Editorial

Estrogen and HDL
All that Glitters Is not Gold
David M. Herrington, John S. Parks

Since the initial report of the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998, the medical community has struggled to understand the unexpected findings from a series of randomized clinical trials that failed to show a beneficial effect of postmenopausal hormone therapy on risk for cardiovascular events. One of the uniformly perplexing features of these trials was the lack of a cardiovascular benefit despite favorable changes in many of the intermediate end points that were previously thought to insure a beneficial effect of estrogen. Chief among these intermediate end points was high density lipoprotein (HDL) cholesterol, which was significantly increased in all of the clinical trials, but whose elevation was apparently not capable of imparting a corresponding reduction in cardiovascular risk. This observation led to speculation that the presumed favorable effects of raising HDL were diminished by other, previously unrecognized, adverse effects. A leading candidate was a proinflammatory effect of estrogen suggested by estrogen induced increases in C-reactive protein (CRP) and other hepatically-derived inflammation proteins. In most discussions, the impact of oral estrogen on HDL and its potential proinflammatory effect were considered separate but offsetting effects with respect to cardiovascular risk.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Abbas et al present new data suggesting that these two effects of estrogen, elevations in HDL without accompanying cardiovascular benefit and increased expression of inflammation proteins, may be more closely linked than previously thought. In a small crossover design clinical trial, they demonstrate that oral estrogen treatment increases serum amyloid A (SAA) incorporation into HDL particles. Previous studies have documented increases in other acute-phase proteins after estrogen therapy, but this is the first report that oral estrogen also leads to increased SAA and HDL SAA content. Previous studies have documented that high levels of SAA in HDL may diminish the reverse cholesterol transport capacity of HDL and also reduce its antioxidant properties. Thus, the authors speculate that oral estrogen treatment could produce HDL particles that have proinflammatory and proatherosclerotic properties rather than the expected anti-inflammatory and antiatherosclerotic properties that are typically associated with “good cholesterol.” SAA incorporation in HDL may also inhibit its ability to deliver free cholesterol to the liver for clearance, thereby contributing to higher levels of HDL cholesterol. Interestingly, transdermal estrogen administration in doses that achieved similar plasma levels of estradiol did not induce SAA levels or its incorporation into HDL, but rather led to a reduction in SAA and HDL SAA content. This observation implicates high intrahepatic levels of estradiol during first-pass metabolism as the chief determinant of these effects of oral estrogen.

When considering the clinical implications of the provocative observation by Abbas et al, it is important to determine whether the modest increases in HDL SAA content are sufficiently large to have a meaningful impact on HDL action. In the setting of more unambiguous inflammatory stimuli and corresponding acute phase responses, SAA has been shown to displace paraoxonase and platelet-activating factor acetylhydrolase from HDL. This displacement results in a reduced ability of HDL to detoxify oxidized phospholipids in low density lipoprotein and to protect against endothelial cell activation. However, in this setting the enrichment of SAA is typically an order of magnitude greater than reported by Abbas et al. It seems unlikely that the 15% enrichment observed after oral estrogen treatment would be sufficient to transform HDL particles from anti- to proatherogenic. It is plausible however, that this degree of enrichment is sufficient to attenuate the favorable properties of the slightly greater number of HDL particles after estrogen treatment. An alternate possibility is that a minor subfraction of HDL is preferentially enriched with SAA, resulting in a small population of proinflammatory HDL particles, SAA appears to preferentially associate with the smaller, more dense HDL subfractions in mice and nonhuman primates. Interestingly, displacement of paraoxonase and platelet activating factor acetylhydrolase from HDL does not seem to be specific to inflammatory incorporation of SAA into HDL. Similar effects on HDL have been observed with overexpression of apoA-II, another indigenous apolipoprotein of HDL. Ultimately, understanding the physiological significance of the intriguing observation by Abbas et al will require documentation of the changes in composition and proinflammatory potential of HDL induced by low grade increases in SAA content.

Beyond the specifics of HDL biology and inflammation, there is a broader lesson to be learned from the data by Abbas et al. Just because a biomarker is associated with coronary heart disease (CHD) events in epidemiologic studies is not a...
guarantee that pharmacologically altering the biomarker will result in changes in CHD risk in the anticipated direction. To successfully forecast clinical consequences requires an extremely detailed understanding of the physiology of the biomarker and its regulation. The data by Abbas et al emphasize the folly of relying simply on HDL cholesterol concentration to infer a clinical effect of hormone therapy. It is questionable whether we actually have such complete knowledge about any cardiovascular risk factor, which is why the assessment of interventions always requires confirmation with properly designed clinical end point trials. In the case of hormone therapy, it appears that we were previously blinded by the glittery array of favorable effects on intermediate end points, such as HDL cholesterol. As a consequence, we failed to recognize the lack of proven efficacy or safety for cardiovascular disease prevention.

References
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Arterioscler Thromb Vasc Biol. 2004;24:1741-1742
doi: 10.1161/01.ATV.0000142357.90351.92

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