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REVIEW ARTICLE

Copper Nutriture and Ischemic Heart Disease: A Brief Review

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ABSTRACT
The idea that dietary fat is poisonous arose nearly ¾ of a century ago. Criteria for associating disease incidence with environmental change were published a couple decades later. Intakes of dietary fat did not increase while ischemic heart disease risk was increasing; in contrast, dietary copper decreased. Intakes of copper calculated from food tables are falsely high by an average of 77%. Approximately half of adults consume less than 0.9 mg of copper per day when chemical analyses are done. This amount is less than nutritional guidelines. When hypercholesterolemia was discovered in copper deficient rats, a search was begun for anatomical, chemical and physiological similarities between animals deficient in copper and people with ischemic heart disease; more than 80 of these similarities have been identified. The copper deficiency theory on the etiology and pathophysiology of ischemic heart disease is the simplest and most general theory that has been proposed because it incorporates other theories on fetal programming, homocysteine and iron overload. It satisfies classical criteria of nutritional deficiency and association of an environmental characteristic with disease prevalence.

Text footnote: [1]References to historical statements can be found in some of my earlier reviews. I have inspected the titles of all articles about cholesterol, copper, coronary disease, trace elements and zinc on PubMed, etc. for decades. Concepts here were gleaned from my collection of nearly 134,000 articles.

History

Ischemic heart disease is largely a disease of the 20th century, becoming the leading cause of death in the US by 1973[1]. The etiology of this illness remains mysterious, although studies of migratory populations reveal it is environmental, not hereditary. In 1965 Sir Austin Bradford Hill [1] offered nine viewpoints regarding deducing causation from an associated environmental feature and presence of an illness.

Hill's fourth point was 'temporality', i.e., the temporal relationship of the association. Many believe that dietary fat is poison and that IHD is a slow and progressive intoxication. As heart disease risk was increasing in the 20th century, the apparently parallel increase in fat intake was found to be an artifact [2]. Also, nearly 50 epidemiologic studies have found no association between dietary fat and heart disease risk [3,4]. In 1976 it was suggested that dietary copper had decreased between 1942 and 1966 [5]. The most robust data on this decline are from analyses of archived wheat grain. These data show that dietary copper has been decreasing since the 1960s (Fan, 2008).

George Mann [6] reviewed the origins of the lipid hypothesis beginning in 1950, early dissension, some cholesterol-lowering trials involving diet or drugs and declared the 'end of an era' prematurely. Even today decreasing cholesterol has a much bigger effect on the *way* that you die then on the *day* that you die because prolongation of life by statins is negligible [7].

Four newer theories to replace that involving dietary fat have emerged; fetal programming by Barker [8], homocysteine by McCully [9] and iron overload by Sullivan [10,11]. The copper deficiency theory is the simplest and most general explanation of the etiology and pathophysiology of ischemic heart disease [12]. Copper metabolism is altered in people with low birth weight, high homocysteine and iron overload.

This theory incorporates those of Barker, McCully and Sullivan because alterations in copper metabolism have been associated with the phenomena. Kuhn [13] argues that theories incorporating other theories contribute to scientific progress. It also satisfies Hill's criteria of analogy, biological gradient, coherence and plausibility.

Theory evolution

Inspired by the wide-spread, inverse association between hardness of drinking water and risk of ischemic disease that now is well-known, a search was begun for trace elements that could affect cholesterol metabolism. Copper deficiency produces hypercholesterolemia in rats [14]. This discovery was unprecedented and has been confirmed in more than 30 independent laboratories worldwide. Thus it satisfies two of Hans Selye's criteria [15] that identify important research: it is both true and surprising. A search then was begun to determine to what degree it was generalizable to satisfy the third criterion.

More than 80 anatomical, chemical and physiological similarities between animals deficient in copper and people with ischemic heart disease have been identified; most of these similarities have been tabulated [16,17]. Copper deficiency is the only nutritional insult to experimental animals that elevates cholesterol, blood pressure, homocysteine and uric acid, has adverse effects on arteries and electrocardiograms, impairs glucose tolerance, promotes thrombosis and oxidative damage and to which males respond differently than females [12].

These similarities were identified by pairing animal experiments with observations on people. Four newly found similarities illustrate the method. Low activity of paraoxonase (also called homocysteine thiolactone hydrolase and PON1) associated with heart disease is described in several articles by Durrington and the Macknesses [4]; its activity is decreased in rats deficient in copper [4].

