NUTRIENT INTERACTION ISSUES

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This presentation covers nutrient interactions, and the impact of these interactions, on nutrient bioavailability. Nutrient bioavailability includes two important components, absorption and utilization (1). Absorption is the process by which a nutrient moves from the intestinal lumen into the body. Until nutrients are absorbed, they are still outside of the body and are not available to perform their functions. Utilization of the absorbed nutrients includes transport to various parts of the body, assimilation by cells, and conversion to biologically active forms.

The major effects of nutrient interactions on bioavailablity and thus nutrient requirements, can be illustrated with zinc and iron. Daily endogenous losses of these minerals has been estimated at 2.2 mg of zinc, 1 mg of iron for men and postmenopausal women, and 1.5 mg of iron for women during their reproductive years. If zinc absorption were 40%, only 5.5 mg of dietry zinc per day would replace body losses, but if absorption were only 10%, 22 mg per day would be needed in the diet. One mg of zinc in the first diet would be equivalent to 4 mg in the second. Women would need about 6.5 mg of iron in a highly available (23% absorbed) form, but they would need 50 mg a day if the iron were in a poorly available form (3% absorbed). One mg of highly available iron would be equivalent to 6 mg of a poorly available form. The higher levels of both minerals are considered nearly impossible to obtain routinely in a diet without supplements. Thus, nutrient interactions which affect bioavailability adversely can impair nutritional status. Some of the examples of nutrient interactions I will discuss have been known for some time and are relatively well understood. However, most are newer research observations. The mechanisms of these interactions and their implications are not yet well understood.

Interactions can affect all of the major categories of nutrients; protein, carbohydrates, fats, vitamins, and minerals. Nutrients in each of these categories can also affect bioavailability of other nutrients. Interactions of nutrients with non-nutrient components of foods can alter availability. The effects of dietary fiber were discussed in the previous presentation. Other examples of non-nutrients which interact with nutrients include oxalate, avidin, and phytate. Oxalate combines with calcium to form an insoluble salt. The avidin in raw egg white renders biotin unabsorbable.

High levels of phytate have been known for some time to impair zinc availability in rats. However, the effect of phytate on zinc absorption in humans had not been confirmed until recently. In a study conducted in a human metabolic unit, young men consumed diets with no phytate or diets with sodium phytate added (2). Zinc absorption was determined with ^{67}Zn, a stable isotope of zinc. The results are shown in the table below.

Table 1. Zinc-phytate interaction

	Basal diet	Basal + Phytate
Dietary zinc (mg)	15	15
Absorption (%)	34.0	17.5
Total fecal zinc (mg)	12.6	15.6
Unabsorbed dietary zinc (mg)	9.9	12.4
Endogenous fecal zinc (mg)	2.7	3.2
Urinary zinc (mg)	0.5	0.4
Zinc balance (mg)	+1.9	-1.0

Average zinc absorption in the young men was over 30% with no phytate in the diet. When phytate was added, at a level resulting in a phytate:zinc molar ratio of 16, zinc absorption was cut in half. When the diet contained phytate, the men were in negative zinc balance, or were losing more zinc than they look in. Not only was zinc absorption impaired, but it appeared that losses of endogenous zinc also increased. The phytate added to the diet not only interfered with absorption of dietary zinc, but impaired reabsorption of endogenous zinc which had been excreted into the gastrointestinal tract. The impairment in zinc absorption is probably due to formation of an isoluble phytate-zinc complex, which can not be absorbed. In contrast, the addition of phytate neither impaired copper absorption nor increased copper losses (3). The effect of foods containing high levels of phytate on zinc absorption in humans is now being investigated. Animal studies suggest an additional variable may play a role in the zinc-phytate interaction. It appears that high levels of dietary calcium enhance the negative effect of phytate on zinc availability (1).

Nutrient-nutrient interactions may affect bioavailability in either a positive or negative way. These interactions may either enhance or inhibit nutrient absorption or utilization. High or low levels of one or more nutrients may affect bioavailability of other nutrients. Examples of enhancement and inhibition of bioavailability and the effects of very high and low levels of nutrients are described later.

The relative proportion of nutrients present in the diet may be the most important factor in determining the impact of nutrient interactions on nutritional status. Using the earlier example of the zinc-calcium-phytate interaction, a diet high in all three may not affect zinc status. Even though the phytate and calcium present form isoluble complexes with zinc, enough zinc is present in uncomplexed, absorbable form to supply the needs of the body. A diet with a marginally adequate level of zinc, but low in calcium and phytate would not produce insoluble zinc complexes, would not impair zinc absorption, and would not result in zinc deficiency. But if a diet with the same marginal level of zinc were high in phytate and calcium, nearly all the zinc might be complexed in an insoluble form and zinc deficiency could result.

There are several mechanisms in addition to complex formation which may be responsible for nutrient interactions. One is competition (4). Competitive interactions cause problems most often when one nutrient is present in high amounts. Competitive interactions are common between minerals. In the intestinal lumen, two nutrients could compete for a common binding ligand. A large excess of one would leave little binding ligand accessible to the other. The two nutrients could also compete for a common receptor site or carrier protein for entry into the intestinal mucosa, or compete for transport through the mucosal cell and into the blood stream. An interaction between iron and zinc has been studied by Solomon. The presence of high levels of iron appears to inhibit zinc absorption. Which type of competitive interaction is responsible for this altered zinc absorption is not yet known. Excess iron at the mucosal cell could prevent much of the zinc present from entering the cell. The interaction could occur within the mucosal cell. If iron status were adequate, so less iron entered the blood stream, the effect on zinc could be reduced. But if the excess iron produced a block to zinc, zinc status could still be affected. The interaction could present a problem when iron supplements are used, particularly in large amounts. Iron supplements are prescribed routinely for pregnant women, who may also have an increased need for zinc. Conclusive results on the effect of iron supplement on the zinc status of pregnant women have not yet been obtained.

