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Mini Review

Zinc supplementation for the treatment or prevention of disease: Current status and future perspectives

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Abstract

Zinc is a nutritionally essential trace element, and thus zinc deficiency may severely affect human health. Many studies were published in which the effect of nutritional zinc supplementation on the incidence or severity of a certain disease was investigated. This review summarizes the main observations and aims to evaluate the use of nutritional zinc supplementation for prevention and treatment of human disease.

Keywords: Zinc; Zinc supplementation; Infection; Immune system; Zinc deficiency; Essential trace element

1. Introduction

The importance of zinc was first documented for *Aspergillus niger* (Raulin, 1869). It took over 75 years to realize that zinc is also an essential trace element for rats (Todd et al., 1935), and an additional 30 years went by before it was recognized that this was also true for humans (Prasad et al., 1963; Sandstead et al., 1967).

Following the initial observation that zinc is required for the catalytic activity of carbonic anhydrase (Keilin and Mann, 1940), it became clear that zinc is a component of more than 300 enzymes from all six enzyme classes (Vallee and Falchuk, 1993). Bioinformatic estimates report that 10% of the human proteome contain zinc binding motives (Andreini et al., 2006). Based on its role in such a plethora of cellular components, zinc has diverse biological functions in enzymatic catalysis (Auld, 2001), redox regulation (Maret, 2006), cellular signal transduction (Beyersmann and Haase, 2001), the immune system (Wellinghausen et al., 1997), and neurons (Frederickson et al., 2005).

Zinc deficiency leads to a retardation of growth and development in children, retarded genital development and hypogonadism, dermatitis and delayed wound healing, alopecia, poor pregnancy outcomes and teratology, and decreased immune function with a resulting increased susceptibility to infections (Maret and Sandstead, 2006). The prevalence of zinc deficiency is estimated to be high, with billions of people at risk, in particular in the developing world (Maret and Sandstead, 2006). In industrialized countries, elderly people are a high risk group for zinc deficiency. In the United States, the Third National Health and Nutrition Survey showed that zinc uptake decreases with age and only 42.5% of the participants who were 71 years or older had an adequate zinc intake (Briefel et al., 2000).

Due to the wide prevalence of zinc deficiency and the multitude of zinc's essential biological functions, nutritional correction of zinc deficiency may have a significant impact on different aspects of human health. Following this rationale, over the years several hundred zinc supplementation studies have been conducted, investigating the effects of nutritional zinc supplementation on different diseases, often with contradictory results.

Zinc supplementation studies are difficult to compare due to a number of reasons. First, the zinc status of the

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subjects has to be known, since zinc deficient subjects will likely react different to zinc supplementation than zinc sufficient ones. Even when values are given, most studies measure total serum or plasma zinc. This is not an optimal method for determining an individual's zinc status, since the bioavailability of the tightly protein bound zinc can differ. Serum and plasma zinc are a suitable parameter for the diagnosis of severe, clinical zinc deficiency, but not for identifying marginal zinc deficiency, which would be the main application for nutritional studies (Aggett, 1991; Haase et al., 2006).

Another major obstacle for the comparison of different studies is based on their design. While some studies are placebo controlled, others rely on untreated control groups, or report single case studies only. In addition, the zinc supplement and the amount of zinc that is administered vary considerably. In some cases, the amount of elemental zinc can not even be determined, since insufficient information about the supplement is provided. For example, several studies in which zinc sulfate was used do not specify its chemical composition. Calculated according to their chemical formulas, the different forms of zinc sulfate contain different quantities of elemental zinc per total weight. $ZnSO_4$ contains 40.5% elemental zinc, while the zinc contents of $ZnSO_4 \times H_2O$ (36.4%) and $ZnSO_4 \times 7H_2O$ (22.7%) are significantly lower. Accordingly, a dose of 220 mg zinc sulfate could correspond to approximately 90 mg (anhydrous form), 80 mg (monohydrate), or 50 mg (heptahydrate) elemental zinc, respectively, depending on the salt form that was administered.

Further factors that should be taken into consideration include the interaction of zinc with other nutrients. This may affect bioavailability, since substances like phytate can bind zinc and reduce its uptake (Lonnerdal, 2000). Also, higher zinc concentrations can interfere with the uptake of other trace elements, in particular copper, and the beneficial effects of zinc supplementation may be abrogated by induction of copper deficiency, which can lead to severe anemia and neutropenia (Prasad et al., 1978; Porter et al., 1977). High zinc concentrations obstruct immune function (Wellinghausen et al., 1997), as demonstrated by *ex vivo* mixed lymphocyte culture inhibition after one week of supplementation with 80 mg elemental zinc per day (aCampo et al., 2001; Faber et al., 2004), a dose that is exceeded in many of the studies cited throughout this review.

This review aims to summarize current knowledge about zinc supplementation and to illustrate where zinc has been shown to have beneficial effects, where it has no effect, and in which cases further studies are advisable.

2. Zinc supplementation for disease prevention

2.1. Healthy persons

Pharmacological doses of zinc given to healthy, zinc sufficient human subjects were reported to reduce serum levels of "anti-atherogenic" high-density lipoprotein (Black et al., 1988; Hooper et al., 1980), revealing a possible health risk of high dose zinc supplementation. However, this is not a general observation and in particular when lower doses are given this does not seem to pose a risk (Bonham et al., 2003b; Boukaiba et al., 1993; Freeland-Graves et al., 1982; Samman and Roberts, 1988).

