Chapter 49

Zinc

Overview

- Zinc is an active component of several important enzymes (including collagenase), and it is widely distributed in animal tissues.
- Zinc affects the metabolism of the pancreas, skin, and male reproductive organs.
- Zinc toxicity affects several different organ systems.
- Zinc is normally absorbed from the intestine at an approximate 20-30% efficiency, and competes with Cu^{++}, Fe^{++}, and Ca^{++} for absorption.
- Zinc deficiency results in growth retardation, delayed wound healing, photophobia, scaly dermatitis, and sometimes loss of taste and smell.
- Vitamin A metabolism is partially Zn^{++}-dependent.

Zinc (**Zn^{++}**) is a widely distributed trace element in animal tissues, concerned with the function of enzymes in several different areas of metabolism. As indicated in **Table 49-1**, this element is associated with enzymes involved in protein biosynthesis and degradation, nucleic acid biosynthesis, carbohydrate and energy metabolism, acid/base balance (CA), cellular protection against free radicals (SOD), interconversion of trans-retinal with retinol, heme biosynthesis, dihydrotestosterone production, and several other reactions. Approximately 50% of Zn^{++} in the body is complexed in bone, and therefore generally unavailable for metabolism. High concentrations are found in the integument, retina, testes, and prostate.

Apart from muscle/organ meats, the richest sources of dietary Zn^{++} are found in whole grains (the germ), seeds, nuts, eggs, and roots of leafy vegetables. Zinc is absorbed from the upper small intestine at an approximate **20-30% efficiency**. It moves by facilitated diffusion into mucosal cells, and from there a portion is transferred across the basolateral membrane (to blood and interstitial fluid) by an energy-dependent process. This is also the site where **Ca^{++}**, **Cu^{++}**, and **Fe^{++}** are absorbed, and these ions, when present in excess amounts, can compete with **Zn^{++}** for uptake. Iron supplements can cause Zn^{++} deficiency, and Zn^{++} supplements are known to cause Fe^{++} and Cu^{++} deficiency. Cereal diets high in Ca^{++} and phytate (which binds Zn^{++}), and marginally low in Zn^{++}, can promote Zn^{++} deficiency (**Table 49-2**). Following transfer to blood, Zn^{++} is primarily bound to albumin. In contrast to Fe^{++}, Zn^{++} is not stored by the body to any great extent, and therefore exhibits a greater turnover.

The most obvious effects of zinc occur on the metabolism, function, and maintenance of the skin, pancreas, and male reproductive organs. Since it is involved in important roles in many different cell types, deficiencies result in broad metabolic changes, including diminished growth (see **Table 49-2**). Zinc is associated with the abundantly secreted **exo-** and **endopeptidases** of the exocrine pancreas, which are necessary for dietary protein digestion

Table 49-1

Zinc

Tissue Distribution	Enzymes
Bone (50%; not available)	Protein metabolism
Muscle	Proteases (collagenase)
Integument (skin, hair & nails)	Peptidases
Retina	Protein synthesis (skin)
Testes & Prostate	Nucleic acid metabolism
Liver	Aspartate transcarbamylase
Kidney	Thymidine kinase (sperm, skin)
Pancreas	RNA & DNA polymerases
Stomach (parietal cells)	Carbohydrate metabolism
Erythrocytes	Aldolase
	Pyruvate carboxylase
	Several dehydrogenases
	Others
	Carbonic anhydrase (CA)
	Superoxide dismutase (SOD)
	Alkaline phosphatase
	Retinal reductase
	Δ-ALA dehydratase (heme)
	5-α-Reductase (dihydrotestosterone)

Modified from Linder MC, 1991.

(see Chapter 7). It is also associated with stored insulin, although it does not appear to play a direct role in insulin action. The sloughing of intestinal mucosal cells and the pancreatic exocrine pathway are thought to be major routes for **zinc elimination** from the body. Smaller amounts are lost through sweat, hair, and skin, while lactation and pregnancy impose additional losses.

Zinc is necessary for **testicular development**, acting as a component of **5-α-reductase**, the enzyme that converts **testosterone** to **dihydrotestosterone** (**DHT**). It also plays a role in the formation of testosterone by testicular Leydig cells, thereby indirectly affecting spermatogenesis. Circulating levels of both testosterone and DHT are reduced in zinc deficiency.

