The hypothesis that iron depletion protects against ischemic heart disease was proposed in 1981 as an explanation for the sex difference in heart disease rates.1–5 The “iron hypothesis” has generated significant debate, especially in the 1990s after publication of supportive findings from Finland.6 Confusion has been introduced into the debate by inappropriate study designs in tests of the hypothesis. A recurring weakness is that stored iron is measured by inappropriate methods. In addition, evidence against a particular mechanism may be erroneously taken as evidence against the core hypothesis. For example, in a particular study design, a finding of no association of stored iron with coronary atherosclerosis would not invalidate an association of stored iron with cardiovascular mortality. Recent studies relevant to the iron hypothesis have been reviewed.5,7–12

In 1994, Ascherio and Willett13 recognized that the iron hypothesis cannot be rejected on the basis of available data, stating that “[s]tronger evidence is needed before the hypothesis is rejected that greater iron stores increase the incidence of coronary heart disease or death from myocardial infarction.” Indeed, nothing in data made available since 1994 excludes the possibility that iron depletion has a large protective effect, large enough to explain the low incidence of myocardial infarction in menstruating women.

A 1997 editorial14 on the iron hypothesis suggests that this once-controversial idea has become more acceptable to many scientists. Gillum14 noted that “this important hypothesis and related research fronts have led to many valuable studies like that of Kiechl et al [see Reference 9], which will greatly enhance our understanding of atherosclerotic vascular disease and may lead to innovations useful in clinical medicine and public health, perhaps in heretofore unanticipated ways.”

Mechanisms of protection have not been completely defined.1–5 Iron depletion probably protects by more than 1 mechanism. Unforeseen modes of action cannot be ruled out. Leading candidates involving the well-known role of iron in free-radical–mediated injury are (1) a decrease in ischemic myocardial injury and/or (2) a decrease in atherogenesis, both effects in association with iron depletion. The relative contribution of these or other mechanisms to protection against clinical events is unknown. Iron depletion may directly protect myocardium against ischemic injury independently of a role in inhibiting atherogenesis. In other words, iron depletion may protect against ischemic events, even in patients with appreciable atherosclerotic disease.1–5

Cardiovascular Disease in Heterozygous Hemochromatosis

In this issue of Circulation, Roest et al15 and Tuomainen et al16 present landmark studies of relevance to the iron hypothesis and to the genetics of cardiovascular disease. Using the newly described genetic polymorphism associated with the majority of patients with hereditary hemochromatosis, Roest et al15 find that heterozygosity for this mutation confers a significant increase in risk of cardiovascular events, including myocardial infarction. The study involved a group of 12 239 women followed up for 16 to 18 years. Incidence-rate ratios of heterozygosity were 1.5 for mortality by myocardial infarction, 2.4 for cerebrovascular mortality, and 1.6 for total cardiovascular mortality. Among hypertensive smokers with the mutation compared with nonsmoking, nonhypertensive normal women, the incidence-rate ratio of heterozygosity was 18.85 for total cardiovascular mortality.

In the study by Tuomainen et al,16 hemochromatosis gene (HFE) Cys282Tyr is found to be associated with a 2.3-fold increased risk of acute myocardial infarction in men ($P=0.03; n=1150$). These findings15,16 confirm the earlier corollary hypothesis linking heterozygosity for hemochromatosis with ischemic heart disease.17 The new data15,16 are also highly supportive of the hypothesis1–5 that iron is an important risk factor for ischemic heart disease in men and in women, as suggested by both groups of authors. The striking increase in incidence among hypertensive women carriers who smoke15 supports the concept that a small burden of stored iron exerts a permissive effect with respect to the impact of other risk factors.

It is conceivable that some effect of the Cys282Tyr polymorphism other than increased iron loading could be the actual basis of the observed associations. However, any such mechanism would be entirely speculative. Given the accumulating literature on iron and cardiovascular diseases, as well as the prior prediction of the observed association,17 a mechanism based on elevated iron stores is far more plausible.

