Zinc and Intestinal Function

Carol E. Semrad, MD

Address
Columbia University College of Physicians and Surgeons, Physicians and Surgeons Building, 10-508, 630 West 168th Street, New York, NY 10032, USA.

Current Gastroenterology Reports 1999, **1**:398–403
Current Science Inc. ISSN 1522-8037

Zinc is an abundant trace element in the human body that is essential for growth and development and immune function. It is important for the formation of biomembranes and zinc finger motifs found in DNA transcription factors and has catalytic function in metalloenzymes. The intestine is the site of zinc absorption and the major route of zinc excretion. Dietary inadequacy or conditions that decrease zinc absorption or increase its losses from the gastrointestinal tract, urine, or skin may quickly cause zinc deficiency due to the limited availability of rapidly exchangeable zinc pools in the body. Diarrhea is both a sign and a cause of zinc deficiency. The mechanism by which zinc deficiency causes diarrhea is not known. At this time, there is no readily available sensitive test for the detection of zinc deficiency, and therefore clinical suspicion remains the main mode of detection. In some individuals with diarrheal disease, zinc supplementation lessens diarrhea. Those receiving prolonged supplemental zinc therapy need to be monitored for copper deficiency.

Introduction

Zinc is a trace element that is essential to all forms of life. Among the trace elements, it is second in abundance to iron in the body. Unlike iron and copper, zinc cannot be oxidized or reduced in biologic systems. Rather, in its stable divalent cation form in the body, zinc complexes with nitrogen, sulfur, and oxygen molecules on the side chains of amino acids to form a stable tertiary conformation and thereby confers protein structure and in some cases catalytic function. For example, there are several hundred zinc metalloenzymes identified to date. In some, such as carbonic anhydrase, carboxypeptidases, and alkaline phosphatase, zinc is directly involved in enzyme catalysis. In others, such as transcarbamylases and alpha-amylase, zinc is necessary to maintain protein structure. In still others, such as aminopeptidases, zinc regulates enzyme activity. Zinc also plays an important role in gene expression. Some transcription factors, steroid and thyroid hormone receptors, and RING (really interesting new gene) finger proteins (*eg*, breast cancer gene *BRCA1*) have two or more zinc finger motifs that bind to DNA. The most common zinc finger motif in transcription factors consists of a short sequence of amino acids (about 25) that contains two cysteine and two histidine residues that bind to a zinc atom. Tandem repeats of this sequence determine the number of zinc fingers formed. The zinc atoms of zinc finger proteins are critical for folding into the finger-like conformations that complex with DNA.

Overall, hundreds of zinc-dependent proteins participate in intermediary metabolism, DNA and RNA synthesis, gene expression, and hormonal homeostasis. Given the vast number of biochemical pathways involved, manifestations of zinc deficiency are often protean (such as anorexia, growth failure, skin rash, and neuropsychiatric problems) and difficult to distinguish from other vitamin, mineral, or protein-calorie deficiencies.

Zinc Food Sources and Bioavailability

Meats, shellfish (especially oysters), and whole grains are the richest source of zinc in the diet. Vegetarian diets that consist predominantly of fruits and vegetables have a low zinc content. Diets containing cereal as the main staple are high in phytates (inositol hexaphosphates), which chelate zinc and decrease its bioavailability. Adults ingest about 8 to 15 mg of zinc each day in their diet; the elderly, on average, ingest less. The recommended daily allowance of zinc is 15 mg for men and 12 mg for women. Breast milk is a rich source of zinc. Infants are at risk for zinc deficiency at the time of weaning, when dietary intake may be inadequate, and in rare inherited diseases of impaired zinc excretion in breast milk or impaired zinc intestinal absorption.

