenotype. It is characterized by an increase in intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), and chylomicron remnants. Sometimes, an additional “hit” is needed to unmask the hyperlipidemia. The second hit is often another disease process or the side effect from a drug. We recently saw a patient at the University of Colorado lipid clinic who

most likely had type III hyperlipidemia unmasked by her autoimmune liver disease. Her case required some thoughtful investigation.

Case Presentation

RC is a 47-year-old woman with primary biliary cirrhosis (PBC) who was referred to our lipid clinic for severe hyperlipidemia. One year after her diagnosis of PBC she developed a severe and progressive pruritus, refractory to ursodiol, cholestyramine, sertraline, rifampin, and steroids. She was referred to our hepatology department in 2011 for a liver transplant. Laboratory results from her initial evaluation are summarized in Table 1.

In 2012, she developed symptomatic palmar xanthomas and tuberoeruptive xanthomas of her elbows and knees. A fasting lipid panel was obtained (Table 2) and showed severe hypertriglyceridemia and hypercholesterolemia.

It was noted on our initial evaluation that



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Laboratory Test	Value	Reference Range
Alpha 1 fetoprotein (ng/mL)	2	0–8
WBC (thous/mm ³)	5.8	3.5–11.0
Hgb (gm/dL)	9.9	12.0–16.0
Hct (%)	29.2	34–47
Platelets (thous/mm ³)	296	150–450
Sodium (mEq/L)	123	135–145
Potassium (mEq/L)	3.6	3.5–5.0
Chloride (mEq/L)	92	98–109
CO ₂ (mmol/L)	22	20–31
BUN (mg/dL)	17	7–23
Creatinine (mg/dL)	0.8	0.6–1.1
Albumin (g/dL)	3.2	3.5–5.0
Alkaline phosphatase (IU/L)	1016	45–129
AST (IU/L)	72	5–40
ALT (IU/L)	111	5–50
Total bilirubin (mg/dL)	8.9	0–1.3

Table 1.

the patient had no past medical history other than her severe PBC. She had been on an oral contraceptive pill (OCP) for many years. She had no known history of elevated lipids and, in fact, had a normal lipid panel documented in both 2005 and 2006 (while on an OCP). Her brother did have type 1 diabetes and a history of hypertriglyceridemia with levels in the 1,000 mg/dL range. She denied excessive alcohol consumption. On physical exam, her BMI was 26.9 kg/m² and vital signs were all normal. She was jaundiced. Numerous palmar and tuberoeruptive xanthomas were noted, with surrounding excoriations and bleeding. Her physical exam was otherwise unremarkable. At the time of this evaluation, she was only taking ursodiol, anti-pruritics, and an OCP.

She was initially diagnosed with lipoprotein X as a consequence of her liver disease, but there was a suspicion that she also had an underlying genetic syndrome leading to her profound hypertriglyceridemia and hypercholesterolemia. Lipoprotein (a) and lysosomal acid lipase levels were both found to be normal; the latter test

excluded adult cholesterol ester storage disease. Her apolipoprotein (Apo) B level was elevated at 267 (normal 55–125 mg/dL), which confirmed that her hyperlipidemia was not all the result of lipoprotein X. Low-dose bile acid sequestrants were re-initiated in addition to 4 grams of lovaza. Her OCP was held. Once the elevated Apo B level was noted, atorvastatin 20mg daily was added to her regimen. One month later in follow-up, her triglyceride level had decreased to 377 mg/dL. Her total cholesterol level remained elevated at 1,220 mg/dL. With the improvement in her hypertriglyceridemia, we felt more comfortable aggressively treating her hypercholesterolemia with higher doses of bile acid sequestrants.

The diagnosis of type III hyperlipidemia was considered because of the patient's palmar and tuberoeruptive xanthomas, history of normal lipid levels, and no family history of premature heart disease. Further testing showed an abnormal genotype of Apo E3/E2. A thorough evaluation showed no second "hit" to explain the hypertriglyceridemia, because

thyroid and renal function were normal and she had no evidence of diabetes. She had no recent weight gain or change in diet/activity level. She was not post-menopausal. She was on an OCP but had several normal lipid panels in the past while she was on this medication. Thus, we believe her primary biliary cirrhosis itself may have been the second hit that led to the clinical manifestation of her type III hyperlipidemia. Alternatively, it may have been the pharmacologic therapy of her severe pruritus that precipitated the hypertriglyceridemia.

