Clinical Feature:
Omega 3 Fatty Acids in the Treatment of Dyslipidemia
—Ronald Goldberg, MD

Lowering triglycerides and reducing CVD risk

Also...
Case Studies from the files of Thomas Dayspring, MD

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The strength of any organization lies in the people who are part of it. The National Lipid Association owes its success to a great many people. I continue to be honored and excited to be involved with this wonderful organization, and I want to acknowledge some of the many members, officers, committee participants, and, of course, staff, who have contributed to our success. Anyone in a leadership position has to be extremely grateful to those who do the work. In this column, I would like to highlight some of these efforts since many members may not be familiar with them. Although one usually does a lot of thanking of people at the end of a term of office, I wanted the members who read The Lipid Spin to see in print the names of at least some of the people who make our organization great. Every one of our members is important. Some of the people mentioned here have worked especially hard to make the NLA what it is today.

The NLA has five regional chapters. The leadership of each region has done a tremendous job in putting on outstanding programs, producing content for educating professionals and the public, and energizing their members. Starting with the founding of the Southeast Lipid Association (SELA) in 1997, we have had people who have contributed enormous efforts to our organization. To mention just a few in SELA: Diane Becker, Maria Lopez-Virella, Vera Bittner, John Guyton, Virgil Brown, Dean Bramlet, Jim Howard, Carol Mason, Terry Jacobson, Daniel Wise, Robin Crouse, Ralph LaForge, Paul Ziajka, Roger Blumenthal. Ron Goldberg. The existence of the Lipid Spin is in large part due to the efforts of Maria Lopez-Virella and Ronald Goldberg who have spent years on this newsletter. Virgil Brown has had a dominant role in getting the NLA started since the first organizational meeting in 2002 and continues to be a leader as the Chair of the American Board of Clinical Lipidology and the editor-in-chief of The Journal of Clinical Lipidology, which had an impressive debut in 2007. Virgil’s work with the International Atherosclerosis Society in developing our connections with lipidologists around the world is continuing.

Our second chapter, the Midwest Lipid Association got a great kickoff with the initial meeting in Chicago in 2004 chaired by Neil Stone and Michael Davidson, who have helped to create the second largest NLA chapter. The annual meeting in Kansas City was enriched by the major efforts of Carlos Dujovne to include as many local contributors as possible. Our officers and board members including Jennifer Robinson, Peter Toth, Bill Harris, Alan Brown, Stephen Crespin, Tara Dall, Lynn Cofer, Eli Roth, Melvyn Rubenfire, Carl Orringer, and Lynne Braun. Ted Mazzone, have started Lipid Insights, complementary membership programs, and local journal clubs as well as being outstanding speakers and contributors to the NLA.

Close on the heels of the MWLA, the Northeast Lipid Association held its inaugural
meeting in New York City in 2005. Led by David Capuzzi along with board members and officers Donald Smith, Penny Kris-Etherton, Linda Hemphill, David Nash, Thomas Tulienko, Mary McGowan, Ira Goldberg, Thomas Dayspring, Edward Fisher, Janet Long, Mark Czirady, and Leonard Keilson, NELA has flourished with an outstanding Boston meeting and the upcoming event this February in Philadelphia.

The Southwest Lipid Association has had great leadership from Christie Ballantyne, Nicole Abate, Kathleen Wyne, Carl Rubenstein, Peter Jones (who as NLA president chaired our first strategic planning meeting), Thomas Blevins, Jonathan Abrams, Kim Birtcher, Anthony Busti, Beth Jackson, Robert Wild, and Jim Falko. The SWLA-hosted annual NLA meeting in Scottsdale in 2007 was our largest so far with 400 attendees.

The Pacific Lipid Association got off to a great start with the first meeting in San Diego in January, 2007. The PLA/NLA annual meeting for this year in Seattle is shaping up to be another outstanding meeting. Many of the leaders of the PLA have contributed to the NLA as speakers, committee members, and NLA officers and board members: Tom Bersot, Matthew Ito, Edward Gill, Eliot Brinton, Karol Watson, Wayne True, Donna Polk, Bryan Pogue, Benjamin Ansell, Alan Bottenberg, Greg Brown, and Mary Ann Champagne.

This is only a partial list. Some people need special recognition for the amount of time and effort that they have contributed to our programs. Michael Davidson has done huge amounts of work in the development of our NLA SAPs as well as the Complex Lipid Management (CLM) and Self Study Module (SSM) self-assessment profiles programs. Jim McKenney has headed the Statin Safety Task Force leading to the production of two extraordinary supplements to the American Journal of Cardiology that will be a resource for years to come. In addition he had been one of the leaders in the Accreditation Council for Clinical Lipidology. Jerome Cohen has chaired the Consumer Affairs Committee which continues to work on ways to educate consumers.

None of the above accomplishments would be possible without the assistance and often the push of Christopher Seymour, our Executive Director, and his staff. The education group including Medical Education Director Nicola Sirdevan along with Jennifer DiPietro and Nicole Woodsmall have helped to produce the content of our meetings and maintain the quality and integrity of our speakers and educational materials. Shannon Sheridan has been a tireless meeting planner: the words do not even begin to cover the depth of detail and effort involved in making our regional and annual meetings go smoothly and occur in wonderful locations with amazing events. With Adam Beamer, Erin Lingerfelt and now Lindsey Otto, those of us working on committees, task forces, and regional and national boards have had our work made easier. Behind the scenes as well, Daniel Sosnoski, publications manager, has worked on everything from the Lipid Spin, the Journal of Clinical Lipidology as well as helping to craft important statements posted on our website as well as media interactions. And let us not forget Clark Morgan, who works magic with the audiovisuals at meetings as well as our web site.

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Omega 3 Fatty Acids in the Treatment of Dyslipidemia

Introduction

Although largely unrecognized by health care practitioners, it has been known for decades that inclusion of large amounts of omega 3 fatty acids (O3FA) in the diet lowers triglyceride levels. Contributing to confusion in this area has been the increasing use of small doses of O3FA to reduce sudden death in subjects with coronary heart disease (CHD), but which have no significant effect on the lipid profile. However recognition of the limitations of statin therapy in recent years, and of the importance of hypertriglyceridemia as a marker of an atherogenic lipoprotein profile beyond LDL-C, has led to renewed interest in O3FA as an anti-dyslipidemic agent especially now that a prescription preparation is available.

Earlier studies demonstrated that the major effect of O3FA on the lipid profile is to lower triglyceride levels between 10-45% depending upon the severity of the hypertriglyceridemia and the dose of O3FA used. At the same time, there is also a tendency for the LDL-C to rise between 0-30%, for LDL particle size to enlarge and for HDL-C to increase between 0-7%. The purpose of this review is to provide a modern perspective based on more recent studies of the role of O3FA as they relate to the management of dyslipidemia.

Actions of Omega-3 Fatty Acids on Lipoproteins

O3FA produce their triglyceride lowering action mainly through a reduction in hepatic triglyceride synthesis and VLDL secretion. At least 2 gms of O3FA is required daily to demonstrate an effect, which is dose related. Although the pool of LDL apo B is unchanged there is a tendency for LDL-C to rise is at least in part related to an increase in LDL particle size without a change in LDL particle number resulting from reduced cholesteryl ester-triglyceride exchange, aided by a treatment-related reduction in CETP activity. Several studies indicate that O3FA treatment also reduces postprandial lipemia though the mechanism for this is unclear, and O3FA may decrease apo C-III levels. Accompanying these effects both apo A-I production and clearance are slowed, with little change or at most a modest increase in HDL-cholesterol.

Utility of Omega-3 Fatty Acids in Dyslipidemic States

Although the labeled indication for P-O3FA currently is for severe hypertriglyceridemia, O3FA have been extensively tested in subjects with milder forms of dyslipidemia.

1. Severe hypertriglyceridemia

The approval of the P-O3FA Omcor/Lovaza, was based on two clinical trials testing its efficacy and safety in subjects with severe hypertriglyceridemia using 4 gm/day. In these studies, triglyceride levels were reduced by 45% and 40%, the HDL-C increased by 13% and 6% and the

In lower risk subjects … in whom long-term CVD risk is high, a case can be made for primary O3FA therapy.

