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*Indicates ABCL Diplomate status
From the NLA President:
Engaging Our Communities

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Thank you for the honor of being able to serve as your next President of the NLA. The 2013–2014 program year will be an exciting time, and I look forward to working with our Board of Directors in the continued growth of our organization to meet the educational and scientific needs of you and your patients. I especially would like to thank my predecessor, Peter Toth, MD, PhD, who just stepped down as NLA President, for his tremendous dedication and service to the association. We hope to build on the previous administration’s momentum, including continuing the NLA’s efforts to raise awareness of Familial Hypercholesterolemia (FH) and making it a major focus in clinical and patient circles.

Our 2013 Annual Scientific Sessions took place in Las Vegas this past May, and I would like to recognize the meeting’s sponsor chapter, the Pacific Lipid Association, and its leadership for making the meeting such an incredible success. Specifically, humble thanks and appreciation are due to my co-chairs for the meeting, Dr. Toth along with J. Antonio G. López, MD, and B. Alan Bottenberg, DO.

We are developing several initiatives that I hope you will find of interest. In particular, we plan to make FH a major focus of the 2014 Annual Scientific Sessions, which will be held May 1-4 in Orlando. We also are partnering with the AHA to develop a scientific statement on pediatric FH, which will be led by NLA member Sam Gidding, MD. In addition, collaborations are underway with the FH Foundation, which will host the FH Summit: Awareness to Action, on September 19 in Annapolis. This Summit will bring together various FH stakeholders to emphasize cooperation and best practices. This Fall we will convene a statin safety expert panel to be chaired by Terry Jacobson, MD. We recently received funding from Merck & Co. to study how electronic medical records can be used to improve LDL-C goal attainment. This project will be chaired by Jerome Cohen, MD, and me. We hope that these continued efforts will reduce the devastating effects of FH.

The NLA’s first meeting in 2014, the Spring Clinical Lipid Update, will take place in Maui, where we will have new opportunities to collaborate with clinicians and organizations in the Pacific Rim and beyond. The Spring CLU planning committee for the host chapters, the Pacific Lipid Association and the Southwest Lipid Association, has already met extensively, and we look forward to relaying details about this exciting program.

Please stay posted for more information about upcoming NLA initiatives in my next Lipid Spin message. Once again, I would like to thank you for this opportunity to serve as your NLA President.
Each of us should strive “to rise above the routines of the daily ward round and to see in every patient an opportunity not only to serve mankind in the best tradition of medical excellence, but to add to the store of medical knowledge.”

—A. McGehee Harvey (1973)

Welcome to this issue of the Lipid Spin! This publication serves a wonderful adjunct to the Journal of Clinical Lipidology in bringing science to the forefront for practical application.

The emphasis in this issue is focused on physical examination. Many have dubbed physical examination a lost art, touting that technology is more convenient and conclusive. However, it should indeed remain on the forefront of each interaction with our patients. This, along with focused inquiry into their medical, family and social history, offers suggestions as to where we should proceed with our investigation and perhaps which technology we should use. Just like a good mystery, we put pieces of a puzzle together to obtain a more complete picture. The term clinical investigator is used predominantly in a research setting, but I find it applicable to health care providers as a whole. What did I want to be when I grew up? You guessed it, a private investigator. I bridged this concept to nursing and medicine and I never have a dull day. I learn something new every day from both patients and colleagues and hope to never lose that benefit of working in cardiology. Lipids are a fascinating piece of this puzzle with still so much to learn. We can and should approach every patient as an opportunity to learn.

As the physical exam offers insight upon where to direct our next step in the investigation, we often utilize other technical modalities beyond our eyes, ears, and hands. We are lucky enough in this day and age to have access to advanced technology to confirm our suspicions. Included in this issue of the Lipid Spin are physical findings that warrant further evaluation. Especially in children and adolescents, these findings can be the clue that leads to an important potentially life-threatening diagnosis.

The applicability of physical examination extends to the population of the world in all ethnicities. Where we become disparate is among dietary patterns, lifestyle and activity levels, responses to medications, and epidemiological trends. This is an important area to acknowledge and understand and we can certainly learn from our colleagues from around the globe. Our Spring Clinical Lipid Update 2014, co-hosted by the Southwest Lipid Association and the Pacific Lipid Association, will serve that capacity. We will learn from international leaders as we dive into international themes and evolutionary topics to include 4000-year-old mummies. Not to worry, we have left enough time to enjoy the island! Save the date for breathtaking Maui in March 2014.

Hope to see you in the Aloha state and enjoy this issue of the Lipid Spin!  ■
Letter From the *Lipid Spin* Editors:
Where Have All the Exams Gone?

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In this issue of *Lipid Spin*, several articles and a tear sheet focus on the importance of the physical exam in the evaluation of the patient with lipid disorders. While the physical examination remains the cornerstone of patient evaluation and ongoing treatment, all too often those of us in a teaching role find this a rapidly disappearing art.

In our lipid clinic, medical housestaff evaluate the patients prior to presenting them to our group for discussion. We then return to see the patient. As a busy referral clinic for patients with lipid disorders, many of these patients exhibit physical findings on examination consistent with either inherited disorders of lipid metabolism or secondary disease states that can cause lipid disorders.

What remains most disturbing to me, is that as an educator, all too often these cases are presented to me without any regard to relevant physical diagnoses. Patients with history and lab results consistent with familial hypercholesterolemia have not had eye exams, skin exams or tendon exams. Patients with possible Type 3 dysbetalipoproteinemia have not had palm or extremity exams, and no investigations have been postulated for physical findings of secondary disease states.

Our trainees are some of the best in the country. They are smart, informed and work hard. I suspect the deficiency is not a lack of interest in the physical exam but rather a dearth of knowledge in Clinical Lipidology. When we return to the patient and highlight obvious exam findings, the excitement and interest is obvious. This moment is what we need to capture as leaders in the field of lipidology.

The future of lipidology is germinating in our trainees. We must foster that interest, feed it, nurture it and grow it. If not, there will be no future leaders. Our trainees, fellows, residents and students are the next generation of lipidologists. Generating interest, with bedside teaching, didactic and interactive learning processes are key to the growth of our field. In the words of Sir William Osler, MD—“Listen to the patient, he (or she) is telling you the diagnosis.”
Chances are that each of us has and takes care of patients from Southeast Asia. This ethnic group is growing significantly in the United States. According to 2010 census data, while the U.S. population grew almost 9.7% between 2000 and 2010, the Asian population alone increased by more than four times that rate—by 43% in that 10-year period. By definition, “Asian” refers to a person having origins in any of the original peoples of the Far East, Southeast Asia or the Indian subcontinent, including Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine islands, Thailand and Vietnam.

Mr. P., 44, presented to his primary care physician’s office in September 2010 for a physical exam. His parents emigrated from India to the United States. His family history reveals a history of early cardiovascular disease in the family. He admits to smoking for several years when he was in his 20s but not currently. The only medication or over-the-counter supplement that he takes on a regular basis is krill oil—a friend told him it was good for his heart and overall health. He also admits to an occasional glass of wine. His job involves sitting at a desk the majority of the time, and he admits to very little activity or exercise. His vital signs reveal a height of 68 inches and a weight of 162 lbs. His BMI is 24. His waist circumference is 36 inches. His BP is 120/76. The rest of his vital signs are within normal ranges for age and sex.

An exam is performed and unremarkable, other than some slight abdominal or midsection fat (Figure 1). Labs reveal: Fasting total cholesterol, 199; triglycerides, 435; HDL-C, 33; non-HDL-C, 166; TSH, 1.8; and glucose, 109. LDL-C was not done secondary to elevated triglyceride levels. A quick calculation of his risk factors showed the presence of both family history and low HDL-C. At this visit he was given extensive counseling regarding diet, exercise and weight loss. He also was advised to follow up in three to six months for repeat assessment and laboratory testing.
Mr. P returns for follow-up in 2012—2 years later—and says he has been working on diet and exercise. He is more physically active now than his previous visit, trying to get out and walk at least twice weekly. In the interim since his last visit, he went to India to visit family. While there, he had lab work performed. He brings in a copy of his lab report for his provider to review. Total cholesterol, 159; HDL-cholesterol, 39; triglycerides, 198; LDL-cholesterol, 89. He is very pleased by these results. He says his “bad cholesterol” is less than 100, which is “at goal.” His physician, having attended National Lipid Association meetings, knows he likely is harboring residual risk that is not apparent through standard lipid profiles and, therefore, orders additional laboratory testing, including an advanced lipid profile: total cholesterol, 189; LDL-cholesterol, 86; HDL-cholesterol, 35; non-HDL-cholesterol, 154; LDL-particle number, 1879; apoB, 108; glucose, 139; and Hg A1c, 7.2. He is now overtly diabetic, based on his Hg A1c and glucose levels. In addition, he now has multiple risk factors—age, an early family history of cardiovascular disease, diabetes mellitus (considered a coronary heart disease risk equivalent) and low HDL-cholesterol. Both his apoB and LDL-p values indicate a discordantly high level of risk as compared to his LDL cholesterol.

