Body Iron Stores, Infection, and Risk of Acute Myocardial Infarction

To the Editor:

Tuomainen et al have noted an association between increased iron stores, as measured by a reduced ratio of serum transferrin receptor concentration to serum ferritin concentration, and excess risk of acute myocardial infarction (AMI).

It has been suggested that iron can catalyze toxic redox reactions, which may lead to an increased risk for coronary heart disease and AMI. Another mechanism by which iron might increase the risk of AMI involves a possible role for iron in facilitating some infections.

Vertebrates have a hypoferremic response during infection that lowers the presence of iron as serum transferrin, temporarily storing the metal as ferritin. Intestinal absorption of iron also declines during infection. Bacterial mechanisms to obtain iron from a host include direct uptake of iron from the labile iron pool, siderophore-mediated iron uptake, and iron uptake by direct interaction with transferrin, lactoferrin, or heme-containing proteins.

Various mechanisms by which infectious processes might induce atherogenesis have been proposed, including cytopathic effects of infection on endothelial and smooth muscle cells, formation of circulating toxins or immune complexes that deposit on vessel walls, elicitation of an inflammatory response, induction of alterations of serum prostaglandin and lipid metabolism, or elicitation of a hypercoagulable state that increases the risk of thrombosis.

Recent research has suggested that numerous organisms may be associated with an increased risk of AMI. These include Helicobacter pylori, Chlamydia pneumoniae, herpes simplex virus, and cytomegalovirus.

Several investigators have noted the importance of iron acquisition for H pylori growth. No studies have reported on the iron requirements of C pneumoniae. However, Raulston et al noted that iron restriction caused a significant reduction in infectivity of C trachomatis elementary bodies. The smaller subunit (R2) of herpes simplex virus ribonucleotide reductase, which catalyzes the reduction of ribonucleotides to deoxyribonucleotides, contains binuclear ferric iron centers; ferrous iron is necessary to generate the binuclear ferric iron centers and to ensure full enzymatic activity. Gumbel et al noted that desferrioxamine, an iron chelator with antiherpetic activity, can inhibit cytomegalovirus in vitro and in vivo.

Further studies are needed to investigate the possible role of infections in the etiology of AMI and of iron in promoting those infections.

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Response

We thank Dr Rabinoff for his interesting comments on our study of body iron and the risk of first acute myocardial infarction. We agree that iron is an essential nutrient and enzyme cofactor in different infectious agents as well as in humans. The role of some infectious agents, especially of Helicobacter pylori, Chlamydia pneumoniae, herpes simplex virus, and cytomegalovirus, in the etiology of cardiovascular disease has been studied by several study groups, but no solid conclusions can yet be drawn. Most of the studies that support this association have been small, and positive publication bias seems very likely. Although we acknowledge that high body iron may predispose to some potentially cardiovascular disease-related infections, we would emphasize the inflammation itself. Plenty of evidence links inflammation and both central and peripheral atherosclerosis. If atherosclerosis is taken as a chronic inflammatory disease, it is likely that any factor that enhances inflammation accelerates the process of atherogenesis.

However, the direct effect of elevated body iron in driving different free radical–generating reactions that propagate lipid peroxidation and cause untargeted direct and indirect oxidative damage in arterial wall and in myocytes is probably far more important. Whether high iron predisposes to coronary heart disease or low iron protects against it remains to be ascertained. Currently, high (elevated) body iron appears to be a risk-increasing factor in cardiovascular disease, independent of infections.

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Long-Term Therapy for Postmenopausal Osteoporosis: Stronger Bones but Weaker Arteries?

To the Editor:

The intriguing article by Jono et al suggests that long-term supplementation with vitamin D for postmenopausal osteoporosis may increase vascular calcification. This is not a new concept and raises important and practical issues.

Alendronate, an inhibitor of osteoclast-mediated bone resorption, is widely promoted for the treatment and prevention of osteoporosis in postmenopausal women. This group of women...
is at higher risk for cardiovascular disease. Vascular calcification has many similarities to that of bone, and vascular wall macrophages may have both osteoblastic and osteoclastic potential.

Calcification alters the mechanical properties of the atherosclerotic plaque. It may lead to increased stress near the shoulder of the plaque, leading to rupture. On the other hand, extensive calcification and fibrosis may stabilize plaque.

