REVIEW

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Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases

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Abstract

Zinc is required for multiple cellular tasks, and especially the immune system depends on a sufficient availability of this essential trace element. During the last decades, many studies attempted to affect the outcome of various diseases by zinc supplementation. These efforts either aimed at supporting immunity by zinc administration or at correcting a loss of zinc secondary to the disease to restore the zinc-dependent functions of the immune system. This review aims to summarize the respective findings and to discuss possible molecular mechanisms by which zinc could influence viral, bacterial, and parasitic infections, autoimmune diseases, and the response to vaccination. Zinc supplementation in diseases such as diarrhea, chronic hepatitis C, shigellosis, leprosy, tuberculosis, pneumonia, acute lower respiratory infection, and leishmaniasis seems beneficial. In contrast, the results for the common cold and malaria are still not conclusive, and zinc was ineffective in most vaccination and rheumatoid arthritis studies. For AIDS and type 1 diabetes, zinc supplementation may even be a risk factor for increased mortality or deterioration of the glucose metabolism, respectively. In these cases, zinc supplementation should be used with care and limited to clearly zinc-deficient individuals.

Key words: zinc, trace elements, infection, vaccination, autoimmunity.

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INTRODUCTION

In 1963, the severe consequences of zinc deficiency in humans were first described by Prasad et al. [121]. Since then, large parts of the molecular basis for the essentiality of zinc have been identified. It was shown that it is a component of more than 300 enzymes from all six classes [160], where it acts as a catalytic, cocatalytic, structural, or regulatory ion. Zinc-dependent biological functions include DNA replication [173], RNA transcription [31, 38, 173], signal transduction [13], enzymatic catalysis [7], redox regulation [87], cell proliferation [17, 55, 83, 119], cell differentiation [112], and apoptosis [151, 155].

In light of these observations it is easy to understand that zinc ions are crucial for multiple aspects of the immune system, including the normal development, differentiation, and function of cells belonging to both innate and acquired immunity [130, 170]. Among the immune cells that are affected by zinc deficiency, T lymphocytes seem to have the highest susceptibility [46] and are influenced on several levels (Fig. 1). Zinc deficiency reduces the number of peripheral and thymic T cells, their proliferation in response to phytohemagglutinin, and the functions of T helper (TH) and cytotoxic T cells, but also acts indirectly by reducing the levels of active serum thymulin. On the molecular level, zinc stimulates the autophosphorylation of the protein tyrosine kinase Lck by non-covalent interaction with the cytoplasmic tails of CD4 and CD8, leading to T cell activation [110, 137, 157]. As one result, the delayed-type hypersensitivity reaction is usually reduced in zinc-deficient individuals. However, other cells are also affected, leading to reduced antibody production and compromised function of cells of the innate immune system, such as natural killer cell activity, cytokine production by monocytes, and the chemotaxis and oxidative burst of neutrophil granulocytes [65, 129].

Another important aspect is the interaction between inflammation and zinc. Pro-inflammatory cytokines have a direct influence on zinc homeostasis. It has been shown that IL-6 induces the expression of the zinc trans-

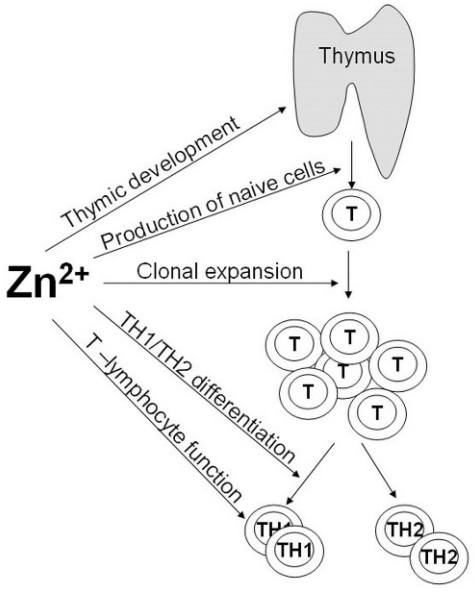

Fig. 1. Multiple effects of zinc on T-lymphocyte generation and function. Zinc deficiency affects T lymphocytes (T) in particular. Zinc ions are required for several steps in T-lymphocyte generation and development and the function of T helper (TH) cells.

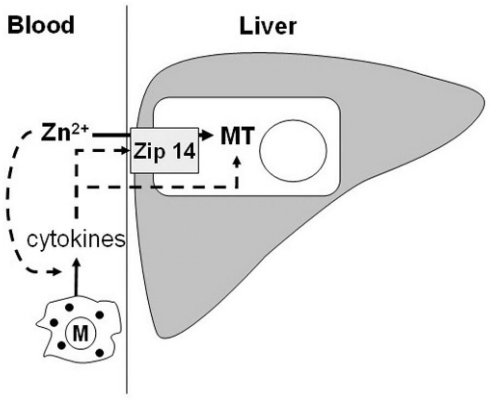

Fig. 2. Inflammation and zinc homeostasis. Pro-inflammatory cytokines induce the production of ZIP14 and metallothionein (MT). This leads to enhanced zinc transport via ZIP14 into liver cells, where it is stored bound to MT. As a consequence of this zinc translocation from plasma into the liver, a significant decrease in plasma zinc occurs during inflammation. On the other hand, zinc affects pro-inflammatory cytokine production by monocytes (M). Hence plasma zinc levels can regulate cytokine secretion. Solid lines show a direct release or translocation of a substance, while dashed lines indicate a modulation of expression.

porter Zrt- and Irt-like protein (ZIP) 14, thereby increasing zinc uptake into hepatocytes [80]. IL-6 also upregulates the zinc binding protein metallothionein (MT) and increases cellular zinc in hepatocytes [143]. Experiments with MT knockout mice confirmed that during endotoxin-induced inflammation, MT is required for zinc sequestration in the liver, leading to a significant reduction in plasma zinc levels [113]. Hence, during the acute-phase response, hypozincemia is caused by ZIP-mediated translocation of zinc into the liver and sequestration bound to MT (Fig. 2). Conversely, zinc affects several aspects of monocyte signal transduction and the secretion of pro-inflammatory cytokines by these cells [58], and zinc supplementation has been shown to reduce the production of tumor necrosis factor (TNF)-α and interleukin (IL)-1β in healthy human subjects [118].

The clinical manifestations associated with zinc deficiency comprise growth retardation, thymic atrophy, hypogonadism, infertility, dermatitis, delayed wound healing, alopecia, poor pregnancy outcomes, teratology, anorexia, diarrhea, and increased susceptibility to infectious diseases caused by bacterial, viral, and fungal pathogens [88, 116, 138]. Those symptoms are hallmarks of the autosomal recessive inheritable disease acrodermatitis enteropathica. It is characterized by low serum zinc levels [97]. These result from reduced enteral zinc absorption, which is based on a mutation in the SLC39A4 gene that encodes the intestinal zinc import protein hZIP4 [79, 81, 167]. Successful treatment of all symptoms was achieved by oral zinc supplementation [48, 100], which is still the standard therapy for acrodermatitis enteropathica.

In addition to the impressive effects on acrodermatitis enteropathica, which demonstrate the physiological importance of zinc, many studies have been performed investigating the effects of zinc supplementation on other diseases. These studies often gave highly contradictory results. Resolving these discrepancies is difficult. A major problem is the different amounts of elemental zinc that were administered, which sometimes differed by more than one order of magnitude. Matters are complicated even further by the fact that the metal content varies significantly between different zinc salts, and several zinc supplements even exist in different salt forms (Table 1). If this form is not specified, the amount of elemental zinc that has been administered cannot be calculated reliably. Furthermore, even if the same supplement is used in various studies, the amount of calculated elemental zinc diverges between different research groups. Other studies do not report the zinc status of the patients, and zinc-deficient subjects will react differently to zinc treatment than zinc-sufficient ones. Even when data regarding the patients zinc status are provided, the parameters measured in most studies are total serum or plasma zinc. The significance of these values is questionable. While they are well suited to detect severe forms of zinc deficiency, they are not adequate parameters to indicate marginal zinc deficiency [2, 56].

Another important difference between studies can result from the differential bioavailability of the zinc supplements [94]. Salts with organic anions such as acetate, methionine, or histidine generally have a higher bioavailability than zinc sulfate, while zinc oxide is of lower availability. Furthermore, zinc uptake does not only vary between different salt forms, but also depends on the source and manufacturing process of the supplements, particularly with regard to ZnO [35] (Table 2).

Table 1. Zinc content of different supplements

Salt form	Chemical composition	Elemental zinc content (% of supplement)[a]
Zinc acetate	Zn $(C_2H_3O_2)_2$ (anhydrous)	35.6
	Zn $(C_2H_3O_2)_2$×2 H_2O	29.8
Zinc aspartate	Zn $(C_4H_6O_4N)_2$	19.8
Zinc gluconate	Zn $(C_6H_{11}O_7)_2$	14.3
Zinc histidine	Zn $(C_2H_8N_3O_2)_2$×2H_2O	16.0
Zinc methionine	Zn $(C_5H_{10}NO_2S_2)_2$	18.1
Zinc orotate	Zn $(C_5H_3N_2O_4)_2$×2 H_2O	15.9
Zinc oxide	ZnO	80.3
Zinc sulfate	$ZnSO_4$ (anhydrous)	40.5
	$ZnSO_4$×H_2O	36.4
	$ZnSO_4$×7 H_2O	22.7

[a] Values were calculated according to the chemical formula.

Concerning bioavailability, one has also to consider the nature of the diet consumed by the subjects. The uptake of zinc is more efficient with an intake of animal protein than with a dietary intake predominantly consisting of cereal protein. The absorption of zinc is negatively influenced by zinc-chelating phytates and phosphates as well as by augmented levels of other bivalent cations, such as Cu, Mg, Ca, Ni, Cd, and Fe. On the other hand, it is increased by high amounts of proteins and single amino acids, in particular histidine and methionine [82, 159]. In turn, high-dose zinc supplementation can also interfere with the uptake of other nutrients. This has been documented for iron [105], and in particular for copper. Impaired copper uptake by excessive zinc supplementation induces severe copper deficiency, which can lead to anemia and neutropenia, abrogating the potential beneficial effects of zinc therapy [114, 120, 139]. Finally, gastric acidity enhances zinc absorption, especially for zinc oxide. This can be a particular problem for the elderly. They have a high incidence of hypo- or achlorhydria [61] and show a general tendency for lower zinc levels, which leads to an impairment of immune function [57, 131].

This review aims to summarize current knowledge about both the beneficial and adverse effects of zinc supplementation on the immune system and to discuss the possible molecular mechanisms by which these effects could be mediated.