At her six-month follow-up visit, a remarkable improvement in her lipid panel was noted. Her xanthomas resolved. Her total cholesterol level was measured at 208 mg/dL and triglyceride level was 119 mg/dL. Her HDL level was measurable at 80 mg/dL and her LDL was 104 mg/dL. An Apo B level was found to be normal at 66 mg/dL. She had gained some weight and had an overall better sense of well-being. Surprisingly, her biliary cirrhosis also improved spontaneously and she had normal bilirubin levels. Her alkaline phosphate level was still elevated but was lower at 381 IU/L. A coronary calcium scan showed a calcium score of 0. The patient has recently undergone a successful live donor liver transplant and we expect that both her lipoprotein X and type III hyperlipidemia also will resolve.

Discussion

Type III hyperlipidemia is a genetic disorder resulting in the accumulation of remnant particles stemming from a defective Apo E, resulting in an elevated cholesterol and triglyceride level.¹ The disease is caused by defective forms of Apo E that ineffectively bind to lipoprotein receptors, leading to accumulation of chylomicron and VLDL remnants. Normal apolipoprotein is E3/E3 and the most common mutation is E2. Interestingly,

Laboratory Test	Value	Reference Range
Cholesterol (mg/dL)	1795	0-199
Triglyceride (mg/dL)	780	<149
HDL (mg/dL)	10	>40

Table 2.

homozygotes with Apo E2/E2 do not always develop hypertriglyceridemia. This highlights the important role a “second hit” plays in the clinical manifestation of this disease. Common precipitants of hypertriglyceridemia include type 2 diabetes, hypothyroidism, renal failure, obesity, alcohol intake, and pregnancy. Many medications also are known to precipitate hypertriglyceridemia, including oral contraceptives, corticosteroids, tamoxifen, select antihypertensives, isotretinoin, bile acid binding resins, cyclophosphamide, antiretroviral regimens, and psychotropic medications.²

Our patient was on an oral contraceptive but had a previously normal lipid profile on this medication, so we do not believe it is the “second hit” that caused the clinical manifestation of her disease. To the best of our knowledge, the association between type III hyperlipidemia and primary biliary cirrhosis has never been described. The striking improvement of our patient’s lipid profile that correlated with the spontaneous improvement in her biliary cirrhosis has led us to suspect that her PBC was the factor that unmasked her type III hyperlipidemia. Severe hypertriglyceridemia has been described with systemic lupus erythematosus (SLE).³ Some speculate that systemic inflammation may lead to disordered lipolysis and hypertriglyceridemia in SLE.² Additionally, autoimmune hyperlipidemia has been described. We postulate that the same mechanism may have precipitated the hypertriglyceridemia in our patient. Alternatively, it may have been the combination of medications used to treat her pruritus that was the “second hit” that

unmasked her type III hyperlipidemia. Our patient was heterozygous for the Apo E mutation with an E2/E3 genotype. Although a high E2/E2 genotype prevalence has been reported in patients with clinical manifestations of type III hyperlipidemia, it has been shown in certain populations that E2/E3 is the prevalent genotype and that heterozygotes also manifest the disease.⁴ Additionally, the hypertriglyceridemic effect of a single E2 allele has been shown in a meta-analysis in which triglyceride levels were higher in Apo E2/E3 vs. Apo E3/E3.⁵

We also believe our patient had an element of lipoprotein X (Lp-X). Her degree of hypercholesterolemia was out of proportion to the elevation of her Apo B level (Apo B level of 267 mg/dL with a simultaneous total cholesterol level of 1,765 mg/dL). Unfortunately, we did not directly measure lipoprotein X levels in this patient. Lp-X is seen in patients with severe cholestasis and consists of an albumin core with Apo C on the surface. Unlike LDL, Lp-X does not contain Apo B and it is not removed by the LDL receptor (therefore, Apo B levels are usually in the normal range if Lipoprotein X is the primary abnormality). Statins are not effective in the treatment of this disease, so bile acid resins and plasmapheresis (not LDL-apheresis) are the cornerstones of therapy.⁶ We initiated bile acid resins in this patient but used very conservative dosing until her hypertriglyceridemia resolved. In contrast to type III hyperlipidemia, Lp-X is usually not associated with premature coronary disease and some believe it may even have anti-oxidant LDL activity. Our patient

had a negative coronary calcium score and it may have been the development of Lp-X that protected against the coronary atherosclerosis usually seen with elevated Apo B levels.