This case is illustrative of commonly seen metabolic patterns in patients of Southeast Asian ancestry—significant percentages have high triglycerides and low HDL-cholesterol. In addition, the standard waist circumference charts that we use as one of the criteria to help define metabolic syndrome in the U.S. populations is different in people of Southeast Asian ancestry—this according to the International Diabetes Federation. Their position advocates that different cut points should be used to define central obesity in this population (Table 1). What most clinicians in the United States use are the National Cholesterol Education Project (NCEP)/Adult Treatment Panel III criteria of 102 cm (40 inches) in men and 88 cm (35 inches) in women. It has been proposed that, in Southeast Asian patients, cut points of 90 cm (35 inches) for men and 80 cm (31.5 inches) for women be used to define central obesity—see Figure 1. Even more stringent guidelines have been proposed in Japanese men.

In Indians, specifically, mortality rates secondary to CVD have increased while decreasing in western countries. In addition, this population also has a higher prevalence of premature coronary artery disease. A number of studies indicate that traditional risk factors do not explain fully the associated increased risk in Asian Indians. Rates of hypertension are lower in Indians when compared to whites. In addition, total cholesterol and LDL-cholesterol are lower among Indians than whites. Data suggest that only 9% of Indians had HDL-cholesterol >50 mg/dL compared to more than 70% of black and white patients. In addition, triglyceride levels tend to be much higher in Indians than in either blacks or whites. It is thought that this so called “atherogenic dyslipidemia” is responsible for the increased risk of cardiovascular disease present in Indians not truly captured by traditional risk factors of elevated total cholesterol and LDL-cholesterol that pertain to either white or black populations. A recent study demonstrated that, among blacks and whites, a TG: HDL-C ratio >3 was associated with a substantially higher proportion of people with a BMI >25. In Indians, BMI was only modestly associated with a TG: HDL-C ratio >3. In the literature, TG: HDL-C ratios of >3 have been demonstrated to signify a higher likelihood of insulin resistance or presence of the metabolic syndrome. So, even slightly increased amounts of central obesity can be associated with insulin resistance and its subsequent problems in the Southeast Asian population.
The reason(s) for racial differences in lipids and lipoproteins in Asian Indians is not clearly elucidated. It has been postulated that a diet high in carbohydrates and low in polyunsaturated fatty acid may contribute to high triglyceride levels, along with the tendency for Southeast Asians to be less physically active than other populations. Genetics likely also play a factor—the hepatic lipase gene has been hypothesized as a possible factor.

When Mr. P first presented to the practitioner, he had two traditional NCEP/ATP III criteria: 1) an early family history of cardiovascular disease and, 2) low HDL-cholesterol. Since he had two risk factors, Framingham risk scoring was done. Calculating this score gave Mr. P a score of 5, which translated to a 10-year calculated risk of 2%. Based on that score, it would not be recommended that he have any pharmacologic treatment; instead, he would have only lifestyle counseling because he fell into a “low risk” group for future cardiovascular events, at least over the next 10 years. We believe, based on his initial elevated non-HDL-cholesterol and then clearly demonstrated later by his advanced lipoprotein testing, that he had a tremendous amount of future cardiovascular risk ahead of him and deserved aggressive treatment.

In summary, there are a number of issues to keep in mind when evaluating patients from India, specifically, or Southeast Asia in general. When you see these patients in your office, keep in mind that lower cutoffs of waist circumference need to be used to define the metabolic syndrome. These cutoffs are $\geq 90$ cm (35.4 inches) for men and $\geq 80$ cm (31.5 inches) for women in this population. If present, at least consider the possibility of insulin resistance and its commonly associated dyslipidemia patterns.

Another point to consider is that, in patients from Southeast Asia, total cholesterol and LDL cholesterol may not be the best “first glance” indicators of risk in these patients. As Mr. P demonstrated, his risk was substantial but not really.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europids*</td>
<td>$\geq 94$ cm</td>
<td>$\geq 80$ cm</td>
</tr>
<tr>
<td>South Asians</td>
<td>$\geq 90$ cm</td>
<td>$\geq 80$ cm</td>
</tr>
<tr>
<td>Chinese</td>
<td>$\geq 90$ cm</td>
<td>$\geq 80$ cm</td>
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<tr>
<td>Japanese</td>
<td>$\geq 85$ cm</td>
<td>$\geq 90$ cm</td>
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<tr>
<td>Ethnic south and central Americans</td>
<td>Use south Asian recommendations until more specific data are available</td>
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<tr>
<td>Sub-Saharan Africans</td>
<td>Use European data until more specific data are available</td>
<td></td>
</tr>
<tr>
<td>Eastern Mediterranean and middle east (Arab) population</td>
<td>Use European data until more specific data are available</td>
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Data are pragmatic cut-offs and better data are required to link them to risk. Ethnicity should be basis for classification, not country of residence. *In USA, Adult Treatment Panel III values (102 cm male, 88 cm female) are likely to continue to be used for clinical purposes. In future epidemiological studies of populations of Europid origin (white people of European origin regardless of where they live in the world), prevalence should be given, with both European and North American cut-offs to allow better comparisons.

Table 1.

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

It is important to emphasize the benefits of regular exercise, which has been shown to improve triglyceride and HDL cholesterol levels, along with a host of benefits on other parameters of wellbeing and health. The American Heart Association recommendation is for patients to strive for 150 minutes (two and half hours) a week of moderate activity—divided in any way that is attainable by patients.

In addition, don’t forget to review the patient’s diet and see where beneficial changes can be made in regards to less carbohydrates and adding lean sources of proteins and good fats. The use of a dietitian can be a useful resource when taking into consideration cultural and ethnic considerations in this arena.

Finally, remember to review all cardiovascular risk factors and modify them if possible. Encourage smoking cessation, treat hypertension to goal and remind patients that even small changes in dietary or lifestyle habits can have beneficial effects on their cholesterol.

Disclosure statement: Dr. Selagamsetty has no disclosures to report. Dr. Uusinarkaus has served on the speakers’ bureaus for Merck & Co., GlaxoSmithKline, Forest Laboratories, AstraZeneca, Kowa Pharmaceuticals America, Amarin Corp., and Vivus Pharmaceuticals. Dr. Uusinarkaus has served on the advisory board for Aegerion Pharmaceuticals.

References are listed on page 30.
This issue of Lipid Spin has a theme of physical findings. One of my colleagues e-mailed me and said I was such an evidence-based guy that he applauded me for choosing a topic that was not evidence based.

While I understand where he was coming from, I submit that nothing could be farther from the truth. Tools for evidence-based practice include history and physical findings from the get-go. This is because those are our best tools for determining how to arrive at a diagnosis.

We can’t treat properly without a diagnosis, nor can we even arrive at a prognosis until we understand the diagnosis. We can’t unleash how to use the best evidence available to integrate patient values and our clinical judgment for optimum choice until we arrive at a diagnosis.

Each of the findings discussed in this issue is helpful, yet not necessarily specific. Other important concepts come into play before we can treat, monitor and look for harm.

A review of some important evidence-based medicine tools useful for diagnosis is in order.

A diagnostic test is ordinarily understood to mean a test performed in a laboratory or an imaging study. However, the principles in this article apply equally well to clinical information obtained from history, physical exam, lab tests and/or imaging procedures.

They also apply when a constellation of findings serves as a diagnostic test. Clinical measurements, including data from diagnostic tests, are expressed as nominal, ordinal or interval scales. Regardless of the data produced, as clinician we reduce the data to a simpler form to make it useful in practice. Most ordinal scales are an example. Murmurs can vary from loud to inaudible, but a simple ordinal scale with grades I through IV serves well. We do this when test results are used for therapy. We either treat or we don’t. Blood pressure is an example. It is measured on an interval scale, yet we decide to treat based on a particular level, such as 140/90. So here we transform the interval data into dichotomous data. Or we turn it into ordinal data and break it down intoprehypertension, or Stage 1 or Stage 2 hypertension.

The diagnostic process is imperfect. We deal with probability. We use “rule out” or “possible,” etc. Increasingly, we use the likelihood that there is a disease as a probability.

A test’s accuracy is considered in relation to a gold standard. That standard could be easy, such as a culture, or it could be invasive, such as a liver biopsy or an autopsy. For some diseases diagnosed at follow-up suffices. Screening for many CVD conditions falls into this type. Because it is costly to obtain hard outcomes and it takes feasibility and time, we are always looking for surrogates, with the understanding that some misclassification is inevitable.
justify risk by pointing out issues of safety and convenience, but simpler tests are useful only when risks of misclassification are known and are acceptably low. To figure this out, we need to know how many are truly positive or negative, as well as how many are falsely so. Most information about these tests is from clinical information, not research, and data on the number of true vs. false negatives often tend to be much less complete than data about positive results.

Always look to see if the test is applied to those thought not to have the condition of interest, as well. How many magnetic resonance imaging (MRI) studies are done this way? For some conditions, there is no gold standard. What about angina? Sometimes we must compare to an imperfect gold standard. Maybe there was an improper gold standard. It may have been because an inadequate spectrum of patients was evaluated. There may have been bias in judgment of the test performance. It could have been because of statistical uncertainty related to small numbers.

The sensitivity and specificity of a test should be established independently of the means by which the diagnosis was established. When the sensitivity and specificity of a test is assessed, the test result should not be a part of the information used to establish the diagnosis. We can use this to our advantage. Many imaging studies are subjective. It is easy to be influenced by the clinical information being over-read or under-read. Both to minimize and take advantage of these biases, some radiologist prefer to read twice, before and after the clinical information that we provide.

We always need to take into consideration our clinical settings. Referral to a teaching hospital, ward or clinic, or emergency room increases the chance of significant disease as a cause of complaints. Relatively more tests and aggressive use of diagnostic tests may be more justified. In primary care practice, however, the chance of finding disease is considerably smaller and tests should be used more sparingly.