The findings may substantially underestimate the impact of stored iron on cardiovascular diseases. Most heterozygotes have stored iron loads well within the reference range. In a study involving 1058 obligate heterozygotes,
Bulaj et al. found that only 20% of male and 8% of female heterozygotes had serum ferritin values higher than normal. Few heterozygotes had the very high levels suggestive of homozygosity. For pathologies related specifically to stored iron load, most heterozygotes would be expected to be indistinguishable from normal subjects. It is likely, however, that many heterozygotes with statistically normal iron loads achieve those levels of stored iron earlier in life than normal subjects. Heterozygous men and women had significantly higher-than-normal mean serum ferritin levels among the 31- to 60-year-old age group. An additional factor tending to obscure the relationship between heterozygosity and disease is the focus of both studies on the Cys282Tyr mutation. A number of subjects without this mutation may nonetheless have higher-than-normal stored iron levels because of other known or unidentified iron-loading mutations.

Franco et al. reported that the HFE genes were not associated with coronary or peripheral atherosclerosis in patients <50 years of age (n=537). Their findings do not invalidate those of Tuomainen et al. or Roest et al. Franco et al. examined the association of HFE genes with structural lesions, whereas the other studies probed the relationship between carrier status and cardiovascular mortality, i.e., a category of cardiovascular events. The role of iron in atherogenesis appears likely to be complex. The new findings suggest that iron could have a clinically more important role in ischemic events than in initiating or promoting vascular structural lesions. Increased events may occur without an increase in atherosclerotic disease. Failure to demonstrate an increase in atherosclerotic lesions in carriers speaks to mechanism; it does not contradict the independent findings that carriers are at an increased risk of events.

A recent study by Nassar et al. considered the prevalence of HFE genes in 2 groups with cardiovascular disease of early (<50 years of age) or late (>65 years of age) onset (n=300). They found similar prevalences of the HFE genes in the 2 groups; however, the early-onset group had significantly higher serum ferritin levels. The study has limited relevance to this discussion because it does not directly address the question of the association of the carrier state with disease, because all subjects in the study had cardiovascular disease.

Association between carrier status and cardiovascular events counters a frequent criticism of the iron hypothesis. It has been argued that the apparent lack of an increase in coronary atherosclerosis in homozygous hemochromatosis is evidence against the iron hypothesis. Even before the publication of the findings on heterozygotes, there had been no study definitively excluding an increased risk of coronary atherosclerosis in homozygotes. The absence of an increased prevalence of coronary lesions in homozygotes, even if true, would not invalidate the hypothesis that iron depletion protects against cardiovascular events. Evidence against 1 possible mechanism is not evidence against the general hypothesis that iron depletion protects against ischemic heart disease. It has also been noted that the "heart lesion of hemochromatosis is relevant to ischemic heart disease precisely because it demonstrates that myocardium can be injured by iron-dependent processes in the absence of coronary occlusion." Vulnerability of myocardium to ischemic injury appears to be significantly regulated by stored iron level and not exclusively by the degree of coronary atherosclerosis.

Homozygotes have iron levels so high that multiple organs are affected. Untreated individuals may tend to die of unrelated causes before clinically significant ischemic myocardial injury occurs. At the extremely high iron levels seen in homozygotes, there is a direct compromise of myocardial function unrelated to coronary artery lesions. At the much lower iron levels associated with heterozygosity, iron-mediated compromise of heart function may arise only after an ischemic event.

Predisposition to myocardial infarction and other cardiovascular events may be the principal hazard of heterozygosity for hemochromatosis. Homozygotes have more iron-related disorders, and these occur earlier in life. Recent findings suggest an analogous pattern in cystic fibrosis. Patients homozygous for cystic fibrosis have severe lung and pancreatic disease early in life. It now appears that cystic fibrosis heterozygotes do not completely escape the deleterious effects of the mutation. Heterozygotes are at higher-than-normal risk of chronic pancreatitis in adulthood but are free of other, more severe manifestations of the homozygous condition. With the quickening pace of gene identification in inherited disorders, there may well be other recessive conditions that turn out not to be benign in the carrier state. The new findings in hemochromatosis suggest that the heterozygous condition puts the carrier at risk of developing a spectrum of disorders that differ qualitatively and quantitatively from those that beleaguer homozygotes.