Therefore, in addition to vitamin D supplementation, long-term therapy for postmenopausal osteoporosis with alendronate may lead to plaque instability and increased cardiovascular events in a population already at increased risk. Diligent post-marketing surveillance of this drug is necessary to monitor these issues.

It would be unfortunate to make bones stronger at the expense of making arteries weaker.

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Response

We thank Dr Goldstein for his interesting comments on our recent article describing the mechanism of stimulatory effects of 1,25-dihydroxyvitamin D3 on in vitro calcification by bovine vascular smooth muscle cells. We agree with Dr Goldstein that long-term therapy for postmenopausal osteoporosis with bisphosphonates including alendronate may lead to plaque instability and cardiovascular events in a population already at increased risk. If calcium content of the calcified plaques is reduced by bisphosphonates, it is likely that the plaques may become more vulnerable to rupture. Because it has been speculated that the vessel is rendered less vulnerable to rupture only when extensive calcification has occurred, the early or intermediate stages of calcification may actually enhance plaque vulnerability. Although there have been no reports concerning adverse events in patients with advanced coronary calcification due to use of bisphosphonates, cautious follow-up may be needed in such cases. However, the role of atherosclerotic calcification in plaque rupture remains unclear. Moreover, bisphosphonates exert both a physicochemical effect, inhibition of calcification, and a biological effect, inhibition of bone resorption. Although the doses required to produce the effect on bone resorption are 1000 times lower than those to inhibit calcification, the compounds may be concentrated in the arterial walls by long-term use of bisphosphonates and modulate arterial functions.

The other effect of bisphosphonates on arterial walls should be considered. Some compounds inhibit the development of atherosclerosis in experimental animals without any marked effect on cholesterol metabolism. Therefore, long-term therapy for postmenopausal osteoporosis with bisphosphonates may exert a preventive effect on atherogenesis, at least in a population without any evidence of cardiovascular disease. In any event, it is necessary to evaluate the long-term effect of alendronate on coronary atherosclerosis and calcification.

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incomparably more precise than data acquired by rescue services. Therefore, data obtained from ICDs are the best way to identify individual circadian rhythms for arrhythmic sudden death.

Because of these limitations, we believe the issue of individual circadian variance for arrhythmic death begs for further analysis and continued discussion.

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Response

The letter from Drs Avila and Brugada is interesting, and we certainly agree with their conclusion that the issue of individual circadian variance for arrhythmic death begs for further analysis and continued discussion. For the patients we studied with recurrent cardiac arrest, the rhythm when the emergency medical services team dispatched for the first cardiac arrest arrived was ventricular fibrillation. It is therefore reasonable to assume that the initial rhythm was ventricular fibrillation or ventricular tachycardia degenerating to ventricular fibrillation. However, we cannot know with certainty what the initial rhythm was for the second arrests.

It is relevant to note that there is a difference between shocks by an implantable defibrillator and sudden death. Most postimplant studies report at least 50% of patients have received $\geq 1$ shock, whereas sudden death rates at 1 year in survivors of cardiac arrest in the prededefibrillator era are reported in the 15% range. Another potential point of difference between our patient population and the 16 patients Avila and Brugada describe may be related to the type of arrhythmia. It appears from their article that perhaps half were treated with an ICD because of an episode of ventricular tachycardia that resulted in syncope or compromising symptoms.

It is only fair to point out that Drs Avila and Brugada found clustering of arrhythmias in only 5 of 16 patients with multiple shocks. There are insufficient data in their article to try to calculate the probabilities of this occurring by chance, but the probability is not zero. Nevertheless, we don’t dispute that some of those 5 surely do have clustering over and above that inherent in the global circadian variation. We suspect that there are individual patients in our sample who also might have clustering, but to determine clustering in a single individual would require many more than 2 episodes, and, sadly, few patients survive $>2$ events.

We should clarify that our analysis of a clustering pattern of arrests within individuals was not based on 6603 patients but on fewer than 500 patients who had an initial and subsequent cardiac arrest. However, that number is sufficient that we had a power of 0.8 of rejecting the null if 5% of our patients had clustering (against a traditional 2-sided 0.05 level test of the null) and a power exceeding 0.99 of rejecting the null if 30% of our patients had clustering.

