ZINC AS AN ESSENTIAL MICRONUTRIENT: A REVIEW.

Maria J Salgueiro*, Bioch; Marcela Zubillaga*, Ph.D; Alexis Lysionek*, Pharm; Maria I. Sarabia*, Pharm; Ricardo Caro*, Ph.D.; Tomás De Paoli†, Ph.D.; Alfredo Hager†, Ph.D.; Ricardo Weill‡, Eng; and José Boccio*, Bioch.

*Radioisotope Laboratory and †Physics Department, School of Pharmacy and Biochemistry, University of Buenos Aires, Junin 956, 1113 Buenos Aires, Argentina.
‡Agrarian Industries Department, School of Agronomy, University of Morón, Buenos Aires, Argentina.

ABSTRACT

Zinc is one of the most important essential tracer metals of human nutrition, and its deficiency is a world nutritional problem. This work compiles past and present information about the role of zinc in human health.

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Key Words: Zinc, Absorption, Metabolism, Deficiency, Toxicity, Fortification.

INTRODUCTION

The first manifestation of zinc deficiency described in humans was its impact on growth in childhood, described by Prasad forty years ago (1-5). Thus, after the essentiality of zinc was proved there was an explosion of research in order to establish the role of zinc in human health (1-3). In the last years zinc deficiency has become a world nutritional problem since it affects developed and developing countries (2, 6). Studies performed in U. S. A., Brazil, Guatemala, Mexico, Chile and Puerto Rico showed that independently of age, sex and race, median intakes range between 50-80% of the recommended dietary allowances (RDA) (7, 8). Zinc supplementation studies proved that zinc deficiency is a worldwide problem (5, 7, 9-20). It is noteworthy that although newborn, children, pregnant women and old people are considered the main risk groups, zinc deficiency may affect the whole population (2, 4, 8, 18, 21, 22). The major problem has been to find a reliable laboratory index of zinc status to estimate the individual zinc nutritional status, at the onset of zinc deficiency or zinc toxicity signs (12, 23). Different laboratory and clinical tests, together with the results of many zinc supplementation trials, have provided the evidence of zinc deficiency in several populations. The laboratory methods proposed to determine zinc status are: serum and plasma zinc concentrations, leukocyte and neutrophil zinc concentrations, the activity of selected enzymes such as 5' nucleotidase and lately, the erythrocyte metallothionein concentration. Table 1 shows some of the zinc status indicators proposed (12, 23-29).

To whom correspondence should be address.
Fax: (5411) 4786-2932. E-mail: jsalgueiro@huemul.ffyb.uba.ar

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TABLE 1: Zinc status indicators

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Proposed as the best indicator of the zinc nutritional status (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma zinc concentrations</td>
<td></td>
</tr>
<tr>
<td>Serum zinc concentrations</td>
<td></td>
</tr>
<tr>
<td>Plasma metallothionein</td>
<td></td>
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<tr>
<td>Erythrocyte metallothionein *</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte zinc concentrations</td>
<td></td>
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<tr>
<td>Leukocyte zinc concentrations</td>
<td></td>
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<tr>
<td>Neutrophil zinc concentrations</td>
<td></td>
</tr>
<tr>
<td>5'-Nucleotidase activity</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase activity</td>
<td></td>
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<tr>
<td>Hair zinc concentrations</td>
<td></td>
</tr>
</tbody>
</table>

The lack of a reliable method to determine the zinc nutritional status also reflects the problem to estimate the metal RDA. Table 2 shows the recommendations proposed by the National Research Council in 1989 (30, 31). Nevertheless, more research is needed because of the difficulty in the application and interpretation of the usual methods to estimate the RDA, when trace metals are evaluated (8, 12, 32, 33).

TABLE 2: Recommended dietary allowances proposed by the National Research Council of United States, 1989.

