Response to Letter by Ryan et al Regarding Article, “Do Hemochromatosis Mutations Protect Against Iron-Mediated Atherogenesis?”

Ryan et al1 propose another factor that may protect patients with hemochromatosis from atherosclerosis, namely, suppression of monocyte chemoattractant protein-1 (MCP-1). To know how much of the antiatherogenic effects of hemochromatosis mutations is due to this suppression will require additional investigation. Lawless et al2 report that MCP-1 is low with the C282Y variant but increased with H63D. This appears consistent with the hypothesis, because some H63D cases have higher hepcidin expression.3–5 In H63D, hepcidin normalized against ferritin is low, but the higher absolute hepcidin concentrations may allow higher macrophage iron in this variant. As noted in my study,6 there is a variable impact of genotype on hepcidin expression. Genotype of subjects in a study to test the hypothesis would need to be determined; however, testing the hypothesis would not rely directly on showing an association of genotype with disease. The hypothesis implies that protection against atherogenesis is inversely proportional to hepcidin expression. In an epidemiological study, the hypothesis suggests that among those with any 1 of the number of iron-overloading genotypes, protection against atherogenesis would be seen as a function of the degree of life-long hepcidin downregulation.

In mice, the effects of Hfe−/− on atherogenesis on an ApoE−/− background may be informative on the question of the effects of Hfe loss and any changes in MCP-1 on atherogenesis. Loss of Hfe in mice increases their survival after infection with Salmonella typhimurium.7,8 Altered macrophage function associated with mutationally low macrophage iron may also lessen atherogenesis in Hfe−/− ApoE−/− double-knockout animals (nutritional iron depletion, sufficient to lessen macrophage iron, diminishes atherosclerosis in the ApoE−/− knockout mouse9). In Hfe knockouts, resting macrophages express MCP-1, and infection with S typhimurium increases macrophage MCP-1.7 Hfe−/− mice are protected from S typhimurium despite the expression of MCP-1. Further study will be required to determine whether these animals exhibit some protection against atherosclerosis as well.

Disclosures

None.

References

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