In summary, we presented an interesting case of type III hyperlipidemia unmasked by biliary cirrhosis with rather severe hypertriglyceridemia and hypercholesterolemia. This case illustrates the complexities in the diagnosis and management of dual lipid disorders and the importance of the identification of a “second hit” in type III hyperlipidemia. ■

Disclosure statement: Dr. Maturu has no disclosures to report. Dr. Forman has no disclosures to report. Dr. Falko has received consultant fees from Kowa Pharmaceuticals, AstraZeneca, and Merck and Co. He's received speaker honoraria from Kowa Pharmaceuticals, Merck and Co., and Aegerion. Dr. Falko was also on the advisory board for AstraZeneca.

References are listed on page 34.

Chapter Update:

Challenges and Opportunities in Increasing SWLA Membership



KARI UUSINARKAUS, MD, FAAFP, FNLA

Treasurer, Southwest Lipid Association
Assistant Professor, University of Colorado
Colorado Springs, CO

Diplomate, American Board of Clinical Lipidology



KRISHNASWAMI VIJAYARAGHAVAN, MD, FACC, FNLA

President, Southwest Lipid Association
Clinical Professor of Medicine, University of Arizona
Vice President, Scottsdale Cardiovascular Center
Scottsdale, AZ

Diplomate, American Board of Clinical Lipidology



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Greetings from the Southwest Lipid Association (SWLA)! Our geographic region extends from the gulf shores of Louisiana to the mountains of Colorado. It also includes vast open spaces in Texas, New Mexico, and Wyoming, along with the deserts of Arizona and the plains of Oklahoma. Because it is such a diverse region, it can be a challenge to address the needs of all clinicians involved in the field of lipidology. The educational and day-to-day practice needs of a dedicated full-time lipidologist practicing in Houston

or Denver are likely quite different from those of a PharmD working in collaboration with rural healthcare providers in New Mexico. Just as this can be a challenge to provide meaningful information and exchange, it also can be a strength. We have such vast geography and many types of patient interactions to draw experiences from. This also gives us the opportunity to educate one another.

People who join medical organizations always want to know, “What am I getting out of my membership?” When the mission or purpose aligns with their interests, they seem to be interested. How do we attract members from different fields related to lipidology in spite of the apathy and disinterest that is highly prevalent out there? Through understanding

people by strengthening our emotional intelligence, improving our leadership skills, and fostering productive teams, the organization will prosper. There is a strong need for understanding people and what will motivate them in various areas of their lives, from what items they purchase to why they donate their money and time to certain organizations. Everyone has a civic duty to participate in educating one another — the community as well as the healthcare professional. This is why having an understanding of what will strengthen motivation and participation in SWLA will help more than just that organization. Clearly, there are many benefits that are spelled out succinctly at **lipid.org**.

Since SWLA is large in actual territorial dimension, we would like to see a

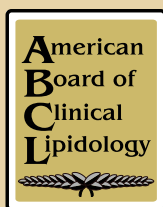
significant growth in our membership. This requires each provider to reach out and let colleagues know of the great organization that is SWLA/NLA. It takes dedication and effort on the part of the National Lipid Association staff and SWLA officers to put together quality meetings and publications and move the organization forward. If we all do a small part, the task can be easily achieved. I would encourage all members of SWLA to reach out to at least one colleague, friend, partner, or other potential member and show him or her the benefits of becoming a member of the NLA/SWLA. If we do this, we can ensure that we will continue to lead the field in the eradication of cardiovascular disease. ■

Disclosure statement: Dr. Ustinarkaus has received speaker honoraria from Vivus, Kowa Pharmaceuticals, Merck, GSK, Forest, Astra-Zeneca, and LipoScience. He's received research honoraria from GSK, Sanofi, SK Life Science, Regeneron Pharmaceuticals, Merck, Eli Lilly, Bristol-Myers Squibb, Orexigen, Gilead, and Pfizer. He's been on the advisory board for Kowa Pharmaceuticals, Aegerion, Janssen Pharmaceuticals, and Amgen. Dr. Vijayaraghavan has received consultant fees from Aegerion. He's received speaker honoraria from Aegerion, AstraZeneca, Medtronic, and Otsuka.

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March 30–May 16, 2015 (application deadline: March 27, 2015)



The ABCL is an independent physician-certifying organization offering the highest benchmark of professional competency in Clinical Lipidology. The program is open to licensed physicians in the US and Canada. Credentialing criteria and application are available at lipidboard.org.