<table>
<thead>
<tr>
<th>Group</th>
<th>Zinc Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>5mg/day</td>
</tr>
<tr>
<td>Children 1-10 years old</td>
<td>10mg/day</td>
</tr>
<tr>
<td>Males &gt; 10 years old</td>
<td>15mg/day</td>
</tr>
<tr>
<td>Females &gt; 10 years old</td>
<td>12mg/day</td>
</tr>
<tr>
<td>Pregnant</td>
<td>15mg/day</td>
</tr>
<tr>
<td>Lactating women 1st semester</td>
<td>19mg/day</td>
</tr>
<tr>
<td>Lactating women 2nd semester</td>
<td>16mg/day</td>
</tr>
</tbody>
</table>

**ZINC DEFICIENCY CONSEQUENCES**

**Immune system.** Zinc is known to play a central and unique role in the immune system. Several studies demonstrated that its deficiency increases the susceptibility to a variety of pathogens and affects non-specific and specific immunity (34-37). Clinical and experimental evidence showed thymic involution (35, 38) that may be mediated in part by glucocorticoids, because zinc deficiency raises blood glucocorticoids concentration (16, 39-41). Effects of zinc deficiency on specific cells of the immune system are lymphopenia, in both lymphoid tissues (central and peripheral), the depression of the T and B lymphocyte function as well as the deceretion of proliferative responses to mitogens (39, 42-44). Although some authors referenced phagocytic activity and neutrocytes bactericidal function deficit, Fraker and King found preliminary evidence, which suggests that granulopoiesis and myelopoiesis have greater resistance than lymphopoiesis in zinc deficiency (45). With regard to soluble mediators of immunity, zinc deficiency reduces thymulin activity and production or biological activity of multiple cytokines such as: IL-1, IL-2, IL-3, IL-4, IL-6, INF-γ, INF-α and TNF-α. Mild zinc deficiency also shows an imbalance of Th-1 cells and Th-2 cells function (39, 46-50). On the other hand, an important finding was that an adequate zinc status contributes to the preservation of the CD4:CD8 ratio, which is crucial in human immunodeficiency virus (HIV) infection for the transition to overt acquired immune deficiency syndrome (AIDS) (15, 39, 46, 51). Thus, plasmatic zinc levels were proposed as a disease
progression marker, altogether with the CD4 lymphocyte amounts and the β2-
microglobulin values (35, 52). It is noteworthy that in several works, all zinc deficiency
signs concerning immune functions were reversed by zinc supplementation (15-17, 22,
34, 35, 39, 40, 44, 46). Fetal zinc deficiency affects immunological development by
reducing natural antibodies. Zinc status is also involved in placental transport of
antibodies from the mother to the fetus, which may result in impaired utero acquisition
of maternal antibodies by the child during mother zinc deficiency (39).

Anorexia nervosa. There is evidence to suggest that zinc deficiency may be involved in
the pathogenesis of anorexia nervosa. In rats, zinc deficiency reduces total food intake
to approximately 50% of the amount of diet consumed by zinc adequate rats, and they
eat with a recurring 3-5 days cyclic pattern. When these rats were forced fed they
became seriously ill, and in some cases they died (53-59). All these signs disappeared
upon zinc repletion. Zinc supplementation studies showed that anorexia nervosa signs
were reversed, as some studies demonstrated that patients stopped loosing weight and
even increased it when zinc was given. In the case of many women, menstruation
returned after zinc therapy (54). The mechanism underlying anorexia nervosa onset is
not known; but it has been suggested that there is an alteration in aminoacid transport
and in its metabolism through the blood-brain barrier, which affects the synthesis of
certain neurotransmitters. These factors could affect appetite (53). Browning et al.
(1998) (55), hypothesized that zinc deficiency induced anorexia, was in relation to a
decrease in neuropeptide Y (NPY) concentration, a potent appetite stimulant, in the
hypothalamus (55). On the contrary, Lee et al. (1998) (53) found, that NPY was
increased during zinc deficiency and that NPY system appears to be intact
postsinaptically. They proposed that it might be that zinc deficiency impairs the
processing of the NPY; thus, it has lower affinity for its receptors causing a decreased
food intake. Nevertheless, they also pointed out that if NPY processing is unaffected,
some other physiologic changes are mediating this sign (53).

