Do body iron stores increase the risk of developing coronary heart disease?¹,²

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Do body iron stores directly increase a person’s risk of developing coronary heart disease (CHD)? The hypothesis, as first posed by Jerome Sullivan in 1981 (1), was that the higher a person’s iron stores—as measured by serum ferritin—the higher the risk. The way to reduce that risk was by eliminating iron stores. In evaluating the research, some have suggested that the evidence may be strong enough to recommend ending iron fortification and supplementation and to start advising people to donate blood to reduce their stores of iron (2, 3).

During the process of developing the new dietary reference intakes (4), the hypothesis was considered in great detail, and it was the conclusion of the Panel on Micronutrients of the US Food and Nutrition Board that there was not enough evidence at the time to support the hypothesis. The decision was based primarily on an evaluation of the epidemiologic evidence. In the space available, I will briefly review that evidence.

The epidemiologic research on this hypothesis may be divided into studies of the association of CHD risk with 1) serum ferritin; 2) other measures of body iron stores, less accurate than serum ferritin, eg, transferrin saturation; 3) blood donation; and 4) heterozygous hemochromatosis.

Salonen et al (5) were the first to report a significant association between serum ferritin concentrations and risk of heart attack, a component of CHD. They found that Finnish men with a serum ferritin concentration ≥ 200 μg/L had an ≈ 2-fold higher risk of heart attack than did men with a concentration < 220 μg/L. They also reported finding a significant linear association between serum ferritin and risk of heart attack. The association between serum ferritin and CHD risk has been investigated in ≈ 20 different studies (6–9). Some of those studies looked at the association with heart attack, some with total CHD, and others with carotid artery disease. In addition, some looked for a low threshold, some—such as Salonen et al—looked for a high threshold, and others looked for a continuous linear association. But no matter what the definition of CHD used or the specific aspect of the hypothesis that was tested, the results were almost entirely negative. In only 3 of the 22 reported studies, including the original paper from Finland, was a statistically significant association found. I agree with the criticism that TS is a much less accurate marker of body iron stores than is serum ferritin in the normal range. But as we will see, those results take on new importance when evaluating the association between hemochromatosis and risk of CHD. Other markers of body iron stores, eg, hemoglobin, hematocrit, and dietary iron intake, were also studied, but again, the results taken together do not support the hypothesis (11–13).

Indirect measures of body iron stores were also used to examine the hypothesis. One such indirect measure is blood donation. Frequent blood donation will reduce body iron stores, and as a result, several researchers have recommended it as a safe and inexpensive method for reducing CHD risk. However, of the 3 studies in this area (14–16), only one found an association overall. That study, by Salonen et al (15), looked at the association between blood donation and heart attack risk. The study is, in my opinion, seriously flawed because men with a history of CHD at baseline were included. Persons with heart disease are much more likely to have a future heart attack than are persons without the disease, and because having CHD is a contraindication for blood donation, it is not surprising that 26% of the non-donors but only 8% of the donors had a history of CHD. As a result of the study design, the nondonors as a group were at a much higher risk of having a future heart attack than were the donors. Finally, in the study by Meyers et al (14), a significant association was not found in men or women as a group. An association was found only for male smokers. No association was found in the study by Ascherio et al (16).

Before the publication of the dietary reference intakes, limited information was available on the relation between hemochromatosis and the risk of heart disease (17, 18). Since then there have been several publications on the topic. The conclusion remains the same, however: there is still no consistent, convincing

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evidence that having hemochromatosis, especially the heterozygous form, is associated with an increased risk of CHD.

Hemochromatosis is a genetic disorder that in the homozygous state leads to iron overload, serious illness, and early death, usually from liver cancer, other liver diseases, cardiomyopathy, or diabetes (19). Persons with the heterozygous form of hemochromatosis are unlikely to develop iron overload, but they tend to have higher body iron stores, as indicated by higher serum ferritin and TS concentrations, than do persons without the condition. Because the heterozygous form of the disease is relatively common—i.e., a prevalence of 10–15% (20–22)—if the iron hypothesis were correct, then heterozygotes would form a substantial pool of persons at increased risk of CHD.

The cysteine-to-tyrosine substitution on the hemochromatosis gene (Cys282Tyr mutation) is thought to account for most of the cases of hemochromatosis. Nine published studies investigated the association between the presence of the Cys282Tyr mutation in an individual and the risk of heart disease (8, 23–30). Note that these studies looked at the association between the presence or absence of a mutation and CHD risk and not whether serum ferritin or some other marker of body iron stores was related to risk. The 3 prospective cohort studies found an association, and the 6 case-control or cross-sectional studies did not.

Roest et al (23) found that Dutch women who were heterozygous for the Cys282Tyr mutation were 1.5 (95% CI: 0.9, 2.5) times more likely to die of a heart attack, 2.4 (95% CI: 1.3, 3.5) times more likely to die of a stroke, and 1.6 (95% CI: 1.1, 2.4) times more likely to die of any cardiovascular disease than were women without the mutation. Toumainen et al (24) reported that heterozygous Finnish men had a 2.3-fold (95% CI: 1.3, 4.8) higher risk of having a heart attack than did men without the mutation. However, although Rasmussen et al (25) reported that heterozygous men and women in the US Atherosclerosis Risk in Communities Study were found to have a 2.7-fold (95% CI: 1.2, 6.1) higher risk of incident CHD than were men and women without the mutation, they also reported that the results were “somewhat unstable due to a few subjects in some strata.” As a result, they advised that their results should be interpreted cautiously.

All of the studies that did not report an association between the Cys282Tyr mutation and disease risk were case-control or cross-sectional studies (8, 26–30). Prospective or cohort studies are generally thought to be superior in design because they can document that the exposure or risk factor precedes the event. But this concern may not be an issue in investigating an association between an inherited mutation and the risk of disease.

The possible association between hemochromatosis and CHD is even further clouded by the fact that elevated fasting serum TS is used as the presumptive diagnosis for the disease (31). Taking that into account and the fact that the heterozygous form of the disease is so common, why hasn’t serum TS been found to be a risk factor for CHD more often? If the iron hypothesis is correct, I think it should have been.

One other issue is often ignored in this discussion: iron deficiency remains the most common nutritional deficiency in the United States (32). Nine percent of toddlers (1–2 y of age) and adolescents (12–15 y of age) and 11% of women of childbearing age (16–49 y of age) in the United States are iron deficient according to data from the third, and most recent, National Health and Nutrition Examination Survey (1988–1994). Given the extent of iron deficiency in the face of fortification and supplementation, any decision to reverse iron fortification and supplementation policy should be based on extremely sound science.

In general, sound clinical practice and public health policy must be based on reasonably sound evidence that what is being recommended is both safe and effective. Given the results to date concerning the iron hypothesis, there can be no doubt about the recommendations. Although further research, including basic research and large-scale epidemiologic studies, is needed to fully assess the association between iron status and risk of cardiovascular diseases, the results to date supporting the iron-CHD hypothesis are weak and inconsistent. Thus, I agree with the conclusion of Corti et al (33): “at the present the currently available data do not support radical changes in dietary recommendations or screening to detect high normal levels nor do they support the need for large-scale randomized trials of dietary restriction or phlebotomy as a means of lowering iron stores.”

REFERENCES