ZOOMING IN ON ZINC


PEGGY GREB (K9832-1)

Zinc likely affects every general function in our bodies. Discoveries from scientists at the ARS Western Human Nutrition Research Center at Davis, California, are unlocking new and important information about this essential mineral.

Some of the findings may lead to a new test that would help predict an individual's ability to use zinc. Other results may modify today's use of iron supplements during pregnancy and breast-feeding. The method most commonly used to check body levels of zinc—a test of serum, from blood—isn't sensitive enough to detect a mild deficiency.

"Mild zinc deficiency may exist in the United States among otherwise healthy infants, toddlers, preschool children, pregnant and lactating women, and seniors," says ARS research

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In a study of how zinc levels between cells are regulated, geneticist Liping Huang studies ZnT transporter proteins in normal rat kidney cells.

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Zinc is a critical part of the mechanism that turns genes on and off. "Genes that are turned on prompt the body to make proteins, enzymes, or hormones; genes that are turned off do not," she says. "In a healthy body, at any given time, some genes are turned on and some are turned off. Without zinc, some genes won't turn on and off properly. Zinc is also a very important part of many enzymes needed for healthy skin and properly functioning immune, nervous, and digestive systems."

Transporter Proteins Move Zinc

To get zinc from foods that we eat into the cells that need it, the body relies on proteins known as zinc transporters. These specialized proteins also take excess zinc out of cells to prevent toxic buildup. Zinc is absorbed into the blood from food in the small intestine. Next, zinc circulating in the blood needs to be transported into cells.

Huang is investigating a family of zinc transporters called ZnTs. "We discovered and characterized—in mice—the function of ZnT4, a transporter that deposits zinc into milk in the mammary glands of mice. In humans, zinc is already known to be essential for proper growth during infancy. So it makes sense that ZnT4 would be found in abundance in the cells of the mammary gland," says Huang.

"Our work suggests two other roles for this transporter protein. First, ZnT4 may move zinc out of the small intestine into the bloodstream. Second, ZnT4 may help store zinc in the cells of the prostate gland," she notes. "The prostate finding is of special interest. Other scientists' studies indicated that men with prostate cancer have dramatically lower levels of zinc in their cancerous cells than their cancer-free counterparts," says Huang. "Healthy men, in fact, have more zinc in their prostate than anywhere else in their bodies. These results suggest that zinc supplements might protect men against prostate cancer." In the United States, prostate cancer is the second leading cause of cancer deaths among men.

Genes: An Ideal Basis for a Test?

Now Huang is hot on the trail of what she thinks are three additional ZnTs. The genetic material the body uses to create transporter proteins might prove ideal as the basis for a new and improved test of zinc in people.

"The amount of a particular zinc transporter protein that an individual produces is partially controlled by genes," Huang explains. "An indirect way to measure the protein is to measure levels of genetic material called messenger RNA, or mRNA. Zinc transporter genes have the instructions the body needs in order to create zinc transporter proteins. The mRNA carries out those instructions." Levels of mRNA may thus be a good indicator of an individual's ability to process zinc.

The goal is a sensitive, accurate test that is also inexpensive, rapid, reliable, and reproducible. Says Huang, "An ideal test could be administered in your doctor's office, with the results ready before you leave. Today, no test of zinc levels in the body meets all of those criteria.

"Zinc is unusual in that it seems to have a large array of transporter proteins to shuttle it in and out of cells," she says. That may be why there are very few diseases or disorders related to zinc imbalances. In contrast, copper and iron, for example, apparently have fewer transporter proteins than zinc. "Not surprisingly," notes Huang, "there are several diseases caused by imbalances of copper and iron."

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This woman is one of 32 volunteers participating in a nutrition study to evaluate the effect of iron supplements on zinc during pregnancy and early lactation.

In her new studies, Huang says she "wants to help develop new national guidelines for zinc intake in food—or in supplements—for different age groups." She will also study whether zinc transporter proteins could prevent the proliferation of prostate cancer cells.

PEGGY GREB (K9827-1)

Registered nurse Earl Laih prepares to inject a pregnant volunteer with a trackable form of zinc. This method lets nutrition scientist Janet C. King (center) measure how much zinc the body uses.

Zinc's Interactions

Meanwhile, a puzzling interaction of iron and zinc is the focus of research by Janet C. King, director of the Western Human Nutrition Research Center. "In a study we did some years ago on the zinc requirements of pregnant women," says King, "we were very surprised to find that iron supplements taken with a meal inhibit zinc uptake."

This finding was important for two reasons. First, iron supplementation is common for women: Iron supplements are prescribed routinely worldwide for fetal growth and also for milk production during breast-feeding. Second, these iron supplements are apparently interfering with zinc during these critical times.

