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## MANAGING LIPOPROTEIN DYSLIPIDEMIAS THROUGH LIFESTYLE AND NUTRACEUTICAL THERAPIES

**F**or the past several decades, the primary blood marker associated with the risk for cardiovascular disease has been cholesterol. Initially it was total cholesterol, then later, LDL cholesterol and HDL cholesterol (deemed “bad” and “good”, respectively) became household terms. This review will attempt to demonstrate that these measurements alone tell only part of the overall cardiovascular risk story, and perhaps have only been surrogate markers for other, more causative, risk factors. We will discuss the anatomy of a lipoprotein particle and review the risk associated with each component (cholesterol, triglycerides, and proteins), as well as the number and size of the particles themselves. A review of the most studied non-pharmacological approaches will follow.

### Introduction

Assessing an individual’s cardiovascular disease risk involves understanding both non-modifiable (age, gender, family history, genetics) and modifiable risk factors (smoking, obesity, sedentary lifestyle, hypertension, and a host of measurable blood markers). Determining which of the modifiable factors is most important in determining risk, and which modification patients will comply with, will best determine the therapies that will have the greatest impact on their health. The list of potential modifiable risk factors and therapies; however, is quite long and expanding. Emerging risk factors are discovered frequently and engender debates among researchers and clinicians concerning the appropriateness of measuring and treating patients based on these new risk factors. In the past several decades, risk factors such as high-sensitivity c-reactive protein (hsCRP) and homocysteine have fallen into this category.

Blood lipoprotein markers, on the other hand, have a long record of use as measurable and treatable markers in the management of cardiovascular disease risk. The discovery of cholesterol deposits within atherosclerotic plaques led to the routine association between cholesterol and atherosclerosis; an association which quickly transferred to the general population and marketers of foods low in cholesterol. Total cholesterol (TC)

alone; however, turns out to be a poor marker for cardiovascular disease risk and in most cases does not predict cardiovascular events in individuals (although lifetime CHD mortality can be correlated to TC in western populations).<sup>1</sup> Further sub-fractions of cholesterol measurements have since been used to improve cardiovascular risk assessment. Low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and the ratio between TC:HDL-C became a more common way of assessing CVD risk.<sup>2</sup> These, along with serum triglyceride (TG) measurements are still the most common lipid markers for measuring cardiovascular risk and also the primary focus of the National Cholesterol Education Panel (NCEP) guidelines for measuring and treating dyslipidemia. However, in order to fully understand and evaluate a patient’s risk, as well as choosing the best laboratory markers for measuring risk, it is vital to understand the anatomy of the lipoprotein particles and how cholesterol, TG and apolipoprotein concentrations are determined.

### Understanding Lipoprotein Particles

Cholesterol and triglycerides are transported throughout the blood stream in particles called lipoproteins. Generally classified by their relative densities (very low-VLDL, low-LDL, intermediate-IDL, high-HDL), lipoproteins have a shell derived

from phospholipids, free cholesterol, and apolipoproteins, and a central core of triglycerides and cholesterol esters (See Figure). It is now well established that measuring cholesterol alone (HDL-C or LDL-C) may not be an accurate measure of the atherogenic potential of lipoprotein particles. The number and size of the various particles, and corresponding apolipoprotein levels, may be more accurate markers for atherogenic potential. We will briefly outline each measurement and discuss its relative benefit in predicting atherogenic potential in individuals. This discussion is important if one is to assess the role of various therapies for their ability to reduce cardiovascular risk.

### LDL-cholesterol

LDL-C is the total amount of cholesterol found in low density lipoprotein particles, measured in mg/dl (milligrams per deciliter or 100 ml of plasma). Because of the way LDL-C is measured, it typically also includes IDL-C and Lp(a)-C (see below). Each of the NCEP Adult Treatment Panel (ATP) guidelines have used LDL-C as the primary target for measuring and treating high blood cholesterol.<sup>3</sup> Not surprisingly, drugs that are able to reduce LDL-C (specifically the HMG-CoA reductase inhibitor drugs called "statins") have become some of the most popular in the Western world. Large clinical trials using these drugs have confirmed the notion that LDL-C reduction decreases the risk for future cardiovascular events.<sup>4</sup> The NCEP ATPIII guidelines recommend the following LDL-C goals: Individuals with High risk (CHD or CHD equivalent like diabetes) <100 mg/dl; Moderate risk (2 or more risk factors) <130 mg/dl; and Low risk (0-1 risk factor) <160 mg/dl. This method does not distinguish between cholesterol residing in lipoproteins of differing atherogenic potential (see below).

### HDL-cholesterol

HDL-C is the total amount of cholesterol found in high density lipoprotein particles, measured in mg/dl. Low HDL-C is an independent risk factor for CVD as the HDL particles are thought to play a role in moving cholesterol from the tissues to the liver for removal, or potentially having anti-inflammatory effects. The NCEP guidelines do not use HDL-C as a target for therapy, but as a guide to determine risk and within the criteria for determining metabolic syndrome. HDL-C below 40 mg/dl in men and 50 mg/dl in women are cut-off points. Patients with insulin resistance or diabetes often have low HDL-C levels.<sup>6</sup> In

general, a 1mg/dl increase in HDL-C results in a 2-4% decrease in cardiovascular risk, this correlation is more in women than men.<sup>5,6</sup> Unfortunately, fewer intervention trials have been performed using HDL-C as a key marker compared to LDL-C.<sup>7,8,9</sup> This is likely due to the fact that fewer agents increase the levels of HDL-C.