Published descriptions of diagnostic tests often include a predictive value or conclusion about the interpretation of a positive or negative test. This is helpful of several tests together. Our history and physicals can be considered as one of several tools. Not infrequently a new test is described in glowing terms, only to be found wanting with wider experience. This can even suggest dishonesty or unfair skepticism. Most often it is related to limitations in methods for which the test was established in the first place. Maybe there was an improper gold standard. It may have been because an inadequate spectrum of patients was evaluated. There may have been bias in judgment of the test performance. It could have been because of statistical uncertainty related to small numbers.

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Published descriptions of diagnostic tests often include a predictive value or conclusion about the interpretation of a positive or negative test. This is helpful
as long as we understand the limitations. Data from large teaching hospitals where prevalence of disease is high can be misleading. Even worse, some authors compare performance of a test in an equal number of patients with and without the disease. While this is an efficient way to describe sensitivity and specificity, any reported positive predictive value means little, because the authors artificially set the prevalence at 50%.

We can use multiple tests in parallel. Generally, this increases sensitivity and the negative predictive value for a given disease prevalence above an individual test. Usually, specificity and positive predictive value are lower than for one test. This is useful when we need very sensitive testing but have available only two or more relatively insensitive tests that measure different clinical phenomena. The price, though, is further evaluation of some patients without disease. For some medical conditions, physical findings and lab results can be great tools, and combinations are called clinical prediction rules or diagnostic decision rules. Sensitivity, specificity and likelihood ratios then can be calculated for these rules.

Likelihood ratios are an alternative way of describing performance of diagnostic tests. They can be used to summarize probability of disease after a positive or negative test. An advantage is that they can be used at multiple test levels. Serial likelihood ratios can also be utilized.

Hx & PE pre-test probability
TEST 1 Pre-test odds x LR = Post-test odds
Test 2 Pre-test odds x LR2 = Post-test odds
Test 3 Pre-test odds x LR3 = Post-test odds
POST-TEST PROBABILITY

****The premise of independence underlies the use of multiple tests, though it seems very unlikely that tests for most diseases are independent of one another. This also depends on how reproducible and accurate the test itself is, and/or how many observers were used, and what their intra- and inter-observer agreement really is. Bottom line: It takes clinical skill, all started by your knowledge and use of history and physical findings.

So think of physical findings as diagnostic tests.

For further elaboration of these concepts, readers may want to review The Evidence Base of Clinical Diagnosis, edited by J. Andre’ Knottnerus. ■

Disclosure statement: Dr. Wild has received honoraria from the National Institutes of Health and the U.S. FDA.

References are listed on page 30.
Lipid Luminations: Translating Physical Studies of Lipoproteins into Clinical Lipidology

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Physical chemistry is, in part, the study of macroscopic and particulate phenomena in terms of laws and concepts of physics, and it can include the physical concepts determining motion, energy, force, time, thermodynamics, light and equilibrium. Physical chemistry, in contrast to chemical physics, is a macroscopic science, because its concepts are relevant to bulk scales rather than molecular and/or atomic scales. Physical methods are applicable to studies of lipids and lipoproteins, with major areas of application including reaction kinetics, surface chemistry of lipoproteins and membranes, equilibria and thermodynamics, thermotropic phase transitions, and colligative properties.

The methods of physical chemistry have informed our understanding of lipoprotein structure, apolipoprotein conformation, the dynamics of lipid exchange and transfer, and the configuration of lipids and proteins on lipoprotein surfaces. Moreover, the tools of physical chemistry have influenced the development of diagnostics for clinical lipidologists, and they have helped uncover the mechanistic relationships between lipoproteins, diabetes and atherogenesis for the academic lipidologist. Nearly every physical method has been applied to the study of lipoproteins, and those that have had the greatest impact on the field of lipoprotein pathobiology are reviewed here.

The Ultracentrifuge: The ultracentrifuge played a central role in clinical lipidology. According to their names, high-, low- and very-low-density lipoproteins (HDL, LDL and VLDL, respectively) have different densities and can be analyzed on the basis of density. W. Virgil Brown has called John W. Gofman the father of modern Clinical Lipidology. In a landmark 10-year study, Gofman and colleagues showed that men who developed ischemic heart disease had lower HDL₂ and HDL₃, combined with higher levels of LDL, intermediate-density lipoprotein (IDL) and small VLDL.¹ A 29-year follow-up to this study² showed that total incident coronary heart disease (CHD) was inversely related to HDL₂-
HDL₂ mass and directly related to LDL-mass, IDL-mass and small and large VLDL-mass concentrations.

Other technologies have been based on differential lipoprotein densities. The vertical spin method has been used to profile lipoproteins in a way that identifies various dyslipidemic states. Furthermore, recognizing that lipoproteins could be distinguished on the basis of differing sizes and densities, others developed preparative ultracentrifugation for large-scale isolation of individual lipoprotein classes. This key technology was essential to defining the composition and properties of lipoproteins and their interactions with plasma lipid-transfer, lipolytic and acyltransferase proteins, as well as cell surface receptors and lipid transporters in the context of normal and pathological states.

Electrophoresis: Early studies showed that plasma proteins could be separated on the basis of charge by electrophoretic methods. With the discovery that albumin-bound buffers improved resolution, paper electrophoresis emerged as a key tool for phenotyping hyperlipoproteinemia. According to their mobilities with respect to α and β globulins, HDL, LDL and VLDL were respectively α-, β- and pre-β-lipoproteins. Gradient gel electrophoresis under non-denaturing conditions, which separates according to size, is another tool that identified small, dense LDL as a CVD risk factor, and subdivided HDL into two HDL₂ and three HDL₃ subfractions.

Circular Dichroic (CD) Spectroscopy: CD spectroscopy reveals the chirality of molecules by measuring the difference in the absorption of left- and right-circularly polarized light. An algorithm based on the CD spectra of a polypeptide containing a known α-helical content permitted laboratory lipidologists to conclude that HDL contained mainly α-helical structures, whereas LDL comprised mostly β-sheet structures. Subsequently, the extant theory of lipid-associated amphipathic helical apolipoproteins was based on model-building and the α-helical content of just a few apolipoproteins revealed by their CD spectra. Ultimately, all apolipoproteins in the gene family of exchangeable apolipoproteins were found to be rich in amphipathic α-helices, and synthetic apolipopeptides based on the amphipathic helical model were shown to be physiologically active.

Differential Scanning Calorimetry (DSC): DSC reveals thermotropic transitions (e.g., melting) and the energy quantity required to complete the transition. For example, DSC reveals that water melts at 0°C with an attendant heat of melting = 80 cal/g. According to the DSC method, the melting behavior of cholesteryl esters (CE) in LDL and in arterial atherosclerotic lesions is similar, exhibiting a transition from liquid crystal to an isotropic liquid phase. Moreover, increasing the triglyceride (TG) content of LDL reduces its CE melting temperature and its binding to the LDL receptor. According to cryo-electron microscopy, increasing the TG content of LDL also changes its structure from ellipsoidal to spherical. The DSC method provided one of the most insightful observations showing that HDL is a uniquely labile lipoprotein. During the heating of HDL in a DSC experiment, its lipid components fuse into a large apo A-II-rich particle, while apo A-I is released in a lipid-free state. These studies indicated that HDL resides in a kinetic trap from which labile apo A-I escapes to the surrounding aqueous phase, lipid-free. This apo A-I lability also is seen when HDL interacts with lipid transfer proteins, lecithin-cholesterol acyltransferase, hepatic lipase, and streptococcal serum opacity factor, all of which disrupt HDL structure and release lipid-free apo A-I.

Mass Spectrophotometric Analyses: Three powerful structural approaches are based on mass spectrometry (MS). They are apolipoprotein configuration analysis by cross-linking (CL) and MS; hydrogen-deuterium (H-D) exchange as assessed by MS; and proteomic analysis by MS. All three methods have been applied to studies of the structure of HDL and reconstituted HDL [(r)HDL]. MS determines the mass of molecules or fragments on the basis of their mass-to-charge ratios.

In the CL-MS application, the ε-amino groups of lysines in rHDL proteins and in HDL containing mainly apo A-I are cross-linked. Subsequent trypsinolysis releases cross-linked peptides that are analyzed by MS. Given that the molecular masses of the tryptic peptides of apo A-I and the cross-linker are known, the site of cross-linking is determined by matching the theoretical and actual molecular masses. With knowledge of the main CL, the configurations of apo A-I on the surface of rHDL and HDL can be determined. According to the CL-MS method, HDL of different sizes and containing no apo A-II had the same CL profiles, suggesting that strong protein-protein interactions on the surface of HDL maintain this constant structure.