The role of zinc in skin and fibrous connective tissue metabolism involves effects on collagen synthesis and degradation (**collagenase** is a zinc-containing enzyme), as well as other proteins. Among the most important zinc-containing enzymes is **carbonic anhydrase** (**CA**), abundantly present in erythrocytes, renal tubular epithelial cells, gastric parietal cells, and pancreatic and biliary ductular epithelial cells. **Superoxide dismutase** (**SOD**), which requires both Zn^{++} and Cu^{++}, plays a defensive role in the cytosol of many cells by disposing of damaging superoxide anions (see Chapter 30). **Retinal reductase** (or dehydrogenase) is also a Zn^{++}-containing enzyme, that plays a role in vitamin A and thus visual pigment metabolism (see Chapter 44). Moreover, Zn^{++} is necessary for the synthesis of **retinol binding**

Table 49-2

Zinc Deficiency

Causes	Symptoms
Increased body loss	Anorexia
Starvation	Impaired taste
Burns	Growth retardation
Diabetes Mellitus	Hypogonadism (males)
Ketoacidosis	Delayed wound healing
Diuretic treatment	Nystagmus
Kidney disease	Photophobia
Proteinuria	Night blindness
Dialysis	Skin lesions
Liver disease	Nail loss
Intravascular hemolysis	Diarrhea
Chronic blood loss	Scaly dermatitis
Parasitism	Thinning & depigmented hair coat
Exfoliative dermatitis	Weight loss and depression
Excessive sweating	
Inadequate dietary intake	
Protein-calorie deficiency	
IV feeding	
High Ca^{++} and phytate diets	
Malabsorption	
Pancreatic insufficiency	
Inflammatory bowel disease	

Modified from Linder MC, 1991.

protein (**RBP**) in the liver, which is required for distribution of vitamin A via blood. These connections to vitamin A metabolism help to explain the photophobia and night blindness associated with Zn^{++} deficiency, as well as the general integrity of the skin. Additionally, the expression/production of growth hormone, which is turned-on by the **retinoic acid-hormone receptor complex**, and the expression of **triiodothyronine** (T_3), whose activity on certain proteins is complimented by vitamin A, can be affected in Zn^{++} deficiency.

Zinc may also be required for the activity of **adrenocorticotropic hormone** (**ACTH**), and for the capacity of erythrocytes, platelets, and other cell membranes to secrete **eicosanoids** (see Chapters 68 and 69). Reports indicate that Zn^{++} is fundamental to **T-cell function** in immunity, and a deficiency of this trace element can lead to thymic atrophy and decreased lymphokine production. Additionally, there may be a depression of natural killer cell and lymphocyte activities, and delayed hypersensitivity. There may also be a direct action of Zn^{++} in antibody production by B-cells. From these observations, it is evident that Zn^{++} is fundamental to growth and remarkable for its broad involvement in metabolism.

Zinc Toxicity

Although Zn^{++} is generally one of the least toxic trace elements, Fe^{++} and Cu^{++} deficiency and pancreatic, intestinal, hepatic, and renal damage are known to occur in animals receiving high doses. Additionally, hemolytic anemia has also been reported. Signs of depression, abdominal discomfort, anorexia, vomiting and diarrhea may precede the appearance of red urine and icterus. Although **Zn^{++} poisoning** has been described in several different animal species (**Table 49-3**), the dog appears to be affected most often. Animals can gain access to excessive amounts of Zn^{++} through **pennies** minted since 1983 (96% Zn^{++}), zinc nuts on collapsible transport cages (e.g., those sometimes used by the airline industry), zinc oxide ointments, zinc phosphide rodenticides, and zinc sulfate solutions used as fungicides on plants and in sheep foot-baths. Zinc is eroded from pennies or metal nuts during retention in the acid milieu of the stomach. Stomach acid also releases phosphine gas from zinc phosphide baits. Phosphine is apparently responsible for the acute effects of this rodenticide toxicity, and then Zn^{++} contributes to hepatic and renal changes present in animals that live several days.

