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 there 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, of the 153 donors and 2529 nondonors in that study, there were 316 heart attacks in the nondonor group and only 1 in the donor group. Clearly, the small number of heart attacks among the donors coupled with inclusion of men with a prior history of heart disease may have led to a biased result. 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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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