### Non-HDL cholesterol

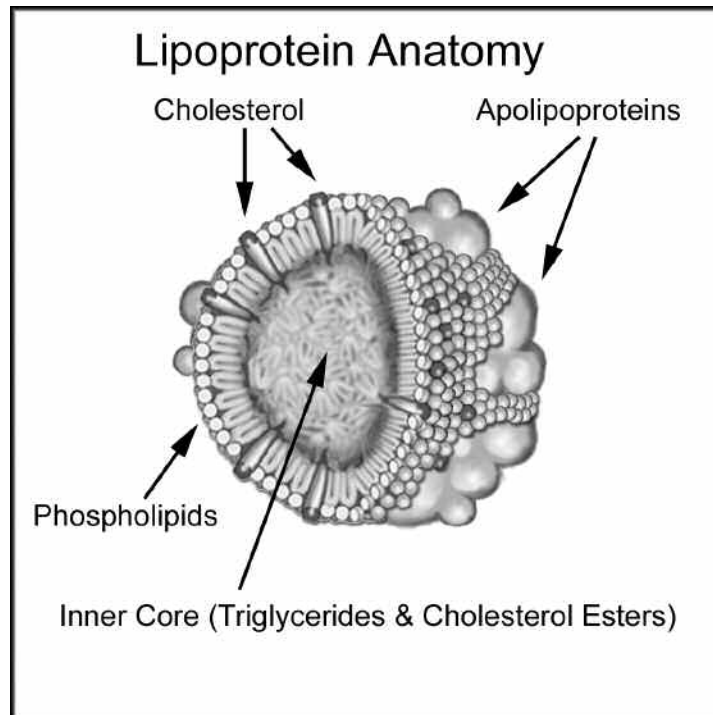
Non-HDL-C is the total amount of cholesterol found in all particles minus the cholesterol in HDL particles and roughly includes LDL-C, IDL-C, VLDL-C and cholesterol in remnant particles. Non-HDL-C is considered to be a strong predictor of future cardiovascular risk and is a secondary target in the NCEP ATPIII guidelines.<sup>3,10</sup> The recommended goals for non-HDL-C are: High (CHD) risk <130mg/dl; Moderate risk <160 mg/dl; and Low risk <190 mg/dl. The increased predictive value of this measurement (over LDL-C alone), especially in patients with very high TG levels, as well as the fact that it is easily derived from routine lipid panels, make this an important alternative for patients with whom other tests may be cost prohibitive.<sup>11</sup>

### Triglycerides

TG levels are measured in mg/dl and reflect the amount of TG in the serum. Fasting TG levels are considered an independent risk factor for cardiovascular disease, although they are metabolically linked with many of the other lipid markers.<sup>12,13</sup> Post-prandial TG levels, when elevated, often are a measure of insulin resistant-driven dyslipidemia and may be detectable before fasting TG are noticeably elevated.<sup>14,15</sup> Post-prandial hypertriglyceridemia is strongly associated with small-dense LDL particles in post-infarct patients with normal fasting TG levels.<sup>51</sup> Since elevated TG (fasting) are also associated with insulin resistance and the metabolic syndrome, NCEP guidelines use fasting TG >150 mg/dl as one of the criteria for diagnosing the metabolic syndrome. In general, TG levels below 150 are considered normal, 150-199 borderline high, 200-499 high and above 500 are considered very high.

### Apolipoprotein B

Apolipoprotein (apo) B (or sometimes apo B-100), reported also as mg/dl, is a protein that is found within the outer shell of all lipoproteins, with the exception of HDL particles. Each VLDL, IDL and LDL particle contains 1 molecule of apo B, so measuring apo B is a rough estimate of the number of the more atherogenic particles (irrespective of the cholesterol contained within them). Apo B is considered to be more predictive of risk than LDL-C,



HDL-C or non HDL-C, especially in metabolic syndrome patients.<sup>16,17,18,19</sup> Apo B may be especially important to measure in diabetic patients with high TG but normal LDL-C.<sup>24</sup> Guideline goals for apo B levels are: High risk <90 mg/dl; Moderate risk <110 mg/dl; and Low risk <130 mg/dl.

### **Apolipoprotein A**

Apolipoprotein (apo) A, reported in mg/dl, is a protein found only within HDL particles. It roughly correlates to the number of HDL particles and is closely linked with HDL-C. While apo A is rarely used alone, the ratio of apo B/apo A is considered to be a very good predictor of future cardiovascular risk, superior to any of the cholesterol measurements or ratios.<sup>16,20,21,22</sup> An apo B/apo A ratio >1 is generally considered to be atherogenic.<sup>23</sup>

### **LDL particle size**

This is a measure of the size (average) or relative abundance of large or small LDL particles. The size can be expressed in nanometers (nm) or angstroms ( $\text{\AA}=1/10$  nm); while persons are often classified as having a pattern A (more large LDL particles-less atherogenic) or pattern B (more small LDL particles- more atherogenic) phenotype. High numbers of small, dense LDL particles, are a strong predictor of cardiovascular disease and is a hallmark of the metabolic syndrome and diabetic atherogenic profile.<sup>24-31</sup> These smaller particles are thought to be more atherogenic because they are taken up more easily within arterial tissue, have increased susceptibility to oxidation and have reduced receptor mediated uptake.<sup>30</sup> Pattern A (large) typically describes particle averages larger than 20.6 nm, while pattern B (small) are those smaller than 20.5 nm, when measured by NMR (nuclear magnetic resonance). Often times the size is measured by gradient gel electrophoresis which results in a consistently larger (~5nm) diameter being report. In these cases, 25.5 nm is considered the differential between large and small particles.<sup>31</sup>

### **HDL-C subfractions HDL2, HDL3**

Like LDL particles, HDL particles vary in size. These can be reported as absolute size (nm) or by the cholesterol amount in each fraction (mg/dl). Some labs (especially those using NMR technology) report different variations of HDL size classifications.<sup>32</sup> Larger particles (HDL2) are considered to be more protective and smaller particles (HDL3), less protective. While therapies which shift HDL particle size from smaller to larger may reduce long-term cardiovascular risk, no such endpoint has been proven as an independent risk factor.<sup>33,34</sup>

### **LDL particle number**

This is simply the number of LDL particles, expressed in nanomoles/liter (nmol/l). Most of the previous measures are in some way related to the number of LDL particles and perhaps are even surrogate markers for LDL particle number. Several studies confirm that LDL particle number is at least as good, and in some cases better, at predicting risk compared to any of the other lipid or lipoprotein measurements.<sup>35,36</sup> NMR technology seems to be the most reliable method for determining both number and size of LDL particles currently.<sup>32</sup>

### **VLDL size and number**

VLDL size (often reported by TG within the particle or other surrogate measures), is becoming important as a key constituent of the atherogenic profile related to insulin resistance, the metabolic syndrome and diabetes.<sup>37,38</sup> It is typically associated with small-dense LDL particles and elevated TG, but may be detected sooner in some at-risk patients.

