COMMENTARY

Is increased tissue ferritin a risk factor for atherosclerosis and ischaemic heart disease?

In 1981 Sullivan postulated a link between tissue iron stores and the risk of heart disease[1] because both the incidence of ischaemic heart disease (IHD) and the serum concentration of ferritin are much lower in premenopausal women than in men of the same age, whereas in men and women over 45 they are similar. There have been several recent challenges to this claim.[2-4]

Iron in a chemically unreactive form is stored intracellularly as ferritin and the concentration of serum ferritin reflects the level of iron in the tissues. Sullivan's hypothesis was supported by a study in Finnish men which showed that high serum ferritin concentrations were associated with an excess risk of myocardial infarction and that the incidence of myocardial infarction and the serum ferritin concentration correlated with the dietary intake of iron, most of which was consumed as haem.[5] Others used the serum transferrin concentration as a measure of iron stores. This was inappropriate because the transferrin concentration reflects the availability of iron to the tissues and varies diurnally and from day to day.[6] When Magnusson *et al* measured the total iron binding capacity (transferrin) and ferritin concentrations they did not find a correlation with myocardial infarction.[3] Nor did Ascherio *et al* find a significant association between total iron intake and risk of coronary heart disease.[4] This is not surprising because, except for haem, the absorption of iron by the gut is well controlled. Men with an intake of haem iron in the top quintile had a higher incidence of fatal coronary disease or non-fatal myocardial infarction than men with an intake in the lowest quintile, although this variable did not show a significant association with the risk of coronary heart disease.[4] So the extent of any association with a higher risk of heart disease remains uncertain.

The distinction between cardiovascular disease and myocardial infarction is important[7 8] but epidemiological evidence is not sufficiently sophisticated to determine whether a detrimental effect of high iron stores operates on the myocardium or on the coronary arteries themselves. Iron promotes the modification of low density lipoproteins (LDL) in vitro and theoretically could enhance atherogenesis. But such modification of LDL is unlikely in the circulation, where any free iron will be captured by transferrin. If it occurs at all, such modification is more likely in the interstitium. Haem iron too can promote LDL modification. Iron could modify LDL in a vessel lesion if haemoglobin were present in the interstitium. This suggests that a high tissue iron store may contribute to atherosclerosis but is not essential to the process. Certainly the incidence of atherosclerosis is not increased in patients with haemochromatosis though they do have cardiomyopathy. We found that the pool of low molecular weight iron was increased in rats with iron overload. This could increase the generation of radicals by redox cycling and eventually cause cardiomyopathy. There is no strong evidence from animal studies, however, that stores of iron in the tissues are involved in the process of atherosclerosis.

Experiments with an iron chelator[9 10] or iron-overloading[11] in animals provided indirect evidence that iron is involved in reperfusion injury after an ischaemic insult. During ischaemia the amount of iron in the low molecular weight pool increased,[12] and iron accumulated in the perfusate when the circulation was restored.[13] A reductive mechanism is probably responsible for the release of iron from ferritin into the low molecular weight pool where it could induce lipid peroxidation and subsequent tissue injury by a Fenton type reaction.[14] Under normal conditions heart function was not affected in iron-loaded rats.[11] But these hearts were much more vulnerable to anoxia than the normal hearts.[11] Clearly, iron plays a crucial part in reperfusion injury of tissues after an ischaemic insult.[14] This suggests that serum ferritin concentrations will be higher in fatal cases of myocardial infarction than in non-fatal cases and that blood donation could reduce the risk of myocardial infarction in men.

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