Reproduction. Zinc plays an essential role in reproduction in males and females. It is
necessary for the synthesis and secretion of luteinizing hormone (LH) and follicle
stimulating hormone (FSH), gonadal differentiation, testicular growth, formation and
maturation of spermatozoa, testicular steroidogenesis and fertilization. The biological
effects of androgens and estrogens are mediated by zinc fingers, located in highly
conserved regions of their nuclear receptors. Zinc supplementation has proven to be
beneficial in sterility and impotence in men and infertility in women. Mechanisms
underlying these functions involved numerous zinc-dependent enzymes and the
complexity of the complete pathway is not fully understood. As zinc is involved in the
production and secretion of LH, FSH and prolactin zinc deficiency depresses
steroidogenesis because it impairs LH function, and steroidogenic enzymes. On the
other hand, rats with zinc deficiency have smaller than normals Leydig cells, and show
an abnormal endoplasmic reticulum (9, 18, 60-66). Om and Chung (1996) (62) reported
that in zinc deficient male rats, LH and testosterone concentrations were reduced, the
hepatic steroid metabolism was altered and sex steroid hormones levels were modified.
They concluded that zinc deficiency contributes to the pathogenesis of male
reproductive disfunction as infertility, hipogonadism and feminization (62).

Pregnancy. Since all the hormones and a wide range of enzymes involved in
reproduction and development are sensitive to zinc status, zinc deficiency has several
deleterious effects on many stages of the pregnancy and on the growth of the newborn.
Several reports showed skeletal malformations (67-69), spontaneous abortion,
prematurity or prolonged gestation and complications during delivery as excessive loss
of blood (5, 9, 14, 70-74). The main teratogenic effects of zinc deficiency are related to neural tube defects in children of mothers with altered zinc status (9).

**Lactating and infants.** During the first few months after birth, milk is the only source of zinc for the newborn. Many factors improve zinc bioavailability from breast milk such as the presence of lactoferrin, the existence of a citrate-rich fraction and the lower casein and phosphorous content (5). Milk zinc concentrations decline as lactation progresses but this is not an inevitable cause of suboptimal zinc intake in the newborn if maternal zinc intake is adequate to meet the demands of lactation (75). However, despite the evidence that zinc absorption from human milk is especially favorable, zinc intake of the fully breast-fed infant may be suboptimal in some circumstances, after the early months of lactation (75). Additionally, since liver zinc reserves are mainly accumulated during the last weeks of gestation, zinc deficiency of the newborn would be more markedly and last longer in premature babies (5). Factors responsible for zinc deficiency in premature infants include not only a defect in transfer of zinc from maternal serum to breast milk that can lead to a severe zinc deficiency in rare circumstances, but also high fecal losses of zinc in the newborn, low body stores of zinc at birth and increased zinc requirements during rapid growth (76, 77). Thus, growth velocity is the main determinant of infant zinc requirements, which are relatively high in the very young infant and decreases with increasing age (75). Zinc deficiency may be a common transient disorder in premature infants characterized by skin lesions resembling acrodermatitis enteropathica, diarrhea, growth stunting and low weight for age (78, 79). Caulfield et al., (1998) (80) suggested that zinc deficiency might be a previously unrecognized cause of impaired disease resistance and decreased vaccine efficacy in infants. In many cases, zinc supplementation corrected the skin lesions and normalized serum zinc levels in the newborn and the mother (78). Potential benefits of maternal zinc supplementation to infants include enhancement of either quantity or quality of human milk and optimization of infant growth, development, and immune function (81). Favier, (1991) (5), reviewed that supplementation of the food of breast-feeding mothers with 15 mg zinc resulted in higher weight gain in their babies than in babies of control mothers. Although more research is needed, growth velocity of breast infants was reported to increase with zinc supplementation in those cases where breast milk did not supply an abundant amount of zinc (82). Folwaczny (1997) (79) suggested that introduction of complementary foods should not be encouraged before 5-6 months of age since exclusive breast-feeding is protective, especially in environments with poor sanitation. However, pregnancy and early childhood are periods of vulnerability to zinc depletion thus, supplementation not only with zinc but also with other micronutrients may be beneficial and particularly justifiable as well as in situations with potential increase losses of zinc, such as diarrhea (82). Due to the frequent use of soy milk instead of breast milk, and the dietary modifications including the intake of cereals and vegetables during the period of transition from milk to solid foods may be difficult to meet the zinc requirements, thus zinc supplementation or fortification may be useful strategies during this period of life (82, 79). At that time, the choice of high quality complementary foods that provide not only zinc but also iron, energy, and protein is likely to be beneficial and zinc interactions are important to be considered when designing mineral supplements for preterm babies, infant formulas and food fortification (81,83).