The ACCL offers two unique pathways to certification and competency assessment in Clinical Lipidology for healthcare professionals. Credentialing criteria for both levels are available at lipidspecialist.org.

- **Clinical Lipid Specialist:** The CLS program is an advanced certification pathway open licensed physicians, pharmacists, nurses, nurse practitioners, physician assistants, registered dietitians, exercise physiologists/specialists, and other healthcare professionals who meet qualifying criteria.
- **Basic Competency in Clinical Lipidology Program:** The BCCL program offers a competency assessment and credentialing pathway for any healthcare professional or paraprofessional with an interest or involvement in the area of dyslipidemia.

Member Spotlight:

Thomas Haffey, DO, FACC, FACOI, FNLA



THOMAS HAFHEY, DO, FACC, FACOI, FNLA

President-elect, Southwest Chapter National Lipid Association
Clinical Professor, Western University/COMP
Denver, CO

Diplomate, American Board of Clinical Lipidology



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Dr. Thomas Haffey's passion for lipids shows in his dedication to the field. As a practicing cardiologist, he spends his days splitting time between seeing patients — a large part of which are dealing with lipid problems — and running research projects at North Suburban Medical Center. Out of office, he dedicates his time to the field of lipidology as well. Dr. Haffey currently sits on the Quality Assurance Committee of the American College of Cardiology, the Governor's ST-Elevation Myocardial Infarction (STEMI) Task Force in Colorado, and is president-elect of the Southwest Chapter of the National Lipid Association (NLA). He has also informally become the official photographer of the NLA. Having taken pictures at almost every meeting since 2006, he estimates to have around 14,000 pictures, which are extremely valuable to the association, members, and staff.

Dr. Haffey's commitment to the NLA and the field of lipidology comes from a personal place. Due to a family history of heart problems, Dr. Haffey made it a point to learn more about it. As the chief fellow in cardiology at William Beaumont Hospital — one of the busiest hospitals in the world — Dr. Haffey never had to order a lipid profile. At that time, there was no therapy and not enough information. Looking back, he's amazed when he realizes how far the field of lipidology has come.

In his "spare" time, Dr. Haffey travels the country giving lectures on heart failure, acute coronary syndrome, and hypertension. As a nationally recognized speaker, he found himself wondering what makes him stand out. In 2006, Dr. Haffey became a member of the first class for the American Board of Clinical Lipidology. After passing the NLA's first certifying exam, he became a Diplomate of Clinical Lipidology.

Dr. Haffey has also dedicated much of his time to Million Hearts, a program that sets

out to reduce heart attacks and strokes by 1 million over a five-year period. They hope to do so by educating the public and focusing clinical attention on the prevention of heart attack and stroke. The Million Hearts program partners with many non-profit organizations to help ensure progress toward that goal. Dr. Haffey believes there is a wonderful opportunity to partner further with Million Hearts and have them place more focus on lipids. His belief is that there is no such thing as a sudden heart attack. He thinks that they can be prevented, or at the very least, delayed. In order to do this, he says that the field has to migrate toward registries and large patient populations to answer questions that occur every day. He believes the current guidelines are somewhat handcuffed by their reliance on double-blind placebo controlled trials, but recognizes that the problem is not just national, but international as well.

From Maui to Milan

After listening to presentations at the NLA's 2014 Spring Clinical Lipid Update in Maui, Hawaii, Dr. Haffey became even more convinced that it is time to



The ceiling of Cesare Sirtori, MD's, palace in Milan.

the NLA could be that body.” As immediate past governor of the Colorado Chapter of the American College of Cardiology, Dr. Haffey has witnessed first-hand the tremendous international growth and

palace in Milan that contains gorgeous artwork, sculptures, and a ceiling Dr. Haffey compared to the Sistine Chapel.