INFECTIOUS DISEASES

Viral infections

Table 3 specifies different zinc supplementation studies dealing with diseases induced by viral pathogens. The common cold is a syndrome caused by a multitude of different viruses, many of them belonging to the rhino- and coronaviruses. For this disease, the use of zinc has been extensively investigated. The individual studies will not be discussed in detail here because they have already been summarized and compared elsewhere [64, 66, 67]. In these studies, which used 4.5–23.7 mg elemental zinc per single dose, the results are as inconsistent as the treatment conditions. In a review by Hulisz [64] it was concluded that zinc can be effective in reducing the duration of the common cold when administered within 24 h after the onset of symptoms. A recent study in children indicates that zinc may also have a prophylactic effect and the administration of zinc results in a lower mean number of colds [78]. However, two meta-analyses did not confirm an effectiveness of zinc-

Table 2. Bioavailability of different zinc supplements

Compound	Relative zinc bioavailability	Species	Experimental setup	References
Zinc acetate[a]	1.4 (high pH)[d, f] 5.7 (low pH)[d, f]	human	single dose of 50 mg zinc, either at high (≥5) or low (≤3) intragastric pH	61
Zinc oxide[b]	0.6 (weight gain) 0.4 (tibia zinc) 0.1 (plasma zinc)[c, e]	chicks	7 d depletion followed by 14 d supplementation with 0, 7.5, and 15 mg Zn/kg diet	168
	0.3–1.0 (weight gain) 0.2–0.9 (tibia zinc)	chicks	4 d depletion followed by 12 d supplementation with ZnO supplements from different sources	35
	0.7 (bone zinc) 0.9 (plasma zinc)[e]	pigs	5 w depletion followed by supplementation with 0, 7.5, and 15 mg Zn/kg diet for 14 w (plasma) or until the animals weighed approx. 100 kg (bone)	169
Zinc histidine[b]	1.2–1.5 (plasma zinc)[d]	human	single dose of 20 mg zinc, followed by measurement of plasma zinc at multiple time points	142
Zinc methionine[b]	1.2 (plasma zinc)[d]	human	single dose of 25 mg zinc, followed by measurement of plasma zinc at multiple time points	132
Zinc metal[b]	0.4–0.7 (weight gain)	chicks	4 d depletion followed by 12 d supplementation with zinc metal from two different sources	35

[a, b] Values are given as increase relative to supplementation with [a] zinc oxide or [b] zinc sulfate.
[c] Estimated from Table 3 (Wedekind and Baker [168]).
[d, e] Plasma zinc was either measured as [d] area under curve for multiple determinations at different time points, or as [e] single values.
[f] Estimated from Table 2 (Henderson et al. [61]).

Table 3. Zinc supplementation and viral infectious diseases

Disease	Zinc species	Zinc dosage[a]	Period	Participants	Effect of zinc supplementation	References
Common cold	more than 12 different studies, analyzing the therapeutic effects of zinc				variable results, reduced duration of symptoms if administered within 24 h of onset	64
	zinc sulfate	15 mg daily	7 mo	100 (Z), 100 (P)	lower mean number of colds demonstrating the prophylactic effect of zinc	78
HIV/AIDS	zinc sulfate	200 mg (=45.5 mg elemental zinc) daily	1 mo	29 (Z), 28 (P)	increase or stabilization in body weight; increase in plasma zinc levels, $CD4^+$ T cells and plasma active zinc-bound thymulin; reduced or delayed frequency of opportunistic infections due to *Pneumocystis jiroveci* and *Candida*, not to *Cytomegalovirus* and *Toxoplasma*	95
	zinc gluconate	45 mg three times daily	15 d	5 (Z), 5 (C)	increased zinc concentrations in red blood cells, $HLA\text{-}DR^+$ cells, stimulation of lymphocyte transformation and phagocytosis of opsonized zymosan by neutrophils	176
	zinc sulfate	10 mg (elemental) daily	6 mo	44 (Z), 41 (P)	no effect on HIV viral load; decreased morbidity from diarrhea	16
	zinc sulfate	220 mg (=50 mg elemental zinc) daily	1 mo	31 (Z), 34 (P)	no improvements in immune responses to tuberculosis, CD4/CD8 ratio, lymphocyte subsets, and viral load	54
	zinc sulfate	25 mg daily	6 mo	200 (Z), 200 (P)	when supplemented to pregnant HIV-positive women, no effect on birth outcomes or T-lymphocyte counts, and negative effects on hematological indicators	40
	zinc sulfate	25 mg daily	6 mo	200 (Z), 200 (P)	increased risk of wasting	163
				50 (Z), 50 (P)	no effect on viral load	163
	zinc gluconate	50 mg daily	6 d	44 (Z), 45 (P)	no improvements in antibody responses to a pneumococcal conjugate vaccine	27
Chronic hepatitis C	polapre-zinc	75 mg (=17 mg elemental zinc) two times daily	24 w	40 (C), 35 (Zn)	zinc supplementation increases serum zinc levels and improves the response to IFN-α therapy	152
	zinc gluconate	78 mg five times daily (=50 mg elemental zinc)	6 mo	18 (Z), 20 (P), 20 (C)	increased serum zinc levels; decreased incidences of gastrointestinal disturbances, body weight loss, and mild anemia	72

Z – zinc, P – placebo, C – control.

[a] Values are given as the amount of supplement unless indicated otherwise. The elemental zinc content is given as provided in the respective publication and may not always correspond to Table 1.

-lozenges in reducing the symptoms of the common cold after seven days [66, 67]. Many potential mechanisms have been suggested that could explain a potential beneficial effect of zinc. These include effects of zinc on viral replication and infection of cells on the one hand and the immune system, in particular cytokine production and modulation of the activity of immune cells, on the other.

Zinc inhibits the formation of viral capsid proteins and the rhinovirus 3C protease, thus preventing the replication of rhinoviruses *in vitro*. However, this remains to be demonstrated *in vivo* [50, 73, 74, 158]. Alternatively, zinc could interact with the binding of the rhinovirus to the intercellular adhesion molecule-1 (ICAM-1), an event that is required for invasion of cells of the nasal epithelium. It was hypothesized that the positively charged zinc ions can bind to the negatively charged regions at the carboxyl termini of rhinovirus coat proteins, thereby preventing the binding to ICAM-1 [64, 102]. In addition, zinc may protect or stabilize the cell membrane [107], which could also contribute to an inhibition of the entry of the virus into the cell. In a similar manner to viral binding of ICAM-1, zinc might also interfere with the binding of leukocyte function-associated antigen-1 to ICAM-1, thus suppressing inflammation [103].

Among the immunomodulatory effects of zinc that could counteract viral infections is its influence on the synthesis of cytokines. *In vitro*, zinc induces the production of antiviral interferon (IFN)-α as well as IFN-γ [19, 136] and it can potentiate the antiviral action of IFN-α, but not of IFN-γ [11]. Besides this, clearance of viral infections requires cytotoxic T lymphocytes, which are highly dependent on zinc, as discussed above.

Other potential mechanisms by which zinc could act against the common cold include an inhibitory effect of zinc on human prostaglandin metabolism [71], which may account for the ability of zinc to reduce symptoms of the common cold. Finally, a zinc-induced alteration of the capillary epithelium might inhibit transcapillary movement of plasma proteins and reduce local edema, inflammation, exudation, and mucus secretion [102].

So far it is not known which of these explanations are relevant for the proposed effect of zinc treatment *in vivo*. The lack of statistical confirmation of effectiveness and the plethora of possible mechanisms illustrate the need for in-depth research, which may allow using zinc with higher efficiency.

Infection with the human immunodeficiency virus (HIV) results in the acquired immune deficiency syndrome (AIDS), a disease where zinc application was tested as a supporting therapeutic intervention [23]. Given the importance of zinc for the development and function of T cells [46, 170], this seems to be a sensible approach. The initial study found an increase in HLA-DR positive cells, a stimulation of lymphocyte transformation by phytohemagglutinin and concanavalin A, and augmented phagocytosis by polymorphonuclear neutrophils [176]. A report by Mocchegiani et al. [95] described even more promising beneficial effects of zinc, including an increase in the number of TH cells and a reduced frequency of opportunistic infections with *Pneumocystis jiroveci* (formerly *P. carinii)* and *Candida*.

To antagonize a loss in TH cells, zinc could either stimulate T-lymphocyte production or enhance their survival. A reason for the former effect may be an action of zinc through thymulin on the maturation of T cells. Thymulin is a zinc-dependent nonapeptide hormone [26] that regulates the differentiation of immature T cells in the thymus [135] and the function of mature T cells in the periphery [24, 134]. On the other hand, an antiapoptotic action of zinc ions [155] at both the peripheral and thymic level could result in an increase in the number of TH cells. It is known that zinc inhibits caspases-3, -6, and -9 [92, 111, 150, 172]. Moreover, zinc can increase the Bcl-2/Bax ratio, thus enhancing the cells' resistance to apoptosis [47].

Unfortunately, the results of the supplementation trials are not consistent. In contrast to the observations of Mocchegiani et al. [95], there was no alteration of the CD4/CD8 ratio in the initial study [176] and several recent papers were unable to find effects of oral zinc on HIV-1 viral load, immune response to tuberculosis, lymphocyte subsets, $CD4^+$, $CD8^+$, and $CD3^+$ cell counts, or antibody response to a pneumococcal conjugate vaccine [16, 27, 40, 54, 163]. In addition, when Fawzi et al. [40] investigated the effects of zinc supplementation on pregnant HIV-positive women, zinc had no effect on pregnancy outcome, but the authors reported lower increases in hemoglobin, red blood cell count, and packed cell volume after the women had given birth. To make matters worse, two studies by Tang et al. [153, 154] indicated an increased risk for the progression to AIDS and a lower survival after zinc intake by HIV-positive individuals. One explanation for these contradictory results may be a different zinc status of the patients. While moderate zinc supplementation to zinc-deficient subjects can advance their immune responses, it may have harmful effects when given to zinc-sufficient ones. Zinc deficiency is frequent in patients with AIDS without treatment; however, anti-retroviral therapy has been shown to counteract the zinc deficiency [133]. Hence, zinc supplementation should be seen as a potential hazard to these patients and be strictly limited to individuals with documented zinc deficiency.

Finally, several studies have investigated the effect of zinc supplementation on hepatitis C, which is induced by an infection with the hepatitis C virus (HCV). After zinc treatment, decreases in the incidence of gastrointestinal disturbances, body weight loss, and mild anemia were found in patients with chronic hepatitis C [72]. In addition, zinc given in combination with IFN-α was more effective against chronic hepatitis C than a therapy with IFN-α alone [152].

In addition to the effects of zinc on immune function and antiviral defense discussed above, its role as an antioxidant may be important in hepatitis. Oxidative stress is a major contributor to cellular damage during viral hepatitis [149]. In mice it was shown that zinc enhances the expression of MT in liver tissues [34], which can function as a free radical scavenger [140, 162] and may prevent oxidative damage to liver tissue [86].

