Copper and the Heart

Maintaining a healthy heart is arguably the most important thing that one can do for the sake of one's overall health. Take a look at the wealth of supplements that are available, which are intended to keep one's heart healthy. The number of these supplements is staggering. Ingredients that are popular for this purpose include, but are not limited to, things like vitamin E, coenzyme Q-10, magnesium, pycnogenol, vitamin C, selenium, fish oil, folic acid, green tea, l-carnitine, and on and on. In line with the importance of the maintenance of a healthy heart, we gathered a core of clinical studies on minerals and their place in helping to maintain a heart healthy status. As one might expect, all of the nutritionally required minerals could be involved in the maintenance of a healthy heart. Magnesium and potassium are most commonly talked about in connection with heart health. In reviewing the latest studies on minerals connected to heart and cardiovascular function, the volume of research that pointed out the importance of copper in the maintenance of the heart and cardiovascular function was of great interest.

Copper Functions

Most scientists attribute copper's biochemical functions to its being part of a number of key proteins, including many vital enzymes. The copper proteins known to be found in living cells are listed in tables 1 and 2.

Table 1.

Copper-containing enzymes in mammals and other phyla,
"Present Knowledge in Nutrition", Zeigler & Filer, 7th Edition.

Enzyme/protein	Distribution & Function
Cytochrome c oxidase[a]	Ubiquitous in mitochrondria; last component in the electron transport chain of oxidative phosphorylation: reduction of O_2.
Cu / Zn superoxide dismutase	Ubiquitous in cytosol; protection against oxygen radicals: dismutation of superoxide to peroxide and O_2.
Tyrosinase (catecholoxidase/phenolase)[a]	Widely distributed; melanin production in mammals (in melanosome) and diverse functions in plants and fungi: oxidative polymerization of tyrosines, oxidation of monophenols and o-diphenols to quinines.
Lysyl oxidase[a,b]	Mammals (vertebrates?), extracellular in connective tissue; cross-linking of collagen and elastin: oxidative cross-linking of lysine residues.
Dopamine-4-monooxygenase[a,b]	Mammals (vertebrates?), in central nervous system and adrenal medullary cells; formation of epinephrine and norpinephrine: hydroxylation of dopamine.
a-Amidating enzyme[b]	Mammals (vertebrates?), in granules of neurohypophysis; modification of neuropeptides: oxidative removal of carbons of C-terminal glycine residue, leaving a-amino.
Amine and diamine oxidases[a,b]	Widely distributed (mammals, plants, fungi, etc.); intracellular and extracellular; oxidative inactivation (?) of histamine, tyramine, and polyamines: oxidative deamination.
Ceruloplasmin[a,c]	Vertebrates, in blood plasma and other extracellular fluids; free radical scavenger and role in promoting flux of iron out of storage sites; oxidation of Fe^{2+} to Fe^{3+}.
Ferroxidase II[a]	Vertebrates (?), in blood plasma; function unknown, but like ceruloplasmin can oxidize Fe^{2+} to Fe^{3+}.
Extracellular SOD	Vertebrates, in blood plasma and probably other extracellular fluids; part of antioxidant defense system(?): dismutation of O^{2-} to H_2O_2 and H_2O.
Ascorbate oxidase[a]	Plants and fungi, mainly intracellular; function unclear but in plants may play a role in fruit maturation and protection of wounds; oxidizes ascorbate, catechols, flavonoids, and hydroxycinnamin acid; in terms of reactivity, belongs to the family of blue copper oxygenases that include laccase and ceruloplasmin.
Laccase[a]	Plants and fungi, mostly extracellular; oxidative polymerization of phenolic compounds to seal wounds (trees); decomposition of lignin (polyphenolic)? (fungi): oxidation of benzene diols; belongs to the family of blue copper oxygenases.
Phenylalanin-4-monooxygenase[a]	Ubiquitous (?) intracellular enzyme; has either iron or copper as a cofactor (Mammalian enzyme is iron dependent); synthesis of tyrosine and degradation of phenylalanine: hydroxylation of phenylalanine.
Metallothionein[c]	Ubiquitous, intracellular, with traces that are extracellular in body fluids; high cysteine-containing divalent metal ion storage protein that has some superoxide dismutase activity when bound to copper.

a Reaction requires molecular mono- or di-oxygen.
b 6-Hydroxy dopa or pyrroloquinoline quinine is a cofactor for the enzyme.
c also plays nonenzymatic roles.