### **Lp(a)**

Lp(a) is a lipoprotein particle with essentially the same structure as a typical LDL particle with one exception, it has the protein apo(a) covalently attached via a disulfide bond to the apo B protein along the surface of the LDL particle (this is a different protein than the apo A attached to HDL particles).<sup>39</sup> The increased atherogenic potential of Lp(a) particles may be related to their being retained more avidly within the arterial wall<sup>40</sup>, their ability to promote coagulation<sup>41</sup>, their decreased interaction with the LDL receptor<sup>39</sup>, or their increased oxidative inflammatory activity.<sup>46</sup> Meta-analyses of both retrospective and prospective studies have associated elevated Lp(a) with increased cardiovascular risk.<sup>42,43,44</sup> Niacin is one of the only reliable agents currently known to lower Lp(a).<sup>39,45</sup>

### **Atherogenic Risk Assessment**

With so many lipoprotein markers to consider (along with homocysteine, hsCRP, hypertension, fibrinolytic markers etc), how does one assess the atherogenic potential of an individual patient? Currently, of all the lipoprotein markers listed above, the combined information of both LDL particle number and size is likely to give the best risk prediction for individuals. These tests are relatively inexpensive and many insurance companies will reimburse the patient. Numerous laboratories now offer various combinations of lipoprotein profiles, reporting VLDL, LDL and HDL heterogeneity along with risk analysis for atherogenic potential and metabolic syndrome. These newer tests will allow physicians to begin treating patients who are developing an atherogenic profile before overt dyslipidemias set in and will allow patient treatment monitoring to assess more than LDL-C reduction. With the growing epidemic of obesity and insulin resistance, resulting in patients with still normal LDL-C, but higher CVD risk (due to elevated small LDL particle, higher TG, larger VLDL and increase particle number), these new tests should be considered in virtually all patients with any risk potential.

## **Managing dyslipidemia using Non-Pharmacological Approaches**

### **Diet**

Human dietary patterns (especially in the Western world) have changed dramatically in the past 100 years. No longer are we bound by seasonal or indigenous foods, but are capable of eating almost anything (natural or artificial) at any moment and at any volume, throughout the year. Years of studies have shown that most of these changes in modern food distribution and

consumption have been universally harmful for the populations that consume them, leading to increased risks of nearly every chronic disease pattern. On the other hand, several different “paradoxes” have been discovered throughout the past several decades (French, Mediterranean, Japanese, Inuit) which reveal that certain groups are less prone to certain diseases, like heart disease, because of one or two major differences from the prevailing “Western diet”. From these paradoxes the role of certain phytonutrients, fatty acids, fiber and macronutrient combinations have helped define which foods (or nutrients within foods) play a role in promoting and preventing CHD.

Hu and Willett have reviewed much of the published literature on diet and heart disease risk.<sup>47</sup> Consistently, saturated fat, trans-fatty acids, high glycemic load, and low folate are related to increased risk of CHD. On the other hand, polyunsaturated fatty acids, monounsaturated fatty acids, omega-3 fatty acids, low glycemic load and diets high in fruits, nuts and vegetables consistently lower risk in populations that consume them.<sup>47,48,49</sup> How individuals (rather than populations) respond to changes in diet, even if they remain compliant, is a bit less predictable. Various genetic differences, primarily in the genes encoding the various apolipoproteins, have been identified that greatly affect how an individual’s lipoprotein markers are altered by changes in diet.<sup>50,51</sup>

#### Low-Fat or Low Carbohydrate Diets

The past decade has witnessed a popular (and scientific) debate about the relative benefits of altering ones dietary intake to include fewer calories from fat and cholesterol, or conversely, fewer calories from carbohydrates. What has emerged from this debate, besides a plethora of packaged foods tailored to one scheme or another, is an understanding of the complex nature of both the fat and carbohydrate categories of macronutrients. In other words, all fats and all carbohydrates are not equally detrimental or beneficial.<sup>53</sup> One important lesson was discovered with the use of hydrogenated polyunsaturated oils (margarine etc.), rich in trans-fats, in place of saturated fats in the attempt to improve health. Intake of food products rich in these hydrogenated fats increases both total and LDL-C and recently has been shown to reduce LDL particle size, decrease apo A levels, and increase both apo B and Lp(a) levels; further promoting an atherogenic profile.<sup>53,54,55</sup> The harmful effects of trans-fats are now well established, requiring mandatory label disclosure on foods in the US.

Low carbohydrate diets of various kinds have recently emerged as an alternative to low-fat diets for weight loss, although many have been skeptical of their safety and ability to protect against CVD (due to lack of fat and protein limits). Recently, several clinical trials have been designed to answer whether the various low-carbohydrate diets have beneficial effects on cardiovascular disease markers. Dumesnil et al.<sup>56</sup> showed that a reduced glycemic index diet (ad libitum) had a greater reduction of markers of atherogenic risk than the American Heart Association (AHA) step I diet (AHA step 1 allows calories from carb=55%,fat=30%, protein=15%)<sup>57</sup> in patients with abdominal obesity. The reduced glycemic index

diet reduced calorie intake, apo B, TG and insulin production while increasing LDL particle size compared to the AHA diet. Others have shown that similar diets that only differ in glycemic index (55-60% carb, <30% fat) generally favor the lower glycemic diet only modestly when compared in terms of weight-loss, while the low-glycemic diet is more favorable in measurable CVD risk factors.<sup>58</sup> Numerous trials have been conducted to show that low-carbohydrate (defined by total carbohydrate or reduced glycemic load) have a more beneficial effect on nearly all measures of insulin resistance and atherogenic lipoprotein measures when compared to conventional or low-fat diets.<sup>59-65</sup> Even the very-low (ketogenic) diets have favorable outcomes for cardiovascular risk in both normal-weight and obese individuals.<sup>66,67</sup>

Generally, the substitution of carbohydrates, especially refined high glycemic carbohydrates with monounsaturated and polyunsaturated fatty acids or protein will tend to have an overall beneficial change in insulin resistance and atherogenicity. While severe carbohydrate restriction may have beneficial short-term weight-loss potential, it is preferable to moderate glycemic load by choosing low glycemic foods that are high in fiber and phytonutrients with the least amount of processing possible.

