

# Iron Overload and Atherosclerosis

SEE ARTICLE ON PAGE 569

In this issue of HEPATOLOGY, Failla et al. show that patients with genetic hemochromatosis have significant eccentric hypertrophy of the radial artery although none of them have arterial hypertension or evidence of cardiovascular disease.<sup>1</sup> The investigators suggest that the structural arterial changes may be accompanied by functional changes in arterial distension (stiffening). The structural alterations were largely reverted by iron depletion; similarly, artery wall stiffening improved, although the initial abnormality was not significant. The investigators conclude that in patients with hemochromatosis, arterial wall thickness is increased before the onset of cardiovascular complications. They did not study potential mechanisms by which iron overload could cause these arterial changes. They did review recent literature, which explores the association between iron and atherosclerosis.

The investigators chose to study arterial alterations in hemochromatosis as a "human model" of the effect of marked iron overload on cardiovascular disease and atherosclerosis. If iron excess contributes to the atherosclerotic process, complications of atherosclerosis should be an early and prominent clinical feature in hemochromatosis. The finding that iron overload leads to marked eccentric hypertrophy of middle-sized arteries in advance of other apparent cardiovascular disease supports this hypothesis. For hepatologists, and in particular for physicians and scientists who work in the field of hemochromatosis and iron overload, the data reported by Failla et al. are astonishing and beg the question whether (and if so why) we have overlooked such an association for more than a century.

Indeed it has become trendy to speculate about the hazards of iron excess, rather than the hazards of iron deficiency, which were a major focus during centuries of limited nutritional iron supply. Today, in significant parts of the industrialized world, particularly in men, iron excess is found more often than iron deficiency.<sup>2</sup> The potential link between iron and atherosclerosis has attracted increasing attention in recent years as shown by the number of published studies (Fig. 1). The "Oxidative Stress Theory" suggests that the production of tissue-damaging free radicals is an essential component in the pathogenesis of numerous chronic diseases and that iron may help to catalyze the reactions producing free radicals.

Excessive iron may promote cardiomyopathy, arthropathy, infection, fibrosis, and diabetes mellitus, as well as some malignant, endocrine, and neurodegenerative disorders (for review see Weinberg<sup>3</sup>). Almost all of the disorders associated with iron loading are manifest in genetic hemochromatosis in which iron stores are markedly increased over a long period of time. Recent discussion has focused on the question whether slight iron excess (in subjects without genetic hemochromatosis) contributes to the two diseases that cause most deaths, *i.e.*, atherosclerosis and neoplasia. Obviously hemochromatosis is an optimal situation in which to study such a potential association. There are several reports that construct links between iron and atherosclerosis or cancer including the current report by Failla et al. All of these articles begin with statements indicating that "genetic hemochromatosis (is) associated with increased cardiovascular morbidity and mortality." Although literally this is true, it is misleading in the present context. There is overwhelming evidence that cardiomyopathy occurs more frequently in patients with hemochromatosis than in normal controls. However, there is also overwhelming evidence that this cardiomyopathy is not caused by coronary artery disease, but by iron-mediated damage to cardiomyocytes. Coronary artery disease, other forms of ischemic heart disease, stroke, and peripheral artery disease are not increased in hemochromatosis. They may even be less frequent than in control populations as assessed by large, partly prospective cohort studies, epidemiologic studies, and autopsy studies. Although Failla et al. mention that "older pathology reports on hereditary hemochromatosis" do not provide evidence of changes in large- and middle-size arteries<sup>4,5</sup> it should be noted that more recent, large, prospective clinical and epidemiologic studies also support the view that atherosclerosis is not prominent in genetic hemochromatosis. Virtually all large cohort studies have shown beyond any doubt that atherosclerosis, coronary artery disease, stroke, and peripheral artery disease are rare clinical features and infrequent causes of death in genetic hemochromatosis.<sup>6-10</sup>

A large autopsy study examined the prevalence of coronary artery disease in patients with hemochromatosis and multiorgan hemosiderosis from a registry of nearly 48,000 autopsies performed at The Johns Hopkins Hospital (Baltimore, MD) between 1889 and 1992.<sup>11</sup> In a 2:1 control-case ratio, 82 controls matched by age, race, and sex were compared with 41 cases with iron overload. Pathologic description of the coronary arteries was carefully recorded as advanced or severe in 12% of iron-overload cases compared with 38% of controls ( $P = .01$ ). The prevalence of three-vessel disease assessed by postmortem coronary arteriography was 11.1% in iron-overload cases compared with 33.3% in controls ( $P = .04$ ). The odds ratio of coronary artery disease with iron overload was 0.18 (95% confidence interval: 0.04-0.73). The investigators cautiously concluded that iron overload resulting from hemochromatosis or multiorgan hemosiderosis is not associated with an increased prevalence of coronary artery disease.<sup>11</sup> The data even suggest that coronary artery disease may be less

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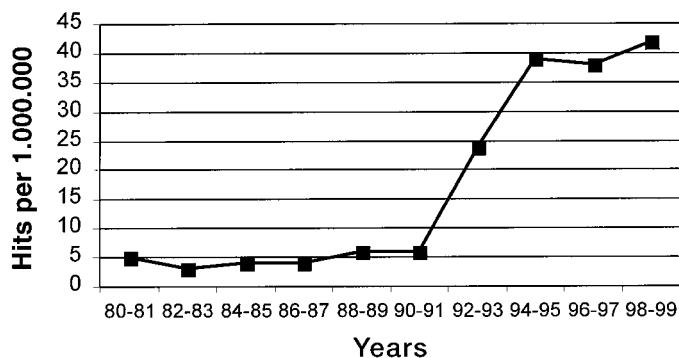


FIG. 1. Number of articles (in the English language) dealing with the link of iron and atherosclerosis published during the last 20 years. Publications were assessed as "PubMed" hits when the topics "iron" and "atherosclerosis" were examined via the Internet on June 22, 2000.

frequent and less severe in iron overload syndromes when compared with control subjects. In addition, there are several autopsy studies in patients with hemochromatosis who died from cardiac causes. These deaths were almost exclusively caused by cardiomyopathy with normal coronary arteries (literature in von Herbay et al.<sup>12</sup>).