Based on the number of enzymes and proteins that copper is involved with, it is clear that copper has a wide reaching impact in the body. Copper is essential for energy metabolism (cellular respiration), brain function (neurotransmitter regulation), soft tissues and bone (collagen synthesis), for nutrient metabolism (particularly for iron), and for oxidative stress defense against free radicals (to decrease the risk of cancer and cardiovascular diseases which can stem from free radical damage).

Copper deficiency leads to an anemia that is not responsive to iron supplementation, as well as poor wound healing, similar to that seen in vitamin C deficiency. Other signs of copper deficiency include weakness, lassitude, joint ache, osteoporosis, small petechial hemorrhaging, and arterial aneurysms, which reflect the vital role for copper in the synthesis of connective tissue, and in particular, collagen synthesis. Hypertrophy of the heart followed by its rupture has been reported in animal studies of the copper deficient. Central nervous system degeneration can be related to copper deficiency's resultant decline in respiratory chain activity and ATP synthesis that is essential to neural activity. Additional signs of copper deficiency reported include: decreased T lymphocytes and neutrophil activities, elevated plasma cholesterol, neutropenia, achromatism, twisted kinky hair, and hemacytic hypochromic anemia. Adrenal steroidogenisis and catecholamine synthesis are impaired in copper deficient conditions. Copper absorption is decreased by phytate and dinositol pentaphospate taken in the same meal. Zinc intake decreases copper absorption, as well. Ascorbic acid decreases copper bioavailability by reducing copper+2 to the more poorly absorbed copper+1.

Research Connecting Copper and Heart Health

Marginal Dietary Copper Restriction Induces Cardiomyopathy In Rats.
Li Y, et al.
J Nutr 2005; 135(9):2130-6.

Prior studies have provided evidence of marginal dietary copper restriction in humans. The present study was undertaken to examine in a rat model the effect of a long-term marginal dietary Cu deficiency on the heart. Male adult rats were fed AIN-76 diet containing 6.0 (control) 3.0, or 1.5 mg Cu/kg starting at 11 weeks of age. Groups of rats were killed at 6, 9, 12, 15, or 18 mo after initiation of feeding, and the same experiment was repeated once. The only systemic change induced by marginal dietary Cu restriction (P < 0.05) was depression of organ Cu concentrations in rats fed 1.5 mg Cu/kg diet. Cardiac pathological manifestations in rats fed lower Cu diets were evidenced by histopathological, ultrastructural, and functional alterations. Myocyte hypertrophy and excessive collagen deposition in the heart occurred in rats fed 1.5 mg Cu/kg diet. Ultrastructural changes, including increased number and volume of mitochondria along with disruption of cristae structure, diastolic and systolic dysfunction, and electrocardiograph alterations, occurred in rats fed 1.5 or 3.0 mg Cu/kg diet. These results demonstrate that, in the absence of most indications of systemic Cu deficiency, heart morphology and function are sensitive to marginal Cu deficiency.

Increased Contractility Of Cardiomyocytes From Copper-deficient Rats Is Associated With Upregulation Of Cardiac Igf-i Receptor.
Dong F ; Esberg LB ; Roughead ZK ;

Table 2.
Nonenzymatic functions of copper-binding proteins,
"Present Knowledge in Nutrition", Zeigler & Filer, 7th Edition.

Protein	Distribution & Function
Albumin	Vertebrates, in blood plasma and extracellular fluids; part of the exchangeable plasma copper pool; carrier of ionic copper in circulation and binder of excess copper; carries a high-affinity N-terminal copper binding site.
Ceruloplasmin	Vertebrates, in blood plasma and extracellular fluids; not part of the exchangeable plasma copper pool; source of copper for cells, scavenger of oxygen radicals; ferroxidase; in terms of reactivity, belongs to the family of blue copper oxygenases that includes laccase and ascorbate oxidase.
Transcuprein	Vertebrates?, in blood plasma; part of the exchangeable plasma copper pool; binds copper with even higher affinity than albumin; exchanges copper with albumin.
Metallothioneins	Ubiquitous, intracellular, with traces that are extracellular in body fluids; high-cysteine divalent metal ion storage protein: affinity for Cu^{2+} is higher than that for most other metal ions.
Factors V and VIII	Mammals, extracellular in blood plasma; nonenzyme proteins necessary for blood clotting; portion homologous to ceruloplasmin.
Cartilage matrix glycoprotein	Mammals, intracellular substituent of chondrocytes and some other cells; considerable homology with ceruloplasmin; like lysyl oxidase, appears to support connective tissue function.
Hemocyanin	Molluscs and arthropods, in the circulatory fluid; substitutes for hemoglobin in carrying oxygen (bound to pairs of copper atoms); belongs to the tyrosinase family of blue copper monooxygenases.
Plastocyanin	Plants, in chloroplasts; part of the electron transport system used in photosynthesis: transfers electrons from cytochrome b6-f to photosystem I.