Several *in vitro* studies indicate that zinc may be able to inhibit viral replication of HCV [174], but also herpes simplex virus [77] and rhinovirus [74], all at concentrations of 100 μM zinc ions in the culture medium. For HIV, a concentration of 100 μg/ml (~1.5 mM) was effective [60]. All these amounts seem to be relatively high. Hence, the *in vivo* relevance of an inhibition of viral replication as a mechanism for antiviral actions of zinc in humans remains to be demonstrated.

Bacterial infections

Different zinc supplementation studies dealing with diseases caused by bacterial pathogens are listed in Table 4. Diarrhea can be either of viral or bacterial origin, but because there seem to be no obvious differences in the effects of zinc treatment, we will discuss all forms together in this paragraph. Diarrhea is a target for successful zinc treatment. This has been extensively studied, and the results have already been summarized in detail, showing that zinc can reduce the duration, sever-

Table 4. Zinc supplementation and bacterial infectious diseases

Disease	Zinc species	Zinc dosage[a]	Period	Participants	Effect of zinc supplementation	References
Diarrhea	multiple different studies				decreased duration, severity and occurrence of diarrhea	63
Shigellosis	zinc acetate	5 mg/kg (=1.3 mg/kg) three times daily	1 mo	16 (Z), 16 (P)	increased intestinal mucosal permeability and better nitrogen absorption; increased serum zinc and alkaline phosphatase activity	3
	zinc acetate	20 mg (elemental) daily	2 w	28 (Z), 28 (P)	increased serum zinc levels, lymphocyte proliferation in response to phytohemagglutinin and plasma invasion plasmid-encoded antigen-specific IgG titers	125
	zinc acetate	20 mg (elemental) daily	2 w	28 (Z), 28 (P)	increased serum zinc levels, serum shigellacidal antibody titers, $CD20^+$ cells, and $CD20^+CD38^+$ cells	124
Lepromatous leprosy	zinc sulfate	220 mg (daily)	18 mo	8 (Z)	reduced dose of clofazimine; withdrawal of steroids; toleration of dapsone; reduced incidence and severity of erythema nodosum leprosum; gradual decrease in the size of granuloma; gradual increase in the number of lymphocytes	89
	zinc sulfate	220 mg (daily)	18 mo	15 (Z), 10 (P)	decreased erythema, edema, and infiltration; regrowth of eyebrows; reduced bacterial index of granuloma; increased serum zinc levels, neovascularization, and endothelial cell proliferation	90
	zinc acetate	200 mg (two times daily)	13 w	17 (Z), 10 (P), 10 (C)	increased serum zinc levels and delayed hypersensitivity reactions; decreased size of skin nodules; disappearance of erythema; regrowth of eyebrows	36
	zinc sulfate	220 mg (daily)	4 mo	40 (Z)	improvements on frequency, duration, and severity of erytheme nodosum leprosum reactions; reduction in steroid requirement	84
Tuberculosis	zinc sulfate	15 mg (daily)	6 mo	40 (Z), 40 (P)	increased plasma retinol concentrations; earlier sputum conversion and resolution of X-ray lesion area	69
Acute lower respiratory infection[b]	zinc gluconate	10 mg (elemental) daily	6 mo	298 (Z), 311 (P)	increased plasma zinc levels; decreased episodes of infection	141
	zinc acetate	10 mg (elemental) two times daily	5 d	76 (Z), 74 (P)	increased serum zinc levels and recovery rates from illness and fever in boys	85
Heliobacter pylori infection	polapre zinc	150 mg two times daily	7 d	28 (C), 33 (Z)	administration of zinc together with antimicrobial therapy increased cure rate of *Heliobacter pylori* infection compared with antibiotic treatment alone	70

Z – zinc, P – placebo, C – control.

[a] Values are given as the amount of supplement unless indicated otherwise. The elemental zinc content is given as provided in the respective publication and may not always correspond to Table 1.

[b] Acute lower respiratory infection may result from infection with viral or bacterial pathogens. In the studies cited here, the pathogens were not specified.

ity, and incidence of diarrhea [41, 63]. Two pooled analyses were conducted by the Zinc Investigators' Collaborative Study Group assessing the use of zinc for the prevention or treatment of diarrhea in children in developing countries [14, 15]. The combined results of seven trials of continuous zinc supplementation confirmed that zinc significantly reduces the incidence and prevalence of diarrhea [14]. When zinc was used for the treatment of acute and persistent diarrhea, the probability of continuation was reduced and the rate of treatment failure or death was diminished by 42%. These results caused the authors to conclude a substantial benefit of zinc supplementation for the treatment of both acute and persistent diarrhea in children [15]. However, a recent report points out that this may not be the case for infants younger than six months of age [166].

Diarrhea leads to increased intestinal loss and malnutrition with micronutrients, including zinc. This loss can be corrected by oral zinc supplementation, which may improve the absorption of water and electrolytes by the intestine [52, 63, 108], lead to a faster regeneration of the gut epithelium [12], and increase the levels of enterocyte brush-border enzymes [49, 106]. Finally, the loss of zinc may negatively affect immune function, which can be antagonized by zinc supplementation to improve the clearance of bacterial pathogens from the intestine [146].

When zinc supplementation was examined in patients with shigellosis, which is induced by different species of *Shigella*, several studies report improvements. These include increased intestinal mucosal permeability, alkaline phosphatase activity and better nitrogen absorption [3], but also augmented lymphocyte proliferation in response to phytohemagglutinin and increased antigen-specific IgG titers [125]. In addition, augmented serum antibody titers together with an increase in $CD20^+$ cells (B cells) and $CD20^+/CD38^+$ cells (plasma cells) were observed [124]. All these effects indicate that the effect of zinc is likely mediated by a modulation of immune function.

Leprosy is induced by infection with the pathogen *Mycobacterium leprae*. Leprosy patients with borderline tuberculoid leprosy, borderline lepromatous leprosy, and lepromatous leprosy have reduced serum zinc levels [51]. Hence, several zinc supplementation studies have been conducted. All of them reported different, but beneficial, effects. One study found a reduction in the required dose of clofazimine, a withdrawal of primarily essential steroids, and an improved toleration of dapsone after zinc treatment. Furthermore, they observed a reduced incidence and severity of erythema nodosum leprosum, a gradual decrease in the size of granuloma, and a gradual increase in the number of lymphocytes [89]. Another study reported a decreased incidence of erythema, edema, and infiltration as well as a reduced bacterial index of granuloma. In addition, there was a regrowth of eyebrows and an increase in neovascularization and endothelial cell proliferation [90]. Those beneficial effects of zinc treatment were confirmed by two other studies [36, 84], which detected decreased size of skin nodules, improved delayed hypersensitivity reactions, a disappearance of erythema and a regrowth of eyebrows [36] as well as improvements regarding frequency, duration, and severity of erythema nodosum leprosum reactions, and a reduction in steroid requirements [84].

Another form of mycobacterial infection is tuberculosis, which is caused by the pathogen *Mycobacterium tuberculosis* and associated with lower serum zinc levels [22]. Here, one study reported an increase in plasma retinol concentration, earlier sputum conversion, and resolution of X-ray lesion areas in response to zinc supplementation [69].

Effective clearance of mycobacterial infections requires a TH1-mediated activation of infected macrophages by IFN-γ [42]. Studies in mice showed that zinc may improve an imbalance in T cell subpopulations, which reflects a disturbed helper/suppressor cell ratio. Here, zinc acts by inducing T cell activation or alteration of lymphokine production, which in turn may activate macrophages to promote bacterial clearance [43]. Zinc can induce the production of IFN-γ in human peripheral blood mononuclear cells [136]. Furthermore, zinc deficiency leads to a TH2 shift, which is mainly characterized by a reduction of IL-2 and IFN-γ [10, 20, 117]. It was also reported that zinc promotes a TH1 immune response by augmenting the gene expression of IL-2 and IFN-γ [8].

Zinc supplementation has also been investigated against acute lower respiratory infection. Two studies reported decreased episodes of infection [141] and increased recovery rates from illness and fever after zinc therapy [85], whereby the effect in the latter study was only significant in boys. Lower respiratory infection may be caused by different bacterial or viral pathogens, the nature of which was not investigated in these studies. Hence it can be concluded that zinc treatment reduces the symptoms, but an effect of zinc on the immune response against the underlying pathogens cannot be concluded from these data. A pooled analysis of four trials in which continuous supplementation was investigated confirmed that zinc is efficient for the prevention of pneumonia. Here, zinc supplementation reduced the incidence of pneumonia in children in developing countries by 41% [14]. Pneumonia is a major factor of childhood mortality; it accounts for approximately 20% of childhood deaths in developing countries [175], making zinc supplementation a promising approach for a significant reduction in childhood mortality. In addition, a recent study indicates that zinc may also be helpful for the elderly. Serum zinc concentrations were negatively associated with the incidence of pneumonia in nursing home residents, indicating that zinc supplementation may be a measure to prevent pneumonia in the elderly [93].

Low gastric mucosal zinc concentrations in *Heliobacter pylori*-infected patients were correlated with the severity of inflammation, measured as infiltration by polymorphonuclear cells into the gastric mucosa [144]. Treatment with polaprezinc (zinc L-carnosine), which is used as an anti-ulcer drug in Japan, led to an improved cure rate when administered together with antimicrobial triple therapy [70]. This indicates that zinc could also be effective as an adjunct therapy for the treatment and eradication of *H. pylori* infection.

Parasitic infections

Various zinc supplementation studies dealing with diseases caused by parasites are listed in Table 5. One of these is acute cutaneous leishmaniasis, induced by different forms of *Leishmania*. Patients with cutaneous, mucosal, and visceral leishmaniasis display lower plasma zinc levels [161]. As a result of zinc therapy, a dose-dependent decrease in erythemas and size of induration

Table 5. Zinc supplementation and parasites

Disease	Zinc species	Zinc dosage[a]	Period	Participants	Effect of zinc supplementation	References
Acute cutaneous leishmaniasis	zinc sulfate	0.83, 1.67 or 3.33 mg/kg (three times daily)	45 d	92 (Z), 12 (P)	increased serum zinc levels and cure rate; decreased erythema and size of induration	147
Malaria	zinc gluconate	10 mg (elemental) daily, 6 days per week	46 w	136 (Z), 138 (P)	reduction in *Plasmodium falciparum*--mediated febrile episodes	145
	zinc acetate/ /zinc gluconate	70 mg (elemental) twice per week	15 mo	55 (Z), 54 (P)	not statistically significant trend towards fewer malaria episodes; no effect on plasma and hair zinc, diarrhea, and respiratory illness	9
	zinc sulfate	12.5 mg daily, 6 days per week	6 mo	336 (Z), 344 (P)	increased serum zinc levels; reduced prevalence of diarrhea	98
	zinc sulfate	20 or 40 mg (elemental) daily	4 d	473 (Z), 483 (P)	increased plasma zinc, no effect on fever, parasitemia, or hemoglobin concentration	177
	zinc sulfate	20 mg (elemental) daily	7 mo	191 (Z), 189 (P)	no significant effect on *P. vivax* incidence; significantly reduced diarrhea morbidity	128

Z – zinc, P – placebo.