Clinical manifestations of zinc deficiency are listed in Table 3 (3, 42, 43, 53, 60, 61, 70, 71, 78, 84-93).
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TABLE 3: Zinc deficiency consequences

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>Oligospermia</td>
</tr>
<tr>
<td>Hipogonadism</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Intercurrent Infections</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Altered immune response</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Increased abortion risk</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Complications during delivery</td>
<td>Mental lethargy</td>
</tr>
<tr>
<td>Prematurity pregnancy</td>
<td>Skin changes</td>
</tr>
<tr>
<td>Neural tube defects of fetus</td>
<td>Taste abnormalities</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>Emotional disorders</td>
</tr>
<tr>
<td>Abnormal dark adaptation</td>
<td>Hyperammonaemia</td>
</tr>
</tbody>
</table>

ZINC FUNCTIONS IN THE ORGANISM

The wide range of functions that zinc plays in the organism may be due to its role as a cofactor of over 200 enzymes and to its structural role in a large number of zinc finger proteins (1, 91, 94, 95). Despite the low values of zinc concentration in most of the organs, zinc metalloenzymes are widespread among all the body tissues and performs crucial roles in a lot of physiological processes. Table 4 summarises the main functions of zinc in humans (1, 3, 9, 18, 22, 37, 62, 67, 87, 91, 94-99).

TABLE 4: Zinc functions in the organism.

<table>
<thead>
<tr>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response onset and regulation</td>
</tr>
<tr>
<td>Antioxidant</td>
</tr>
<tr>
<td>Enzymatic cofactor</td>
</tr>
<tr>
<td>Spermatogenesis and steroidogenesis</td>
</tr>
<tr>
<td>Vitamin A metabolism</td>
</tr>
<tr>
<td>Insulin storage and release</td>
</tr>
<tr>
<td>Energetic metabolism</td>
</tr>
<tr>
<td>Proteins synthesis</td>
</tr>
<tr>
<td>Stabilization of macromolecules</td>
</tr>
<tr>
<td>Regulation of the DNA transcription</td>
</tr>
<tr>
<td>Cellular division</td>
</tr>
</tbody>
</table>

One of the most important functions of zinc is related to its antioxidant role and its participation in the antioxidant defence system. The mechanism of this action is not clear, but zinc deficiency provokes oxidative damage that reminds the effects produced by free radicals action (72 100-103). Some authors suggest that zinc inhibits free radical propagation reactions because the metal increases metallothionein synthesis. In this way, metallothionein acts as a free radical scavenger protecting the cell membranes (21, 104). On the other hand, several studies suggest an interrelation between zinc and vitamin E for this action. Kim et al. (1998) (105) proposed that the role of zinc as an antioxidant by itself has to be reviewed. They support this point of view on account of studies that suggest impaired absorption of lipid soluble vitamins as E and A, probably due to defective formation of chylomicrons in the enterocyte during zinc deficiency. Thus, some of the oxidative damage in zinc deficient animals may be linked to the impaired vitamin E status during zinc deficiency, as in many cases supplemental vitamin E showed to prevent some of these lesions (105).
ZINC DEFICIENCY CAUSES

Zinc deficiency causes are classified in two groups (2). In the first group there are several syndromes related to metabolic or genetic malfunctions, which determine zinc deficiency such as: malabsorption syndromes, acrodermatitis enteropathica, Crohn’s disease, alcoholism, liver cirrhosis, chronic renal diseases, etc. In this group the treatment of Wilson’s disease with penicillamine also provokes zinc deficiency (30, 42, 43, 76, 84-86, 104). In the second group there are the nutritional causes, which are the most important and common (34, 106, 107) such as: decreased zinc intake or the consumption of poor zinc content foods (107). Table 5 shows the most common zinc sources.