As correctly cited by Failla et al., peripheral artery disease is uncommon in patients with genetic hemochromatosis and insulin-dependent diabetes.<sup>13,14</sup> These studies show that even in the presence of strong risk factors for atherosclerosis, such as insulin-dependent diabetes mellitus, iron overload does not promote peripheral artery disease.

A recent study searched Multiple-Cause Mortality Files compiled by the National Center for Health Statistics for the years 1979 to 1992 for all records listing hemochromatosis.<sup>15</sup> These data were used to calculate age-adjusted and age-specific mortality rates, identify medical conditions associated with a known diagnosis of hemochromatosis at death, and calculate proportionate mortality ratios for these medical conditions. As expected from previous studies, the association of cardiomyopathy and hemochromatosis was increased about 4.8-fold over the expected ratio. However, deaths in which other cardiac disorders were present, including acute myocardial infarction, other ischemic heart disease, old myocardial infarction, angina pectoris, and other chronic ischemic heart disease, were not higher than expected in patients with hemochromatosis but tended to be lower in patients who died with hemochromatosis.<sup>15</sup>

Failla et al. mention some experimental evidence that iron may contribute to the atherosclerotic plaque formation and human studies that have reported a correlation between iron stores and the risk of coronary disease or atherosclerosis.<sup>16,17</sup> Along these lines, Sullivan suggested that iron depletion protects against ischemic heart disease and argued that the difference in the incidence of heart disease between men and women may be caused by differences in their iron stores.<sup>18</sup> The maximal gender difference in serum ferritin level is reached at approximately 45 years of age and is about 300%. The maximal gender difference in heart disease is also reached at approximately 45 years and is also about 300%.<sup>19</sup> The iron hypothesis could explain the gender difference in coronary disease as well as the low prevalence of coronary disease in regions with a high prevalence of iron deficiency.<sup>18</sup> However, iron deficiency may be only one consequence of a globally insufficient diet, which limits atherogenesis for other reasons.

The iron hypothesis could also explain the protective effect of medication that causes gastrointestinal blood loss, e.g., aspirin, or inhibits iron absorption, e.g., cholestyramine, and the risk of an increasing effect of oral contraceptives, which are known to decrease menstrual blood loss (for review and literature see de Valk and Marx<sup>20</sup>). If the iron hypothesis is true, easy and effective ways to reduce the risk of cardiovascular events would be through blood donation and abolition of iron fortification of food and multivitamin preparations.<sup>20</sup> If such an iron hypothesis is true, coronary heart disease should be a prominent feature of hemochromatosis and other forms of severe iron overload.

Some epidemiologic studies (mainly from Finland) support the hypothesis that high iron levels or iron stores (usually serum iron or ferritin were measured) and heterozygous presence of the hemochromatosis gene Cys282Tyr mutation are associated with an increased risk of myocardial infarction.<sup>16,17,21-26</sup> As also mentioned by Failla et al., asymptomatic carotid atherosclerosis assessed by duplex sonography has been linked to high iron stores.<sup>16</sup> Lowering of iron stores reduced, and iron accumulation increased, cardiovascular risk.<sup>26</sup> The latter results, although intriguing, could not be confirmed by further studies measuring carotid intima-media thickness as an indicator for early asymptomatic atherosclerosis.<sup>27,28</sup>

The vast majority of recent epidemiologic data, including results from prospective, cross-sectional, case-control and autopsy studies, have failed to support the original hypothesis that high body iron stores or heterozygosity for the Cys282Tyr mutation of HFE increase the risk of coronary heart disease, myocardial infarction, or atherosclerosis.<sup>29-48</sup> In the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, serum iron levels and transferrin saturation were not related to myocardial infarction.<sup>37,38</sup> Sempos et al. even found an inverse association between transferrin saturation and coronary heart disease.<sup>39</sup> Regnstrom et al. studied serum ferritin levels and serum iron levels in 94 young male survivors of myocardial infarction 4 to 6 months after the event.<sup>40</sup> They found no differences in ferritin levels in myocardial infarction patients compared with healthy controls and the patients had even lower serum iron levels.

In sum, recent literature does not support the hypothesis that iron contributes to atherosclerosis to a major degree although further prospective studies are required to elucidate this association. There is overwhelming evidence that atherosclerosis, coronary artery disease, stroke, and peripheral artery disease are neither prominent clinical features nor frequent causes of death in genetic hemochromatosis. In view of this solid background, the new and provocative findings of Failla et al. are difficult to reconcile. The investigators themselves admit problems fitting their data to the well-known and well-studied clinical features of hemochromatosis. Only further studies will be able to resolve this apparent paradox. It must also be kept in mind that many populations have a high prevalence of the hemochromatosis gene Cys282Tyr mutation, which is a relatively young mutation (probably less than 2,000 years old). If iron excess, even of a minor degree, is so dangerous in contributing to atherosclerosis and cancer, it is difficult to explain the extraordinary evolutionary advantage to HFE heterozygotes.

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