A number of factors affect the bioavailability of zinc. Phytates, high dietary fiber, and oxalate form insoluble complexes with zinc and decrease its absorption. A number of ions (Ca^{2+}, Fe^{2+}, Cd^{2+}, and Sn^{2+}), when given in oral solutions, compete with Zn^{2+} for uptake in the intestine. Elemental calcium supplements have been reported to depress plasma zinc concentrations in humans [1]. The clinical significance of this finding is unclear, as manifestations of zinc deficiency did not occur in the reported study, and balance studies show that calcium supplementation has no effect on zinc absorption or excretion [2,3]. Iron decreases $^{65}ZnCl_2$ absorption in whole-body studies [4,5]. However, iron does not decrease zinc absorption when ^{65}Zn is administered as part of a test meal [5]. This finding suggests

that supplemental iron does not interfere with zinc absorption from food. Copper does not decrease zinc absorption in the intestine, but zinc decreases copper absorption and causes copper deficiency. Factors that enhance zinc absorption include cysteine, histidine, and organic acids (citric, acetic, and butyric acid). The mechanism by which these ligands enhance zinc absorption is not known.

Zinc Absorption, Transport, and Body Pools

Zinc is absorbed predominantly in the duodenum and jejunum. Absorption decreases with age; however, zinc excretion also decreases with age. Consequently, overall zinc balance is not affected [6]. Zinc in the intestinal lumen comes from two sources, the diet (about 10 mg) and digestive juices (about 3 mg). Pancreatic juice has the highest concentration of zinc and may contain a ligand that promotes absorption of zinc in the intestine. The predominant forms of zinc (free, ligand-bound, and salt) and their concentrations in the intestinal lumen after a standard diet have not been measured. The mechanism of zinc transport in intestinal epithelial cells is just beginning to unfold (Fig. 1). A proton-coupled divalent cation transporter (DCT1) that has substrate specificity for Fe^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, and Pb^{2+} has been identified in the brush-border membrane of the proximal small intestines of rats [7••]. It is not known to what extent this transporter or other processes, such as internalization of zinc bound to extracellular ligands or diffusion of the uncharged zinc species (*eg*, $ZnCl_2$), contributes to zinc uptake in the intestine [8]. Development of a specific DCT1 inhibitor will help resolve this question.

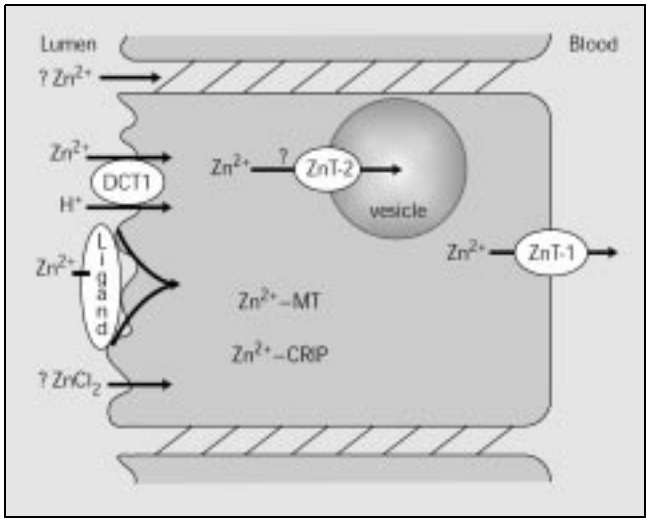

Figure 1. Proposed mechanisms for zinc uptake and transport in mammalian small intestine. CRIP—cysteine-rich intestinal protein; DCT1—divalent cation transporter; Ligand—histidine, cysteine, and others. MT—metallothionein; Znt—zinc transporters.

Once taken into intestinal epithelial cells, zinc binds to metallothioneins or other intracellular proteins such as cysteine-rich intestinal proteins and is also transported into organelles and across the basolateral membrane into the blood. The zinc transporter ZnT-1 [9], a member of the family of zinc/cadmium/cobalt transport proteins that protects cells from metal toxicity, has been localized to the basolateral membrane of the intestinal epithelial cells of rats and is a likely candidate for zinc export from cells [10••]. Another zinc transporter, ZnT-2, has been localized to intracellular vesicles in rat kidney cells [11••]. ZnT-2 may be important in transporting zinc into vesicles, thereby protecting cells from zinc toxicity.