Outside of work, Dr. Haffey is very family oriented and is extremely proud of their accomplishments. His wife, Marilyn, is a retired lieutenant colonel, black belt in taekwondo, and is a wonderful artist with a portrait hanging in the corporate headquarters of the American College of Cardiology. Dr. Haffey's daughter, Marie, works on a committee for helping people with disabilities in Colorado and his son, Thomas, Jr., holds a world record for building the largest penny pyramid in the world! The Haffey family is full of talent and bright minds. ■

go international. He has seen interest in Australia, East Asia, Egypt, and especially Europe. “There's a great interest in Europe,” he says, “and right now there is no overall body that influences or inspires people in the field of lipidology and I think

influence in recent years. On a trip to Milan with his wife, Dr. Haffey reached out to Cesare Sirtori, MD, a well-known identifier of apoA1 Milano, who he had previously connected with at the Maui meeting. Dr. Sirtori invited them to his

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Education and Meeting News and Notes

Abstracts Now Being Accepted for 2015 NLA Scientific Sessions

The National Lipid Association (NLA) is now accepting abstracts for the 2015 Scientific Sessions in Chicago, June 11–14, 2015. This is your opportunity to submit your science for inclusion in the NLA's 2015 Poster Hall. The Scientific Session provides abstract presenters and especially young investigators with many opportunities to present their science to attendees during the Abstract Session and in the poster hall. Submit your abstract by using the online abstract submission system. Accepted abstracts will be published in the 2015 Annual Scientific Sessions edition of the *Journal of Clinical Lipidology*. The deadline for submission is February 23, 2015 at 5:00 p.m. EST. **Visit lipid.org/abstracts to submit.**

Save the Date! NLA Spring Clinical Lipid Update in Denver

Save the date for the NLA Spring Clinical Lipid Update. The 2015 Spring CLU will take place in Denver Feb. 27–March 1, 2015 at the Grand Hyatt Denver. Reserve your room today by calling **888-421-1442** and ask for the NLA room rate. A special room rate starting at \$179 per night plus tax has been arranged. This group rate will be available until **Jan. 19, 2015**, or until the room block is filled. Please make your reservation early as we do anticipate the room block will sell out.

New Recommendations and Guidelines Tab Featured on Clinical Lipidology Resource Center

A new Recommendations and Guidelines tab was recently launched on the

Clinical Lipidology Resource Center to coincide with the launch of the NLA's Recommendations for Patient-Centered Management of Dyslipidemia. The new site features relevant articles and guidelines, slide presentations from NLA thought leaders, and audio and video interviews discussing important issues. To view this site, visit **nlaresourcecenter.lipidjournal.com/Home/Recommendations**.

New Complex Lipid Management Self-Assessment Program 16 Now Available

The Complex Lipid Management Self-Assessment Program 16: (CLM-SAP 16) Hypertriglyceridemia–Diagnosis, Pathophysiology, Clinical Significance, and Treatment is an online self-assessment program that will objectively validate and enhance your clinical knowledge of hypertriglyceridemia. Hypertriglyceridemia is associated with an increased risk of cardiovascular events and acute pancreatitis. The reduction in elevated levels of non-HDL-C, a marker of increased concentrations of circulating triglyceride-rich lipoproteins, is associated with reduced atherosclerotic cardiovascular risk. Similarly, a reduction in markedly elevated serum triglyceride levels decreases the risk of pancreatitis. This program will provide strategies to integrate evidence-based medicine into daily practice in order to appropriately assess, manage, and treat patients with hypertriglyceridemia.

Get real time feedback after each question, including a detailed critique and bibliographic references for further reading and receive a PDF copy of the program upon claiming CME/CE credit.

Complete via computer or from tablet app for iPad and Android devices. Check **lipid.org/education/clmsap/16** for more information.

Mentors Needed for Mentor/Mentee Program

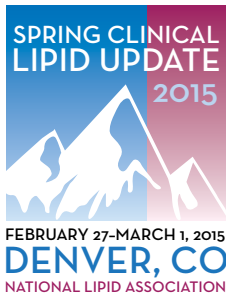
Become a mentor to an early career member today! Take time to complete an application on **lipid.org** listed under the “Education” tab and scroll down to the Mentor/Mentee Program. Your participation will benefit new and existing early career members and/or fellows-in-training.

Listen to ReachMD's Latest Podcasts Featuring NLA Members

Host Alan Brown, MD, joins several prominent members of the National Lipid Association during the latest recordings of the ReachMD podcasts. In the first, Dr. Brown interviews Kevin Maki, PhD, FNLA, CLS, to discuss the evidence for LDL and other non-HDL targets for primary and secondary prevention of heart disease from the standpoint of the NLA's Recommendations.

In the second, Dr. Brown is joined by Carl Orringer, MD, FNLA, Associate Professor of Medicine at the Cardiology Division, University of Miami Medical Center and Director of the Preventive Cardiovascular Medicine and LDL apheresis program to discuss the management of patients with triglycerides 200–499 mg/dl. To listen to these podcasts and many more, visit **lipid.org/communications/reachmd**.