Omega 3 fatty Acid Preparations

Until the availability of a prescription omega-3 fatty acid (P-O3FA) preparation in 2004 (Lovaza, formerly

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OMEGA 3s
LDL-C rose by 31% and 17%, respectively. These effects are similar to those of the fibrates, which have traditionally been the first pharmacotherapeutic choice in patients with severe hypertriglyceridemia. There has been a single head-to-head comparison between P-O3FA (4 gm/day) and gemfibrozil (1200 mg/day) in subjects with severe hypertriglyceridemia in which the two agents lowered triglyceride levels by 37% and 40% respectively while increasing HDL-C (11% vs 17%) and LDL-C (30% vs 34%) similarly. This suggests that either of these classes of agents may be chosen as initial therapy, but that the two agents are likely to have additive effects when used together because of their differing mechanisms of action. This needs to be assessed in a controlled clinical trial. Given the increased risk of rhabdomyolysis with statin + fibrate combinations, one advantage for initial treatment with O3FA rather than a fibrate is that subsequent addition of statin therapy once the triglyceride level is <500 mg/dl, is safer than if the patient is taking a fibrate. Other possible advantages for O3FA over fibrates include a lack of interaction with other drugs, safety in subjects with chronic kidney disease, and better evidence for CVD protection in statin treated subjects.

2. Atherogenic lipoprotein phenotype

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) based its recommendations for pharmacotherapy primarily on LDL-C, and secondarily on non-HDL-C cutpoints when triglyceride level >200 mg/dL. In high-risk subjects, these cutpoints are 70-100 mg/dL for LDL-C and 100-130 mg/dL for non-HDL-C, whereas for lower risk subjects the recommended cutpoints are at least 30 mg/dL higher. Thus, in those with a CHD risk equivalent, O3FA would principally be used as add-on therapy to statins. In lower risk subjects, who do not necessarily qualify for statin treatment, but in whom long-term CVD risk is high, a case can be made for primary O3FA therapy.

Combination Therapy With Statins In Subjects With Cardiovascular Disease

A large proportion of subjects with a CVD risk equivalent have an atherogenic lipoprotein phenotype. Although statin treatment is effective in reducing CVD events, the triglyceride-lowering action of these agents is less impressive. Because high-risk subjects treated with statins continue to experience CVD events, and non-HDL-C is a better predictor of events than LDL-C, agents that are effective at lowering triglyceride and VLDL-C such as O3FA may add to the benefit of primary statin therapy. An equally important rationale for combination statin+O3FA treatment relates to the cardioprotective properties of O3FA that appear at least in part to be independent of lipoprotein effects. Studies such as the GISSI Prevenzione study demonstrated that treatment with 1 gm/day of P-O3FA, which did not lower triglyceride levels significantly, was accompanied by reduced CVD mortality, especially sudden death.8 Similarly studies evaluating the associations between fish intake and CVD show a benefit for low doses of O3FA on CVD death.9

A standard dose of 4gm O3FA /day added to statin therapy in dyslipidemic subjects with coronary heart disease (CHD) was previously shown to cause a durable 20-30% lowering of triglyceride levels, a 30–40% decrease in VLDL-C and an 18% reduction in non-HDL-C with little change in LDL-C or HDL-C.10 More recently, the efficacy of P-O3FA (4gm/day) versus placebo to reduce non-HDL-C when added to simvastatin 40 mg/day was studied in 254 hypertriglyceridemic men (mean baseline triglyceride 282 and 287 mg/dl) for 8 weeks only.11 The median reduction in non-HDL-C resulting from add-on O3FA was 9% versus 2% in placebo group. The median triglyceride reduction was 30% versus 7%, the VLDL-C decrease was 28% versus 7%, there was a slight increase in HDL-C (3.4% versus -1.2%) and no change in LDL-C. Despite this rather modest effect on the

Figure 1. Median percent change in non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), calculated very-low-density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) from baseline to the end of treatment.

(From Davidson, MH., Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007: 29; 1354-67.)
non-HDL-C, as many as 52% of those who were not at their non-HDL-C goal at baseline achieved it on the combination treatment compared to only 24% on the statin+placebo combination (Fig 1). Doses smaller than 4 gm/day of O3FA added to statins are less efficacious for lipid lowering. Whether the full dose of the prescription preparation has a greater cardioprotective effect compared to low dose O3FA has not been formally tested.

The results of the recently published JELIS (Japan EPA Lipid Intervention Study) trial provide new information on this question. In JELIS, 18,645 patients with a total cholesterol level of >250 mg/dL were randomized to receive statin therapy (pravastatin 10 mg or simvastatin 5 mg) alone or in combination with 1.8 gm daily of EPA for 5 years. The purified EPA preparation was chosen because it is an approved treatment for hyperlipidemia in Japan. The average age of participants was 61 years, 31% were men, 16% had diabetes and about 20% had CHD. The average baseline LDL-C was 183 mg/dL, triglyceride was 155 mg/dL, and HDL-C was 59 mg/dL. As one might expect from the relatively small dose of O3FA used, the lipid changes in that group were modest; there was no difference in LDL-C reduction (~25% in each group) or in HDL-C in the two groups while the triglyceride level fell only 9% in the EPA compared to the control group. Among the statin-only group 3.5% had a major coronary event, whereas among the statin+ EPA group 2.8% had an event. The hazard ratio was 0.81 (95% confidence interval was 0.69-0.95) and p=0.011 (Fig 2). Importantly the reduction in events was due to fewer non-fatal events (Fig 3, p=0.015) rather than a significant reduction in sudden death or fatal myocardial infarction (MI) as has been shown in most intervention studies with low dose O3FA. This suggests that in JELIS, the cardioprotective effect of O3FA was less likely to be due to its anti-arrhythmic properties which have been used to explain the effect of low dose O3FA to reduce sudden death. Since the protective effect against sudden death occurs at relatively low doses e.g. 0.35–1.0 gm O3FA daily and because of the high fish intake in Japan, it was proposed that the placebo group was protected against sudden death allowing the higher dose effect on non-fatal MI to manifest in the O3FA group. This concept is supported by the fact that in addition to the anti-arrhythmic properties, at a dose of 1.4 gm/day O3FA appear to have plaque-stabilizing effects that might protect against plaque rupture and acute coronary syndrome which might be expected to protect against MI. Whatever the explanation, these studies demonstrate a significant cardioprotective effect of O3FA, and specifically that addition of O3FA can expand the cardioprotective effect of statin therapy.

The Use of Omega-3 Fatty Acids in Selected Dyslipidemic States

The anti-dyslipidemic effects of O3FA both as monotherapy, as well as add-on therapy to statins, coupled with its CVD protective effect and safety record, suggest a role for O3FA in selected high-risk dysmetabolic states, even in the absence of overt CVD. These include diabetes, chronic renal insufficiency, human immunodeficiency virus (HIV) disease and possibly metabolic syndrome. In addition, because of their safety they may have utility in children with significant diet-resistant dyslipidemia.

1. Diabetes

Diabetes is considered to be a CHD risk equivalent by NCEP ATP III. The majority of type 2 diabetic subjects have triglyceride levels >150 mg/dL and/or reduced HDL-C often with the small dense LDL phenotype. Thus, such individuals are recommended for primary statin therapy; however, statin-treated individuals remain at significant risk for CVD and thus should benefit from the additional lipid-modifying and cardioprotective effects of O3FA. As in the general population, inverse associations between fish intake and CVD have been noted in subjects with diabetes and higher degrees of fish intake were accompanied...
by less angiographic progression of CHD in diabetic women.\textsuperscript{17} In an open label study, 1.8 gm/day of EPA reduced carotid wall thickness progression over 2 years compared to no additional treatment in 60 subjects with type 2 diabetes.\textsuperscript{18} Older individuals with type 2 diabetes, particularly those with renal disease, are at increased risk for rhabdomyolysis related to statin+fibrate combination therapy, and niacin may not be well-tolerated in these individuals. Studies with O3FA in diabetic subjects have shown similar effects on the lipid profile to that reported in non-diabetic subjects, without any alteration of glycemic control or other significant adverse effects.\textsuperscript{19}

In a short-term study of 26 type 2 diabetic subjects, 4.8 gm/day of O3FA reduced the concentration of large VLDL and small HDL particles, without significant changes in LDL particle size or number.\textsuperscript{20} In addition, add-on O3FA (3.6 gm/day) administered to type 2 diabetic subjects who had not reached lipid targets despite treatment with pravastatin+fenofibrate, significantly lowered plasma homocysteine levels in addition to its additional lowering of triglyceride levels.\textsuperscript{21} Trials to test the long-term benefits of O3FA treatment on CVD outcomes in subjects with glucose intolerance include the Outcome Reduction With Initial Glargine Intervention (ORIGIN) testing the effects of O3FA on cardiovascular mortality in subjects with impaired fasting glucose, impaired glucose tolerance, and early diabetes (clinicaltrials.gov/ct/show/NCT00069784) and A Study of Cardiovascular Events in Diabetes (ASCEND) evaluating the effects of either aspirin, EPA and DHA, or placebo by factorial design on non-fatal stroke or MI, and vascular death (clinicaltrials.gov/ct/show/ NCT00135226).