Zinc has a profound impact on virtually all cells of the immune system (Rink and Haase, 2007), and while low dose zinc supplementation to healthy persons does not affect blood leukocyte or lymphocyte subsets (Bonham et al., 2003a), it can increase the response of lymphocytes to stimulation with mitogens (Duchateau et al., 1981a). The severity of immunosenescence, which is the age related decline of immune function, corresponds to the age dependent decline in zinc status, and is counteracted by zinc supplementation (Haase et al., 2006). Zinc supplementation has been shown to improve the cell-mediated immune response of healthy elderly (Fortes et al., 1998), the delayed type hypersensitivity reaction (DTH) (Duchateau et al., 1981b; Cossack, 1989; Prasad et al., 1993), and plasma thymulin activity (Boukaiba et al., 1993; Prasad et al., 1993). However, when a group of elderly was investigated who were not zinc deficient according to their plasma zinc levels, no effect of zinc supplementation was observed (Bogden et al., 1990), indicating that the efficiency depends on the individuals zinc status. In elderly, zinc-deficient persons, a shift in the T helper cell balance towards Th2 is observed (Cakman et al., 1996). This corresponds well to a study in which mild zinc deficiency was induced experimentally in healthy human volunteers. Here, the production of typical Th1 cytokines, the recruitment of naïve T cells, and levels of cytotoxic T cells were decreased (Beck et al., 1997). The impact of mild zinc deficiency on the immune system shows that it can lead to an impairment of the immune defense. The reduction of the Th1 response in healthy individuals indicates that zinc deficiency could promote neoplasia and increase the susceptibility to viral infections.

2.2. Vaccination

Following an initial report that zinc supplementation can increase the number of positive responses and IgG titers after tetanus vaccination (Duchateau et al., 1981b), some studies tried to verify this effect for other vaccinations, but with limited success (Table 1). Among those was the investigation of the influence of zinc on cholera vaccination in Bangladeshi children (Albert et al., 2003; Qadri et al., 2004) and Norwegian medical students (Karlsen et al., 2003). Zinc treatment led to increased formation of vibriocidal antibodies (Albert et al., 2003; Karlsen et al., 2003), but suppressed the formation of antibodies against Cholera toxin (Karlsen et al., 2003; Qadri et al., 2004). The reason for this differential effect remains unclear.

Two other studies investigated the effect of zinc supplementation on influenza vaccination in the elderly, both

Table 1
Effect of zinc supplementation on vaccination

Vaccination	Zinc species and dosage	Period	Participants	Effect of zinc	Reference
Tetanus	ZS 440 mg (daily in 2 doses)	1 mo. prior to vacc.	11 (Z), 11 (C)	Anti-tetanus toxin IgG titer increased	Duchateau et al. (1981b)
Cholera	ZA 20 mg (daily, elemental)	6 w., starting 3 w. before vacc.	125 (Z), 124 (P)	Lower increase in cholera toxin IgA and IgG	Qadri et al. (2004)
	ZA 20 mg (daily, elemental)	6 w., starting 3 w. before vacc.	125 (Z), 124 (P)	Increased serum zinc and vibriocidal antibody titers	Albert et al. (2003)
	ZS 600 mg (daily in 3 doses)	9 d. starting 2 d. before vacc.	15 (Z), 15 (P)	Lower increase in serum IgA and IgG titers; increased fecal antibody titers (IgA) increased vibriocidal AB titers	Karlsen et al. (2003)
Influenza	ZS 440 mg (daily in 2 doses)	28 d., starting 7 d. before vacc.	43 (Z), 41 (P)	No effect	Remarque et al. (1993)
	ZS 400 mg (daily in 2 doses)	60 d. total, starting 15 d. before vacc.	194 (Z), 190 (P)	Increased plasma zinc; no effect on vaccination	Provinciali et al. (1998)
	ZS 120 mg (2–3 times per week after hemodialysis)	1 mo.	13[a] (Z), 13[a](P) 11[b](P)	Increased serum zinc; no effect on vaccination	Turk et al. (1998)

Z, zinc; P, placebo; C, control; ZA, zinc acetate; ZS, zinc sulfate; d., days; w., weeks; mo., months.
[a] Hemodialysis patients.
[b] Healthy subjects.

finding no effect of zinc (Provinciali et al., 1998; Remarque et al., 1993). Also, influenza vaccination in hemodialysis patients, a population with a high incidence of zinc deficiency, was not altered by zinc supplementation (Turk et al., 1998). However, a correlation between zinc status and vaccination response is suggested by another report stating that hemodialysis patients who did not respond to diphtheria vaccination did have significantly lower serum zinc levels than responders and age-matched controls (Kreft et al., 2000).

At present the majority of the data contradicts the hypothesis that zinc supplementation can increase the success rate or antibody titer after vaccination. However, cellular immunity does not recover very quickly in zinc deficient individuals, and a sufficient duration of zinc administration prior to vaccination to sufficiently restore T helper function may be necessary. In the studies that did not find an effect, zinc was given between 0 to 3 weeks prior to immunization, while the positive outcome was observed after one month of zinc administration (Duchateau et al., 1981b). Also, all studies without an effect of zinc had continued the supplementation regime after the immunization. Since T cells are inhibited by relatively low doses of zinc (Wellinghausen et al., 1997) and the formation of IgA and IgG requires T cell help, supplementation after the vaccination may suppress T cells and make the immunization less effective.

3. Therapeutic zinc supplementation

3.1. Infectious diseases

Zinc is essential for the immune system and zinc deficiency has dramatic implications for immune function (Fraker and King, 2004; Shankar and Prasad, 1998; Wellinghausen et al., 1997). Hence, it is not surprising that zinc deficiency increases the risk for several infectious diseases like diarrhea, pneumonia, and malaria (Fischer Walker and Black, 2004). Accordingly, zinc supplementation has been suggested to be beneficial and has been investigated in different experimental settings (Table 2).

One disease for which the use of zinc has been extensively investigated is the common cold, and the results have already been summarized in detail elsewhere (Hulisz, 2004). These results are contradictory to some extent, and design and sample size of several studies have been criticized. Overall, it can be concluded that zinc is effective in shortening the duration of the common cold, but only if it is administered no later than 24 h within the onset of the symptoms (Hulisz, 2004). The mechanism by which zinc acts against the common cold is still not completely understood. It has been found that zinc inhibits the rhinovirus 3C protease, and hereby viral replication, but this effect was only observed in vitro and not in vivo (Turner, 2001). Also discussed is an interference of zinc with the binding of the rhinovirus to its cellular receptor, the adhe-