King conducted the study with 13 pregnant women, aged 22-40. "We followed their zinc uptake and use from the beginning of pregnancy through the first 3 months of breast-feeding," she says. Four of these women were also taking prenatal iron supplements of at least 100 milligrams a day under the orders of their doctors. That's in contrast to the Recommended Dietary Allowance of 18 milligrams for women of childbearing age.

At regular intervals throughout the study, volunteers were given an easily detected form of zinc in a beverage and another as an injection. These trackable kinds of zinc known as stable isotopes occur naturally. The amounts of the stable isotopes were measured in blood and urine samples collected a few hours later. From these measurements, scientists determined the amount of the zinc that each volunteer absorbed and used. Of all the volunteers, only the four who took the prescribed iron supplements didn't show any increase in zinc absorption from the zinc supplements during the early months of breast-feeding.

King and her colleagues reported their findings in the *American Journal of Clinical Nutrition* and other scientific publications.

King is now working on a follow-up study with pregnant volunteers aged 22-40 years. Each volunteer receives 15 milligrams of zinc from food and supplements every day. Some volunteers receive prenatal iron supplements of 65 milligrams a day.

King notes, "Some take their iron supplement in the morning, with their breakfast, and others at bedtime, without a meal. We want to determine whether zinc uptake is affected by taking the iron supplement at a particular time of day and with or without a meal."

Concepcion Mendoza, a postdoctoral fellow in King's laboratory, is leading this study. Fernando Viteri, a faculty member at the University of California at Berkeley, is also a collaborator.

Studies in Brazil and South Korea are providing more information about the interplay of zinc and iron or zinc and phytate—a form of phosphorus. Center scientists collaborated in these investigations.

"More than half of the people in the world don't get enough zinc," King points out. "In countries where grains or legumes such as beans make up a significant component of the day's meals, zinc deficiency is a special concern. That's because the zinc in grains and legumes is less available to the body than the zinc in beef, pork, and dark-meat chicken."

The Brazilian experiment looked at the zinc used by 15 pregnant women in Rio de Janeiro. The volunteers, aged 21-34, were given daily iron supplements of 50 or 100 milligrams for most of the last half of pregnancy.

Volunteers ate their normal foods, including meats. Findings showed that the 100-milligram iron supplements interfered with the uptake of zinc but that the 50-milligram iron supplements did not.

Carmina L. Vargas Zapata and Carmen M. DonAngelo of the Federal University of Rio de Janeiro conducted the research.

Zinc and Phytate Link Probed

A study in South Korea is exploring the interaction of phytate and zinc in the body. Phytate is an essential nutrient. "The phytate in grains such as rice and corn is thought to interfere with the uptake and use of zinc," says Huang, a collaborator in the study.

Scientists are working with groups of female volunteers—ages 18-24 and 60-70. In the three-phase experiment, the researchers are altering the relative amount of phytate to zinc the volunteers consume. In the first phase, the women eat familiar fare, predominantly rice and vegetables. This diet provides about 20 parts phytate to 1 part zinc.

PEGGY GREB (K9829-1)

Zinc absorption could be affected by iron supplements. Nutrition scientist Concepcion Mendoza (left) instructs a study volunteer on when to take her iron supplements.

In the second phase, the volunteers eat foods with less phytate, resulting in a ratio of about 8 parts phytate to 1 part zinc. That's about the ratio of phytate to zinc that Americans consume. The scientists lowered the phytate consumption by providing white rice in place of higher phytate brown rice.

For the third phase of the study, the volunteers eat their familiar foods, including high-phytate rice. But they also take a 25-milligram zinc supplement each day. This regimen again gives them a ratio of about 8 parts phytate to 1 part zinc.

Hee Young Paik of Seoul National University is directing the study and providing blood samples from the volunteers to Huang, at her Davis lab, for analysis of zinc transporters.

Is an mRNA-based Zinc Test Ahead?

Huang is looking at the levels of mRNA—created from zinc transporter genes—in the samples. She wants to see which, if any, of the transporters predict an individual's zinc uptake and use. If there is a correlation between zinc use and the level of zinc transporter mRNA, the mRNA could become the basis of a better test for the body's use of zinc.

She is also determining whether the levels of ZnT proteins vary with age. "If there are significant differences in the way we process zinc as we age," Huang says, "then the dietary allowance of zinc may need to be adjusted."

Scientists have known for decades that zinc is essential for human health. Foods that are good sources of zinc include beans, whole grains, shellfish, red meat, and dark-meat poultry.—By **Marcia Wood,** ARS.

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