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Letter by Sullivan Regarding Article, “HFE C282Y Homozygosity Is Associated With Lower Total and Low-Density Lipoprotein Cholesterol: the Hemochromatosis and Iron Overload Screening Study”

To the Editor:

Adams et al¹ report lower serum cholesterol and low-density lipoprotein levels in hemochromatosis patients homozygous for C282Y. They suggest a role for excess iron in this effect; however, ironically, an alternative mechanism may involve a relative lack of intracellular iron in certain cell types in homozygous patients. The classical finding of parenchymal iron loading in hemochromatosis with sparing of reticuloendothelial cells, together with more recent studies,² suggests that macrophage iron retention is defective in homozygotes. This cellular defect is linked to a profoundly diminished hepcidin level in hemochromatosis.² Another clinical situation associated with diminished hepcidin production and iron-free macrophages is iron deficiency. Iron deficiency may also be associated with lower levels of cholesterol and low-density lipoprotein.^{3–5} Perhaps iron-poor macrophages in either iron deficiency or inherited iron overload negatively regulate systemic cholesterol level. The role of macrophage iron metabolism in regulation of lipid level is a fruitful area for future research.⁶

Protection against cardiovascular disease by iron depletion has been proposed.^{7,8} A frequent objection to this hypothesis has been that it is incompatible with the apparently lower prevalence of cardiovascular disease in hemochromatosis. The physiology of hepcidin suggests an explanation for the contradiction of a protective role for iron depletion, despite less cardiovascular disease in massive iron overload. Both iron deficiency and homozygosity for C282Y are characterized by very low levels of hepcidin with consequently low iron concentrations in the macrophage. It has been proposed that homozygous hemochromatosis may confer some specific protection against atherogenesis because of diminished iron load in atherosclerotic plaque macrophages.^{2,8} One possible contributing mechanism

for such protection could involve the associated lower levels of cholesterol and low-density lipoprotein reported by Adams et al.¹

Disclosures

None.

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