<table>
<thead>
<tr>
<th>TABLE 5: Zinc content of foods</th>
<th>mg %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>3.20</td>
</tr>
<tr>
<td>Liver</td>
<td>5.10</td>
</tr>
<tr>
<td>Egg</td>
<td>1.35</td>
</tr>
<tr>
<td>Milk</td>
<td>0.38</td>
</tr>
<tr>
<td>Refined cereals</td>
<td>0.50</td>
</tr>
<tr>
<td>Whole wheat*</td>
<td>10.00</td>
</tr>
<tr>
<td>Whole corn*</td>
<td>2.50</td>
</tr>
<tr>
<td>Whole rye*</td>
<td>1.30</td>
</tr>
<tr>
<td>Carobs</td>
<td>2.65</td>
</tr>
<tr>
<td>Onion</td>
<td>1.40</td>
</tr>
<tr>
<td>Peanut</td>
<td>2.00-3.00</td>
</tr>
<tr>
<td>Chocolate</td>
<td>1.00-2.00</td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>1.50</td>
</tr>
</tbody>
</table>

All values are given as mg of zinc per 100g of food
*Low bioavailability

As it can be observed, zinc content in food is very low even in those foods considered as zinc rich foods (8, 108, 109). In the case of unrefined cereals although they have a high content of zinc, the presence of other components in the grain causes the low bioavailability of the metal from these sources (2, 8, 107). On the other hand, massive consumption foods such as milk and refined cereals, considered as the ideal carriers in food fortification procedures, have a very low content of zinc. Therefore, as nutritional causes are the most important all around the world and food fortification is an effective and economic strategy to prevent nutritional deficiencies, fortification of milk and refined cereals with a proper zinc compound may be the key to overcome zinc deficiency (110).

ABSORPTION

In mammals, zinc absorption takes place in the small intestine through two mechanisms: active and passive transport. Active transport is saturable at high concentrations of the metal in the intestine lumen, and its efficiency increases during low intake periods. On the contrary, passive transport is a diffusion mechanism, which is inalterable during low intake periods and its efficiency is proportional to zinc lumen concentrations (21, 109). There are many factors that may modify zinc absorption and they may be considered as activators or inhibitors of this process. Among absorption activators there are picolinic acid secreted by the pancreas, vitamin B6 that increases...
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Picolinic acid secretion, citrate and amino acids such as glycine, histidine, lysine, cysteine and methionine (8, 21, 111, 112). In the group of absorption inhibitors, there are phytic and oxalic acids, tannins, fibre, selenium, iron and calcium (2, 3, 7, 21, 113-122). With regard to iron and calcium, there is great controversy about their role as inhibitors, but it appears that they only interfere with zinc absorption at higher concentrations than those found at nutritional levels (8, 114, 117-119, 123). Figure 1 shows zinc absorption that occurs by both active and passive mechanisms.

INTESTINE

Dietary Zinc \( Zn^+ \) → \( Zn^+ \) Enteroocyte

Absorption

Endogenous Secretion

\( Zn^+ \) → \( Zn^+ \) Albumin

\( Zn^+ \) → \( Zn^+ \) Blood

Endogenous Reabsorption

\( Zn^+ \) → \( Zn^+ \) Excretion

FIGURE 1. Zinc Absorption: Zinc absorption may occur by an active or a passive transport, and zinc that is not absorbed is excreted with the feces. There is also an endogenous zinc secretion into the intestinal lumen. Both dietary and endogenous zinc are under the same homeostatic regulation in the intestine, and they may be reabsorbed at distal segments of the intestine or finally excreted with the feces.