#### Dietary Fiber

Increased consumption of dietary fiber has long been associated with numerous health benefits, including the reduced risk of cardiovascular diseases.<sup>68</sup> Both insoluble and soluble fibers have been implicated in CVD reduction by different mechanisms. For instance, oat fiber (mostly soluble) is capable of reducing LDL particle size and number, while wheat fiber (mostly insoluble) had no effect in overweight elderly men.<sup>69</sup> The use of soluble fibers from oat, psyllium, and flax (among others) have resulted in beneficial, though modest, lipoprotein changes in several clinical trials.<sup>70-75</sup> A recent clinical trial showed that the addition of 15 grams/day of psyllium fiber to 10mg simvastatin was similar in lipid-lowering as 20mg of simvastatin without psyllium. Here fiber is being used as a dietary supplement, rather than being incorporated into food.<sup>76</sup>

#### Nutraceutical management of dyslipidemia

Diet and lifestyle changes (like exercise<sup>77-83</sup>) can be effective in reducing cardiovascular risk in most individuals who remain compliant. For many; however, reaching the lipoprotein marker targets set by the NCEP ATPIII guidelines may be more difficult to attain; especially those with previous cardiovascular disease or patients with diabetes. In many cases, physicians immediately choose a pharmaceutical regimen (usually a statin or statin combination) to bring down the LDL-C to within the guideline recommendations. This review will not discuss all the pharmaceutical options that effect lipoprotein markers. Instead, we will discuss the numerous effective options that are available without a prescription as nutraceuticals or dietary supplements here in the United States. Many of these ingredients will offer significant benefits to patients (even beyond the ability to

manage dyslipidemia) and when combined together, or with diet and lifestyle changes, may delay or prevent the need for pharmaceuticals altogether. Space will not permit discussion of every possible agent that has some effect on one of the lipoprotein markers mentioned, we will attempt to review the most studied along with others with fewer, but promising mechanisms or secondary benefits.

### Niacin (Nicotinic Acid)

The lipid-altering effects of the B vitamin niacin were first reported in 1955<sup>111</sup> and have been repeatedly demonstrated in clinical trials and clinical practice since then. In a 1989 study of patients with high cholesterol and established coronary artery disease, niacin at an average dose of 1400 mg/day significantly lowered total cholesterol by 13% and significantly increased HDL by 31%.<sup>112</sup> In Keenan et al.'s study of generally healthy adults with elevated LDL-C levels, niacin at 1500 and 2000 mg/day significantly reduced LDL-C (19% and 26%, respectively), total cholesterol (13.3% and 18.4%, respectively), and the ratio of total cholesterol to HDL-C (19.4% and 20.4%, respectively) compared to control.<sup>113</sup> Recent trials have shown that niacin can also improve dyslipidemia in diabetic populations by beneficially altering multiple lipid parameters, including triglycerides, HDL-C, LDL particle size, and Lp(a) levels.<sup>114,115</sup>

Niacin's ability to alter a specific lipoprotein class varies with the lipid disorder of the patient.<sup>116</sup> In general, niacin can lower fasted serum TG by 20-50%, LDL-C by 5-25%, and Lp(a)-C by 15-25%. Niacin is also one of the few and most effective agents available for increasing HDL-C levels (15-35%). A positive effect on lipoprotein subclasses is also exhibited; niacin can increase the concentration of larger, buoyant LDL particles (pattern A)<sup>117,118</sup> and raise levels of the cardioprotective large HDL particles.<sup>119</sup> Most importantly, long-term niacin therapy has been shown to lower CVD and total mortality.<sup>120</sup>

Niacin's lipid-regulating effects are likely due to a number of complex and interrelated effects on lipid and lipoprotein metabolism.<sup>116</sup> One key action of niacin is inhibiting free fatty acid mobilization from peripheral adipose tissue to the liver. Consequently, hepatic synthesis of triglycerides, synthesis and secretion of VLDL, and synthesis of LDL from VLDL are decreased.<sup>121</sup> Niacin also appears to reduce the catabolism of apo A-I, subsequently elevating apo A-I levels may leading to the enhanced HDL production that is observed with niacin administration.<sup>116</sup>

Niacin preparations are typically classified as immediate-release (IR), extended-release (ER), or sustained-release (SR, also called long-acting or timed-release niacin). The different formulations result in different release times with IR dissolving and being absorbed much more quickly than the other formulations. The rate of absorption plays a central role in determining how niacin is metabolized in the liver, in turn affecting the efficacy, safety, and side effect profile of the formulation.<sup>117,122,123</sup> This general classification system has its limitations; even within each classification there are differences among preparations that may influence dissolution and

absorption rates and therefore cause differences in efficacy and side effects.<sup>124</sup> In general; however, IR niacin more significantly increases HDL-C but results in more cutaneous flushing of the face and trunk.<sup>122,123</sup> Slower-releasing niacin is more effective at lowering LDL-C but is more often associated with hepatotoxic effects.<sup>121,122,125</sup> The most common symptom of niacin administration, flushing, can be minimized with measures such as gradually titrating the dose, taking an adult aspirin (325 mg) 30-60 minutes prior to the initial dose, taking niacin with food, and avoiding alcohol, spicy foods, or hot beverages near the time of niacin dosing.<sup>117</sup> Other side effects of niacin administration include gastrointestinal distress and elevated uric acid and homocysteine.<sup>117,126</sup> Elevated glucose levels may also occur;<sup>123</sup> although this is usually mild and recent trials have shown that niacin can be a safe therapeutic option even for patients with diabetes.<sup>114,115,127</sup>

The therapeutic dose range of niacin is from 250 mg to 3000 mg/day depending on formulation (release profile). Maximal effects on HDL-C and triglycerides tend to occur at doses of 2000 mg/day, while LDL-C levels may further improve with higher doses.<sup>123</sup> However, with all formulations higher doses tend to increase the incidence of intolerance. With slower-releasing niacin, doses above 2000 mg/day should be avoided.<sup>121,122</sup>

In recent years an alternative niacin formulation, inositol hexanicotinate (IHN), has captured a large share of the niacin market due to claims that it causes less flushing than other niacin formulations.<sup>128</sup> Data regarding IHN metabolism is limited, and while IHN is often marketed as a dietary supplement that can improve cholesterol levels and heart health, there is limited scientific evidence supporting its use for these purposes. In fact, most of the small studies examining IHN's effects on lipids were published over 20 years ago.<sup>129-131</sup> Currently, a randomized, double-blind, controlled trial is being conducted at the University of Minnesota Medical School to compare the lipid-altering effects and metabolism of IHN and a sustained-release niacin formulation that is known to beneficially alter blood lipids. Until results of this and other well-controlled trials are obtained, IHN cannot be recommended as a substitute for niacin in lipid-altering therapies.