2. Chronic Kidney Disease

Chronic kidney disease (CKD) is considered to be a CHD-risk equivalent and is commonly associated with dyslipidemia. Thus there may be value in adding O3FA to statin therapy, especially in subjects with increased non-HDL-C. Although there have been no systematic trials of O3FA treatment in dyslipidemic subjects with CKD, the fact that fenofibrate and full doses of gemfibrozil are not recommended in these individuals, and there is little experience with niacin, point to a rationale for O3FA in dyslipidemic subjects with CKD. O3FA have a record of safe use in subjects with IgA nephropathy, where they appear to attenuate progression of disease possibly through anti-inflammatory effects, and in renal transplant recipients,\textsuperscript{22} although no overall benefit was shown in this meta-analysis. Finally, O3FA may be useful in subjects with severe hypertriglyceridemia due to nephrotic syndrome.

3. HIV Disease

CVD has emerged as an important concern among the HIV-infected population. Dyslipidemia due both to the infection and as a consequence of antiretroviral therapy, is likely to be an important determinant. It is recommended that dyslipidemia be actively identified and treated according to NCEP ATP-III guidelines in these subjects. Although statin therapy will be preferred in subjects with elevated LDL-C levels, hypertriglyceridemia is
common, especially in patients treated with protease inhibitors. As a consequence statins may either not be the agent of choice, or if used as primary therapy may not be sufficient. In addition, many antiretroviral drugs inhibit the P450 3A4 cytochrome enzyme system which is important in the clearance of several statins and therefore increase the risk of rhabdomyolysis with those statins. This also increases the risk associated with fibrate use in statin-treated patients and has thus led to interest in the use of O3FA. Four randomized trials of O3FA in patients with HIV and hypertriglyceridemia receiving highly advanced antiretroviral therapy but not administered statins have been reported in the past few years. Collectively they show similar efficacy and tolerability to what has been demonstrated in other studies, with no effects of O3FA on viral or immunologic parameters. Studies of combination therapy of O3FA with statins that are not metabolized through 3A4 are needed to more fully assess the role of O3FFA in the management of the dyslipidemia that accompanies HIV disease.

4. Other states

Dyslipidemic subjects with a high risk for CVD such as those with familial combined hyperlipidemia or older subjects with the metabolic syndrome could be considered for O3FA treatment. The use of O3FA in children has been fairly widely reported for conditions such as IgA nephropathy and appears to be well-tolerated and safe. Hence, O3FA may be useful in the management of hypertriglyceridemia in children and adolescents. Finally, although all triglyceride-lowering drugs including P-O3FA are listed as category C drugs in relation to pregnancy, P-O3FA may be the safest first choice in pregnant women with severe hypertriglyceridemia.

Conclusion

Although statin treatment in high-risk subjects reduces CVD, it is recognized that such individuals remain at considerable risk for CVD events. O3FA treatment has been shown to reduce CVD risk in statin-treated subjects and at prescription strength doses it has significant triglyceride lowering properties and will increase the proportion of statin-treated subjects reaching their non-HDL-C goal. Thus a case can be made for the use of O3FA at prescription strength in high-risk patients particularly those receiving statin therapy.

References


Possible Clinical Applications for Omega 3 Fatty Acid Therapy

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Therapy</th>
</tr>
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</table>
| 1. Severe hypertriglyceridemia | - monotherapy  
- combination therapy with fibrate |
| 2. Atherogenic lipoprotein phenotype with CVD | - combination therapy with statin |
| 3. Atherogenic lipoprotein phenotype without CVD  
   (a) Type 2 diabetes  
   (b) Chronic renal failure  
   (c) HIV disease  
   (d) Metabolic syndrome (high risk) | - combination therapy with statin  
- combination therapy with statin  
- monotherapy or combination therapy with statin  
- monotherapy or combination therapy with statin |
| 4. Hypertriglyceridemia in children | - monotherapy |


This article focuses on actual lipid disorders from actual patients and how one clinical lipidologist, evaluates the available clinical and laboratory data and then arrives at a therapeutic solution. Dr. Dayspring has been in practice 33 years and lectures extensively throughout the country on lipid/lipoprotein issues. He authored the chapter in *Therapeutic Lipidology* dealing with phytosterolemia and the absorption, synthesis and excretion of cholesterol and noncholesterol sterols.

**Case One**

A 26-year-old woman presents to her gynecologist with amenorrhea and questions about conceiving. She has a history of polycystic ovary syndrome (PCOS) since age 16. Her height is 5’1”, and her weight is 210. BP is 116/92. Her laboratory data (unless otherwise indicated all values are mg/dL) are as shown in the box below:

The provider forwarding this case asked for a discussion of the lipid metabolic pathways that create this potentially high risk profile typical of PCOS patients. An increasing number of the lipid/lipoprotein abnormalities providers now see are related to insulin resistance. It does make sense to try and fully understand why patients such as this may have significant risk for CHD yet have at goal or borderline LDL-C levels. These are precisely the patients where clinicians have to be less LDL-C centric. PCOS is an insulin resistant state, associated with androgen excess, obesity, insulin resistance, amenorrhea, infertility as well as a multitude of metabolic abnormalities that increase cardiovascular risk.¹

The key to understanding CV risk attributable to lipids is to recognize the crucial fact that lipids like TG, phospholipids and cholesterol and other sterols go nowhere in the human body unless a lipoprotein traffics them somewhere. Thus, comprehension of atherogenesis and its prevention or treatment must be focused on lipoproteins. The only way sterols penetrate the arterial wall is as passengers inside of lipoprotein particles. It really does not matter how much cholesterol is in a given lipoprotein per se, it is the number and the various qualities of that vehicle (particle) that determines the destiny of the

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**From the Files**

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<table>
<thead>
<tr>
<th>Original profile (over a year ago):</th>
<th>One month later the patient started metformin. Her current labs (a year later from above) are:</th>
<th>NMR LipoProfile (lipoprotein concentrations via nuclear magnetic resonance spectroscopy)</th>
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<tbody>
<tr>
<td>TC = 221</td>
<td>TC = 203</td>
<td>LDL-P = 1820 nmol/L (desirable &lt; 1300, perfect &lt; 1000)</td>
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<tr>
<td>TG = 286</td>
<td>TG = 379</td>
<td>Small LDL-P = 1556 nmol/L (perfect &lt; 600)</td>
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<tr>
<td>HDL-C = 49</td>
<td>HDL-C = 37</td>
<td>LDL particle size = 19.5 nm (quite small)</td>
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<tr>
<td>LDL-C = 115</td>
<td>LDL-C = 90</td>
<td>Cutoff between Pattern A (normal) and Pattern B (small is 20.5)</td>
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<tr>
<td>VLDL-C = 57</td>
<td>VLDL-C = 75</td>
<td>Large HDL-P 3.9 umol/L (quite low)</td>
</tr>
<tr>
<td>Non-HDL-C = 221 – 49 = 172</td>
<td>Non-HDL-C = 166</td>
<td>Small HDL-P was not provided (but likely it is quite high)</td>
</tr>
<tr>
<td>TC/HDL-C = 4.5</td>
<td>TC/HDL-C = 5.4</td>
<td>Large VLDL-P 23.1 nmol/L (extremely high, normal &lt;0.5)</td>
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<tr>
<td>TG/HDL-C = 5.8</td>
<td>TG/HDL-C = 10.24</td>
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<tr>
<td>FBS 82.</td>
<td>Fasting insulin 26.</td>
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</tbody>
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¹ Thomas Dayspring, MD, FACP, October 2017

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The key to understanding CV risk attributable to lipids is to recognize the crucial fact that lipids like TG, phospholipids and cholesterol and other sterols go nowhere in the human body unless a lipoprotein traffics them somewhere. Thus, comprehension of atherogenesis and its prevention or treatment must be focused on lipoproteins. The only way sterols penetrate the arterial wall is as passengers inside of lipoprotein particles. It really does not matter how much cholesterol is in a given lipoprotein per se, it is the number and the various qualities of that vehicle (particle) that determines the destiny of the
lipids being trafficked. We need to know which of the various lipoproteins are potentially atherogenic (capable of arterial wall entry and macrophage ingestion) and which are not. Having that knowledge, we must then determine how best to utilize the laboratory to diagnose risk accurately: i.e., should we be ordering lipid or lipoprotein measurements.