Table 2
Zinc supplementation and Infectious diseases

Disease	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Malaria	ZA/ZG 70 mg (elemental, twice per week)	15 mo.	55 (Z), 54 (P)	No effect on plasma and hair zinc, trend towards fewer malaria episodes (not statistically significant), no effect on diarrhea or respiratory illness	Bates et al. (1993)
	ZG 10 mg (elemental, daily, 6 days per week)	46 w.	136 (Z), 138 (P)	Reduction in *Plasmodium falciparum*-mediated febrile episodes	Shankar et al. (2000)
	ZS 12.5 mg (daily, 6 days per week)	6 mo.	336 (Z), 344 (P)	Increased serum zinc, no effect on malaria, but reduced prevalence of diarrhea	Muller et al. (2001)
HIV/AIDS	ZG 45 mg (three times daily)	15 d.	5 (Z), 5 (C)	Increased zinc in red blood cells and number of HLA-DR+ cells, stimulation of lymphocyte transformation and phagocytosis of opsonized zymosan by PMN	Zazzo et al. (1989)
	ZS 200 mg (daily)	1 mo.	29 (Z), 28 (P)	Increase or stabilization in plasma zinc and body weight; increase in CD4+ T cells and plasma active zinc-bound thymulin; reduced or delayed frequency of opportunistic infections due to *Pneumocystis carinii* and *Candida*, not to *Cytomegalovirus* and *Toxoplasma*	Mocchegiani et al. (1995)
	ZS 10 mg (daily, elemental)	6 mo.	44 (Z), 41(P)	No effect of HIV-1 viral load, but reduction of morbidity from diarrhea	Bobat et al. (2005)
	ZS 220 mg (daily)	1 mo.	31 (Z), 34 (P)	No effects on immune response to tuberculosis, CD4/CD8 ratio, lymphocyte subsets and viral load	Green et al. (2005)
	ZG 50 mg (daily)	6 d.	44 (Z), 45 (P)	No improvement of antibody responses to a pneumococcal conjugate vaccine	Deloria-Knoll et al. (2006)
Recurrent aphthous stomatitis	ZS 660 mg (daily in 3 doses)	3 mo.	20 (P, Z)	No therapeutic effect	Wray (1982)
	ZS 220 mg (daily)	1 mo.	20 (Z), 20 (P)	Increased serum zinc, serum albumin, and serum alkaline phosphatase activity; aphthae disappeared; reduced recurrence scores	Orbak et al. (2003)
Common cold	>12 different studies			variable results, zinc reduces duration of symptoms if administered within 24h of onset	Hulisz (2004)
Acute lower respiratory infection	ZG 10 mg (daily, elemental)	6 mo.	298 (Z), 311 (P)	Increased plasma zinc, decreased episodes of infection	Sazawal et al. (1998)
	ZA 20 mg (daily in 2 doses, elemental)	5 d.	76 (Z), 74 (P)	Increase in serum zinc and recovery rates from illness and fever in boys	Mahalanabis et al. (2004)
Leprosy	ZS 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	Mathur et al. (1983)
	ZS 220 mg (daily)	18 mo.	15 (Z), 10 (P)	Increased serum zinc; decreased erythema, edema and infiltration; regrowth of eyebrows; reduced bacterial index of granuloma; increased neovascularization and endothelial cell proliferation	Mathur et al. (1984)
	ZA 400 mg (daily in 2 doses)	13 w.	17 (Z), 10 (P), 10 (C)	Increased serum zinc and delayed hypersensitivity reactions; decreased size of skin nodules; disappearance of erythema; regrowth of eyebrows	el-Shafei et al. (1988)
	ZS 220 mg/d.	4 mo.	40 (Z)	Improvements regarding frequency, duration and severity of erytheme nodosum leprosum reactions; reduction in steroid requirement	Mahajan et al. (1994)
Tuberculosis	ZS 15 mg (daily)	6 mo.	40 (Z), 40 (P)	Increased plasma retinol concentrations; earlier sputum conversion and resolution of X-ray lesion area	Karyadi et al. (2002)
Acute cutaneous leishmaniasis	ZS 2.5, 5 or 10 mg/kg (daily in three doses)	45 d.	92 (Z), 12 (C)	Increased serum zinc; decreased erythema and size of induration; increased cure rate	Sharquie et al. (2001)
Diarrheal diseases	Multiple studies of different design			Decreased duration, severity and occurrence of diarrhea	Hoque and Binder (2006)

Z, zinc; P, placebo; C, control; d., days; w., weeks; mo., months; ZA, zinc acetate; ZS, zinc sulfate; ZG, zinc gluconate.

sion molecule ICAM-1, or an interaction of zinc with host immune function (Hulisz, 2004).

Another disease where zinc supplementation is successfully applied are the different forms of diarrhea. On the one hand, diarrhea leads to increased intestinal loss of micronutrients, including zinc, which is corrected by zinc supplementation. On the other hand, several studies, which have already been summarized previously (Fischer Walker and Black, 2004; Hoque and Binder, 2006), demonstrated that zinc can also reduce the duration, severity, and incidence of diarrhea. Especially in malnourished children in the developing world, zinc administration, in addition to the standard oral rehydration, is a cost-effective and efficient way to reduce mortality from diarrhea.

Zinc is of particular importance for the development of T cells (Fraker and King, 2004; Wellinghausen et al., 1997). Hence, it seems reasonable to use it as a supporting therapeutic intervention for patients with HIV/AIDS. Initial studies seemed promising, reporting that short term supplementation of a relatively small group of five patients led to an improvement of immune function, namely an increase in the number of activated (HLA-DR positive) T cells, augmented lymphocyte transformation by phytohaemagglutinin and concanavalin A, and increased phagocytosis by polymorphonuclear neutrophils (Zazzo et al., 1989). This was supported by a paper that even described an increase in the number of T helper cells and a protective effect against infections with *Pneumocystis carinii* and *Candida* (Mocchegiani et al., 1995). However, recent papers did not find an effect on immune response, vaccination, CD4/CD8 ratio, or viral load (Bobat et al., 2005; Deloria-Knoll et al., 2006; Green et al., 2005). The only positive effect was a reduction of morbidity from diarrhea (Bobat et al., 2005).

