IRON AND ATHEROSCLEROSIS: IRON CHELATORS DECREASE ADHESION OF MONOCYTES TO VASCULAR ENDOTHELIUM

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Abstract

Besides the fact that it is a vital element in life, iron may also participate in diverse pathological processes. It has been hypothesised that iron is involved in the development of atherosclerosis and related cardiovascular diseases. Several epidemiological studies as well as *in vivo* and *in vitro* experiments are in favour for this iron hypothesis, although some studies have yielded conflicting results. This review describes iron as a risk factor of atherosclerosis, through its involvement in the process of monocyte adhesion to endothelium, a crucial event of atherosclerotic plaque formation. Furthermore, the benefits of iron chelators in preventing this process are reviewed

Key Words: Iron, atherosclerosis, monocytes, inflammation, endothelium, risk factors.

Introduction

Iron is an essential dietary components, which is necessary for oxygen transport in the body and many cellular functions such as respiration. It also plays a role in the immune response by catalysing the formation of oxygen radicals. There is considerable evidence for the role of oxidative stress in the development of atherosclerosis and related cardiovascular diseases. It has been hypothesised that iron-mediated oxidation is involved in this process.

Inflammatory changes coupled with dyslipidemia may lead to atherosclerotic plaque formation and, furthermore, to plaque rupture and arterial thrombosis. Transendothelial migration of leukocytes is a fundamental and one of the earliest inflammatory mechanism in atherogenesis.(1) This process is partly mediated by the interaction between endothelial adhesion molecules and their ligands on monocytes, which is enhanced by the inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1).(1) Elevated concentrations of endothelial adhesion molecules have been shown to be present in human atherosclerotic plaques, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial selectin (E-Selectin).(2) A significant correlation has also been found between the degree of macrophage infiltration and endothelial ICAM-1, VCAM-1 and E-selectin expression.(2) The arrest and firm adhesion of the leukocytes on endothelium occur via activation of the integrins: very late antigen-4 (VLA-4) and lymphocyte function-associated antigen-1 (LFA-1).(3) One important role of iron in the development of atherosclerosis may be facilitating the event of monocyte adhesion to endothelium. The potential counteracting effects of iron chelators in this process are described.

Iron and atherosclerosis - evidence

In 1981 Jerome Sullivan(4) suggested that the reduction of risk for ischemic heart disease in premenopousal women could be the result of iron depletion. Many epidemiological studies in the past decade tested this iron hypothesis. Some showed that body iron stores are positively correlated to the incidence of cardiovascular diseases,(5-11) while other studies had yielded conflicting results.(12-18) In 1999, de Valk and Marx(19) concluded that studies published so far provided a strong epidemiological evidence for the iron hypothesis.

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The mechanism by which iron may stimulate atherogenesis is still unclear. Labile iron has been found in human atherosclerotic lesions.(20) Regulatory functions of endothelium in the process of leukocyte adhesion, NO production, vascular smooth muscle proliferation and platelet aggregation, may be modulated by iron. Patients with hereditary hemochromatosis (HH), a disease resulting in iron-overload, had significant alterations of the radial artery wall.(21) The structural alteration leading to a functional problem (stiffening), was largely reverted by iron depletion.(22) Iron overload showed to stimulate the formation of atherosclerotic lesions in hypercholesterolemic rabbits.(23) Iron overload also increased the susceptibility of rat hearts to oxygen reperfusion damage.(24,25) Dietary iron showed to initiate the formation of atherosclerotic plaques in animals fed with a high-cholesterol diet,(26) while dietary iron restriction protected the apoE-deficient mice from developing the lesions.(27)

Iron-catalysed free radical formation may modulate the inflammatory atherogenic response of monocytes and endothelium. *In vitro* iron upregulated interleukin-6 (IL-6) production by endothelial cells,(28) while iron chelators inhibited activation of endothelium by TNF-α.(29,30) Expression of IFN γ -inducible genes in monocytic cells was affected by iron and iron-chelation.(31) Moreover, iron was shown to increase secretion of TNF-α(32) and IL-1(33) by monocytes.

Iron chelators prevention of atherosclerotic events?

Deferoxamine (DF), a hexadentate iron chelator, is capable of chelating trivalent iron, decreasing the availability of iron for the production of oxygen radicals.(34) DF has shown to improve early functional and structural vascular dysfunctions of endothelium due to iron-induced oxidative stress.(35) Several studies showed a protective effect of iron chelators in the post-ischaemic cardiac injury in animals, suggesting the benefits of iron chelators in protection against cardiovascular event.(36-40) In animal models, deferiprone (LI),(41) an orally active chelator, has also been shown to protect against atherogenesis.

DF has specifically down regulated the expression of endothelial adhesion molecules involved in monocyte recruitment, namely VCAM-1, ICAM-1 and ELAM-1, after TNF-? treatment(29;30) or cytomegalovirus infection.(42) Furthermore, antioxidants have been shown to protect against the endothelial dysfunction associated with atherosclerosis.(43) These radicals may be involved in the expression and DNA binding of transcription factors such as nuclear factor α (NF-α)(44) important for the transcription of a large number of genes, including these adhesion molecules.(45,46)

Besides the protective effects, depending on the dosage and type of chelators, chelator-induced manipulations of iron metabolism can result in cellular toxicity. The removal of iron from critical cellular sites, may be lethal for healthy cells.(47) Several chelators such as nitrilotriacetate (NTA) and ethylenediaminetetraacetic acid (EDTA) are capable of potentiating iron-mediated free radical generation,(34) suggesting the effects of these chelators in promoting atherosclerosis. Therefore, the potential of iron chelators as anti-atherosclerotic agents depends on their biochemical properties. Further investigations involving different chelators could provide more clues for possible disease prevention.

Conclusion

There is growing evidence for the role of iron in the development of atherosclerosis and related cardiovascular diseases. There are several possible mechanisms by which iron may play a role in atherogenesis. Iron may promote the adhesion of monocytes to endothelium by modulating the expression of adhesion molecules and the release of inflammatory cytokines, which may be restrained by iron chelators.

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