Nutrition Discussion Forum

How reliable and robust are current biomarkers for copper status? – comments by Brewer and Althaus

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We read the paper by Danzeisen *et al.* [1] with interest and would like to take issue with the authors on a number of topics.

First, in the early part of the paper, the authors raise the spectre of rather widespread human Cu deficiency. We disagree that Cu deficiency occurs to any significant extent in human populations, except in special, relatively rare, situations. Most of the evidence the authors cite is in animals, where severe Cu deficiency causes the problems they identify. However, the human data presented, for example on bone mineralization, is old and has had no recent support. There is no evidence of increased infection in human populations due to Cu deficiency or marginal Cu status. The evidence of low Cu being aetiologically involved in Alzheimer's disease is countered by much data suggesting that free Cu is too high in Alzheimer's. Cu deficiency does occur in the face of Zn administration, if the Zn dose is high enough (25–50 mg), taken often enough (at least twice per d), and taken in the absence of food. However, most individuals take Zn once per d and take it with food, and have no problems with Cu status. Extensive bowel surgery or bowel disease may lead to poor-enough absorption of Cu to lead to Cu deficiency, but this is rare. There are rare patients who exhibit severe Cu deficiency for unknown reasons. We do accept the authors' assertion that severely malnourished children may have Cu deficiency along with their other nutritional deficiencies. However, we believe the available evidence indicates Cu deficiency in most human populations is relatively rare, and that there is no good evidence that Cu deficiency is involved in such common problems as osteoporosis and infection.

Second, the authors use most of their paper to review possible markers of Cu status, both deficiency and excess, and highlight that most of them are unsatisfactory. Regarding the lowering of serum ceruloplasmin in Cu deficiency as a marker, they state it may be a good marker for moderate to severe Cu deficiency, but apparently not mild Cu deficiency. In their analysis of this point they ignore a body of data using ceruloplasmin as a very sensitive marker of decreased Cu status in animal studies[2–9], and in cancer[10–12], macular degeneration[13], and most recently in idiopathic pulmonary fibrosis (Flaherty KR, Arenberg DA, White ES, *et al.*, unpublished results). We maintain that ceruloplasmin is a sensitive marker of Cu depletion and of marginal Cu status.

Third, in discussing their concern about widespread Cu deficiency, they discuss allowable limits of Cu in drinking water. For example, the US limit is 1·3 mg/l. They say this type of regulation is 'predominantly a conservative approach in Cu-exposure regulation. This approach may not be suitable for an essential trace metal, since a low intake of Cu is as dangerous as a too-high intake.' This statement shows a surprising lack of awareness of recent literature, which among other things, has focused on the risks of Cu in drinking water. Sparks and colleagues find that adding as little as 0·12 mg/l (one-tenth the US limit) Cu to drinking water greatly exacerbates amyloid deposits and cognitive abilities in rabbits and other models of Alzheimer's disease[14–16]. Other researchers have confirmed the potential brain damage from low levels of Cu in drinking water in mice[17]. Mice that drank water containing only 0·12 mg Cu/l had twice as much Cu in the cells lining their brain blood vessels, had about one-third fewer LDL receptor-related protein (LRP) molecules in their brains, and one-third more amyloid β in their brains than control mice. LRP shuttles amyloid β out of the brain, into the systemic circulation. Using human cells, these investigators found that Cu damaged LRP molecules, giving a molecular mechanism for how excess Cu might be involved in the pathogenesis of Alzheimer's disease. Squitti *et al.* have found an excess of 'free' (non-ceruloplasmin) serum Cu in Alzheimer's disease[18,19]. Finally, Morris and colleagues have found that a high intake of Cu (mostly from supplements; drinking water wasn't studied) along with a high-fat diet caused cognitive decline over the 4-year study[20]. We suspect that Cu in drinking water and Cu in supplements, essentially unbound Cu, unlike food Cu, bypasses the liver for a time and is available to directly penetrate the blood–brain barrier.

Thus, as opposed to Danzeisen *et al.* [1], who fear widespread Cu deficiency, we fear widespread free Cu excess. The authors are correct that there is no current way to evaluate Cu excess, although the calculation of non-ceruloplasmin Cu in the serum, which they heavily criticize, is acceptable for some purposes (expanded free Cu pool in Wilson's disease, excess free Cu in Alzheimer's disease). However, a new and direct measure has been developed: one of us (J. A.) has invented a mobile apparatus that can measure both free and bound Cu. It is called Freebound (patent pending). This approach has already confirmed the findings of Squitti *et al.* that free Cu is high in Alzheimer's disease (J Althaus and J Quinn, unpublished results). Use of this approach should be a good answer to the search for indicators of high free Cu status.

Conflict of interest

J. A. works for Pipex Pharmaceuticals. Pipex has applied for a patent for Freebound. G. J. B. has equity in and is a paid consultant to Pipex.

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