### Pantethine

Pantethine is the metabolic precursor of the water-soluble B vitamin, pantothenic acid. In the serum pantethine is hydrolyzed to form pantothenic acid and cysteamine.<sup>132</sup> Pantethine, but not pantothenic acid, has been shown in a number of trials over the last 30 years to effectively reduce serum triglycerides, LDL-C, and apo B, while increasing HDL-C and apo A-I.<sup>133-135</sup> Cysteamine is believed to be the agent responsible for pantethine's lipid-altering ability and appears to exert its effects primarily through the inhibition of two hepatic enzymes: acetyl-CoA carboxylase and HMG-CoA reductase.<sup>136,137</sup>

Pantethine has been tested over a wide dose range from less than 300 mg to more than 1800 mg per day. Most of the evidence suggests that the therapeutic range of this agent is between 600-1200 mg/day with usual dosing at 300 mg two to four times per day. The average response over this dose range is 10-15 percent

reduction in total cholesterol and LDL-C, 15-20 percent reduction in triglycerides, and a 15-20 percent improvement in HDL-C. Pantethine administration significantly decreases apo B levels by an average of 15 percent and increases apo A-I levels by an average of 20 percent.<sup>138</sup> These lipid changes are usually noted within 2-4 weeks and the effects appear to be maintained with the same dose. Pantethine appears most effective in individuals with mild to moderate dyslipidemia and is less effective in some subgroups including those with renal failure or uremia, those on diuretics and/or beta-blockers, and those with familial hyperlipidemia<sup>139</sup> or extremely high LDL-C concentrations (>250 mg/dL).<sup>140</sup> Pantethine is well tolerated with occasional reports of gastrointestinal discomfort and diarrhea, most frequently when administered in higher doses (i.e.,  $\geq 1200$  mg/d).

While most studies report increases in HDL-C values after pantethine treatment, the effect may be a function of pretreatment values, with the greatest response reported among those individuals with lower HDL-C concentrations. For example, Zhu et al. in a small randomized trial reported a 45 percent increase in HDL-C levels among those participants with abnormally low values but only a 6 percent increase among those with normal pretreatment HDL values.<sup>141</sup> However, a recent crossover trial showed little effect on HDL in a population with low HDL values.<sup>135</sup> A few studies that have investigated the effects of pantethine on HDL sub-fractions suggest that pantethine exclusively increases the cardioprotective HDL2 sub-fraction while leaving the HDL3 fraction largely unchanged.<sup>138</sup>

Triglyceride reduction may be pantethine's most consistent lipid-altering effect. In a crossover trial by Gaddi et al., administration of 900 mg of pantethine per day resulted in an average triglyceride reduction of 23 percent.<sup>134</sup> All of this effect was quickly lost when patients were switched from pantethine to placebo. Rubba et al. showed an 11 percent reduction in VLDL-triglyceride levels among patients with normal triglyceride levels after 30 days of pantethine administration at 300 mg, three times per day.<sup>140</sup> Capurso et al. demonstrated that pantethine administration effectively reduces serum triglyceride levels by 9 percent in hypertriglyceridemic patients after 60 days of treatment with 900 mg/d.<sup>142</sup>

In a recent controlled cross-over study, Pins et al. confirmed results of many previous pantethine studies.<sup>143</sup> In this trial of 48 hyperlipidemic adults, 6-weeks pantethine administration at 600 and 900 mg/day decreased triglycerides, LDL-C, and apo B, and increased apo A-I. Notably, LDL particle size was also beneficially affected in this trial, and improvements in these parameters were significantly greater with 900 mg/day than with 600 mg/day.<sup>135,144</sup>

Pantethine therapy may provide clinical benefit beyond lipid management. Pantethine administration may improve platelet function<sup>145</sup> and possess antioxidant properties<sup>146,147</sup>. Pantethine may also have hepato-protective effects. Osono et al. demonstrated that fatty liver disease could be ameliorated in many patients after six months of pantethine administration at 600 mg/d.<sup>148</sup> Additionally, findings from our recent clinical trial using pantethine showed post-treatment reductions in abdominal fat with administration of 900 mg/day.<sup>143</sup>

## Policosanol

Policosanol is rapidly becoming a very commonly used dietary supplement that has been shown in a number of trials to improve blood lipids and other markers of cardiovascular disease risk.<sup>85,86</sup> Additionally, a recent prevention study demonstrated that policosanol reduced all mortality and all cardiovascular, coronary, cerebrovascular, and vascular serious adverse events in older patients.<sup>87</sup> This supplement, which is a mixture of aliphatic (open-chain) alcohols derived from purified sugar cane wax, has virtually no side effects and has demonstrated excellent safety and tolerability even in long-term studies of two and three years.<sup>85,86,88-90</sup>

The effectiveness of policosanol as a lipid-altering agent has been well documented in clinical trials of different hypercholesterolemic populations, including the elderly, postmenopausal women, and those with type 2 diabetes. A review<sup>85</sup> of randomized, placebo-controlled, double-blind studies in these populations found policosanol at doses of 5-20 mg/day to significantly improve a number of lipid parameters, most notably LDL cholesterol (19-31%). Policosanol also lowers total cholesterol (13-23%) and increases HDL cholesterol (8-29%). While most reports indicate that policosanol has no effect on triglycerides, a handful of studies have demonstrated significant reductions in triglycerides with doses of 10-40 mg/day.<sup>89,91-93</sup> There is some evidence that policosanol's lipid-altering effects are dose-dependent up to 20 mg/day, with little or no additional benefit at higher doses.<sup>86,91,94</sup>