Zinc is exported from the basolateral membrane of intestinal epithelial cells into the mesenteric circulation, where it binds to plasma proteins, predominantly albumin. Protein-bound zinc is then transported via the portal circulation to the liver, where it is taken up and released and then distributed to other tissues. In the serum, zinc is bound predominantly to albumin (about 85%), and to a lesser extent to α2-macroglobulin (about 16%) and amino acids (1% to 2%) [12]. Changes in the circulating concentrations of these proteins, especially albumin, can dramatically alter plasma zinc levels.

There are no body stores of zinc. Inadequate zinc absorption causes an immediate decrease in protein turnover and cell growth to preserve zinc body pools, which may rapidly result in signs of zinc deficiency. Muscle may be broken down to maintain plasma zinc levels with inadequate zinc absorption.

Zinc Excretion

The intestine is the major route of zinc excretion. Stool losses arise from unabsorbed zinc (dietary and endogenous) and zinc present in sloughed epithelial cells. Smaller amounts of zinc are lost in urine, desquamated skin, hair outgrowth, semen, and menses. The amount of zinc lost in the stool ranges from 1 mg/d on a low-zinc diet to 5 mg/d on a high-zinc diet. Higher amounts of zinc are lost in individuals with increased gastrointestinal fluid losses (Fig. 2) [13]. Zinc can also be lost in excess amounts in the urine. Increased urinary excretion of nitrogen, which happens in stress (infection, trauma, major surgery, or burns), is associated with increased urinary loss of zinc. This loss may be caused by protein catabolism. High concentrations of amino acids in parenteral nutrition increase the fraction of amino acid–bound zinc filtered by the kidneys and result in increased loss of zinc in the urine.

Conditions Predisposing to Zinc Deficiency

A number of diseases, drugs, dietary substances, and physiologic conditions predispose individuals to zinc deficiency. These are summarized in Table 1 and in the text below.

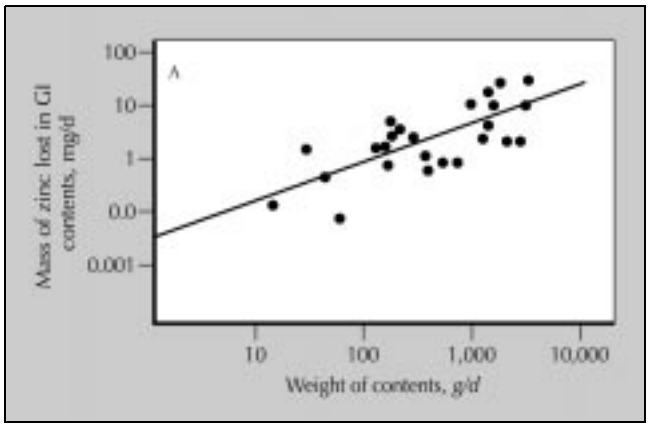

Figure 2. Log–log plot of regression analysis of the amount of zinc lost in gastrointestinal contents and the weight of the contents. *From* Wolman *et al*. [13]; with permission.

Table 1. Conditions Predisposing to Zinc Deficiency

Malabsorptive diseases (Crohn's disease, short-bowel syndrome, HIV disease, celiac disease, intestinal bypass)
Enterocutaneous fistula
Pancreatic cutaneous fistula
Chronic diarrhea
Malnutrition
Alcoholism
Cirrhosis
Pancreatic insufficiency
Diabetes
Anorexia nervosa
Cystic fibrosis
Extensive burns
Drugs/dietary substances (phytates, high dietary fiber, penicillamine, sodium valproate, diethylene triamine penta-acetate)
Nephrotic syndrome
Pica
Parenteral nutrition
Sickle cell anemia
Acrodermatitis enteropathica
Pregnancy

Dietary deficiency

Dietary inadequacy is probably the most common cause of zinc deficiency worldwide. Among the factors that predispose individuals to zinc deficiency are cereal-based diets high in phytates, malnutrition, alcoholism, anorexia nervosa, and aging. In alcoholics, zinc deficiency may be caused by a combination of decreased zinc intake and increased zinc losses in the urine, especially in individuals with liver disease. There are also physiologic states in which zinc requirements are increased. These include pregnancy, lactation, and infant and childhood growth.