Zinc Therapy in Copper Toxicosis

As indicated above, the **intestinal absorption of Cu^{++}** can be reduced by dietary Zn^{++}. This interaction forms the basis for Zn^{++} therapy in Cu^{++} toxicosis (see Chapter 50). Zinc induces synthesis of **metallothionein**, a protein that binds both Cu^{++} and Zn^{++} in mucosal cells of the small intestine. Thus, Cu^{++} absorption is reduced and the complexed Cu^{++} is held within mucosal cells of the gut until they are sloughed. The binding of Zn^{++} to metallothionein is apparently weaker than the binding of Cu^{++}, therefore this protein does not significantly reduce Zn^{++} absorption.

Zinc Deficiency

Zinc deficiency is not uncommon, and may occur because of **inadequate intake** or availability, **malabsorption**, or **increased rates of loss** from the organism. Growth retardation, skin lesions, and impaired sexual development in young males are recognized symptoms. Loss of taste and smell and impaired wound healing have also been described. The mechanism of Zn^{++} involvement in taste is unclear, but it may be a preneural event involving Zn^{++} attachment to **gustin**, a salivary protein. As indicated above, Zn^{++} plays a promotional role in skin and connective tissue metabolism, which has been recognized since ancient times when **calamine lotion (99% ZnO + 1% Fe_2O_3)** was first used on the skin. The connection is thought to be in the conversion of retinol to retinal, and then to

Table 49-3

Zinc Toxicosis

Susceptible Animals	Causes	Symptoms
Dogs	Zinc oxide ointments	Anorexia
Cats	Zinc sulfate solutions	Vomiting
Birds	Zinc metal nuts	Diarrhea
Ferrets	Zinc pennies (minted after 1983)	Hemolytic anemia
	Zinc phosphide	Renal dysfunction
		Hepatic dysfunction
		Pancreatic dysfunction

retinoic acid (retin A), which is necessary for epithelial cell differentiation (see Chapter 44), and also in the action of Zn^{++} as a cofactor for collagenase.

Increased Zn^{++} losses occur in **burn victims**, and in patients with **kidney damage**. In the latter, glomerular leakage of Zn^{++} attached to albumin is thought to be the main factor. Similarly, patients may lose substantial amounts of Zn^{++} during renal dialysis, and those on total parenteral nutrition (IV feeding) may receive less Zn^{++} than they require if the trace element has not been added to administered fluids. A variety of conditions and treatments, including inflammation, stress, cancer, glucocorticoid disturbances or treatments, starvation, or hemolysis may affect serum levels of Zn^{++}. Several of these factors apparently act by inducing hepatic **metallothionein**, which, like the same compound in mucosal cells of the gut, is thought to withdraw some of the metal from blood and hold it intracellularly. This acute phase may help subdue bacterial infections, for infusion of Zn^{++} into the blood of experimental animals brought into an inflammatory state by endotoxin has been shown to enhance virulence of the inflammatory process.

OBJECTIVES

- Explain why iron supplements can cause zinc deficiency, and compare iron to zinc absorption and storage by the body.
- Identify the tissue distribution of zinc, as well as the enzymes which depend upon this trace element as a cofactor.
- Discuss and understand the varied causes and symptoms of zinc deficiency, and know why zinc is fundamental to growth, development and optimal activity of the organism.
- Explain why zinc is used in calamine lotion.
- Understand how zinc affects the reproductive physiology of males.
- Know the relationship between zinc and metallothionein, and understand why zinc may be therapeutic in copper toxicity.
- Outline the causes and symptoms of zinc toxicosis, and identify animals that appear to be most susceptible.
- Summarize the relationships between zinc and the pancreas.
- Explain the connection between zinc deficiency and photophobia.

QUESTIONS

1. Which one of the following is NOT a zinc-containing enzyme?

a. Glycogen phosphorylase
b. Collagenase
c. Carbonic anhydrase
d. Retinal reductase
e. 5-α-Reductase

2. Which one of the following competes with zinc for intestinal absorption?

a. Cl^-
b. K^+
c. Na^+
d. Alanine
e. Cu^{++}

3. Zinc is closely associated with which one of the following vitamins?

a. A
b. B_{12}
c. C
d. D
e. E

4. Ingestion of which one of the following would most likely cause zinc toxicosis?

a. A new pencil
b. A newly minted penny
c. A small section of electrical cord
d. A pair of plastic sunglasses
e. An old sock

5. Which one of the following proteins is known to bind zinc?

a. Fibrinogen
b. Sucrase
c. Prothrombin
d. Metallothionein
e. Tropomyosin

ANSWERS

1. a
2. e
3. a
4. b
5. d