In comparison trials of policosanol and popular lipid-altering drugs, policosanol has produced lipid profiles comparable or superior to those achieved with simvastatin,<sup>95,96</sup> pravastatin,<sup>92</sup> lovastatin,<sup>97,98</sup> probucol,<sup>99</sup> acipimox,<sup>100</sup> and atorvastatin<sup>93</sup>. Policosanol at 10 mg/day improved HDL-C to a greater degree and exhibited greater safety and tolerability than lovastatin at 20 mg/day.<sup>98</sup> After 12 weeks of therapy, policosanol also improved LDL-C, total cholesterol, and the LDL-C:HDL-C ratio to similar or greater degrees than lovastatin. In an 8-week comparison of pravastatin and policosanol (10 mg/day) in older patients with hypercholesterolemia and high cardiac risk,<sup>92</sup> policosanol significantly lowered LDL-C (19.3%), total cholesterol (13.9%), and the ratios of LDL-C/HDL-C (28.3%) and total cholesterol/HDL-C (24.4%). Pravastatin significantly lowered LDL-C (15.6%), total cholesterol (11.8%), and the ratios of LDL-C/HDL-C (18.9%) and total cholesterol/HDL-C (15.7%). Policosanol, but not pravastatin, significantly increased HDL-C (18.4%) and reduced triglycerides (14.1%).

Policosanol appears to exert its lipid-altering effects by decreasing hepatic cholesterol synthesis, possibly by suppressing action of HMG-CoA, a key enzyme in the first step of cholesterol biosynthesis. It may also improve LDL levels by increasing LDL binding, uptake, and degradation. It is unknown what component or components of policosanol are responsible for these effects, or whether these effects are caused by policosanol's open-chain alcohols themselves or their fatty acid metabolites.<sup>85,86</sup> It is therefore important to note when reviewing the literature that not all policosanol formulations are identical. While most formulations are composed primarily of octacosanol, triacontanol, and hexacosanol, the precise

percentages of these and other minor alcohol constituents may vary among different manufacturers and formulations,<sup>101</sup> thus affecting efficacy.

Policosanol appears to have numerous cardiovascular benefits beyond effects on lipids. Policosanol may slow development of atherosclerosis by having a protective effect on the vascular endothelium<sup>102</sup> and by decreasing foam cell formation,<sup>103</sup> LDL oxidation,<sup>104,105</sup> and smooth muscle proliferation.<sup>106</sup> At doses of 10-50 mg/day, policosanol has also demonstrated the ability to reduce platelet aggregation in individuals with and without hypercholesterolemia.<sup>85,86,92,107</sup> This inhibitory effect on platelet aggregation is likely the mechanism by which policosanol reduces symptoms of intermittent claudication.<sup>108-110</sup>

### Plant Sterols and Stanols

Plant sterols (phytosterols) and stanols are compounds from various plant sources which are structurally similar to cholesterol. The most common are sitosterol, campesterol, stigmasterol and related stanols. Ingestion of these compounds at effective doses have been shown to lower both total and LDL-C by approximately 10%.<sup>149</sup> The use of plant sterols has been almost exclusively as a food additive (margarine, orange juice, salad dressing), where the FDA permits the following claim: "Foods containing at least 0.65 grams per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 grams, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease."<sup>150</sup> Sterol and stanol intake is also included in the NCEP ATPIII guidelines, as part of the Therapeutic Lifestyle Changes (TLC) protocol, recommending 2 g/day as a means to promote cholesterol reduction.<sup>154</sup>

Sterols inhibit the absorption of cholesterol from the gastrointestinal tract. This includes both ingested cholesterol as well as cholesterol that is secreted with bile which is efficiently re-absorbed in the gut. Sterols combine and co-precipitate with cholesterol in gut, resulting in reduced absorption of dietary cholesterol and bile recycling. Additionally, when plant sterols are ingested, they are taken up by the same enterocytes that also transport cholesterol. Both plant sterols and cholesterol are substrates for the enzyme acyl coenzyme A: cholesterol acyltransferase (ACAT). Cholesterol must be esterified by ACAT in order to be transported out of the enterocyte. However, plant sterols are poor substrates for ACAT and tie-up many of these enzymes, preventing them from access to cholesterol molecules. This causes the enterocyte to transport the unesterified cholesterol back into the lumen of the intestinal tract where it can be transported out of the body with the feces.<sup>151,152</sup> This unique activity within the enterocytes is likely the reason that plant sterols do not need to be consumed with each meal in order to have their benefit.<sup>153</sup>

Current studies have focused on combination therapies between plant sterols and other lipid-lowering regimens (statins, niacin, fibrates, diet).<sup>155,156,157</sup> Currently, little is known about the sterol effects on lipoprotein particle size and number, although conflicting reports would suggest it is moderate at best.<sup>157,158</sup> In diabetic patients, 1.8g/day of plant sterols alone

reduced both LDL-C and non-HDL cholesterol.<sup>159</sup>

The GRAS (generally recognized as safe) status of plant sterols will permit more functional foods to incorporate these compounds and distribute them through the United States. Plant sterols are also available as dietary supplements in various forms (tablets and capsules primarily) and various brands. Most commercially available sterol products are derived from soy. Decreased absorption of carotenoids and certain fat-soluble nutrients has been reported with sterol intake, although clinical trials have not noted significant clinical concerns at therapeutic doses.<sup>149</sup> With the current data available, clinicians should recommend increased consumption of plant sterols in the form of functional foods or dietary supplements to patients with mixed dyslipidemias (especially elevated LDL-C).

