Interrelationships Among Protein, Zinc, and Copper in Human Nutrition[1]

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ABSTRACT

Recent research suggest interactions among protein, zinc, and copper, with the possibility that the absorption and utilization of the trace elements are affected. Although reports from animal studies indicate that protein metabolism is altered by low zinc intakes, investigations with human subjects do not confirm this when zinc intakes are marginal. High protein intakes may cause increased urinary excretion of zinc, but this is not clearly documented, as for calcium. The absorption of copper is difficult to evaluate in the usual balance method with human subjects because of the route of excretion. A few studies in which both protein and copper were variables do not indicate any effect of protein on copper retention, but this relationship appears not to have been investigated in humans. Most human studies indicate that zinc does not alter the utilization of copper, but at least one study with humans and reports from animal models suggest an antagonistic effect and decreased retention of copper when the intake of zinc is elevated. Data from several human studies indicate that the apparent absorption of copper ranges from 0 to 60% and of zinc from 7.1 to 62.1%. In most studies, the apparent absorption of zinc is in the range of 20–35%. The possibility exists that the interrelationship among protein, copper, and zinc is important to human health; thus further investigations seem to have merit.

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During recent years, human utilization of nutrients has received increasing attention. Utilization depends upon the myriad relationships among nutrients, including the effects of one nutrient upon another, the effects of other components of the food upon one or more nutrients, and the physiological state of the individual at the time the food or nutrient is consumed. In addition, studies of nutrient interrelationships may be complicated by species, age, and sex differences. The human does not respond to factors influencing nutrient utilization as do animal species, although much of our present knowledge about nutrient function has been derived from investigations with animal models. Therefore, the objective of this article, based on information from human studies, is to focus on relationships between protein, zinc,

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and copper nutrition.

The potential importance of the relationships among nutrients in the human has been suggested from studies indicating that the level of dietary protein may be an important factor in calcium utilization (Johnson et al 1970, Kim and Linkswiler 1979, Margen et al 1974, Walker and Linkswiler 1972) and in the incidence of osteoporosis in the American population. The importance of the relationship between protein and zinc has been suggested from studies with animals in which roles for zinc were demonstrated in the synthesis of nucleic acids (Sandstead and Rinaldi 1969, Terhune and Sandstead 1972) and protein (Sandstead and Terhune 1972). Sandstead (1973) suggested a possible role for zinc in the utilization of dietary protein in the human. Klevay (1975) has hypothesized that the ratio of zinc to copper in the diet may be a major contributing factor in the development of cardiovascular problems in the U. S. population. These reports serve as examples of the possible importance of nutrient interrelationships and interactions in human health and provide adequate rationale for periodic reviews of available information and for additional studies designed to elucidate further these interrelationships.

EXPERIMENTAL APPROACHES WITH HUMAN SUBJECTS

Most of the current information about nutrient utilization has come from balance studies with human subjects. This method presents some difficulties, but a reasonable alternative has not been developed. Some of the shortcomings of the balance method can be minimized with appropriate controls. Details of our approach to the controlled balance study have been provided previously (Ritchey and Korslund 1976). We have conducted studies with growing children, young adults, and with elderly adults. Elements essential to a reliable study include clear communication with the participating subjects so that they understand the objectives of the study and the constraints to be imposed upon them, personnel who demonstrate interest in the study and the welfare of the subjects, appropriate control of diets and water intake, medical supervision and support as required for the specific study, adequate adjustment periods during which the experimental routine is established but data are not usually used to calculate nutrient retentions, reasonably acceptable menus that do not compromise the objectives of the study, and a well-organized and capable team of investigators (Ritchey and Korslund 1976). Almost without exception, the participants have been cooperative, interested, and helpful in the conduct of a given experiment. Few incidences of cheating have occurred; the data are as reliable as one can anticipate from this type of study and probably as reliable as from a similar study employing animals.

In studies involving trace elements, both food and water intake must be controlled. We routinely provide menus based on a cycle of three or four days. Each menu is analyzed before the study and throughout the experimental portion to give an accurate record of nutrient intake for each subject. An example of a menu is given in Table I. In these studies distilled, ion-free water is provided ad libitum, but no other source of water is permitted. Throughout the metabolic studies, complete collection of urine and feces is made to provide reliable information on the excretion of nutrients.

Other laboratories have conducted studies using a similar approach, thus providing most of our current information on nutrient availability and nutrient interactions. For the most part, these studies use healthy human subjects in contrast to patients in a hospital environment.

PROTEIN-ZINC INTERACTIONS

In a short-term study with children (Meiners et al 1977), the possible influence of dietary zinc on nitrogen retention was studied. The investigators found that nitrogen utilization and the urinary excretion of urea nitrogen, uric acid, and creatinine were not different in subjects consuming 5.5 or 10.5 mg of zinc daily (Table II). Because these findings contrast with reports from animals (Sandstead and Rinaldi 1969, Sandstead and Terhune 1972, Terhune and Sandstead 1972), the study of the children may not have been sufficiently long to cause a zinc effect. However, zinc appeared not to be a limiting factor in nitrogen retention on a low protein intake, a possibility which has been suggested (Sandstead 1973a). Previous studies of the rat (Hsu and Anthony 1975) have suggested that zinc affects protein metabolism and DNA synthesis (Sandstead and Rinaldi). Human studies are limited by the need to maintain a nutrient level at which a deficiency is not effected; thus the critical response to a very low nutrient intake may not be demonstrated in these studies.