Zinc deficiency has been reported in individuals receiving parenteral nutrition. Initially, this was due to failure to include zinc in the solution. However, even when zinc is added to parenteral solutions, deficiency can occur through inefficient delivery to tissues or increased losses from the body secondary to the underlying disease that warranted parenteral nutrition. Those malnourished before the initiation of parenteral nutrition may be more prone to zinc deficiency.

Malabsorptive diseases

A variety of diseases (intestinal and extraintestinal), drugs, dietary products, and procedures (such as intestinal resection or bypass surgery) cause nutrient malabsorption. Diseases that most commonly cause zinc deficiency are Crohn's disease, short-bowel syndrome, HIV disease, celiac disease, and enterocutaneous fistulae. Pancreatic insufficiency may also cause zinc deficiency. The etiology is poorly understood.

Diarrheal diseases

The association between zinc deficiency and acute diarrheal diseases has been best studied in children. Every year, about 3 million children worldwide die of diarrheal diseases despite widespread use of oral rehydration solutions. Children with malnutrition have the highest morbidity and mortality rates and are more likely to have prolonged and more frequent episodes of diarrhea. They are also more likely to be zinc deficient due initially to decreased dietary intake and then to increased losses in the stool. Results from studies conducted in a variety of countries suggest that zinc supplementation lessens the duration and frequency of diarrheal episodes in children, particularly those who are malnourished [14,15]. A recent large double-blinded, randomized, controlled study in India showed a similar reduction in the duration (23% reduction in the risk of continued diarrhea on a given day) and severity (39% reduction in the mean number of watery stools per day) of diarrhea in children supplemented with zinc [16•]. Zinc supplements were started within 3 days of the onset of diarrhea. The best responses were observed in children with stunted growth. Equivalent studies have not been conducted in adults with acute diarrheal diseases.

Chronic diarrhea caused by infection, inflammatory bowel disease, hormone-producing tumors, and other conditions causes increased intestinal zinc losses that may result in zinc deficiency. Zinc deficiency may then worsen the diarrhea.

Genetic diseases

Only a few inherited disorders of zinc transport have been reported in mammals. Acrodermatitis enteropathica is a rare inherited autosomal recessive disease caused by decreased intestinal zinc absorption [17]. Infants present with growth retardation, dermatitis, alopecia, and diarrhea between three and 18 months of age. Death occurs unless zinc is supplemented in the infant's diet. The gene responsible for the disorder has not yet been identified. Plasma zinc and alkaline phosphatase levels are characteristically very low. Pharmacologic doses of oral zinc result in rapid improvement of symptoms, presumably due to the absorption of zinc by diffusion or another alternative pathway.

Zinc deficiency has been reported in infants of lactating women who fail to secrete zinc into breast milk but otherwise have a normal zinc status. Pharmacologic doses of zinc do not correct the low zinc concentration in mother's milk. Consequently, these infants must be supplemented with zinc. An animal model for this disease is the lethal milk (*lm/lm*) mouse [18]. Offspring of *lm/lm* mice have stunted growth and dermatitis. They die unless fostered by normal mothers or given zinc supplementation. Unlike the human disease, zinc supplementation to *lm/lm* mothers increases their milk zinc concentration and can also restore health to the offspring. The lethal milk gene was recently cloned and found to be a zinc transporter (ZnT4) that is expressed in mammary epithelia and in the brain and has homology to ZnT2 and ZnT3 [19••]. Affected offspring with the *lm/lm* genotype also develop zinc deficiency in adult life, suggesting that ZnT4 may be involved in intestinal transport of zinc as well.