[a] Values are given as the amount of supplement unless indicated otherwise. The elemental zinc content is given as provided in the respective publication and may not always correspond to Table 1.

and an increased cure rate were found [147]. A direct anti-leishmanial effect was shown for zinc which could be demonstrated *in vitro* by zinc-induced inhibition of several enzymes from *Leishmania* [5, 6]. However, the lowest concentration investigated in the assays was 150 μM, and many inhibitions were only observed at even higher concentrations. Therefore, the physiological relevance of these observations may be limited.

Another area of zinc application is malaria. During acute malaria, plasma zinc levels are reduced and inversely correlate to C-reactive protein, indicating a decrease of zinc as a consequence of the acute-phase response [33]. There are some studies dealing with the usefulness of zinc supplementation against this disease, with contradictory results. Two papers reported beneficial effects, including a reduced incidence in *P. falciparum*-mediated febrile episodes [145] and a trend toward fewer malaria episodes [9]. However, the last-mentioned study was statistically not significant and found no zinc-mediated effect on diarrhea and respiratory infection [9]. Two other studies also found no effect of zinc on the incidence of malaria, but demonstrated that zinc supplementation decreased morbidity from diarrhea [98, 128]. In addition to these trials, which focused on the prevention of malaria by zinc supplementation, the therapeutic value of zinc as an adjunct to standard chemotherapy for the treatment of acute malaria has also been investigated in a large multicenter study in Ecuador and four African countries [177]. Here, no effect of zinc was found on any of the parameters that were investigated.

With regard to a potential mechanism, it seems remarkable that zinc protects against morbidity mediated by *P. falciparum*, but not by *P. vivax*. This selectivity indicates that zinc may act on a specific pathogenic process, for example the sequestration of mature parasite-infected erythrocytes in the microvasculature, which is associated only with *P. falciparum* [145].

AUTOIMMUNE DISEASES

Table 6 summarizes zinc supplementation studies in patients who suffer from one of two autoimmune diseases, namely rheumatoid arthritis (RA) and type I or insulin-dependent diabetes mellitus (IDDM). When the effect of zinc supplementation on RA patients was investigated, one study detected positive changes after zinc therapy regarding joint swelling, morning stiffness, and walking time [148]. However, two other studies found no antirheumatic activity of zinc [91, 126]. Conversely, it was shown that zinc supplementation modulated *ex vivo* phagocytosis and oxidative burst in phagocytes from RA patients [62, 109]. At present, these contradicting data do not allow concluding an effectiveness of zinc for treating RA.

Patients with RA show reduced serum zinc levels [101, 178], which may be due to a malabsorption of zinc [99]. A way in which zinc deficiency could affect the pathogenesis of RA is its influence on pro-inflammatory cytokine secretion. In patients with RA, the serum zinc level correlates negatively with levels of TNF-α and IL-1β as well as parameters for inflammation such as acute-phase proteins and erythrocyte sedimentation. This corresponds to a cellular *in vitro* model for zinc deficiency in which the levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-8 were

Table 6. Zinc supplementation and autoimmune diseases

Disease	Zinc species	Zinc dosage[a]	Period	Participants	Effect of zinc supplementation	References
Type 1 diabetes	zinc gluconate	30 mg (daily)	3 mo	18 (P, Z)	increased plasma zinc levels and selenium glutathione peroxidase activtiy; decreased plasma thiobarbituric acid reactive substances	39
	zinc gluconate	50 mg (elemental) daily	1 mo	7 (Z), 6 (C)	increase in HbA1c and mononuclear leukocyte zinc	25
	zinc glycine	7.5 to 15 mg daily	4 mo	20 (Z), 17 (C)	increase in HbA1c	29
Rheumatoid arthritis	zinc sulfate	220 mg three times daily	12 w	9 (Z), 12 (P)	positive changes regarding joint swelling, morning stiffness, walking time; no improvements regarding grip strength	148
	zinc sulfate	220 mg three times daily	6 mo	12 (Z), 9 (P)	no antirheumatic activity, only increase in alkaline phosphatase level	91
	zinc sulfate	220 mg (=45 mg elemental) three times daily	8 w to 24 mo	22 (Z)	no improvements	126
	zinc aspartate	130 mg two times daily	15 d	10 (Z), 10 (C)	reduced capacity of monocytes to release reactive oxygen species after *in vitro* stimulation	62
	zinc gluconate	45 mg (elemental) daily	2 mo	11 (Z), 11 (P)	increased plasma zinc levels, phagocytosis of blood polymorphonuclear cells and mean phagocytotic activity	109

Z – zinc, P – placebo, C – control.
[a] Values are given as the amount of supplement unless indicated otherwise. The elemental zinc content is given as provided in the respective publication and may not always correspond to Table 1.

increased [8], and to other observations demonstrating that monocytic production of pro-inflammatory cytokines is inhibited by zinc ions [164, 165].

IDDM is typically accompanied by a loss of zinc due to increased urinary excretion, resulting in a decrease in total body zinc. This secondary zinc deficiency might contribute to diabetic complications [21]. On the one hand, zinc is necessary for insulin maturation and storage as a solid hexamer bound with two zinc ions per hexamer in insulin secreting pancreatic β cells [30, 37, 53]. On the other hand, zinc deficiency comprises the potential to hinder immune function, interacting with pro-inflammatory cytokine production as discussed above. Both effects suggest a potential benefit for zinc as a supporting therapeutic intervention in diabetic patients.

Besides its action on the immune system, zinc supplementation may have an additional effect on patients with IDDM or RA. Zinc deficiency is known to induce oxidative stress [18], and in both diseases, reactive oxygen species contribute to the pathogenesis [1, 104]. The influence of zinc on redox metabolism is well established [87, 115] and several mechanisms have been suggested by which zinc can act as an antioxidant. Because zinc itself is not redox active in biological systems, its antioxidant function is indirect, for example through the expression of MT [59, 87]. Moreover, zinc can bind to thiolate groups and protect them from oxidation by lowering their susceptibility to oxidation [87]. Other trace metals can also play a role in RA. Excess iron aggravates inflammation [1] and zinc has been shown to counteract transition metal-mediated oxidation by interfering with the Haber Weiss cycle [18]. Finally, zinc is important for antioxidant enzymes. It was suggested that zinc may exert an effect on lipid peroxidation by protecting the active site of the selenium-glutathione peroxidase, which is important for detoxification of reactive oxygen species, against the binding of toxic ligands with subsequent inactivation of the enzyme [39]. In addition, the zinc-containing metalloenzyme Cu/Zn superoxide dismutase, which catalyzes the degradation of superoxide to hydrogen peroxide, is effective against IDDM [76] and RA [1] *in vivo*.

How much does the zinc deficiency observed in both types of patients contribute to oxidative damage? Although this has not been directly investigated so far, the improvement in parameters for oxidative stress in diabetic patients indicates that the antioxidant effect of zinc is relevant for disease progression *in vivo*. One study found a positive effect on oxidative stress, measured by an increase in selenium-glutathione peroxidase activity, and a decrease in plasma thiobarbituric acid reactive substances, which are an indicator for lipid peroxidation [39]. On the other hand, two other studies detected an increase in the glycosylated form of hemoglobin, HbA1c, indicating a further deterioration of metabolic control [25, 29]. Taken together, it seems that zinc supplementation can be helpful against oxidative stress, but its effect on glucose metabolism may limit its usefulness in diabetic patients.

VACCINATION

Antibody production during both the first and an immunological memory response is disturbed by zinc deficiency [28, 44, 45], suggesting that zinc supplementation could improve vaccination results. Experiments in mice showed that antibody production in response to T cell-dependent antigens is more sensitive to zinc deficiency than in response to T cell-independent antigens [96] and zinc deficiency impairs TH cell function [43].

The various effects of zinc supplementation on different forms of vaccination are listed in Table 7. Although both the elderly and hemodialysis patients have a high risk for being zinc deficient, there was no influence of zinc on influenza vaccination in either group [122, 127, 156]. Conversely, there is one study from which a relationship between zinc status and vaccination response can be concluded. In this report, a correlation between failure to respond to diphtheria vaccination by elderly chronic hemodialysis patients and low serum zinc level was found [75]. Other studies analyzed the effect of zinc on cholera vaccination and had contradictory results. On the one hand, an increase in vibriocidal antibody titers after zinc therapy could be found [4, 68], while on the other, a suppression of antibody formation against cholera toxin was detected [68, 123].

So far, only one study has reported an entirely beneficial effect of zinc on vaccination. In contrast to all other studies, the patients started with zinc treatment one month prior to tetanus vaccination, but stopped taking zinc during vaccination. Following this treatment the patients showed an increase in the anti-tetanus toxin IgG titer and also in the number of circulating T lymphocytes and an improved delayed type hypersensitivity reaction toward several different antigens [32]. Potentially, zinc is required to restore normal TH cell function, but because it has a direct inhibitory effect on T lymphocytes [171], supplementation during vaccination may hinder efficient vaccination response. It may be a promising approach to investigate the time- and concentration-dependent effect of zinc on vaccination in order to define an optimal treatment protocol.

CONCLUSION

It is well established that zinc status is an essential aspect of an intact immune system. However, in the studies discussed above it could not always be distinguished if zinc acts solely as an immune-modulator or to what extent other functions, for example its antioxidant properties, contribute to an *in vivo* effect of zinc supple-

Table 7. Zinc supplementation and vaccination

Disease	Zinc species	Zinc dosage[a]	Period	Participants	Effect of zinc supplementation	References
Tetanus	zinc sulfate	220 mg two times daily	1 mo prior to vaccination	11 (Z), 11 (C)	increased anti-tetanus toxin IgG titer	32
Cholera	zinc acetate	20 mg (elemental) daily	6 w	125 (Z), 124 (P)	increased serum zinc levels and vibriocidal antibody titer	4
	zinc sulfate	200 mg (=45 mg elemental zinc) three times daily	9 d	15 (Z), 15 (P)	lower increase in antibody titers (IgA and IgG); increased fecal antibody titer (IgA) and vibriocidal antibody titer	68
	zinc acetate	20 mg (elemental) daily	6 w	125 (Z), 124 (P)	lower increase in antibody titer (IgA and IgG)	123
Influenza	zinc sulfate	220 mg two times daily	4 w, starting 1 w prior vaccination	43 (Z), 41 (P)	no effect on vaccination	127
	zinc sulfate	200 mg two times daily	60 d, starting 15 d prior vaccination	194 (Z), 190 (P)	increased plasma zinc levels; no effect on vaccination	122
	zinc sulfate	120 mg (2–3 times per week after hemodialysis)	1 mo	13 (Z), 13 (P), 13 (C)	increased serum zinc levels; no effect on vaccination	156

Z – zinc, P – placebo, C – control.