In a study with a mixture of meat and soy proteins, Greger et al (1978a) reported that nitrogen retention was not affected by zinc intake. Zinc retention was not changed when 30% of the meat was replaced by soy protein. However, the protein source appears to affect zinc absorption. The work of Price et al (1970) indicated that absorption of zinc from plant foods was somewhat lower than that from mixed diets (Table III). The interpretation may be somewhat confounded by the difference in protein level, however.

Level of protein may influence zinc excretion in elderly subjects (Burke et al 1981). Urinary excretion of zinc by subjects consuming a diet containing 45 g of protein was about 0.19 mg/day, but zinc excretion by subjects ingesting 100 g of protein was about 0.31

Table I
Example Menu[a] used in Human Study[b]

Meal	Food	Amount (g)
Breakfast	Special K	20
	Sugar	10
	Orange juice	150
	Milk, whole	140
Lunch	Tomato soup	100
	Milk	100
	Lettuce	30
	Tomato	30
	Carrot sticks	15
	Mayonnaise	10
	Saltines	11
	Lemonade	200
Snack	Graham cracker	28
	Pears, canned	90
	Kool Aid	200
	with sugar	25
Dinner	Chicken	40
	Macaroni	65
	Tomato, canned	100
	Bread	28
	Margarine	10
	Ice cream	90
	Cookie	40
	Pineapple juice	200

[a] One day's intake, containing, by analyses, 5.61 mg of zinc.
[b] Taken from Ritchey et al (1979).

Table II
Effect of Zinc Intake on Daily Nitrogen Retention and Nitrogen-Containing Compounds in Urine in Preadolescent Girls[a]

Zinc Content of Supplemental N			Urinary Excretion		
Source of Supplemental N	Zinc (mg)	Nitrogen Retention (g)	Urea N (g)	Uric Acid (g)	Creatinine (g)
Amino acids	5.5	1.01±0.18	1.66±0.23	0.13±0.01	560±91
Amino acids	10.5	1.00±0.35	1.55±0.15	0.16±0.02	520±94
Ammonium citrate	10.5	0.81±0.39	1.86±0.22	0.15±0.01	612±96
Ammonium citrate	5.5	0.90±0.32	1.64±0.04	0.15±0.01	608±86

[a] Mean ± SD; from Meiners et al (1977).

mg/day. In this study the source of protein was not different. This finding is similar to reports concerned with the level of protein and urinary calcium excretion (Johnson et al 1970, Kim and Linkswiler 1979, Margen et al 1974, Walker and Linkswiler 1972).

The interaction between zinc acid level and source of dietary protein remains unclear. Experiments with human subjects under carefully controlled conditions are needed to clarify our understanding of these interactions because animal responses cannot always be extrapolated to humans.

PROTEIN-COPPER INTERACTIONS

Copper absorption cannot be readily assessed because of the primary excretion route. Copper is absorbed from the stomach and upper small intestine. At least two absorption mechanisms, one involving amino acids and a second in which copper is bound to two protein fractions, have been described (Burch et al 1975). Under normal circumstances very little copper is excreted in the urine; most is excreted through the biliary tract. Separation of absorbed copper from fecal copper presents problems not readily resolved in the usual human balance approach.

Retention of copper may be affected by amount and source of protein. In the study by Price et al (1970), copper retentions were slightly higher in diets with a mixture of plant and animal proteins, but these diets were also higher in total protein than were plant proteins (Table III). Fecal copper levels were similar for all dietary treatments, suggesting that copper utilization was not affected by protein. Greger et al (1978b) found no difference in apparent copper absorption when the copper intake was 2.9 mg/day and the protein source was either a mixed diet or a diet in which 30% of the meat was replaced by soy protein. In a recent study (Mareckova et al 1978), renal patients were consuming 20 g of protein and 0.8 mg of copper daily but were not able to maintain increases in ceruloplasmin. The investigators suggested the low copper intake as the limiting factor.

Apparent absorption of copper (in reality, apparent utilization of dietary copper) varies considerably with subjects and dietary variables (Table IV). In studies examining variables of protein and zinc, the utilization of copper ranged from 0 to approximately 60% of intake.

Table III
Apparent Absorption of Zinc as Affected by Source and Amount of Protein in Preadolescent Girls[a]

Protein		Zinc		
Source	Intake (g/day)	Intake (mg)	In Feces (mg)	Apparent Absorption (%)
Plant	25	4.83	3.98	17.6
Plant	25	4.53	3.31	26.9
Mixed	46	6.88	4.68	32.0
Mixed	46	6.93	4.58	33.9

[a] Data from Price et al (1970).