NLA Events Calendar



2015 National Lipid Association Clinical Lipid Update—Spring

Hosted by the Pacific and Southwest Chapters
February 27–March 1, 2015
Grand Hyatt Denver
Denver, Colorado



2015 National Lipid Association Scientific Sessions

Hosted by the Midwest Lipid Association
June 11–14, 2015
Palmer House Hotel
Chicago, IL



2015 National Lipid Association Clinical Lipid Update—Fall

Hosted by the Northeast and Southeast Chapters
September 18–20, 2015
Omni William Penn Hotel
Pittsburgh, PA

Lipid Academy

February 26–27, 2015
Denver, CO
June 10–11, 2015
Chicago, IL
September 17–18, 2015
Pittsburgh, PA



Masters in Lipidology

February 26–27, 2015
Denver, CO
June 10–11, 2015
Chicago, IL
September 17–18, 2015
Pittsburgh, PA



Latest Happenings

Annual Dues

Check your mail in November for the 2015 dues statements.

Lipid Insights

Latest virtual program available on demand at lipid.org/node/1303. Check your email for information on upcoming programs.

CLM-SAP 16

Free CME activity on Triglycerides launched in early October 2014. More information on page 20.

Abstracts

The submission deadline for the 2015 Annual Scientific Sessions Abstracts is Feb. 23, 2015 at 5:00 pm EST.

Lipidology Resource Center

New NLA Recommendations Tab now available. Look for updates to the Triglyceride Tab soon! To view these additions, visit nlaresourcecenter.lipidjournal.com.

ABCL and ACCL

Spring 2015 Testing Window: March 30–May 16, 2015
Summer 2015 Testing Window: June 29–August 15, 2015
Fall 2015 Testing Window: October 5–November 21, 2015
More certification information on page 27.

Foundation Update



ANNE C. GOLDBERG, MD, FNLA

President, Foundation of the National Lipid Association
Associate Professor of Medicine
Washington University School of Medicine
St. Louis, MO

Diplomate, American Board of Clinical Lipidology



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The Foundation of the National Lipid Association (FNLA) has been hard at work in the past few months, and we have many new initiatives and accomplishments to show for it.

Most recently, the FNLA helped launch an awareness campaign centered on elevated triglycerides and the role they play in a patient's life. The "What's Your Number?" campaign kicked off in conjunction with September's National Cholesterol Education Month, and encouraged patient education and discussion about lipid management and the resulting consequences of high cholesterol and triglycerides. The Foundation's initiatives for this campaign have included media interviews, the launch of a patient resource page on LearnYourLipids.org, and the creation of a patient tool that was mailed to NLA members in this LipidSpin for display in their office. In addition, you can view our "What's Your Number?" infographic on page 35.

To coincide with this campaign launch, the FNLA recently acquired a Cholestech machine, which will facilitate future efforts to conduct cholesterol screenings at patient events. The first screening was done Sept. 20 at the Yankee FanFest in the Health and Wellness Village. Volunteers from the Northeast Chapter of the NLA manned the booth and educated attendees about the importance of cholesterol and providing appropriate screenings.

The event was a tremendous success, and the Foundation looks forward to being able to participate in more patient events around the country to provide screenings and feedback on managing cholesterol. In addition, the Foundation will be sponsoring a special abstract award at the 2015 NLA Annual Scientific Sessions in Chicago from June 11–14, 2015. In honor of Donald Hunninghake, MD, a pioneer in lipid research, the Foundation is offering The Foundation of the National Lipid Association Donald Hunninghake Familial Hypercholesterolemia Abstract Award for the best submitted abstract specifically in the area of familial hypercholesterolemia (FH) research.

The Foundation has had a significant focus



Kenneth A. Kellick, PharmD, FNLA, gives a cholesterol screening test at Yankee Radio Network FanFest September 20, 2015.

geared toward patient awareness and education concerning disorders such as FH, and this award has been created in order to continue that focus and to further encourage clinicians in their research and study of such disorders. The winner will be determined by the Foundation of the NLA Board of Directors once the abstract committee has approved the abstracts in this category. The award will be presented to the winner at the Honors and Awards Ceremony at the NLA 2015 Annual Scientific Sessions. Please check lipid.org/abstracts for more information on submitting an abstract in this category for consideration of this award. ■