[a] Values are given as the amount of supplement unless indicated otherwise. The elemental zinc content is given as provided in the respective publication and may not always correspond to Table 1.

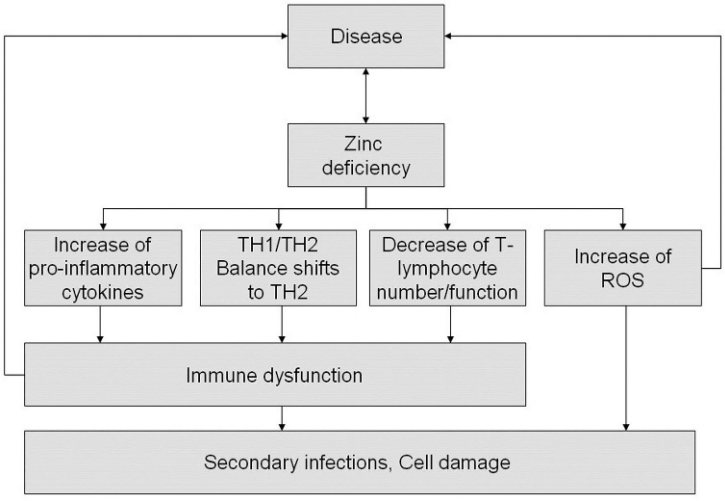

Fig. 3. Interaction between zinc homeostasis and disease. While many diseases affect zinc homeostasis, the latter can modulate several components of the immune system, but also general metabolic processes such as the production of reactive oxygen species (ROS). These can lead to complications such as secondary infections and cellular damage, but also contribute to the initial disease.

mentation. Due to the clear effects of zinc deficiency and supplementation on numerous immune parameters, especially pro-inflammatory cytokines and T lymphocytes, it can be safely assumed that its effect on the immune system contributes significantly to the results observed in supplementation trials for different diseases.

In most cases it is not known to what extent zinc deficiency is causal for a disease or if it occurs secondary to the disease and only contributes to its severity or the occurrence of complications or secondary infections (Fig. 3). In any event, zinc supplementation can be effective in correcting both states. Therapeutic zinc supplementation in diseases such as acute lower respiratory infection, chronic hepatitis C, diarrhea, shigellosis, leprosy, tuberculosis, and acute cutaneous leishmaniasis is beneficial. Unfortunately, these observations cannot be generalized. The results for the common cold and malaria are still not conclusive, and zinc was ineffective in many vaccination trials as well as most RA studies. It is unclear if this can be overcome by changes in dosage or duration. In AIDS and type 1 diabetes, zinc supplementation may even be a risk factor for increased mortality or deterioration of the glucose metabolism, respectively. In these cases, zinc supplementation should be avoided, or at least limited to clearly zinc--deficient individuals.

Future work should aim at two aspects. First, by paying more attention to zinc dosage and the patient's zinc status before and during the supplementation, it should be possible to administer the optimal amount of zinc and thereby significantly improve the therapeutic effects. Here the standard parameter, i.e. total serum or plasma zinc, does not adequately reflect the patient's zinc status, but the development of new methods such as the use of fluorescent probes for the measurement of labile intracellular zinc [56] may lead to improvement. Secondly, elucidating the molecular mechanisms by which zinc acts will help to provide a successful treatment, in particular when zinc is given in combination with other substances. Here an important first step will be evaluating which *in vitro* observations are relevant. Given that many effects can only be seen when supra-physiological concentrations of zinc are used, as in the different cases of the inhibition of viral replication, the likelihood for an *in vivo* relevance is questionable. There is still great potential for improving the use of zinc as a therapeutic agent and successful application for the modulation of the immune response.

REFERENCES

1. Aaseth J., Haugen M. and Førre O. (1998): Rheumatoid arthritis and metal compounds – perspectives on the role of oxygen radical detoxification. Analyst, **123**, 3–6.
2. Aggett P. J. (1991): The assessment of zinc status: a personal view. Proc. Nutr. Soc., **50**, 9–17.
3. Alam A. N., Sarker S. A., Wahed M. A., Khatun M. and Rahaman M. M. (1994): Enteric protein loss and intestinal permeability changes in children during acute shigellosis and after recovery: effect of zinc supplementation. Gut, **35**, 1707–1711.
4. Albert M. J., Qadri F., Wahed M. A., Ahmed T., Rahman A. S., Ahmed F., Bhuiyan N. A., Zaman K., Baqui A. H., Clemens J. D. and Black R. E. (2003): Supplementation with zinc, but not vitamin A, improves seroconversion to vibriocidal antibody in children given an oral cholera vaccine. J. Infect. Dis., **187**, 909–913.
5. Al-Mulla Hummadi Y. M., Al-Bashir N. M. and Najim R. A. (2005): The mechanism behind the antileishmanial effect of zinc sulphate. II. Effects on the enzymes of the parasites. Ann. Trop. Med. Parasitol., **99**, 131–139.
6. Al-Mulla Hummadi Y. M., Najim R. A. and Al-Bashir N. M. (2005): The mechanism behind the antileishmanial effect of zinc sulphate. I. An *in-vitro* study. Ann. Trop. Med. Parasitol., **99**, 27–36.
7. Auld D. S. (2001): Zinc coordination sphere in biochemical zinc sites. Biometals, **14**, 271–313.
8. Bao B., Prasad A. S., Beck F. W. and Godmere M. (2003): Zinc modulates mRNA levels of cytokines. Am. J. Physiol. Endocrinol. Metab., **285**, 1095–1102.

9. Bates C. J., Evans P. H., Dardenne M., Prentice A., Lunn P. G., Northrop-Clewes C. A., Hoare S., Cole T. J., Horan S. J., Longman S. C., Stirling D. and Aggett P. J. (1993): A trial of zinc supplementation in young rural Gambian children. Br. J. Nutr., **69**, 243–255.
10. Beck F. W., Prasad A. S., Kaplan J., Fitzgerald J. T. and Brewer G. J. (1997): Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. Am. J. Physiol., **272**, 1002–1007.
11. Berg K., Bolt G., Andersen H. and Owen T. C. (2001): Zinc potentiates the antiviral action of human IFN-alpha tenfold. J. Interferon Cytokine Res., **21**, 471–474.
12. Bettger W. J. and O'Dell B. L. (1981): A critical physiological role of zinc in the structure and function of biomembranes. Life Sci., **28**, 1425–1438.
13. Beyersman D. and Haase H. (2001): Functions of zinc in signaling, proliferation and differentiation of mammalian cells. Biometals, **14**, 331–341.
14. Bhutta Z. A., Black R. E., Brown K. H., Gardner J. M., Gore S., Hidayat A., Khatun F., Martorell R., Ninh N. X., Penny M. E., Rosado J. L., Roy S. K., Ruel M., Sazawal S. and Shankar A. (1999): Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J. Pediatr., **135**, 689–697.
15. Bhutta Z. A., Bird S. M., Black R. E., Brown K. H., Gardner J. M., Hidayat A., Khatun F., Martorell R., Ninh N. X., Penny M. E., Rosado J. L., Roy S. K., Ruel M., Sazawal S. and Shankar A. (2000): Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am. J. Clin. Nutr., **72**, 1516–1522.
16. Bobat R., Coovadia H., Stephen C., Naidoo K. L., McKerrow N., Black R. E. and Moss W. J. (2005): Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double--blind placebo-controlled trial. Lancet, **366**, 1862–1867.
17. Bohnsack B. L. and Hirschi K. K. (2004): Nutrient regulation of cell cycle progression. Annu. Rev. Nutr., **24**, 433–453.
18. Bray T. M. and Bettger W. J. (1990): The physiological role of zinc as an antioxidant. Free Radic. Biol. Med., **8**, 281–291.
19. Cakman I., Kirchner H. and Rink L. (1997): Zinc supplementation reconstitutes the production of interferon-α by leukocytes from elderly persons. J. Interferon Cytokine Res., **17**, 469–472.
20. Cakman I., Rohwer J., Schutz R. M., Kirchner H. and Rink L. (1996): Dysregulation between TH1 and TH2 T cell subpopulations in the elderly. Mech. Ageing Dev., **87**, 197–209.
21. Chausmer A. B. (1998): Zinc, insulin and diabetes. J. Am. Coll. Nutr., **17**, 109–115.
22. Ciftci T. U., Ciftci B., Yis Ö., Guney Y., Bilgihan A. and Ogretensoy M. (2003): Changes in serum selenium, copper, zinc levels and Cu/Zn ratio in patients with pulmonary tuberculosis during therapy. Biol. Trace Elem. Res., **95**, 65–71.
23. Coovadia H. M. and Bobat R. (2002): Zinc deficiency and supplementation in HIV/AIDS. Nutr. Res., **22**, 179–191.
24. Coto J. A., Hadden E. M., Sauro M., Zorn N. and Hadden J. W. (1992): Interleukin 1 regulates secretion of zinc-thymulin by human thymic epithelial cells and its action on T--lymphocyte proliferation and nuclear protein kinase C. Proc. Natl. Acad. Sci. USA, **89**, 7752–7756.
25. Cunningham J. J., Fu A., Mearkle P. L. and Brown R. G. (1994): Hyperzincuria in individuals with insulin-dependent diabetes mellitus: concurrent zinc status and the effect of high-dose zinc supplementation. Metabolism, **43**, 1558–1562.
26. Dardenne M., Savino W., Borrih S. and Bach J. F. (1985): A zinc dependent epitope of the molecule of thymulin, a thymic hormone. Proc. Natl. Acad. Sci. USA, **82**, 7035–7038.
27. Deloria-Knoll M., Steinhoff M., Semba R. D., Nelson K., Vlahov D. and Meinert C. L. (2006): Effect of zinc and vitamin A supplementation on antibody responses to a pneumococcal conjugate vaccine in HIV-positive injection drug users: a randomized trial. Vaccine, **24**, 1670–1679.
28. Depasquale-Jardieu P. and Fraker P. J. (1984): Interference in the development of a secondary immune response in mice by zinc deprivation: persistence of effects. J. Nutr., **114**, 1762–1769.
29. de Sena K. C., Arrais R. F., das Gracas Almeida M., de Araujo D. M., dos Santos M. M., de Lima V. T. and de Fatima Campos Pedrosa L. (2005): Effects of zinc supplementation in patients with type 1 diabetes. Biol. Trace Elem. Res., **105**, 1–9.
30. Dodson G. and Steiner D. (1998): The role of assembly in insulin's biosynthesis. Curr. Opin. Struct. Biol., **8**, 189–194.
31. Dreosti I. E. (2001): Zinc and the gene. Mutat. Res., **475**, 161–167.
32. Duchateau, J., Delepesse G., Vrijens R. and Collet H. (1981): Beneficial effects of oral zinc supplementation on the immune response of old people. Am. J. Med., **70**, 1001–1004.
33. Duggan C., MacLeod W. B., Krebs N. F., Westcott J. L., Fawzi W. W., Premji Z. G., Mwanakasale V., Simon J. L., Yeboah-Antwi K. and Hamer D. H. (2005): Plasma zinc concentrations are depressed during the acute phase response in children with falciparum malaria. J. Nutr., **135**, 802–807.
34. Durnam D. M. and Palmiter R. D. (1981): Transcriptional regulation of the mouse metallothionein-I gene by heavy metals. J. Biol. Chem., **256**, 5712–5716.
35. Edwards H. M. and Baker D. H. (1999): Bioavailability of zinc in several sources of zinc oxide, zinc sulfate, and zinc metal. J. Anim. Sci., **77**, 2730–2735.
36. el-Shafei M. M., Kamal A. A., Soliman H., el Shayeb F., Abdel Baqui M. S., Faragalla S. and Sabry M. K. (1988): Effect of oral zinc supplementation on the cell mediated immunity in lepromatous leprosy. J. Egypt. Public Health Assoc., **63**, 311–336.
37. Emdin S. O., Dodson G. G., Cutfield J. M. and Cutfield S. M. (1980): Role of zinc in insulin biosynthesis: some possible zinc-insulin interactions in the pancreatic B-cell. Diabetologia, **19**, 174–182.
38. Falchuk K. H. (1993): Zinc in developmental biology: the role of metal dependent transcription regulation. Prog. Clin. Biol. Res., **380**, 91–111.
39. Faure P., Benhamou P. Y., Perard A., Halimi S. and Roussel A. M. (1995): Lipid peroxidation in insulin-dependent diabetic patients with early retina degenerative lesions: effects of an oral zinc supplementation. Eur. J. Clin. Nutr., **49**, 282–288.
40. Fawzi W. W., Villamor E., Msamanga G. I., Antelman G., Aboud S., Urassa W. and Hunter D. (2005): Trial of zinc supplements in relation to pregnancy outcomes, hemato-