Table IV
Utilization of Copper by Humans Consuming a Variety of Diets

Copper				
Intake (mg)	Retention (%)	Subjects	Dietary Variables	Reference
1.25	28.0–36.8	Adolescent females	Zinc, protein	Greger et al 1978c
2.90	57.2–59.7	Adolescent females	Zinc, protein	Greger et al 1978b
2.32	11.6–56.9	Elderly adults	Zinc	Burke et al 1981
2.10	62.1±19.9	Adult females	···	King et al 1978
1.63	31.6–47.1	Adolescent females	Protein	Price et al 1970
2.0	···[a]	Adult females	Zinc	Taper et al 1980

[a] Fecal excretions exceeded intake for all treatment groups.

Table V
Apparent Absorption of Zinc by Human Subjects Consuming a Variety of Diets

Zinc				
Intake (mg)	Absorption (%)	Subjects	Dietary Variables	Reference
8–24	7.8–11.5	Adult females	Zinc	Taper et al 1980
4.6–14.6	7.1–62.1	Preadolescent girls	···[a]	Ritchey et al 1979
11.5–14.7	7.8–11.3	Adolescent females	Zinc	Greger et al 1978c
12.2–16.7	9.8–14.4	Adult males	Zinc	Spencer et al 1976
11	46	Adult females	···	King et al 1978
7.8–23.3	1.5– 2.4	Elderly adults	Zinc	Burke et al 1981

[a] Dietary variables ranged widely in the several studies included.

COPPER-ZINC INTERACTIONS AND ZINC UTILIZATION

Zinc and copper have been recognized as potential antagonists for a long time. Effects of zinc on copper utilization were observed in rats by Van Campen (1966). Klevay (1975) presented epidemiological and metabolic data in suggesting that an imbalance of zinc and copper intake is a major causative factor in cardiovascular disease. Strain et al (1975) reported that changes in the serum ratios of zinc and copper were caused by therapeutic dosages of zinc in a patient with classical acro-dermatitis enteropathia. Thus, the interaction between zinc and copper in the human is a cause for concern.

Taper et al (1981) found that dietary zinc did not influence copper retention. Copper retentions were similar in young adult females ingesting dietary zinc ranging from 8 to 24 mg/day. In those diets, zinc absorption ranged from 7.8 to 11.5% (Table V). In a summary of zinc absorption by preadolescent children, Ritchey et al (1979) found a range from 7.1 to 62.1%. These data were extracted from several studies, differing in protein source, protein level, and in other nutrients, but they suggest a reasonable estimate of zinc utilization in the growing child. Although the range is quite wide, the mean absorption was 27.0%, with most of the studies having zinc absorption from 17 or 18% to 30–34%.

The apparent absorption of zinc ranged from 7.8 to 11.3% in a study with adolescent females on a diet of commonly consumed foods (Greger et al 1978c). In adult males, Spencer et al (1976) reported absorptions from 9.8 to 14.4% when intakes were above 12 mg/day; at an intake of 6.5 mg, subjects excreted more zinc in the feces than they ingested. Using a tracer technique, King et al (1978) found zinc to be 46% absorbed. In a group of elderly subjects, apparent zinc absorption was 1.5 and 2.4% on intakes of 7.8 and 23.3 mg, respectively (Burke et al 1981).

A recent paper suggests that the relationship between zinc and copper may, in turn, affect the excretion of ascorbic acid in the human. Keltz et al (1978) found that supplements of zinc decreased the urinary excretion of ascorbic acid. This effect was opposite that for increased intakes of copper (Osaki et al 1964) and suggests that the zinc-copper antagonism can have a role in the use of other nutrients.

The absorption of zinc can be affected by numerous other dietary components, including protein, copper, phytates, calcium, and others. The mechanism for absorption is not well understood, but an active mechanism seems to be involved. Competition between copper and zinc for common binding sites within the intestinal mucosa may be the basis for the apparent antagonism.

Utilization of zinc is critical in certain population groups who have marginal intakes of this nutrient (Sandstead 1973a). Most investigators assume the absorption rate of zinc to be in the range of 20–30% (Burch et al 1975, Ritchey et al 1979, Sandstead 1973a), but in certain subjects and because of dietary variables, the absorption may be quite different (Table V). One controlling mechanism for zinc absorption may be the individual's need for zinc at that time. Need is important in the utilization of other nutrients, such as calcium and iron, and may partially explain the variation in zinc absorption rates.

FUTURE WORK

The few studies on human subjects seem to raise as many questions about as they provide insights into the interrelationship among protein, zinc, and copper. The possibility that these interactions are critical for human health should provide sufficient stimulation for additional investigations. Further research on the absorption mechanism and the development of more precise techniques for evaluating nutrient utilization, particularly the trace minerals, is essential to understanding. Although additional studies with animal models will be helpful in the elucidation of nutrient relationships, human studies are also required if we are to achieve adequate understanding of the nutritional needs of the human.

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