Iron Metabolism and Development of Atherosclerosis

To the Editor:

Juan and colleagues1 showed impressive data supporting the role of hemeoxygenase-1 (HO-1) in cytoprotective response and iron homeostasis. They demonstrated that gene transfer-mediated overexpression of HO-1 in vascular cells could facilitate iron metabolism and attenuate atherogenesis in mice prone to develop premature and severe atherosclerosis.

It is believed that inflammation and oxidation are important mechanisms involved in the complex pathological process of atherogenesis.2 Moreover, it has been demonstrated that free oxygen radicals act directly on the endothelial cells and have a close interaction with lipid peroxidation, causing a modification of LDL and facilitating LDL deposition, with the consequent formation of atherosclerotic plaques. Free radical production is catalyzed and accelerated in the presence of iron.3 A possible association between body iron status and the risk of coronary heart disease was first supported by findings from a Finnish study4 relating increased levels of both serum ferritin and dietary iron to an increased risk of myocardial infarction in men. In contrast, more recently published data, like the study by Ascherio and colleagues,5 do not support the hypothesis that reduced body iron stores lower coronary artery disease (CAD) risk. There are only a few reports investigating the correlation between serum concentrations of ferritin and anatomic diagnosis of coronary atherosclerosis (defined as more than 50% diameter stenosis) assessed by coronary arteriography.

We studied a total of 100 men and women (41 women, 59 men, mean age 63.7; range 31 to 82 years) with cardiovascular disease and stable angina pectoris referred for coronary angiography. Baseline data collection comprised conventional risk factors for coronary artery disease, lipids, fasting total homocysteine, C reactive protein, serum ferritin levels and transferrin saturation, and clinical characteristics. Serum ferritin levels and transferrin saturation (serum iron concentration divided by total iron-binding capacity) were used as measures of the amount of circulating iron available to tissues. Two experienced cardiologists blinded for clinical and laboratory data reviewed the cinefilms.

The risk of CAD assessed by coronary angiography (defined as more than 50% diameter stenosis of at least one coronary artery) was not related to ferritin concentrations or transferrin-saturation levels in white men or women. Estimates of the relative risk of coronary heart disease for the quintile with the highest concentration of serum ferritin as compared with the lowest quintile were 0.83 (95% CI, 0.63 to 1.24). Moreover, transferrin saturation did not correlate with CAD (P=0.29). The presence of angiographic CAD was associated with patient age (P=0.048), male sex (P<0.01), high LDL-cholesterol levels (P=0.02), low HDL-cholesterol levels (P=0.02), high plasma fibrinogen levels (P<0.01), and high fasting total homocysteine levels (P=0.04). Thus, in patients referred for coronary angiography, higher ferritin concentrations and transferrin saturation levels were not associated with an increased extent of coronary atherosclerosis. Therefore, our results and data from others8 do not support the hypothesis that body iron stores, as measured by serum ferritin and transferrin saturation, are related to the risk of coronary heart disease assessed by coronary angiography. Attenuation of atherogenesis by overexpression of HO-1 in vascular cells, as demonstrated by Juan and colleagues,3 may act primarily by other (or at least additional) mechanisms beyond iron overload.

Response

Dr Auer and colleagues raised an issue concerning the coherent data supporting the link between iron status and the development of atherosclerosis. In our study of apolipoprotein E (apoE)-deficient mice,1 we demonstrated that hemeoxygenase-1 (HO-1) overexpression in vascular tissues reduced the iron overload and formation of the lesion in animals, thereby suggesting a role for iron in atherogenesis. The iron hypothesis, however, was not overwhelmingly supported by epidemiological studies, including the one carried out by Dr Auer and colleagues. Vascular iron content is an important factor that influences the extent of oxidative injury in vasculature and lesion development.

In our study,1 we measured the serum ferritin concentration in animals and found no significant difference in ferritin levels between the control group and the group receiving HO-1 gene transfer, although the vascular iron deposition and lesion formation were significantly attenuated in HO-1-treated animals. Furthermore, we demonstrated that the protective effect of HO-1 was evident only when HO-1 was overexpressed in vascular tissues, but not in liver, indicating that the protection by HO-1 is mediated through a local effect. We are skeptical that measuring serum ferritin level and transferrin saturation so commonly used in epidemiological studies as an index of body iron stores is a sensitive and reliable indicator of fluctuation in vascular tissue iron content and its local iron effect.

We agree with Dr Auer and colleagues on the point that additional mechanisms may have roles in the antiatherogenic effect of HO-1. We broached that subject in the Discussion section of the paper.

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