Letter from the LipidSpin Editors

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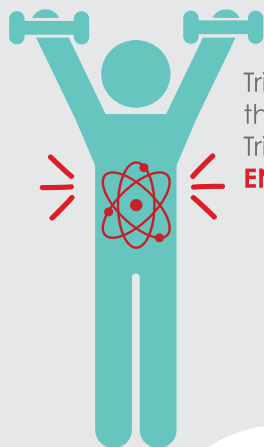
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Case Study

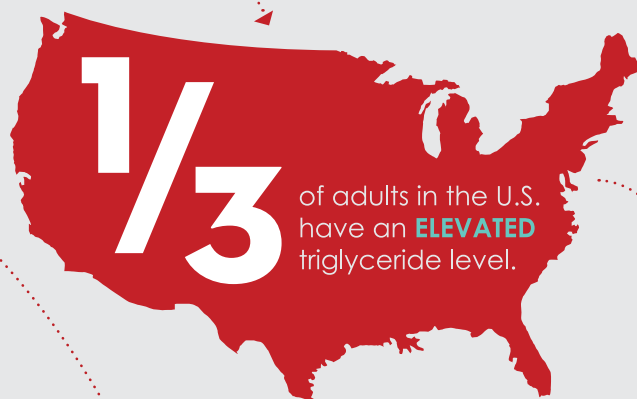
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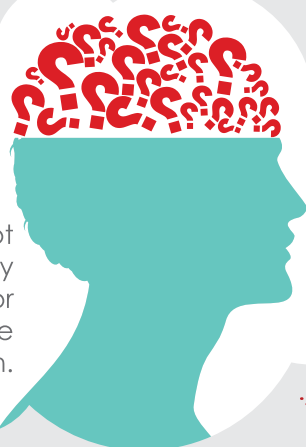
WHAT'S YOUR NUMBER?



Triglycerides are a form of **FAT** that circulates in your blood. Triglycerides are used as an **ENERGY SOURCE** by your body.



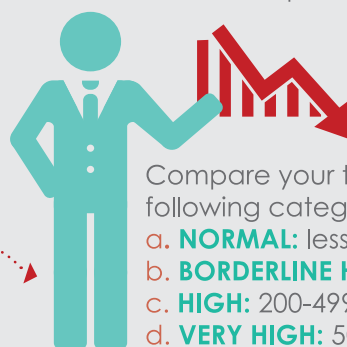
Patients may not recognize any **SYMPTOMS** or be aware of the condition.



Although your body needs some triglycerides, **TOO MUCH** may lead to heart disease, stroke or severe abdominal pain due to **IRRITATION** of the pancreas.



Your clinician will check your triglyceride level with a simple **BLOOD TEST**, usually as part of a full lipid profile test that will report your Total Cholesterol, LDL cholesterol and HDL cholesterol.



Compare your triglyceride level to the following categories:

- a. **NORMAL:** less than 150 mg/dL
- b. **BORDERLINE HIGH:** 150-199 mg/dL
- c. **HIGH:** 200-499 mg/dL
- d. **VERY HIGH:** 500 mg/dL or more

Speak to your health care provider about the results of your entire lipid profile, including your triglyceride level. If your patients' triglyceride level is 150 mg/dL or above, you need to engage in a more comprehensive discussion about triglycerides with them.

KNOW YOUR CHOLESTEROL

Reduce Your Risk of Heart Attack and Stroke

STEP 1



Learn about your risk of heart attack and stroke.



Ask yourself ...

Are you overweight?
Do you exercise?
Do you eat healthy?
Do you smoke?



Do you have high blood pressure?

Do you have diabetes?



Has anyone in your family had a heart attack or a stroke?

STEP 2



Talk to your healthcare provider.



Ask about your risk for heart disease and stroke.



Get your cholesterol checked.



Know your cholesterol goal.

STEP 3



Once you know your goal, take action!



Follow the diet you and your provider agreed to.

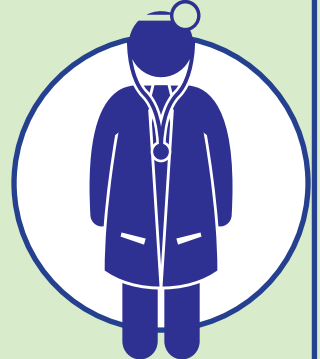


Keep a daily journal of what you eat and how many minutes you exercise.



Follow your provider's advice—if you are on medicine, take it.