H-D exchange complements CD methods by identifying specific amino acid residues that are nonexchangeable because they are hidden within α-helices. Briefly, the protein protons are exchanged for deuterons by dilution into D₂O. The pH is reduced to quench additional exchange, and the protein is trypsinized. The liberated peptides are separated and their molecular masses determined. The additional molecular mass of nonexchanged deuterons and the known molecular masses of the tryptic peptides reveal which residues are nonexchangeable because they reside in α-helices. The
α-helix of lipid-free apo A-I as assessed by H-D and CD analysis agreed well; moreover, the location of the α-helices for the most part supported what was predicted by computational methods. However, when apo A-I in rHDL was similarly analyzed, only a few amino acids at each end of the protein contained exchangeable deuterons so that when associated with lipid, apo A-I is ~95% α-helical. H-D analysis also has revealed differences in the structural dynamics of apo A-I point variants. Apo A-I Iowa (G26R) is associated with systemic amyloidosis; apo A-I Milano (R173C) is associated with hypoalphalipoproteinemia and, apparently, cardioprotection. According to H-D exchange studies, the helical structures of both are less stable than those of native apo A-I. Although they will not replace X-ray crystallography for structural analysis, H-D exchange studies have the advantage of giving information about proteins in aqueous solutions.

Proteomics, which is more a discovery-driven platform than a hypothesis-driven platform, is the large-scale study of structure, occurrence and function of proteins, especially by MS. According to shotgun proteomics, HDL contains multiple complement-regulatory proteins, serpins with serine-type endopeptidase inhibitor activity, and acute-phase response proteins, which suggests that HDL may play a role in regulating the complement system by protecting tissue from proteolysis and inflammation. With improved methodologies, other studies have identified numerous HDL proteins associated with complement function, coagulation, neurogenesis, development, insulin signaling and collagen binding. MS proteomics has advantages and disadvantages. Because of the sensitivity of MS, this approach can detect very low levels of proteins with a heretofore unsuspected role in lipoprotein metabolism. However, the importance of low copy-number proteins is uncertain, and it will be important to determine quantitative stoichiometric relationships between these low-level species in a way that leads to mechanistic insights.

The Future: Physical methods will continue to play an important role in identifying structure-function relationships among lipoproteins and in defining atherogenic vs. atheroprotective processes. As current methods are refined, new physical approaches will be applied to studies of lipoproteins.

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References are listed on page 30.
In keeping with the theme of this issue of *Lipid Spin*, I have chosen waist circumference as the physical finding that can lead us to so much more in terms of atherosclerosis risk assessment. As we know, nearly 80 million Americans have metabolic syndrome, and enlarged waist circumference is the physical expression of this syndrome.1 To borrow a phrase from my good friend and mentor, Tom Dayspring, metabolic syndrome patients are diabetics in-training. It is my goal in this article to provide an understanding of the physiologic pathways that result in carbohydrate-induced lipogenesis and why that potato we consume can contribute to visceral adiposity. This new understanding of how our diet choices have failed us is, I believe, the first line of defense we as health care providers have to save both lives and money.

For more than 30 years our national dietary focus has been to reduce red meat in our diets. As a result, we have been rewarded with an epidemic of prediabetes and diabetes. I believe this focus has not resulted in better health and, in fact, has not been a good choice. As we have focused on less protein in our diets, we have dramatically increased our carbohydrate intake. This also has resulted in a negative impact on our collective lipid panels.

Maki et al published in the *Journal of Clinical Lipidology* last year that the impact of lean red meat on our lipid panel was not significantly different from that of poultry or fish. I think this concept is important, because we need to move away from carbohydrates and increase our protein choices.2

As various forms of carbohydrates enter the glycolytic pathway, they are converted to two primary intermediate compounds, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. These two compounds begin the conversion of carbohydrate to triglyceride. They can spin off glycerol or enter the mitochondria of the hepatic cell. In the mitochondria, the transformation of carbohydrate continues as it passes through the Krebs cycle and emerges as citrate that is further converted to acyl coA. Remember that triglycerides are in reality triacylglycerols (Figure 1).

This lipogenic pathway takes on even more importance when we think about the various forms of carbohydrate in the American diet. Glucose, sucrose (the combination of glucose plus fructose to make common table sugar), dairy lactose (glucose plus galactose), and mannose primarily are used for fuel or stored for energy as fat. When we consume these carbohydrates, our bodies respond with an increase in pancreatic insulin secretion. Influenced by this are various hormones...
that are responsible for satiety, including leptin and ghrelin. The glucose that passes through the blood brain barrier results in changes in regional blood flow that also cause us to know we are full and decrease our appetite.3

This activity occurs as glucose is transported across cell membranes via the glucose transporter type 4, or GLUT 4. It is critical to recognize that fructose is different. Fructose, which has been called the natural sugar in days past, has flown under the radar in terms of its lipogenic potential. Fructose is transported by the GLUT 5 transporter, not found in the beta cells of the pancreas or the blood brain barrier. This has severe metabolic consequences. After the ingestion of fructose, the pancreas does not receive the signal to produce insulin. Since fructose is not transported into the brain, we do not feel full as a result. A recent article in JAMA demonstrated how differently the ingestion of glucose versus fructose affected regional cerebral blood flow. In that study, glucose in effect made the brain sense satiety and fructose did not.3

The net result of this difference in metabolism has broad implications for the American diet. Fructose ingestion may well be a major factor in the epidemic of weight gain, metabolic syndrome, diabetes and, ultimately, cardiovascular disease. Fructose consumption also increases inflammatory

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**Figure 1.**

Kidney, Liver, Pancreas, and Blood Flow Diagram
biomarkers. This, of course, negatively affects the endothelium. It decreases adiponectin, which helps insulin resistance develop. It decreases leptin, which inhibits central signaling so appetite is not affected. Fructose also decreases ghrelin, a gut hormone that is orexigenic. A recent article also demonstrated that fructose increased uric acid, a more recently recognized dysfunction in metabolic syndrome.

High fructose corn syrup (HFS) has become a staple of the American diet. It was first discovered in 1967 as HFCS 42%. It was further refined in 1977 as HFCS 55%. More current versions contain 90%. It has gained rapid popularity with industry for several reasons. It is cheap, stable and easy to produce, and it lends itself to multiple food sources, including soda, multiple processed packaged foods and even fruit juices that we give our children. HFCS is produced by taking corn—a relatively cheap and abundant commodity—adding glucose isomerase to it and converting the corn to HFCS.

HFCS is ubiquitous in the American diet. Between 1970 and 1990, our use increased 1,000%. Per capita consumption increased from 0.5 pounds a year to 62.4 pounds a year. A large part of its appeal is how sweet HFCS tastes. On a relative scale, with table sugar—sucrose—assigned a sweetness rating of 100, glucose would rate 43, and HFCS would rate 173.

All of this becomes more frightening as we realize that the vast majority of HFCS we consume is metabolically shunted to lipogenesis. As our liver struggles under the metabolic assault of the carbohydrates we consume, it must find some way to process the load. With deposition of fat and non-alcoholic fatty liver disease (NAFLD), or steatohepatitis being the last resort, our liver packages all this newfound fat as very-low-density lipoprotein (VLDL) and releases it into the circulation. This ultimately results in the production of atherogenic apolipoprotein B (apoB) containing low-density lipoprotein (LDL) particles. When we consider the effect of cholesterol ester transfer protein on these particles, they become smaller in size, requiring even more of them to carry the cholesterol load our bodies produce. The net result of this cascade of events is, of course, atherogenic disease of our arteries and the cardiovascular events that result.

Thus, we have come full circle. That patient who sits in our waiting room every day with elevated waist circumference is at risk for everything mentioned in this article. Such a simple clinical observation can result in the recognition of the at-risk patient long before any event may occur. At that point we can intervene with appropriate dietary and lifestyle advice, as well as any pharmacologic interventions that are appropriate.

With all the technology and sophisticated serum markers we utilize, please don’t forget the marker that is virtually free. We have the opportunity to save the health care system vast amounts of money. For both health and economic reasons, our patients will thank us for doing this.

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References are listed on page 31.
Practical Pearls:
Polycystic Ovarian Syndrome

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She is sitting in your office waiting room. That fat, hairy woman for whom you can pretty much guarantee her chief complaint — amenorrhea, abnormal hair growth or knee pain. You know the Pandora’s Box of diagnoses she really should be worried about: diabetes, hyperlipidemia, endometrial cancer. So many problems, so little time, so little compensation.

The average woman with polycystic ovarian syndrome (PCOS) fits this picture, but not all do. Approximately 30% of women with PCOS are thin. The chief complaints of women affected by PCOS are infertility, abnormal uterine bleeding, hirsutism and acne. PCOS affects approximately 6% to 7% of reproductive-age women and can be diagnosed, by meeting two of three criteria set in 2003 by the Rotterdam Consensus: hyperandrogenism (either clinically or biochemically), oligomenorrhea or amenorrhea, and polycystic ovaries noted on ultrasound. The Androgen Excess Society expanded the definition in 2006 by requiring hyperandrogenism to be present among the three Rotterdam criteria. Potential diagnoses of hyperandrogenisims such as androgen-secreting tumors, Cushing’s syndrome, non-classical congenital adrenal hyperplasia, exogenous androgens and acromegaly must be excluded.

No clear etiology of PCOS has been defined. Insulin resistance with subsequent decreased levels of sex hormone-binding globulin and more available circulating androgen is central to the pathophysiology. Hyperinsulinemia can stimulate further androgen production by the ovaries and by the adrenal glands. Obesity can independently exacerbate PCOS and its symptoms.

The physical exam reveals many aspects of PCOS. Through excessive hair growth, male-pattern baldness and acne, hyperandrogenism can significantly impact women’s lives. Hirsutism can be evaluated using the Ferriman-Gallwey score (Figure 1). First described in 1961, this scale was

modified in 2001 for grading 19 corporal locations with a score of 0 (no hair growth) to 4 (extensive hair growth). These locations include upper lip, chin, lower abdomen and inguinal area. Acne also may disfigure with deep pustular nodules along the patient’s cheeks, jawline, chin and upper neck (Figure 2). A pelvic exam can demonstrate clitoromegaly, a subtle but important finding on physical exam, and ovarian enlargement. A transvaginal ultrasound will give the classic appearance of “string-of-pearls” for polycystic ovaries (Figure 3).