This lactone is an irreversible inhibitor of lysyl oxidase which depends on copper to initiate cross-linking of collagen and elastin in arteries [18]. Borowczyk et al. [19] found that urinary thiolactone predicts myocardial infarction. High thiolactone may impair arterial repair [20].

Lavi et al. [21] reviewed the presence of elevated isoprostanes in various disease states related to atherosclerosis. F_2-isoprostanes are increased in rats deficient in copper [22].

Tivesten et al. [23] measured dehydroepiandrosterone (DHEA) in serum of nearly 2500 Swedish men and found that low levels predicted increased risk of coronary heart disease death after five years. Serum DHEA is decreased in rats deficient in copper [24].

Glucose intolerance has long been associated with heart disease risk [25]. Glycated hemoglobin is associated with coronary artery stenosis and heart disease severity [26,27]. Rats deficient in copper have increased glycosylated hemoglobin [28].

Dietary copper

Copper intakes in nutrition surveys generally are calculated from food tables [29]. Several articles reveal that these calculated values for dietary copper exceed analytical values by an

average of 77%. Thus only intakes based on contemporaneous analytical chemistry are valid. Approximately half of adults consume less than 0.9 mg of copper per day [29] when analyses are done. This amount is the Recommended Dietary Allowance for copper [30] for the US; recommendations for the UK and Europe are higher.

Approximately 35 men and women of middle age have been depleted of copper in metabolic wards where experimental conditions were controlled carefully and dietary copper was measured [12]. Cardiac function was monitored with many Holter cardiograms. Hypercholesterolemia and ventricular tachycardia were among the findings [31].

Assessing copper nutriture

Obvious causes of copper deficiency include bariatric or other gastrointestinal surgery, dental adhesives high in zinc, hemochromatosis, iron or zinc supplementation, lead poisoning, malabsorption and soft drink excess [32]. Ischemic heart disease is more subtle. Dietary deficiency must be considered.

According to the Oxford Textbook of Medicine [33], low nutrient intakes can reduce nutrient concentrations in tissues and compromise metabolic pathways. More than sixty medical articles reveal deficiency in ischemic heart disease and related diseases by these criteria [29]. For example, Oster et al. [34] reported that cardiac output correlates positively with cardiac copper in heart disease patients.

Functional improvement from nutrient supplementation is the third criterion of deficiency [33]. Elimination of premature ventricular beats [35] with copper supplemenation and improvement of cardiac output from micronutrients including copper [36] are examples.

Anemia has preoccupied students of copper metabolism for three quarters of a century. Deficiency can occur without it. Less known are adverse effects of deficiency on arterial connective tissue. Owen's five volumes (e.g., [37]) and those of Underwood [38] are invaluable.

Four tests of copper nutriture (status) generally are available: ceruloplasmin in plasma and copper in liver, plasma or serum and urine [39]. Urinary copper is useless because it generally is unaffected by months of experimental, copper depletion of middle-aged men and women.

Liver copper is the best indicator. Deficiency experiments with animals reveal that plasma can be normal or increased even though copper in liver or other organs is low.

Normal serum copper is ill-defined and needs improvement in sensitivity to deficiency [39 40]. Several articles reveal that C-reactive protein and serum copper are correlated because of the acute phase response to inflammation; some serum copper values may be falsely high.

People should be evaluated with some of the newer, potentially more sensitive, indices of copper nutriture such as erythrocyte and extracellular superoxide dismutases, leukocyte copper, platelet cytochrome C oxidase or serum lysyl oxidase. Erythrocyte superoxide dismutase may be most sensitive [39]. Values of some of these have been found impaired in ischemic heart disease [29]

Copper supplementation

Copper gluconate is the only copper supplement listed by the United States Pharmacopeial Convention; it probably is best for oral use. We have used copper sulfate effectively with human volunteers. Cupric oxide should be avoided [41].

Conclusions

The background and evolution of the copper deficiency theory of ischemic heart disease are reviewed briefly. There are many anatomical, chemical and physiological similarities between animals deficient in copper and people with ischemic heart disease. This theory is the simplest and most general theory on its etiology and pathophysiology. The theory satisfies classical criteria of nutritional deficiency and for association of an environmental characteristic with disease prevalence.

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