Invited commentary

Role of trace elements in coronary heart disease

It is well established that hypercholesterolaemia is an important inducer of coronary heart disease (CHD). It is therefore anticipated that reducing levels of plasma cholesterol should decrease both incidence and mortality of the disease. Unfortunately, no matter how successfully we deal with hypercholesterolaemia, CHD does not disappear, because high cholesterol levels are not the only causative factors.

Several lines of evidence indicate that the development of atherosclerosis is related to free radical processes, lipid peroxidation and oxidative modifications of low-density lipoproteins (LDL). Free radicals may arise from a number of sources and cellular mechanisms, and their production occurs under both normal and pathological circumstances. Fortunately, the cell possesses highly efficient protective mechanisms, including antioxidants such as α-tocopherol, ascorbate, β-carotene, glutathione, and metal-binding proteins such as transferrin and caeruloplasmin, and enzymes such as manganese superoxide dismutase (MnSOD), copper–zinc superoxide dismutase (Cu,ZnSOD), selenoenzyme glutathione peroxidase (GSH-Px) and the iron-containing enzyme catalase (Halliwell, 1996). All these antioxidants are designed to prevent the occurrence of free radical-induced injury under normal conditions. However, it has been argued that these protective mechanisms may be overwhelmed and severe free radical-mediated injury may occur.

The process of LDL oxidation has been repeatedly demonstrated to be dependent on high concentrations of transition metals such as Cu and Fe *in vitro* (Minotti, 1993; Ziouzenkova *et al*. 1998). The molecular mechanism by which Cu and Fe initiate oxidation of LDL is not fully clear. It is also uncertain if the *in vitro* model reflects some aspects of LDL oxidation *in vivo*. Nevertheless, Cu-mediated oxidation is frequently used to assess the susceptibility of LDL to oxidation *in vitro*, which is regarded as a possible risk factor for atherosclerosis. *In vitro* studies also show that LDL oxidation can proceed when antioxidants are depleted. The oxidative process can be inhibited by metal chelators (EDTA, desferrioxamine) and by antioxidants (BHT, vitamin E, glutathione) *in vitro*, which further strengthens the possible involvement of a free radical chain reaction.

Cu could be a potential inducer of LDL oxidation. On one hand, Cu has the ability to oxidize LDL *in vitro* (Ziouzenkova *et al*. 1998). On the other hand, it is a constituent of Cu,ZnSOD which is involved in preventing oxidative injury. In addition, caeruloplasmin, a multifunctional protein which contains most of the Cu in blood, is thought to possess antioxidant functions which could be beneficial in resisting disease. In contrast, high caeruloplasmin levels have been speculated to be a risk factor for atherosclerosis, based on its pro-oxidant properties (Fox *et al*. 1995). Indeed, it has been reported that patients suffering from cardiovascular disorders exhibit elevated serum caeruloplasmin (Reunanen *et al*. 1992; Mänttari *et al*. 1994). Caeruloplasmin, however, is increased by inflammation. It remains to be seen whether elevated caeruloplasmin in cardiovascular disease is not simply due to inflammation. An inflammation-induced elevation of rat serum caeruloplasmin levels did not render LDL + VLDL more prone to oxidation (DiSilvestro & Jones, 1996). Similarly, in the Rotterdam study described in this month's issue (Klipstein-Grobusch *et al*. 1999) the inflammation-induced elevation of caeruloplasmin in CHD patients was associated with inflammatory processes and not with the pro-oxidant activity of caeruloplasmin. The possibility that inflammation has the ability to alter the susceptibility of LDL to oxidation cannot be ruled out.

Median intake of Cu from food is lower than the estimated safe and adequate daily dietary intake (ESADDI) values for most age, sex, and racial/ethnic subgroups (Third Report on Nutrition Monitoring in the United States, 1995). Cu deficiency has been classified as a potential public health issue. Nutrient supplements and highly fortified foods are widely consumed by Americans today. Potentially, some of these supplements could adversely affect the health of users because of antagonistic interactions among nutrients. The nutrients which are particularly interesting from this point of view are Fe, Cu and Zn. Their excess or deficiency has been implicated in LDL oxidation, hypercholesterolaemia and CHD.