Oligomenorrhea and other menstrual irregularities are common complaints. Oligomenorrhea is defined as menstrual cycles occurring at an interval of less than 21 days or greater than 35 days. With the lack of a moliminal symptom such as breast tenderness or mood-changes, oligomenorrhea can be suggestive of anovulation. These women often seek medical attention for infertility and, with ovarian stimulation, are prone to hyperstimulation and pregnancies complicated by multiple gestations. Without ovulation, women with PCOS are at increased risk of endometrial cancer as they age.

The prevalence of concomitant cardiometabolic syndrome is between 33% and 47%. This is from two to three times that of the general population and may be related to obesity. Therefore, those with PCOS should be screened regularly for cardiovascular risk factors.

Approximately 70% of American women with PCOS have dyslipidemia with mildly elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL) cholesterol and higher triglycerides than normal. This often responds to lifestyle intervention. It is wise to remember that statins are contra-indicated in women at risk for pregnancy. Cholesevelam is the only lipid modifying agent that is pregnancy class B. All agents except statins (which are class X) are class C. Target goals are those for metabolic syndrome in patient with PCOS (3 of 5 characteristics including low HDL cholesterol (50 mg/dL in women), high Triglycerides (>150 mg/dL), elevated fasting glucose (>110 mg/dL) and elevated waist circumference (>35 inches in Caucasians and >3.5 inches in Asians. Carbohydrate intolerance also needs to be assessed at regular intervals, because the incidence of impaired glucose intolerance is approximately 20% a year. Screening for diabetes is recommended in any patient with PCOS, regardless of age, given that inherent insulin resistance often is aggravated by obesity. Acanthosis nigricans can herald this insulin resistance on physical exam, marking the neck, axillae, chest and vulva with its classic velvety, hyperpigmented appearance. A quantitative scale of acanthosis nigricans has been devised and validated to aid with longitudinal evaluation. Notably, patients with PCOS also often have excess skin tags.

To properly evaluate this prevalent disorder, the American College of Obstetrics and Gynecology recommends examining the patient for the stigmata mentioned above. Additionally, assessment for cardiometabolic syndrome in blood pressure, waist circumference, body mass index, fasting lipid panel and a complete metabolic profile, including fasting glucose and liver enzymes, should be completed. Liver enzymes need to be evaluated for fatty liver and/or nonalcoholic steatohepatitis (NASH). Hyperandrogenism should be documented by obtaining a free androgen index [the ratio of testosterone to sex hormone-binding globulin (SHBG)] and exclusion of other etiologies by obtaining a thyroid-stimulating hormone level, a prolactin and 17-hydroxyprogesterone level at 0800hrs to rule out non-classic congenital hyperplasia, hypothyroidism and/or hyperprolactinemia. A pelvic ultrasound to document polycystic ovaries also is recommended, because it also evaluates for endometrial pathologies. Evaluation for Cushing’s syndrome and androgen-secreting tumors is left to the discretion of the practitioner. Cushing’s syndrome, likewise, usually has characteristic stigmata and patients with virilizing ovarian or adrenal tumors usually have rapid onset virilization with serum androgens (T or DHEAS) in a very high range. Additionally, patients with PCOS often have depression and/or anxiety disorders for which they should be screened and diagnosed.

The evaluation of a patient with polycystic ovarian syndrome takes time and likely needs to be spread over several visits. This allows you to tackle the multiple complaints your female patient has to offer and permits her Pandora’s Box of medical complexities to be addressed effectively and comprehensively.

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*As of July 23, 2013*
A 37-year-old patient was referred to our lipid clinic from his primary care provider. A basic lipid panel revealed: total cholesterol (TC) 715 mg/dL, triglyceride (TG) 901 mg/dL; HDL-C 45 mg/dL, Lipoprotein(a) [Lp(a)] mass was elevated (44 mg/dL); Lp(a)-cholesterol levels were not measured. The patient, who was generally very healthy, had not seen a physician for several years. He presented with bilateral palmar xanthomas (see Photo 1). He had noticed them for approximately 2 years but did not know what they were. Flat macules were diffusely spread across his palmar surfaces and the flexor surfaces of the fingers. He sought treatment after a physician friend saw his hands and urged him to see his primary care physician and to have his cholesterol levels measured.

His medical history was unremarkable; his family history was somewhat unknown, but he reported that he thought there was early cardiac death on his mother’s side, though not in his immediate family. He exercised strenuously four days a week and followed a low-carbohydrate diet that was high in vegetables and lean meats. He had never had a weight problem. He was not on any prescription medications but took omega 3 fatty acid capsules daily, exact dosage unknown. He had no drug allergies, no history of cigarette smoking and no surgeries. He denied any other physical complaints.

Vital signs: Height, 6 feet, 0 inches; weight, 148 pounds; BMI 20.1; BP 120/82; P 60.

We suspected type III dysbetalipoproteinemia or “remnant disease” because of the physical presentation and the levels of very high triglycerides and total cholesterol. Advanced lipoprotein testing was ordered. A secondary cause workup included urine analysis (UA), thyroid function tests (TFTs), HBA1c and a complete metabolic panel (CMP).

Planar xanthomas of the palms, as seen in the patient, are also called xanthoma striatum palmare (XSP). They are rare but considered pathognomonic of dysbetalipoproteinemia.1 In addition, the condition is characterized by very elevated cholesterol and triglycerides, as seen in the patient’s initial laboratory findings. Dysbetalipoproteinemia reflects an accumulation of remnant lipoproteins: both intestinally produced chylomicron remnants and hepatically produced VLDL remnants. It is sporadic because most cases are recessive and two defective Apolipoprotein E (ApoE) alleles (ApoE 2/2) are required, plus additional environmental factors are necessary for full expression of the dyslipidemia.2 This genetic lipid disorder is associated with premature coronary and/or peripheral vascular disease.3 It is seen when factors that increase remnant lipoprotein production overwhelm the receptor-mediated clearance pathways. Conditions such as hypothyroidism, weight loss...
gain, estrogen status or uncontrolled diabetes could precipitate the development of dysbeta
talipoproteinemia.\(^3\) XSP develop because of lipid leakage from vessels into
surrounding tissues; macrophages then phagocytize the lipids.\(^1\)

Interestingly, our patient did not have any identifiable metabolic causes of his dyslipidemia; his secondary cause work-up was negative.

His advanced lipoprotein testing showed the following notable results:

- ApoE genotype: 3/3
- Apolipoprotein (ApoB): 245 mg/dL (very high)
- NMR Data:
  - LDL-P: 3,450 nmol/L (very high)
  - VLDL-P: 1,028 nmol/L (very high)
  - Large VLDL-P: 21.7 (very high)
- Lp(a) mass: 45 mg/dL (high)
- Lp(a)-C: <3 mg/dL (normal)
- Campesterol: 12.14 µg/mL (high)
- Sitosterol: 6.20 µg/mL (high)
- Cholestanol: 11.16 µg/mL (high)

The most surprising initial finding was the very high levels of both ApoB and LDL-P in addition to the apoE 3/3 genotype; these findings are not suggestive of dysbeta
talipoproteinemia. In true dysbeta
talipoproteinemia, LDL-P will be low, which could falsely suggest low cardiovascular risk. The ApoB also will be low because of the short half-life of the LDL and VLDL particles despite their high numbers. In dysbeta
talipoproteinemia, risk is high because of the atherogenicity of remnant lipoproteins; one cannot rely solely on ApoB and LDL-P to predict risk.

We initiated aggressive lipid management via drug therapy and prescribed Lovaza 4 grams daily, Trilipix 135 mg daily, and Crestor 10 mg daily. Zetia 10 mg daily was added later. The patient also underwent carotid intima media thickness (CIMT) testing that revealed: left side, 0.538 mm; 20th percentile for his age and gender; carotid plaque was not visualized on either side. He also elected to initiate care with a cardiologist and went through extensive cardiac testing, including a nuclear stress test and computed tomography (CT) angiogram, both of which were negative. He met with a dietitian and, though his diet was already quite healthy, he moved toward a more vegan diet, basically eliminated all animal fats and further reduced his refined carbohydrate intake. From a scientific standpoint we were intrigued by his case, which phenotypically looked like dysbeta
talipoproteinemia, though ApoB levels and apoE 3/3 were not consistent with this disorder. It should be noted that the patient also was quite interested in understanding the genetic cause of his lipid disorder and was hopeful we could help him shed more light on his complex case. There are rare naturally occurring apoE mutations other than apoE 2/2 that have been associated with a dominant form of dysbeta
talipoproteinemia that is expressed at an early age; the genetic defect alone is sufficient to trigger dyslipidemia without requiring secondary factors.\(^4\) We were fortunate that the patient enrolled in a research study that provided apoE gene sequencing for research purposes only, but no mutations were found. The patient continues to be involved in a genetic research study; at this time no further results are available. Overall, this case reveals that the physical presentation of lipid disorders can sometimes be misleading: We initially presumed the patient to have dysbeta
talipoproteinemia, given the presence of the XSP. While his electrophoresis did “look” like dysbeta
talipoproteinemia, his ApoB and LDL-P levels most definitely did not and his apoE initial testing did not support this diagnosis.