Clinical Manifestations of Zinc Deficiency

The signs of pure zinc deficiency have been best described in individuals with acrodermatitis enteropathica and in those receiving parenteral nutrition solutions that lack zinc (Table 2). These individuals present with growth failure or weight loss, skin rash, diarrhea, hair loss, impaired taste, visual disturbances, behavioral disorders, recurrent infections, and impaired wound healing. The rash is characteristically an erythematous, scaly, pustular dermatitis found around the mouth or on the nasolabial folds, arms, or groin. A bullous dermatitis can be seen with severe deficiency. Even mild zinc deficiency has been associated with growth retardation in children [20]. Most cases of zinc deficiency occur in the setting of malnutrition, alcoholism, or intestinal malabsorptive diseases. In these cases, signs of zinc deficiency such as skin rash, growth failure, recurrent infections, and poor wound healing are difficult to distinguish from signs of protein–calorie malnutrition and other vitamin and mineral deficiencies.

Table 2. Clinical Manifestations of Zinc Deficiency

Growth retardation
Skin rash
Diarrhea
Hypogeusia
Behavioral changes (apathy, irritability, depression, impaired cognition)
Hair loss
Ataxia
Impaired wound healing
Hypospermia
Night blindness
Corneal edema/opacities
Glucose intolerance

How Does Zinc Deficiency Cause Diarrhea?

It has been known for many years that zinc deficiency causes diarrhea. The mechanism remains unknown. The histology of the small intestine in humans and animals with zinc deficiency is for the most part normal. Disaccharidase activity in zinc-deficient rats is normal when the overall decrease in mucosal protein content is taken into account [21]. Intestinal permeability is not altered in rats with select dietary zinc deficiency [22]. However, zinc deficiency may adversely affect intestinal permeability in malnourished animals. Malnutrition causes increased intestinal permeability to small solutes in guinea pigs [23]. This abnormality can be prevented by treating malnourished animals with pharmacologic doses of zinc.

Intestinal transport abnormalities have been reported in zinc-deficient animals. Sodium and water transport is decreased in the small intestine and colon of zinc-deficient rats when compared to controls, but glucose transport remains normal [24]. Recent studies show that uroguanylin message RNA is upregulated in zinc-deficient rats [25•], evidence that may link this hormone to the sodium and water transport abnormalities observed. Uroguanylin, a natural ligand for the *Escherichia coli* stable toxin (STa) receptor (guanylate cyclase GC-C) [26], has been shown to elevate cyclic GMP concentrations in intestinal epithelial cells, to inhibit sodium and chloride absorption, and, to a lesser extent, to stimulate chloride secretion [27]. Uroguanylin has been localized to enterochromaffin cells in the proximal small intestine [28]. These cells have the capability of secreting their hormone products basolaterally or apically. It is not clear why zinc deficiency would cause upregulation of a secretory hormone that may promote zinc loss from the intestine and perhaps from the kidney, where activation of GC-C results in a natriuresis. Normally, the body conserves zinc when its absorption decreases. Measurement of uroguanylin protein levels in zinc-deficient animals and humans is necessary to determine the role of uroguanylin in zinc deficiency–related diarrhea. Impaired immune function in the gut may play a role in the etiology of diarrhea due to zinc deficiency, but there are no studies to support this hypothesis.

Assessment of Zinc Status

No sensitive test exists for the detection of zinc deficiency (Table 3). A number of factors affecting zinc concentration in the blood make interpretation of plasma and serum zinc levels difficult. Severe zinc deficiency, along with a number of other conditions (*ie*, infection, stress, steroids, pregnancy, and hypoalbuminemia), decreases plasma and serum zinc levels. Hemolysis, contamination with zinc during blood collection, and fasting may increase plasma and serum zinc levels. For these reasons, plasma and serum zinc levels are a poor indicator of zinc status in the body. Radioisotope tracer studies are the best measure of zinc status, but they require expertise and radioactive

Table 3. Laboratory Assays for Assessing Zinc Status

Plasma and serum zinc concentration*
24-hour urinary zinc
Erythrocyte zinc content
Leukocyte zinc content
Hair zinc content
Saliva zinc concentration
Nail zinc content
Rectal mucosal zinc content
Serum alkaline phosphatase*
Serum and erythrocyte metallothionein†
Erythrocyte ^{65}Zn uptake study
^{67}Zn, ^{68}Zn, or ^{70}Zn stable-isotope study†
^{65}Zn, ^{69m}Zn, or ^{63}Zn radioisotope whole-body study‡