logic indicators, and T cell counts among HIV-1-infected women in Tanzania. Am. J. Clin. Nutr., **81**, 161–167.
41. Fischer Walker C. and Black R. E. (2004): Zinc and the risk for infectious disease. Ann. Rev. Nutr., **24**, 255–275.
42. Flynn J. L., Chan J., Triebold K. J., Dalton D. K., Stewart T. A. and Bloom B. R. (1993): An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. J. Exp. Med., **178**, 2249–2254.
43. Fraker P. J., De Pasquale-Jardieu R., Zwickl C. M. and Luecke R. W. (1978): Regeneration of T-cell helper function in zinc-deficient adult mice. Proc Natl. Acad. Sci. USA, **75**, 5660–5664.
44. Fraker P. J., Gershwin M. E., Good R. A. and Prasad A. S. (1986): Interrelationships between zinc and immune function. Fed. Proc., **45**, 1474–1479.
45. Fraker P. J., Jardieu P. and Cook J. (1987): Zinc deficiency and the immune function. Arch. Dermatol. Res., **123**, 1699–1701.
46. Fraker P. J. and King L. E. (2004): Reprogramming of the immune system during zinc deficiency. Annu. Rev. Nutr., **24**, 277–298.
47. Fukamachi Y., Karasaki Y., Sugiura T., Itoh H., Abe T., Yamamura K. and Higashi K. (1998): Zinc suppresses apoptosis of U937 cells induced by hydrogen peroxide through an increase of Bcl-2/Bax ratio. Biochem. Biophys. Res. Comm., **246**, 364–369.
48. Gartside J. M. and Allen B. R. (1975): Treatment of acrodermatitis enteropathica with zinc sulphate. Br. Med. J., **3**, 521–522.
49. Gebhard R. L., Karouani R., Prigge W. F. and McClain C. J. (1983): Effect of severe zinc deficiency on activity of intestinal disaccharidases and 3-hydroxy-3-methy-glutaryl coenzyme A reductase in the rat. J. Nutr., **113**, 855–859.
50. Geist F. C., Bateman J. A. and Hayden F. G. (1987): *In vitro* activity of zinc salts against human rhinoviruses. Antimicrob. Agents Chemother., **31**, 622–624.
51. George J., Bhatia V. N., Balakrishnan S. and Ramu G. (1991): Serum zinc/copper ratio in subtypes of leprosy and effect of oral zinc therapy on reactional states. Int. J. Lepr. Other Mycobact. Dis., **59**, 20–24.
52. Ghishan F. K. (1984): Transport of electrolytes, water, and glucose in zinc deficiency. J. Pediatr. Gastroenterol. Nutr., **3**, 608–612.
53. Gold G. and Grodsky G. M. (1984): Kinetic aspects of compartmental storage and secretion of insulin and zinc. Experientia, **40**, 1105–1114.
54. Green J. A., Lewin S. R., Wightman F., Lee M., Ravindran T. S. and Paton N. I. (2005): A randomised controlled trial of oral zinc on the immune response to tuberculosis in HIV-infected patients. Int. J. Tuberc. Lung Dis., **9**, 1378–1384.
55. Grummt F., Weinmann-Dorsch C., Schneider-Schaulies J. and Lux A. (1986): Zinc as a second messenger of mitogenic induction. Effects on diadenosine tetraphosphate (Ap4A) and DNA synthesis. Exp. Cell Res., **163**, 191–200.
56. Haase H., Hebel S., Engelhardt G. and Rink L. (2006): Flow cytometric measurement of labile zinc in peripheral blood mononuclear cells. Anal. Biochem., **352**, 222–230.
57. Haase H., Mocchegiani E. and Rink L. (2006): Correlation between zinc status and immune function in the elderly. Biogenterology, **7**, 421–428.
58. Haase H. and Rink L. (2007): Signal transduction in monocytes: the role of zinc ions. Biometals, **20**, 579–585.
59. Hao Q. and Maret W. (2005): Imbalance between pro-oxidant and pro-antioxidant functions of zinc in disease. J. Alzheimers Dis., **8**, 161–170.
60. Haraguchi Y., Sakurai H., Hussain S., Anner B. M. and Hoshino H. (1999): Inhibition of HIV-1 infection by zinc group metal compounds. Antiviral Res., **43**, 123–133.
61. Henderson L. M., Brewer G. J., Dressman J. B., Swidan S. Z., DuRoss D. J., Adair C. H., Barnett J. L. and Berardi R. R. (1995): Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. JPEN J. Parenter. Enteral Nutr., **19**, 393–397.
62. Herold A., Bucurenci N., Mazilu E., Szegli G., Sidenco L. and Baican I. (1993): Zinc aspartate *in vivo* and *in vitro* modulation of reactive oxygen species production by human neutrophils and monocytes. Roum. Arch. Microbiol. Immunol., **52**, 101–108.
63. Hoque K. M. and Binder H. J. (2006): Zinc in the treatment of acute diarrhea: current status and assessment. Gastroenterology, **130**, 2201–2205.
64. Hulisz D. (2004): Efficacy of zinc against common cold viruses: an overview. J. Am. Pharm. Assoc., **44**, 594–603.
65. Ibs K. H. and Rink L. (2003): Zinc-altered immune function. J. Nutr., **133**, 1452S–1456S.
66. Jackson J. L., Lesho E. and Peterson C. (2000): Zinc and the common cold: a meta-analysis revisited. J. Nutr., **130**, 1512S–1515S.
67. Jackson J. L., Peterson C. and Lesho E. (1997): A meta--analysis of zinc salts lozenges and the common cold. Arch. Intern. Med., **157**, 2373–2376.
68. Karlsen T. H., Sommerfelt H., Klomstad S., Andersen P. K., Strand T. A., Ulvik R. J., Ahren C. and Grewal H. M. (2003): Intestinal and systemic immune responses to an oral cholera toxoid B subunit whole-cell vaccine administered during zinc supplementation. Infect. Immun., **71**, 3903–3913.
69. Karyadi E., West C. E., Schultink W., Nelwan R. H., Gross R., Amin Z., Dolmans W. M., Schlebusch H. and van der Meer J. W. (2002): A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am. J. Clin. Nutr., **75**, 720–727.
70. Kashimura H., Suzuki K., Hassan M., Ikezawa K., Sawahata T., Watanabe T., Nakahara A., Mutoh H. and Tanaka N. (1999) Polaprezinc, a mucosal protective agent, in combination with lansoprazole, amoxycillin and clarithromycin increases the cure rate of *Helicobacter pylori* infection. Aliment. Pharmacol. Ther., **13**, 483–487.
71. Kelly R. W. and Abel M. H. (1983): Copper and zinc inhibit the metabolism of prostaglandin by the human uterus. Biol. Reprod., **28**, 883–889.
72. Ko W. S., Guo C. H., Hsu G. S., Chiou Y. L., Yeh M. S. and Yaun S. R. (2005): The effect of zinc supplementation on the treatment of chronic hepatitis C patients with interferon and ribavirin. Clin. Biochem., **38**, 614–620.
73. Korant B. D. and Butterworth B. E. (1976): Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. J. Virol., **18**, 298–306.
74. Korant B. D., Kauer J. C. and Butterworth B. E. (1974): Zinc ions inhibit replication of rhinoviruses. Nature, **248**, 588–590.
75. Kreft B., Fischer A., Kruger S., Sack K., Kirchner H. and Rink L. (2000): The impaired immune response to diphtheria vaccination in elderly chronic hemodialysis patients is related to zinc deficiency. Biogerontology, **1**, 61–66.

