Body Iron Stores and Coronary Heart Disease

Over the past 20 years, the hypothesis that body iron stores are associated with risk of coronary heart disease (CHD) has generated extensive debate (1–4). This debate has intensified in the last 4 years after reports from three studies that carriers of the recently discovered HFE C282Y mutation commonly seen in hereditary hemochromatosis have significantly increased risk of CHD (5–9). Clinical trial has recently been proposed as the ultimate resolution to assess protective effects of iron depletion against CHD among C282Y heterozygotes (9). In this issue of Clinical Chemistry, Bozzini et al. (10) show that neither a biochemical marker (serum ferritin) nor a genetic marker (C282Y carrier status) of body iron stores was significantly associated with angiographically documented coronary atherosclerosis.

Do increased body iron stores increase risk of CHD? Are individuals who are heterozygotes for the common C282Y mutation at especially high risk of CHD? Can iron depletion reduce the risk? These questions have important implications given the common practice of fortification of food and supplements with iron in industrialized countries and the high frequency of HFE C282Y carriers (~9% of them are of northern European descent) (11). Moreover, the “Oxidative Stress Theory” suggests that iron, as a potent catalytic agent, could promote formation of highly reactive oxygen species and lipid peroxidation, a crucial step in atherosclerosis (4). Thus, evaluation of the iron hypothesis for CHD will lead to advances in our understanding of its pathogenesis. To date, conflicting results have been reported from epidemiologic studies (4, 8, 9, 12–14) conducted in different countries and populations using different biochemical and genetic markers of body iron stores.

Among biochemical markers of iron stores, serum ferritin is generally considered the best measure that can be readily assessed in epidemiologic studies. Nine of the 11 cross-sectional or case-control studies (13) [including the study of Bozzini et al. (10)] reported no association between serum ferritin and CHD or atherosclerosis, with the exception of the Italian Bruneck Study (15) and a study of young Iranian male CHD patients (16). All of these studies evaluated serum ferritin among patients with CHD, but ferritin, an acute-phase protein, can be increased by myocardial damage and inflammation (17). A positive association could therefore be biased by postmyocardial infarction damage and inflammation. Chronic inflammation (as measured by fibrinogen, C-reactive protein, albumin, leukocytes, and erythrocyte sedimentation rate) has consistently been found to be associated with increased CHD risk (18). In the present Italian study of Bozzini et al. (10), serum C-reactive protein, but not ferritin, was significantly higher among CHD patients than the CHD-free controls, although the two markers were significantly correlated with each other. On the other hand, the lack of an association with serum ferritin in a case-control study could also reflect bias by factors related to treatment, such as aspirin, or behavioral changes, such as a healthy diet or increase in exercise.

Prospective cohort studies measure biomarkers using blood samples collected before the disease is diagnosed. Because CHD patients are prospectively ascertained and CHD-free controls arise from the same cohort, many potential biases can be avoided. Eight prospective cohort studies have reported results for the relationship of serum ferritin with risk of CHD or atherosclerosis (12, 13); only two found a significant positive association (12, 13, 19). The first positive finding was based on the Finnish Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) (20, 21) in men, which reported a twofold increased risk of CHD (a total of 83 incident cases) among men with serum ferritin >200 µg/L. The other was based on the Italian Bruneck Study (19) and found a positive association between serum ferritin and ultrasound measures of progression of carotid atherosclerosis over a 5-year follow-up period. The Bruneck Study (11) presented results on the basis of a combined sample of men and women that is hard to interpret given the large gender difference in ferritin concentrations. Transferrin saturation percentage is the most widely used indicator for screening iron overload. However, none of the five cohort studies assessing transferrin saturation reported increased risk of CHD (12).

In addition to assessing the effect of iron overload, several recent studies have specifically addressed the hypothesis that “iron depletion” is associated with lower risk of CHD. In a recent prospective analysis of the second National Health and Nutrition Examination Study, Sempos et al. (13) observed either no association (in Caucasian men) or a possible nonsignificant increased risk (in Caucasian women) of cardiovascular or CHD death among individuals with low ferritin concentrations. In the current study (10), the observed higher prevalence of iron depletion in CHD-free vs CHD women was mainly explained by age and other CHD risk factors. In addition to the use of biomarkers, the comparison of blood donors with nondonors appears to provide a good test of the iron-depletion hypothesis because of the marked contrast in body iron stores of regular donors compared with those of nondonors (14). However, of three published studies on blood donation (14, 22, 23), only the Finnish KIHD study found a significant inverse relation with CHD (23).