Further sequencing of his apoE did not reveal any other genetic abnormalities to help guide a diagnosis. There are myriad abnormal genes that can influence lipid metabolism; with this patient it could be some type of overproduction of VLDL in association with defective LDL receptors, a defect in ApoB, or PCSK9 gain of function mutation. In real-life practice situations, precise labels and detailed genetic analysis are not necessary to provide adequate treatment, though the final genetic testing results will prove very interesting. The most important service we provided for this patient—who was quite concerned about his risk and his abnormal levels—was to treat his lipoproteins and help reassure him that his risk was minimized with this proper and aggressive treatment. The treatment produced marked improvements in his lipoprotein levels as summarized in the following chart:

<table>
<thead>
<tr>
<th>Lipid</th>
<th>March 2012</th>
<th>Feb 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>768 mg/dL</td>
<td>211 mg/dL</td>
</tr>
<tr>
<td>LDL-C:</td>
<td>204 mg/dL</td>
<td>67 mg/dL</td>
</tr>
<tr>
<td>HDL-C:</td>
<td>50 mg/dL</td>
<td>82 mg/dL</td>
</tr>
<tr>
<td>Triglycerides:</td>
<td>927 mg/dL</td>
<td>151 mg/dL</td>
</tr>
<tr>
<td>ApoB:</td>
<td>245 mg/dL</td>
<td>93 mg/dL</td>
</tr>
<tr>
<td>LDL-P</td>
<td>3,450 nmol/L</td>
<td>1,509 nmol/L</td>
</tr>
<tr>
<td>HDL-P</td>
<td>22.8 µmol/L</td>
<td>48.9 µmol/L</td>
</tr>
<tr>
<td>Large VLDL-P:</td>
<td>21.7 nmol/L</td>
<td>&lt;0.8 nmol/L</td>
</tr>
<tr>
<td>Small LDL-P:</td>
<td>2,167 nmol/L</td>
<td>832 nmol/L</td>
</tr>
<tr>
<td>Campesterol:</td>
<td>12.4 µg/mL</td>
<td>1.92 µg/mL</td>
</tr>
<tr>
<td>Sitosterol:</td>
<td>6.20 µg/mL</td>
<td>1.94 µg/mL</td>
</tr>
<tr>
<td>Cholestanol:</td>
<td>11.16 µg/mL</td>
<td>4.26 µg/mL</td>
</tr>
</tbody>
</table>

Considering his starting levels, these are nice improvements, though his levels remain above the most aggressive lipoprotein goals. There are new lipid drugs available and in development, and he ultimately may require them or respond better to them. His xanthomas have improved ever so slightly and we will follow the patient closely. As mentioned previously, further genetic information will be very interesting and we currently await those results.

Disclosure statement: Ms. Davila has no disclosures to report.

References are listed on page 31.
Multiple observational studies have found an inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular disease (CVD).\textsuperscript{1-3} The cumulative mechanism(s) by which HDL-C is associated with reduction in CVD is/are intricate and multifactorial.\textsuperscript{2} Pharmacologic approaches to increase HDL-C have been successful, but the studies assessing the cardio protective effect(s) of these interventions often has been conflicting and is debatable.\textsuperscript{4} The Adult Treatment Panel (ATP) III report also has recognized the ambiguity of cardiovascular benefits associated with increasing HDL-C without addressing low-density lipoprotein cholesterol (LDL-C) and, hence, mostly have targeted LDL-C with additional recommendations for lowering HDL-C as secondary targets.\textsuperscript{5} After appropriately lowering LDL-C, residual risk still exists and it is then that targeting HDL-C to try to eliminate residual risk.\textsuperscript{6} HDL-C scavenges excess cholesterol from peripheral vascular macrophages and transports it back to the liver for elimination in the bile. This process is known as “reverse cholesterol transport.”\textsuperscript{1-3} Apolipoprotein (Apo) A1 is the functional unit of HDL-C that controls its ability to efflux cholesterol from the periphery.\textsuperscript{2,7} HDL-C also possesses anti-inflammatory, anti-oxidant and anti-thrombotic properties.\textsuperscript{3} It prevents endothelial damage and slows atherosclerotic plaque formation.\textsuperscript{1} Once HDL-C scavenges cholesterol from the periphery, it is converted to cholesterol ester by lecithin-cholesterol acyltransferase. The cholesteryl ester transfer protein (CETP) mediates the bidirectional and equimolar distribution of cholesterol esters along with triglycerides between lipoproteins and fuels reverse cholesterol transport.\textsuperscript{8} Inhibition of CETP in humans is known to increases HDL-C, something learned from studies of genetic polymorphism in which genetic mutation decreases the quantity or activity of CETP.\textsuperscript{4} This evidence has given rise to a novel class of drugs called CETP inhibitors. Niacin and fibric acid derivatives also are known to increases HDL-C levels. The mechanism via which niacin increases HDL-C is not well established, but studies have shown that niacin works via G-protein-coupled receptors to exert its action.\textsuperscript{9} Fibrates activate transcription of peroxisome proliferator-activated receptors that induce transcription of Apo A1 and Apo A2. They also decrease the production of Apo C-III and stimulate lipolysis by.
increasing the activity of lipoprotein lipase.\textsuperscript{10}

Torcetrapib was the first CETP inhibitor to be investigated. It increased HDL-C by 72% and decreased LDL-C by 24.9% when administered in combination with atorvastatin.\textsuperscript{11} However, torcetrapib increased production of aldosterone and cortisol, which was speculated to have influenced electrolyte abnormalities and elevation in blood pressure, causing an increase in morbidity and mortality—93 deaths in the torcetrapib group versus 59 in the atorvastatin-only group. As a result, the trial had to be terminated.\textsuperscript{4,6,11}

After termination of the trial, reports of all-cause death and cardiovascular events during follow-up were similar in both groups.\textsuperscript{11} Dalcetrapib is a CETP modulator and second in this class after torcetrapib to be discontinued for futility.\textsuperscript{4} Dalcetrapib caused anticipated physiological changes of raising HDL-C by 31% to 40% with minimal decreases in LDL-C.\textsuperscript{4} Dalcetrapib is less potent and so did not elevate HDL-C as much as torcetrapib did. It also did not have as many significant adverse effects as torcetrapib.\textsuperscript{4} However, it failed to show meaningful efficacy in patients with CVD.\textsuperscript{4} Two more drugs, evacetrapib and anacetrapib, are currently being investigated. Evacetrapib also has shown a significant dose-dependent increase in HDL-C—up to 128.8%—while decreasing LDL-C and triglycerides at highest dosage without any adverse effects.\textsuperscript{12} Results from the DEFINE—Determining the Efficacy and tolerability of CETP INhibition with Anacetrapib\textsuperscript{13}—trial of anacetrapib showed a 138% increase in HDL-C and a 40% decrease in LDL-C in patients on anacetrapib and statin compared to placebo.\textsuperscript{6} No significant changes in morbidity and mortality were noted, including adverse effects.\textsuperscript{6} The phase III trial known as REVEAL—Randomized EValuation of the Effects of Anacetrapib through Lipid-modification\textsuperscript{14}—is on the way to investigate whether a therapeutic increase in HDL-C is protective against cardiovascular events.

CETP inhibitors such as anacetrapib and evacetrapib have shown reduction in LDL-C not seen in dalcetrapib, along with a significant increase in HDL-C. They also don’t have any of the adverse effects seen with torcetrapib, but they have yet to be proven to be cardio protective in a clinical trial. They also have shown a significant LDL-C-lowering effect that may make it difficult to conclude how much of the benefit is the result of a decrease in LDL-C versus an increase in HDL-C. A study in Japanese-American men with genetically inactivating CETP mutation showed an increased risk of CVD in men with an HDL-C range from 41 to 60. It was thought likely to be the result of a

What we currently know about HDL-C, its role in atherosclerosis and effects of HDL-C modulation is just the tip of an iceberg, and any definitive conclusion based on current evidence is premature.

<table>
<thead>
<tr>
<th>Class of drugs</th>
<th>CETP inhibitors</th>
<th>CETP modulator</th>
<th>Nicotinic acid formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Torcetrapib (Phase III Trial)\textsuperscript{11}</td>
<td>Anacetrapib (DEFINE trial)\textsuperscript{1}</td>
<td>Evacetrapib (Phase II trial)\textsuperscript{12}</td>
</tr>
<tr>
<td>% HDL-C increase</td>
<td>72</td>
<td>138</td>
<td>53 - 129 (Dose dependent)</td>
</tr>
<tr>
<td>% LDL-c decrease</td>
<td>24.9</td>
<td>40</td>
<td>14 - 36 (Dose dependent)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Decreased</td>
<td>Reduced</td>
<td>Reduced (Dose dependent)</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Elevated blood pressure, aldosterone, and electrolyte disturbances</td>
<td>Insignificant compared to placebo</td>
<td>Insignificant compared to placebo</td>
</tr>
<tr>
<td>Trial Status</td>
<td>Stopped because of adverse effects</td>
<td>Ongoing Phase III trial REVEAL</td>
<td>Completed Phase II trial. Ongoing Phase III trial</td>
</tr>
</tbody>
</table>

Table 1. Randomized clinical trials of HDL-C-modifying drugs.
negative impact on the role of CETP as a contributor in reverse cholesterol transport making CETP deficiency a positive risk factor for CVD.8 Men with HDL-C greater than 60 in this study had relatively lower CVD, which was attributed to the possible atheroprotective effect of elevated HDL-C resulting from increase reverse transport.8 Apo-B containing molecules such as LDL-C and VLDL also are involved in transporting cholesterol back to the liver, and inhibiting CETP would impede the transfer of cholesterol ester to these particles and negatively impact reverse cholesterol transport.15 These observations make it important to further investigate the role of CETP in reverse cholesterol transport.

