Trace Elements, Atherosclerosis, and Abdominal Aneurysms

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Atherosclerosis is the leading cause of acute myocardial infarction and cerebral infarction in the industrialized world. The atherosclerotic process begins early in life, perhaps in infancy or in utero. Although much has been learned about atherosclerosis since Anitchkov and Chalatow fed cholesterol to rabbits in 1913, its cause remains mysterious.

The amount and location of atherosclerosis are difficult to measure in individuals before death, although methods are improving. Late lesions associated with illness are easier to evaluate than early, subclinical lesions. For these reasons, much that is known about the etiology of atherosclerosis is inferred from the epidemiology of ischemic heart disease and stroke. Abdominal aneurysms share some biochemistry, epidemiology, and pathophysiology with atherosclerosis, but associations are imperfect. Before the origin of a disease is known, medical scholars are confronted by a bewildering array of apparently dissimilar observations.

Copper and zinc were implicated in the origin and mechanisms of ischemic heart disease in 1973 with the induction of hypercholesterolemia in rats by a high ratio of zinc to copper. These experiments, prompted by the inverse relationship between risk of ischemic heart disease and the hardness of available drinking water first noted by Kobayashi, led to a collection of other associated elements; this collection has been revised and expanded. It will be argued here that trace elements, particularly zinc and copper, may be involved in the destructive and reparative aspects, respectively, of abdominal aneurysm formation.

Destruction of normal aortic anatomy during the formation of aneurysms seems to be mediated, inter alia, by collagenase, gelatinase, and plasmin. Some of these enzymes depend upon zinc for their activity.

Captopril is a thiol that was designed specifically to bind the zinc at the active site of angiotensin converting enzyme because of its similarity to carboxypeptidase A. If the matrix metalloproteinases become better characterized as to their dependence on zinc, treatment of small aneurysms with captopril may be beneficial. Because some patients with aneurysms are treated for hypertension, it may be of epidemiologic interest to compare the effect of captopril with other treatments on the expansion rate of small aneurysms. In contrast, zinc supplements may be harmful, both because they may relieve zinc deficiency, which may decrease metalloproteinase activity, and because they may interfere with copper utilization.
Whatever the cause of the damage to arteries that eventually leads to aneurysms, it seems unlikely that development of pathology will be slowed if reparative processes are impaired. Mechanisms by which copper deficiency can damage the cardiovascular system have been reviewed.\textsuperscript{15-19} Only a few of these mechanisms will be emphasized here.

The Western diet that is closely associated with high risk of cardiovascular disease frequently seems to be low in copper. Pooled data from 10 analytic surveys\textsuperscript{20} reveal that approximately one-third of daily diets contain less than 1 mg, and 60\% contain less than 1.5 mg, the lower limit of the estimated safe and adequate copper intake for adults.\textsuperscript{21} Daily copper intakes of less than 1 mg have been proved insufficient for more than 31 men and women who responded to diets low in copper with potentially harmful changes in lipids,\textsuperscript{22,23} glucose tolerance,\textsuperscript{24} blood pressure,\textsuperscript{25} and electrocardiograms.\textsuperscript{22,26}

Copper deficiency is the only nutritional insult that has been shown to produce abnormal electrocardiograms, glucose intolerance, hypercholesterolemia, hypertension, hyperuricemia, injury by free radicals, and thrombosis in animals, and to which males respond differently than females.\textsuperscript{18} It also is impossible to synthesize normal collagen, elastin and proteoglycans without adequate copper.\textsuperscript{27,28} Although data are not perfectly consistent,\textsuperscript{29-31} it seems likely that abnormalities of copper utilization contribute to the formation of aneurysms.

In summary, two important trace elements, zinc and copper, deserve increased attention in the pathogenesis of abdominal aortic aneurysms. If the matrix metalloproteinases resemble carboxypeptidase, an established drug, captopril may be useful. If data do not support the use of captopril, other, more appropriate drugs can be developed. If the association between copper utilization and aneurysm formation becomes closer, it may be that people who eat more copper do better than people who eat less. Although assessment of copper nutrure is difficult, attempts to do so may be rewarding. Zinc supplements should be avoided.

REFERENCES


8. \textsc{Thompson, R. W., D. R. Holmes, R. A. Mertens, S. Liao, M. D. Botney, R. P.}