76. Kubisch H. M., Wang J., Luche R., Carlson E., Bray T. M., Epstein C. J. and Phillips J. P. (1994): Transgenic copper/zinc superoxide dismutase modulates susceptibility to type 1 diabetes. Proc. Natl. Acad. Sci. USA, **91**, 9956–9959.
77. Kümel G., Schrader S., Zentgraf H., Daus H. and Brendel M. (1990): The mechanism of the antiherpetic activity of zinc sulphate. J. Gen. Virol., **71**, 2989–2997.
78. Kurugöl Z., Akilli M., Bayram N. and Koturoglu G. (2006): The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. Acta Paediatr., **95**, 1175–1181.
79. Küry S., Dréno B., Bézieau S., Giraudet S., Kharfi M., Kamoun R. and Moisan J. P. (2002): Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. Nat. Genet., **31**, 239–240.
80. Liuzzi J. P., Lichten L. A., Rivera S., Blanchard R. K., Aydemir T. B., Knutson M. D., Ganz T. and Cousins R. J. (2005): Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. Proc. Natl. Acad. Sci. USA, **102**, 6843–6848.
81. Lombeck I., Schnippering H. G., Ritzl F., Feinendegen L. E. and Bremer H. J. (1975): Absorption of zinc in acrodermatifis enteropathica. Lancet, **1**, 855.
82. Lonnerdal B. (2000): Dietary factors influencing zinc absorption. J. Nutr., **130**, 1378–1383.
83. MacDonald R. S. (2000): The role of zinc in growth and cell proliferation. J. Nutr., **130**, 1500–1508.
84. Mahajan P. M., Jadhav V. H., Patki A. H., Jogaikar D. G. and Mehta J. M. (1994): Oral zinc therapy in recurrent erythema nodosum leprosum: a clinical study. Indian J. Lepr., **66**, 51–57.
85. Mahalanabis D., Lahiri M., Paul D., Gupta S., Gupta A., Wahed M. A. and Khaled M. A. (2004): Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. Am. J. Clin. Nutr., **79**, 430–436.
86. Manuel Y., Thomas Y. and Pellegrini O. (1992): Metallothionein and tissue damage. IARC Sci. Publ., **118**, 231–237.
87. Maret W. (2006): Zinc coordination environments in proteins as redox sensors and signal transducers. Antioxid. Redox Signal., **8**, 1419–1441.
88. Maret W. and Sandstead H. H. (2006): Zinc requirements and the risks and benefits of zinc supplementation. J. Trace Elem. Med. Biol., **20**, 3–18.
89. Mathur N. K., Bumb R. A. and Mangal H. N. (1983): Oral zinc in recurrent Erythema Nodosum Leprosum reaction. Lepr. India, **55**, 547–552.
90. Mathur N. K., Bumb R. A., Mangal H. N. and Sharma M. L. (1984): Oral zinc as an adjunct to dapsone in lepromatous leprosy. Int. J. Lepr. Other Mycobact. Dis., **52**, 331–338.
91. Mattingly P. C. and Mowat A. G. (1982): Zinc sulphate in rheumatoid arthritis. Ann. Rheum. Dis., **41**, 456–457.
92. Mesner P. W., Bible K. C., Martins L. M., Kottke T. J., Srinivasula S. M., Svingen P. A., Chilcote T. J., Basi G. S., Tung J. S., Krajewski S., Reed J. C., Alnemri E. S., Earnshaw W. C. and Kaufmann S. H. (1999): Characterization of caspase processing and activation in HL-60 cell cytosol under cell-free conditions. Nucleotide requirement and inhibitor profile. J. Biol. Chem., **274**, 22635–2264.
93. Meydani S. N., Barnett J. B., Dallal G. E., Fine B. C., Jacques P. F., Leka L. S. and Hamer D. H. (2007): Serum zinc and pneumonia in nursing home elderly. Am. J. Clin. Nutr., **86**, 1167–1173.
94. Mittmann U. (2001): Bioverfügbarkeit von Zink-Präparaten. J. Pharmakol. Ther. **5**, 143–153.
95. Mocchegiani E., Veccia S., Ancarani F., Scalise G. and Fabris N. (1995): Benefit of oral zinc supplementation as an adjunct to zidovudine (AZT) therapy against opportunistic infections in AIDS. Int. J. Immunopharmacol., **17**, 719–727.
96. Moulder K. and Steward M. W. (1989): Experimental zinc deficiency: effects on cellular responses and the affinity of humoral antibody. Clin. Exp. Immunol., **77**, 269–274.
97. Moynahan E. J. (1974): Acrodermatitis enteropathica: a lethal inherited human zinc-deficiency disorder. Lancet, **2**, 399–400.
98. Müller O., Becher H., van Zweeden A. B., Ye Y., Diallo D. A., Konate A. T., Gbangou A., Kouyate B. and Garenne M. (2001): Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomised double blind placebo controlled trial. Br. Med. J., **322**, 1–6.
99. Naveh Y., Schapira D., Ravel Y., Geller E. and Scharf Y. (1997): Zinc metabolism in rheumatoid arthritis: plasma and urinary zinc and relationship to disease activity. J. Rheumatol., **24**, 643–646.
100. Neldner K. H. and Hambidge K. M. (1975): Zinc therapy in acrodermatitis enteropathica. N. Engl. J. Med., **292**, 879–882.
101. Niedermeier W. and Griggs J. H. (1971): Trace metal composition of synovial fluid and blood serum of patients with rheumatoid arthritis. J. Chronic Dis., **23**, 527–536.
102. Novick S. G., Godfrey J. C., Godfrey N. J. and Wilder H. R. (1996): How does zinc modify the common cold? Clinical observations and implications regarding mechanism of action. Med. Hypotheses, **46**, 295–302.
103. Novick S. G., Godfrey J. C., Pollack R. L. and Wilder H. R. (1997): Zinc-induced suppression of inflammation in the respiratory tract, caused by infection with human rhinovirus and other irritants. Med. Hypotheses, **49**, 347–357.
104. Oberley L. W. (1988): Free Radicals and Diabetes. Free Radical Biol. Med., **5**, 113–124.
105. Olivares M., Pizarro F. and Ruz M. (2007): New insights about iron bioavailability inhibition by zinc. Nutrition, **23**, 292–295.
106. Park J. H., Grandjean C. J., Antonson D. L. and Vanderhoof J. A. (1985): Effects of short term isolated zinc deficiency on intestinal growth and activities of brush border enzymes in weaning rats. Pediatr. Res., **19**, 1333–1336.
107. Pasternak C. A. (1987): A novel form of host defense: membrane protection by Ca^{2+} and Zn^{2+}. Biosci. Rep., **7**, 81–91.
108. Patrick J., Michael J., Golden M. N., Golden B. E. and Hilton P. J. (1978): Effect of zinc on leukocyte sodium transport *in vivo*. Clin. Sci. Mol. Med., **54**, 585–587.
109. Peretz A., Cantinieaux B., Neve J., Siderova V. and Fondu P. (1994): Effects of zinc supplementation on the phagocytic functions of polymorphonuclears in patients with inflammatory rheumatic diseases. J. Trace Elem. Electrolytes Health Dis., **8**, 189–194.
110. Pernelle J. J., Creuzet C., Loeb J. and Gacon G. (1991): Phosphorylation of the lymphoid cell kinase p56lck is stimulated by micromolar concentrations of Zn^{2+}. FEBS Lett., **281**, 278–282.

111. Perry D. K., Smyth M. J., Stennicke H. R., Salvesen G. S., Duriez P., Poirier G. G. and Hannun Y. A. (1997): Zinc is a potent inhibitor of the apoptotic protease, caspase-3. A novel target for zinc in the inhibition of apoptosis. J Biol Chem., **272**, 18530–18533.
112. Petrie L., Chesters J. K. and Franklin M. (1991): Inhibition of myoblast differentiation by lack of zinc. Biochem. J., **276**, 109–111.
113. Philcox J. C., Coyle P., Michalska A., Choo K. H. and Rofe A. M. (1995): Endotoxin-induced inflammation does not cause hepatic zinc accumulation in mice lacking metallothionein gene expression. Biochem J., **308**, 543–546.
114. Porter K. G., McMaster D., Elmes M. E. and Love A. H. (1977): Anaemia and low serum-copper during zinc therapy. Lancet, **2**, 774.
115. Powell S. R. (2000): The antioxidant properties of zinc. J. Nutr., **130**, 1447–1454.
116. Prasad A. S. (1984): Discovery and importance of zinc in human nutrition. Fed. Proc., **43**, 2829–2834.
117. Prasad A. S. (2000): Effects of zinc deficiency on Th1 and Th2 cytokine shifts. J. Infect. Dis., **182**, 62–68.
118. Prasad A. S., Bao B., Beck F. W., Kucuk O. and Sarkar F. H. (2004): Antioxidant effect of zinc in humans. Free. Radic. Biol. Med., **37**, 1182–1190.
119. Prasad A. S., Beck F. W., Endre L., Handschu W., Kukuruga M. and Kumar G. (1996): Zinc deficiency affects cell cycle and deoxythymidine kinase gene expression in HUT-78 cells. J. Lab. Clin. Med., **128**, 9–11.
120. Prasad A. S., Brewer G. J., Schoomaker E. B. and Rabbani P. (1978): Hypocupremia induced by zinc therapy in adults. JAMA, **240**, 2166–2168.
121. Prasad A. S., Miale A., Farid Z., Sandstead H. H. and Schulert A. R. (1963): Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. J. Lab. Clin. Med., **61**, 537–549.
122. Provinciali M., Montenovo A., Di Stefano G., Colombo M., Daghetta L., Cairati M., Veroni C., Cassino R., Della Torre F. and Fabris N. (1998): Effect of zinc or zinc plus arginine supplementation on antibody titre and lymphocyte subsets after influenza vaccination in elderly subjects: a randomized controlled trial. Age Ageing, **27**, 715–722.
123. Qadri F., Ahmed T., Wahed M. A., Ahmed F., Bhuiyan N. A., Rahman A. S., Clemens J. D., Black R. E. and Albert M. J. (2004): Suppressive effect of zinc on antibody response to cholera toxin in children given the killed, B subunit-whole cell, oral cholera vaccine. Vaccine, **22**, 416–421.
124. Rahman M. J., Sarker P., Roy S. K., Ahmad S. M., Chisti J., Azim T., Mathan M., Sack D., Andersson J. and Raqib R. (2005): Effects of zinc supplementation as adjunct therapy on the systemic immune responses in shigellosis. Am. J. Clin. Nutr., **81**, 495–502.
125. Raqib R., Roy S. K., Rahman M. J., Azim T., Ameer S. S., Chisti J. and Andersson J. (2004): Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. Am. J. Clin. Nutr., **79**, 444–450.
126. Rasker J. J. and Kardaun S. H. (1982): Lack of beneficial effect of zinc sulphate in rheumatoid arthritis. Scand. J. Rheumatol., **11**, 168–170.
127. Remarque E. J., Witkamp L., Masurel N. and Ligthart G. J. (1993): Zinc supplementation does not enhance antibody formation to influenza virus vaccine in the elderly. Aging Immunol. Infect. Dis., **4**, 17–23.
128. Richard S. A., Zavaleta N., Caulfield L. E., Black R. E., Witzig R. S. and Shankar A. H. (2006): Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am. J. Trop. Med. Hyg., **75**, 126–132.
129. Rink L. and Gabriel P. (2001): Extracellular and immunological actions of zinc. Biometals, **14**, 367–383.
130. Rink L. and Haase H. (2007): Zinc homeostasis and immunity. Trends Immunol., **28**, 1–4.
131. Rink L. and Seyfarth M. (1997): [Characteristics of immunologic test values in the elderly]. Z. Gerontol. Geriatr., **30**, 220–225.
132. Rosado J. L., Munoz E., Lopez P. and Allen L. H. (1993): Absorption of zinc sulfate, methionine, and polyascorbate in the presence and absence of a plant based rural mexican diet. Nutr. Res., **13**, 1141–1151.
133. Rousseau M. C., Molines C., Moreau J. and Delmont J. (2000): Influence of highly active antiretroviral therapy on micronutrient profiles in HIV-infected patients. Ann. Nutr. Metab., **44**, 212–216.
134. Safie-Garabedian B., Ahmed K., Khamashta M. A., Taub N. A. and Hughes G. R. (1993): Thymulin modulates cytokine release by peripheral blood mononuclear cells: a comparison between healthy volunteers and patients with systemic lupus erythematodes. Int. Arch. Allergy Immunol., **101**, 126–131.
135. Saha A. R., Hadden E. M. and Hadden J. W. (1995): Zinc induces thymulin secretion from human thymic epithelial cells *in vitro* and augments splenocyte and thymocyte responses *in vivo*. Int. J. Immunopharmacol., **17**, 729–733.
136. Salas M. and Kirchner H. (1987): Induction of interferon-γ in human leukocyte cultures stimulated by Zn^{2+}. Clin. Immunol. Immunopathol., **45**, 139–142.
137. Salgueiro M. J., Zubillaga M., Lysionek A., Cremaschi G., Goldman C. G., Caro R., De Paoli T., Hager A., Weill R. and Boccio J. (2000): Zinc status and immune system relationship. Biol. Trace Elem. Res., **76**, 193–205.
138. Salgueiro M. J., Zubillaga M., Lysionek A., Sarabia M. I., Caro R., De Paoli T., Hager A., Weill R. and Boccio J. (2000): Zinc as an essential micronutrient: a review. Nutr. Res., **20**, 737–755.
139. Salzman M. B., Smith E. M. and Koo C. (2002): Excessive oral zinc supplementation. J. Pediatr. Hematol. Oncol., **24**, 582–584.
140. Sato M. and Bremner I. (1993): Oxygen free radicals and metallothionein. Free Radic. Biol. Med., **14**, 325–337.
141. Sazawal S., Black R. E., Jalla S., Mazumdar S., Sinha A. and Bhan M. K. (1998): Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. Pediatrics, **102**, 1–5.
142. Schölmerich J., Freudemann A., Köttgen E., Wietholtz H., Steiert B., Lohle E., Häussinger D. and Gerok W. (1987): Bioavailability of zinc from zinc-histidine complexes. I. Comparison with zinc sulfate in healthy men. Am. J. Clin. Nutr., **45**, 1480–1486.
143. Schroeder J. J. and Cousins R. J. (1990): Interleukin 6 regulates metallothionein gene expression and zinc metabolism in hepatocyte monolayer cultures. Proc. Natl. Acad. Sci. USA, **87**, 3137–3141.
144. Sempertegui F., Diaz M., Mejia R., Rodriguez-Mora O. G., Renteria E., Guarderas C., Estrella B., Recalde R., Hamer D. H. and Reeves P. G. (2007): Low concentrations of zinc in gastric mucosa are associated with