It has been shown that zinc deficiency is prevalent among HIV infected persons, especially in malnourished patients or users of illicit drugs. In these cases, zinc deficiency is a predictor of higher mortality, although it is unclear if the zinc status has a direct influence on survival rates, or just correlates with the severity of the disease (Baum et al., 2000, 2003). However, it can not be generalized that patients with AIDS are zinc deficient, since antiretroviral therapy can normalize the zinc status (Rousseau et al., 2000). This is of particular importance because two nutritional studies showed that increased intake of zinc in HIV-1 infected patients led to an augmented risk for the progression to AIDS (Tang et al., 1993) and lower survival (Tang et al., 1996). In the quartile of patients with the highest total daily zinc intake (>20 mg/day) combined from food and supplements, the risk for progression to AIDS and poorer survival was doubled compared to the quartile with the lowest intake of zinc (<11.6 mg/day) (Tang et al., 1993, 1996). A recent study has addressed the safety of zinc supplementation, using a moderate dose of 10 mg elemental zinc per day and the authors came to the conclusion that zinc supplementation has no adverse effects (Bobat et al., 2005). However, it was performed in HIV-infected South African children, a population with high prevalence of malnutrition and limited access to medication. Although the zinc status of the children has not been determined, it can be assumed that many of them were zinc deficient (Bobat et al., 2005; Green and Paton, 2006). Zinc supplementation with HIV positive patients should be performed cautiously with constant monitoring of the patient's zinc status. While moderate supplementation to zinc-deficient patients can help stabilize their immune system, supplementation to zinc-sufficient ones may accelerate disease progression and increase mortality.

Leprosy patients with borderline tuberculoid leprosy, borderline lepromatous leprosy, and lepromateous leprosy were all found to have significantly reduced serum zinc levels compared to healthy controls (George et al., 1991). Four different studies reported beneficial effects of zinc treatment on medication requirements and an improvement of several immune parameters (el-Shafei et al., 1988; Mahajan et al., 1994; Mathur et al., 1983, 1984), indicating that zinc supplementation may support immune function and also counteract symptoms secondary to zinc deficiency in leprosy. Another study reports that zinc has similar effects on another form of mycobacterial infection, tuberculosis (Karyadi et al., 2002).

Another pulmonary disease, acute lower respiratory infection, has also been reported to be beneficially affected by zinc supplementation. Two studies, during which relatively low doses of 10 mg elemental zinc per day were given to children, reported generally decreased episodes of infection (Sazawal et al., 1998) and increased recovery rates (Mahalanabis et al., 2004). Inexplicably, the latter study only found a significant effect in boys but not in girls (Mahalanabis et al., 2004).

Zinc administration has also been tested during parasite infection, namely malaria and cutaneous leishmaniasis. Plasma zinc levels generally decline during the acute phase of an infection. This has been confirmed for acute malaria infection and can be at least partially restored by nutritional zinc supplementation (Duggan et al., 2005). The incidence of *Plasmodium falciparum*-mediated febrile episodes was reported to be reduced by zinc supplementation compared to the placebo group of preschool children located in a malaria endemic region of Papua New Guinea (Shankar et al., 2000), and a lower incidence of malaria in zinc-supplemented children from Gambia was reported (Bates et al., 1993). The latter was not statistically significant, and zinc did not have an effect on diarrhea or respiratory infection (Bates et al., 1993). An effect of zinc on the incidence of *P. falciparum* induced malaria was not confirmed by a larger study in Burkina Faso, however this time they found a reduction in the prevalence of diarrhea in zinc treated malaria patients (Muller et al., 2001). Acute cutaneous leishmaniasis was positively affected by application of zinc sulfate (Sharquie et al., 2001), with a dose-dependent healing rate of >96% in patients treated with the highest dose of 10 mg zinc sulfate per kg body weight, compared to 0% in the control group. However, this study was not blind or placebo controlled, and the control patients had

significantly different size, number, and localization of the lesions.

There is in vitro evidence that zinc has a direct anti-leishmanial effect, inhibiting several enzymes from *Leishmania* (Al-Mulla Hummadi et al., 2005a,b). On the other hand, zinc may interact with the patient's immune system. A successful response against the intracellular parasite requires a Th1 immune response. Zinc deficiency leads to a reduction of Th1 cytokines (Beck et al., 1997), and patients with cutaneous, mucosal, and visceral leishmaniasis display significantly lower plasma zinc levels than control subjects (Van Weyenbergh et al., 2004). Thus, correcting zinc deficiency could support the Th1-mediated defense against *Leishmania*.

Investigation of the use of zinc supplementation for the treatment of recurrent aphtous stomatitis has led to contradicting results. While it was reported that zinc sulfate (660 mg per day) has no effect and therefore is not a recommended treatment (Wray, 1982), a later report did find significant improvements (Orbak et al., 2003). Remarkably, the latter study used only a third of the dose from the previous one. Hence, a moderate zinc supplementation could be more effective for the treatment of recurrent aphtous stomatitis than the application of a very high dose.

3.2. Genetic disorders

Zinc supplementation studies have been conducted in patients with different genetically based disorders (Table 3). The classical zinc deficiency syndrome Acrodermatitis enteropathica (AE) is based on a mutation of the intestinal zinc transport protein hZIP-4 (Kury et al., 2002; Wang et al., 2002), which mediates zinc uptake from food in the duodenum and jejunum. AE is characterized by skin lesions, developmental retardation, alopecia, and immune deficiency. All these symptoms are caused by zinc deficiency and are completely reversed by nutritional supplementation with zinc. To date, continuous nutritional supplementation with high doses of zinc is the standard treatment for AE (Maverakis et al., 2007).

Another disease where zinc is routinely used is Wilson's disease, an autosomal recessive disorder with excessive accumulation of copper in the body. Here, the interference of high zinc doses with copper uptake is utilized to reduce the copper uptake and the resulting symptoms (Brewer et al., 1994; Hoogenraad et al., 1984, 1987; Rossaro et al., 1990).

Down syndrome, or trisomy of chromosome 21, is associated with reduced plasma zinc levels (Fabris et al., 1984). Several reports of a normalization of thymulin levels, thyroid hormones and functions of several different immune cells indicate that zinc has several positive effects on the health of patients with Down syndrome (Bucci et al., 1999; Chiricolo et al., 1993; Franceschi et al., 1988; Licastro et al., 1992, 1993, 1994a,b; Lockitch et al., 1989; Napolitano et al., 1990).