Although there are many ways to separate lipoproteins in research labs, in the real world it is for the most part done by ultracentrifugation (VAP and others), nuclear magnetic resonance spectroscopy (NMR) or electrophoresis (Berkeley and others). A convenient way of classifying lipoproteins is to identify them by their surface “apolipoproteins” that provide the particle with structure, stability and solubility. One to four molecules of ApoA-I enwrap each HDL particle, classically called the alphalipoproteins, and a single molecule of apoB surround each of the betalipoproteins: Chylomicrons, VLDLs, IDLs and LDLs as well as another type of LDL termed Lp(a). We have known for some time that the apoB particles are potentially atherogenic, but before we recognized the concept of dysfunctional or proatherogenic HDLs it was thought that all apoA-I particles were always cardioprotective. However, newer data has now introduced the concept dysfunctional or proatherogenic HDLs, present in proinflammatory states like insulin resistance. Multiple epidemiological and therapeutic trials have shown that ApoB or the apoB/A-I ratio is the best predictor of CV risk. It should be apparent that measuring apoB or apoA-I is one method of collectively quantitating how many of the lipoproteins exist in a deciliter (dL) of plasma. If one uses NMR instead of apoB, we get actual concentrations of the individual lipoprotein species: VLDL-P, IDL-P, LDL-P, and HDL-P. Although the apoB “dump trucks” are the potential “illegal dumpers” of cholesterol, because of its very long half-life, LDL particles make up > 90% of the betalipoproteins in most people, making LDLs the prevalent trafficker of sterols into our patient’s arteries. Many consider apoB to be synonymous with LDL-P, but several studies now exist where LDL-P was a better predictor of risk than was apoB suggesting to me that if we are to spend extra healthcare dollars on lipoprotein testing, LDL-P, rather than apoB is the way to go. Multiple studies have shown that it is particle number, not how much cholesterol is in the various particles, (LDL-C, VLDL-C, and HDL-C) that are the best correlates of CV risk. Patients with too many betalipoproteins or, worse yet, too many beta and too few alphalipoproteins have the highest CV risk. If one uses traditional lipid profiles, the lipid concentration surrogate(s) (predictors) of apoA-I is HDL-C and that of apoB are: TC, LDL-C and best of all, Non-HDL-C. VLDL-C is a notoriously poor predictor of apoB since VLDL-C is calculated as TG/5—patients with high TG might simply have large, TG-rich particles rather than too many TG-containing particles: thus TG and VLDL-C go up, but VLDL-apoB or VLDL-P may or may not. In recent data from the Framingham Offspring Trial, just published in the Journal of Clinical Lipidology, Non-HDL-C was a better predictor of risk than LDL-C, but LDL-P was the best of all. Since >90% of the apoB particles are LDLs, it now seems the real reason Non-HDL-C is a better predictor of risk than is LDL-C is that Non-HDL-C correlates better with LDL-P than does LDL-C. Interestingly, from that same population, in a separately published paper in JAMA, apoB was surprisingly no better than the TC/HDL-C ratio in predicting risk.

Back to the case: This woman, with her insulin resistance, in part related to her androgen excess so typical of PCOS, is greatly over-producing apoB-containing TG-rich VLDLs (note the large VLDL-P of 23.1). Of course, if her liver is making too many large VLDLs, her serum TG will be high and de facto her VLDL-C (TG/5) is quite high at 75 (379/5 normal < 30). As the VLDLs are exposed to lipoprotein lipase (LPL), the TG-rich VLDLs ultimately undergo lipolysis (hydrolysis or breakdown of its lipid contents). Once TG is depleted, the majority of the now smaller VLDLs
or IDLs are rapidly removed by hepatic LDL receptors (LDLr) which attach to the particle’s apoB/E: however, some undergo further lipolysis upon exposure to hepatic lipase and form LDLs, which because of their lack of apoE and reduced LDLr clearance, have a long half-life and accumulate, raising apoB/LDL-P.

In patients with insulin resistance, the lipolysis is often significantly delayed, lasting 8–12 hours or more, rather than 2–6 hours as is normal because the increased numbers of VLDLs compete with TG-rich chylomicrons for lipoprotein lipase (LPL), and increased amounts of apoC-III prevent the interaction of surface apoC-II with LPL. As the TG-rich particles circulate they create endothelial damage by increasing blood viscosity, impairing endothelial nitric oxide production, upregulating inflammatory, and coagulable proteins. Also with increased plasma residence time, the VLDLs can be acted upon by cholesteryl ester transfer protein (CETP) which swaps their TG and for cholesteryl ester (CE) within HDLs and LDLs. This radically changes the composition of the VLDLs, HDLs and LDLs, with the former become CE-rich (raising VLDL-C) and the latter two becoming TG-rich and CE-poor (lessening HDL-C and LDL-C). HDLs and LDLs that now carry too much TG, also undergo lipolysis as they pass through the liver: hepatic lipase hydrolyzes both their TG and surface phospholipids, resulting in much smaller HDLs and LDLs. Some of the HDLs can become so small they pass through the glomeruli and are excreted (contributing to the very large HDL-P level, low large HDL species, low HDL-C and presence of predominantly small HDL-P). Of course the VLDL-C increases as it receives CE that used to be in LDLs and HDLs (smaller, cholesteryl-rich VLDLs or chylomicrons are called remnants). Because the LDLs are so much smaller (in this case 19.5 nm) it takes extremely large numbers to traffic (carry) the 90 mg/dl of cholesterol that is in this woman’s plasma. The volume of a sphere is calculated as 4/3piR³ meaning it is related to the third power of the particle radius explaining why any shift of particle size translates into significantly different volume capacities. There are several clues in this patient’s lipid profile that would have predicted the NMR findings of LDL-P, VLDL-P excess and small LDL phenotype of, increasing the catabolism of or removing the existing LDLs from plasma. The most potent lowering apoB/LDL-P monotherapy drugs are statins (with varying potencies) which upregulate hepatic LDL receptors capable of attaching to apoB and clearing LDL-P from plasma (a process now called indirect reverse cholesterol transport). However, if one adds ezetimibe or a bile acid sequestrant to the statin, there will be further depletion of hepatic cholesterol pools and upregulation of many more LDL receptors than the statin can upregulate by itself: hence combo-therapy as an initial choice can make great sense getting to goal. The patient’s glucose is normal on the metformin: if it were not colesevelam, a bile acid polymer might be an interesting add-on to the statin as it has recently shown an ability to improve glycemic parameters. Ultimately in this patient one will have to significantly diminish TG synthesis and that is where fibrates, niacin and high dose N-3 fatty acids can help out. By reducing production of hepatic TG, and enhancing lipolysis of TG-rich lipoproteins, these drugs will produce less TG-rich VLDLs which will have downstream benefits on HDL and LDL composition: LDL size increases making the LDL more amenable to LDL receptor removal and the larger HDLs are not subject to renal excretion increasing HDL-P and HDL-C. Blood viscosity and the other aforementioned

There are several clues in this patient’s lipid profile that would have predicted the NMR findings of LDL-P, VLDL-P excess and small LDL phenotype.
rheological abnormalities also improve. In this women with insulin resistance the TG are clearly the problem and if the patient does not achieve lipid or lipoprotein goal with the statin or statin/ezetimibe/BAS I would consider fenofibrate or fenofibrate plus N-3 FA as additional therapy rather than niacin. Others would simply add N-3 FA to the initial therapy. Since this is a young woman we hope she really tries the lifestyle so we can minimize the drugs. Also take note that if N-3 fatty acids are prescribed for TG-benefit, one must use 4000 mg daily as lesser doses are ineffective.