Therapeutic use of niacin in its chemical form, nicotinic acid, has been shown to increase HDL-C and decrease LDL-C, VLDL and triglycerides levels in a dose-dependent manner. The ARBITER 6-Halts trial showed a significant decrease in carotid intima-medial thickness as a potential benefit of niacin’s HDL-C-increasing effect in patients with atherosclerotic disease who were on statin monotherapy.16 A more recent study, the AIM-High trial, concluded that niacin showed no additional benefit in patients with optimum LDL-C levels, regardless of the increase in HDL-C and reduction in triglycerides.17 Another large multi-center randomized trial, known as HPS2-Thrive and coordinated by University of Oxford, compared extended-release niacin 2 grams plus laropiprant 40 milligrams versus placebo in patients with pre-existing occlusive vascular disease who were treated with a statin.18 Laropiprant does not have an effect on HDL-C levels. When added to extended-release niacin, though, it reduces the incidence of flushing and, thus, makes the drug more tolerable. The results of this trial showed no meaningful reduction in cardiovascular events in patients in whom LDL-C was optimally managed with statin therapy.18

Apo-A1, the functional unit of HDL-C, regulates its ability to mobilize cholesterol from peripheral macrophages. A rare mutation in Apo-A1 known as “APO-A1 Milano” is characterized by elevated levels of Apo-A1 activity with extremely low levels of HDL-C.7,19 Some people carrying this mutation are thought to be free of CVD, irrespective of lifestyle. This mutation is associated with a rapid increase in the efflux capacity, which ramps up reverse cholesterol transport. In animal studies, this effect is seen within 48 hours.7 This evidence supports the importance of HDL-C quality over quantity. Further investigation of the components of HDL-C and their dynamics is important to understanding its role in reverse transport.

What we currently know about HDL-C, its role in atherosclerosis and effects of HDL-C modulation is just the tip of an iceberg, and any definitive conclusion based on current evidence is premature. There is a discrepancy between the observation that people with low HDL-C are at higher risk of CVD and the evidence that raising HDL-C does not offer incremental protection. This evidence begs the question: If the LDL-C level is optimum, would exceptionally high HDL-C levels confer any cardio protective benefit? Is there any specific sub-group that would benefit from HDL-C-lowering therapy?

Future studies will be able to give us some direction and may be answer some of these critical questions.

Disclosure statement: Dr. Lokhandwala has no disclosures to report. Dr. Dhoble has no disclosures to report.

References are listed on page 31.
Randy Burden, PharmD, often traveled to the eight northern Pueblo tribes in New Mexico as part of his job with the U.S. Indian Health Service cardiovascular risk reduction program. At each site visit, he became engulfed in addressing lipid disorders, diabetes, the metabolic syndrome, and blood pressure problems in his patient population. During that period, he realized he specifically wanted to focus on one of these precursors to heart disease, a leading cause of death for Native Americans.

U.S. Indian Health Service colleague Ralph La Forge, MSc, introduced Dr. Burden to the NLA in 2004, and he has been a member ever since. Today, he works as a pharmacist clinician where his role is akin to that of a disease management specialist. His practice closely mirrors that of the patient-centered medical home, which uses registries and other forms of health information exchange to help patients get indicated care when and where they need it in a culturally and linguistically appropriate manner.

In addition to attempts at preventing onset or progression of disease, Dr. Burden’s team uses therapeutic lifestyle approaches to address their concomitant diseases. Watching patients take ownership of their health is almost as rewarding as seeing improved clinical outcomes, Dr. Burden says.

“It’s great when they make that connection and realize that what we’re doing improves their quality of life, as if we’re the coaches and they’re the quarterbacks who are getting kudos for making the right play,” he said.

Dr. Burden’s “whole person” approach extends into other aspects of his professional and personal life, such as his work as the pastor of health and wellness at a community church in Albuquerque.

“We have a congregation of 800, and what we try to do is mix health care into the context of a faith-based community setting,” Dr. Burden said. “There’s a strong link between what I do at work and what I do in the church, and we want people to realize how important it is to integrate these areas in their own lives.”

Looking ahead, Dr. Burden hopes to see the practice of Clinical Lipidology extend to patient care in ways that include looking at the spiritual aspects of the patient. He also would like to see the utilization and broader recognition of Clinical Lipid Specialists within the medical community.

In his free time, Dr. Burden likes to stay busy with outdoor activities such as fly fishing, swimming, biking and running.

“I’m convinced that as HCPs, we have to be an example to our patients and we cannot live in a fish bowl,” he said. “We will be more successful if we practice what we preach, because we also face the same challenges as our patients.”
Fall CLU Early Bird Registration Extended

The final program has been mailed for the NLA’s Fall Clinical Lipid Update: Clinical Tools for the Practicing Lipidologist: Recent Advances in Genetics, Lifestyle and Pharmacy in Baltimore, MD. The conference, scheduled for September 20-22, is hosted by the Southeast and Northeast regional chapters of the NLA. Register online at lipid.org/fallclu before August 9 to take advantage of the early-bird registration rate of $425.

On Demand Highlights from the Annual Scientific Sessions Now Available

Highlights from the National Lipid Association’s 2013 Annual Scientific Sessions are now available on demand. You can now view selected presentations with audio from the sessions. Please go to lipid.org/education/highlights to view the highlights.

ATP IV Guidelines

The NLA recently met with representatives of the ATP IV Guidelines to discuss the development and dissemination plan following the NHLBI’s announcement on June 19 that all future work on the guidelines will be done in collaboration with organizations. Plans are underway to publish an executive summary of the ATP IV Guidelines in the Journal of Clinical Lipidology in December 2013.

Pediatric FH Meeting During 2013 Annual Scientific Sessions

The NLA hosted a meeting to discuss issues and ideas about pediatric FH during our annual meeting in Las Vegas this past May. Chaired by Sam Gidding, MD, the meeting featured representation from the NLA, Foundation of the NLA, and partner organizations. Please stay posted for more updates regarding pediatric FH efforts in the coming months.

NLA Web Task Force Seeks Nominations

The NLA Web Task Force is seeking three to four nominations from the general membership. Conference Calls are scheduled bi-monthly. Members of the Task Force should include a cross-section of those with expertise in education issues, practice management, advocacy, membership and other committees that are pertinent to web content and user application in web-based or mobile environments. Members need not have any particular technical expertise but should be active in typical social networking venues as well as the Community features of the NLA website. To read the committee charge and self-nominate or nominate another NLA member, please go to lipid.org/communications/committees/webtaskforce.

Help Kick Off the New NLA Web Community

The new NLA website features an all new public discussion format that is easier to use and better integrated with other areas of the site. The NLA invites you to jump over to lipid.org/forum, select an area where you have something to contribute, and share a post or two. Nothing engages our members like a discussion in progress. We’ll see you there!

USAGE Campaign Awards

The USAGE Campaign, which launched in 2012 as a joint initiative by the NLA, Kowa Pharmaceuticals America and Eli Lilly & Co. has won five nationally renowned public relations awards. The USAGE Campaign, which involved the largest known cholesterol survey conducted in the U.S., was conducted with more than 10,100 statin users and explored patient perceptions and behaviors regarding statin medication. Here is a list of awards that the campaign has won thus far:

- PRSA New York Big Apple Awards: Best Healthcare Campaign, Consumer Marketing/Products and Best Campaign in 2012
- Bulldog Media Awards: Gold Award for Best Education/Public Service Campaign
- PRSA National Bronze Anvils: Best Media Relations: Health Care Products
- PRSA National Silver Anvils: Award of Excellence: Health Care Products
- PRSA New Jersey Pyramid Award: Best in Health Care
Impact of Inflammatory Biomarkers on Relation of High Density Lipoprotein-Cholesterol with Incident Coronary Heart Disease and Cardiovascular Disease: Cardiovascular Health Study

David M. Tehranifar, MD, MBA, Donald M. Lloyd-Jones, MD, Phyllis K. Stein, PhD, David Yanet, PhD, Calvin H. Hirsch, MD, Nathan D. Wong, PhD

Disclosures: Healthcare, Aviir.

Background: Inflammatory factors and low high-density lipoprotein cholesterol (HDL-C) relate to increased coronary heart disease (CHD) risk, but whether inflammation attenuates protection from CHD with high HDL-C is unknown.

Methods: In 5,888 older adults aged 65 to 98 without cardiovascular disease, we examined if the inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6), and lipoprotein-associated phospholipase A2 (Lp-PLA2) modify the protective relation of HDL-C on CHD. Cox models were run separately for HDL-C and CRP, HDL-C and IL-6, and HDL-C and Lp-PLA2, as tertiles. Also, an inflammation index of z-score sums of CRP, IL-6, and Lp-PLA2 was categorized in tertiles. We calculated CHD and CVD incidence for each HDL-C/infammation group and performed Cox regression, adjusted for standard CVD risk factors and tertiles, separately for each inflammation group, to incident CHD and CVD events occurring over a mean of 11.3 and 10.3 year follow-up respectively.