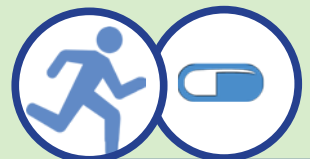
STEP 4



Follow up with your provider to see if you're meeting your goals.



Get your cholesterol checked again.



If you eat healthy, exercise more and take your cholesterol medicine, you are less likely to have a heart attack or stroke.



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Published October 2014

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FOR YOUR PATIENTS

Triglycerides—What's Your Number?



What are triglycerides?

- Triglycerides are a form of fat that circulates in your blood. Triglycerides are used as an energy source by your body.
- After eating, any calories that are not used immediately get stored as triglycerides inside fat cells.
- Although your body needs some triglycerides, too much may lead to heart disease, stroke, or pancreatitis.

Causes of elevated triglycerides:

- Diet high in fat, certain carbohydrates, or sugar
- Too much alcohol
- Not enough exercise
- Being overweight
- Certain medical conditions (e.g. high blood sugar)
- Certain medications
- Heredity

Triglyceride levels:

- Your clinician will check your triglyceride level with the same blood test used to measure cholesterol.
- Recent food intake can increase triglycerides, so it is important to fast for 8-12 hours before your blood test. You may drink water or coffee (with nothing in it) during the time you are fasting
- Compare your triglyceride level to the following categories:
 - Normal: less than 150 mg/dL
 - Borderline High: 150-199 mg/dL
 - High: 200-499 mg/dL
 - Very High: 500 mg/dL or more
- If your triglycerides are 500 mg/dL or more, you are at risk for pancreatitis. Pancreatitis can cause many other health problems and may be life-threatening. If your triglycerides are very high, your clinician will talk to you about making aggressive lifestyle changes and possibly taking medication to lower your triglycerides.

Ways to lower triglycerides:

• Diet

- **Cut back on fat.** Eliminate the trans fats and decrease the amount of saturated fats that you eat. Eat less processed foods, fast food, fried foods, beef, pork, whole milk, and ice cream.
- **Increase fiber intake.** Fiber makes you feel full longer, so you may eat less. Most green, yellow, and orange vegetables; brown rice; whole grains, like oatmeal, are high in fiber.
- **Eat healthier calories.** Only eat small portions of "starchy" foods (ex. pasta, rice, potatoes, corn, peas). Eat more vegetables than fruit. Limit fruit and fruit juice; these have natural sugar. Decrease sweets.
- **Increase omega-3 intake.** Certain fish, like salmon and tuna, have good amounts of omega-3.
- **Read nutrition labels.** This can help you determine the right portion size and keep track of your daily intake of calories, fats, and sugars.
- **Drink alcohol only in moderation.** Men should have no more than 2 drinks per day and women no more than 1 drink per day.



• Exercise

- **Exercise at least 30 minutes, 5 times a week.** People with diabetes should exercise at least every other day. This can be done with many fun activities such as walking your dog, biking, playing a sport, going to the gym, swimming, dancing, or even taking the stairs at work.

• Weight loss

- Lose weight by eating a healthy diet and doing regular exercise. Losing 5-10% of your body weight can lower triglycerides about 20%. Do not take supplements to lose weight unless your clinician tells you it is safe to do it.

• Medications

- In addition to healthy lifestyle changes, your clinician may recommend that you take prescription medication and/or fish oil supplements to lower your triglyceride levels.
- For best results, it is important to take your medication as prescribed. Talk to your clinician, if you have any questions or concerns about your medications.

• Diabetes

- If your blood sugar is high, your triglycerides may also be high. Take your diabetes medication as prescribed. Test your blood sugar as recommended. Stay on schedule for your follow-up appointments for diabetes.

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Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 011; 123: 2292-2333.

This information is intended for providers and patients.

Health Care Providers—access this tear sheet at www.learnyourlipids.com





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NATIONAL LIPID ASSOCIATION SCIENTIFIC SESSIONS

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New in 2015!

In honor of Donald Hunninghake, MD, a pioneer in lipid research, the Foundation of the NLA is offering **The Foundation of the National Lipid Association Hunninghake FH Abstract Award** for the best submitted abstract in the area of familial hypercholesterolemia (FH) research. The winner will be determined by the Foundation of the NLA Board of Directors and a monetary award will be presented at the Honors and Awards Ceremony at the NLA's 2015 Annual Scientific Sessions. Please visit www.lipid.org/abstracts for more information.