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EDITORIAL COMMENT

Apolipoprotein A-I and High-Density Lipoprotein

Is This the Beginning of the Era of Noninvasive Angioplasty?*

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The quest for finding new therapies to alter the natural history of atherosclerotic cardiovascular disease (ASCVD) involves a series of steps that provide insight into the pathophysiology, leading to new targets for therapy. For example, interventions to lower low-density lipoprotein cholesterol (LDL-C) have become an established approach for the prevention and treatment of ASCVD on the basis of decades of research that included epidemiologic studies, characterization of naturally occurring genetic defects in humans, genetic mutations in animals, experimental studies that altered LDL-C levels in animals, and finally randomized clinical trials in humans. Advances in these areas usually occur simultaneously and contribute to our understanding of the disease process, ultimately resulting in improved therapies.

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Decades of information from large clinical studies have established that a low level of high-density lipoprotein cholesterol (HDL-C) is a risk factor for ASCVD (1). Animal studies have shown that infusion of HDL can slow, arrest, or in some cases regress the process of atherosclerotic plaque formation (2). An improved understanding of the metabolism of HDL has helped elucidate probable mechanisms by which HDL decreases the progression of atherosclerosis and hence offers potential targets for drug development.

Apolipoprotein (apo) A-I, which is synthesized by the liver and intestine, is the most abundant HDL protein and plays a major role in HDL metabolism. The nascent cholesterol-poor HDL particle containing apo A-I acquires cholesterol and phospholipids from peripheral cells, facilitated by adenosine triphosphate-binding cassette protein-1, thus initiating a process known as reverse cholesterol transport. The enzyme lecithin:cholesterol acyltransferase then esterifies the unesterified cholesterol within the HDL particle, and the esterified cholesterol is taken up by the liver through scavenger receptor class type BI. In addition, the cholesteryl ester in HDL can be exchanged for triglycerides from other lipoproteins through the action of the cholesteryl ester transfer protein (CETP). Other actors in this complex metabolic pathway include phospholipid transfer protein and various lipases (lipoprotein, hepatic, and endothelial). In addition to reverse cholesterol transport, HDL also may confer protection against atherosclerosis by preventing oxidation of LDL, promoting the availability of nitric oxide, and modulating expression of endothelial cell adhesion molecules.

Some studies have suggested that apo A-I may be a better marker of ASCVD than total cholesterol and HDL-C, particularly after statin therapy (3). Animal studies have suggested that interventions modulating apo A-I will likely reduce the burden of atherosclerosis (4,5). Several naturally occurring mutations of apo A-I have been described in humans. Low HDL-C levels and premature atherosclerosis have been described in humans with the complete deletion of the *APOAI* gene (6,7).

In this issue of the *Journal*, Hovingh et al. (8) describe a new *APOAI* mutation, L178P, which was associated with an increased risk for atherosclerosis as assessed by increased carotid intimal-medial thickness (IMT), impaired flow-mediated dilation (FMD), and increased premature coronary artery disease (CAD) events. They initially identified six probands, all from the same geographic region of the Netherlands, with a point mutation in the *APOAI* gene that resulted in the substitution of a proline for the usual leucine residue at position 178. Six kindred with 54 heterozygotes for the mutation and 147 family controls were identified. The *APOAI* gene defect was associated with a 52% mean reduction in apo A-I levels and a 62% decrease in HDL levels (17 vs. 47 mg/dl). Median FMD was noted to be significantly reduced in patients with the mutation after statistical correction for the significant age difference between the groups. Similarly, carotid IMT was increased in patients carrying the mutation compared with controls. The increase in IMT with this mutation in apo A-I was similar to the increase in IMT observed in familial hypercholesterolemia with high LDL-C. Patients with the mutation also had a 14-fold increase in risk for CAD events, but in the entire study sample (cases and controls), only 10 subjects had CAD events, leading to a very wide confidence interval for the odds ratio (2.3 to 87.1). Although risk for premature CAD events was increased, it is not possible to conclude from the data presented whether this mutation confers the same degree of risk for premature ASCVD events as does familial hypercholesterolemia. Despite the limitation of sample size, the consistency of the results suggests that the presence of the mutation does indeed confer a higher risk for ASCVD.