Results: The unadjusted CHD and CVD incidence (per 1,000 person years) was higher for each category of inflammation and lower for each category of HDL-C. For CHD incidence, compared to high-HDL/low-inflammatory (reference), increased Hazard Ratios (HR) were observed for those in the mid-HDL/high-inflammation category (HR=1.35, p<0.01) which had similar risk to those in the low-HDL/low-inflammation group (HR=1.43, p=0.05). Similar associations were seen with CRP and IL-6 individually, but not with Lp-PLA2.

Conclusion: The protective relation of HDL-C to incident CHD and CVD is attenuated with increasing inflammation.

Methods: The CHS is a prospective study focused on identifying CVD risk factors and outcomes in older community dwelling adult population.

Results: The unadjusted CHD and CVD incidence (per 1,000 person years) was higher for each category of inflammation and lower for each category of HDL-C. For CHD incidence, compared to high-HDL/low-inflammatory (reference), increased Hazard Ratios (HR) were observed for those in the mid-HDL/high-inflammation category (HR=1.35, p<0.01) which had similar risk to those in the low-HDL/low-inflammation group (HR=1.43, p=0.05). Similar associations were seen with CRP and IL-6 individually, but not with Lp-PLA2.

Results Summary: Across groups defined by HDL-C categories paired inflammatory biomarkers, CRP, IL-6, and Lp-PLA2, individually and collectively, on the association of HDL-C with incident CHD and cardiovascular disease (CVD) are attenuated with increasing inflammation.

Objective: We investigated the impact of inflammatory markers CRP, IL-6, and Lp-PLA2, individually and collectively, on the association of HDL-C with incident CHD and cardiovascular disease (CVD) in older individuals without CVD at baseline from the Cardiovascular Health Study (CHS).

Incident CHD Events by Category

<table>
<thead>
<tr>
<th>Incident CHD (per 1,000 person years)</th>
<th>Reference</th>
<th>Mid-HDL/High Inflammation</th>
<th>High-HDL/Low Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>0.6</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>IL-6 (ng/mL)</td>
<td>0.6</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Lp-PLA2 (mg/L)</td>
<td>0.6</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Conclusions: Among those with the highest HDL-C values (≥60 mg/dL), greater levels of CRP (≥5.0 mg/dL), IL-6 (≥6.0 ng/mL), and Lp-PLA2 (≥10 mg/L) were associated with greater risks for CHD and CVD. Our results show that anti-inflammatory effects of high HDL-C for incident CHD and CVD is attenuated with increasing inflammation.
The Foundation of the NLA constantly strives to support research, medical education and community outreach activities, particularly those that fall within our primary areas of focus for grant funding: children, genetic disorders, Familial Hypercholesterolemia (FH), primordial prevention, and underserved populations.

Collaborations between the Foundation and the NLA have resulted in many “firsts,” including the launch of our inaugural FH awareness campaign in May 2011. The Foundation’s commitment to diagnosing and treating this genetic disease encourages us to continue moving forward. Our patients require more than the expertise and therapy we provide—they seek to understand their condition and how it impacts their loved ones.

We are committed to taking the time necessary to reach out and inform patients about this inherited yet treatable condition, because we believe that healing begins with understanding.

With this in mind, we are cultivating a grassroots outreach effort about FH awareness in observance of National Cholesterol Education Month this September. In particular, National FH Awareness Day is September 20, and we hope our outreach activities will encourage individuals to sign up for the FH registry (thefhfoundation.org/register/the-fh-registry) organized by the FH Foundation.

Please watch your mail in September for FH awareness materials and invite your colleagues and patients to learn more about this underdiagnosed condition. Awareness saves lives, and it could be their own.

In other areas, I am pleased to report the following:

- Lifetime Membership has done amazingly well, with more than $100,000 set aside for future lipidology training. One of our goals is to have 100% participation from the NLA and FNLA boards (we have 33 board members so far). To show your support, please go to lipid.org/membership/lifemember by December 31;
- An update to the FH Pocket Guide was released at the Annual Scientific Sessions in May (guidelinecentral.com/medical-society/national-lipid-association); and
- Our next Foundation fundraiser, the delectable Fell’s Point Food Tour, will take place on Saturday, September 21, in conjunction with our Fall Clinical Lipid Update in Baltimore. Join us for this guided, narrated walking tour of Fell’s Point and learn about the historic, cultural and architectural significance of the area. We’ll meet in the hotel lobby promptly at 6:30 p.m. for a short walk to the water taxi, which we will take across the harbor to Fell’s Point. Cost is $75 per person, and all proceeds will benefit the Foundation. To register, please go to lipid.org/fallclu and click on the “Register” tab.


Specialty Corner References


Practical Pearls References


Case Study References


Chapter Update References


10. deGoma E, deGoma R, Rader D. Beyond high-density lipoprotein cholesterol levels:evaluating high-density lipoprotein function as influenced by novel therapeutic approaches. Journal of the American College of Cardiology, 51(23), 2199-2211.

Member Spotlight References

Events Calendar

2013 Scientific Meetings

2013 National Lipid Association Clinical Lipid Update—Fall
Hosted by the Southeast Lipid Association and the Northeast Lipid Association
September 20–22, 2013
Hyatt Regency Baltimore Hotel
Baltimore, Maryland
www.lipid.org/fallclu

2014 Scientific Meetings

2014 National Lipid Association Clinical Lipid Update—Spring
Hosted by the Pacific Lipid Association and the Southwest Lipid Association
March 13–16, 2014
Grand Wailea Hotel
Maui, Hawaii

2014 National Lipid Association Scientific Sessions
Hosted by the Southeast Lipid Association
May 1–4, 2014
Hyatt Regency Grand Cypress Hotel
Orlando, Florida

2014 National Lipid Association Clinical Lipid Update—Fall
Hosted by the Midwest Lipid Association and the Northeast Lipid Association
August 22–24, 2014
JW Marriott Hotel
Indianapolis, Indiana

Save the Date for Breathtaking Maui
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Topics will include:
• Diagnosis and Lipid Management in the Metabolic Syndrome: Developments from Around the World
• Cardiovascular Risk in Asians and Pacific Islanders
• New Targets in Atherogenesis

More details available soon! Stay tuned to www.lipid.org for updates.
**Physical Findings in Lipid Disorders**

1. **Lipemia retinalis** is a rare physical finding which happens with severe hypertriglyceridemia (usually with triglyceride level greater than 2000mg/dL). It was originally described in Familial Chylomicronemia. It is characterized by white discoloration of the retinal vessels seen when the eyes are examined with an ophthalmoscope. Typically, lipemia retinalis is asymptomatic and doesn’t cause vision changes; however it can reflect the risk of acute pancreatitis. This condition is reversible if the triglyceride level is reduced.

2. **Eruptive xanthomas** are small bumps with yellowish tips and dark pink bases that appear mainly over the chest, shoulders, buttocks, and extensor surfaces of the upper limbs. It is associated with very high triglyceride levels (triglyceride level greater than 2000mg/dL), that occur in conditions such as Familial Hypertriglyceridemia and Familial Chylomicronemia. The bumps resolve completely after lowering the triglyceride level, but may cause permanent darkening of the skin in those affected areas.

3. **Tendon xanthomas** are nodular accumulations of cholesterol that occur in genetic disorders associated with severely elevated low density lipoprotein cholesterol (LDL-C). It appears most commonly in patients with Familial Hypercholesterolemia, and Familial Defective Apo B-100, but also can appear in Beta Sitosterolemia. The Achilles tendon is the most common site, however cholesterol can deposit in other extensor tendons in the hands and feet. Achilles tendon xanthomas can sometimes be tender and can be diagnosed by palpating the Achilles tendon, but the diagnosis can be confirmed by biopsy. Management focuses on treating underlying hypercholesterolemia and improvement can occur with intensive therapy.

4. **Xanthelasma** are yellow plaques that usually occur near the inner part of the eyelids. They are associated with abnormal lipid levels and may not go away after treatment. Patients are often concerned by their appearance.

5. **Conjunctival xanthelasma** is an eye condition characterized by grayish clouding in the cornea. It presents in Familial Hypercholesterolemia, Familial Defective Apo B-100 and Dysbetalipoproteinemia. It appears before the age of 50, and should be distinguished from the xanthelasmas that can occur with advanced age; in this case it is called “xanthelasma senilis” and may be associated with high HDL-C.

6. **Tuberculous xanthomas** are non-tender nodules which appear usually in pressure areas such as the elbows and knees. They are associated most commonly with autosomal dominant hypercholesterolemia and also with Beta Sitosterolemia. Management focuses on treating underlying hypercholesterolemia, and they can improve with intensive therapy.

7. **Palmar xanthomas** are yellowish lesions that can look like bumps or lines found in the creases of the palms. This is found in Dysbetalipoproteinemia. Very low-density lipoprotein (VLDL-C) is elevated and the patient usually has very high triglycerides and total cholesterol. Dysbetalipoproteinemia increases the risk for atherosclerosis.

8. **Xanthelasmas** are yellow plaques that usually occur near the inner part of the eyelids. They are associated with abnormal lipid levels and may not go away after treatment. Patients are often concerned by their appearance.

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Name: ____________________________  Date: __________  Health Care Provider: ____________________________

Medications Recommended: ____________________________________________________________

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