The efficiency of this process ranges between 15 and 40% (121). Zinc that is not absorbed is excreted with the feces. There is also an endogenous zinc secretion into the intestinal lumen. This endogenous zinc comes from pancreatic, biliar and intestinal secretions as well as from desquamated mucosal cells (13, 21, 121, 122, 124). Once inside the intestine, both dietary and endogenous zinc are under the same homeostatic regulation, and they might be reabsorbed at distal segments of the intestine, or finally excreted with the feces (21). Homeostasis regulation of zinc is very important at the intestinal level. Some authors explain that during low zinc intake periods, there is a marked decrease of endogenous zinc secretion instead of an increase in zinc absorption (13, 21, 121, 124-127). Recent works proposed the intestinal metallothionein as one of the proteins involved in this secretion process (127). Once zinc is absorbed, it may form an intestinal pool bound to the intestinal metallothionein or it may be transported from the enterocyte to the blood (21, 121, 124).

TRANSPORT

Zinc transport in blood is carried out by albumin, although other plasma components may also bind the metal such as: \( \alpha_2 \)-macroglobulin, transferrin, cysteine and histidine. It appears that in such conditions as pregnancy and malnutrition, with low plasma albumin concentrations, zinc absorption decreases (21, 121).
Most of plasma zinc reaches the liver, where it is stored bound to hepatic metallothionein. Metallothioneins are the main proteins involved in zinc metabolism and they are cytosolic proteins with high cystein content. These metalloproteins can bind seven atoms of zinc per molecule of protein, but they can also bind copper with higher affinity. Metallothionein isoforms 1 and 2 are highly expressed in liver, intestine, kidney and pancreas and their expression may be induced by many factors such as zinc rich diets, IL-1, IL-6, glucocorticoids, stress, etc. Their biochemical roles are associated with heavy metals detoxification, free radicals scavenging, redistribution of body zinc in acute infection or stress, and it appears that mainly hepatic metallothionein can act as a zinc reservoir that may convey protection against zinc deficiency (21, 72, 104, 109, 127-132). Intestinal metallothionein appears to act as a negative regulator of zinc absorption, and may participate in the intestinal mucosa-lumen zinc efflux, but more research is needed to clarify this (127). Figure 2 summarizes the biological cycle of zinc, as it was explained above.

FIGURE 2. Zinc metabolism: Dietary zinc absorption takes place in the small intestine. Zinc may form an intestinal pool bound to the intestinal metallothionein or may be transported by albumin in plasma, to the liver. Once in the liver, it may form a hepatic pool bound to the hepatic metallothionein or may be distributed to the rest of the body to performed a wide range of biological and biochemical functions. Zinc is excreted through feces from pancreatic, biliar and intestinal secretions, and mucosal desquamated cells. Endogenous zinc secretions and dietary zinc that was not absorbed may also be reabsorbed at distal segments of the intestine.

In the last years, it has been described a family of mammalian zinc transporters that play an important role in the regulation of zinc metabolism at the intracellular level. The divalent cation transporter-1 (DCT-1), is not zinc specific, and it has transport activity for many other trace metals and specially for iron. The others four zinc transporters 1, 2, 3 and 4 (ZnT-1, ZnT-2, Zn-T3 and ZnT-4) known until today, are zinc specific. Their general structure consists in 6 transmembrane domains, an intracellular histidine rich region and the amino and carboxy terminus, which resides intracellularly. ZnT-1 is widely expressed in the organism, and it functions as a zinc exporter. It was demonstrated the direct regulation of the ZnT-1 gene by zinc in the mouse intestine and liver, independently of the level of metallothionein. ZnT-2 is expressed in intestine, kidneys and testes. It functions as a zinc exporter, but it has the capacity of zinc compartmentalization into intracellular vesicles. ZnT-3 expression is restricted to the
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brain, suggesting an important role for zinc in the central nervous system, and it is also expressed in testes. ZnT-3 transporter activity is associated with vesicular packaging of zinc, and it could be involved in spermatogenesis and related to insulin secretion. ZnT-4 is expressed in the mammary gland and the brain. A single point mutation in ZnT-4 gene resulting in a premature termination of the protein causes the lethal mouse syndrome. This syndrome is characterised by a marked decrease of zinc transport from the mammary gland to the milk (127, 133-135).