Ren J ; Saari JT
Am J Physiol Heart Circ Physiol. 2005;
289(1):H78-84

Hearts from severely copper-deficient rats show a variety of pathological defects, including hypertrophy and, in intact hearts, depression of contractile function. Paradoxically, isolated cardiomyocytes from these rats exhibit enhanced contractile properties. Because hypertrophy and enhanced contractility observed with other pathologies are associated with elevation of insulin-like growth factor-I (IGF)-I, this mechanism was examined for the case of dietary copper deficiency. Male rats were provided diets that were deficient or adequate in copper for 5 weeks. IGF-I was measured in serum and hearts by an ELISA method, cardiac IGF-I and IGF-II receptors and IGFBP-3 were measured by Western blotting analysis. and mRNAs for cardiac IGF-I and IGF-II were measured by RT-PCR. Contractility of isolated cardiomyocytes was assessed by a video-based edge-detection system. Copper deficiency depressed serum and heart IGF-I and heart IGFBP-3 protein levels and increased cardiac IGF-I receptor protein. Cardiac IGF-II protein and mRNA for cardiac IGF-I and IGF-II were unaffected by Cu deficiency. A Cu deficiency-induced increase in cardiomyocyte contractility, as indicated by increases in maximal velocities of shortening and relengthening and decrease in time to peak shortening, was confirmed. These changes were largely inhibited by use of H-1356, an IGF-I receptor blocker. The researchers concluded that enhanced sensitivity to IGF-I, as indicated by an increase in IGF-I receptor protein, accounts for the increased contractility of Cu-deficient cardiomyocytes and may presage cardiac failure.

Congestive Heart Failure In Copper-deficient Mice.

Eisherif L ; Ortines RV ;
Saari JT ; Kang Y J
Exp Bioi Med (Maywood). 2003;
228(7):811-7

Copper Deficiency (CuD) leads to hypertrophic cardiomyopathy in various experimental models. The morphological, electrophysiological, and molecular aspects of this hypertrophy have been under investigation for a long time. However the transition from compensated hypertrophy to decompensated heart failure has not been investigated in the study of CuD. We set out to investigate the contractile and hemodynamic parameters of the CuD mouse heart and to determine whether heart failure follows hypertrophy in the CuD heart. Mice were fed CuD or copper-adequate (CuA) diet starting from the third day post delivery and the weanling pups were fed the same diet for a total period of 5 weeks (pre- and postweanling). At week 4, the functional parameters of the heart were analyzed using a surgical technique for catheterizing the left ventricle. A significant decrease in left ventricle systolic pressure was observed with no significant change in heart rate, and more importantly contractility as measured by the maximal rate of left ventricular pressure rise and decline were significantly depressed in the CuD mice. However, left ventricle end diastolic pressure was elevated, and relaxation was impaired in the CuD animals; the duration of relaxation was prolonged. In addition to significant changes in the basal level of cardiac function, CuD hearts had a blunted response to the stimulation of the beta-adrenergic agonist isoproterenol. Furthermore, morphological analysis revealed increased collagen accumulation in the CuD hearts along with lipid deposition. This study shows that CuD leads to systolic and diastolic dysfunction in association with histopathological changes, which are indices commonly used to diagnose congestive heart failure.

Marginal Copper Deficiency And Atherosclerosis.

Hamilton IM ; Gilmore WS ; Strain JJ
Bioi Trace Elem Res. 2000;
78(1-3):179-89

Copper is an essential trace element in the maintenance of the cardiovascular system. Copper-deficient diets can elicit, in animals, structural and functional changes that are comparable to those observed in coronary heart disease. In this study, the effect of dietary-induced copper deficiency on aortic lesion development was measured by quantitative image analysis in C57BL/6 mice that are susceptible to diet-induced aortic lesions. The diets administered were severely copper deficient (0.2 mg/kg diet), marginally deficient (0.6 mg/kg diet), or copper adequate (6.0 mg/kg diet). Similarly, increased aortic lesion areas and elevated serum cholesterol were demonstrated in both deficient groups, compared with the copper-adequate group. Evidence for graded differences in copper status among the dietary groups was shown by the dose-response increase in liver copper concentration, copper-zinc superoxide dismutase and cytochrome-c oxidase activities, together with serum caeruloplasmin oxidase with increasing intakes of dietary copper. Despite the difference in copper status between the copper marginal and severely deficient groups, similar lesions found in both groups of mice suggest a threshold effect of copper deficiency on lesion formation.