There are clinical similarities between patients with sickle cell anemia and zinc deficiency. Patients with sickle cell disease have been shown to have increased urinary excretion of zinc and, subsequently, reduced plasma, erythrocyte, and hair zinc levels (Prasad et al., 1975). Sickle cell anemia patients seem to benefit from zinc supplementation, since zinc positively influences serum hormone levels, physical development, and affects immune function, e.g., reducing the incidences of bacterial infections (Prasad et al., 1981, 1999; Prasad and Cossack, 1984; Zemel et al., 2002).

3.3. Diabetes

A general observation in diabetes, type 1 as well as type 2, is a loss of zinc due to increased urinary excretion. The resulting decrease in total body zinc may contribute to diabetic complications (Chausmer, 1998). Mechanistically, zinc has been described as having an insulinomimetic effect (Coulston and Dandona, 1980; May and Contoreggi, 1982). This may be based on its physiological role in insulin receptor signal transduction, and in particular on its function as a regulator of protein tyrosine phosphatases (Haase and Maret, 2003, 2005a,b). Hence, zinc supplementation may be deemed appropriate for diabetic patients. Furthermore, oxidative stress has been indicated as a significant contributor to the pathogenesis of diabetes. Many studies cited in Table 4 report positive effects on oxidative stress measured by thiobarbituric acid reactive substances, an indicator for lipid peroxidation (Anderson et al., 2001; Faure et al., 1995; Roussel et al., 2003).

HbA1c, glycosylated hemoglobin, is frequently used as a biomarker for glycaemic control in diabetes. Two studies with type 1 diabetic patients showed an increase (Cunningham et al., 1994; de Sena et al., 2005), while another study, in type 2 patients, found a decrease HbA1c (Al-Maroof and Al-Sharbatti, 2006). Several others did not find effects on HbA1c or glucose metabolism (Anderson et al., 2001; Roussel et al., 2003; Niewoehner et al., 1986). Promising results were found in a study investigating the effect of zinc supplementation on subjects with diabetic neuropathy. Reduced blood sugar levels were observed as well as improvement in motor nerve conduction velocity (Gupta et al., 1998). Although zinc has in vitro effects on redox (Maret, 2006) and cellular glucose metabolism (Tang and Shay, 2001), only a redox effect is reproducible in vivo in different studies, whereby the influence on glucose metabolism remains unclear. The effect of zinc on glucose metabolism may be species specific. While the zinc status did affect glucose levels in experimental animals, intravenous injection of zinc (25 mg) had no effect on plasma glucose in healthy or diabetic human subjects (Brandao-Neto et al., 1999). Furthermore, all in vitro experiments that indicated an effect of zinc on the cellular level were performed in a murine cell line (Tang and Shay, 2001). Taken together, there is a discernible indication that zinc is helpful against oxidative stress in diabetic patients, but the effects of zinc supplementation on glucose metabolism in humans require more detailed investigations.

Table 3
Zinc supplementation and genetic disorders

Disease or disorder	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Sickle cell disease	ZA 45 mg (daily in 3 doses)	6 to 18 mo.	4 (P, Z)	Increase in plasma zinc and serum testosterone, decrease in plasma lactic dehydrogenase levels	Prasad et al. (1981)
	ZA 45 mg (daily in 3 doses)	6 to 18 mo.	7 (Z), 7 (P)	Increase in plasma zinc and serum testosterone, decrease in plasma lactic dehydrogenase levels	
	ZA 30 mg (daily in 2 doses)	1 y.	5 (Z), 5 (P) 5 (P, Z)	Increase in plasma and erythrocyte zinc, greater increase in height, body weight and serum testosterone levels	Prasad and Cossack (1984)
	ZA 50 to 75 mg (daily, elemental)	3 y.	11 (Z), 11 (P)	Increase in plasma, lymphocyte and granulocyte zinc and IL-2 production; decreased incidence of bacterial infections, number of hospitalizations and vaso-occlusive pain crisis	Prasad et al. (1999)
	10 mg (daily, elemental)	1 y.	20 (Z), 22 (P)	Increased plasma zinc levels, height, sitting height, knee height and arm circumference	Zemel et al. (2002)
Acrodermatitis enteropathica	3 mg/kd daily (elemental) as a starting dose			Complete clearance of all symptoms	Maverakis et al. (2007)
Down syndrome	ZG 25 to 50 mg/day	6 mo.	64 (P, Z)	Increase in serum zinc levels, no effect on several immune parameters	Lockitch et al. (1989)
	ZS 1 mg/kg (daily)	4 mo.	25, 14 (C)	Normalization of serum zinc, thymulin, thyroid stimulating hormone and 3,3′,5′ triiodothyonine; decreased incidence of infectious diseases	Licastro et al. (1992)
	ZS 1 mg/kg (daily)	4 mo.	51 (Z), 15 (C)	Normalization of plasma zinc, thymulin, TSH and reversal T3	Licastro et al. (1993)
	ZS 1 mg/kg (daily)	4 mo.	51 (Z), 23 (C)	Normalization of plasma zinc, thymulin, TSH and reversal T3; increased granulocyte activity	Licastro et al. (1994b)
	ZS 1 mg/kg (daily, elemental)	4 mo.	21 (Z), 18 (C)	Normalization of plasma zinc and thymulin levels; increased lymphocyte proliferation (PHA, Con A), polymorphonuclear activity and CD3+ DR+ cells; reduced incidence of infections	Licastro et al. (1994a)
	ZS 1 mg/kg (daily)	2 mo.	18 (Z)	Increased plasma serum thymic factor level; reduced inactive serum thymic factor molecules; normalization of plasma zinc, thymulin activity and absolute number of CD2+ lymphocytes; reduced recurrent infections	Franceschi et al. (1988)
	ZS 1 mg/kg (daily)	4 mo.	15 (Z), 10 (C)	Increased thymidine incorporation of PHA stimulated lymphocytes; decelerated DNA repair	Chiricolo et al. (1993)
	ZS 1 mg/kg (daily)	6 mo.	32 (Z), 52 (P)	Reduced thyroid-stimulating hormone levels in hypozincemic subjects	Bucci et al. (1999)
	ZS 1 mg/kg (daily)	9 mo.	22 (Z)	Increased growth, growth hormone and somatomedin C levels	Napolitano et al. (1990)
Wilson‘s disease	ZS 660 mg (daily in 3 doses)	1.5 to 7 y.	5 (Z)	Increased plasma zinc and decreased plasma copper; reduction in symptoms (necrosis and inflammation in the liver, Kayser–Fleischer rings); normalization of serum albumin, prothrombin and urinary copper excretion	Rossaro et al. (1990)
	ZS 600 to 900 mg (daily in 3 doses)	2 y.	2 case reports	Reduction in body stores of copper and in Kayser-Fleischer rings	Hoogenraad et al. (1984)
	ZS 300 to 600 mg (daily in 3 doses)	1 to 323 m.	27 (Z)	Disappeared Kayser-Fleischer rings; normalization of free plasma copper concentration	Hoogenraad et al. (1987)
	ZA 150 mg (daily in 3 doses, elemental)	3 to 9 y.	13 (Z)	Decreased urinary and plasma copper levels	Brewer et al. (1994)