*Useful measure in individuals receiving parenteral nutrition.
†Experimental tests under development.
‡Best test of zinc status. Utility limited by cost, availability, and requirement of radioactive isotopes.

material, which limits their use. Tests for zinc deficiency that hold the most promise include plasma and erythrocyte metallothionein concentrations and stable isotope studies. These studies are experimental and require further validation before they can be put into general use. Low serum alkaline phosphatase levels are associated with hypozincemia and zinc deficiency. Measurements of alkaline phosphatase levels have been used to screen children for zinc deficiency and to follow zinc status in those on parenteral nutrition [29,30]. This test is inexpensive and easy to follow with zinc repletion. Functional tests of zinc status such as dark adaptation, taste acuity, skin testing, and measurements of wound healing lack specificity. In individuals predisposed to zinc deficiency, low blood zinc or alkaline phosphatase levels may be helpful in the diagnosis of zinc deficiency. However, until a sensitive test is developed to assess zinc status, recognition of those at risk or with clinical manifestations of zinc deficiency remains the mainstay in diagnosis.

Intestinal Diseases and Zinc Treatment

Individuals with chronic diarrhea or malabsorptive diseases should receive zinc supplementation to prevent deficiency. Zinc should be supplemented according to the amount lost in diarrhea or intestinal effluent. In adults, diarrhea or ileostomy effluent contains about 17 mg of zinc per kg [13]. Proximal small intestinal fluid effluent via fistula or stoma contains about 12 mg of zinc per kg [13]. Failure to supplement zinc may result in worsening of intestinal outputs caused by zinc deficiency. Zinc supplementation should also be considered in individuals who are at risk for zinc deficiency and develop diarrhea (Table 1). Oral multivitamin and mineral preparations usually contain 10 to 20 mg of elemental zinc. Zinc sulfate, 220 mg, contains 50 mg of elemental zinc. For adults receiving parenteral nutrition with gastrointestinal outputs of less than 300 g/d, 3 to 5 mg of zinc is usually given [13]. In patients with larger gastrointestinal fluid losses, higher amounts of zinc should be added to the solution, typically 10 to 25 mg/d. Even with zinc supplementation, those at risk should be monitored for signs of zinc deficiency because plasma and serum zinc levels do not necessarily reflect zinc status.

In children, most studies support a role for zinc in the treatment of acute diarrheal diseases, particularly in those who are malnourished. In the largest study conducted, children were treated with 20 mg of elemental zinc (as zinc gluconate) once a day. However, general use of zinc in the treatment of childhood diarrheal diseases is not recommended until the optimal dose and form (elemental or as a multimineral) of zinc and the timing, duration, and complications accompanying treatment have been established. It is not known whether prophylactic zinc supplements or foods fortified with zinc decrease the number of diarrheal episodes in children. The role of zinc in the treatment of acute diarrheal diseases in adults has not been studied.

Complications of Zinc Treatment

Copper deficiency is the main complication of prolonged zinc therapy. Zinc inhibits copper absorption in the intestine. One theory holds that zinc increases synthesis of intracellular metallothioneins that have a higher affinity for copper than zinc. Copper bound to metallothioneins is then lost from the gastrointestinal tract in sloughed epithelial cells. Zinc may also compete with copper for uptake by DCT1, thereby decreasing copper absorption. Doses of zinc as low as 18 mg/d interfere with copper absorption [31]. Malnourished individuals with marginal copper status may be at highest risk for zinc-induced copper deficiency. The ability of zinc to inhibit copper absorption is so effective that zinc is the first line of treatment in individuals with Wilson's disease, a hereditary disease of excess copper accumulation in the body.

Zinc has minimal toxicity when compared to other heavy metals. Elemental zinc doses of 100 to 200 mg/d have been reported to decrease serum high-density lipoprotein concentrations, depress immune function, and cause clinical signs of copper deficiency (such as anemia, neutropenia, and hair depigmentation) [32]. Doses higher than 200 mg/d frequently cause nausea and vomiting. Acute intoxication, arising from doses higher than 500 mg, can cause epigastric pain, nausea, vomiting, and lethargy.

