DIETARY COPPER: A POWERFUL DETERMINANT OF CHOLESTEROLEMIA

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ABSTRACT

A new hypothesis suggests that deficiency of copper is important in the etiology and pathophysiology of ischemic heart disease. Several chemicals, called cholesterotrophic and cuprotrophic, that affect cholesterolemia also affect copper metabolism. Responses to some of these chemicals that have been tested in humans were compared on a molar basis. Dietary copper was approximately one hundred times as active in lowering cholesterol in plasma than was clofibrate which, in turn was six times as active as dietary fat. Dietary copper may be a powerful determinant of cholesterolemia.

INTRODUCTION

A new hypothesis, called the zinc/copper hypothesis, on the etiology and pathophysiology of ischemic heart disease has been in development for approximately a decade (1-9). According to this hypothesis "a metabolic imbalance in regard to zinc and copper is a major factor" in the etiology of ischemic heart disease. This imbalance, either a "relative or absolute deficiency of copper characterized by a high ratio of zinc to copper", results in hypercholesterolemia, myocardial and arterial damage, and increased mortality. Among the phenomena associated with a high ratio of zinc to copper and either high risk of mortality or hypercholesterolemia are diets high in fat or sucrose, pregnancy, nephrotic syndrome, chronic hemodialysis, hypertension, and the low amounts of copper found in the presumably normal areas of infarcted hearts. Associated with a low ratio of zinc to-copper and either low risk of mortality or hypocholesterolemia are diets high in fiber, hepatic cirrhosis, infectious hepatitis, strenuous exercise, and the availability of hard water. The hypothesis, based on a wide variety of epidemiologic and experimental observations (1-7), has been extended (8,9) with emphasis on pathology, pharmacology, and physiology (8). Recent emphasis also has been placed on risk factors, on links between the
lipid hypothesis and the zinc/copper hypothesis, and on the numerous similarities between animals deficient in copper and people with ischemic heart disease (9). The most important of these similarities are hypercholesterolemia, abnormalities of the electrocardiogram, glucose intolerance, and hyperuricemia.

Five characteristics of people, from among a few hundred characteristics, can be used to identify individuals who seem to be at increased risk of ischemic heart disease. These characteristics, called risk factors, are hypercholesterolemia, hypertension, abnormalities of the electrocardiogram, glucose intolerance, and the smoking of cigarettes (10). By considering these characteristics one can identify the 20% of a population in which ultimately one will find 40% of the ischemic heart disease (11). Hyperuricemia also is predictive of risk (11).

Hypercholesterolemia from impaired copper nutrition has been observed in several species of animals studied in several independent laboratories (for references see (8)). Hypercholesterolemia also has been produced in a man fed a diet low in copper (12).

This diet (12), which was made from conventional foods, contained 0.83mg of copper per day. This daily amount of copper is not unusually low in comparison to other contemporary diets in industrialized countries. Numerous articles (for references see (8)) show daily intakes less than 2mg to be common; five articles are among the more accessible (13-17). Data in these reports are based on direct, chemical analysis rather than by calculation from analysis of foods. In our experience (18) calculation is unreliable for copper. It is estimated that 75% of diets in the United States contain less than 2mg of copper (19) daily. It is generally believed (20) that 2mg of copper are required each day to compensate for the urinary and fecal loss of adults. Diets containing 0.83mg may represent the lower 15% of daily intakes.

There is no Recommended Dietary Allowance for copper; the estimated safe and adequate intake is 2-3mg per day (21). It has been suggested that this intake is neither safe nor adequate (22).

Cholesterotropic and cuprotropic chemicals

The association between cholesterolemia and risk has prompted extensive studies of the metabolism of cholesterol and has led to a large number of attempts to minimize cholesterolemia (e.g. see (23)) on the assumption of beneficial effects. A large number of agents have been shown to affect the metabolism of cholesterol.

Several quite diverse chemicals alter both cholesterolemia and copper metabolism. This duality of action prompted the suggestion that a new class of chemicals, those both cholesterotropic and cuprotropic, has been identified (24,25). The origin of the suffix -tropic is from the Greek τροπ-, which indicates a turning in direction in response to a stimulus. In this sense the chemicals
are the stimuli that change the directions of cholesterol and copper. Some of these chemicals are hypercholesterolemic and copper inhibiting: ascorbic acid, cadmium, cholesterol plus cholic acid, fructose, glucose, histidine, sucrose, and zinc. Others are hypcholesterolemic and copper enhancing: calcium, clofibrate, guaran (the principal polysaccharide from guar seeds), and sodium phytate.

The chemical dissimilarity of the cholesterotropic and cuprotropic chemicals that have been identified has been discussed (25). They range from salts of elements and small molecules to complex carbohydrates. The effects of these agents on cholesterol metabolism may be mediated by alterations in copper metabolism (25).

In the study (12) of human experimental copper depletion, the subject experienced an increase in cholesterol in plasma of 32mg/dl in depletion and a decrease of 36mg/dl in repletion. These changes represent a change of at least 424mg of cholesterol/dl per millimole of copper. In the large scale, clinical trial (26) of clofibrate, the decrease in serum cholesterol was 3.60mg/dl per millimole of drug. Similar calculations using standard equations (27,28) for calculating the change in serum cholesterol associated with changes in dietary fat reveal a maximum change of 0.55mg of cholesterol/dl per millimole of fat, if the diet is changed from one containing coconut oil to one containing safflower oil. These oils are quite different in their degree of saturation and chain length of the fatty acids.