Z, zinc; P, placebo; C, control; mo., months; y., years; ZA, zinc acetate; ZS, zinc sulfate; ZG, zinc gluconate.

Table 4
Zinc supplementation and diabetes

Disease or disorder	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Type I diabetes	ZG 30 mg (daily)	3 mo.	18 (P, Z)	Increased plasma zinc levels and selene glutathione peroxidase activtiy; decreased plasma thiobarbituric acid reactive substances	Faure et al. (1995)
	ZG 50 mg (daily, elemental)	1 mo.	7 (Z), 6 (C)	Increase in HbA1c and mononuclear leukocyte zinc	Cunningham et al. (1994)
	Zinc glycine 7.5 to 15 mg (daily)	4 mo.	20 (Z), 17 (C)	Increase in HbA1c	de Sena et al. (2005)
Type II diabetes	ZS 30 mg (daily, elemental)	3 mo.	43 (Z), 43 (P)	Decrease in HbA1c; increase in serum zinc	Al-Maroof and Al-Sharbatti (2006)
	ZS 660 mg (daily in 3 doses)	6 to 8 w.	9 (Z), 4 (P)	Increase in serum zinc and T lymphocyte response to phytohemagglutinin	Niewoehner et al. (1986)
	ZG 30 mg (daily)	6 mo.	54 (Z), 56 (P)	Decreased plasma lipid peroxidation as measured by thiobarbituric acid reactive substances	Anderson et al. (2001)
	ZG 30 mg (daily)	6 mo.	28 (Z), 28 (P), 60 (C)	Increased plasma zinc; decreased plasma lipid peroxidation as measured by thiobarbituric acid reactive substances	Roussel et al. (2003)
Diabetic neuropathy	ZS 660 mg (daily)	6 w.	15 (Z), 15 (P), 20 (C)	Increased serum zinc levels; improvements regarding fasting blood sugar, post prandial blood sugar as well as peripheral neuropathy as measured on median and common peroneal nerves	Gupta et al. (1998)

Z, zinc; P, placebo; C, control; w., weeks; mo., months; ZS, zinc sulfate; ZG, zinc gluconate.

3.4. Arthritis

Serum zinc levels are significantly reduced in patients with rheumatoid arthritis (RA) (Niedermeier and Griggs, 1971; Zoli et al., 1998), potentially due to malabsorption of zinc by RA patients (Naveh et al., 1997). Moreover, a negative correlation between the serum level of zinc and the levels of the pro-inflammatory cytokines IL-1β and TNF-α was found (Zoli et al., 1998). An initial report from Simkin (1976) also described a beneficial effect of zinc supplementation on RA with positive effects of zinc on morning stiffness and joint swelling. Two later studies of similar design, administering the same dose of zinc sulfate, were unable to confirm this finding (Mattingly and Mowat, 1982; Rasker and Kardaun, 1982). Two further studies found reduced in vitro release of reactive oxygen species by monocytes (Herold et al., 1993) and activation of polymorphonuclear cell phagocytosis (Peretz et al., 1994) in patients with RA as a result of zinc supplementation, but the clinical consequences of these observations were not investigated and remain unclear. Taken together, zinc treatment does not seem beneficial in cases of RA (Table 5).

A similar activation of neutrophil chemotaxis, but without an effect on the disease, was found after zinc supplementation in patients with psoriatic arthritis (Leibovici et al., 1990). However, in this case another study exists that reports a favorable development of psoriatic arthritis with an improvement of several symptoms and a reduction in the intake of analgesics (Clemmensen et al., 1980).

3.5. Dermatological conditions

Delayed wound healing and skin lesions are among the symptoms of zinc deficiency, and the effect of zinc supplementation on several dermatological conditions has been investigated (Table 6). In contrast to its reported effects on psoriatic arthritis (Leibovici et al., 1990), zinc treatment seems to be without effect on psoriasis (Burrows et al., 1994).

Acne is a condition for the treatment of which zinc is frequently recommended either by topical or oral application. While some reports do not find an effect after oral zinc supplementation (Orris et al., 1978; Weismann et al., 1977), others report significant improvements (Goransson et al., 1978; Hillstrom et al., 1977; Verma et al., 1980). There were no obvious differences in study design or the amount or salt form of zinc so that no conclusive statement about the effectiveness of zinc for the treatment of acne can be made. In this respect it should be noted that overdosage has repeatedly been reported when oral zinc supplementation was applied for the treatment of acne. The resulting interference with copper uptake has led to severe anemia, leukopenia, and neutropenia at doses that exceeded 100 mg elemental zinc per day (Porea et al., 2000; Salzman et al., 2002).

