Many Potential Explanations for the Homocysteine Paradox

In our editorial, we listed several potential explanations for the homocysteine paradox, including the possibility that mild hyperhomocysteinemia is a marker of another deleterious factor. Klevay proposes that copper deficiency might be such a factor. He notes that dietary deficiency of B vitamins (particularly folate and vitamin B12) is a frequent cause of elevated plasma total homocysteine, and that a subset of hyperhomocysteinemic subjects could have coexisting copper deficiency. Klevay hypothesizes that supplementation with copper might improve the outcome of homocysteine-lowering intervention trials through two mechanisms: (1) it may contribute to homocysteine lowering by increasing the activity of methionine synthase, and (2) it may increase the activity of the collagen crosslinking enzyme, lysyl oxidase, which can be inhibited by homocysteine thiolactone.

The intervention trials clearly demonstrate that B vitamins (folic acid, vitamin B6, and vitamin B12), without copper supplementation, are sufficient to lower plasma total homocysteine in most subjects. It seems likely, therefore, that copper deficiency was not a major cause of hyperhomocysteinemia in these subjects. The second proposed mechanism is plausible but untested. Homocysteine thiolactone can lead to aberrant N-homocysteinylation of proteins, and copper deficiency might potentiate the elevation of homocysteine thiolactone by decreasing the activity of paraoxonase, an enzyme that has homocysteine thiolactonase activity. The pathophysiological importance of homocysteine thiolactone remains unproven, but the potential effects of copper on homocysteine thiolactone and lysyl oxidase activity clearly merit further investigation. We wish to reemphasize, however, that coexisting copper deficiency is only one of many potential explanations (along with chronic kidney disease and several other putative factors) for the homocysteine paradox.

Disclosures

None.

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