Final caution: Since metformin can improve her fertility and most lipid-modulating drugs must be used with caution, one must address contraception before using the above therapies in such a patient. Often such women for a variety of reasons are prescribed oral contraceptives which would solve that problem. If however, the patient wants to conceive, lipid management would consist of aggressive lifestyle therapeutics, and high dose N-3 FA. Two articles of great interest to women with CV risk were just published. The first is data from the ERA (Estrogen Replacement in Atherosclerosis Study) in menopausal women revealing that the degree of coronary atherosclerosis in postmenopausal women is linked to a dysregulation of TG/HDL metabolism. Subpopulations of TG-rich and HDL lipoproteins are better predictors of disease than the actual TG and HDL cholesterol concentrations. The second article sheds light on which women may be responsive to estrogen administration with respect to atherosclerosis. The conclusion was that estrogen and sex hormone binding globulin (SHBG) are associated with reduced subclinical atherosclerosis progression in healthy postmenopausal women. These associations are partially mediated by their beneficial effects on lipids. Among women taking estradiol, the most beneficial hormone profile associated with CIMT progression was increased free estradiol and SHBG with concomitant decreased free testosterone. In the PCOS case just discussed, the patient likely has increased testosterone and decreased SHBG and this may help explain why such patients have increased CV risk.

Case Two

The second case is timely in view of the recent controversy regarding ezetimibe and this case was written before the ENHANCE data were released. The case is a menopausal woman with a family history of premature heart disease, who is a “naturalist” with a love of herbal medication. She uses 4000 mg of pure natural fish oils/day. Her past history includes a cholecystectomy. She has a normal BMI. Two months prior she had a lipid panel as shown below at left, and her repeat panel after taking ezetimibe (Zetia) 10 mg daily is shown at right:

<table>
<thead>
<tr>
<th>Original panel</th>
<th>After 3 months of Zetia 10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC = 221</td>
<td>TC = 225</td>
</tr>
<tr>
<td>LDL-C = 155</td>
<td>LDL-C = 164</td>
</tr>
<tr>
<td>HDL-C = 42</td>
<td>HDL-C = 48</td>
</tr>
<tr>
<td>TG = 121</td>
<td>TG = 63</td>
</tr>
<tr>
<td>VLDL-C = 24</td>
<td>VLDL-C = 12</td>
</tr>
<tr>
<td>Non-HDL-C = 179</td>
<td>Non-HDL-C = 177</td>
</tr>
<tr>
<td>TC/HDL-C = 5.2</td>
<td>TC/HDL-C = 4.6</td>
</tr>
<tr>
<td>TG/HDL-C = 2.8</td>
<td>TG/HDL-C = 1.3</td>
</tr>
</tbody>
</table>

The patient was 100% compliant with medication, so both she and her clinician were disappointed with this response, as the published data and ezetimibe’s package inserts would have one expect a 15–20% drop in LDL-C. The provider wondered if the absence of the gall bladder might affect ezetimibe’s action. The answer to that is quite simple: No. The gall bladder (GB) is irrelevant to a patient’s lipids: it is simply a storage organ for bile acids, phospholipids and cholesterol in their journey from the liver to the gut. Without the GB, the bile and cholesterol simply flows to the intestinal lumen without being stored. So having or not having a GB plays has no effect on the amount of biliary sterols or bile acids that reach the intestine in a 24-hour period. With an intact GB, those molecules are delivered postprandially: without a GB they are constantly delivered.

Before we figure out what ezetimibe did or did not do, we need to review how the intestine and liver handle sterols (this happens to be what my chapter in Therapeutic Lipidology covers). Cholesterol exists in either an esterified or unesterified (free) state. The free cholesterol (FC) is an alcohol (sterol) with a hydroxy (-OH) group at the #3 position and the ester (cholesteryl ester or CE) has a fatty acid replacing the -OH. Every cell in the body can synthesize cholesterol in a complex series of over 37 conversions with the rate limiting step being catalyzed by HMG CoA reductase. For FC to be stored for future use or to be transported by lipoproteins, esterification occurs within the endoplasmic reticulum of cells using an enzyme called acylcholesterol acyl transferase 2 (ACAT-2) or within lipoproteins using an enzyme called lecithin cholesterol acyltransferase (LCAT). If a cell wants to export CE, it must de-esterify it, using an esterolase, to FC (the
CASE STUDIES

The cholesterol consumed in the diet (300–600 mg daily) consists of both FC and CE (20% CE and 80% FC). The same amounts of noncholesterol sterols are also usually ingested whereas all of the cholesterol excreted in the bile is FC (1200 mg/day). The CE in the diet is acted upon by intestinal esterolases in which transform some of it to FC. The CE that is not converted to FC cannot be absorbed by the intestine. So if one eats 500 mg of cholesterol, maybe 100–200 mg is CE only some of which is converted to FC. This joins with the 1200 mg of bile FC. Thus the vast amount of FC in the intestine is of biliary origin, not dietary origin. It should be obvious why restricting cholesterol in the diet is unlikely to play a major role in lipid control. Within cells the majority of FC synthesis is from FA byproducts, and thus restriction of saturated fat should be the major dietary advice to lower cholesterol.

As soon as FC (CE cannot be transferred from hepatocyte to bile) is secreted from the liver to the bile, through the hepatobiliary canalicular membrane via an ATP binding cassette transporter G5 and G8 (ABCG5, ABCG8), it mixes with biliary bile acids and phospholipids forming biliary micelles. Since the bile acids and phospholipids are amphipathic molecules (have both a polar and nonpolar surface: i.e. water soluble and non-water soluble) they are soluble in aqueous intestinal juices. Once in the intestine dietary noncholesterol (plant and shellfish) sterols and fatty acids also enter the micelles. The micelles, once loaded up with lipids, enter to the microvilli of the intestinal brush border. Fatty acids pass via diffusion and fatty acid transport proteins into the enterocyte. The sterols are pulled in by what used to be called a sterol permease (a protein that permits sterols to enter) but has now been identified as the Niemann-Pick C1 Like 1 (NPC1L1) protein. There are other proteins and processes involved with sterol entry (see Therapeutic Lipidology for more advanced discussion). Only FC enters the micelle and only FC or unesterified noncholesterol sterols can gain entry into the enterocyte: CE is not absorbed.\(^7,8\) NPC1L1 has also been indentified at the hepatobiliary canaliculi where it can facilitate the backwards movement of biliary cholesterol into the hepatocyte.

So at any given moment, small intestinal sterols come from 1) exogenous sources (eating), and 2) hepatic excretion of endogenously produced cholesterol: bile enters the intestine as constant diffusion in those lacking a gall bladder or in those with a GB, postprandially after GB contraction. Over a 24-hour period, the same amount of biliary FC enters the gut: the gall bladder plays no role in sterol regulation. The majority of intestinal sterols are of biliary, not dietary origin. Many are surprised to learn that vegetarians, eating no cholesterol, have the same cholesterol absorption rates as meat eaters. They are simply absorbing their biliary cholesterol.

Although the average person absorbs about 50% of the FC in the proximal small intestine, the cholesterol absorption varies tremendously between individual patients. Some are hyper (70–90%) and some are hypoabsorbers (20–30%). If someone is a hypoabsorber, they have very little expression of NPC1L1, which is required for sterol delipidation of micelles and entry into the enterocyte. It is very likely that the patient under discussion is a hypoabsorber of cholesterol due to very little intestinal expression of NPC1L1 protein. Ezetimibe’s main mechanism of action blocks NPC1L1 protein from working. Persons who have reduced expression of NPC1L1 protein obviously will be hypoabsorbers of sterols and have very little response to ezetimibe. Conversely, someone with upregulation of NPC1L1 will be over absorbers of sterols and hyper-responders to ezetimibe.\(^9\)

There are ways to evaluate intestinal sterol absorption: 1) measure plasma noncholesterol sterol levels: they will be extremely low/high in hypo/hyper absorbers. This is only practical in research settings. 2) Observe the response to a statin. This patient has a high LDL-C level; if that is not explained by over-absorption of cholesterol, it has to be due to over-production. Any person who is over-producing cholesterol will have lots of HMG CoA reductase. The more of that enzyme that is present, the more efficacious is a statin. If one prescribes what NCEP calls the standard dose of a statin, there should be a reduction of LDL-C by 35% in the average person. However, if the same dose is given to someone with increased HMG CoA reductase, the LDL-C reduction will be significantly greater. This patient’s lack of response to ezetimibe suggests she is an over-producer and predicts she might respond well to even small doses of a statin.