An interaction between zinc and copper has been demonstrated. This interaction is also likely to be competitive. Copper deficiency, rarely observed in humans, was seen when very high levels of zinc were used therapeutically and copper intake was low (1).

Another mechanism for nutrient interactions is substitution. It is often a favorable type of interaction. In the presence of inadequate vitamin E, selenium is known to substitute for the vitamin in the inactivation of potentially harmful oxygen radicals. Folic acid supplements will prevent the anemia associated with vitamin B-12 deficiency. However, folate will not prevent the irreversible neurological damage resulting from vitamin B-12 deficiency. Observation of anemia leads to diagnosis of vitamin B-12 deficiency before irreversible neurological damage occurs, so the effect of folate is not considered advantageous in this situation. Another example of substitution is the substitution of tryptophan for niacin (5). Niacin deficiency will not result from a diet low in niacin, but with sufficient tryptophan, since tryptophan can be partially converted to niacin.

Function changes can result in nutrient interactions. For example, a deficiency of folic acid over a sufficient period of time results in changes in intestinal mucosa morphology. The intestinal villa become flattened, with less area. The function of the intestinal mucosa is impaired, resulting in inefficient absorption of most nutrients. Copper deficiency results in anemia in the presence of adequate iron. One hypothesis for the mechanism of this interaction is that copper deficiency produces a functional defect in the bone marrow. This defect impairs formation of red cells by the marrow. Some scientists think the mechanism responsible for anemia is a lack of copper oxidase activity which is necessary for iron transport.

Biochemical changes can result in interactions. Protein energy malnutrition (PEM) and other nutrient deficiencies can result in decreased levels of enzymes. These enzymes catalyze chemical reactions necessary for proper utilization of nutrients. Some of the deficiency symptoms may not be readily apparent in the presence of general malnutrition. During recovery from PEM, symptoms of deficiency of other nutrients may become apparent. Requirements are exaggerated by rapid growth during repletion which results in a greatly increased need for most vitamins and minerals. The xerophthalmia of viamin A deficiency, and even blindness, have been observed when PEM is treated with protein and calories, but no vitamin A supplements.

The chemical or biochemical interactions produced by a nutrient may be advantageous for one nutrient, but deleterious for another. Ascorbic acid supplements will enhance the absorption of iron, probably by assuring it is in the reduced, best absorbed form. However, recent work suggests that these same supplements may have an adverse effect on copper status. They may have reduced the oxidase activity of ceruloplasmin, a copper-containing enzyme (6). The effect of iron on copper absorption is being evaluated with a stable copper isotope.

Often the mechanism of an interaction is not understood. Some recently discovered interactions whose mechanisms are not yet understood are described below.

Recent research with laboratory rats in Beltsville suggests that diets high in a carbohydrate, fructose, exaggerate the effect of copper deficiency (7). The impact of this interaction on copper status in humans is under investigation.

A recent experiment at the Western Human Nutrition Research Center was conducted to study the effects of vitamin B-6 deficient diets on vitamin B-6 status and also on the metabolism of several minerals. The study revealed interactions between vitamin B-6 and zinc and between vitamin B-6 and calcium (8, 9). When the diet was deficient in vitamin B-6, zinc absorption and retention were higher than usual. With higher levels of B-6, zinc absorption was lower and zinc retention declined. While zinc absorption and retention were higher with low vitamin B-6, the additional amount of zinc did not appear to be available for the body to use. The plasma level of zinc declined significantly with low B-6, then increased as vitamin B-6 was added to the diet. These results suggest that the enhance absorption was accompanied by impaired utilization.

Another type of effect was observed with calcium. Though calcium balance did not change markedly, urinary calcium fell to very low levels during B-6 depletion, suggesting a change in calcium metabolism.

In the above study, as in other studies conducted earlier, we used stable isotope of minerals as tracers to obtain definitive information on mineral absorption. Stable isotopes are valuable new tools to nutritionists, which allow the metabolic fate of minerals to be followed without exposure to radioactivity. They can therefore be used safely in pregnant women and in children. Interactions between several minerals can be determined simultaneously.

The importance of nutrient interactions on bioavailability suggest that information on the nutrient content alone of the diet is not sufficent. Requirements vary depending on bioavailability. The addition of bioavailability factors to recommended intakes of nutrients or to nutrient data bases would be advantageous. Enough data are available on some nutrient interactions to introduce such factors. Dietary iron absorption can be calculated based on five factors: total iron, heme iron, non-heme iron, ascorbic acid, and amount of meat (5). Tryptophan can be expressed in niacin equivalents (5). Sixty mg of tryptophan is equivalent to 1 mg of niacin. Evidence in rats and now in humans suggests that a phytate:zinc ratio in excess of 20 adversely affects zinc status in rats (10). A ratio of 16 impaired zinc absorption in humans. A zinc:copper ratio which exceeds 10 may adversely affect copper status (4). These examples, as well as most other interactions become a problem when a nutrient or other dietary component is present in unusually high or low amounts.

Insufficient data are currently available to establish bioavailability factors for most nutrient interactions. In addition, as more data become available, an approach to introducing and applying these factors must be agreed upon and consistent to avoid confusion.

New techniques are available and others are being developed to facilitate evaluation of nutrient interactions. These include use of stable isotopes or radioactive tracers to determine mineral absorption and utilization; the slope-ratio assay, often used in laboratory animals; and identification of sensitive indicators of nutritional status, so minor changes in status can be detected.

As the data become available on interactions and bioavailability, I urge those developing nutrient data bases to work toward taking bioavailability factors into account in nutrient composition data.

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