The increased susceptibility of LDL to peroxidation in Cu deficiency is due to a combination of two factors: an inadequate antioxidant defence mechanism due to a reduction of Cu,ZnSOD, and an increase in body Fe stores due to the antagonistic relationship between Cu and Fe (Owen, 1978). Fe is a strong oxidant and is known to catalyze LDL oxidation *in vitro*. Its role in atherogenesis *in vivo* remains uncertain. In 1981, Sullivan proposed that the difference in heart disease risk between the sexes might be explained by differences in body Fe stores. Subsequently, many epidemiological reports concerning Fe and heart disease have been published (Laufer, 1990; Salonen *et al*. 1992; Ascherio *et al*. 1994; Meyers, 1996; Tzonou *et al*. 1998). Fe might contribute to coronary artery disease, the leading cause of death in western countries, at two critical stages of the disease: atherogenesis and reperfusion. In the former case it appears that LDL in the artery wall must be oxidatively modified to attract macrophages and thus lay the foundation for atherosclerotic lesions. In the case of reperfusion injury, oxygen free radicals are formed upon reflow after ischaemic events.

Chelation of free Fe decreases functional damage. CHD mortality rates were found to be best correlated with liver Fe–serum cholesterol in men and both sexes combined (Laufer, 1990).

It is suggested, however, that an inadequate antioxidant defence mechanism by itself is not sufficient to increase blood cholesterol and to induce atherogenesis. Similarly, an increase of body Fe stores alone does not induce hypercholesterolaemia. However, atherogenesis can develop when a generator of reactive oxygen species is present in a suppressed antioxidant status (Fields *et al*. 1993). In support of this hypothesis are data from studies where rats fed on a high-Fe diet inadequate in α-tocopherol and β-carotene exhibited increased lipid peroxidation and hypercholesterolaemia. In addition, rats fed on a low-Se diet and treated with adriamycin, a free radical generator, exhibited hypercholesterolaemia. Furthermore, Cu deficiency and increased intake of dietary Fe was responsible for free radical generation and elevation of blood cholesterol. In contrast, Cu-deficient rats which consumed a low-Fe diet did not develop hypercholesterolaemia although their antioxidant defence system was compromised.

Since Zn is an essential component of Cu,ZnSOD, the deficiency of Zn could induce an increase in tissue oxidative damage. Zn deficiency is associated with an increase of Cu and Fe due to the antagonistic relationships between these metals. Indeed, the oxidative damage which occurred in Zn-deficient rats (DiSilvestro & Blostein-Fujii, 1997) could be due to increases of tissue Fe. A decrease of Cu induces both an elevated Zn status and an increase in serum cholesterol. It has been suggested that an imbalance between Cu and Zn may be a factor in the aetiology of CHD. However, Tiber *et al*. (1986) could not find a correlation between plasma levels of Cu and Zn and serum levels of lipids or lipoprotein in sixty adult male patients with confirmed CHD.

Data summarized here illustrate the potential that essential trace elements have for inducing atherogenesis. In *in vitro* studies, one could easily isolate a single nutrient and study its effect on CHD. *In vivo*, however, we face the reality and consequences of nutrient–nutrient interactions. It seems reasonable to suggest that there is a need to shift from the concept of a single nutrient to a global perspective of balance. This need should be reflected both in the way we design studies, the way we care for patients, and the way we exercise public health interventions. We should not overlook the possibility that CHD may not be induced by an excess or a deficiency of only one element, but may be induced by a combination of deficiencies and excess of numerous potential atherogenic agents. Consequently, detection and correction of imbalances among trace elements could ultimately diminish individual risk factors and reduce the incidence of atherosclerotic heart disease.

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