Homocysteine Is Not So Paradoxical

To the Editor: Rodionov and Lentz summarized the homocysteine paradox. Hyperhomocysteinemia disrupts vascular structure and function in animals and predicts risk of “coronary events, stroke, venous thromboembolism, and death,” yet clinical benefit in intervention trials remains unproved. They offer several plausible explanations.

Trials usually involve dietary supplementation with folate and vitamins B-6 and B-12. It also seems plausible that results would have been better if the intervention trials included copper.

High homocysteine concentrations lead to increased homocysteine thiolactone, an irreversible inhibitor of lysyl oxidase which depends on copper to initiate the cross-linking of collagen and elastin in arteries. Insufficient lysyl oxidase leads to vascular disease. Thus decreasing homocysteine may not lead to vascular repair without extra copper which also can lower plasma homocysteine.

The Western diet is often low in copper according to pooled data from several articles on more than 900 adult diets chemically analyzed. Sixty-two percent and 36% of diets of 80 randomly selected adults in Baltimore were below the recommended dietary allowance and the estimated average requirement for adults, 0.9 and 0.7 mg daily, respectively. Diets low in copper tend to be low in folate as well and vice versa.

Copper deficiency is the only nutritional insult that elevates cholesterol, blood pressure, homocysteine, isoprostanes, and uric acid, has adverse effects on electrocardiograms and arteries, impairs glucose tolerance and paraoxonase activity, and promotes thrombosis and oxidative damage. More than 80 anatomic, chemical, and physiological similarities between animals deficient in copper and people with ischemic heart disease have been identified.

Copper supplementation (with other micronutrients) of people with ischemic heart disease produced objective and subjective improvement of heart failure. It is likely that the copper contributed to this improvement.

Copper supplementation (with zinc) improved survival in a long-term double-blind study of ocular disorders. Larger and longer trials of homocysteine-lowering therapy with folate, etc. may be useless if homocysteine, per se, is not the injurious molecule. It seems unreasonable to do the same experiments over and over with an expectation of different results.

Inclusion of copper in a supplement, however, may promote vascular healing by a different mechanism than assumed in past trials. As the thiolactone is destroyed by paraoxonase (activity of which is decreased by copper deficiency), improved copper nutrition may stimulate an increase in lysyl oxidase activity and repair of damaged or decreased collagen and elastin.

Disclosures

None.

References

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doi: 10.1161/ATVBAHA.108.172072
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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