Six experiments (29-34) involving 145 subjects have shown decreased cholesterolemia of men and women ingesting calcium salts (usually carbonate) as supplements to their usual diets. These changes were less than 1.96mg cholesterol/dl per millimole of calcium.

The changes in cholesterolemia from these agents are summarized in Table 1. The range of responses is several hundredfold. Data were selected, when a choice was available, to minimize this range. The change in cholesterolemia from copper seems to be approximately one hundred times the response to clofibrate.

Responses of people to cholesterotropic agents calculated on a molar basis do not seem to be readily available. The use of molar comparisons is common in the pharmacology of drugs that are chemically similar. This concept may be useful in the comparison of agents that are dissimilar chemically but which produce a common pharmacological effect.

Only a few of the cholesterotropic and cuprotropic chemicals that have been identified have been studied in humans. There is no need to feed cholesterol plus cholic acid to humans because few would suggest increased cholesterolemia is desirable. The hypercholesterolemic response of animals and the coincident decrease in liver copper to this combination of agents may explain the slight increase in plasma cholesterol found in patients treated for gallstones with chenodeoxycholic acid, however (35).
Table 1  Decreased cholesterolemia from oral agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cholesterol Change</th>
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<tbody>
<tr>
<td></td>
<td>mg/dl per millimole</td>
</tr>
<tr>
<td>Copper</td>
<td>&gt;474*</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>3.60</td>
</tr>
<tr>
<td>Calcium</td>
<td>≤1.96+</td>
</tr>
<tr>
<td>Fat</td>
<td>≤0.55°</td>
</tr>
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*Several daily doses of copper; e.g. from the mean loss during depletion of 0.11mg to the mean intake of 4.83mg during repletion (12), could have been used to calculate the response. As one doesn't know which of these would be the most accurate, 4.83mg was selected to produce a minimal value for cholesterol change.

+This response is the unweighted mean calculated from six studies (29-34). Because the experimental designs, dosage schedules, etc., were quite variable some assumptions were made and some data were selected. The effect of assumption and selection was to maximize the value for cholesterol change.

°This response is based on the Keys' equation (28) as it is greater than that from the equation derived by Hegsted, et al. (27).

Experiments with animals have revealed the cuprotropic characteristics of some of the cholesterotropic agents known for activity in humans. Romasz et al. (36) found that as the dietary calcium of rats was increased and the concentration of cholesterol in serum decreased, the concentration of copper in liver increased. This change is indicative of improved nutriture (nutritional status). Clofibrate enhances the utilization of copper of rats fed a diet low in copper and concomitantly lowers cholesterolemia (24). It is unknown whether or not polyunsaturated fat has a beneficial effect on copper nutriture; however, preliminary data on men (37) are consonant with a decreased retention of zinc from a diet high in polyunsaturated fat. Polyunsaturated fat fed to rats decreased the amount of zinc in liver without affecting liver copper (38).

Perhaps dietary fat is cuprotropic as well as cholesterotropic and, thus, is similar to clofibrate and calcium. The response (on a molar basis) of cholesterolemia to these agents is quite small in comparison to dietary copper. This smaller response is consonant with their actions on cholesterol being indirect and being mediated via dietary copper.
The mechanism by which alterations in copper metabolism affect cholesterol metabolism is understood incompletely. Liver copper seems involved as shown by the negative correlations between plasma cholesterol and copper in liver microsomes (39) and liver (24,40,41). Copper deficiency increases the incorporation of tritiated mevalonate into plasma cholesterol; incorporation and liver copper were negatively correlated (42).

Kinetic analyses identified a pool of cholesterol that was larger and was changing more slowly in copper deficiency than with normal nutriture (43). The activities of lecithin:cholesterol acyltransferase (44,45) and lipoprotein lipase (46) are decreased in copper deficiency.

CONCLUSIONS

Published data (24,39-46) do not explain completely the effects of copper on cholesterol metabolism. Copper is a versatile nutrient (47). Underwood (48) has reviewed numerous systemic effects of copper deficiency discovered in the last half century. Owen (e.g., 49) has written five volumes on the biology of copper. Copper was mentioned in 30 topical sessions at the 69th annual meeting of the Federation of American Societies for Experimental Biology. Some of the recent and increasing interest in research on the biology of copper derives from the similarities between animals deficient in copper and people with ischemic heart disease. Opportunities for research are numerous. Perhaps effects of copper nutriture on cholesterol metabolism are mediated via cellular receptors, energy conversion, enzyme kinetics, or membrane modification. Time will tell.

Available data support the belief that dietary copper may be one of the more powerful determinants of cholesterolemia. As dietary copper has been controlled only rarely in studies of cholesterol metabolism, copper nutriture may have contributed to biological variability, and may have influenced experimental results. Insufficient dietary copper may be an important determinant of risk of ischemic heart disease.

ACKNOWLEDGEMENT

The verification by Marilyn R. Lawler, Ph.D., R.D. and Janet R. Mahalko, R.D., of calculated responses to dietary fat is appreciated.

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