Conclusions

Zinc deficiency is probably more common than reports would indicate. This may be due to the lack of a sensitive assay for its detection and the lack of recognition for signs of zinc deficiency. Diarrheal and malabsorptive diseases are important causes of zinc deficiency. In such cases, zinc

deficiency may then worsen diarrhea. Supplemental zinc treatment is not without complications, and it should be targeted to those individuals with signs of zinc deficiency or those who are predisposed to deficiency. Until the role of zinc in the treatment of acute diarrheal diseases is further clarified, zinc supplementation should not be routinely given. In those individuals who require long-term zinc supplementation, intermittent measurements of plasma zinc levels and monitoring for signs of both zinc and copper deficiencies are recommended.

References and Recommended Reading

Recently published papers of particular interest are highlighted as:

- • Of importance
- •• Of major importance

1. Argiratos V, Samman S: **The effect of calcium carbonate and calcium citrate on the absorption of zinc in healthy female subjects.** *Eur J Clin Nutr* 1994, **45:**198–204.
2. Snedeker SM, Smith SA, Greger JL: **Effect of dietary calcium and phosphorous levels on the utilization of iron, copper, and zinc by adult males.** *J Nutr* 1982, **112:**136–143.
3. McKenna AA, Ilich JZ, Andon MB, *et al.*: **Zinc balance in adolescent females consuming a low- or high-calcium diet.** *Am J Clin Nutr* 1997, **65:**1460–1464.
4. Sandstrom B, Davidsson L, Cederblad A, *et al.*: **Oral iron, dietary ligands and zinc absorption.** *J Nutr* 1985, **115:**411–414.
5. Valberg LS, Flanagan PR, Chamberlain MJ: **Effects of iron, tin and copper on zinc absorption.** *Am J Clin Nutr* 1984, **40:**536–541.
6. Turnlund JR, Durkin N, Costa F, *et al.*: **Stable isotope studies of zinc absorption and retention in young and elderly men.** *J Nutr* 1986, **116:**1239–1247.
7. •• Gunshin H, Mackenzie B, Berger UV, *et al.*: **Cloning and characterization of a mammalian proton-coupled metal-ion transporter.** *Nature* 1997, **388:**482–488.

This paper reports cloning and characterization of DCT1, the first mammalian divalent cation uptake process identified. DCT1 is upregulated by iron and shows substrate specificity for zinc as well as iron.

8. Reyes JG: **Zinc transport in mammalian cells.** *Am J Physiol* 1996, **270:**C401–410.
9. Palmiter RD, Findley SD: **Cloning and functional characterization of a mammalian zinc transporter that confers resistance to zinc.** *EMBO J* 1995, **14:**639-649.
10. •• McMahon RJ, Cousins RJ: **Regulation of the zinc transporter ZnT-1 by dietary zinc.** *Proc Natl Acad Sci U S A* 1998, **95:**4841–4846.

The authors show that ZnT-1 is localized to the basolateral surface of intestinal villous epithelial cells using immunofluoresence. Whereas an oral load of zinc increased intestinal ZnT-1 mRNA levels, protein expression was not increased (the reverse was observed in liver tissues). Clearly, other factors are involved in the regulation of ZnT-1 transport proteins.

11. •• Palmiter RD, Cole TB, Findley SD: **ZnT-2, a mammalian protein that confers resistance to zinc by facilitating vesicular sequestration.** *EMBO J* 1996, **15:**1784–1791.

These authors report on identification of a zinc transporter that is localized on intracellular vesicles. Using zinc-specific fluorescent probes, they demonstrated that ZnT-2 transports zinc into vesicles, thereby protecting transfected cells from toxicity.

