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Lipid Analyses: Early-Warning Assessment Tools for Cardiology and More

Exploratory studies in human subjects are testing the hypothesis and the potential use of synthetic HDL as a new treatment modality for acute coronary syndromes. Single high dose infusions and repeated injections of lower doses of apolipoprotein A-I variants or mimetics complexed to phospholipids have produced remarkable effects on the progression and regression of atherosclerosis in animal models. In 2007, a group of researchers studying the composition of HDL unexpectedly identified multiple complement-regulatory proteins and a diverse array of distinct serpins with serine-type endopeptidase inhibitor activity. Collectively, the observations of this group (published in the *Journal of Clinical Investigation*) suggest that HDL plays previously unsuspected roles in regulating the complement system and protecting tissue from proteolysis and that the protein cargo of HDL contributes to its anti-inflammatory and anti-atherogenic properties. REF #1-2

Apolipoprotein A-I (apoA-I) is the most abundant protein in HDL, accounting for approximately 70% of the total protein content of HDL. Studies suggest that the terminal helices of apo A-I penetrate into the phospholipid bilayer of membranes, promoting cooperative interactions between other α-helical segments and lipids to create an apo/lipid structure that dissociates from membranes. Immunohistochemical studies have found that specific epitopes derived from hypochlorous acid (HOCI) produced by myeloperoxidase (MPO), a heme protein secreted by phagocytes, colocalized with apo A-I. HDL or lipid-free apolipoprotein A-I exposed to HOCI was less able to remove cholesterol from cultured cells requiring the cell membrane transporter A1. The possibility has been raised that MPO, by virtue of its ability to form HOCI, may promote atherogenesis by counteracting the established antiatherogenic effects of HDL and ATP-binding cassette transporter A1 pathway. REF #3

Abdominal obesity is the body fat parameter most closely associated with metabolic syndrome and cardiovascular risk, and lifestyle interventions are the initial therapies recommended. The search for more effective and better-tolerated drugs for the control of obesity and metabolic syndrome continues. Reliable indices of coronary risk assessment and targets for drug treatment are important to the management of patients. Measurements of apolipoproteins are internationally standardized, automated, cost-effective, and convenient. Apolipoprotein B, apolipoprotein A-I, and the apo B/apo A-I ratio have been reported to be better predictors of cardiovascular events than LDL-C, and they even retain their predictive power in patients receiving lipid-modifying therapy. This profile could replace serum cholesterol and HDL cholesterol in the estimation of cardiovascular disease risk. Defining the therapeutic target of statin therapy in terms of serum apolipoprotein B rather than LDL cholesterol could also help to optimize statin treatment. REF #4-7

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a member of the phospholipase A_2 superfamily, a family of enzymes that hydrolyze phospholipids. Circulating Lp-PLA2 is a marker of inflammation that plays a critical role atherogenesis; its inhibition may have antiatherogenic effects. The Rotterdam Study was a population-based follow-up study of 7983 subjects to investigate Lp-PLA2 as an independent predictor of coronary heart disease and stroke. The study showed the relationship between Lp-PLA2 and coronary heart disease was present in both subjects with non-HDL cholesterol levels below the median and those with non-HDL cholesterol levels above the median. Numerous studies have been published supporting Lp-PLA2 as a predictive marker. REF #8-11

Ultrasound technologies have long been used to study vessel physiology. Ultrasound assessment of brachial artery vasoreactivity using high-resolution B-mode ultrasound emerged as a clinical research tool for studying endothelium-dependent vasomotor function in the early 1990s. The vascular endothelium, as the largest paracrine organ, maintains vascular health and modulates vascular tone, cell growth, platelet and leukocyte interactions, thrombogenicity, and inflammation. Nitric oxide, a potent endogenous vasodilator, is secreted by the endothelium in response to various chemical and physical stimuli, such as shear stress from increased blood flow. Nitric oxide bioavailability is reduced in a pro-oxidant milieu, as seen in the presence of cardiovascular disease.

Ultrasound is used to study the brachial artery's response to increased flow induced by hyperemia (flow-mediated dilation [FMD]). The technique of brachial artery reactivity has matured into a commonly used research tool to evaluate risk factor status and preclinical disease states, and to improve endothelial function with targeted specific interventions and risk factor modifications. Numerous studies have been published on endothelial function, including those that measured the effects of juice powder concentrate, flavonoid-rich dark chocolate, and high-fat meals enriched with walnuts or olive oil. Even epigallocatechin gallate (EGCG) has been shown to have a protective effect on the endothelium related to decrease in ADMA level in at least one animal study. REF #12-16

In 2006, the *American Journal of Cardiology* published a study that analyzed the relations between changes in the endothelium-dependent flow-mediated dilation of the brachial artery and changes in the plasma markers of metabolic control (glucose, insulin, adiponectin, resistin, and lipid profiles), markers of inflammation (high-sensitivity C-reactive protein [CRP], interleukin-6, soluble CD40 ligand, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1), and markers of vasoreactivity(asymmetric dimethylarginine [ADMA] and endothelin-1). The researchers sought to elucidate the roles of these markers in mediating the vascular protective effects of rosiglitazone. Data from this study showed that rosaglitazone treatment significantly improved flow-mediated dilation and nitroglycerin-induced vasodilation of the right brachial artery. REF #17

Clinician/Researcher of the Month

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Dr. Valori Treloar is a board-certified dermatologist who trained at the Boston University-Tufts University Joint Training Program in Dermatology after graduating from the Boston University School of Medicine. She is the only dermatologist to earn certified nutrition specialist status from the American College of Nutrition, and maintains a private practice in Newton, MA. Dr. Treloar is co-author of the book *The Clear Skin Diet: How to Defeat Acne and Enjoy Healthy Skin* (Cumberland House Publishing, 2007) along with Alan Logan, ND. The book has received positive reviews and features a forward by Dr. Bill Danby of Dartmouth University. REF #18

Dr. Bland and Dr. Treloar discuss the rising incidence of acne, much of which is attributable to the influence of a Western diet. Very obvious changes in skin complexion have been observed among what were once considered "clear-skin nations," including Japan, Portugal, and Peru, as well as within the Inuit culture. They also discuss the work of Dr. Loren Cordain, who published a landmark paper in the *Archives of Dermatology* in 2002. REF #19

Dr. Treloar provides useful insights about her approach to gathering information from patients and working with them to achieve a successful outcome from their treatment. She also discusses how she works cooperatively with other physicians and providers in her community, and makes an effort to increase awareness about functional medicine whenever there is opportunity.

Dr. Bland recommends *The Clear Skin Diet* to listeners as a valuable resource, as well as an interesting and unique collaboration between a naturopath and a board-certified dermatologist.

In Closing: The Cochrane Collaboration

The Cochrane Collaboration is a group of individuals who pool their expertise to evaluate the evidence base for different types of medical therapies. The group has recently published a review on the use of probiotics for the maintenance of remission in Crohn's disease. This publication is available online at http://www.thecochranelibrary.com.

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