### Fish, Fish Oil and Omega-3 fatty acids

The role of omega-3 fatty acids from fish and fish oil in preventing cardiovascular events is well established.<sup>160-164</sup> Concerning lipoprotein markers, the reduction of serum triglycerides is by far the most significant and consistent clinical response to fish oil ingestion. A meta-analysis of 65 published reports showed TG reduction averaging 25% with fish oil consumption (4g/day EPA and DHA).<sup>165</sup> The American Heart Association recommends 2 to 4 grams of EPA and DHA for patients with hypertriglyceridemia.<sup>164,165</sup> Coincident with the dose-dependent decrease in TG, is a small increase in LDL-C and HDL-C (not total-C). This is expected with large drops in TG, as a shift in VLDL metabolism moves cholesterol back to LDL particles. This shift is likely to improve the atherogenic profile by altering lipoprotein particle number and size, although clinical trials are mixed on this aspect.<sup>167-170,212</sup> One recent trial in hyperlipidemic children given 1.2 g/day of DHA showed a dramatic (91%) increase in larger LDL particles with a concomitant decrease (48%) in small-dense LDL particles, compared to placebo in 6 weeks.<sup>211</sup>

Increasing fatty fish consumption within the diet and/or supplementing with several grams of the omega-3 fatty acids EPA and DHA, should be considered for anyone with risk for cardiovascular disease. We have recently reviewed the use of fish oil in clinical practice, with an emphasis on cardiovascular uses.<sup>161</sup>

### Tocotrienols

Tocotrienols are within the vitamin E family, very closely related to tocopherols, but with a unsaturated isoprenoid side chain. Found abundantly in rice bran oil, palm oil and annatto, tocotrienols may play a role in the natural approach to cholesterol management. A significant body of research is available which shows direct reduction of total and LDL-C<sup>171,172,173</sup> with the ingestion of gamma-tocotrienols as well as closely related compounds. Consistent human data; however, has been generally lacking for tocotrienols.<sup>179,180</sup> The mechanism is thought to be a suppression of the enzyme HMG-CoA reductase, by a unique process of post-transcriptionally modifying the synthesis of the enzyme itself, while also modifying the intracellular mechanisms to increase the degradation of the enzyme.<sup>174,175</sup>

Like tocopherols, tocotrienols describe a group of molecules ( $\alpha, \beta, \gamma, \delta$ ) rather than a single molecule. The various potential blends of these compounds, as well as the presence of tocopherols, has been shown to significantly impact activities, leading to negative or inconsistent clinical results.<sup>176,177</sup> Some researchers believe these results are due to too much (>30%)  $\alpha$ -tocopherol within the tocotrienol blend, or too little  $\gamma$ - and  $\delta$ -tocopherol.<sup>177,178</sup> Larger controlled clinical trials of specific blends need to be performed before giving specific recommendation on dosing (typically 200mg of specific or blended tocotrienols) and expected outcomes. No side-effects are noted with tocotrienol intake.

### Red Yeast Rice

Red yeast rice (RYR), also called Xuezhikang, is a product which results from the fermentation of rice with the red yeast (*Monascus purpureus* Went.) The resulting fermented product contains small amounts of compounds known as monocolins. Monacolin K, the lovastatin-like component, is considered to be a key active ingredient (although only accounting for about 0.2% by weight) of the lipid-lowering effects attributed to RYR.<sup>187,188</sup> This component is also the cause of the regulatory issues preventing sales of RYR in the United States.

Like the statin drugs, the primary mechanism attributed to RYR preparations is HMG-CoA reductase inhibition. Human clinical trials using 2.4 grams/day of RYR (providing 4.8 mg monocolin K) or 1.2 grams/day resulted in multiple clinical changes; such as reduced LDL-C (20-30%), reduced TG (13-30%) and increased HDL-C (15-20%, although some trials showed no significant change in HDL-C); although many of these trials were uncontrolled.<sup>181-183</sup> Since there are many different (at least 10) monocolins which can be made during the fermentation process, the combination and relative amounts of each may play a role in determining the effectiveness of different commercial preparations; accounting for some of the clinical inconsistency.<sup>184</sup> Recent studies have shown other benefits associated with RYR therapy, such as reduced high sensitivity C-reactive protein (hsCRP), reduction in Lp(a) and improved endothelial dysfunction.<sup>182,185,186</sup>

FDA considers RYR products with monocolin K ("lovastatin") to be drugs, and since these RYR preparations have not been approved as new drugs by FDA, they cannot be sold legally in the United States as dietary supplements.<sup>189</sup> These products are available in other nations and via internet sales. How FDA will regulate distribution of RYR products via these channels is currently unknown.

The use of RYR products, like statin drugs, may deplete tissues of coenzyme Q10 (CoQ10). Mice given a RYR preparation in various doses showed a dose-dependent depletion of hepatic and cardiac CoQ10 levels.<sup>190</sup> Likewise, a case report noted rhabdomyolysis in a kidney transplant patient taking cyclosporine and RYR.<sup>191</sup> These reports suggest that the same precautions and contraindications for statin therapy may be warranted for patients given RYR.

### Berberine

Berberine is an alkaloid found in numerous plants used in

traditional Chinese medicine, as well as the widely used Western herb, goldenseal (*Hydrastis canadensis* L.). It is most noted as a compound with antimicrobial, antifungal and immune enhancing properties.<sup>192-195</sup> Through a genetic screening process, berberine was found to significantly upregulate the LDL receptor (LDLR) gene mRNA. Subsequently, in vitro and animal data suggested a novel cholesterol-lowering activity. A recent clinical trial was performed using berberine (500 mg, twice per day) or placebo for 3 months in hypercholesterolemic patients. In the subset of patients who not taking other drugs or herbal remedies, berberine significantly lowered total-C (29%), TG (35%), and LDL-C (25%). No increase in HDL-C was noted.<sup>196</sup> This recent data, combined with the clinical use of berberine for congestive heart failure and hypertension, has made berberine an emerging nutraceutical for cardiovascular health.<sup>198</sup> More and larger clinical trials are needed to confirm the use of berberine, but the current information, along with the safety profile (berberine improves liver enzymes and is hepatoprotective)<sup>196,197</sup>, make berberine a promising option as a monotherapy or in conjunction with other natural or pharmaceutical therapies.<sup>199</sup> Furthermore, recent animal studies suggest berberine may have insulin sensitizing activity which may make it even more applicable in patients with both insulin resistance and dyslipidemias, like metabolic syndrome patients.<sup>200,201</sup>

### Polymethoxylated flavones

Flavonoids are ubiquitous polyphenol compounds found in numerous plant species, many which have demonstrated biological action. Several citrus flavonoids, including the polymethoxylated flavones tangeretin and nobiletin, have recently been identified to have activities which limit the production of apo B and LDL particles, potentially preventing atherosclerosis.<sup>202,203,204</sup> In an animal model (hamster), polymethoxylated flavones fed at .25% to 1% were able to reduce TG, total-C, VLDL and LDL-C in a dose-dependent fashion. There was no change in HDL-C.<sup>205</sup> While no human studies have been published to date (making it difficult to suggest an active dose), these flavonoids have gained the attention of many researchers and have become available on the market in various forms. These and other flavonoids may play an important role in future studies as part of a natural combination therapy for reducing atherogenic lipoprotein markers.

