Iron Chelation and Vascular Function
In Search of the Mechanisms

Dardo E. Ferrara, W. Robert Taylor

In 1981, Sullivan suggested that a state of iron depletion (ie, reduced iron stores without anemia) was potentially protective against coronary heart disease (CHD). This original “iron hypothesis” was an attempt to explain the known sex difference in cardiovascular (CV) risk and the subsequent loss of the protective effect of female gender with menopause. This initial hypothesis was based in part on the observation that men exhibited an age-dependent increase in the accumulation of iron that was not seen in women until after menopause. This, coupled with the observation that hysterectomy without oophorectomy was associated with an increased CHD risk, supported the concept that a diminution in iron stores was protective against CHD. Basic and clinical data have recently begun to provide plausible explanations for a link between iron and atherosclerosis.2,3

The amount of free ferrous (Fe2+) iron is normally maintained at a very low level in humans. Of all the iron in the body (4 g), ~2/3 is found in association with hemoglobin in the ferrous form and the majority of the remainder is stored as ferritin. The sequestration of iron in the form of ferritin may have cytoprotective effects to guard against oxidative damage. Ferritin comprises 24 subunits of 2 types (H- and L-chains). The H-chains contain the metal-binding site and can oxidize Fe2+ to Fe3+, a process required to take up iron. The synthesis of ferritin is tightly regulated in concert with that of ferritin mRNA. Conversely, when cellular iron is high, the opposite regulation takes place. Synthesis of ferritin H-chains is also upregulated by heme oxygenase-1 (HO-1).8 Heme oxygenases catalyze the conversion of heme into CO, iron, and biliverdin, the latter being subsequently reduced to bilirubin.9 Of the 3 isoforms of heme oxygenase, HO-1 is regulable and is induced in response to a variety of stimuli, including heme, angiotensin II (Ang II), nitric oxide (NO), inflammatory cytokines, and other agents that promote oxidative stress.9,10 The release of iron by HO-1 results in increased synthesis of ferritin, which has the potential to limit the contribution of the labile iron pool to oxidative reactions (Figure 1). Therefore, HO-1 is thought to have potent antioxidant effects by degrading prooxidant heme and facilitating iron sequestration, while at the same time generating the antioxidants biliverdin and bilirubin.

Although the majority of the in vitro and animal research supports a role of iron in the pathogenesis of atherosclerosis, prospective human studies have provided inconsistent evidence in terms of clinical cardiovascular outcomes.11 Some investigators have hypothesized that iron may be primarily involved in the early events of atherosclerosis, and focusing on CV morbidity and mortality (reflecting later stages of the disease) may not give insight into the potential mechanistic role of iron.2 Recent emphasis has been placed on endothelial dysfunction as an early surrogate marker of atherosclerosis. In this regard, Zheng et al12 have studied the effects of blood donation on iron stores and markers of vascular function. They compared high-frequency donors (≥8 donations in the past 2 years) and low-frequency donors (1 to 2 donations) and found that although the hematocrit did not differ between the groups, serum ferritin was significantly decreased and flow-mediated dilation (FMD) was significantly increased in high-frequency blood donors. Serum markers of inflammation did not differ between groups but 3-nitrotyrosine, a marker of oxidative stress, was decreased in the high-frequency-donor group. Some improvement in FMD has also been described in patients with hemochromatosis after phlebotomy.13 Duffy et al found that acute administration of deferoxamine (an extracellular iron chelator) in patients with CHD decreased serum iron levels and improved NO-mediated dilation.14 Finally, the cell-permeable chelator dexrazoxane has been shown to abrogate homocysteine-induced reductions in FMD in healthy subjects.15 This action was attributed to its high affinity to the intracellular labile iron pool and was associated with increased bioavailability of NO in response to flow. Taken together, it seems likely that both extracellular and intracellular iron-dependent reactions contribute to impair FMD. In keeping with this, researchers have demonstrated...
that non-protein bound iron may play a role in direct inactivation of endothelium-derived NO.16

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Ishizaka et al17 investigated the effects of Ang II on ferritin induction and iron accumulation in rat aortic tissue and attempted to link these phenomena with the effects of deferoxamine on vascular reactivity. They found that Ang II increased ferritin protein expression in endothelial and adventitial cells, which was associated with occasional iron deposits in the adventitia. Moreover, they confirmed once again that Ang II can promote oxidative stress and lipid peroxidation. Importantly, they also showed that chronic administration of deferoxamine partially blunted Ang II–induced expression of HO-1, ferritin, and MCP-1 and subsequent lipid peroxidation. As a physiological correlate, they demonstrated that treatment with deferoxamine improved Ang II–induced impaired aortic relaxation. As expected, treatment with iron dextran increased the induction of ferritin but failed to increase redox-sensitive and inflammatory markers (HO-1, MCP-1, and 4HNE). It is important to note that the authors could not find a statistically significant increment in iron deposits in the vascular tissue of Ang II–treated animals. Like many good studies, the study by Ishizaka et al raises additional important questions. The precise mechanisms responsible for the beneficial effects of deferoxamine on vascular reactivity remain elusive. In addition, the authors did not demonstrate a strong causal relationship between altered iron metabolism and Ang II–induced oxidative stress and subsequent impaired vascular function. However, the authors’ findings do point to deferoxamine as an antioxidant drug that may potentially reverse the impaired vascular function and subsequent atherosclerosis. Because deferoxamine has been shown to diminish the toxic effects of ROS by mechanisms independent of iron chelation,18,19 additional elucidation of the mechanisms would provide a deeper understanding of the equivocal results of some iron depletion studies. Although the present study suggests that the Fenton reaction may be involved in Ang II–induced oxidative stress, the upregulation of HO-1 followed by ferritin may only represent part of a concerted defense mechanism and, in this sense, may be simply markers of oxidative stress. Whether HO-1 or superoxide may release an excess of iron (from heme or ferritin, respectively) so that iron can participate in oxidative reactions remains speculative.20 Finally, the direct effects of iron and deferoxamine on the NO signaling pathway need to be addressed in the future.

In conclusion, the study by Ishizaka et al presents important findings supporting a potential link between use of iron chelators, oxidative stress, and CV risk. These results reemphasize the potential of targeting antioxidant defense mechanisms to prevent atherosclerotic disease. Further studies are needed to demonstrate that chelation of iron is indeed the key factor responsible for the improvement of vascular function. Ongoing prospective outcome studies on the clinical role of iron depletion will ultimately shed light on the mechanisms and functional relevance of iron chelation therapy.21

References


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