TOXICITY

Although the knowledge of zinc toxicity is scarce, the most important evidence is its interference with copper metabolism (21, 136-139). Among patients with Wilson’s disease, zinc is the treatment of choice because high concentrations of zinc significantly limits the amount of copper absorbed, slowing the progression of the disease (140). Patients with acrodermatitis enteropathica need high doses of zinc to prevent zinc deficiency, but most of them develop copper deficiency (26). Myelocytic anaemia and neutropenia are usually, the manifestation of this interaction between copper and zinc (21, 136, 137). The hypothetical mechanism for zinc-copper interaction is related with their similar chemical and biochemical properties. Some authors proposed a direct interference at the intestinal level. Others suggest that as high dietary zinc induces the increase of intestinal metallothionein, and this metalloprotein binds copper with higher affinity, so it may act as a sequestrant of the absorbed copper (141-146). Lonnerdal reviewed all these hypotheses and it can be concluded from his work that at nutritional doses of both metals, no clear interference was found (138). Another aspect of zinc toxicity is related with the pancreas as the target organ. Acute toxicity studies showed that although multiple organs are exposed to zinc toxicity, the pancreas is the most affected, but the reason is not clear (104, 147). Kelly et al. (1996) (104) suggest a protective role for metallothionein against zinc toxicity as a redundant mechanism for protection because zinc transporters involved in zinc efflux from the cell, are the most efficient mechanism (104, 133). The signs and symptoms that an acute oral zinc dose may provoke are: tachycardia, vascular shock, dyspeptic nausea, vomits, diarrhea and pancreatic and hepatic parenchyma damage (104, 148). Nevertheless, it is well known that the amounts of zinc that provokes toxic effects are much higher than those contained in regular diets (Table 6 (137, 149)). Thus, food fortification appears as a safe strategy in order to prevent zinc deficiency.

<table>
<thead>
<tr>
<th>TABLE 6: Oral acute toxicity of common zinc compounds</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Cl2Zn</td>
</tr>
<tr>
<td>SO4Zn7H2O</td>
</tr>
<tr>
<td>Zn-gluconate</td>
</tr>
</tbody>
</table>

All values are given as mg of compound per kg of body weight. 1Lowest published toxic dose. 2Lethal dose 50 (LD50)

ZINC COMPOUNDS

Zinc compounds commonly used as nutritional supplements or in food fortification are zinc oxide and zinc sulphate (150). However, both of them have serious disadvantages. Zinc sulphate has an adequate bioavailability but it interacts with the food matrix modifying the food sensorial characteristics, making food flavour
unacceptable. Zinc oxide does not interact with the food matrix because as it is insoluble it precipitates in liquid foods. In the case of solid foods, it can be deposited at the bottom of the package, because of the different density or granulometry between its particles and those of the solid food. Therefore, their use is restricted to solid foods. At present, a new zinc compound is in study. This product is a zinc gluconate stabilized with glycine. The new source has demonstrated the same bioavailability in aqueous solution, and the same metabolic behaviour, than zinc sulphate (151). The advantages that this product presents are: high solubility, soft taste, no modification of the sensorial food characteristics and low cost. Therefore, it should be taken into account for food fortification or supplementation procedures as a proper zinc compound.

CONCLUSIONS

Although more research is needed in order to clarify the role of zinc in human health, it is clear that its deficiency has become a worldwide nutritional problem.

- Zinc deficiency affects developed and developing countries.
- Nutritional causes are the most important. Diet is the only source of zinc but zinc content of food is very low.
- Zinc deficiency produces multiple clinical consequences, which ranges between mild and serious dysfunctions
- The lack of a reliable method to assess zinc nutritional status interferes with the diagnosis of zinc deficiency and the estimation of the RDA.

Therefore, food fortification with a proper zinc compound appears as an effective, safe and economic strategy to prevent zinc deficiency.

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Accepted for publication October 13, 1999.