Iron and the Genetics of Cardiovascular Disease

A preponderance of evidence supports a familial aggregation of premature myocardial infarction. Roughly 5% to 7% of individuals in the general population fall into the high-risk group. Some high-risk families appear to be at increased risk because of familial predisposition to known risk factors such as hyperlipidemia or hypertension. However, in most studies, no aggregation of the known risk factors is seen in a large proportion of the high-risk families.

These studies suggest a heritable risk factor (or factors) for myocardial infarction that preferentially affects those younger than 50 years of age and is independent of traditional risk factors. Furthermore, this unknown, heritable factor selectively increases the risk of male family members. Women in the coronary-prone families are relatively protected from the unknown factor(s).

These patterns make sense if the mysterious risk factor is a gene favoring iron absorption. Stored iron increases with age in normal people. Accumulation is accelerated in hemochromatosis heterozygotes. Iron stores in older normal subjects eventually approximate those seen in younger heterozygotes. As they age, heterozygotes would be at progressively less relative disadvantage, thus
explaining the selective effect of the heritable factor on persons under age 50. Women in high-risk families are spared from the effect of the unknown heritable risk factor. Such a pattern is expected if the unknown factor is the hemochromatosis gene. Iron acquisition in affected women is delayed in comparison with men by continual loss of iron in menstrual blood. The relationship of the mystery factor to known risk factors is unsurprising, because heterozygous hemochromatosis is not known to be associated with increases in the traditional risk factors. The proportion of carriers in the general population is 10% to 13%, more than enough to account for the percentage of families with the unknown heritable risk factor given that not all carriers have abnormal levels of stored iron.

The findings of Roest et al15 and Tuomainen et al16 provide empirical support for the hypothesis that heterozygosity confers increased risk.17 The findings15,16 are significant because they provide strong support for a link between iron and cardiovascular diseases. Roest et al15 and Tuomainen et al16 also give specific support to the corollary hypothesis17 that the much-discussed unknown factor is an inherited predisposition to accumulate iron.

Conclusions
Among the important unresolved questions raised by the iron hypothesis are the following: Does deliberate iron depletion, eg, by regular blood donation, protect against cardiovascular diseases? Does the public need to be informed of the risks of stored iron before a definitive trial is completed?

Three studies published in 1997–9 are confirmatory of the key prediction1–5 that volunteer blood donation is associated with a significant decrease in vascular events and in atherosclerosis. Donors must be in relatively good health before they are permitted to donate and may thus be expected to have lower disease rates than nondonors. However, in the new studies of heart diseases in blood donors,7–9 donors and nondonors alike were in a similar state of health at entry as defined by subject criteria in the study designs. For this reason, the bias inherent in simple comparisons of disease rates in donors and nondonors is significantly mitigated. The iron hypothesis must ultimately be tested in a randomized, prospective clinical trial of the effects of iron depletion, eg, in blood donors.

The practical implications of the risk factor status of stored iron depend on a weighing of the risks and benefits of iron depletion induced under medical supervision. As to the possible risks of iron depletion, a sense of proportion must be maintained. Undeniably, ischemic heart disease is a significantly greater public health problem than iron depletion. There is no epidemic of deaths due to iron depletion or even to iron-deficiency anemia. Iron-deficiency anemia can generally be treated successfully and, unlike ischemic heart disease, is not often in itself an actual cause of death among affluent populations.

The investigation of the leading cause of death in the industrialized world imposes a duty to rigorously examine traditional practices. According to conventional wisdom, being a carrier for a hemochromatosis gene confers no risk. However, carriers have only slightly larger loads of storage iron than unaffected individuals. A true estimate of the risk of such nearly “normal” levels of stored iron would require an additional control group: those with no stored iron at all, ie, iron-depleted subjects. Definitive trial data on the safety of maintaining iron in storage are surprisingly absent. Support for the safety of maintaining iron in storage is based on traditional practice, not on scientifically valid data. In the absence of appropriate clinical trial findings on the safety of stored iron, advice to the public must necessarily be based on medical judgment. In my view, the totality of evidence suggests that iron depletion is safer than maintaining iron in storage. A consensus is urgently needed on what specific public health recommendations should be made in light of available data.

References


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