12. Foote JW, Delves HT: **Albumin bound and alpha-2-macroglobulin bound zinc concentrations in the sera of healthy adults.** *J Clin Pathol* 1984, **37:**1050–1054.
13. Wolman SL, Anderson G, Marliss EB, *et al.*: **Zinc in total parenteral nutrition: requirements and metabolic effects.** *Gastroenterology* 1979, **76:**458–467.
14. Ruel MT, Rivera JA, Santizo M-C, *et al.*: **Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children.** *Pediatrics* 1997, **99:**808-813.
15. Hambidge KM: **Zinc and diarrhea.** *Acta Paediatr Suppl* 1992, **381:**82–86.
16. • Sazawal S, Black RE, Bhan MK, *et al.*: **Zinc supplementation in young children with acute diarrhea in India.** *N Engl J Med* 1995, **333:**839–844.

Report from a large study involving 937 children in India. The authors investigated the effect of zinc supplementation on acute diarrhea in this double-blinded, randomized, and controlled trial. All children also received oral rehydration solution and vitamin supplements. Dietary intakes were not measured.

17. Atherton DJ, Muller, DPR, Aggett, PJ, *et al.*: **A defect in zinc uptake by jejunal biopsies in acrodermatitis enteropathica.** *Clin Sci (Lond)* 1979, **56:**505–507.
18. Piletz JE, Ganschow RE: **Zinc deficiency in murine milk underlies expression of the lethal milk (lm) mutation.** *Science* 1978, **199:**181–183.
19. •• Huang L, Gitschier J: **A novel gene involved in zinc transport is deficient in the lethal milk mouse.** *Nat Genet* 1997, **17:**292–297.

The first identification of an inherited defect in a zinc-transport gene in mammals is reported here.

20. Walravens PA, Hambidge KM, Koepfer DM: **Zinc supplementation in infants with a nutritional pattern of failure to thrive: a double-blind, controlled study.** *Pediatrics* 1989, **83:**532–538.
21. Zarling EJ, Mobarhan S, Donahue PE: **Does zinc deficiency affect intestinal protein content or disaccharidase activity?** *J Lab Clin Med* 1985, **106:**708–711.
22. Moran JR, Lewis JC: **The effects of severe zinc deficiency on intestinal permeability: an ultrastructural study.** *Pediatr Res* 1985, **19:**968–973.
23. Rodriguez P, Darmon N, Chappuis P, *et al.*: **Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc.** *Gut* 1996, **39:**416–422.
24. Ghishan FK: **Transport of electrolytes, water and glucose in zinc deficiency.** *J Pediatr Gastroenterol Nutr* 1984, **3:**608–612.
25. • Blanchard RK, Cousins RJ: **Upregulation of rat intestinal uroguanylin mRNA by dietary zinc restriction.** *Am J Physiol* 1997, **272:**G972–G978.

The authors identify zinc deficiency as the first known regulator of the hormone uroguanylin in rats.

26. Fan X, Hamra FK, Freeman RH, *et al.*: **Uroguanylin: cloning of preprouroguanylin cDNA, mRNA expression in the intestine and heart and isolation of uroguanylin and prouroguanylin from plasma.** *Biochem Biophys Res Commun* 1996, **219:**457–462.
27. Hamra FK, Eber SL, Chin DT, *et al.*: **Regulation of intestinal uroguanylin/guanylin receptor-mediated responses by mucosal acidity.** *Proc Natl Acad Sci U S A* 1997, **94:**2705–2710.
28. Perkins A, Goy MF, Li Z: **Uroguanylin is expressed by enterochromaffin cells in the rat gastrointestinal tract.** *Gastroenterolgy* 1997, **113:**1007–1014.
29. Kararskis EJ, Schuna A: **Serum alkaline phsophatase after treatment of zinc deficiency in humans.** *Am J Clin Nutr* 1980, **33:**2609–2612.
30. Gordon W, White PJ: **Zinc deficiency in total parenteral nutrition.** *S Afr Med J* 1978, **54:**823–824.
31. Festa MD, Anderson HL, Dowdy RP, *et al*: **Effect of zinc intake on copper excretion and retention in men.** *Am J Clin Nutr* 1985, **41:**258–292.
32. Fosmire GM: **Zinc toxicity.** *Am J Clin Nutr* 1990,**51:**225–227.