Hereditary hemochromatosis causes progressive accumulation of iron in most tissues and has been used as a “human model” to evaluate the effect of marked iron overload on CHD (8). Autopsy or mortality studies have consistently shown that atherosclerosis, CHD, stroke, and peripheral artery disease are neither prominent clinical features nor frequent causes of death in clinically diagnosed hemochromatosis patients (8). Because most of these studies included patients with severe iron overload, individuals with moderate iron overload were not represented.
The recent discovery of the HFE gene mutation provides a new opportunity to address the iron hypothesis. Of the two common mutations of the HFE (C282Y and H63D), C282Y carrier status has recently been associated with significantly increased risk of CHD incidence or cardiovascular mortality in three cohort studies (5–7). The first study (5) was from a subgroup of the original Finnish KIHD cohort. Eight (11.8%) of 68 individuals diagnosed with acute myocardial infarction and 77 (6.7%) of 1150 non-CHD participants were carriers of C282Y. The crude relative risk of myocardial infarction was 2.0 (95% confidence interval (CI), 0.9–4.1), and the adjusted relative risk was 2.3 (95% CI, 1.1–4.8). In a cohort of 12 239 Dutch postmenopausal women, the C282Y carrier status was assessed among 531 (57 carriers; 10.7%) women who died of cardiovascular disease and 555 (43 carriers; 7.7%) randomly selected women who did not die of cardiovascular disease (6). This study reported a 1.5-fold increased risk of myocardial infarction death (95% CI, 0.9–2.5), a 2.4-fold increased risk of cerebrovascular death (95% CI, 1.3–4.4), and a relative risk of 1.6 (95% CI, 1.1–2.4) for total cardiovascular death. However, the numbers of C282Y carriers in the cause-specific subgroups were not given. In this study, a subgroup analysis suggested that C282Y heterozygotes who were both smokers and had hypertension had a strongly increased risk of cardiovascular death (relative risk, 18.9; 95% CI, 8.4–42.4). The wide CI reflects the small number of deaths in the smoker/hypertensive category; further study is needed to confirm or refute this finding. The third study, the United States Atherosclerosis Risk in Communities study (7), reported a C282Y carrier frequency of 9.9% among 243 CHD cases and 6.1% among 535 selected noncases. The crude relative risk of CHD associated with C282Y carrier status was 1.6 (95% CI, 0.9–3.0) and was 2.7 (95% CI, 1.2–6.0) after controlling for other risk factors, especially lipid concentrations. In addition to the current study by Bonzini et al. (10), all six previous case-control studies reported no association between atherosclerosis or cardiovascular events and heterozygosity for HFE C282Y (24–29). Although survival bias could not be ruled out in all these case-control studies, the three prospective studies did not specifically report a stronger impact of C282Y heterozygosity on fatal CHD.

It has been reported that heterozygotes for hereditary hemochromatosis have slightly but significantly increased serum ferritin and serum iron (30). However, it remains uncertain whether heterozygotes of C282Y indeed have increased iron stores because some studies, including the Finnish KIHD study and the study in this issue, found that serum ferritin concentrations were not correlated with C282Y carrier status (5, 10, 25). One recent study (31) suggested that non-transferrin-bound iron or low-molecular weight iron is increased in circulation of C282Y heterozygotes, leading to higher transferrin saturation. However, transferrin saturation was not associated with increased risk of CHD in epidemiologic studies as discussed previously (12). Moreover, in all three cohort studies (5–7) and seven case-control studies (10, 24–29) of HFE mutation and CHD risk, the numbers of individuals homozygous for C282Y were too small to evaluate a gene-dose effect, and a larger study is needed to address this issue.

In summary, the totality of available evidence from a variety of studies using different measures of body iron stores (ranging from blood donation, biochemical and genetic markers to hemochromatosis patients) do not provide persuasive evidence to support the iron hypothesis, although further studies are warranted. The majority of HFE heterozygotes have distributions of iron storage indicators that overlap substantially with controls. The potential influence of nongenetic factors (such as gender, chronic blood loss, regular blood donation, excessive iron intake, or other dietary modifiers that increase or decrease iron stores) on phenotype expression needs to be carefully evaluated. Previously published studies either lacked comprehensive nongenetic information or were too small to examine gene-environment interactions. A larger comprehensive prospective study or a pooled analysis of existing genetic studies might provide a more coherent picture before a large and expensive trial of genetic screening and iron depletion can be seriously entertained.

References

Supported by Research Grants CA 78293, CA 42182, CA 58684, CA 70817, and CA 90598 from NIH.


Jing Ma*
Meir J. Stampfer1,2
1 Channing Laboratory
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA 02115
2 Departments of Epidemiology and Nutrition
Harvard School of Public Health
Boston, MA 02115

*Author for correspondence. Fax 617-525-2008; e-mail jing.ma@channing.harvard.edu.