Clinical Expression in Patients With Hypertrophic Cardiomyopathy Caused by Cardiac Myosin-Binding Protein C Gene Mutation

To the Editor:
Hypertrophic cardiomyopathy is a primary cardiac disorder, mostly genetically transmitted, with a heterogeneous clinical and morphological expression. Analysis of the clinical expression of several genetic alterations has previously focused mainly on unfavorable manifestations. In this regard, recent articles by Charron and colleagues$^3$ and by Niimura and colleagues$^2$ that describe delayed expression of cardiac hypertrophy and a favorable clinical course in patients with mutations in the gene for cardiac myosin-binding protein C (MyBP-C) are indeed important contributions to an understanding of phenotype-genotype correlations at the mild end of the spectrum of the disease. However, these reports did not include precise morphological distribution of left ventricular hypertrophy, which is of clinical importance in the diagnosis and management of patients with this disorder.

We had opportunities to study 6 probands from 6 small Japanese families living in Kochi prefecture who were found to have the same mutation in the cardiac MyBP-C gene: a 1-base deletion at codon 593 from TCC (Ser) to CC in exon 18.3 Of 30 adult family members screened, 14 were identified as having this MyBP-C mutation. Although disease penetrance was incomplete, 90% of all patients and 80% of those under the age of 50 years had cardiac hypertrophy. The mean maximal wall thickness was 21±3 mm. Most patients revealed hypertrophy of both the ventricular septum and the free wall: 14 with Maron type III, 1 with type I, 1 with type IV, and 2 with diffuse concentric hypertrophy. There was no patient with apical hypertrophy, which was characteristically reported among Japanese patients.$^4$

It would be interesting and clinically valuable to know what kind of morphological patterns of left ventricular hypertrophy, assessed by 2-dimensional echocardiography, have been seen in the patients reported by Charron and colleagues.

Concerning the natural history, sudden cardiac death was not observed during a follow-up period of 54.5±57.1 months (range, 1 to 160 months) in our patients, and 3 patients reached the age of $>70$ years. However, it is worth noting that 4 patients gradually progressed to the stage of left ventricular dilation and dysfunction later in their lives, a fact that has not been reported previously.

This phenotype-genotype information will be of significant importance for the practicing clinician, because left ventricular hypertrophy, as well as left ventricular dilation and dysfunction, often occurs in elderly patients, particularly in association with systolic hypertension.

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Response

We thank Dr Doi et al for their comments about our article on phenotype-genotype analysis related to the cardiac myosin binding protein C (MyBP-C) gene in familial hypertrophic cardiomyopathy (FHC). They screened Japanese families, found a mutation in the MyBP-C gene in 6 of them (14 adult members), and analyzed some of their clinical features. They found that penetrance of the disease was incomplete, as in our experience, but was as high as 80% before 50 years of age. First, the penetrance of the disease depends heavily on the diagnostic criteria used, as was recently shown in children. Therefore, it would be interesting to know the diagnostic criteria used by Doi et al. Second, in addition to the causative mutation or gene, many factors could modulate the expression of the disease and could explain the difference observed between the Japanese and French populations. These factors include mean age, sex ratio, modifier gene (such as the ACE I/D polymorphism), and unknown environmental factors.

Interestingly, a mean follow-up of 34 months was available in families studied by Doi et al, and no sudden cardiac death was observed. This confirms the good prognosis observed in our study in young subjects. The fact that 4 patients progressed to left ventricular dilation and dysfunction is also in accordance with our findings, because we observed 4 cardiac deaths or transplantations related to congestive heart failure (mean age, 65±9 years) in our population. This evolution appears not specific of families with a mutation in the MyBP-C gene, because it was described in families with a mutation in the β-myosin heavy chain gene.

Finally, the distribution of left ventricular hypertrophy (LVH) was not described in our study (it was not our purpose, because the distribution of LVH appears to be of little interest for prognostic implications). However, in 46 subjects with LVH, of the 76 carriers of a mutation in the MyBP-C gene, we found 2 (4.3%) subjects with Maron type I hypertrophy, 19 (41.3%) with type II, 24 (52.2%) with type III, and 1 with type IV (2.2%). As previously shown in FHC related to other genes, the morphological distribution of LVH was therefore variable in families related to the MyBP-C gene, even within a given family.

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Individual Circadian Variation and Sudden Death
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