Zinc administration has so far been found to be ineffective for the treatment of atopic eczema (Ewing et al., 1991),

Table 5
Zinc supplementation and arthritis

Disease or disorder	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Rheumatoid arthritis	ZS 660 mg (daily in 3 doses)	12 w.	9 (Z), 12 (P)	Positive changes regarding joint swelling, morning stiffness, walking time; no improvements regarding grip strength	Simkin (1976)
	ZS 660 mg (daily in 3 doses)	6 mo.	12 (Z), 9 (P)	No anti-rheumatic activity, only increase in alkaline phosphatase level	Mattingly and Mowat (1982)
	ZS 660 mg (daily in 3 doses)	8 w. to 24 mo.	22 (Z)	No improvements	Rasker and Kardaun (1982)
	Zn-Aspartate 260 mg (daily in 2 doses)	15 d.	10 (Z), 10 (C)	Reduced release of reactive oxygen species by monocytes after in vitro stimulation	Herold et al. (1993)
	ZG 45 mg (daily, elemental)	2 mo.	11 (Z), 11 (P)	Increased plasma zinc, phagocytosis of blood polymorphonuclear cells, and mean phagocytotic activity	Peretz et al. (1994)
Psoriatic arthritis	ZS 660 mg (daily in 3 doses)	6 w.	13 (Z), 26 (C)	Activation of neutrophil chemotaxis, but no effect on disease	Leibovici et al. (1990)
		6 w.	24 (Z, P)	Reduction in joint pains and daily intake of analgesics; reduction in serum immunoglobulins; increase in serum albumin and zinc levels	Clemmensen et al. (1980)
	ZS 660 mg (daily in 3 doses)	6 mo.	11 (Z)	Reduction in joint pains, morning stiffness and daily intake of analgesics; reduction in serum immunoglobulins; increase in serum albumin and zinc levels; increase in mobility; decrease in swelling of several joints; improvement of the overall condition	

Z, zinc; P, placebo; C, control; d., days; w., weeks; mo., months; ZS, zinc sulfate; ZG, zinc gluconate.

but there are single reports that it was successfully used to treat rosacea (Sharquie et al., 2006) and recurring oral ulcers (Merchant et al., 1977). Another form of ulcers, chronic leg ulcers, were seemingly unaffected by zinc in two studies (Floersheim and Lais, 1980; Greaves and Ive, 1972), but another report did find an effect, and especially a correlation between serum zinc levels and healing (Hallbook and Lanner, 1972). This indicates once again that the patients zinc status may be a crucial indicator for the effectiveness of any zinc supplementation.

There exists a report about the high effectiveness of zinc supplementation against viral warts (Al-Gurairi et al., 2002). However, several methodological weaknesses in this paper were pointed out by Gibbs (2003), questioning the validity of the results. Another striking effect is the complete resolution of the yellow nail syndrome after zinc supplementation, but this is based on a single case report without any controls (Arroyo and Cohen, 1993) and awaits verification in a larger, placebo controlled study.

3.6. Miscellaneous diseases

In addition to the cases discussed above, zinc has also been applied in an attempt to treat several other diseases, with some examples being mentioned here (Table 7). Two studies exist that investigate the effect of zinc supplementation in cancer patients during radiotherapy, showing that it can reduce side effects such as radiation induced oropharyngeal mucositis and taste abnormalities (Ertekin et al., 2004; Ripamonti et al., 1998). In this respect, it should be noted that there is also a potential relationship between zinc and the incidence of cancer, e.g., a correlation between nutritional zinc supplementation and the incidence of prostate cancer. While several reports state that a moderate intake of zinc can decrease the risk for prostate cancer, data from the Health Professionals Follow-up study suggest that an intake of more than 100 mg per day could promote the incidence of aggressive prostate cancers (Jarrard, 2005). The effectiveness of zinc against prostate cancer is still a matter of intense debate and subject of ongoing research (Costello et al., 2005).

For age-related macular degeneration (AMD), a few smaller studies exist, some of which found significant effects of zinc supplementation (Newsome et al., 1988), while others did not (Stur et al., 1996). In the age-related eye disease study, which monitored 3640 participants for over 5 years, a significant effect of zinc alone, as well as in combination with anti-oxidants (vitamins C and E, beta carotene), was found on the odds of developing advanced AMD. This strongly suggests that nutritional zinc supplementation, either alone or even more effective when taken with anti-oxidants, is advantageous for elderly patients at risk for macular degeneration (AREDS Research Group, 2001).

Zinc supplementation has also been examined in patients with several psychiatric illnesses. When zinc was supplemented in addition to standard anti-depressant therapy in 6 patients, reduced symptoms of unipolar depression

Table 6
Effect of zinc supplementation on dermatological conditions

Disease or disorder	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Chronic leg ulcers	ZS 660 mg (daily in 3 doses)	4 mo.	18 (Z), 18 (P)	No effect	Greaves and Ive (1972)
	ZS 660 mg (daily in 3 doses)	3 mo.	24 (Z), 23 (P)	Increased serum zinc; no effect on healing	Floersheim and Lais (1980)
	ZS 600 mg (daily in 3 doses)	4 mo.	13 (Z), 14 (P)	Improved healing-rate, correlated to serum zinc levels	Hallbook and Lanner (1972)
Recurring oral (aphthous) ulcers	ZS 220 to 660 mg (daily)		17 (Z), 15 (P)	Reduction in frequency of episodes	Merchant et al. (1977)
Psoriasis vulgaris	ZS 660 mg (daily in 3 doses)	6 w.	13 (Z), 26 (C)	Normalization of neutrophil random migration and directed chemotaxis	Leibovici et al. (1990)
Psoriasis	ZS 220 mg (daily)	3 mo.	13 (Z), 11 (P)	No effect	Burrows et al. (1994)
Yellow nail syndrome	ZS 300 mg (daily)	2 y.	1(Z)	Total resolution of yellow nails and lymphoedema	Arroyo and Cohen (1993)
Atopic eczema	ZS 185 mg (daily in 3 doses, = 67.5 mg elemental Zn)	2 mo.	22 (Z), 20 (P)	No effect	Ewing et al. (1991)
Rosacea	ZS 300 mg (daily in 3 doses)	3 mo.	19 (P, Z)	Decreased papules, pustules and erythema	Sharquie et al. (2006)
Acne vulgaris	ZS 600 mg (daily in 3 doses)	1 to 3 mo.	20 (Z), 19 (P)	Increase in serum zinc levels; no effect	Weismann et al. (1977)
	ZS 600 mg (daily in 3 doses)	3 mo.	29 (Z), 27 (P)	Decrease in number of papules, infiltrates and cysts; increase in serum vitamin A levels	Verma et al. (1980)
	ZS 600 mg (daily in 3 doses)	6 w.	27 (Z), 27 (P)	Reduction in the numbers of lesions and scores	Goransson et al. (1978)
	ZS 400 mg (daily in 2 doses)	3 mo.	48(Z), 43(P)	Reduced papules and pustules	Hillstrom et al. (1977)
Moderate acne	ZS 411 mg (daily in 3 doses)	2 mo.	12 (Z), 10 (P)	Increase in serum zinc levels; no effects	Orris et al. (1978)
Viral warts	ZS 10 mg/kg (daily in 3 doses), up to 600 mg per day	2 mo.	23 (Z), 20 (P), 20 (C)	Increased serum zinc; complete clearance of warts in most patients	Al-Gurairi et al. (2002)