increased severity of Helicobacter pylori-induced inflammation. Helicobacter, **12**, 43–48.
145. Shankar A. H., Genton B., Baisor M., Paino J., Tamja S., Adiguma T., Wu L., Rare L., Bannon D., Tielsch J. M., West K. P. Jr. and Alpers M. P. (2000): The influence of zinc supplementation on morbidity due to *Plasmodium falciparum*: a randomized trial in preschool children in Papua New Guinea. Am. J. Trop. Med. Hyg., **62**, 663–669.
146. Shankar A. H. and Prasad A. S. (1998): Zinc and immune function: the biological basis of altered resistance to infection. Am. J. Clin. Nutr., **68**, 447–463.
147. Sharquie K. E., Najim R. A., Farjou I. B. and Al-Timimi D. J. (2001): Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. Clin. Exp. Dermatol., **26**, 21–26.
148. Simkin P. A. (1976): Oral zinc sulphate in rheumatoid arthritis. Lancet, **2**, 539–542.
149. Stehbens W. E. (2004): Oxidative stress in viral hepatitis and AIDS. Exp. Mol. Pathol., **77**, 121–132.
150. Stennicke H. R. and Salvesen G. S. (1997): Biochemical characteristics of caspases-3, -6, -7 and -8. J. Biol. Chem., **272**, 25719–25723.
151. Sunderman F. W. (1995): The influence of zinc on apoptosis. Ann. Clin. Lab. Sci., **25**, 134–142.
152. Takagi H., Nagamine T., Abe T., Takayama H., Sato K., Otsuka T., Kakizaki S., Hashimoto Y., Matsumoto T., Kojima A., Takezawa J., Suzuki K., Sato S. and Mori M. (2001): Zinc supplementation enhances the response to interferon therapy in patients with chronic hepatitis C. J. Viral. Hepat., **8**, 367–371.
153. Tang A. M., Graham N. M., Kirby A. J., McCall L. D., Willett W. C. and Saah A. J. (1993): Dietary micronutrient intake and risk of progression to acquired immunodeficiency syndrome (AIDS) in human immunodeficiency virus type 1 (HIV-1)-infected homosexual men. Am. J. Epidemiol., **138**, 937–951.
154. Tang A. M., Graham N. M. and Saah A. J. (1996): Effects of micronutrient intake on survival in human immunodeficiency virus type 1 infection. Am. J. Epidemiol., **143**, 1244–1256.
155. Truong-Tran A. Q., Carter J., Ruffin R. E. and Zalewski P. D. (2001): The role of zinc in caspase activation and apoptotic cell death. Biometals, **14**, 315–330.
156. Turk S., Bozfakioglu S., Ecder S. T., Kahraman T., Gurel N., Erkoc R., Aysuna N., Turkmen A., Bekiroglu N. and Ark E. (1998): Effects of zinc supplementation on the immune system and on antibody response to multivalent influenza vaccine in hemodialysis patients. Int. J. Artif. Organs, **21**, 274–278.
157. Turner J. M., Brodsky M. H., Irving B. A., Levin S. D., Perlmutter R. M. and Littman D. R. (1990): Interaction of the unique N-terminal region of tyrosine kinase p56lck with cytoplasmic domains of CD4 and CD8 is mediated by cysteine motifs. Cell, **60**, 755–765.
158. Turner R. B. (2001): The treatment of rhinovirus infections: progress and potential. Antiviral Res., **49**, 1–14.
159. Valberg L. S., Flanagan P. R. and Chamberlain M. J. (1984): Effect of iron, tin and copper on zinc absorption in humans. Am. J. Clin. Nutr., **40**, 536–541.
160. Vallee B. L. and Falchuk K. H. (1993): The biochemical basis of zinc physiology. Physiol. Rev., **73**, 79–118.
161. Van Weyenbergh J., Santana G., D'Oliveira A. Jr., Santos A. F. Jr., Costa C. H., Carvalho E. M., Barral A. and Barral-Netto M. (2004): Zinc/copper imbalance reflects immune dysfunction in human leishmaniasis: an *ex vivo* and *in vitro* study. BMC Infect. Dis., **4**, 50.
162. Viarengo A., Burlando B., Ceratto N. and Panfoli I. (2000): Antioxidant role of metallothioneins: a comparative overview. Cell. Mol. Biol. (Noisy-le-grand), **46**, 407–417.
163. Villamor E., Aboud S., Koulinska I. N., Kupka R., Urassa W., Chaplin B., Msamanga G. and Fawzi W. W. (2006): Zinc supplementation to HIV-1-infected pregnant women: Effects on maternal anthropometry, viral load, and early mother-to-child transmission. Eur. J. Clin. Nutr., **60**, 862–869.
164. von Bulow V., Dubben S., Engelhardt G., Hebel S., Plumakers B., Heine H., Rink L. and Haase H. (2007): Zinc-dependent suppression of TNF-alpha production is mediated by protein kinase A-induced inhibition of Raf-1, IkappaB kinase beta, and NF-kappaB. J. Immunol. **179**, 4180–4186.
165. von Bulow V., Rink L. and Haase H. (2005): Zinc-mediated inhibition of cyclic nucleotide phosphodiesterase activity and expression suppresses TNF-alpha and IL-1 beta production in monocytes by elevation of guanosine 3',5'-cyclic monophosphate. J. Immunol., **175**, 4697–4705.
166. Walker C. L., Bhutta Z. A., Bhandari N., Teka T., Shahid F., Taneja S. and Black R. E. (2007): Zinc during and in convalescence from diarrhea has no demonstrable effect on subsequent morbidity and anthropometric status among infants <6 mo of age. Am. J. Clin. Nutr., **85**, 887–894.
167. Wang K., Zhou B., Kuo Y. M., Zemansky J. and Gitschier J. (2002): A novel member of a zinc transporter family is defective in acrodermatitis enteropathica. Am. J. Hum. Genet., **71**, 66–73.
168. Wedekind K. J. and Baker D. H. (1990): Zinc bioavailability in feed-grade sources of zinc. J. Anim. Sci., **68**, 684–689.
169. Wedekind K. J., Lewis A. J., Giesemann M. A. and Miller P. S. (1994): Bioavailability of zinc from inorganic and organic sources for pigs fed corn-soybean meal diets. J. Anim. Sci., **72**, 2681–2689.
170. Wellinghausen N., Kirchner H. and Rink L. (1997): The immunobiology of zinc. Immunol. Today, **18**, 519–521.
171. Wellinghausen N., Martin M. and Rink L. (1997): Zinc inhibits IL-1 dependent T cell stimulation. Eur. J. Immunol., **27**, 2529–2535.
172. Wolf C. M. and Eastman A. (1999): The temporal relationship between protein phosphatase, mitochondrial cytochrome c release, and caspase activation in apoptosis. Exp. Cell Res., **247**, 505–513.
173. Wu F. Y. and Wu C. W. (1987): Zinc in DNA replication and transcription. Annu. Rev. Nutr., **7**, 251–272.
174. Yuasa K., Naganuma A., Sato K., Ikeda M., Kato N., Takagi H. and Mori M. (2006): Zinc is a negative regulator of hepatitis C virus RNA replication. Liver Int., **26**, 1111–1118.
175. Zar H. J. and Madhi S. A. (2006): Childhood pneumonia – progress and challenges. S. Afr. Med. J., **96**, 890–900.
176. Zazzo J. F., Rouveix B., Rajagopalon P., Levacher M. and Girard P. M. (1989): Effect of zinc on the immune status of zinc-depleted AIDS related complex patients. Clin. Nutr., **8**, 259–261.
177. Zinc Against Plasmodium Study Group (2002): Effect of zinc on the treatment of Plasmodium falciparum malaria in children: a randomized controlled trial. Am. J. Clin. Nutr., **76**, 805–812.
178. Zoli A., Altomonte L., Caricchio R., Galossi A., Mirone L., Ruffini M. P. and Magaro M. (1998): Serum zinc and copper in active rheumatoid arthritis: correlation with interleukin 1 beta and tumour necrosis factor alpha. Clin. Rheumatol., **17**, 378–382.