Conversely, if a statin is given to a hyperabsorber of cholesterol there will be a very poor response to the statin (“hyporesponder”). If someone is over-absorbing cholesterol there will be a marked reduction of cellular expression of HMG CoA reductase and hence less cholesterol synthesis.

Many are surprised to learn that vegetarians, eating no cholesterol, have the same cholesterol absorption rates as meat eaters. They are simply absorbing their biliary cholesterol.
Persons with little HMG Co A reductase expression will not respond well to statins. This is why when one prescribes a statin and sees reduced response, it may make increasing the dose of the statin futile. The problem is not hypersynthesis but rather hyperabsorption and the clear therapeutic response is to add ezetimibe. Since in most of our patients we have no clue who is a hyper or hypoabsorber or synthesizer, it may make sense to combine statin and ezetimibe therapy to achieve goal. This also makes sense for another reason: namely statin tachyphylaxis. This was first described with atorvastatin but has been seen with all statins. The statin works well but over time the LDL-C starts to rise somewhat again. The reason is becoming better understood. When one reduces cholesterol synthesis with a statin, the liver must obtain cholesterol elsewhere: it does that upregulating LDL receptors and clearing apoB LDL particles with their cholesterol from plasma. This clearly and rapidly reduces apoB and LDL-C. However, there is also another response to the decreased cholesterol synthesis by nuclear transcription factors which reduce excretion of cholesterol into the bile (down regulation of hepatobiliary ABCG5, G8 transporters, reduce bile acid synthesis, and increase biliary cholesterol to return to the liver through upregulation of NPC1L1 protein in hepatobiliary canaliculi. In the intestine there is an upregulation of NPC1L1 and downregulation of G5 and G8 with an overall effect of increasing intestinal absorption of FC.\(^7,10\)

An interesting study was published this year showing the effect of ezetimibe when given to pure vegans who eat almost no cholesterol. Humans synthesize enough cholesterol to satisfy cellular requirements. As explained above, since vegans have the same sterol absorption rates as meat eaters, they reabsorb their biliary cholesterol and thus ezetimibe reduces cholesterol absorption the exact same in vegans or in beef eaters, clearly suggesting the main action of ezetimibe is to block the absorption of biliary cholesterol, not dietary cholesterol.\(^10\)

Back to the case at hand, the proper choice in nonresponders to ezetimibe, who are likely over-synthesizers of cholesterol, is a statin, dosed appropriately to get her to goal. One should keep in mind that in this and other patients statin tachyphylaxis may occur. The statin will deplete cholesterol synthesis in the body. As cellular sterol levels decrease, there can be downregulation of the nuclear transcription factor that regulates sterols, namely the liver X receptor (LXR). LXR downregulation leads to an upregulation of proteins that will restore sterol levels to normal; i.e., increased NPC1L1 (increasing intestinal sterol absorption) and decreased ABCG5, G8 (decreasing intestinal and hepatic excretion of sterols). Obviously any statin-induced absorption of and decreased excretion of sterols in part defeats the amount of cellular cholesterol the statin will diminish.

Lastly, this naturalist may not want a chemical like a statin! Well lovastatin, simvastatin, and pravastatin are all distillates of their fungal precursors. Formerly they were called the “natural statins.” So the easiest way to control the LDL-C long term in this patient is to use one of the natural statins with ezetimibe (to prevent statin tachyphylaxis).

**References**

Polycystic Ovarian Syndrome, Insulin Resistance, and Lipids

Polycystic ovarian syndrome (PCOS), a disorder of androgen excess, is a highly prevalent disease affecting approximately 10% of reproductive-age women. The androgen excess appears to be driven by an underlying insulin-resistant state. Patients with PCOS have a high prevalence of the metabolic syndrome and as a result are at increased risk for type II diabetes as well as increased risk for cardiovascular disease. Impaired glucose tolerance (IGT) or overt type II diabetes develops by the age of 30 in 30–50% of obese women with PCOS. This article will focus on the lipid abnormalities that are typical of PCOS, the role of advanced lipid testing in assessment of these abnormalities, and an updated treatment approach focusing on insulin resistance.

PCOS is a clinical diagnosis associated with chronic anovulation and clinical or biochemical signs of hyperandrogenism, and in some patients polycystic ovaries. Complications of PCOS include infertility, menstrual dysfunction, hirsutism, acne and obesity. Some studies in PCOS patients show evidence of increased hsCRP, increased PAI-1, endothelial dysfunction, hyperhomocysteinemia, and increased carotid intimal medial thickness (CIMT), especially if age is above 45 years. Studies using coronary calcium scores as a surrogate showed young, obese women with PCOS have a high prevalence of early asymptomatic coronary atherosclerosis compared to obese controls.

The lipid abnormalities in PCOS patients are similar to metabolic syndrome patients and type II diabetics: low HDL-C (<50 mg/dL), low HDL2 subfraction, low Apo-A1, high triglycerides (>150 mg/dL), and increased small dense LDL particle concentration. The low HDL-C is independent of body weight. Compensatory hyperinsulinemia, often seen in these young patients, is frequently sufficient to keep glucose, even postprandial glucose levels, in the normal range. Insulin levels may be helpful to confirm insulin resistant state but may be normal as well. The American Association of Clinical Endocrinologists states “Because accurate assessment of insulin sensitivity is impossible in the clinical practice setting, it is prudent to regard all obese women with PCOS as likely having insulin resistance and being at risk for the insulin resistance syndrome (IRS) and to assume that most non-obese women with PCOS have the IRS as well.”

Referral of PCOS patients to a cardiometabolic lipid clinic may be appropriate, especially if other risk factors for cardiovascular disease exist. Also, patients with PCOS frequently have a discrepancy between calculated LDL cholesterol (LDL-C) and LDL particle concentration (LDL-P), as measured by NMR, or Apo B. An example is Sarah, a 20-year-old woman referred to our lipid clinic by her gynecologist due to diagnosis of PCOS and strong family history of premature coronary artery disease. Her BMI is 33.3 kg/m², waist circumference 38.5 inches, blood pressure 130/84, fasting glucose 76 mg/dL, 2-hour glucose after 75 g glucose challenge 111 mg/dL. She had a normal comprehensive metabolic panel, and TSH was normal at 1.21 µIU/ml. Clinical symptoms included fatigue, polydipsia, polyphagia, hirsutism and irregular menses. Her lipid panel revealed total cholesterol 167 mg/dL, LDL-C 69 mg/dL, HDL-C 64 mg/dL, triglycerides 174 mg/dL, and non-HDL-C 103 mg/dL. An NMR showed LDL-P 1794 nmol/L (optimal LDL-P <1000), small LDL-P 1421 nmol/L (optimal <850), large VLDL-P 7.8 nmol/L (high risk >5 nmol/L), and small LDL particle size consistent with pattern B. The calculated LDL cholesterol of 69 mg/dL meets even the most aggressive goal for lipid management, yet the NMR unmasks a severe dyslipidemia consisting of numerous small LDL particles.

Treatment with oral contraceptives has been a traditional approach that helps correct the reproductive and menstrual abnormalities thus providing symptom relief. Hormonal therapy, however, may be associated with adverse metabolic consequences such as decreased insulin sensitivity, impaired glucose tolerance, increased triglycerides, and increased risk of thrombosis. An adjunctive approach would address the insulin resistance which is at the core of the cardiovascular pathophysiology of this disorder. Hyperinsulinemia is in part due to genetic predisposition and obesity. Excess insulin leads to decreased sex hormone binding globulin (SHBG) synthesis in the liver and therefore increased levels of circulating free testosterone. PCOS is also managed with therapies that address the altered androgen metabolism. Spironolactone, an androgen...
antagonist, may be used to treat the hirsutism but neither spironolactone nor hormonal contraceptives address the underlying insulin resistance which will persist.