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The investigators demonstrate the power of combining genotyping with careful phenotyping to provide more compelling evidence that the genetic mutation contributes to ASCVD. They began by identifying 94 individuals with a well-defined phenotype, HDL-C that is less than the fifth percentile for age and gender, which can easily be measured quantitatively with standard assays. After identification of a mutation associated with low plasma levels of HDL-C and apo A-I, they not only examined the association between genotype and the phenotype of low HDL-C, but they also used noninvasive imaging measures (FMD and IMT) that provide quantitative information on vascular structure and function. Finally, they examined whether there was an association between the genotype and clinical evidence of premature CAD. This approach of careful quantitative phenotyping using both plasma measurements and vascular imaging modalities provides important evidence for understanding how genetic mutations in metabolic pathways lead to atherosclerosis and also suggests that the clinical efficacy of therapies that target the identified metabolic pathways may be monitored by using quantitative plasma measurements (biomarkers) and quantitative vascular imaging modalities.

A different mutation in *APOAI*, in which cysteine is substituted for arginine at position 173, was first noted in a family from Limone sul Garda, Italy, and was associated with low levels of HDL-C (<15 mg/dl) but not with any evidence of clinical atherosclerosis. This mutation, known as apo A-I_{Milano}, allows for formation of disulfide bonds with other apo A-I_{Milano} particles and with apo A-II, with more rapid metabolism than normal apo A-I particles (9). Carotid IMT in patients with apo A-I_{Milano} is not increased despite the profoundly reduced levels of HDL-C (10).

In addition to mutations that are associated with reduced levels of HDL-C, clinical studies focusing on individuals with high levels of HDL-C have identified mutations or polymorphisms in the gene encoding CETP. Mutations leading to CETP deficiency are associated with increased levels of HDL-C and apo A-I, but studies are conflicting as to how this may influence the risk for CAD. However, genetic variants have been associated with reduced activity, increased HDL-C, reduced risk for CAD (11), and increased longevity (12).

Data from genetic and metabolic studies have been used to build a paradigm in which increased concentrations of atherogenic particles (as observed in mutations in the LDL receptor, apo B, and apo E) lead to lipoprotein deposition in arteries with development and progression of atherosclerosis, whereas high levels of HDL prevent or reverse atherosclerosis. The development of novel pharmacologic therapies has allowed clinical trials to test this paradigm. In the recently reported Apo A-I Milano Trial, patients with acute coronary syndromes who received five weekly infusions of recombinant apo A-I_{Milano}/phospholipid complex, an HDL mimetic, had modest but statistically significant regression of coronary atherosclerosis as measured by intravascular ultrasound (13). Although this was a small study (n = 47 completed) with brief duration (5 weeks), the results suggesting that modulation of HDL-C levels may enhance regression of atherosclerosis differ from the results of clinical trials with statins, which primarily lower atherogenic particles. Multiple clinical trials using quantitative coronary angiography and now intracoronary ultrasound have shown that statins can stop or slow atherosclerosis but do not on average lead to regression of the lesion or improvement in lumen diameter.

In follow-up to the Apo A-I Milano Trial, several compounds are being tested in animals and humans, such as reconstituted HDL (14), phospholipid liposomes in unilamellar vesicles (15), and orally administered apo A-I mimetic peptides (16). Another approach, the inhibition of CETP, also is in clinical development, with one agent, torcetrapib, showing marked increases in plasma levels of HDL-C (17) Several agonists of peroxisome proliferator-activated receptors (PPARs) alpha, gamma, and delta that raise HDL-C are also under development. Several agents, such as niacin, fibrates, and PPAR gamma agonists, raise HDL-C and are currently available.

The era of noninvasive interventions for CAD began with statins and other lipid-lowering therapies that promote stabilization of lesions and stop the progression of atherosclerosis. If therapies that modulate HDL indeed provide additive benefit to statin therapy and promote regression of atherosclerosis, we may soon enter into the era of noninvasive angioplasty. However, the new targets of pharmacologic therapy identified by genetic studies must still pass rigorous testing in clinical trials to assess not only the effects on atherosclerosis but also, ultimately, the benefits on reducing cardiovascular events without substantially increasing risk for adverse events.

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