### Guggul

Gugulipids come from the resin of the mukul myrrh tree (*Commiphora mukul*). Used in India for centuries, gugulipids were researched significantly since the 1960's for obesity and lipid disorders.<sup>206</sup> The active ingredients are the guggulsterones, which can be extracted with ethyl acetate and standardized within the extract. Gugulipid has been reported to lower total-C, TG and LDL-C and raise HDL-C levels. Guggul's primary mode of action seems to be the ability to increase the number of hepatic LDL receptors.<sup>207</sup> Guggul has also been reported to increase bile secretion and decrease cholesterol synthesis, possibly due to the increased LDL receptors on hepatocytes.<sup>208</sup>

Clinical trials using various preparations of guggul have been performed with moderate success in reducing total

cholesterol and LDL-C when measured, although most studies did not look at other lipid or lipoprotein markers.<sup>209</sup> The most recent, and most widely known, clinical trial failed to show any benefits with using either 1000 mg or 2000 mg/day of a guggul extract (2.5% guggulsterones) and even raised LDL-C levels compared to placebo in hypercholesterolemic subjects.<sup>210</sup> While the study was only 8 weeks, these data have placed caution for the use of guggul extracts as a primary therapy for dyslipidemia.

### Artichoke

Artichoke (*Cynara scolymus* L.) leaf extracts, along with other natural choleric agents, have been popular dietary supplements for managing dyspepsia, liver abnormalities and hypercholesterolemia.<sup>213,214,215</sup> They are thought to work by increasing bile synthesis and output, and in conjunction with a bile-sequestering soluble fiber, effectively move cholesterol out of the body.<sup>216,217</sup> In vitro studies in rat hepatocytes also reveal an inhibitory action against the HMG-CoA reductase enzyme which limits production of cholesterol.<sup>218</sup>

Currently, there are few human clinical trials assessing the role of artichoke extracts as a monotherapy for the reduction of cholesterol or other lipoprotein markers.<sup>219</sup> Certain extracts have shown promising results (25:1 aqueous extract)<sup>220</sup>, while others have shown little.<sup>219,221</sup> Recently; however, other activities such as antioxidant, increased nitric oxide formation and improved endothelial function have been associated with artichoke extracts, potentially leading to other beneficial roles in patients with atherosclerosis and cardiovascular disease.<sup>222,223,224</sup> Artichoke extracts should be considered in dyslipidemic patients with dyspepsia and liver complaints, but should be taken with a water-soluble fiber (psyllium, oat bran) regimen to maximize cholesterol-reducing potential.

### Garlic

Garlic (*Allium sativum* L.) has long been used for medicinal purposes throughout the world. Various preparations have been used for cardiovascular purposes, especially elevated cholesterol levels. There have been nearly 50 studies conducted to assess the lipid-lowering effects of garlic in humans over the past 40 years with a wide range of results.<sup>225</sup> Two recent meta-analysis suggest that the best and most controlled trials show garlic preparations are better than placebo in cholesterol reduction, but have modest effects at best.<sup>226,227</sup> This may not reflect the only benefit for garlic in relation to lipids and cardiovascular disease. Garlic prevents LDL oxidation, accounting for profound anti-atherosclerotic activity<sup>228,229</sup>, improves fibrinolytic activity<sup>225</sup>, inhibits platelet aggregation<sup>225</sup>, and acts as an anti-hypertensive agent.<sup>230</sup>

Garlic, like many herbal products, can differ quite dramatically (chemically and medicinally) depending on how it is processed. Positive and negative results have been reported with raw garlic (cultivated, wild, elephant), garlic oils, garlic extracts, odor-less garlic extract (standardized to the alliin precursor alliin) and aged garlic extracts. Proper manufacturing techniques, especially involving enteric-coating processes, can also alter the therapeutic potential of garlic products.<sup>231,232</sup> Therefore, it is important to understand the data and dose of the

specific product chosen in order to get the expected benefits.

### Other natural agents

The list of agents which have been studied for their ability to lower cholesterol or other lipoprotein markers is exhaustive. We list several here (with references) that have been studied in humans, which may be of some interest because of their use for other related conditions; however, their blood lipid-altering effects are modest and require further research.

They include: Fenugreek<sup>209,233</sup>, walnuts<sup>234,235</sup>, carnitine<sup>236,237</sup>, taurine<sup>238,239</sup>, soy constituents<sup>240</sup>, red wine<sup>241,242,243</sup>, rice bran oil (contains tocotrienols)<sup>244</sup>, green tea extracts<sup>245,246</sup>, pomegranate juice<sup>247</sup>, and conjugated linoleic acid (CLA)<sup>248</sup>.

### Conclusion

Cardiovascular diseases, such as atherosclerosis, are complex and multifactorial. Lipoprotein metabolism plays an important role in determining patient risk- although many other factors should be considered when assessing overall risk. We have shown that measuring and treating total or LDL-C alone is inadequate to reduce the atherogenic burden for many patients, especially those with metabolic syndrome and related atherogenic disorders. We have outlined the various important lipoprotein markers, such as LDL particle number and size, as important tests to help determine risk. Furthermore, we have outlined most of the non-pharmacological approaches to lower a person's risk based on these new markers. Physicians should have a number of approaches, especially when used in combination, to design treatment protocols which are well-researched, safe and effective for the majority of their dyslipidemic patients.

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