The initial treatment of PCOS should be aimed at weight loss because even a small reduction of body weight by 2–5 % and loss of visceral fat can restore ovulation, lower insulin levels, increase insulin sensitivity, increase SHBG and reduce testosterone levels and acne. LDL-C and LDL-P will generally improve with the weight loss. Our approach has been to prescribe exercise in the form of pedometers and step counts. Exercise for 60–90 minutes/day is recommended for weight loss and weight maintenance; this includes a minimum of 10,000 steps/day plus at least 30 minutes of moderate exercise. Our diet recommendations focus on high fiber, whole-grain food and lower intake of simple carbohydrates. We also advise eliminating intake of trans fat (partially hydrogenated oil).

If lifestyle change alone fails to produce weight loss, we consider the addition of metformin or thiazolidinediones (TZDs). Although not FDA approved for treatment of PCOS, metformin is commonly used in PCOS. Many studies have demonstrated safety and efficacy in this patient population. Metformin is a category B drug in pregnancy, and has no known fetal toxic effects, so it can be used fairly safely in young women. Metformin reduces plasma insulin levels, reduces blood pressure and reduces LDL-C. In our clinical experience, we see a more dramatic decrease in LDL-P than LDL-C with metformin than with lifestyle change alone. The Indian Diabetes Prevention program and US Diabetes Prevention program are major randomized trials that have shown that the use of metformin decreases relative risk of progression to diabetes among patients with IGT at baseline. There have been no randomized trials to date assessing the effect of metformin on the progression to type 2 diabetes in patients with PCOS specifically. Appropriate starting dose is 500 mg twice daily with food or long-acting formulation once daily.

Multiple studies of thiazolidinediones (TZDs) (troglitazone, Rosiglitazone, and Pioglitazone) have shown benefit in the treatment of metabolic abnormalities of PCOS. TZDs have also been shown to decrease androgen levels, improve ovulation, and reduce progression to overt type II DM in patients with PCOS and IGT. Lipids also improve with use of TZDs, although effects vary by specific TZD. Pioglitazone is more likely to produce a drop in triglycerides and an increase in HDL-C, whereas all TZDs shift LDL particles to large buoyant particles. However, TZDs may cause increased body weight. TZDs are considered category C drugs in pregnancy and, therefore, need to be used with caution in women of child-bearing potential.

The Androgen Excess Society released a position paper recommending that all women with PCOS be screened with glucose tolerance test at diagnosis and every 2 years thereafter. They also state use of metformin to treat or prevent progression to impaired glucose tolerance may be considered but not mandated until randomized controlled trials demonstrate efficacy. The American Association of Clinical Endocrinologists recommends metformin for initial intervention in most women with PCOS, particularly if overweight.

In summary, PCOS is a syndrome of androgen excess that is driven by insulin resistance. This frequently results in impaired glucose tolerance, lipid abnormalities such as high triglycerides, low HDL-C, and increased LDL-P or Apo B, all easily evaluated in many patients by looking for an elevated non-HDL-C. These patients have an increased risk of cardiovascular disease in a manner similar to patients with the metabolic syndrome and diabetes. Patients with PCOS will therefore likely benefit from cardiovascular prevention efforts. Therapeutic lifestyle changes should be initiated but at times additional pharmacotherapy which addresses insulin resistance will help correct a large portion of the metabolic and dyslipidemic complications of this syndrome.

References:


Continued on page 20
On-Treatment HDL-C Levels Matter In Statin-Treated Subjects with CVD
—Even in Those with LDL-C < 70 mg/dL

Despite the success of statins in reducing cardiovascular disease (CVD) events in high-risk individuals, there remains a substantial residual risk in treated subjects. One possible explanation for this might be the common occurrence of low HDL-cholesterol (HDL-C) levels, which have been shown to remain predictive of CVD events in statin-treated patients. However, it could be argued that if LDL-C levels are reduced to very low levels, low HDL-C may no longer be relevant. This question was tested in a post-hoc analysis of participants in the Treating to New Targets (TNT) trial, many of whom achieved an LDL-C <70 mg/dL on statin therapy.

The TNT trial randomized 10,001 men and women with CVD and whose LDL-C was <130 mg/dL on atorvastatin (atorva) 10 mg daily, to continued atorva 10 mg or atorva 80 mg daily and demonstrated that the group receiving 80 mg atorva, whose average LDL-C was 77 mg/dL, had a 22% reduction in CVD events compared to the group treated with 10 mg of atorva (mean LDL-C 101 mg/dL). Of these, 9770 had HDL-C measurements and were stratified into quintiles of HDL-C (measured after 3 months of treatment), namely <38, 38–<43, 43–<48, 48–<55 and >55 mg/dL. Subjects with higher HDL-C were more likely to be female, leaner, less likely to be a smoker and had lower triglyceride and apo B levels.

The overall risk of major CVD events differed significantly across the HDL-C quintiles (p=0.04), in which, compared to those with HDL-C <38 mg/dL, those with values in the 43–<48, 48–<55 and >55 mg/dL ranges had a 20%, 8% and 25% reduction in hazard rates. Both the LDL-C/HDL-C and the total/HDL-C ratios were highly predictive of major events. When analyzed separately by treatment group, among those receiving atorva 10 mg the highest HDL-C quintile had a significant 29% risk reduction compared to the lowest quintile, and among those treated with 80 mg atorva the reduction was 19% (not significant). However among subjects with an on-treatment LDL-C <70 mg/dL, the risk of a major CVD event differed significantly by HDL-C quintile (p=0.03), with subjects in the highest HDL-C quintile having a significant, 39% lower hazard ratio than those in the lowest quintile. Overall, an increase of 1 mg/dL increment in HDL-C at 3 months could be expected to reduce CVD risk by 1.1% (p=0.003).

Thus the findings in this study indicate that low HDL-C remains a powerful predictor of increased cardiovascular risk in statin-treated subjects, that this effect remained significant even after all other baseline factors, including the LDL-C and apo B levels were taken into account, and that even among patients with LDL-C levels < 70 mg/dL, the risk of major CVD events was reduced in those with higher than lower HDL-C levels.

Although not formally evaluated in this study, most of those with low HDL-C were also obese and had elevated triglyceride levels, raising the possibility that the presence of the metabolic syndrome in these subjects may have an important effect on outcomes. These findings also point to a need for additional measures beyond high-dose statin therapy to reduce risk, aimed either at residual apo B-containing particles and/or at improving the quality and quantity of HDL.

Reference:
Proceedings from the NLA 2nd Annual Masters Summit now online

The National Lipid Association offers an annual Masters Summit as its highest level of medical education. We presented the second of these symposia as a satellite event at the American Heart Association's 2007 Scientific Sessions in Orlando last November. Like the inaugural event, attendance was tremendous and seating was filled to capacity. The topic of the Summit was The Role of the Digestive Tract in Lipid Metabolism and CV Risk, and it brought together 7 thought leaders to discuss current developments in this area of lipid science.

If you were not able to attend the Summit in person, you can now view the proceedings online. Visit www.nlacme.com for the complete audio recordings and speakers slides. These are arranged as a 3-hour CME activity with post-test and evaluation included.

ACC Symposium—Popular Particle Mechanics

At ACC this year, the NLA will present a symposium titled Popular ‘Particle’ Mechanics, designed to explore the science of lipoproteins, from their structure to their role in metabolism, placing particular emphasis on their pathogenic role for arteries. This 3-hour program will be held March 29, 2008 at the McCormick Place Convention Center in Chicago.

At this event, top experts in lipidology will also explore issues related to LDL-C lowering, non-HDL-C, and a look at where we stand with respect to HDL-C metabolism. If you’re planning to attend ACC you’ll definitely want to take part in this program. Look for upcoming advertisements in NLA literature and visit www.lipid.org to register.

NLA now offering Speaker’s Bureau

A long-term NLA initiative is now ready, and we would like your help as we begin to organize a clearinghouse for members who would like to be considered for speaking engagements: The NLA Speaker’s Bureau. To participate, visit the NLA homepage at www.lipid.org, and from there, select “Account” at the top of the page.