Regression Of Dietary Copper Restriction-induced Cardiomyopathy By Copper Repletion In Mice.

J Nutr. 2004; 134(4):855-60
(ISSN: 0022-3166) t
Elsherif L ; Wang L ; Saari JT ; Kang Y J

Dietary copper deficiency (CuD)(3) leads to cardiac hypertrophy in various animal models. We showed recently that heart failure develops after hypertrophy in FVB mice fed a CuD diet. The present study was undertaken to determine whether CuD-induced cardiac failure is reversible upon copper repletion (CuR). Dams of FVB mice were fed a CuD diet (0.3 mg/kg) starting from day 3 post delivery; the weanling pups were fed the same diet until CuR with 6.0 mg/kg Cu in the diet at 4 or 5 weeks of age. CuR at 4 weeks of age prevented the body weight loss; at 5 wk of age, it resulted in the regaining of the lost weight caused by CuD. A significant regression of CuD-induced cardiac hypertrophy was observed in the CuR mice. Histopathological examination revealed that CuR eliminated CuD-caused lipid deposition in the myocardium, and electron microscopy demonstrated that CuD-induced ultrastructural changes such as mitochondrial swelling and organelle structural disarray were all reversed in the CuR mice. Hemodynamic analysis showed that the CuD-depressed systolic and diastolic parameters such as the maximal rate of left ventricular pressure rise (+dP/dt) and decline (-dP/dt), and the contraction and relaxation times were completely recovered in the CuR mice. Furthermore, the CuD-blunted myocardial responses to the beta-adrenergic agonist, isoproterenol, were also restored in the CuR mice. This study thus demonstrates for the first time that CuR results in the regression of heart failure induced by CuD as demonstrated by the reversal of depressed cardiac hemodynamic and contractile function and the restored responsiveness to beta-adrenergic stimulation.

Cardiovascular Disease From Copper Deficiency--a History.

Klevay LM
J Nutr. 2000; 130(2S Suppl):489S-492S

Although the nutritional essentiality of copper was established in 1928, a preoccupation with hematology delayed the discovery of cardiovascular disease from copper deficiency for more than a decade. Anatomical studies of several species of deficient animals revealed, interalia, aortic fissures and rupture, arterial foam cells and smooth muscle migration, cardiac enlargement and rupture, coronary artery thrombosis and myocardial infarction. Abnormal biochemistry in deficiency probably contributes to these lesions, e.g., decreased activities of lysyl oxidase and superoxide dismutase which result in failure of collagen and elastin cross-linking and impaired defense against free radicals. Copper deficiency also decreases copper in hearts and other organs and cells and increases cholesterol in plasma. Abnormal physiology from deficiency includes abnormal electrocardiograms, glucose intolerance and hypertension. People with ischemic heart disease have decreased cardiac and leucocyte copper and decreased activities of some copper-dependent enzymes. Copper depletion experiments with men and women have revealed abnormalities of lipid metabolism, blood pressure control, and electrocardiograms plus impaired glucose tolerance. The Western diet often is as low in copper as that proved insufficient for these people. Knowledge of nutritional history can be useful in addressing contemporary nutritional problems.

The research on copper has shown a wide array of negative health changes to be associated with its deficiency and marginal deficiency. In addition, it has been observed that the Western diet is often very low in copper content. Even lower now that so many rely on bottled water, as opposed to tap water. Disorders of the heart due to copper deficiency have been clearly demonstrated, and their end results are severe. Various forms of heart failure and cardiovascular lesions (leading to coronary artery disease) are found in the copper deficient. Recently, research has shown that copper repletion can help improve the heart conditions found in the copper deficient. This was a very critical and hopeful finding. It should be noted that excess zinc, as well as phytate intake, in conjunction with copper intake has been demonstrated to impede the absorption and utilization of copper. In supplementing copper, it should be noted that Albion Advanced Nutrition has had independent scientific research done on its Copper Chelazome, which have shown that its absorption and utilization is not impeded by the intake of zinc. In addition, phytates do not inhibit the absorption of chelates to the degree that they do with the other mineral forms. The copper forms available from Albion Advanced Nutrition are: Copper Chelazome® Amino Acid Chelate and Copper Lysine Amino Acid Chelate. The Chelazome® Amino Acid Chelate is a Copper Glycinate Amino Acid Chelate.

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