Z, zinc; P, placebo; C, control; w., weeks; mo., months; y., years; ZS, zinc sulfate.

were observed (Nowak et al., 2003). It has also been reported that zinc sulfate treatment reduced symptoms in children with attention deficit hyperactivity disorder (Bilici et al., 2004). In addition, there are case studies that describe a beneficial effect of zinc treatment on patients with anorexia nervosa (Bryce-Smith and Simpson, 1984; Safai-Kutti and Kutti, 1986). Due to similarities of the symptoms of patients with zinc deficiency and anorexia nervosa, it has been suggested that zinc nutrition is involved in the etiology of this disorder (Bakan, 1979), but it should also be considered that the observed low serum zinc values may simply be a result of dietary inadequacy (Sandstead, 1986).

Many of these reports seem promising, however they usually only represent single studies, sometimes with low numbers of participants. Confirmation by investigation of the effects in larger study groups or identification of the underlying molecular mechanism would strengthen the supposed usefulness for zinc supplementation in these diseases.

4. Conclusion

Despite the high number of studies, the effectiveness of nutritional zinc supplementation can only be concluded for a limited number of diseases, while many others still require closer investigation. From the data it seems clear that zinc supplementation is recommendable for Acrodermatitis enteropathica, Wilson's disease, diarrhea, and leprosy. While zinc is effective for the causal treatment of some diseases, like AE, many other diseases lead to a decrease in zinc status, like increased urinary excretion in diabetes and sickle cell disease. In addition to the primary effects of the disease, this can cause secondary complications due to zinc deficiency, which can also be treated with zinc supplementation.

In many cases, contradicting results were described. Adequate and comparable supplementation protocols are required, since the daily doses of elemental zinc differ, sometimes by one order of magnitude. Also, there is considerable variation between the bioavailability of the different salt forms of zinc, making comparisons virtually impossible. Zinc bioavailability correlates with solubility in aqueous solution, with zinc sulfate and acetate being highly soluble and easily absorbed, while zinc carbonate and oxide are practically insoluble and have significantly lower bioavailability (Allen, 1998). Also, zinc absorption is negatively influenced by dietary factors like zinc-chelating phytates, and supported by high amounts of protein and single amino acids, in particular

Table 7
Effect of zinc supplementation on miscellaneous diseases

Disease	Zinc species and dosage	Period	Participants	Effect of zinc supplementation	Reference
Head and neck cancer	ZS 150 mg (daily in 3 doses, elemental)	10 to 13 w.	15 (Z), 15 (P)	Decrease in degree of mucositis, decelerated development of confluent mucositis and faster improvements	Ertekin et al. (2004)
	ZS 135 mg (daily in 3 doses, elemental)	11 w.	9 (Z), 9 (P)	Reduced worsening and quicker recovery of taste acuity	Ripamonti et al. (1998)
Unipolar depression	ZA 25 mg (daily, elemental)	3 mo.	6 (Z), 8(P)	Reduction of symptoms	Nowak et al. (2003)
Attention deficit hyperactivity disorder	ZS 150 mg (daily)	3 mo.	95 (Z), 98 (P)	Increased serum zinc and free fatty acid levels; reduced hyperactive, impulsive and impaired socialization symptoms	Bilici et al. (2004)
Anorexia nervosa	ZS 45 to 90 mg (daily, elemental)	4 to 16 mo.	5 (Z)	Increased weight gain	Safai-Kutti and Kutti (1986)
	ZS 45 to 150 mg (daily in 3 doses, elemental)	4 mo.	1 case report	Increased weight gain; improved taste; no depression	Bryce-Smith and Simpson (1984)
Macular degeneration	ZS 200 mg (daily in 2 doses)	1 to 2 y.	80 (Z), 71 (P)	Less visual loss; lesser decrease in mean visual acuity; eyes remained stable or showed less accumulation of visible drusen	Newsome et al. (1988)
	ZS 200 mg (daily)	24 mo.	56 (Z), 56 (P)	Increased serum zinc levels	Stur et al. (1996)
	zinc oxide 80 mg elemental zinc per day	average of 6.3 y.	903 (P), 904 (Z), 945 (A), 888 (Z + A)	Significantly decreased odds for developing AMD in groups treated with zinc alone and zinc + antioxidants	AREDS Research Group (2001)

Z, zinc; P, placebo; A, antioxidants; w., weeks; mo., months; y., years; ZA, zinc acetate; ZS, zinc sulfate.

histidine and methionine (Lonnerdal, 2000). Another aspect is the gastric pH, especially for the insoluble zinc salts, which can be partially converted into more soluble zinc chloride in the presence of gastric acid (Allen, 1998).

In certain cases, like Wilson's disease and AE, high doses of zinc are required to inhibit copper uptake, or to be taken up in sufficient quantity, respectively. In other cases, less zinc may actually be more effective. 30 years ago it was already recognized that a daily dose of 660 mg zinc sulfate may be too high for long term therapy (Porter et al., 1977), and detrimental effects on copper homeostasis and immune function could occur. Not only is the dosage important, but some effects of zinc are gradual and require time, as observed by the complete recovery of AE patients, which requires months. Since the half life of naïve T cells is three months, an effect of zinc supplementation on cellular immunity (e.g., for influencing vaccination efficacy) cannot be expected within a few days or weeks, and supplementation protocols must reflect this.

Finally, one of the main factors that have to be taken into consideration is the individual zinc status of the single patient. Zinc-deficient patients may respond completely different than zinc-sufficient ones, as seen when treating HIV/AIDS patients. Therefore, the zinc status has to be quantified by a reliable method, which is not available at the moment. Only then will it be possible to fully compare study results, identify diseases where zinc supplementation is recommendable, and develop supplementation protocols that maximize the health benefits of zinc supplementation.

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