Once there, you will see a new item in the upper left box, titled, “Speakers Bureau Records.” Select that option and you will be presented with a list of topics in lipidology, and radio buttons you can use to select your specialty and indicate whether you have published in a particular area and if you have speakers materials available. The more members who complete this information, the more robust our speakers bureau will be. Then, when members are looking for local or national experts on particular topics, this information will be available. If you’d like to participate, please visit your Account page and update this information.

Register now for the Annual Scientific Sessions

The highlight of every year is the NLA Scientific Sessions. This year, we’re holding the Scientific Sessions in Seattle, Washington. Don’t miss this opportunity to get up to speed with recent developments in lipid science and clinical care. This is also an opportunity to prepare for ABCL and ACCL certification, with more than 30 hours of lipid-focused CME/CE credit offered, or sit for an exam if you now qualify.

See page 22 for the NLA Education Course Catalogue for more information.

Visit the online registration page and learn more at www.lipid.org/sessions.

NLA Announces 2008 Annual Scientific Sessions Poster Session

The NLA is now accepting poster session submissions for presentation at our Annual Scientific Sessions in May in Seattle. Only a limited number of abstracts will be accepted and the submission deadline is March 7, 2008, so hurry and submit your abstract today at www.lipid.org/poster/. Accepted abstracts will be published in the Journal of Clinical Lipidology.

Take the Needs Assessment Survey

We can meet your needs better when you tell us what you want from your Association. Our annual Needs Assessment Survey is now underway. It only takes 5 minutes to complete. Hundreds of you have already weighed in and we appreciate your participation. If you haven’t taken the survey yet, do it today. Your responses will be used to shape and improve our programs. Visit www.lipid.org and select the link at the very top of the page titled, “click here to take the survey.”

NLA Statement on ENHANCE

On January 16, 2008, in response to member concerns with advice to patients, the NLA published a press release regarding the limited availability of data on the ENHANCE Trial. That statement is available at the homepage of www.lipid.org, and also provided on our press page.
**New Item for NLA Members Coming Soon**

As part of our “Beyond Cholesterol” physician and patient education campaign, we’re now in the production phase of desktop stands that will be mailed to all members of the NLA in the spring. Accompanying information will explain the use of the stands, which are designed to facilitate discussion of lipid panel results with your patients. The NLA Consumer Affairs Committee helped to design this useful tool and we thank them for their work on this project.

**Extended-type for stationery:**

\[\text{MEMBER} \quad 	ext{NATIONAL LIPID ASSOCIATION 2008}\]

**From the NLA Office**

**NL A Membership Logo available**

Now there’s a way to let the world know you’re a member of the NLA—the NLA member logo. We have two available for use by members in good standing. Select the one that best suits your needs at [www.lipid.org](http://www.lipid.org) (download from your “Account” page).

**Round-type for general use:**

\[\text{MEMBER} \quad \text{NATIONAL LIPID ASSOCIATION 2008}\]

**Practical Pearls continued from page 17**


**From the President continued from page 3**

boards have had our work made easier. Behind the scenes as well, Daniel Sosnoski, publications manager, has worked on everything from the *Lipid Spin*, the *Journal of Clinical Lipidology* as well as helping to craft important statements posted on our website as well as media interactions. And let us not forget Clark Morgan, who works magic with the audiovisuals at meetings as well as our web site.

Obviously, there is not space to mention everyone who has made a contribution. I would like to include the name of every member who has helped our organization, but that would probably take an entire issue of the *Lipid Spin*. Again, I want to thank everyone who has helped to make the National Lipid Association what it is today. Please continue to contribute our great organization.
Save the Date

Online Courses

**Through March 2008**
Meeting Highlights: Presentations from the 2006 NLA Scientific Meetings
Sponsored – CME, CE
Available at www.NLACME.com

**Online: Through October 2008**
CME Newsletter: Diabetes & Dyslipidemia: Reports from the ADA Scientific Sessions
Sponsored by SCEPTER
Endorsed – CME, CE
Available at www.NLACME.com

Webcast: Targeting Cardiovascular Risk in Patients With Diabetes: Impact of Dyslipidemia Management
Sponsored by SCEPTER
Endorsed – CME, CE
Available at www.NLACME.com

**Online: Through December 2008**
CME Newsletter: Cardiovascular Disease & Dyslipidemia
Sponsored by SCEPTER
Endorsed – CME, CE
Available at www.lipid.org/education/masters

Meetings and Events

**February 22–24, 2008**
Northeast Lipid Association 4th Annual Scientific Forum
Philadelphia, PA
Sponsored – CME, CE
Details at www.lipid.org

**February 24, 2008**
Nutrition Counseling Workshop
Philadelphia, PA
Sponsored – CME, CE
Details at www.lipid.org/education/nutrition

Lipid Clinic Operations and Development Course
Philadelphia, PA
Sponsored – CME
Details at www.lipid.org/education/lcido

**March 29, 2008**
Popular “Particle” Mechanics an NLA Symposium
Chicago, IL
Sponsored – CME
Details at www.lipid.org

**April 5, 2008**
Comprehensive Cardiometabolic Risk-Reduction Program (CCRR) at Lahey Clinic Medical Center
Boston, MA
Sponsored – CME
Details at www.cardiometrisk.com

**May 28–29, 2008**
Lipid Management Training Course
Seattle, WA
Sponsored – CME, CE
Details at www.lipid.org/education/lmtc

Masters in Lipidology Advanced Training and Board Review Course
Seattle, WA
Sponsored – CME, CE
Details at www.lipid.org/education/masters

**May 29, 2008**
Lipid Clinic Operations and Development Course
Seattle, WA
Sponsored – CME
Details at www.lipid.org/education/lcido

**May 29–June 1, 2008**
2008 NLA Annual Scientific Sessions
Seattle, WA
Sponsored – CME, CE
Details at www.lipid.org

**May 30, 2008**
Nutrition Counseling Workshop
Seattle, WA
Sponsored – CME, CE
Details at www.lipid.org/education/nutrition

Participants attending the Masters in Lipidology Advanced Training and Board Review Course
Global Approaches to CVD Prevention
Challenges and Controversies in Clinical Lipidology

National Lipid Association
2008 Scientific Sessions
Seattle

Registration Now Open
—visit www.lipid.org/sessions

Calling for Abstracts

Abstract Submission Deadline: March 7, 2008
The National Lipid Association is accepting a limited number of posters so get your submissions in early!

Abstracts for scientific posters will be accepted online from NLA members who are Young Investigators (in-training residents and fellows or <5 years in practice), or are in Academic Programs, Practice, or Industry.

All accepted poster abstracts will be reproduced in the NLA’s May/June 2008 issue of the Journal of Clinical Lipidology.

Young Investigator Award
NLA members who are Young Investigators (in-training residents and fellows or <5 years in practice) who submit posters will be eligible to win the NLA 2008 Young Investigator Award. Also the lead presenter will receive a $300 travel voucher and free meeting registration.

Conference Highlights
• Challenging Case Presentations
• Masters in Lipidology Board Review Course
• Lipid Management Training Course
• Lipid Clinic Operations and Development Course
• Nutrition Counseling Workshop
• ABCL and ACCL Certification Exams and Convocation Ceremony
• Satellite Breakfast and Dinner Symposia Daily

To obtain more information and to register for the meeting visit: www.lipid.org
Questions? Phone 904-998-0854
A National Lipid Association Symposium

Popular ‘Particle’ Mechanics

Saturday, March 29, 2008
11:00 AM–11:30 AM Registration & “Brown Bag Lunch” • 11:30 AM–2:00 PM Symposium
McCormick Place Convention Center • Room S403A/B • Chicago, IL

Lipoproteins:
What Else Appears to Be Pathogenic?
— W. Virgil Brown, MD, Chair • Atlanta, GA

Optimizing Targets - What Are the Best Measures for Cardiovascular Risk Detection?
— Peter W. Wilson, MD

Considering Secondary Targets - Is There More Beyond LDL?
— Alan S. Brown, MD

HDL Function – What Is It? How Can It Be Improved?
— Bruce Greg Brown, MD

Apolipoproteins - A Target for Therapy in At-Risk Patients?
— Frank M. Sacks, MD

To register
www.lipid.org/particle

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